COMPASS

A Publication Dedicated to Research Updates | **SUMMER** 2018

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 10 research grants, totaling $1.3 million – our largest contribution to date. 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 individuals living with SMA and advance our understanding of the disease. The first FDA-approved treatment for SMA – Spinraza in December 2016 – was a major clinical milestone that gave families and individuals living with SMA hope for improved outcomes and longer life expectancies.

Just recently, research on pre- and post-symptomatic treatment with Spinraza paved the way for a recommendation from the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) to include SMA in newborn screenings. Current studies demonstrate that treatment before symptoms are shown greatly improves motor function for individuals with SMA and may even lead to some children with SMA achieving the ability to walk. Research also helps us better understand the progression of SMA over time.

The approval of Spinraza and a recommendation to include SMA in newborn screenings highlight the need for continuous research in disease development to enable physicians to approach care from a comprehensive and personalized perspective. While it's critical to understand how specific genes play a role in the manifestation of SMA, it's equally important to identify which symptoms have the greatest effect on individuals' quality of life. This year we identified grant recipients who are studying a wide array of topics related to SMA. Each study will add to our growing understanding of SMA and play a significant role in improving the lives of those living with the disease.

Meet Our Recipients: Understanding the Pathology of SMA

Basic research lays the foundation for understanding SMA, including what causes it and how it affects different parts of the human body. In order to create optimal treatments that can help all those living with the disease, researchers across the country are looking at how to expand this understanding of the disease.

SMA modulators as a means to revealing disease mechanisms

Dr. Umrao Monani of Columbia University was awarded $150,000 for a two-year study.

- **Objective:** This study will identify genes that may affect SMA severity and test the potential effects of these genes on the disease.
- **Research Strategy:** To study these genes, researchers will create mice with two genes identified that may affect the severity of SMA. By breeding these mice with mice that have SMA, they will be able to look at how these genes might mitigate SMA severity.

To learn more about SMA and its effects, please visit **www.cureSMA.org**, which provides information and resources for patients.

- **Significance:** This project hopes to uncover how these genes lessen disease severity. Researchers believe that, once we understand more about these genes, we may be able to develop therapies that target them. As not much is known about how low survival motor neuron (SMN) protein causes neuromuscular disease, this study will seek to address how this understanding can be used to advance current SMA therapies.

The Spinal Muscular Atrophy Research Team (SMART) has generously donated $150,000 to support this grant to Dr. Monani. SMART is a grass roots organization based in Buffalo, NY that started in 2009 to raise awareness and funds for research aimed at finding a cure for SMA and related diseases. Since 2009, SMART has raised greater than $1,200,000 for SMA research. For more information, visit their website www.smarthope.com.

Hear from Umrao Monani, PhD

Dr. Monani, who is an associate professor at Columbia University, is studying how specific genes, other than SMN, impact the physical manifestation of SMA.

"I'm convinced there are better and more effective treatments down the road, and we have to invest in basic research."

Dr. Monani points out that for those who have lived with SMA for long periods of time, it is critical to understand what's happening with these genes and their subsequent proteins to develop novel means of treating the disease.

"We still have to find means by which to offer comfort and solace to those who have been suffering from the disease for a long period of time."

Dr. Monani highlights that researchers examining the basic science of SMA are doing so "with an eye on finding good treatments for the disease." He believes this basic research will have a significant impact on the treatment of SMA.

Role of astrocyte produced miR-146a in SMA pathology

Dr. Allison Ebert of the Medical College of Wisconsin was awarded $150,000 for a two-year study.

- **Objective:** This study will determine the role that astrocytes, star-shaped cells known to support motor neurons in the brain and spinal cord, play in motor neuron dysfunction and death in SMA.
- **Research Strategy:** Researchers will utilize three modeling systems to identify astrocyte involvement in SMA pathology including: patient-derived stem cells, mouse modeling, and cerebral spinal fluid from individuals with SMA.
- **Significance:** This three-pronged study has the potential to impact the understanding of astrocyte-mediated motor neuron loss and may help researchers identify a novel pathway for therapeutic intervention that could complement existing therapies.

