COMPASS

A Publication Dedicated to Research Updates WINTER 2015

Cure SMA Awards Five New Basic Research Grants for $640,000

In this issue of Compass, Cure SMA is proud to announce five new basic research grant awards, for a total of $640,000. These were selected by our Scientific Advisory Board (SAB) from 29 grant applications submitted to our Fall 2014 Request for Proposals (RFP).

THE THREE STAGES OF THE RESEARCH PROCESS

I. BASIC RESEARCH TO UNDERSTAND THE CAUSE AND BIOLOGY OF SMA

II. DRUG DISCOVERY TO CONVERT BASIC RESEARCH IDEAS INTO PRACTICAL NEW DRUG CANDIDATES

III. CLINICAL TRIALS TO TEST THE DRUG CANDIDATES

Our strategic research approach includes three areas—basic research, drug discovery, clinical trials—working together toward our vision of a treatment and cure for SMA. Cure SMA has invested $57 million in research since 1984, with $35 million in the past decade alone.

We also fund research in a fourth area, clinical care research, that investigates issues like breathing or nutrition that impact daily life for individuals with SMA.

In addition to the basic research funding announced here, Cure SMA is currently in the process of announcing over $225,000 in clinical care grants and $775,000 in new drug discovery funding.

Why We Fund Basic Research

Basic research, which investigates the cause and biology of SMA, is the critical first step in our comprehensive research strategy. Through basic research, we can begin to identify the most effective strategies for drug discovery.

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.

Advancing Future Breakthroughs

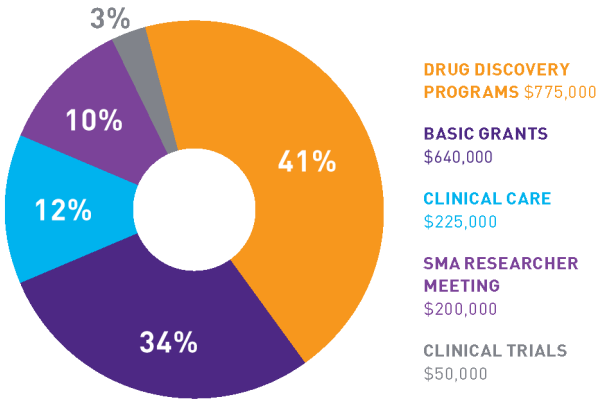
Cure SMA has been investing in basic research for three decades, with nearly $10 million in grants in the last decade alone. The three stages of our research model—basic research, drug discovery, and clinical trials—all work together to build on past discoveries and inform future discoveries. And through our RFPs, we're looking for specific projects that will also build on past discoveries, and inform future discoveries.

We know that the *SMN1* mutation prevents SMN protein from forming correctly. Now we're looking at what other genes might be involved in turning SMN on or off, or meditating SMN function.

We know that motor neuron cells stop working correctly and die when there is not enough SMN protein, but we need a greater understanding of what's going wrong in SMA. What is the exact timing when defects occur, and what other cell types are affected by low SMN levels?

Continued on next page

cure SMA



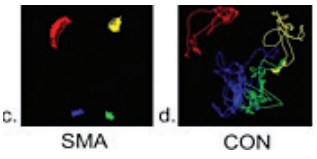
We've created animal models of SMA, but we need more tools to better understand SMA and to test drugs in mice and humans.

Our 2014 RFP invited researchers to submit projects that would address these priorities, to directly inform current drug development efforts, or lead to new drug development approaches for SMA.

How Our New Basic Research Grants Are Moving Research Forward

Our first new grant was given to Dr. Sara Custer at Indiana University. Dr. Custer received the **Audrey Lewis Young Investigator Award**. Audrey Lewis founded Families of SMA, now Cure SMA, 30 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.

Dr. Custer's project will identify gene changes that occur with lowered SMN, leading to new drug targets and therapeutic avenues for SMA.



Trajectory of movement for each extremity in an infant with SMA (c) and an age-matched infant without SMA (d). Kindly provided by Dr. Lowes.

