COMPASS

A Publication Dedicated to Research Updates | **SUMMER** 2017

Cure SMA Awards 10 New Grants in Basic Research

In this issue of Compass, we are proud to announce over $1.03 million in new funding.

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 a maximally effective SMA therapies for all types and stages of the disease. Basic research is our investment in future drug development for SMA.

Continuing Need for Basic Research

The FDA approval of Spinraza has ushered in a new stage in the SMA community. As we enter this new era, Cure SMA remains committed to the needs of the SMA community. While we celebrate the long awaited approval of Spinraza, there remains much to be done and many questions to be answered as we continue to work to most effectively treat SMA. While Spinraza will offer tremendous benefit to those with SMA, there is also a need for continued research and development investment. It will likely take a combination of therapies to achieve the greatest possible effect for each and every SMA patient at every age and stage of disease.

Our hope is that Spinraza is just the leading edge of a robust drug pipeline, with a breadth and depth that reflects our goal of treatments for all ages, stages, and types of SMA. We've seen many advances in recent years, from new techniques in gene therapy, which Cure SMA is funding with an award to Nationwide Children's Hospital through our translational grant program, to drugs that affect muscle and nerve function that could be used in combination with drugs like Spinraza that target the underlying genetics of SMA. We're actively working on additional treatments that target the underlying genetics of SMA as well as therapies that target other systems, pathways, and processes affected by SMA. Our goal is a combination of therapeutic approaches that can be tailored to each individual SMA patient.

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.

For more information on these grants, our research model, and the latest research news visit **www.cureSMA.org**

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These questions include:

- What are the functions of the SMN protein and how does SMN perform those functions?
- 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?

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.

New Grants to Learn More About the When and Where of SMN

Our grant to Dr. Jocelyn Cote will fund research into understanding the function of the SMN protein, focusing on the role SMN plays in protein production.

Our grant to Drs. Oliver Gruss and Utz Fischer will analyze the impact of SMN on cellular signaling networks in an effort to understand the role SMN plays in the overall activity of the cell.

Dr. Christian Lorson has found that some types of neurons get "sick" when SMN levels are low, while others do not. Our grant will focus on how astrocytes, another cell type present in the central nervous system, protect some neurons while leaving others vulnerable to low levels of SMN.

Our grant to Dr. Christine DiDonato focuses on skeletal muscle proteins and their sensitivity to calcium, which impacts their ability to contract and generate force. Our grant to Dr. Stephen Kolb will look at when SMN is needed to clarify the critical issue of timing for SMN increasing therapies.

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New Grants to Study SMA Modifiers and Identify New Drug Targets

In our grant to Dr. Arthur Burghes genes that vary between these discordant siblings, siblings with the same copy number of *SMN2* but presenting with different disease severity, will be compared. This will give insights as to what genes may be able to modify SMA disease severity.

In SMA, actin, which is a protein that helps muscles to contract doesn't work properly Our grant to Dr. Remy Bordonne will support the discovery of genes, called SMN-modifier genes, that rescue defects in actin functioning, in cells with low SMN protein levels.

Our grant to Dr. Alberto Kornblihtt seeks to identify drugs which use epigenetic, strategies to enhance the production of functional SMN protein from the *SMN2* gene. Epigenetics refers to changes that affect how much protein is made from a gene without altering that gene's sequence.

Our grant to Dr. Jean Giacomotto will allow for the optimization of his previously developed zebrafish model to make it compatible with drug discovery. After optimization, a pilot screen will be performed to identify drug candidates which improve SMA symptoms in the fish.

Dr. Yongchao Charles Ma has found that the activity of Cdk5, cyclin-dependent kinase 5, is significantly increased in SMA motor neurons. The grant investigates the underlying reasons for this hyperactivity and if its inhibition can be used as a therapeutic strategy.

