Basic Research Grants Funded for 2007

Yukio Sasaki, Ph.D., Emory University, Dysfunction of Axon Guidance in Spinal Muscular Atrophy for $108,000.
Recent studies suggest that SMA could be caused by developmental defects in neuromuscular interactions between motor neurons and muscle. Therefore, it is important to investigate the role of the survival motor neuron (SMN) protein, the causal gene product of SMA, in several aspects of this process, including initial growth of the motor nerves to the muscle (called axon outgrowth and guidance) and in establishment of the subsequent interactions between the motor nerve and muscle in forming a functional neuromuscular synapse. This research project focuses on how SMN protein works at the distal tips of axons in response to axon guidance cues during axon outgrowth and will increase our understanding of the mechanisms of disease onset

Douglas A. Kerr M.D. / Ph.D., Johns Hopkins University School of Medicine, Transplantation of Human Embryonic Stem Cell-Derived Motor Neurons in Large Mammals $172,800.
In this project, we will transplant human embryonic stem cell derived motor neurons into a dog model of paralysis to extend our recent rat studies showing the formation of functional motor units using mouse embryonic stem cells and a sophisticated cocktail of factors. If we are to consider this as a possible human therapy for paralysis, we need to establish both the safety and efficacy of human ES cells in a large animal model of lower motor neuron injury. Ultimately, we hope to use these studies as a springboard to clinical trials in humans with paralysis from a variety of causes including SMA, traumatic spinal cord injury, and ALS.

Charlotte J. Sumner, M.D., Johns Hopkins University, Targeting the muscle and the neuromuscular junction for SMA therapeutics for $172,800.
SMA is caused by deficiency of survival motor neuron (SMN) protein, but it remains unclear whether primary abnormalities in the muscle play an important role in the disease or whether motor neurons will degenerate regardless of the health of the muscle. In order to evaluate the role of muscle in this disease, we will perform a more comprehensive evaluation of the evolution of pathological changes in SMA and deliver therapy specifically to the muscle to evaluate whether this will improve the health of the motor nerve. These studies should provide important insights into whether therapy delivered to muscle alone could be of benefit in SMA patients.

Butchbach, Matthew E. R., Ph.D., Ohio State University, Mechanisms of Butyrate Neuroprotection in a Mouse Model of Spinal Muscular Atrophy for $110,000.
Butyrates and butyrate-like compounds, such as phenylbutyrate, have been suggested to be potential drug treatments for SMA. These compounds improve survival of a mouse model of SMA but do not increase SMN levels in the spinal cord of these mice. In this grant, we will examine potential mechanisms by which these drugs exert their protective effects in the spinal cord of SMA mice. This information will provide greater understanding about the effectiveness of these drugs in treating SMA and will lead to the design of newer drugs with better protective properties. The proposal will also generate a novel model to monitor SMN2 induction and splicing which can be used to identify new therapies for SMA.

Hans Keirstead, Ph.D., University of California, Irvine, Functional Characterization of High Purity Motoneuron Cultures Derived from Human Embryonic Stem Cells $200,000.
Human embryonic stem cells (hESCs) can form any cell in the body, and therefore have great potential to treat human diseases that might benefit from replacement of lost cells. One strategy for cell replacement is to direct hESCs to become particular cell types prior to transplanting them into the body. Motor neurons are the desired cells for cellular replacement strategies to treat SMA. Our laboratory has succeeded in generating high purity and functional human motor neurons from hESCs with the support of past FSMA funding. Our new grant focuses on the functional characterization of this cell population, the genetic modification of these cells to allow for extension of axonal processes, and the development of a means to specifically draw these processes to muscles in the limb. All work will be conducted in an FDA-compliant manner, under the supervision of a Regulatory Quality Assurance officer. At the conclusion of these studies, we will have defined a clinically relevant cell population for therapeutic application.

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Sibylle Jablonka, Ph.D., University of Wuerzburg, Analysis of cAMP Effects in a Cell Culture Model of SMA with FSMA funding of $47,325.
This project will use motor neuron screening assays developed in the lab to help identify substances, initially cyclic AMP analogues ,able to compensate for the morphological and functional defects of SMN-deficient motor neurons.
Co-funded with Initiative "Forschung und Therapie für SMA"

Brunhilde Wirth, Ph.D, Eric Hahnen, Ph.D, MBA, University of Cologne, Characterization of new drugs for SMA therapy with FSMA funding of $11,734.
This project will assess the potential efficacy of a highly potent second-generation histone deacetylases inhibitor (SAHA) in SMA animal models.
Co-funded with Initiative "Forschung und Therapie für SMA"

Alex E. MacKenzie, M.D., Ph.D., Children's Hospital of Eastern Ontario, SMA cellular assay optimization and SMN2 inducing small molecule assessment for $80,049.
This project will assess the potential efficacy of a new drug candidate found in the lab in a panel of SMA cellular assays.

Jean-Yves Masson, Ph.D., Laval University, DNA damage signaling and repair in Spinal Muscular Atrophy for $80,553.
This proposal aims to understand how DNA damage can affect SMA pathology because proteins involved in DNA repair are sometimes physically linked to the SMN protein and neurons in general suffer naturally from a high level of DNA damage.