Cure SMA Awards 10 New Grants in Basic and Clinical Care Research

In this issue of Compass, we are proud to announce nearly $1 million in new research funding: $890,000 for basic research and $100,000 for clinical care research.

Basic Research Grants
Basic research is the first step in our comprehensive research model. We fund basic research to investigate the biology and cause of SMA, in order to identify the most effective strategies for drug discovery. We also use this funding to develop tools that facilitate SMA research.

Without basic research, the SMA drug pipeline would not continue to grow and diversify. We need both a breadth and a depth of options in our quest for an effective SMA therapy. Basic research is our investment in future drug development for SMA.

Broadening the Drug Pipeline and Developing Combination Therapies
Because of a genetic mutation in the survival motor neuron gene 1 (SMN1), individuals with SMA don’t produce survival motor neuron protein (SMN protein) at high enough levels, causing motor neurons to shrink and eventually die. This results in muscle weakness that impacts daily activities as well as the basic functions of life, such as breathing and eating.

Prior basic research projects uncovered the SMN1 gene and the link to SMN protein. However, there are many unanswered questions about the SMN protein. By funding research into these unanswered questions, we can develop new treatment strategies that will add to the breadth of the SMA drug pipeline, as well as develop combination therapies. A broad pipeline is particularly important as we seek to develop treatments for all ages, types, and stages of SMA.

These questions include:

- What other cells, tissues, and processes are affected by the loss of SMN protein?
- How, where, and when do we need to restore SMN protein in order to benefit those with SMA?
- How can we use this knowledge to develop new combination treatments for SMA, or to evaluate if treatments are effective?

New Grants to Broaden the Drug Pipeline
Our grant to Dr. Christine Beattie will fund research on how the loss of SMN protein affects the development of motor neurons, as well as other proteins and RNAs that might interact with SMN protein during the development of motor neurons.

Our grant to Dr. Arthur Burghes will provide resources to look at the cellular function of SMN protein, hoping to learn more about what SMN does to a cell to help it function.

Dr. Jocelyn Cote has discovered that SMN plays a critical role in the regulation of protein production, called “translation.” Our grant will help further investigate the impact this has on the body.
Through a new and unique mouse model, Dr. Christine DiDonato has discovered that increasing SMN in the central nervous system does not completely alleviate the symptoms of SMA, suggesting there are also defects in the skeletal muscles. Our grant will fund additional work with this mouse model to better understand where and how SMA therapies should be targeted.

Our grant to Dr. Rashmi Kothary will support investigation into how SMN protein affects muscle satellite cells, which help the body respond to muscle damage.

New Grants to Deepen the Drug Pipeline
Our grant to Dr. Antoine Cléry will fund a project investigating different molecules that might affect the splicing of SMN2.

Axons are long projections that grow out of motor neurons, and send information to other neurons or muscles. Our grant to Dr. Charlotte Sumner will fund research into how and when motor axons are affected by the loss of SMN protein, and when in development axons can be fixed by oligonucleotides, which are small snippets of synthetic genetic material that bind to ribonucleic acid (RNA) to correct the splicing of SMN2.

Dr. Megerditch Kiledjian has identified a previously unknown protein variant that could lead to increases in SMN2 mRNA and SMN protein. His grant will fund additional work to understand this protein variant.

Next Steps
After basic research, the next phase in our research model is drug discovery. Drug discovery takes what we have learned through basic research about the causes and biology of SMA, and converts that knowledge into new drug candidates that can be tested in clinical trials. In the next few months, we will be announcing several new drug discovery grants that will help us continue to move research forward.

Deepening the Drug Pipeline
All individuals with SMA have at least one copy of survival motor neuron gene 2 (SMN2), which is often called the SMA “backup gene.” SMN2 also produces SMN protein, but most of the protein produced by SMN2 is lacking a key piece, called exon 7.

Of the 18 treatments currently in development, half are focused on modulating this SMN2 gene—either by prompting SMN2 to make more protein, or by fixing the splicing of SMN2, meaning that SMN2 could produce a complete protein.

This new round of grants includes several projects that will further investigate this therapeutic approach as well more novel ones, thereby deepening our knowledge of a promising treatment avenue.

**Continued from cover**
Identification of SMN:HuD bound RNAs critical for motor neuron development.
Christine Beattie, PhD, at the Ohio State University for $140,000.

Objective: We have found that motor neurons do not develop properly in a SMA animal model in fish, and we hypothesize that this contributes to the motor neuron dysfunction in this disease.

Research Strategy: We are looking at proteins and RNAs that SMN interacts with to ask whether they are important for motor neuron development.

Significance: In SMA, motor neurons fail to function properly, but we do not yet understand why at the molecular level. If we understood this, we could better design therapeutics to specifically target the exact defect.

Defining the contribution of RNP assembly pathways to the SMA phenotype.
Arthur Burghes, PhD, at the Ohio State University for $140,000.