ONGOING BASIC RESEARCH PROJECTS CURRENTLY BEING FUNDED BY CURE SMA

- **Identification of SMN:HuD bound RNAs critical for motor neuron development**
Christine Beattie, PhD, Ohio State University

- **Defining the contribution of RNP assembly pathways to the SMA phenotype**
Arthur Burghes, PhD, Ohio State University

- **Assessing mediators of muscle weakness in SMA mice**
Christine DiDonato, PhD, Lurie Children's Hospital of Chicago

- **Muscle satellite cell biology and muscle regeneration in Smn- depleted mice**
Rashmi Kothary, PhD, Ottawa Hospital Research Institute

- **Novel approaches against spinal muscular atrophy by targeting splicing regulators**
Antoine Clery, PhD, ETH Zurich

- **Assessing the reversibility of proximal axon abnormalities in SMA mice,** Charlotte Sumner, MD, Johns Hopkins Hospital

- **Novel Strategies to Increase SMN2 RNA**
Megerditch Kiledjian, PhD, Rutgers, The State University of New Jersey

- **A pilot, open-label, dose response study investigating the effect of low-dose Celecoxib on SMN2 in patients with Spinal Muscular Atrophy**
Hugh McMillan, PhD, and Alex McKenzie, PhD, Children's Hospital of Eastern Ontario Research Institute

- **The Development of a Clinically Relevant Outcome Measure for SMA Therapeutic Trials**
Chad Heatwole, MD, University of Rochester

- **Preclinical development of a JNK drug candidate to alter disease progression in SMA**
Charlotte Sumner, MD, Johns Hopkins Hospital and Imago Pharmaceuticals

- **Slowing SMN degradation to treat SMA**
Barrington Burnett, PhD, Uniformed Services University

- **Pharmacological inhibition of p38αMAPK as a candidate therapeutic approach for SMA**
Livio Pellizzoni, PhD, Columbia University

- **Development of a drug to increase SMN2 transcription**
Kevin Hodgetts, PhD, Brigham and Women's Hospital

More About Our New Basic Research Grants

Investigating the Mechanism by Which SMN Regulates Translation: Identification of Novel Therapeutic Targets

Jocelyn Cote, PhD, at the Ottawa Hospital Research Institute for $140,000

Objective: We have been the first to describe a new function for SMN in the regulation of protein production and we propose to perform experiments to gain a better understanding of how SMN goes about doing this new function- and to determine the consequences of losing this function in cells from SMA patients.

Research Strategy: We propose to use a series of biochemical, molecular and cellular approaches that will allow us to learn about a new function for SMN in the regulation of protein production.

Significance: The current proposal will provide crucial insights into a novel function for SMN in spinal cord motor neurons. Identification of the targets that are misregulated due to loss of this novel SMN function in SMA should lead to a more complete understanding of disease mechanism and has the potential to identify new therapeutic targets. *This international grant is supported by funding from Families of SMA Canada.*

Regulatory Cues Modulating the Activity of SMN in Human Cells

Oliver Gruss, PhD, at the Rheinische Friedrich-Wilhelms-Universitat Bonn in Germany and Utz Fischer, PhD, at the Julius-Maximilians-Universitat Wurzburg in Germany for $140,000

Objective: Our projects aims at understanding the details of how SMN protein works in the cell. We will analyze the impact of SMN on cellular signaling networks to try to understand the role SMN plays the overall activity of the cell.

Research Strategy: We will use biochemical and biological assays to perform experiments on function and regulation of the SMN protein and the other proteins with which SMN associates.

Significance: Our study will provide new understanding into how SMN functions and its role within cells. These insights will deepen our knowledge on the role of SMN in things such as motor neuron degeneration and therefore, will aid in therapy development.

Examining the Role of Astrocytes and the Influence upon Lower Motor Neuron Susceptibility in SMA

Christian Lorson, PhD, at the University of Missouri for $75,000

Objective: Despite the lack of SMN in every cell in the body in SMA, not all cell types, or even neurons, become "sick" when SMN levels are very low. The goal of this project is to understand why some neurons get sick while other neurons do not get sick.

