Basic Research Grants Funded for 2009

Development of Therapeutic Strategies Based on Stem Cell Transplantation for SMA. Giacomo Comi, M.D., University of Milan with Funding from FSMA of $80,000.

Background: The objective of this project is to contribute to the development of a stem cell therapy for Spinal Muscular Atrophy, which is caused by mutations in the Survival Motor Neuron gene.
Primary Research Question: We will investigate the therapeutic potential of transplanted Neural Stem Cells (NSCs).
Research Plan: We will evaluate whether NSC engraftment into the spinal cord modifies disease progression in a transgenic mouse model of SMA. We will investigate strategies that can be combined with cell transplantation to promote motor axon growth toward muscles. Furthermore, we will evaluate the molecular mechanisms responsible for the therapeutic effect of NSCs.
Anticipated Results: This study is anticipated to contribute to, and assess the feasibility of, the development of a cell-based therapy for SMA.
Co-funded with SMA Europe.

Mechanism of Drug Action in SMN2 Up-regulation. Megerditch Kiledjian, Ph.D., Rutgers, The State University of New Jersey for $160,000.

Background: There are no current effective treatments for SMA although increased expression of the SMN2 gene is known to reduce the severity of SMA. Therefore, small molecule drugs that increase SMN2 expression should be beneficial for SMA patients. The recent optimization of a potential drug candidate in the Quinazoline family that can increase SMN2 expression holds great promise, as does the recent identification of the enzyme DcpS as the cellular target of the Quinazoline compounds.
Primary Research Question: Our objective is to determine the exact way that inhibiting DcpS leads to increases in SMN2 expression.
Research Plan: We will test to see if the Quinazoline compounds lead to increased amounts of SMN protein by: regulating promoter activity (driving the gene engine); increasing SMN2 mRNA stability (maintaining the presence of the protein template for longer periods); or by enhancing protein translation in cells (directly increasing the amount of protein being made).
Anticipated Results: Knowing how the Quinazolines work will provide further insights and may lead to greater optimization of the efficacy of this drug class. This knowledge may lead us to more effective second generation therapeutic interventions that target DcpS in SMA patients

Development of a Model to Monitor SMN Expression In Living Mice: Applicability to Drug Discovery. Matthew Butchbach, Ph.D., The Ohio State University for $140,000.

Background: Butyrates and butyrate-like compounds, such as phenylbutyrate, have been suggested to be potential drug compounds for treating SMA patients. These compounds improve survival of a mouse model of SMA but do not increase SMN in the spinal cord. It is possible that they may induce SMN expression in vivo at levels which are below the detection limit of currently available assays.
Primary Research Question: In this grant, we will try to develop a more sensitive tool for testing SMN enhancing drugs.
Research Plan: We will generate a novel mouse model to monitor SMN2 induction and splicing in the spinal cord of living SMA mice.
Anticipated Results: This information will be extremely useful in understanding the effectiveness of SMN-inducing drugs in treating SMA and will lead to the design of newer drugs with better protective properties.

A Molecular Understanding of Why Alterations of SMN Give Rise to SMA. James Allen, Ph.D., Arizona State University for $153,000.

Background: Spinal Muscular Atrophy is a neurodegenerative disorder due to the loss of motor neurons with three clinical forms that arise from changes in a gene identified as SMN1. The gene encodes the survival of motor neurons protein, or SMN protein.
Primary Research Question: Why the observed changes in this gene give rise to the observed clinical characteristics remains unknown. A critical reason for our limited understanding of why SMA arises from these changes is the lack of understanding at the molecular level of how SMN functions in cells.
Research Plan: To overcome this limitation, we propose to determine the three-dimensional structure of SMN, including both the form found in healthy patients as well as the predominant form found in SMA

patients.
Anticipated Results: Once these studies are completed, we anticipate that the resulting molecular structures will lead to an improved understanding of SMN and insight into novel protein-based therapies for the treatment of SMA.

Modifiers of SMN Using Transgenic Drosophila as a Model System. Anindya Sen, Ph,D., Harvard Medical School for $126,510.

Background: Spinal Muscular Atrophy is an autosomal recessive neurodegenerative disease that is the leading cause of genetically-linked infant mortality. The observation of fundamental importance with respect to developing treatments for SMA is that the severity of the disease relies critically on the amount of Survival Motor Neuron (SMN) protein present in the affected individual.
Primary Research Question: Are there genes which can regulate the amount of SMN protein made?
Research Plan: We will use a model genetic system that easily allows identification of genes that interact with and regulate SMN activity.
Anticipated Results: We will identify different factors that regulate SMN with an aim to find new therapeutic strategies for SMA by identifying novel drug targets.

Quantitative Proteomic Study of the Motor Neuron SMN Complex. Jocelyn Cote, Ph.D., University of Ottawa for $173,400.

Background: Loss of a protein named SMN (for "Survival of Motor Neurons") causes SMA. SMA results in the loss of function of spinal cord motor neurons, which are the cells responsible for voluntary movements. Research in recent years has identified an essential function for the SMN protein, which should be equally important for all cells in the body.
Primary Research Question: How does the loss of SMN result in a motor neuron specific disease?
Research Plan: Our current research strategy will use novel, state-of-the-art approaches to identify the proteins that interact specifically with SMN in motor neurons.
Anticipated Results: Identification of new interactions with the SMN protein may provide crucial insights into the function of SMN important for motor neurons and to the etiology of SMA. Identifying SMN interactions will also help identify new targets for the development of novel approaches for therapeutic intervention.
Funded by FSMA Canada.

Characterization of mRNAs within SMN-associated RNA Granules in Motor Neurons. Ching Wang, M.D., Ph.D., Stanford University Medical Center for $200,000.

Background: Defects in the communications between the nuclei and the distal nerve terminals is likely one of the causes of motor neuron degeneration in SMA. The SMN protein is crucial for the assembly and trafficking of some messenger RNA (mRNA) within RNA granules.
Primary Research Question: These RNA granules likely transport specific mRNAs to the neuronal terminals to serve specific functions within motor neurons such as neurite outgrowth, pathfinding, and maintaining the integrity of neuromuscular junctions. We want to determine if this is true.
Research Plan: In this research project we plan to isolate and characterize the components of the SMN-associated mRNA within the RNA granules. We will first isolate the RNA granules in the nerve terminals and then isolate the mRNA species within these RNA granules. To confirm that SMN interacts with these mRNAs we will use a novel technique to reduce the intracellular level of SMN and to observe its effects on the distribution of these SMN-associated mRNAs and on neuronal growth and morphology.
Anticipated Results: We will have a greater understanding of the exact role of SMN protein in motor neuron axons.