Objective: SMN protein is known to function in the cellular process call RNA protein assembly. This project hopes to definitively show whether or not RNA protein assembly is the critical pathway that is disrupted in SMA when SMN protein levels are low.

Research Strategy: A series of biochemical, molecular and cellular approaches will be used to explore the therapeutic potential of increasing the levels and/or activity of regulators of SMN function in order to compensate for loss of SMN.

Significance: The identification of the molecular targets that are misregulated due to loss of this novel SMN function in SMA should lead to a more complete understanding of disease mechanism.

Assessing mediators of muscle weakness in SMA mice.
Christine DiDonato, PhD, at Lurie Children’s Hospital of Chicago for $70,000.

Objective: We will study a special SMA mouse that we have generated that has increased SMN levels in its motor nerves and low SMN levels everywhere else. We have shown that this mouse develops muscle weakness as a young adult, which we believe is due to a problem in the skeletal muscle.

Research Strategy: We will study the skeletal muscles of these mice and various control mice to determine if there are structural defects within the muscle cell. Specifically, we will determine if SMN is indeed localized to the sarcomere and whether there is a problem with muscle cell fusion.

Significance: Our research using these newly developed mice has uncovered the fact that specifically increasing SMN only within the central nervous system does not completely correct everything, as we have unmasked a skeletal muscle problem. This may have important implications for current and future therapies.

The role of SMN as a translational regulator.
Jocelyn Cote, PhD, at the University of Ottawa for $30,000.

Objective: We have been the first to describe a new function for SMN in the regulation of protein production (called translation) and will perform further experiments to gain a better understanding of how SMN is involved in this new function.

Research Strategy: We will study the skeletal muscles of these mice and various control mice to determine if there are structural defects within the muscle cell. Specifically, we will determine if SMN is indeed localized to the sarcomere and whether there is a problem with muscle cell fusion.

Significance: The proposed studies will provide insight into the importance of muscle cell biology at multiple stages of SMA disease progression, using SMN depleted-mice.

Muscle satellite cell biology and muscle regeneration in Smn-depleted mice.
Rashmi Kothary, PhD, at the Ottawa Hospital Research Institute for $140,000.

Objective: Our goal is to better understand how depletion of SMN impacts the generation and function of muscle satellite cells, which help muscle respond to damage, and the capacity of skeletal muscle to regenerate.

Research Strategy: We will study what aspects of muscle satellite cell biology and muscle regenerative capacity are affected upon SMN depletion using genetic mouse models, single myofiber culture, cell biology, and cell transplantation.

Significance: The proposed studies will provide insight into the importance of muscle cell biology at multiple stages of SMA disease progression, using SMN depleted-mice.
Novel approaches against spinal muscular atrophy by targeting splicing regulators.
Antoine Cléry, PhD, at ETH Zurich for $90,000.

Objective: We aim to identify a new generation of molecules that control the protein splicing regulators of the SMN2 pre-mRNA. Understanding this could lead to promising drugs against SMA and other splicing-related diseases.

Research Strategy: We will screen chemical compound libraries against protein splicing regulators bound to their SMN2 RNA. In addition, we will use our protein structural data to specifically assess the role of a protein-splicing regulator called SRSF1 protein.

Significance: Finding new therapeutic strategies to approach SMA and other splicing-related diseases is a very promising method to correct splicing defects.

Novel Strategies to Increase SMN2 RNA.
Megerditch Kiledjian, PhD, at Rutgers, The State University of New Jersey, for $140,000.

Objective: In order to increase levels of SMN2 mRNA and SMN protein, we have identified a variant form of a protein that when expressed in cells leads to increased SMN2 mRNA and protein. Our goal is to further understand the molecular basis for how this occurs.

Research Strategy: We will be using SMA cell lines from type I patients to determine the molecular mechanism underlying this new way of increasing SMN protein levels in patient cells. We will also devise novel therapeutic strategy in cells with the goal to ultimately treat SMA.

Significance: Therapeutic approaches to increase SMN2 expression should be beneficial in SMA patients. Our objective is to decipher the molecular mechanism underlying this new mode of SMN2 upregulation and implement strategies to utilize in therapeutic intervention for SMA patients.

Assessing the reversibility of proximal axon abnormalities in SMA mice.
Charlotte Sumner, MD, at Johns Hopkins University for $140,000.

Objective: Our objective is to further characterize how the loss of SMN protein causes axonal defects in motor neurons, and to determine whether and when during development they can be reversed by SMN2 splice-switching oligonucleotides.

Research Strategy: We are currently utilizing mouse models to further define this axonal pathology over time and its relationship to motor neuron death. We are also testing whether prenatally delivered SMA therapeutics can prevent these pathologies.

Significance: It is unknown how SMN protein deficiency causes dysfunction and ultimately death of motor neurons. We anticipate that these studies will provide important insights regarding the earliest functional and cellular abnormalities of SMN-deficient motor neurons, which might then guide the timing of therapeutic intervention.