Research Strategy: By examining the differences between astrocytes from different regions within the central nervous system, we hope to identify new factors that help "protect" some neurons while understanding why other neurons are not "protected."

Significance: This proposal is designed to investigate why lower motor neurons are specifically impacted in SMA. This understanding is important from a biological perspective as well as for designing optimized drugs.
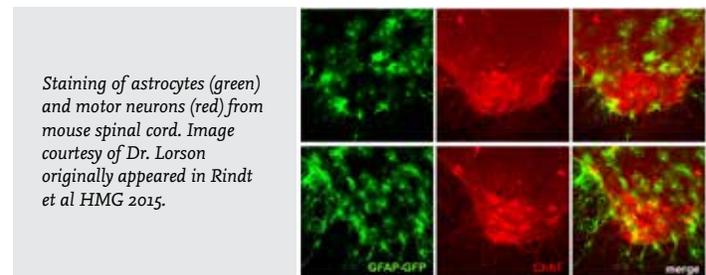
Staining of astrocytes (green) and motor neurons (red) from mouse spinal cord. Image courtesy of Dr. Lorson originally appeared in Rindt et al HMG 2015.

Skeletal Muscle Activators as Potential Modulators of Muscular Weakness in SMA

Christine DiDonato, at the Ann & Robert H. Lurie Children's Hospital of Chicago for $140,000

Objective: This proposal focuses on skeletal muscle proteins and their sensitivity to calcium, which impacts their ability to contract and generate force. Skeletal muscles activators could foreseeably be used alone or in combination with SMN-inducing drugs to provide enhanced benefit to SMA patients.

Research Strategy: We will first investigate how proteins known to modulate muscle activity in SMA skeletal muscle are mis-regulated. Normal versions of these mis-regulated proteins will be expressed in a mouse model of SMA to determine their effect on the ability of SMA muscle to contract properly.

Significance: These studies will allow us to gain insight into the potential mis-regulation of proteins that may contribute to reduced force production and endurance in SMA muscle and how one might benefit from enhancing calcium sensitivity to improve muscle contraction. This work will have important parallels to the Cytokinetics drug compound, tirasemtiv or CK-107, which works by sensitizing the muscle to calcium to improve contraction and force generation.
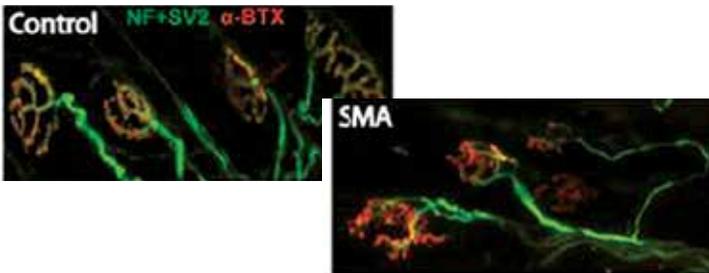
The junction between motor neurons and muscle in healthy (control) and SMA mice. Image courtesy of Dr. DiDonato.

Identification of SMA Modifiers and Deletion/Duplication Junctions in the SMA Region

Arthur Burghes, PhD, at the Ohio State University for $140,000

Objective: The project objective is twofold. First, we want to identify the genes in humans that cause a milder or no phenotype in siblings despite having the loss of SMN1 and the same copy number of *SMN2*. The second objective is to identify parts of the *SMN1* gene which may be deleted or duplicated without the absence of the whole gene. Doing so would improve carrier screening.

Research Strategy: We will determine all variants that differ between discordant siblings and concordant siblings. These will then be compared and all variants that differ in concordants will be eliminated from the discordant file. The remaining variants can mark the modifying gene(s) in SMA. Novel genome sequencing techniques will be used to look for deleted and duplicated parts of *SMN1*.

Significance: The identification of modifiers of SMA allows for accurate DNA testing that can predict severity of disease as well as targets for therapeutic intervention in SMA. The identification of parts of the SMN1 gene which may be deleted or duplicated will aid carrier testing by identifying when this is the case.

