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). This year, we are proud to announce that we have awarded 7 research grants, totaling $1.15 million. These grants will further our mission to drive breakthroughs in treatment that will lead the way to a world without SMA. In this issue of Compass, you will get to know our recipients, learn about the important research they are conducting, and see how these awards help advance treatment for people living with SMA and their families. We understand that our commitment to the treatment and cure of SMA is not about just 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. The two FDA-approved treatments for SMA – Spinraza in December 2016 and Zolgensma in May 2019 – have been major clinical milestones that gave families and individuals living with SMA hope for improved outcomes and longer life expectancies.

AUDREY LEWIS YOUNG INVESTIGATOR AWARDS

Audrey Lewis founded Families of SMA, now Cure SMA, 34 years ago. Audrey 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 for SMA.

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 two recipients of the 2019 Audrey Lewis Young Investigator Award, Krysta Engel, PhD, at the University of Colorado and Veronica Pession, PhD, at the Salk Institute.

Krysta Engel, PhD, at the University of Colorado is a post-doctoral researcher, working in the laboratory of Dr. Matthew Taliaferro. She was awarded $150,000 for her project, “Transcriptome-wide interrogation of SMN-mediated RNA localization mechanisms in neurons.”

Meet Dr. Engel

What do you hope to learn from this research project?
The goal of this study is to gain a detailed understanding of an understudied role of SMN in promoting the transport of RNA molecules to the projections of neuronal cells and how this is misregulated in SMA.

How will this project work?
We will quantify the extent to which individual RNAs are transported to projections in cells that either contain or lack SMN. Those that are differentially transported depending on whether or not SMN is present will be prime candidates for further study, and represent potential molecular explanations behind SMA phenotypes as well as potential therapeutic targets.

What is the significance of your study?
Insights gained from completion of this study will be the first comprehensive characterization of how RNA localization is disrupted in cells deficient in SMN. Given that SMN is known to be involved in RNA transport and defects in RNA transport are associated with other neurological diseases, this study will give a foothold into understanding the contribution of RNA mislocalization to SMA.

To learn more about SMA and its effects, please visit www.cureSMA.org, which provides information and resources for patients.
Veronica Pessino, PhD, at the Salk Institute for Biological Sciences working in the laboratory of Dr. Samuel Pfaff was awarded $150,000 for her project, “Identifying SMN and microRNA-218 impacts on the local transcriptome of neuromuscular junctions.”

Meet Dr. Pessino

What do you hope to learn from this research project?
We know the cause of SMA is the lack of a protein called survival motor neuron (SMN), however it is unclear why lack of this protein specifically hurts motor neurons and their ability to communicate with muscles through neuromuscular junctions (NMJs). The objective of this work is to understand SMN’s involvement in communication maintenance, and the mechanisms behind NMJ breakdown, while testing a potential remedy for improved NMJ communication when SMN levels are low in SMA patients.

How will this project work?
In order to understand NMJ maintenance, we must first identify what molecules are most important and locally enriched at that part of the motor neuron by (1) sequencing all the local transcripts from NMJs in cultured cells, and dissected out of mice, and (2) comparing the sequencing results from normal cells/mice to those that model SMA and are lacking the SMN protein. Previously, we identified a molecule, miR-218, that we showed is involved in NMJ support, and may be able to buffer the negative effects of missing SMN, so we’ll insert miR-218 in abundance into the cells and mice and quantify its effect on their survival.

What is the significance of your study?
Once we understand what maintains a functional NMJ, and how SMN protein is involved in that maintenance, we will have new molecules to target and potentially prevent NMJ breakdown from happening, and therefore, SMA from progressing. Furthermore, this work will characterize the effects of miR-218 abundance, and if they are positive, miR-218 could be a promising therapy to keep SMA patients from progressing in disease.

Meet Dr. Jablonka

What do you hope to learn from this research project?
The project aims at understanding the cellular mechanisms leading to affected cluster formations of the active zone-associated voltage-gated calcium channels (VGCCs) in Smn-deficient motor neurons due to dysregulations of their auxiliary subunits. We will further expand our study on the modulation of these VGCC-subunits to compensate affected VGCC-cluster formations that in turn might support proper differentiation of and neurotransmission in SMA motor axon terminals.

How will this project work?
We will use molecular, live-cell imaging and electrophysiological assays to perform experiments on function, regulation as well as modulation of auxiliary voltage-gated calcium channel subunits. Results from subunit-knockdown experiments and subunit-targeted approaches will be visualized by confocal and high-resolution microscopy.

What is the significance of your study?
Our project promises to systematically evaluate the impact of auxiliary subunits on proper voltage-gated calcium channel cluster formations in motor axons and neuromuscular endplates. In particular, external modulation of these subunits in Smn-deficient motor neurons may provide a novel strategy to improve synaptic function in SMA.

Meet Dr. Kornblihtt

What do you hope to learn from this research project?
We hope to discover potential drugs that, by affecting epigenetic features of the SMN2 gene, help to produce more functional SMN protein.

How will this project work?
We will use epigenetic strategies developed in our lab to investigate how to promote functional SMN protein production from the SMN2 gene.