We thank the following families and foundations for their generous contributions toward these grants:

The Jacob Isaac Rappoport Foundation (ourshootingstar.com) toward Dr. Burghes, and
The Miller McNeil Woodruff Foundation (imwithmiller.com) toward Drs. Sumner and Alderfer.
The grants to Drs. Cote and Kothary were funded by Families of SMA Canada.

Visit our website to read how these scientists got involved in SMA research, and to learn more about these research projects. Visit www.cureSMA.org/news and choose “Research” from the right sidebar.
In addition to funding basic research, drug discovery, and clinical trials, Cure SMA funds research in a fourth area: clinical care. The purpose of clinical care research is to understand the issues that affect daily life for people with SMA, from breathing to nutrition, and to improve their quality of life today.

In this issue of Compass, we announce two clinical care grants, totaling $100,000 in new funding. These grants will support two new pilot studies into clinical care:

- Dr. Tariq Rahman is studying the use of the WREX exoskeleton in children with SMA. An exoskeleton is a robotic system that can help support movement and/or improve range of motion for individuals who have conditions that cause muscle weakness, including SMA.

- Dr. Melissa Alderfer is studying a psychological assessment screening tool. The goal of her research is to adapt this tool for use with families affected by SMA to identify potential stressors and resources within the family for coping with difficult treatment choices, fatigue and stress, limitations on independence, uncertainty, financial hardship, and other factors that often accompany a diagnosis like SMA.

Pilot studies are often a first step when testing a new or innovative treatment option. They help researchers evaluate the feasibility of larger studies, and pinpoint ways that they can modify their approach in order to produce the most meaningful results. This information is then used to support larger and lengthier studies.

In addition to these two new pilot studies, several pilot studies in care (many funded by Cure SMA) are ongoing or have recently been completed.

Along with the investigators, the Cure SMA Medical Advisory Council is assessing the information that has already been learned from these pilot studies. The goal is to scale these up, to see what impact the discoveries might have on the wider SMA population, and lead toward defining and improving the standard of care for all those affected by SMA.

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**Outcome Measures Using WREX – An Upper Extremity Exoskeleton for Children with SMA.**

Tariq Rahman, PhD, at the Alfred I. DuPont Hospital for Children for $50,000.

**Objective:** Individuals with SMA often have difficulty moving their arm in space, which can affect performance of activities of daily living. Several upper extremity orthotic systems have been introduced to the therapy community, but most have had no commercial success due to impracticality, cost, and appearance.

**Research Strategy:** We will perform a small study to examine the benefits of an upper extremity exoskeleton for people with SMA. We will use standard range of motion testing as well as three tools to measure the effects of the WREX over the course of one year.

**Significance:** More data is needed to show the benefits that the WREX medical device can have for individuals with SMA. The results from this study will be used as the basis for larger, multi-site trial.

**Screening for Psychosocial Risk among Families of Children With Spinal Muscular Atrophy.**

Melissa Alderfer, PhD, at the Alfred I. DuPont Hospital for Children for $50,000.

**Objective:** The purpose of this study is to create a tool to screen families of children with spinal muscular atrophy (SMA) for psychosocial risk factors such as financial difficulties, limited social support, patient and sibling behavioral problems, and family problems.

**Research Strategy:** The Psychosocial Assessment Tool (PAT), originally created to assess psychosocial risk among families of children with cancer, will be adapted for use with families of children with SMA.

**Significance:** This project is the first in a series of studies that will produce a reliable and valid screening tool, feasible for use in SMA clinics that will ensure psychosocial needs of families of children with SMA are appropriately and efficiently identified and addressed.
One of the most significant aspects of the Annual SMA Conference is the bringing together of families and researchers in the same event. The 2016 Annual SMA Conference is poised to set a record, with well over 1,400 families and researchers already registered.

As the world’s largest gathering of SMA families and researchers, the conference is an ideal forum to come together and evaluate current developments in SMA research, and chart out the next steps toward a treatment and cure. The Saturday afternoon Research Q&A Session will be a pivotal opportunity to advance those goals.

Currently, there are 18 drugs in development, with six in clinical trials. With several of those drugs progressing into Phase 2 and Phase 3 clinical trials, we believe we are closer than ever to an approved treatment for SMA.

The final stage in gaining an approved treatment is a new drug application (NDA) with the FDA. With this in mind, we’ve gathered an expert panel who will walk our community through the NDA process, including a time for questions and answers.

Following that panel, representatives from all six programs currently in clinical trials will present updates, followed by another Q&A session.

Our thanks to Biogen for their generosity as the presenting sponsor of the 2016 Annual SMA Conference.

Keep an eye on your mailboxes! The fall 2016 issue of Compass will cover these panels as well as other research developments from the 2016 Annual SMA Conference.