Identification of the Protective Mechanism of a SMN Modifier Gene using S. pombe as a Model Organism

Remy Bordonne, PhD, at CNRS-Centre National de Recherche Scientifique in France for $30,000

Objective: In SMA, actin, which is a protein that helps muscles to contract doesn't work properly. The goal of this project is to discover genes that rescue defects in actin functioning, in cells with low SMN protein levels.

Research Strategy: We will use S. pombe, a yeast, to try to understand how a SMN-modifier gene protects the formation and function of actin networks, which are critical for muscle contraction.

Significance: Understanding how this protective SMN-modifier gene protects actin networks could potentially lead to the development of therapeutics which improve muscle contraction in SMA.
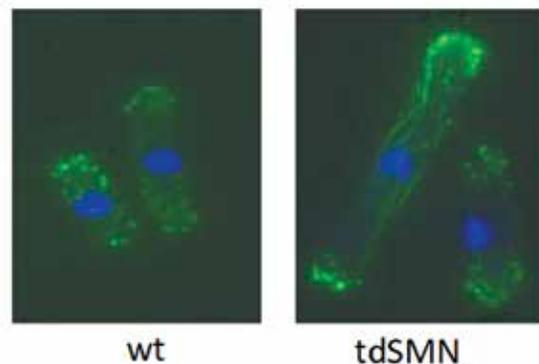
Actin filaments in healthy (wt) and SMA cells. Image courtesy of Dr. Bordonne

Epigenetics in *SMN2* E7 Alternative Splicing

Alberto Kornblihtt, PhD, at the Universidad de Buenos Aires in Argentina for $140,000

Objective: Epigenetics refers to changes, which without altering the DNA sequence, affect how much protein is produced from each gene. We will use epigenetic strategies to enhance the production of SMN protein from the SMN2 gene, with the goal of compensating for the missing SMN1 gene in SMA patients.

Research Strategy: We will use epigenetic strategies developed in our lab to investigate how to promote functional SMN protein production from the SMN2 gene.

Significance: 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.
This international grant is supported by funding from Families of SMA Argentina.

Zebrafish Models of Spinal Muscular Atrophy Optimized for Chemical Genetics and Drug Discovery: From Proof-of-Principle to New Insights and Treatments

Jean Giacomotto, PhD, at the University of Queensland in Australia for $75,000

Objective: In SMA, the lack of additional "druggable" targets, beyond SMN, creates a gap in the traditional drug discovery pipeline. In order to address this issue, we have created a zebrafish model of SMA designed to be suitable for large-scale drug screening.

Research Strategy: We will optimize our zebrafish model to make it compatible with drug discovery and run a pilot screening study using a pool of pharmacologically active compounds to potentially find beneficial drugs for SMA.

Significance: This research will generate the first animal model of SMA compatible with large-scale drug discovery experiments. This model can then be used to screen drugs and identify those which may warrant further drug development for SMA.


Zebrafish model of SMA. Image courtesy of Dr. Giacomotto.
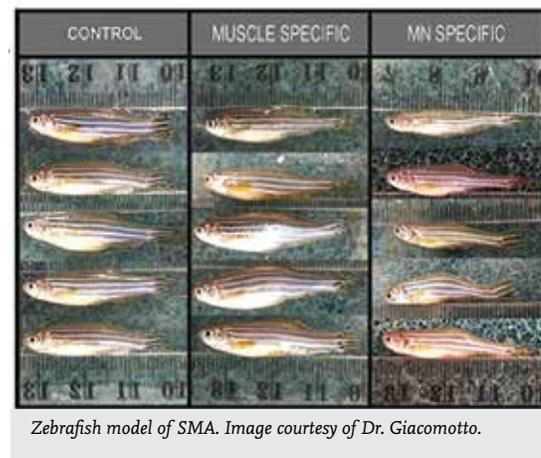
Regulation of Motor Neuron Defects by Cdk5 Signaling in SMA

Yongchao Charles Ma, PhD, at the Ann & Robert H. Lurie Children's Hospital of Chicago for $75,000

Objective: We have found that the activity of a protein called Cdk5, cyclin-dependent kinase 5, is significantly increased in motor neurons affected by SMA. In this project we hope to find out why this protein displays increased activity and to test whether inhibiting hyperactive Cdk5 activity can be used as a therapeutic strategy.

