This year, we are proud to announce that we have awarded six new research grants, totaling $750,000, to further our mission to drive breakthroughs in the treatment of spinal muscular atrophy (SMA). Basic research is the first step in developing treatments and a cure for SMA. Basic research projects investigate the biology and cause of SMA to identify the most effective strategies for drug discovery. 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 grant 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 have 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 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 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 then ranks the submitted proposals on both their scientific merit and their relevance to Cure SMA’s research priorities. Funding is awarded to the highest ranked projects.

Cure SMA’s top basic research priorities currently include:

- Learning more about when and where the survival motor neuron (SMN) protein is needed and how it functions in the body.
- Finding new ways to treat SMA, especially those that can be used in combination with approved drugs.
- Using cellular or animal models to better understand the SMA disease process.
- Developing new tools for SMA research, such as new SMA animal models and new ways of tracking disease progression.

* Bolded terms are defined in the glossary on page 3.

To learn more about SMA and its effects, please visit www.cureSMA.org, which provides information and resources for patients.
Dr. Bowerman is a Senior Lecturer in Neuromuscular and Skeletal Disorders at the Keele University School of Medicine in the United Kingdom. She first became involved in SMA research approximately 20 years ago as a postgraduate fellow.

Currently, researchers in Dr. Bowerman’s lab work on many projects aimed at better understanding the symptoms experienced by individuals living with SMA.

Infants and children with SMA lose muscle very quickly. Muscle loss can have negative effects on different organs and tissues in the body. In her project, Dr. Bowerman and her lab will study how muscle loss affects the rest of the body. To do so, they will use mouse models of SMA in which the SMN protein is only missing in muscle. This will allow them to study how the muscle loss that occurs in SMA impacts the health and function of other organs and tissues.

Learning more about the role of muscle in SMA will help increase our understanding of how low levels of the SMN protein cause the symptoms of SMA. It will also inform the development of future SMA treatments.

Dr. Ebert is an associate professor of cell biology, neurobiology, and anatomy at the Medical College of Wisconsin. She originally became involved in SMA research about 15 years ago when she was a postdoctoral fellow. As part of her postdoctoral research, she worked with an SMA research expert, Chris Lorson, to develop a new human stem cell model for SMA. Today, Dr. Ebert leads a basic research laboratory where her research group studies how non-neuronal cells contribute to motor neuron loss in neurological diseases.

The brain and spinal cord are made up of neuronal and non-neuronal cells. Neuronal cells, like motor neurons, perform advanced functions like carrying messages from the brain to muscles. Non-neuronal cells, like astrocytes, support the structure and function of the more complex neuronal cells. Dr. Ebert’s previous research has shown that in SMA, astrocytes undergo changes that prevent them from being able to adequately support motor neurons.

In this project, Dr. Ebert’s research group will use a human stem cell model to determine how the loss of a specific protein, teneurin (TENM4), affects the ability of astrocytes to support motor neurons. Utilizing a range of laboratory techniques, including microscopy and protein biochemistry, they will investigate how astrocytes develop and function in the absence of the TENM4 protein. Dr. Ebert and her colleagues will also determine whether supportive function can be restored to astrocytes by adding back the missing protein.

Learning more about the effects of SMA on non-neuronal cells will contribute to researchers’ overall understanding of the disease process. Dr. Ebert also hopes the results of this project will uncover new targets for SMA therapeutics that, combined with existing therapies, can achieve the best possible outcomes for people with SMA.

Lyndsay Murray, PhD, at the University of Edinburgh in Scotland was awarded $150,000 for her research project, “Investigating the viability of vulnerable motor axons following SMN restoration in mouse models of SMA.”

Dr. Murray leads a research laboratory at the University of Edinburgh in Scotland. She became involved in SMA research during graduate school, when she was one of the first scientists to describe how the connections between motor neurons and muscle break down in SMA mice. After graduate school, Dr. Murray continued to research SMA, and in 2014, she established her own lab in Edinburgh.

