# COMPASS

A Publication Dedicated to Research Updates | Spring 2020

This year, we are proud to announce that we have awarded seven (7) research grants, totaling $1.1 million, to further our mission to drive breakthroughs in treatment that will lead the way to a world without SMA. Basic research is the first step in our comprehensive research model. Cure SMA has a rich history of supporting research aimed at improving quality of life, expanding treatment options, and advancing the understanding of spinal muscular atrophy (SMA). In this issue of Compass, you will meet our recipients, learn about the important research they are conducting, and see how these awards help advance treatment for people living with SMA. We understand that our commitment to the treatment and cure of SMA is not just about seeking solutions, but about helping to create them. We dedicate ourselves to accelerating research to improve outcomes for all individuals living with SMA and advance our understanding of the disease.

There are now two treatments approved by the U.S. Food and Drug Administration (FDA) that target the underlying genetics of SMA—with another treatment currently under review with the FDA and expected to be approved in Spring 2020. While the advent of these treatments for SMA have given families and individuals living with SMA hope for improved outcomes and longer life expectancies, we're on the verge of further breakthroughs that will continue to change the course of SMA for everyone affected. In the end, it will likely take a combination of therapeutic approaches—tailored to everyone's age, stage, and type of SMA—to achieve the greatest possible effect for all patients with SMA.

Basic research is our investment in continued drug development for SMA and without it, the SMA drug pipeline would not continue to grow and diversify. The awards highlighted here seek to explore novel targets for potential combination therapies, understand the pathology of SMA more fully and develop model systems that more closely recapitulate the human disease. We thank these—and all researchers—for their ongoing commitment to the treatment of all people with SMA and to the SMA Community.

## AUDREY LEWIS YOUNG INVESTIGATOR AWARDS

*Audrey Lewis founded Families of SMA, now Cure SMA, more than 35 years ago. She recognized early on the importance of attracting new and talented researchers to SMA, with the hope that they would commit their careers to developing a treatment and cure.*

*Cure SMA honors Audrey's legacy with the Audrey Lewis Young Investigator Award, periodically given to younger researchers working in the SMA field. The goal is to make a positive impact on the early phase of a talented researcher's career, enabling them to focus on the SMA field.*

***Cure SMA is pleased to announce the three recipients of the 2020 Audrey Lewis Young Investigator Award: Emily Welby, Ph.D., of the Medical College of Wisconsin; Timra Gilson, Ph.D., of Indiana University; and Dmytro Morderer, Ph.D., of the Mayo Clinic in Jacksonville, Fla.***

cure SMA Make today a breakthrough.

### Emily Welby, Ph.D.

***Dr. Welby, of the Medical College of Wisconsin, is a post-doctoral researcher in the laboratory of Dr. Allison Ebert. She was awarded $150,000 for her project titled, "The role of astrocytes in SMA motor neuron synapse defects."***

**What do you hope to learn from this research project?**

Astrocytes, a type of cell in the central nervous system, are critical for supporting the health of motor neurons. Hence, it is possible that dysfunctional astrocytes may play a role in some of the motor neuron defects observed in SMA. We think that the supportive role of astrocytes in ensuring proper formation and activity of neuronal synapses, the part of the neuron important for transmitting electrical signals to other cell types, might be impaired in SMA.

Understanding these abnormalities and how they affect synapse formation will give novel insights into motor neuron vulnerability in SMA and may lead to the identification of potential novel therapeutic targets.

**How will this project work?**

Our initial data suggests that astrocytes in SMA may have abnormalities in the molecules they express at the cell surface, which are needed in astrocyte-neuron communication to form proper connections between the cells (synapses). To assess if this is true, we will characterize the cell surface proteins expressed by astrocytes generated from SMA patient-derived stem cells and study these proteins within our astrocyte-motor neuron culture system, to see if they affect synapse formation.

**What is the significance of your study?**

The proposed study has the potential to significantly impact the understanding of astrocyte-mediated motor neuron loss and led to the identification of novel targets to that could help restore motor neuron synapse health in SMA.

## Timra Gilson, Ph.D.

*Dr. Gilson, of Indiana University, works in the laboratory of Dr. Elliot Androphy. She was awarded $150,000 for her project titled, "αCOP complex dependent axonal transport of RNA."*

**What do you hope to learn from this research project?**
We will study the role of αCOP, a cellular component that aids in protein transport between different parts of the cell, in SMA. We have previously shown that motor neurons unable to extend a neurite—or projection from the body of the cell—due to SMN depletion, are rescued for neurite length by over expression of αCO protein. Similarly, in the zebrafish model of SMA, over-expression of αCOP restores normal neurite outgrowth. In this project we want to understand how the over-expression of αCOP rescues neurite outgrowth in SMN motor neurons and promotes a longer lifespan in SMA mice.