What is the significance of your study?
This research may result in therapies that work by epigenetic mechanisms. These therapies could potentially be used in combination with SMN-enhancing drugs, such as Spinraza, to improve effectiveness in patients.

Meet Dr. Jablonka

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Cure SMA, FAME (Families of SMA, Argentina), and the Weisman Family Foundations have awarded a $200,000 research grant to Alberto Kornblihtt, PhD, at the Universida de Buenos Aires, Argentina, for his project, “Epigenetics in SMN2 E7 Alternative Splicing II.”
Cure SMA and Cure SMA Canada have awarded a $150,000 research grant to Jocelyn Cote, PhD, at the University of Ottawa for his project, "Investigating the contributions of CARM1 and HuR misregulation to SMA skeletal muscle and NMJ defects."

Meet Dr. Cote

What do you hope to learn from this research project?
We have discovered that an important regulatory protein (called CARM1) is abnormally over-expressed in SMA muscles. We propose to study how this protein may contribute to the development of the problems that are observed in SMA muscles and postulate that targeting this protein may represent a novel therapeutic strategy to complement existing approaches restoring SMN mainly in spinal cord motor neurons.

How will this project work?
We propose to use a series of biochemical, molecular and cellular approaches that will allow us to determine what pathways are affected by the abnormal expression of CARM1 in SMA muscles. We want to learn how these pathways impact normal muscle development and connection of the motor neuron with muscles and muscle function. For those experiments we are using various cell culture and mouse models of SMA, but also validating our results using SMA patient cells to ensure that our findings are relevant to the human condition.

What is the significance of your study?
With the availability of new therapeutic options that focused on SMN restoration, it is very important to fully understand the role of SMN in all tissues, including skeletal muscle, in order to inform the development of more efficient or combinatorial therapeutic approaches. Since most of the current therapies are aimed at improving motor neuron numbers and function, it is also crucial to ensure that motor neurons can form stable, functional connections with skeletal muscle.

Cure SMA has awarded a $200,000 research grant to Charlotte Sumner, MD, at Johns Hopkins University, for her project, "Neurofilaments as markers of neurodegeneration in SMA."

Meet Dr. Sumner

What do you hope to learn from this research project?
The objective of this application is to evaluate blood neurofilament light chain (NF-L) levels as a biomarker of SMA disease activity and therapeutic responsiveness.

How will this project work?
We will measure blood NF-L levels in SMA mice at baseline at different time points and determine changes when SMN is increased in specific cell types or when mice are treated with SMN-inducing therapeutics. We will also determine NF-L levels in patient blood and CSF samples isolated from patients who are initiating nusinersen.

What is the significance of your study?
If successful, these results would provide further insights regarding the time course of neurodegeneration in SMA and the impact of therapeutic intervention. These observations could aid in optimizing therapeutic efficacy of currently available drugs and future therapeutics in SMA patients.

Cure SMA has awarded a $150,000 research grant to Laxman Gangwani, PhD, at the Texas Tech University Health Sciences Center, for his project entitled, "Function of Senataxin as a Protective Modifier of Spinal Muscular Atrophy."

Meet Dr. Gangwani

What do you hope to learn from this research project?
We hope to learn if and how Senataxin protein functions as a protective modifier of SMA and develop a novel (SMN-independent) therapeutic strategy for the treatment of SMA.

How will this project work?
We will create and characterize a novel genetically modified mouse which overexpresses the Senataxin protein. We will cross this new mouse model with an SMA mouse model and look for improvement in SMA disease in these mice.

What is the significance of your study?
Findings from this study will provide a genetic proof-of-concept and will establish Senataxin protein as a viable SMN-independent therapeutic target that could be used as a stand-alone treatment or in combination with SMN-dependent treatments for SMA.

Neurofilaments are released from axons during their disintegration.
Cure SMA Annual Researcher Meeting Review

The annual SMA Researcher Meeting is the largest research meeting in the world specifically focused on SMA. This year, we had a record setting 735 attendees join together in Anaheim, CA. The goal of the meeting is to create open communication of early, unpublished data, accelerating the pace of research. The meeting also furthers research by building collaborations—including cross-disciplinary dialogue, partnerships, integration of new researchers and drug companies, and educational opportunities for junior researchers.

One of the most important themed sessions each year is our special session. This year’s special session was entitled, ‘Spinal and Neuromuscular Circuitry: Exploring defects in SMA and Potential Therapeutic Targets’. Understanding how the intricate circuitry connecting nerves and muscles functions and what defects in that circuitry are present in SMA will help researchers better understand the pathology of SMA. Furthermore, identifying defects in the circuitry may identify potential targets for future therapeutics. The goal of this session was to better understand this circuitry in the context of SMA and discuss how this knowledge may impact further therapeutic development.

This year’s session highlights the importance of the identification of non-SMN targets—additional systems, pathways, and processes such as the neuromuscular circuitry featured in the session—that can serve as the basis for an SMA drug and the development of combination therapies. In this session, researchers and clinicians were encouraged to think about how components of the circuitry system could be potential non-SMN drug targets and how those non-SMN approaches might be used in combination with SMN-enhancing approaches with the goal of treatments for all types, ages, and stages of SMA.

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