Today, Dr. Murray’s research group uses SMA mouse models to better understand how motor neurons and muscles recover when treatment is given. They want to find new ways to speed and improve the recovery of motor neurons affected by SMA.

Motor neurons carry messages from the brain to muscles. In people with SMA, SMN protein deficiency can cause motor neurons to become unhealthy, causing muscle wasting (shrinkage). Dr. Murray’s group believes that in infants with SMA, a specific sub-group of motor neurons are developmentally immature and vulnerable to disease. They believe that these immature motor neurons do not respond well to currently approved treatments for SMA.

In their current project, Dr. Murray’s group wants to learn more about these immature motor neurons and how to support them. The researchers will use high power microscopes to study immature motor neurons in an inducible SMA mouse model. The inducible SMA mouse is normally deficient in the SMN protein. However, Dr. Murray and her colleagues can use a chemical switch to turn on the expression of the SMN protein in the inducible mouse.

This technique will enable Dr. Murray’s research lab to study how immature motor neurons function with and without the SMN protein. They will also investigate whether a combination of approved SMA treatments can help protect these motor neurons. Insights from this research could improve the effectiveness of current treatments and result in better outcomes for people with SMA.
Gene is deleted or mutated occurs when the — A shortage of the SMN protein that SMN protein deficiency — A gene that has qualities to mimic a biological process or disease that a researcher wants to study gene - A DNA sequence that contains the instructions to produce a specific protein at a specific time and in specific cells. Genes are organized into chromosomes and stored inside the nuclei of cells human stem cell model – A cell that begins undifferentiated or “blank” and can be manipulated in the laboratory to develop into a specialized cell, such as an astrocyte, for research motor neuron - The type of nerve cell that sends messages between the brain and muscles. These signals direct the movement and control of the head, neck, chest, abdomen, legs, and limbs mutation - A mistake in a gene that will be copied into RNA when the gene is turned on. The mutation may affect the structure and function of the protein that is made from the instructions in that gene nucleus/nuclei - A specialized organelle within most types of cells that contains the cell’s genes on structures called chromosomes. The nucleus acts as the cell’s control center because it contains the instructions for how to make the proteins needed for the cell to function protein - A molecule made up of amino acids strung together in a specific order that is encoded by the protein’s gene. The specific sequence of amino acids determines the protein’s structure and function in the cell RNA - A chemical copy of a gene that provides the instructions for the specific amino acid sequence that is needed to make a specific protein RNA splicing – Chemically trimming an RNA molecule to prepare it to take the instructions for a specific protein from a gene in the nucleus to elsewhere in the cell survival motor neuron 1 gene (SMN1) - A gene that contains the instructions for the SMN protein, which is required for motor neuron health and function. Deletion or mutation of the SMN1 gene results in SMN protein deficiency. To be affected by SMA, an individual must inherit two faulty SMN1 genes, one from each parent survival motor neuron 2 gene (SMN2) - The SMN protein’s “back-up” gene. Like the SMN1 gene, the SMN2 gene also encodes the SMN protein. However, much of the SMN protein made from the SMN2 gene is shortened and doesn’t function well survival motor neuron protein (SMN) - A protein made from the instructions encoded in the SMN1 gene and the low-functioning SMN2 gene. The health and function of motor neurons is dependent on the SMN protein SMN protein deficiency — A shortage of the SMN protein that occurs when the SMN1 gene is deleted or mutated

In people with SMA, deletion or mutation of the SMN1 gene results in SMN protein deficiency. Previous research has shown that the presence of the SMN protein is required for motor neurons to stay healthy and function properly. However, researchers continue to try and understand more about the timing and cellular pathways involved in motor neuron death caused by SMN deficiency.

By adding to the knowledge about SMN’s role in the health and function of motor neurons, Dr. Kolb’s project will enhance the understanding of how current treatments work. The results of this project may also inform future SMA drug development.
**Motor neurons** are cells in the central nervous system that relay information from the brain to muscles. In people with SMA, **motor neurons** can become unhealthy, causing muscles to lose strength and function. **Motor neurons** contain a chemical messenger called **RNA** in their **nuclei**. RNA messages change depending on what is happening inside a **motor neuron**. For example, the **RNA** found in a healthy **motor neuron** will contain different messages than those found in an unhealthy **motor neuron**.