Our second new grant was given to Dr. Francesco Lotti at Columbia University. He will study how the function of the SMN protein is controlled. Greater understanding of this process will reveal new ways of making the SMN protein work more efficiently.

Our third new grant was given to Dr. Mustafa Sahin at Boston Children's Hospital. Dr. Sahin's project aims to understand how a particular cellular pathway called mTOR goes awry when SMN protein is lowered. This work could identify genes that compensate for the loss of SMN protein.

Our fourth and fifth grants were given to Dr. Linda Lowes at Nationwide Children's Hospital, and Dr. Chad Heatwole at the University of Rochester. Both of these projects are focused on developing new clinical trials outcome measures for infants and adults with SMA. As more novel drugs begin testing in human clinical trials, it is essential that we have sensitive measures in people of all ages and with all types of SMA.

Thank you for your continued support of our basic research projects!

We thank the following families and foundations for their generous contributions toward these grants: The Jacob Isaac Rappoport Foundation (ourshootingstar.com) toward Drs. Custer, Sahin, and Lotti; The Miller McNeil Woodruff Foundation (imwithmiller.com) toward Dr. Lowes; The Spinal Muscular Atrophy Research Team (smarthope.com) toward Dr. Heatwole.

ONGOING BASIC RESEARCH PROJECTS CURRENTLY BEING FUNDED BY CURE SMA.

- The When and Where Requirements of SMN in Mild SMA to Christine DiDonato, PhD, at Northwestern University for $140,000.
- To Characterize the Role of SMN Protein in Myoblast Fusion to Barrington G. Burnett, PhD, at Uniformed Services University of the Health Sciences for $100,000.
- Multi-Center Electrophysiological Evaluation of Clinically Relevant Phenotypes in SMA Mouse Models to Laurent Bogdanik, PhD & Cathleen Lutz, PhD, at The Jackson Laboratory for $90,000.
- Investigate Ubiquitination-Dependent SMN Transport to Ke-Jun Han, PhD, at the University of Colorado for $95,000.
- Arginine Methylation as a Regulator of SMN Activities in Motoneurons to Jocelyn Côté, PhD, at the University of Ottawa for $140,000.
- The Non-SMN Mediated Benefits of The HDAC Inhibitor Trichostatin A to Rashmi Kothary, PhD, at The Ottawa Hospital Research Institute for $100,000.
- Investigating The P53 Signaling Pathway in Pathogenesis of Mouse Models of SMA to Lyndsay Murray, PhD, of the University of Edinburgh for $80,000.

How Our New Basic Research Grants Are Moving Research Forward

Gene changes in a NSC-34 model of SMA.

Sara Custer, PhD, at Indiana University for $140,000 over two years.

Objective: Identifying gene changes in motor neurons with lowered SMN protein levels.

Research Strategy: Using a motor neuron cell model of SMA, we will determine the gene changes caused by low SMN and also examine the biological consequences of these changes on motor neuron biology and SMA pathology.

Significance: Determining the gene changes caused by low SMN protein levels in our cells should identify genes that are specifically important for motor neuron health. This will reveal new drug targets and thus new avenues for therapeutic intervention in SMA, beyond the SMN protein. These pathways could be critical to motor neuron health and may also be relevant to multiple motor neuron diseases.

Development of A Clinically Relevant Outcome Measure for SMA Therapeutic Trials.

Chad Heatwole, MD, at the University of Rochester for $140,000 over two years.

Objective: The objective of this project is to develop, validate, and utilize a reliable, responsive, and patient-meaningful disease-specific patient reported outcome measure for SMA clinical trials. Patient-reported outcomes are typically required by the FDA in pivotal drug trials.

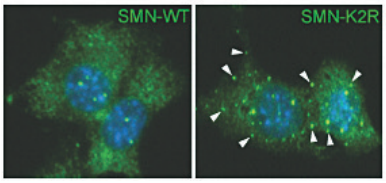
Research Strategy: This research will: (1) utilize a large cross-sectional study to identify those symptoms that are most important to SMA patients; (2) develop and validate a reliable, responsive, and patient-meaningful patient reported outcome measure for SMA patients; and (3) implement this instrument in SMA clinical trials and in clinic settings as a means to track patient-meaningful responses to treatment.

