Basic Research Grants Funded for 2014

Gene changes in a NSC-34 model of SMA. Sara Custer, PhD, at Indiana University, for $140,000 over two years.
Objective: Identifying gene changes in motor neurons with lowered SMN protein levels.
Research Strategy: Using a motor neuron cell model of SMA, we will determine the gene changes caused by low SMN and also examine the biological consequences of these changes on motor neuron biology and SMA pathology.
Significance: Determining the gene changes caused by low SMN protein levels in our cells should identify genes that are specifically important for motor neuron health. This will reveal new drug targets and thus new avenues for therapeutic intervention in SMA, beyond the SMN protein. These pathways could be critical to motor neuron health and may also be relevant to multiple motor neuron diseases.

Role of Sumoylation in SMN Function and SMA Pathology. Francesco Lotti, PhD, at Columbia University, for $140,000 over two years.
Objective: The identification of biological pathways that regulate SMN function is critical in revealing strategies for SMA therapy. However, little is known about the modifications to the SMN protein after it is made (called post translational modifications or PMTs) or how PMTs control SMN function. This project will investigate the hypothesis that PMTs of the SMN protein regulate SMN cellular functions.
Research Strategy: The team will investigate the requirement of PMTs in SMN protein function using well-established cell and mouse model systems of SMA. The goal is to determine whether PMTs are required for SMN protein to work properly.
Significance: Successful completion of this project will reveal the role of PTMs in the regulation of SMN biology. In addition, to the importance to unraveling novel regulatory networks that control fundamental cellular processes, importantly this project also has the potential to link PTMs of the SMN protein to SMA pathology.

mTOR and Protein Synthesis in SMA. Mustafa Sahin, MD, PhD, at Boston Children's Hospital, for $140,000 over two years.
Objective: The lab recently discovered that a pathway regulating protein synthesis in neurons is suppressed in SMA. This is called the mTOR pathway. This study current aims to understand this defect better in order to find and develop new therapeutic routes for the treatment of SMA.
Research Strategy: The lab will apply its expertise in studying neuronal protein synthesis and its regulation to how it is altered in SMA. A combination of cell culture and mouse experiments will be used.
Significance: SMA treatment may be most successful by combining treatment types - treatments that increase protein synthesis with those that increase SMN expression. Thus, the findings of this project may impact clinical trial design in the future.

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Development of An Innovative Outcome Measure to Define Disease Progression in SMA Type I for Use in the Home or Clinic. Linda Lowes, PhD, at Nationwide Children's Hospital, for $80,000 over one year.

Objective: This project will develop an outcome measure to help advance clinical trials in infants with SMA type I that can be used in the clinic or the patient's home.

Research Strategy: The project team will utilize Microsoft Kinect to record the infant's movement. Investigators will visit the homes to instruct 15 families on how to use our system, teaching them to record the baby's movement, once a month for 12 months.

Significance: It is difficult for fragile infants with SMA to participate in clinical trials. At home testing would ease the burden on the infant and family.

Development of A Clinically Relevant Outcome Measure for SMA Therapeutic Trials. Chad Heatwole, MD, at the University of Rochester, for $140,000 over two years.

Objective: The objective of this project is to develop, validate, and utilize a reliable, responsive, and patient-meaningful disease-specific patient reported outcome measure for SMA clinical trials. Patient-reported outcomes are typically required by the FDA in pivotal drug trials.

Research Strategy: This research will: (1) utilize a large cross-sectional study to identify those symptoms that are most important to SMA patients; (2) develop and validate a reliable, responsive, and patient-meaningful patient reported outcome measure for SMA patients; and (3) implement this instrument in SMA clinical trials and in clinic settings as a means to track patient-meaningful responses to treatment.

Significance: At the completion of our work the SMA research community will have a valid outcome measure to aid in therapeutic assessment that will encourage therapeutic development for adult SMA patients.

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