In her current project, Dr. Molotsky will analyze **RNA** from the individual spinal cord **motor neurons** of SMA mice at different stages of disease progression. By determining how **RNA** messages change as these **motor neurons** become unhealthy, Dr. Molotsky will learn more about which cellular processes are disrupted in the **motor neurons** of people with SMA. Her research may also reveal new targets for future SMA drugs.

Dr. Tellier became a principal investigator at the University of Leicester in the UK in January of 2023. For many years, his research has focused on molecules that activate **genes** by binding to them. Recently, Dr. Tellier became involved in SMA research when, together with Dr. Sylvain Egloff, he found that one of the molecules he is studying regulates the activity of the **survival motor neuron 1 (SMN1)** and **survival motor neuron 2 (SMN2)** genes.

Both the **SMN1** and **SMN2** **genes** encode the **SMN protein**, which is necessary for **motor neuron** health and function. In SMA, a mutation in the **SMN1 gene** results in low levels of the **SMN protein**, causing **motor neuron death**. Although the **SMN2 “back-up” gene** also encodes the **SMN protein**, most of the **SMN protein** it produces is shortened and unstable.

Dr. Tellier previously discovered that a small, non-coding RNA molecule called “7SK” binds to and activates the expression of the **SMN1** and **SMN2** genes. Furthermore, he found that 7SK also interacts with the **SMN protein** itself to form a complex. In his current research project, Dr. Tellier and his fellow researchers want to determine if the 7SK-**SMN protein** complex plays a role in **SMN1** and **SMN2 gene** activation. He will also investigate whether mutations in the **SMN1 gene** that cause SMA disrupt the function or formation of this complex.

To accomplish these objectives, Dr. Tellier and his research group will create new cell lines. A cell line is a defined population of cells that share a group of identical traits and can be kept alive, or cultured, in a laboratory for an extended period. These new cell lines will have special characteristics that will allow Dr. Tellier and his colleagues to track the expression of the **SMN1** and **SMN2 genes**, as well as the activity of the **SMN protein**.

From the results of this project, Dr. Tellier and his colleagues hope to learn more about the regulation of **SMN1** and **SMN2**, including whether the **SMN protein** increases the expression of its own **genes**. Because all three currently approved SMA treatments work by increasing **SMN protein** levels, this information will have important implications for current and future SMA treatments. In addition, Dr. Tellier’s new cell lines will not only be useful in this project, they may also be utilized in future SMA research by other scientists.

**Special thanks to the Concepcion Family, Nunemaker Family, Weisman Family, Luke 18:1 Foundation and Dhont Foundation for their generosity to Cure SMA in our quest to invest in basic research that will ultimately drive the next generation of SMA treatments.**

**Figure 1.** Cure SMA Basic Research Grant recipients plan to use a variety of approaches to learn more about SMA disease and treatment.
Cure SMA Launches Phase 9 of the SMA Industry Collaboration

Established in 2016, the SMA Industry Collaboration (SMA-IC) is a multi-faceted partnership that brings together pharmaceutical companies, Cure SMA, and other nonprofit organizations to share information, ideas, and data. The SMA-IC works together to address scientific, clinical, and regulatory topics critical to advancing drug development in spinal muscular atrophy (SMA). It is currently comprised of our partners at Scholar Rock, Biogen, Novartis, Biohaven Pharmaceuticals, Genentech/Roche, Alcyone Therapeutics, NMD Pharma, and SMA Europe.

Through the SMA-IC, we fund research to ensure that effective, safe treatments can progress through clinical trials quickly and gain approval from the United States Food and Drug Administration (FDA) and international regulators. Our research also ensures these treatments address the unmet needs of the SMA community, and that the community’s priorities and goals are incorporated into the development, review, and approval of therapies. The SMA-IC consists of four topic groups; prior year accomplishments and Phase 9 priorities for the 2024 calendar year are outlined below.

