

# COMPASS

A Publication Dedicated to Research Updates | **SPRING 2023**

This year, we are proud to announce that we have **awarded five new research grants**, totaling **\$575,000**, to drive breakthroughs in treatments for spinal muscular atrophy (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 SMA.

In this issue of Compass, you will meet our new 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 also about helping to create them. We dedicate ourselves to accelerating research to improve outcomes for all individuals living with SMA and to advancing our understanding of the disease.

There are now three treatments approved by the U.S. Food and Drug Administration (FDA) that target the underlying genetics of SMA—with several others in

various phases of clinical trials. While the advent of these treatments for SMA has 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 continued investment in further drug development for SMA. Without it, the SMA drug pipeline would not continue to grow and diversify.

The awarded researchers highlighted here seek to explore novel targets for potential combination therapies and understand the pathology of SMA more fully. We thank these—and all researchers—for their ongoing commitment to the treatment of all people with SMA and to the SMA Community.

## About Cure SMA's Research Grants

Each year, Cure SMA invites scientists from around the world to submit funding proposals for basic research projects that address specific unanswered questions in SMA biology. Our Scientific Advisory Board ranks the submitted proposals on both their scientific merit and relevance to the Cure SMA research priorities. This year, Cure SMA's top basic research priorities include:

- Identifying the roles the survival motor neuron protein (SMN) plays throughout the body.
- Understanding the details of how SMN-dependent therapies work.
- Finding treatment targets other than SMN.
- Combining SMN-dependent therapies and other treatments to achieve the best possible outcomes.

In 2022, Cure SMA awarded a total of \$575,000 to five scientists to explore these questions.



To learn more about SMA and its effects, please visit [www.cureSMA.org](http://www.cureSMA.org), which provides information and resources for patients.



**Cure SMA awards Saravanan Arumugam, PhD \$100,000 grant for his research, “The Role of Cytosolic and Mitochondrial Ca<sup>2+</sup> Homeostasis in the Pathogenesis of SMA”**

“The concentration of calcium inside cells affects many processes. Calcium is especially important in motor neurons, where it plays a major role in communication with muscles. Without active communication between motor neurons and muscle cells, muscles will atrophy and weaken.

SMA is caused by a deficiency in the survival motor neuron (SMN) protein that results from mutations in the survival motor neuron gene, *SMN1*. The regulation of calcium, called ‘calcium homeostasis,’ is altered in SMN-deficient motor neurons. This dysregulation results in poor motor neuron health and decreased communication with muscle cells. Our project seeks to learn more about how calcium homeostasis is disrupted in SMA motor neurons.

Mitochondria are the main organelles that regulate calcium inside cells. In SMA, the function of mitochondria in motor neurons is altered. Through this work, we seek to understand if restoring mitochondrial function in SMA motor neurons improves disrupted communication with muscles. This will be done by testing whether several compounds that are known to support mitochondrial function can restore calcium homeostasis and normalize ionic currents in cultured SMA neurons.”

– Saravanan Arumugam, PhD, Universidad de Seville



**Cure SMA Awards \$100,000 grant to Anton Blatnik, PhD for his research, “The Role of Sm Assembly in SMA Pathogenesis”**

“This project aims to address the long-standing question, ‘Which function(s) of SMN are directly responsible for the development of SMA?’ Specifically, I aim to expand the understanding of the role of the SMN protein in Sm-ring assembly.

The SMN protein has a number of functions in cells throughout the body. In SMA, there is SMN protein

deficiency, disrupting many of the processes that are important for cell health. One such process is Sm protein ring assembly. Sm proteins bind together to form rings that act as the core structures for larger protein complexes. These complexes are involved in processing RNA that is transported out of the nucleus and translated into protein elsewhere in the cell. Although SMN protein deficiency in SMA likely results in reduced Sm-ring assembly, a causal link between reduced Sm-ring assembly and the development of SMA has not been established.