**How will this project work?**
αCOP is known as a transport protein, meaning that it moves other proteins and molecules within cell. We will investigate how these molecules are selected and moved by αCOP, and how this influences SMA severity in cells and SMA mice.

**What is the significance of your study?**
Understanding how over-expression of αCOP is increasing transport of select molecules to the axons of motor neurons could lead to new insights about SMA pathology.

## Dmytro Morderer, Ph.D.

*Dr. Morderer, of the Mayo Clinic in Jacksonville, works in the laboratory of Dr. Wilfried Rossoll. He was awarded $150,000 for his project titled, "Effect of SMN deficiency on ribonucleoprotein assembly."*

**What do you hope to learn from this research project?**
In our SMA research, we use cellular and animal models of SMA to find out how low levels of SMN affect molecular processes that occur in cells. We are mostly focused on studying the assembly of complexes that include both RNA and protein molecules, also called ribonucleoproteins. The SMN protein is an important regulator of ribonucleoprotein formation, and when this protein is missing or mutated, the molecular assembly and functions of ribonucleoproteins are impaired. The objective of this proposal is to find out what proteins bind RNA differently, and how the assembly of ribosomes—large complexes of RNA and protein that act as cellular factories for protein synthesis—are impaired in SMA.

**How will this project work?**
We will fix all RNA-binding proteins to their RNAS in both normal cells and cells with low levels of SMN protein (SMA cells). This will allow us to identify and quantify all these proteins that were bound by RNA and compare their abundance in normal and SMA cells. We will also take healthy mice and SMA mice, isolate the ribosomes in their motor neurons, and determine differences in protein and RNA content between ribosomes from unaffected and SMA model mice.

**What is the significance of your study?**
Despite the great progress in SMA therapy and years of extensive research, we still don't know why motor neurons die when they have low levels of SMN protein. Our project is aimed to find out what cellular processes are impaired by low levels of SMN, so that we can identify specific therapeutic targets for novel treatments that can be combined with existing SMN-enhancing therapeutics.

# BASIC RESEARCH GRANTS

## Lyndsay Murray, Ph.D.

*Dr. Murray, of the University of Edinburgh, was awarded a $170,000 research grant for her project titled, "Developing strategies to support enlarged motor units following SMN restoration in mouse models of SMA."*

**What do you hope to learn from this research project?**
The benefits of currently approved therapeutics decrease as disease progresses, and we want to understand why. Using a mouse model of SMA, we have recently shown that when treatment is delayed, motor neuron size increases dramatically. By understanding what happens to these large motor neurons, we can develop strategies to support them.

**How will this project work?**
We will treat a mouse model of SMA after its symptoms have started with a drug like Spinraza. We will then examine what happens to these large motor neurons over time and investigate what aspects of the cells' activities are disrupted. Also, since previous work has shown that large motor neurons often suffer from heightened levels of stress, we will give a widely available approved supplement that should reduce stress and investigate whether this helps motor neurons.

**What is the significance of your study?**
This work will give insight into why a delay in treatment results in poorer outcomes in individuals affected by SMA, and therefore has the potential to improve outcomes for those treated after symptoms have started. Furthermore, understanding how to support enlarged motor units may led to novel therapeutic opportunities.

## Umrao Monani, Ph.D.

*Dr. Monani, of Columbia University, was awarded a $190,000 research grant for his project titled, "Genetic suppressors of the SMA phenotype."*

**What do you hope to learn from this research project?**
My lab uses mouse models to understand the biology underlying SMA, with a goal to eventually find the most optimal treatment for the human disease. We were amongst the first to demonstrate how important SMN is to the development and health of the structures where the motor neurons communicate with muscle cells. The principal objective of this research project is to exploit differences in the SMA phenotype (characteristics or traits) observed in model mice as compared to non-SMA controls to identify new genes associated with the disease.

**How will this project work?**
To identify the novel gene(s) associated with SMA, regions of the genome linked to severe or mild disease severity will be sought. These regions will eventually be narrowed using genetic markers until the specific gene or genes of interest are identified.

