Basic Research Grants Funded for 2005

Dr. Louise Simard, Center of Research Hospital Sainte-Justine , "Study SMN function and SMN gene expression during neuronal differentiation using a site-specific stable integration P19 cell system" for $71,055.
Two important questions in SMA research relate to SMN's function in motor neurons as well as spatial and temporal regulation of SMN expression. Answers to both questions impact on the development of effective therapies. In light of emerging data suggesting that SMA is a developmental disorder, it is expected that a combination of different therapies may be necessary to treat all forms of SMA. The proposed work addresses these two questions and represent important pieces of the puzzle that is SMA and how best to treat this deadly disease.

Dr. Christian Lorson, University of Missouri, "Development of SMN rAAV Vectors" for $124,072.
One of the underlying defects in SMA is that the RNA generated from the SMN2 gene is truncated and, in turn, generates a truncated and defective protein. This proposal is designed to identify molecules that are delivered via a viral intermediate that can stimulate full-length SMN expression from the SMN2 gene.

Dr. Matthew Butchbach, Ohio State University, "Protective Effects of Butyrate Analogues & Prodrugs on a Mouse Model of SMA" for $104,407.
Butyrates and butyrate-like compounds such as phenylbutyrate have been suggested to be potential drug compounds for treating SMA patients. In this grant, the effectiveness of different butyrate-like compounds in delaying motor neuron loss in a mouse model for SMA will be tested. Potential mechanisms by which these drugs exert their protective effects will be examined. This information will be extremely useful in understanding the effectives of these drugs in treating SMA and will lead to the design of newer drugs with better protective properties.

Dr. Ravindra Singh, University of Massachusetts , "Characterization of a novel intronic element as the potential therapeutic target of SMA" for $194,314.
SMN1 and SMN2 represent the two nearly identical copies of the survival of motor neuron gene in humans. The most frequent cause of SMA is the loss of SMN1 accompanied by the inability of SMN2 to compensate due to an inhibitory mutation at position 6 in exon 7 (C6U transition in transcript) that causes exon 7 exclusion. We have recently identified a novel inhibitory element within intron 7 of SMN2. Upon blocking this element with antisense oligos, exon 7 inclusion was found to be restored in SMN2. In this grant we will characterize this element in detail. Because SMN2 is present in most SMA patients, the outcome will have direct therapeutic implications.

Dr. Honglai Zhang, Albert Einstein College of Medicine , "Role of SMN complex in regulation of GAP-43 mRNP localization to Axon of Motor Neuron" for $150,000.
SMA is is caused by mutation of a gene which encodes SMN protein whose normal function in neuron is not understood. In this proposal I will test the hypothesis that one important function for SMN is to participate in the GAP-43 mRNA localization, which may be essential for neurite outgrowth and structure of motor neuron.

Dr. Hans Keirstead, University of California, Irvine, "Derivation and functional characterization of high purity motoneuron cultures from human embryonic stem cells" for $231,063.
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. Sites of disease strongly influence maturation of transplanted cells, and so one strategy to circumvent this is to direct the human embryonic cells to become particular cell types prior to transplanting them into disease sites. Directing the fate of hESCs to clinically useful cell populations is the greatest challenge facing hESC research. For the first time, our laboratory has demonstrated that hESCs can be directed into a high purity brain/spinal cord population. Moreover, due to our possession of and experience in growing hESCs, we feel that we are in a unique position to derive high purity motoneuron cultures from hESCs and test their functional

characteristics. In this application, we are proposing multiple culture manipulations in order to generate high purity motor neuron cultures from hESCs. At the conclusion of these studies, we will have developed a method for the generation of high purity functional human motor neurons from hESCs that will provide a biological tool for further research and therapeutic development.

Dr. Vicki McGovern, Ohio State University, "Does SMA result from defects in motor neuron development in the mouse" for $104,407.
The aim of this proposal is to determine when and where SMN protein is required in development. We believe that in SMA mice motor neuron connections are not formed properly due to low levels of SMN protein. By increasing SMN levels in the embryo during motor neuron development we hope to correct the axonal defects and thereby eliminate SMA in the mouse. We will also examine how motor neurons in SMA mice function. A better understanding of how motor neurons are affected in SMA will help us develop more effective treatments for the disease.

Dr. Natalia Singh, University of Massachusetts, "Characterization of protein(s) that contributes to SMN exon 7 skipping through a novel inhibitory element" for $186,824.
SMN2 is a disease-modifying gene for SMA. Thus, means to increase the amount of full-length SMN2 transcript by promoting exon 7 inclusion during splicing, represent one of the potential SMA therapies. Recently we identified a novel inhibitory element located at the 3'end of exon 7 and unique to humans. We call it the 3'-Cluster. The proposed study will identify and characterize the protein that specifically binds to the 3'-Cluster causing skipping of SMN2 exon 7. The study will advance our understanding of the mechanism of exon 7 splicing and present a new target for SMA therapy.

Dr. Brunhilde Wirth, University of Cologne, "Characterization of new drugs for SMA therapy" for $144,000.
Spinal muscular atrophy (SMA) is caused by homozygous absence of the survival motor neuron gene 1 (SMN1). The SMN2 gene, a nearly identical copy of SMN1, has shown to be a promising target for SMA therapy since both genes are ubiquitously expressed and encode identical proteins. Transcriptional SMN2 activation or modulation of its splicing pattern to increased FL-SMN levels is likely to slow down disease progression and therefore a crucial challenge of SMA research. Besides valproic acid, we identified novel candidate drugs able to significantly increase SMN transcript and protein levels in several experimental paradigms including fibroblasts derived from SMA patients as well as rat and human hippocampal brain slices. In vitro and in vivo validation of these compounds are main aims of the outlined project.