Hear from Allison Ebert, PhD

Dr. Ebert, who is an associate professor at Columbia University, is looking at how support cells in the central nervous system, called astrocytes, play a role in SMA. She explains that the grant from Cure SMA will allow her lab to examine tissue from individuals with SMA to better understand the effect that astrocytes have on motor neurons.

"Right now, the current therapy that's available is showing tremendous benefits, but it's not a cure. By understanding disease mechanisms, we can identify additional targets to make interventions more complete and consistent across all patients and even more effective."

Dr. Ebert describes how the value of basic research is immeasurable in understanding how cells function when an individual has SMA, as well as what changes are occurring within a patient's body during treatments. In particular, she notes that using patient tissue will help create a "bigger picture" understanding for researchers.

"Collaboration between clinicians and patients in terms of basic science is very, very beneficial."

Dr. Ebert highlights the importance of collaboration within the research community. She believes that by working with both clinicians and patients, we can better understand SMA and help educate the broader medical community to reach common goals.

The shifting landscape of SMA research: towards a better understanding for a role for SMN in aging

Dr. Rashmi Kothary of the Ottawa Hospital Research Institute was awarded $50,000 for a one-year study.

- **Objective:** This study will expand our understanding of symptoms that are present in less severe cases of SMA and identify possible disease pathologies that may arise during aging for individuals with SMA.
- **Research Strategy:** Researchers will observe mice in order to gain insight into how specific aspects of SMA, such as the formation of muscle, change during aging.
- **Significance:** The underlying disease pathology of SMA may be masked by the currently short life span of many individuals with the disease. Understanding how SMA manifests in older patients will help ensure that additional therapeutic options are researched and made available.

This grant to Dr. Kothary was generously co-funded with Cure SMA – Canada.

Clinical and pathologic correlations in patients with early infantile-onset SMA

Dr. Kathryn Swoboda of the Massachusetts General Hospital was awarded $150,000 for a two-year study.

- **Objective:** This study will expand the understanding of how tissues besides motor neurons are affected by SMA and the impact of the disease on the growth and function of different parts of the body.
- **Research Strategy:** Researchers will examine tissue from patients who had SMA type I to identify problems that may not be immediately obvious. Researchers will examine both the types of cells and structures within these tissues.
- **Significance:** Recent studies have indicated that individuals with SMA type I may have additional health-related problems, including difficulties with blood sugar levels, digestion, intestinal function, and heart function. This study will help determine the most important problems that individuals with SMA type I are facing and help guide physicians to provide the most appropriate clinical monitoring and therapies.

This grant was generously co-funded by the Weisman Family Foundations.

Effects of diminished SMN on segmental spinal cord innervation of motor neurons

Dr. Robert Kalb of the Northwestern University Feinberg School of Medicine was awarded $75,000 for a one-year study.

- **Objective:** This study will determine if there are abnormal connections to motor neurons related to SMA and precisely map motor neuron connections, whether defective or not.
- **Research Strategy:** Researchers will examine the "wiring diagram" of motor neuron connections in mice using a virus-based tracing system.
- **Significance:** By identifying how motor neuron connections may be defective or not, therapies can be designed to address the potential loss of connections, which could lead to improved movement for individuals with SMA.

Meet Our Recipients: Advancing Therapeutic Pathways for SMA

While we have seen remarkable advancements in the treatment of SMA, we know that more work is needed to optimize these treatments. Not only are researchers looking at how to advance existing therapies, they are also examining how to improve clinical trials and identify new therapeutic pathways to create combinatorial treatments.

Testing the potential of SMN-AS1 as a therapeutic target in SMA

Dr. Charlotte Sumner of Johns Hopkins University was awarded $150,000 for a two-year study.

- **Objective:** This study will further assess the therapeutic potential of inhibiting a specific non-coding RNA, called SMN-AS1, as a novel treatment approach for individuals with SMA.
- **Research Strategy:** Researchers will examine SMA mice in which the SMN-AS1 locus has been deleted, in order to understand how this affects SMN gene and protein expression during neural differentiation and development, and the impact it has on disease outcomes.
- **Significance:** The results of this study will support further investment in developing SMN-AS1 as a novel therapeutic target to be used in combination with SMN-upregulating therapies.