**What is the significance of your study?**
Despite progress in treating SMA, not much is known about how low SMN protein causes neuromuscular disease. The significance of the project stems from attempts to address this important question as a means of improving current SMA therapies by understanding other genes which may be influencing disease severity.

## Stephen Meriney, Ph.D.

*Dr. Meriney, of the University of Pittsburgh, was awarded a $190,000 research grant for his project titled, "A novel treatment targeting persistent neuromuscular dysfunction in a mild mouse model of SMA."*

**What do you hope to learn from this research project?**
My lab uses SMA model mice to characterize disease-induced changes in the neuromuscular synapse, explore alterations in behavior and muscle strength, and develop and test of a novel symptomatic treatment approach. Our novel treatment approach is designed to be used in combination with existing therapies for SMA. The objective of the proposed work is to test the effectiveness of a novel treatment strategy designed to combat muscle weakness for mild forms of SMA in model mice.

**How will this project work?**
The strategy is to use a mild SMA mouse model to test a novel small molecule that increases calcium influx into motor nerve terminals. This small molecule (GV-58) holds voltage-gated calcium channels open longer than normal and can significantly increase neurotransmitter release from motor nerve terminals, allowing for increased muscle contraction.

**What is the significance of your study?**
Patients with mild forms of SMA would benefit greatly from a treatment that targets muscle weakness at the neuromuscular synapse directly. The proposed project would test a novel molecule that might strengthen the neuromuscular synapse in mild SMA.

## Rashmi Kothary, Ph.D.

*Dr. Kothary, of the Ottawa Hospital Research Institute, was awarded a $100,000 research grant for his project titled, "Characterization of canonical disease features in a novel mouse model of SMA Type 3 and 4." This grant to Dr. Kothary was funded by Cure SMA Canada.*

**What do you hope to learn from this research project?**
This study aims to characterize our recently developed novel mouse model of mild SMA. We will complete the basic characterization of traditional SMA features, such as neuromuscular junction pathology, EMG, MUNE, and CMAP. In addition, exercise challenges will be performed to understand the ability of SMN-depleted mice to withstand various types of physical exertion and fatigue. Importantly, this will inform us on the role of SMN in maintenance of the motor unit during adult life and allow us to better model SMA Type 3 and 4.

**How will this project work?**
We will take advantage of a new mild mouse model of SMA that has been generated in our laboratory.

**What is the significance of your study?**
A mouse model of mild SMA will allow for better characterization of molecular changes within skeletal muscle and motor neurons, and to determine whether these differ in any way to those identified in the models of more severe SMA. The proposed studies will substantially inform the biology and treatment of mild SMA.

**CURE SMA WISHES TO RECOGNIZE AND THANK THE FOLLOWING DONORS WHOSE CONTINUED ANNUAL SUPPORT BENEFITS CURE SMA'S RESEARCH AND CARE PROGRAMS:**

**The Weisman Family Foundation, The Toby & Nataly Ritter Family Foundation, The Louis A. Ritter Foundation, The Irene Ritter Foundation, Meredith Greenbaum, Victoria Ritter, The Theodore and Renee Weiler Foundation, The Miller McNeil Woodruff Foundation, and The Dhont Family Foundation.**

# MORE ABOUT OUR BASIC RESEARCH GRANTS PROGRAM

**We've invested over $80 million in SMA research since 1984. Basic research is one of the cornerstones of Cure SMA's research strategy. Each year, our Scientific Advisory Board identifies specific priorities for funding, which are then released in a request for proposals. Once submitted, all proposals are evaluated using an NIH-like scoring system based on both scientific quality and relevance to the Cure SMA research mission. Current and future basic research projects will build on these priorities. For example:**

- We want to learn more about the SMN protein. We're investigating what critical functions it performs, and where it most needed in the body tissues of those with SMA.
- We're investigating the practicalities of SMN-based therapies (also called "SMN-enhancing" therapies). We want to know how when and where SMN needs to be replaced in order to provide maximal benefit for those with SMA. We also want to know if we can increase muscle strength without improving motor neuron function.
- We're looking for other targets—additional systems, pathways, and processes—that can serve as the basis for an SMA drug, and we're asking how we can best measure the effectiveness of these "non-SMN" approaches.
- We're exploring ways that SMN-enhancing approaches and non-SMN approaches might be used in combination with each other, in order to provide treatments for all types, ages, and stages of SMA.

**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 effective SMA treatments. Basic research is our investment in continued drug development for SMA.**

To learn more about SMA, basic research, and these recently awarded grants, visit www.curesma.org.

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