

Basic Research Grants Funded for 2010

George Mentis, Ph.D., Columbia University, "SMA as a progressive synaptic disease" for \$200,000.

Background Information: The effects of SMA disease on motor neurons within the central nervous system have been relatively unexplored with much of the emphasis thus far being paid on the neuromuscular junction. I aim to explore in substantial detail the time-course and pathologic characteristics of motor neurons in a mouse model of SMA.

Primary Research Question / Objective: The primary question sought in this study, is to determine the onset of motor neuron loss and the differential functional effects of the disease in different types of motor neurons. Particular emphasis will be paid into the relationship between pre motor and motor neurons.

Research Strategy: To determine the beginning of motor neuron loss and identify as well as characterize the pathological features of motor neurons by employing powerful combinatorial anatomical, physiological and immunohistochemical approaches.

Anticipated Results: I anticipate the results of this study to provide vital information on the onset of the disease and shed light into the patho-physiological mechanisms of motor neuron degeneration.

Importance / Significance: The potential importance of a systematic analysis of both cell-autonomous and non-autonomous effects of the SMA mutation is that it should allow both a better understanding of the disease mechanism and a more rational targeting of therapeutic strategies.

Brian Kaspar Ph.D., Nationwide Children's Hospital at Ohio State University, "Optimizing Titer and Window of Opportunity for Targeting Motor Neurons via an AAV9 Vector in Newborn Non-human Primates" for \$100,000.

Background Information: We have discovered that a gene therapy can rescue SMA mice for normal function and lifespan by delivering the SMN gene through the blood. Our virus targets the spinal cord motor neurons and muscle efficiently. We are trying to move this product forward for clinical trials.

Primary Research Question / Objective: Our research has primarily been performed in mice. We now need to test the principle of our therapy in larger species closer to humans. We plan to use non-human primates to determine the optimal way to move forward for treatments of humans.

Research Strategy: We have established a rigorous and ambitious research study with all of the components in place (virus, nonhuman primates and staff) to perform the studies. Briefly, we will test our therapeutic approach by injecting non-human primates with the virus into their blood stream and evaluating the number of motor neurons targeted.

Anticipated Results: We anticipate achieving our aims of effectively targeting motor neurons with our viral mediated approach. We will collect the data in a manner that will help guide a planned clinical trial to treat SMA.

Importance / Significance of the Project: Currently there are no effective treatments for SMA patients. We have found the remarkable ability to rescue a mouse model of this disease. We plan to collect important data on feasibility and safety to move to clinical trials.

Hans Keirstead, Ph.D., University of California Irvine, "Stem Cell Derived Motor Neuron Replacement in Established Models of SMA" for \$105,000.

Background Information: Human embryonic stem cells can differentiate into all cell types, including nerve cells. Therefore, they can be used for multiple therapeutic applications, including SMA.

Primary Research Question / Objective: These experiments test the ability of transplanted human embryonic stem cell-derived motor neuron progenitor cells (hESC-MNPs) to develop a therapy for spinal muscular atrophy (SMA) disease.

Research Strategy: We will use an established SMA mouse model for our studies with a goal of ameliorating tissue loss and functional decline by hESC-MNP transplantation. We will hESC-MNPs into a SMA murine model, and study their engraftment, differentiation and repair potential of diseased tissue.

Anticipated Results: We anticipate determining the survival, differentiation, and benefit of our transplanted cell population into SMA mouse models.

Importance / Significance of the Project: Extension of this transplantation paradigm to multiple animal models of motor neuron loss will illustrate robustness of the approach, increase the likelihood of positive outcomes when applied to humans, and increase the likelihood of FDA approval for the approach.