Research Strategy: We plan to use a combination of genetic, biological, and biochemical approaches to investigate how increased Cdk5 activity leads to motor neuron degeneration. We will test reducing the activation of Cdk5 as a therapeutic strategy in SMA mouse models.

Significance: Our study will help us understand more about motor neuron degeneration in SMA. The findings could potentially lead to the development of new therapeutic strategies which could be used in combination with SMN-enhancing therapeutics, such as Spinraza, to achieve maximal therapeutic benefit.

SMA motor neuron cultures. Image courtesy of Dr. Ma
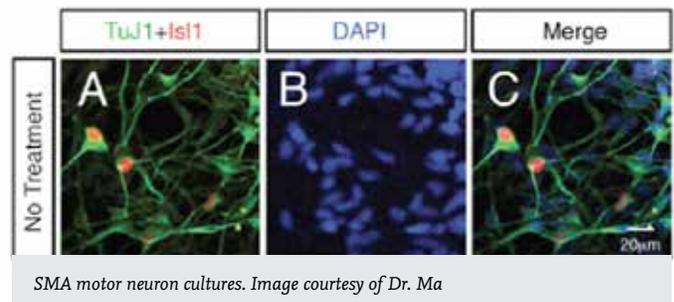
Arrested Development or Neurodegeneration? An approach to understand developmental motor neuron pathology in SMA

Stephen J Kolb MD PhD, at The Ohio State University for $75,000

Objective: We will create a large animal pig model of newborn infants with SMA. We will use this model to understand the pathological findings that are seen in motor neurons in infants with SMA.

Research Strategy: We will create the model by delivery of a virus that will knockdown the expression of SMN in fetal piglets in utero. Once these piglets are born, we will study the motor neurons and determine if the pathological findings are the same as in infants with SMA.

Significance: This project will address the urgent question of timing to optimize delivery of SMN increasing therapies in infants with SMA, and allow us to predict the long-term success of these therapies by modeling the consequences of low SMN during fetal development.

RUSP Nomination for SMA Accepted into Evidence Review

Left to Right: Representative Becky Ruth, Grace Grutter, and Leslie Derrington at a newborn screening hearing in Missouri. Grace and Leslie testified in support of newborn screening legislation sponsored by Rep. Ruth.

The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) announced that they have accepted spinal muscular atrophy into the review process for the Recommended Uniform Screening Panel (RUSP). The RUSP is a list of conditions that all newborns in the US are recommended to be screened for.

The RUSP application for SMA now moves into evidence review, which is a six to nine month process. Once the evidence review is completed, the committee will make a recommendation to the Secretary of Health and Human Services, who will determine whether SMA will be added to the RUSP. The review by the HHS Secretary can also take several months, meaning a final decision on the RUSP application could come in mid-2018.

"We are pleased that the committee has taken this significant first step toward recommending SMA for inclusion on the RUSP," said Jill Jarecki, PhD, Cure SMA's chief scientific officer. "Adding SMA to the federal guidelines would help ensure that all babies born with SMA receive the best change for prompt, effective treatment. As the committee continues their review, we will continue our advocacy for SMA screening implementation. Thank you again to our working group for their hard work on the nomination."

At the meeting, the committee heard testimony from the SMA community in support of the application. Dr. Jarecki testified, along with Debra Schaefer, who has had two granddaughters affected by SMA: one who passed away in 2012, and one who was diagnosed in utero and has benefited from early treatment with Spinraza.

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