The first aim of this project is to demonstrate that the association of Sm-rings with RNA is dependent on the presence of the SMN protein, and that this association functions as a signal to move these RNAs to specific locations within the cell. The second aim is to establish a causal link between reduced Sm-ring assembly and impaired processing of newly synthesized RNAs.”

– Anton Blatnik, PhD, The Ohio State University



**Cure SMA awards \$150,000 grant to Alberto Kornblihtt, PhD for his research, “Epigenetics in SMN2 E7 Alternative Splicing”**

“The goal of this project is to understand how the epigenetics of the *SMN2* gene interact with an antisense oligonucleotide (ASO1) that resembles Spinraza (nusinersen). Epigenetics are factors that affect how much protein is produced from a gene without changing the genetic code itself. These factors include things like chemical changes to the DNA or other molecules that bind to the gene.

SMA is caused by recessive mutations of the survival motor neuron 1 (*SMN1*) gene. These mutations result in reduced levels of the survival motor neuron (SMN) protein, which cause motor neuron death and muscle atrophy. In addition to the *SMN1* gene, everyone has at least one copy of a second gene, *SMN2*. *SMN2* also encodes the SMN protein and can act as a ‘back-up’ gene to the mutated *SMN1* gene. However, because of a small difference in the *SMN2* gene sequence, the majority of protein that is made from *SMN2* is shortened or ‘truncated’ and doesn’t function very well. Truncation of the *SMN2* protein occurs when the *SMN2* gene is copied or ‘transcribed’ into mRNA, and a portion of the gene known as ‘exon 7’ is spliced out of the mRNA sequence.

The Kornblihtt lab has identified epigenetic factors that affect the splicing of *SMN2* mRNA and the effectiveness of AS01. Like Spinraza, AS01 binds to *SMN2* mRNA to promote the inclusion of exon 7 and increase the amount of full-length SMN protein. This project is designed to learn more about how the interplay between AS01, epigenetic factors, and the *SMN2* gene affects the production of full-length SMN protein.”

– Alberto Kornblihtt, PhD, Universidad de Buenos Aires

*\*Thank you to the Dhont Family Foundation for their support of this important basic research project.*



**Cure SMA awards \$150,000 grant to Florence Rage, PhD for her research, “Deciphering the Mechanisms of RNA Transport along Axons to Understand the Progression of SMA”**

“We would like to develop tools that can establish a link between the regulation of mRNA transport and SMA. We are looking for direct evidence of a connection between mRNA mis-localization and the disruption of neuromuscular junction formation that is observed in SMA.

Proteins are large and complex molecules that provide structure and perform many critical functions in cells throughout the body. Cells must constantly manufacture new proteins to meet the body’s needs, and each gene in our DNA contains instructions for how to manufacture a specific protein. When more of a certain protein is needed, copies of its genetic instructions are made in the cell nucleus in the form of mRNA. The mRNA is then transported out of the nucleus and translated into protein.

SMA is caused by mutations in the survival motor neuron 1 gene (*SMN1*). As a result of these mutations, cells do not make enough SMN protein. The SMN protein is thought to play an important role in the transport of mRNA from the nucleus of motor neurons along their axons. Axons are nerve fibers that carry messages from motor neurons to muscle cells. As such, uninterrupted mRNA transport along the axon is critical to maintaining the synthesis of proteins that are needed to support nerve-muscle communication.

The goal of this project is to study how disrupting mRNA transport affects the function of motor neurons. A gene editing technique called clustered regularly interspaced short palindromic repeats (CRISPR) will be used to disrupt the trafficking of a specific mRNA called *ANXA2*. The *ANXA2* gene encodes the annexin A2 protein, which has important functions in the axons of motor neurons. A variety of techniques will be used to track the transport of *ANXA2* mRNA. Finally, we will characterize how the disruption of *ANXA2* mRNA impacts motor neuron function.”