Significance: At the completion of our work the SMA research community will have a valid outcome measure to aid in therapeutic assessment that will encourage therapeutic development for adult SMA patients.

Role of Sumoylation in SMN Function and SMA Pathology.

Francesco Lotti, PhD, at Columbia University for $140,000 over two years.

Objective: The identification of biological pathways that regulate SMN function is critical in revealing strategies for SMA therapy. However, little is known about the modifications to the SMN protein after it is made (called post translational modifications or PMTs) or how PMTs control SMN function. This project will investigate the hypothesis that PMTs of the SMN protein regulate SMN cellular functions.



Inhibition of SMN PMT alters its sub-cellular location. Image kindly provided by Dr. Lotti.

Research Strategy: The team will investigate the requirement of PMTs in SMN protein function using well-established cell and mouse model systems of SMA. The goal is to determine whether PMTs are required for SMN protein to work properly.

Significance: Successful completion of this project will reveal the role of PTMs in the regulation of SMN biology. In addition to the importance in unraveling novel regulatory networks that control fundamental cellular processes, importantly this project also has the potential to link PTMs of the SMN protein to SMA pathology.

mTOR and Protein Synthesis in SMA.

Mustafa Sahin, MD, PhD at Boston Children's Hospital for $140,000 over two years.

Objective: The lab recently discovered that a pathway regulating protein synthesis in neurons is suppressed in SMA. This is called the mTOR pathway. The current study aims to understand this defect better in order to find and develop new therapeutic routes for the treatment of SMA.

Research Strategy: The lab will apply its expertise in studying neuronal protein synthesis and its regulation to determining how it is altered in SMA. A combination of cell culture and mouse experiments will be used.

Significance: SMA treatment may be most successful by combining treatment types: for example, treatments that increase protein synthesis may be combined with those that increase SMN expression.

Development of An Innovative Outcome Measure to Define Disease Progression in SMA Type I for Use in the Home or Clinic.

Linda Lowes, PhD, at Nationwide Children's Hospital for $80,000 over one year.

Objective: This project will develop an outcome measure to help advance clinical trials in infants with SMA type I that can be used in the clinic or the patient's home.

Research Strategy: The project team will utilize Microsoft Kinect to record the infant's movement. Investigators will visit the homes to instruct families on how to use our system, teaching them to record the baby's movement, once a month for 12 months.

Significance: It is difficult for fragile infants with SMA to participate in clinical trials. At home testing would ease the burden on the infant and family.

The Cure SMA Research Funding Process

There's great promise in the SMA research landscape. In the last decade, we've seen more discoveries made, more researchers studying SMA, and more industry and regulatory partners investing in clinical trials than ever before.

Even with this progress, there's also a pressing need for continued and growing investment. And as the pace of research increases, it's important for us to be strategic in how we select the right projects to fund—the projects that show the most promise for sustaining this momentum.

The SAB meets in Washington DC to review basic research proposals.

Key to this process is our Scientific Advisory Board (SAB). Our SAB is a group of recognized group of experts in SMA and motor neuron biology. They provide strategic and practical guidance in shaping our research programs.

At the close of each RFP, they review each of the proposals we receive, looking to see which projects are the most intriguing, which have a well constructed study plan, and which match up with the most pressing unanswered questions about SMA.

Most importantly, they are looking for the projects that show the most promise in getting us closer to our goal of a treatment and cure for SMA. Once this evaluation is complete, we award research grants to the top proposals, although several excellent proposals remain unfunded each year.

With the size of our community, the strength of our connections, and the expertise of our SAB, we're able to direct research at unparalleled scale and efficiency.

Each of these five awards builds on the successes of our past funding. We look forward seeing the results of these projects, and learning how those results will then lay the foundation for our next round of research funding.

Cure SMA
925 Busse Road
Elk Grove Village, IL 60007
1-800-886-1762

Return Service Requested

Non-Profit Organization
U.S. Postage
PAID
Permit No. 1705
Chicago, IL