2023 SMA Industry Collaboration Accomplishments

**Topic Group 1: Approaches to Enabling Drug Development and Clinical Trials**

The Approaches to Drug Development Topic Group is actively working to engage regulatory authorities to deepen their understanding of SMA and the perspectives of individuals living with SMA on which treatment outcomes are clinically meaningful. In 2022, Cure SMA launched the Cure SMA Risk/Benefit Survey to learn about the SMA community’s current views on treatment risks and benefits. Respondents were asked how willing they were to live with 11 different SMA treatment risks in exchange for the possibility of certain treatment benefits (Figure 1).
These results were then compared with those obtained from a similar study carried out in 2017, to determine if community perspectives have changed as more treatment options have become available. The findings will be shared with the FDA. A summary document for the SMA community is also available on the Cure SMA website.

Figure 1. Sample survey question

The Approaches to Drug Development Topic Group also strives to help prospective trial sites improve their preparedness to conduct SMA clinical trials. In 2018, the Industry Collaboration launched the Cure SMA Clinical Trial Readiness Program to equip sites with resources to support effective, patient-centered management of SMA clinical trials. Last year’s program activities focused on how changes in the screening landscape, staffing shortages, and facility constraints are affecting site capacity and recruitment for SMA trials. In early 2023, an analysis of the current SMA clinical trial landscape was launched to understand current site capacity and projected recruitment needs for SMA trials over the next five years. The analysis showed that despite the increase in SMA trial sites across the U.S. since 2017, greater site capacity is still needed to accommodate the increase in trial participant recruitment needs. To better understand current experiences with site capacity and recruitment for SMA trials, Cure SMA spoke with various industry sponsors and SMA trial sites. The learnings from these discussions informed the development of a survey to understand site capacity for SMA trials. The survey was distributed to SMA trial sites across the U.S. between June 28, 2023 – August 11, 2023. Key findings from the survey results indicate most sites still have the capacity to conduct additional SMA trials. Additionally, the survey analysis revealed that increasing the number of clinical trial staff and streamlining physical therapist (PT) training for trials were reported as the most helpful factors to increase site capacity. Findings from the 2023 survey informed topic group efforts to revamp the Cure SMA Clinical Trial Readiness Toolkit and the Best Practices for Clinical Research Coordinators Toolkit; updated materials will be available on the Cure SMA website in spring 2024.

Topic Group 2: Education and Awareness to Promote Broad and Inclusive Research, Treatment, and Care of SMA Patients

The Education and Awareness Topic Group seeks to engage individuals and families affected by SMA to understand and identify disparities in SMA care, treatment, and clinical trial research. Last year, the Topic Group developed and launched the 2023 Clinical Trial Experience Survey (CTES) to evaluate the motivators, barriers, stressors, and benefits associated with trial participation from the perspective of caregivers and adults living with SMA. Similar research was carried out in 2019 to obtain the views of prior trial participants. Since the publication of that research, the SMA diagnosis and treatment landscape has changed radically. Due to these changes, Cure SMA expanded the CTES to obtain current perspectives from prior SMA clinical trial participants, people who considered participating in a SMA clinical trial but did not enroll, and those who had never considered clinical trial participation. The final analysis will be developed into a manuscript for peer review, and is also being utilized to create a multi-pronged awareness campaign to increase clinical trial awareness, knowledge, and access among the SMA community. The campaign will feature a searchable SMA clinical trial registry, 1-page handouts, and videos. All materials will be available on the Cure SMA Clinical Trials website in early spring.

