Basic Research Grants Funded for 2017

Dr. Arthur Burghes at The Ohio State University for $140,000 for two years to study, "Identification of SMA modifiers and deletion/duplication junctions in the SMA region".
The objective of the project is twofold. First, to identify the genes in humans that cause a milder or no phenotype in siblings despite having the loss of SMN1 and the same copy number of SMN2. The second aim is to identify deletion and duplication junctions to improve carrier screening. The strategy is to determine all variants that differ between discordant siblings and concordant siblings. These are then compared and all variants that differ in concordants will be eliminated from the discordant file. The remaining variants can mark the modifying gene in SMA. Junctions will be identified in both carriers and patients using novel genome sequencing techniques.

Dr. Jocelyn Cote at the Ottawa Hospital Research Institute for $140,000 for two years to study, "Investigating the Mechanism by Which SMN Regulates Translation: Identification of Novel Therapeutic Targets". (Families of SMA Canada)
We have been the first to describe a new function for SMN in the regulation of protein synthesis and we propose to perform experiments to gain a better understanding of how SMN goes about doing this new function, and also determine what might be the consequences of losing this function in cells from SMA patients. We propose to use a series of biochemical, molecular and cellular approaches that will allow us to (i) *determine the composition of the regulatory complex(es) in which SMN functions to regulate translation in motoneurons*;(ii) *identify the subset of mRNAs that are regulated by SMN at the translational level and determine whether these are misregulated in SMA*; and (iii) *explore the therapeutic potential of increasing the levels and/or activity of regulators of SMN function in SMA cells in order to compensate for loss of SMN*. For those experiments we are using cell culture and mouse models of SMA, but also validating our results using SMA patient cells to insure that our findings are relevant to the human condition.

Drs. Oliver Gruss and Utz Fischer at Rheinische Friedrich-Wilhelms-Universitat Bonn and Julius-Maximilians-Universitat Wurzburg in Germany for $140,000 for two years to study "Regulatory cues modulating the activity of SMN in human cells".
Our project aims at understanding the molecular details of the mode of action of SMN mutations which are a major cause for SMA. We will expand the analysis of SMN on cellular signaling networks to try to understand the integration of SMN activity into the overall biosynthetic activity of cells. We will use biochemical and cell biological assays to perform experiments on function and regulation of the SMN complex. Metabolic labeling of RNA and proteins as well as high-resolution immunofluorescence microscopy will be paralleled by inhibition and knockdown experiments.

Dr. Christine DiDonato at the Ann & Robert H. Lurie Children's Hospital of Chicago for $140,000 for two years to study "Skeletal muscle activators as potential modulators of muscular weakness in SMA".
We aim to study the long term effect on muscle and nerve using a therapy that enhances muscle force production through altering calcium sensitivity. Hence muscle contraction is enhanced when the nerve isn't working optimally. We will use vascular delivery of an AAV9 containing Troponin C variant that

enhances sensitivity to calcium to improve muscle contraction. This AAV9 system can be compared to the Cytokinetics drug compound as it also slows the rate of calcium release from the troponin complex and sensitizes the sarcomere to calcium. Importantly it is active in both fast and slow skeletal muscle fibers.

Dr. Remy Bordonne at CNRS-Centre National de Recherche Scientifique in France for $30,000 for one year to study "Identification of the protective mechanism of a SMN modifier gene using S. pombe as a model organism".
Our goal is to understand how a SMN-modifier gene rescues defects in actin dynamics observed in cells carrying a SMN mutated allele. The yeast S. pombe will be used as a model organism to analyze the effect of a protective SMN-modifier gene on the formation and function of actin networks

Dr. Yong-Chao Ma at the Ann & Robert H. Lurie Children's Hospital of Chicago for $75,000 for one year to study, "Regulation of Motor Neuron Defects by Cdk5 Signaling in SMA".
We have found that the activity of Cdk5 is significantly increased in motor neurons affected by SMA. In this project we hope to elucidate the underlying mechanism and to test whether inhibiting hyperactive Cdk5 activity can be used as a therapeutic strategy for SMA. We plan to use a combination of genetic, cell biological and biochemical approaches to investigate how increased Cdk5 activity leads to motor neuron degeneration. We will also test mitigating aberrant Cdk5 activation as a therapeutic strategy for rescuing motor neuron defects in SMA mouse models.

Dr. Jean Giacomotto at University of Queensland in Brisbane, Australia for $75,000 for one year to study, "Zebrafish models of Spinal Muscular Atrophy optimized for chemical genetics and drug discovery. From proof-of-principle to new insights and treatments".
We have recently developed an innovative zebrafish model of SMA. We will optimize this model to make it compatible with drug discovery and run a pilot screening study using a drug-enriched chemical library. We will use a state-of-the-art genetic system to create healthy SMA carrier fish, giving us the opportunity to generate large number of animals affected by the disease. A pool of pharmacologically active compounds will then be tested to find beneficial drugs against SMA.

Dr. Christian Lorson at the University of Missouri for $75,000 for one year to study, "Examining the role of astrocytes and the influence upon lower motor neuron susceptibility in SMA".
SMA is caused by mutations in a gene that expresses in every cell in the body, however, not all cell types, or even neurons, become "sick" when SMN levels are very low. The goal of this project is to understand why some neurons get sick while other neurons do not get sick. By examining the differences between astrocytes from different regions within the central nervous system, we hope to identify new factors that help "protect" some neurons while understanding why other neurons are not "protected."

Dr. Steven Kolb at The Ohio State University for $75,000 for one year to study, "Arrested Development or Neurodegeneration? An approach to understand developmental motor neuron pathology in SMA.".
We will create a large animal model of newborn infants with SMA. We will use this model to understand the pathological findings that are seen in motor neurons in infants with SMA. We will create a newborn SMA model by delivery of a virus that will knockdown the expression of SMN in fetal piglets *in utero* by ultrasound-guided cannulation of the umbilical vein. Once these piglets are born, we will systematically study the motor neurons and determine if the pathological findings are the same as in infants with SMA.

Dr. Alberto Kornblihtt at the Universidad de Buenos Aires in Argentina for $140,000 for two years to study, “Epigenetics in SMN2 E7 Alternative Splicing”.

Whereas genetics involves inheritable changes in the DNA sequence of an individual, epigenetics refers to changes that, without altering the DNA sequence, affect how much active protein is produced from each gene. We plan to use epigenetics strategies to
enhance the production of an active SMN protein from the SMN2 gene, necessary to fully make up for the faulty copies of the SMN1 gene present in patients with spinal muscular atrophy (SMA). We wish to identify drugs that, by affecting epigenetic features of the SMN2 gene, ensure that the SMN2-produced protein contains all the key building blocks needed for its correct functioning.