Hear from Dr. Charlotte Sumner

Dr. Sumner, a researcher at Johns Hopkins University, will use gene-editing technology to remove specific SMA-related genes from mice, look at how the disease changes in the absence of these genes, and identify potential combinatorial treatment pathways.

"The support from Cure SMA allows us to do an experiment we couldn't do otherwise, and if it's successful, it would give us a new therapeutic target for SMA that didn't exist."

Dr. Sumner emphasizes that the effectiveness of current therapies for SMA varies for different patient populations. She notes that it's important for those across the health care industry – from scientists to insurers – to not generalize patients as researchers continue to explore different therapeutic pathways and identify therapeutic benefits.

"This is just the beginning. While recent research is a really important demonstration that this field can make substantial progress that's remarkable for a neurodegenerative disease, it makes me want to double down and work even harder to make new therapies even better."

Dr. Sumner says that the field of SMA has seen "remarkable progress," and highlights that there is more to do to understand how treatments for SMA can be optimized and bring change to patients.

Serum-derived exosomes as a biomarker for spinal muscular atrophy

Dr. Robin Parks of the Ottawa Hospital Research Institute was awarded $150,000 for a two-year study.

- **Objective:** This study will explore the development of a novel assay, based on a simple blood sample, which can be used to characterize SMA disease severity and response to treatment.
- **Research Strategy:** Researchers will use blood samples from individuals with SMA both before and after treatment with nusinersen. Researchers will monitor levels of SMN protein within the blood, identifying whether or not an increase in the amount of protein occurs.
- **Significance:** The successful completion of this work will lead to the development of a simple, minimally invasive assay that can be used to monitor the response of patients with SMA to therapy. This would enhance researchers' ability to monitor a patient's response to treatment in clinical trials.

This grant was generously funded by Cure SMA – Canada.

Study of combinatorial therapy based on SPINRAZA together with a novel protective genetic modifier

Dr. Brunhilde Wirth of the Institute of Human Genetics, Cologne was awarded $150,000 for a two-year study.

- **Objective:** The main goal of this project is to develop a combinatorial therapy using Spinraza together with antisense oligonucleotides (ASOs).
- **Research Strategy:** Researchers have identified specific genes in people who have SMN1 deletions, but no SMA symptoms. They believe these genes may be able to help protect these individuals from developing SMA symptoms. A combinatorial therapy aimed at modulating these genes will be studied in SMA mice.
- **Significance:** By developing a combinatorial therapy that targets both SMN-dependent and SMN-independent pathways, researchers believe that additional functional support may be given to affected cells.

Meet Our Recipients: Understanding the Needs of Individuals with SMA

Patients are central to all of the research being conducted on SMA. Because of this, a key focus of research is to improve our understanding of the needs of those living with SMA. By expanding our understanding, we can in turn ensure that future research is in areas that are most important to patients.

Determine the motor unit response following SMN restoration in late-onset spinal muscular atrophy

Dr. Bakri Elsheikh of the Ohio State University was awarded $150,000 for a two-year study.

- **Objective:** This study will determine the clinical effect of nusinersen in adults with SMA, explore the physiological effects by which nusinersen results in motor function improvement, lead to a better understanding of the natural history of SMA, and identify the best outcome measure for tracking responses to nusinersen in adults with SMA.

- **Research Strategy:** Researchers will follow 44 adults with genetically confirmed SMA over a 14-month period in order to assess the change in their muscle strength, as well as motor and pulmonary function, following treatment with nusinersen.
- **Significance:** The results of this study will help address the significant gap in the SMA community's understanding of the effects of nusinersen in adult forms of SMA and will clarify the long-term natural history and outcome measures of mild forms of SMA. Additionally, the results of the study will also advance the understanding of the effect of SMN protein restoration on motor unit function, thus establishing the basis for therapies to address aspects of motor unit function that are not adequately restored by nusinersen.

Hear from Dr. Bakri Elsheikh

Dr. Elsheikh, who conducts research at the Ohio State University, has identified a "clear" unmet need for individuals with SMA type II or III: a lack of data on how existing treatments are effective for adults.

"Working with SMA patients is a passion."