– Florence Rage, PhD, Institute of Molecular Genetics of Montpellier



**Cure SMA awards \$75,000 grant to Lyndsay Murray, PhD for her research, “Evaluating the Impact of Sequential Versus Simultaneous Administration of SMN-Inducing Compounds on Motor Unit Recovery in Mouse Models of SMA”**

“We aim to understand how motor neurons recover when individuals affected by SMA are treated with FDA-approved drugs. We also want to determine whether combining approved therapies can help motor neurons recover more effectively.

Spinraza (nusinersen) and Evrysdi (risdiplam) are FDA-approved drugs that are used to treat SMA. Both drugs act by modifying the splicing of *SMN2* mRNA so that more full-length SMN protein is made. Increased levels of SMN protein may help motor neurons and the muscles they communicate with recover from damage caused during disease progression. To gain insight into motor neuron and muscle recovery in treated SMA-affected individuals, we use a mouse model of SMA and treat the mice with Spinraza-like and Evrysdi-like drugs.

In our previous research, we looked carefully at muscles in treated mice and found that motor neurons didn’t fully recover when a drug similar to Spinraza was given to the mice. We now aim to give these mice combinations of Spinraza-like and Evrysdi-like drugs to determine whether using the two drugs together allows motor neurons to more fully recover.”

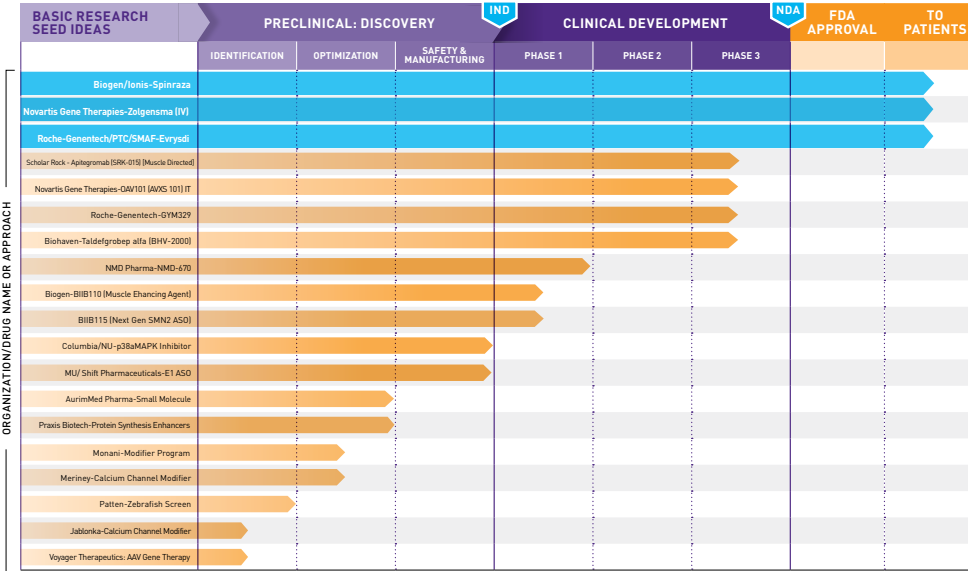
– Lyndsay Murray, PhD, University of Edinburgh

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## SMA DRUG PIPELINE

We're funding and directing research with more breadth and depth than ever before. We know what we need to do to develop and deliver new therapies, which could also work in combination, to reach our goal of treatments for all ages and types. And we're on the verge of further breakthroughs that will continue to change the course of SMA, and eventually lead to a cure.



IND = Investigational New Drug    NDA = New Drug Application    Last updated: March 2023

## Thank You to the Nunemaker Family

Special thanks to the Nunemaker Family for partnering with Cure SMA in our quest to invest in research that will focus on ways to enhance muscle strength and function as well as investigating nerve muscle connections and the regeneration of nerves. To achieve these goals, the Nunemakers have generously offered to match all gifts up to \$250,000.

To join the Nunemakers in investing in the future of SMA, please visit:

[donate.curesma.org/Nunemaker](https://donate.curesma.org/Nunemaker)



To learn more about SMA and its effects, please visit [www.cureSMA.org](http://www.cureSMA.org), which provides information and resources for patients.

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