Figure 2. Core Data Fields Captured by the Community Update Survey (CUS)

Topic Group 3: Cure SMA Patient-Reported Data

The goal of this Topic Group is to collect patient-reported data to better understand SMA, the evolving phenotypes as new therapies are approved, and the continued burden of SMA. In 2023, the Topic Group launched the 7th Annual Cure SMA Community Update Survey (CUS). The survey is distributed each year to capture longitudinal self- and
caregiver-reported data on the characteristics, experiences, and outcomes of individuals with SMA (Figure 2). Our top priority is to represent the patient voice from the whole community, so we can drive research and care to meet patient needs. Every piece of data collected allows Cure SMA to track changes in the attitudes, feelings, and actions of the SMA community over time. Findings are shared with federal and state policymakers, insurers, and other key officials to support the ongoing care and program needs of the SMA community.

Cure SMA is also working to develop a manuscript to highlight findings of a longitudinal analysis of data captured from the 2017 – 2023 CUS (Figure 3). The objective of the analysis is to describe factors related to motor function changes over time among children living with SMA Type 1. Factors analysed include age at first treatment, use of mono- vs. combo therapy, SMN2 copy number, gender, race, and age at time of survey completion. Results from the analysis revealed motor function gains over time decreased with every week delay in treatment initiation. Results also showed that individuals that utilized combination therapy over mono-therapy experienced greater gains in motor function over time, while males and non-white individuals experienced a decrease in motor function over time.

For additional information, or to access manuscripts, toolkits, and other resources generated by the SMA-IC, please visit https://www.curesma.org/sma-industry-collaboration/.

**Phase 9 (2024) SMA Industry Collaboration Priorities**

During Phase 9, we will build upon previous achievements to further refine outcome measures and enhance knowledge of the SMA patient experience. Additionally, we will work to identify and address disparities that limit patient access to clinical research, treatment, and care. Key projects include:

- Update of the Cure SMA Toolkit on Best Practices for SMA Physical Therapists and Clinical Evaluators
- Creation of a Global Set of Patient Centered Outcomes for SMA
- Development of a Survey to Identify Unmet Needs and Access Disparities for SMA Treatment and Care
- Development of a Survey to Evaluate the Diagnostic Journey of Adult Onset SMA
- Launch of the 8th Annual Cure SMA Community Update Survey
- Pan European Survey on Treatment Decision Making
- Development of a Guide on Patient-relevant Design of SMA Clinical Trials

**Conclusion**

Thanks to the dedication of our community and the ingenuity of our researchers, we now have three approved disease-modifying treatments that target the underlying genetics of SMA and are expected to change the phenotype. However, many unmet needs remain for the SMA community. The SMA-IC provides opportunities for Cure SMA to collaborate with academics, industry, regulatory agencies, and individuals living with SMA and their families, to actively identify and advance goals important to the SMA community. Cure SMA appreciates the invaluable funding support for the SMA-IC, provided by our partners at Scholar Rock, Biogen, Novartis, Biohaven Pharmaceuticals, Genentech/Roche, Alcyone Therapeutics, and NMD Pharma.
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.

**New Planned Research Funding**

Cure SMA Announces $2.5 Million in

**Organizations/Drug Name or Approach**

- **Biosgen/Sentis-Spinraza**
- **Novartis-Zolgensma (IV)**
- **Roche-Genentech/PTC/SMAF-Evrysdi**
- **Scholar Rock - Algopenrion GM-010 [Muscle Directed]**
- **Novartis-GX101 (ArNOX 101)**
- **Roche-Genentech-GYM329**
- **Biohaven-Taldegrasp alpha (BHv-2020)**
- **NMD Pharma-NMD-670**
- **BIB115 (Rox Gen SMN ASO)**
- **Columbia/NI-P38aMAPK Inhibitor**
- **MU Shift Pharmaceuticals-E1 ASO**
- **Aurimedi Pharma-Small Molecules**
- **Praxis Biotech-Protein Synthesis Enhancers**
- **Menax-Modifier Program**
- **Meriney-Calcium Channel Modifiers**
- **Patten-Zebrafish Screen**
- **Jablonka-Calcium Channel Modifiers**
- **Wyper Therapeutics-AAV Gene Therapy**

**IND = Investigational New Drug  NDA = New Drug Application  Last updated: April 2024**

**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.