Basic Research Grants Funded for 2008

Charles Y. Cho, Ph.D., Genomics Institute of the Novartis Research Foundation (GNF), Functional Genomic Screens for Novel Regulators of SMN2 Expression and Splicing for $153,750.

In SMA the discovery of new drugs often begins with large-scale high throughput screens to find compounds that increased SMN levels. An important complementary approach to SMA drug discovery would be to identify new protein targets than regulate SMN levels. To identify new protein targets for SMA drugs, we have begun functional genomic screens for genes whose inhibition increases SMN levels (in collaboration with Elliot Androphy's lab). We are using a technique, called RNAi, that can inactive nearly all of the predicted 25,000 genes in the human genome. Genes found to regulate SMN expression, splicing, or stability will be further studied in SMA motor neuron models and ultimately help to find new protein targets for drugs.

Elliot J. Androphy, M.D. University of Massachusetts Medical School, Identification of factors that control SMN protein levels for $152,073.

Current approaches to identify a medical treatment for SMA involve screening for chemicals that increase levels of the survival motor neuron (SMN) protein. Even after successful screens, we do not know how these candidate drugs act. Our project uses RNAi, a powerful genetic approach, to specifically reduce the amount of virtually every protein in the cell. In collaboration with the Genomics Institute of the Novartis Research Foundation, we will use an RNAi gene library to broadly query all cellular proteins that regulate SMN expression. The results from this project will 1) identify factors that control SMN expression, 2) identify candidate targets for therapeutic intervention, and 3) provide a method to assess how compounds currently in development work.

Christine DiDonato, Ph.D., Northwestern University, New Mouse Models for Pre-clinical Compound Testing for $160,000.

Mouse models of SMA are used to test the potential of therapeutic agents. Our proposal focuses on developing two new mouse models of SMA that present with symptoms at the 3-4 week age. These models are important because we currently lack a mouse model of SMA that has symptom onset at this intermediate age. One model contains SMN2, to allow testing of compounds that specifically act upon this target, while the other model will help identify compounds that bypass SMN function when Smn levels are low.

Megerditch Kiledjian, Ph. D., Rutgers, The State University of New Jersey, Mechanism of Action for a Drug Mediated up Regulation of SMN2 for $80,000.

Unfortunately there are no effective treatments for Spinal Muscular Atrophy, although increased expression of the SMN2 gene can reduce the severity of SMA. Therefore therapeutic approaches to increase SMN2 expression would be beneficial in SMA patients. The recent identification by an FSMA-deCODE Genetics collaboration of a potential drug in the quinazoline compound family that can increase SMN2 expression derived holds great promise. Our objective is to decipher the molecular mechanism of drug action in order to understand how it increases SMN2 expression and gain insights into further optimization of its efficacy for therapeutic intervention in SMA patients, which could lead to new, improved drugs.

Ryan Burnett / Joel Gottesfeld, Ph.D, The Scripps Research Institute, Novel Histone Deacetylase Inhibitors as Therapeutics for Spinal Muscular Atrophy for $54,639.

This proposal is aimed at the development of therapeutic candidates to treat the inherited neurodegenerative disease Spinal Muscular Atrophy (SMA). SMA is a genetic disease that results in under-expression of a key protein, SMN, in neurons. Classes of small molecules known as histone deacetylase inhibitors (HDACi) have been shown to increase the amount of SMN present in established cells derived from SMA patients as well as in mouse models of the disease. Our lab has developed a new generation of HDAC inhibitors that retain the ability to increase SMN expression in SMA cell lines while being much less toxic.

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Kum- Loong Boon, Ph.D, The Ohio State University, Analysis of motoneuron specific expression of SMN in promoting normal motor axon outgrowth and β-actin mRNA transport for $64,000.

To further understand the cause of SMA and to design optimal drug therapeutics, we need to understand how SMN functions in motoneurons. Decreasing SMN during early development causes the motor axons to grow out improperly in zebra fish. In this proposal, I will test whether increased SMN protein expressed in only motor neurons can rescue this defect. If it can, I will also test different mutant forms of SMN in motor neurons for their ability to rescue. This experiment will help find the region of SMN protein responsible for normal motor axon outgrowth. In addition, I will study the role of SMN in transporting axonal factors required for axonal growth (such as β-actin mRNA) into the motor axons. Results of these experiments will further our understanding of how decreases in SMN in motor neurons cause SMA.

Brunhilde Wirth, Ph.D, Eric Hahnen, Ph.D, MBA, University of Cologne, Analysis of natural and drug-induced epigenetic changes in SMN2 for $160,000.

SMA is caused by absence of the SMN1 gene, and the SMN2 copy number strongly influences the severity of the disease. Nevertheless, identical SMN2 copy number can correlate with all three types of SMA, which raises the possibility that non-inherited changes in DNA called epigenetic can influence the SMN2 expression level. We will search and characterize these epigenetic differences in the SMN genes. Furthermore various drugs, such as histone deacetylase inhibitors, act through epigenetic modifications of SMN. This will be analyzed at a comprehensive level. Additionally because various patients react very differently to HDAC inhibitors we will search for pathways responsible for variable responses, including epigenetic ones. Finally by treating SMA mice with various drugs we will analyze in vivo the epigenetic changes that occur in the target tissues (spinal cord and muscles).

Christina, B. Brahe, PhD ., Istituto di Genetica Medica, Rome, ITALY; Louise R. Simard, Ph.D., University of Manitoba, Winnipeg, Manitoba CANADA, SMN Biomarker: Towards a validated international Standard Operating Procedure with FSMA of $50,000.

The combined efforts of active clinical research worldwide have facilitated the development of reliable and reproducible clinical tools, including assays to monitor potential biomarkers to monitor drug response. This project aims to develop an international standard operating procedure to determine whether SMN RNA levels are altered in SMA patients participating in clinical drug trials. In addition, these procedures will be very useful for testing the effects of drugs in SMA cell lines and SMA mice.
Co-funded by Famiglie SMA in Italy

Jean-Yves Masson, Ph.D., Laval University, DNA damage signaling and repair in Spinal Muscular Atrophy and neuronal cells for $84,000.

Spinal Muscular Atrophy affects the motor neurons which influence the voluntary muscles that are used for activities such as walking and swallowing. However, although the SMN gene has been identified as responsible for this disease, how mutations in SMN lead to SMA is still unclear. We found that proteins involved in DNA repair are directly linked to SMN. This proposal aim to understand how DNA damage can affect SMN and consequently SMA since neurons suffer naturally from a high level of DNA damage.