Dr. Elsheikh believes that this grant is particularly meaningful to his research because he sees practical, clinical, and scientific value in understanding how treatments affect older populations. He notes that this project will help researchers better understand how to restore proteins that affect motor function and has the potential to improve targeted patient outcomes.

"One size will not fit all – and we need to identify outcome measures that we can use based on the sub-populations."

Dr. Elsheikh points out clinical results are already "very promising," and there is a significant need to continue research. Specifically, Dr. Elsheikh wants individuals with SMA and their families to know that there are centers providing adults with access to SMA treatment and that they should speak with a neurologist to identify where they can receive these treatments.

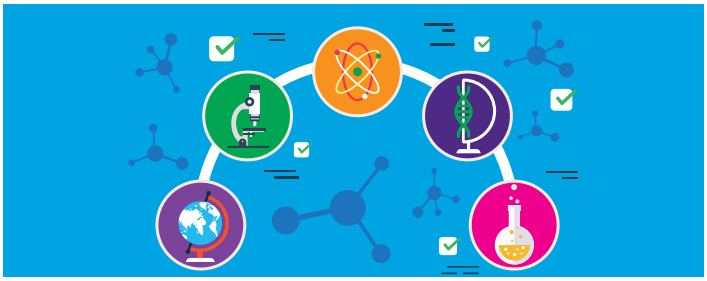
To learn more about where you can access treatments, please visit Cure SMA's website, which provides information and resources for patients.

Development of a clinically relevant outcome measure for pediatric SMA therapeutic trials

Dr. Chad Heatwole of the University of Rochester was awarded $150,000 for a two-year study.

- **Objective:** This study will develop, validate, and utilize a reliable, responsive, and patient-meaningful, disease-specific, observer-reported outcome measure for SMA clinical trials and monitoring.
- **Research Strategy:** Researchers will utilize a large cross-sectional study to identify the symptoms of SMA that are the most important to infants and children with SMA.
- **Significance:** By completing this research, the SMA research community will have a valid outcome measure to aid in the assessment of therapies and encourage therapeutic development for pediatric SMA patients.

We would like to thank each recipient for their continuous commitment to improve SMA care, as well as the entire SMA research community, which works tirelessly to improve treatment options and quality of life for families and individuals affected by the disease. Ultimately, Cure SMA recognizes and celebrates the amazing impact that research has had, and will continue to have, on treating SMA. We are dedicated to working hand-in-hand with the research community to help advance this work and look forward to the innovations that are yet to come.



Cure SMA Receive Gifts for Research

In Honor of William N. Kanehann

Cure SMA is extremely pleased to announce a generous $620,000 gift has been made to the organization. The donation was made anonymously in honor of William N. Kanehann. Billy had SMA and died in 2013 at the age of 23. We are grateful for this amazing donation in memory of his life.

This gift will be dedicated to supporting new translational SMA research with the goal of identifying new drug targets which will lead to practical new drugs and combination therapies for SMA.

Funding for this research will help discover new systems, pathways and processes that are affected in SMA. Approaches that work on these new areas could then be used in combination with the current treatment approaches being tested in clinical trials and now

approved that work on increasing SMN levels. This important work will allow us to develop maximally effective treatments for all types, ages and stages of SMA.

As the SMA research landscape has developed and the drug pipeline has grown to include the first-ever FDA approved treatment, the needs for new translational SMA research have also developed. Cure SMA continues to invest in research by funding the areas of greatest need, and where we are best positioned to make a significant difference.

Weisman Family Foundations

The Weisman Family Foundations awarded $65,800 to Cure SMA in order to further new scientific research and to help provide access to treatments, trials, and care.

A generous donation is made each year by the Weisman Family Foundations. The Weisman family has given over $1.2 million to Cure SMA through contributions from their foundation and associated family foundations.

We are especially honored to have once again been chosen as beneficiaries of a gift from this incredible family and foundation.

On behalf of the entire SMA community, thank you to Loree, Ward, Lyza and Lena Weisman, The Weisman Family Foundation, The Toby & Nataly Ritter Family Foundation, The Louis A. Ritter Foundation, and The Irene Ritter Foundation for their generous contributions to Cure SMA.

To learn more about SMA and its effects, please visit **www.cureSMA.org**, which provides information and resources for patients.

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