COMPASS

A Publication Dedicated to Research Updates SUMMER 2015

Cure SMA Announces $775,000 in New Drug Discovery Grants to California Institute for Biomedical Research (Calibr) and Nationwide Children's Hospital

Developing a treatment and cure for SMA is the driving force behind Cure SMA, and the goal of our three-stage research model.

Drug discovery is the pivotal second stage of that research model. The model begins with basic research, which investigates the causes and biology of SMA. Drug discovery then takes these basic research ideas and converts them into practical drug candidates that can be tested in the third stage: clinical trials.

Through this step-by-step model and through the diversity of therapeutic approaches we've identified, we are able to minimize the most common challenges of drug discovery by building a diverse "pipeline" of drug candidates. Fifteen years ago, we had just two potential drugs in the pipeline. Today we have eighteen, including seven now in clinical trials. Cure SMA has funded half of these drug programs.

While there is real promise in the research landscape right now, which gives us great reason for hope, we know that much work remains to be done. There's a pressing need for continued and growing investment in drug discovery, to respond to the complexities of the process and lead into clinical trials. This is why we aggressively invest in promising programs.

For more information on these grants, our research model, and the latest research news, visit

www.cureSMA.org

This latest round of funding includes:

- $330,000 to the Calibr small molecule program, led by Peter Schultz, PhD, bringing the total invested in that program to over $1 million.
- $445,000 to the Nationwide Children's Hospital gene therapy program, led by Brian Kaspar, PhD, bringing the total invested in that program to $845,000: $745,000 for the CSF gene therapy program and $100,000 for the systemic gene therapy program.

Attacking SMA from All Sides

Through our research model, we've identified four therapeutic approaches that may be used to treat SMA. The Calibr and Nationwide Children's programs address two of these approaches: correction of the mutated survival motor neuron gene 1 (*SMN1*) and modulation of survival motor neuron gene 2 (*SMN2*), the SMA "backup gene." Both of these approaches are notable since they address the underlying genetics of SMA.

Survival motor neuron (SMN) protein is critical to the function of the nerves that control our muscles. Individuals with spinal muscular atrophy don't properly produce this protein at high enough levels, due to the mutation in *SMN1*. The Nationwide Children's Hospitals gene therapy project aims to correct this mutation, using a virus to "infect" cells with new *SMN1* DNA.

In addition, all individuals with SMA have one or more copies of *SMN2*. However, *SMN2* makes only a small amount of functional SMN protein. The Calibr project is one of several that is looking for ways to prompt the *SMN2* gene to make more protein.

HOW OUR NEW DRUG DISCOVERY GRANTS ARE MOVING RESEARCH FORWARD

Calibr
California Institute for Biomedical Research

About the CALIBR Program

This partnership first began in 2012, when we awarded $700,000 to Peter G. Schultz, PhD, and his team for their drug discovery program, "Optimization of Small Molecules that Increase *SMN2* Levels for the Treatment of Spinal Muscular Atrophy."

Peter Schultz, PhD

Small molecules are chemicals that can treat or cure a disease. The Schultz group previously discovered several different compound classes that enhance SMN protein levels. Our funding to CALIBR has been focused on turning these compounds into a useable drug through a process called medicinal chemistry.

Progress to Date

As with all our drug discovery grants, this program was awarded by the Cure SMA Translational Advisory Council (TAC), a group of drug discovery and SMA experts. Funding for this project is provided after achieving a series of predetermined milestones, which are reviewed and approved by a sub-group of the TAC convened specifically to oversee this program.

To date, the research team has completed the following:

- They have demonstrated that compound treatment elevates SMN protein levels in a severe mouse model of SMA.
- They have identified new related compounds, called analogs, that require less drug to increase SMN levels.
- They have identified new analogs with more drug reaching the brain.

Recently, we expanded our funding of this project to include a collaborative effort with Dr. Chien-Ping Ko of the University of Southern California. Currently, Dr. Ko and the team are testing compounds for benefit in a severe mouse model of SMA. They will be assessing weight gain, motor function, survival, and motor neuron morphology at synapses in the central nervous system and at the muscle.

Next Steps for New Funding

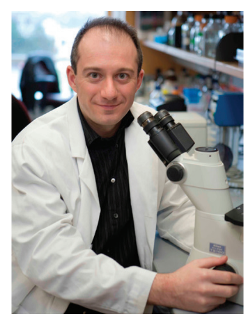
The new goals of the project, which will also be funded through a series of predetermined milestones, focus on continuing to optimize compounds in order to identify a drug candidate suitable for human testing. These goals include demonstrating a survival benefit in a severe model of SMA, further enhancement of brain exposure, and optimization of safety and selectivity of the lead compounds.

These optimized compounds will hopefully lead to a clinical development candidate. The candidate would then undergo the series of studies required for an Investigational New Drug (IND) application, the first step to obtaining FDA approval for a human clinical trial.

NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.℠

About the Nationwide Children's Hospital Program

Brian Kaspar, PhD, principal investigator in the Center for Gene Therapy at Nationwide Children's, and his team have made promising strides toward therapies to treat SMA.



Brian Kaspar, PhD

Gene therapy, also known as gene transfer, may increase SMN levels by using a viral vector to deliver the *SMN1* gene to affected cells. Dr. Kaspar's laboratory discovered that adeno-associated virus serotype 9 (*AAV9*) had the unique ability to cross the blood-brain barrier and the blood-cerebrospinal fluid (CSF) barrier.

We thank the following families and foundations for their generous contributions toward these grants: The Jacob Isaac Rappoport Foundation and The Miller McNeil Woodruff Foundation toward Dr. Kaspar, and The Michael and Chandra Rudd Foundation toward Drs. Kaspar and Schultz.

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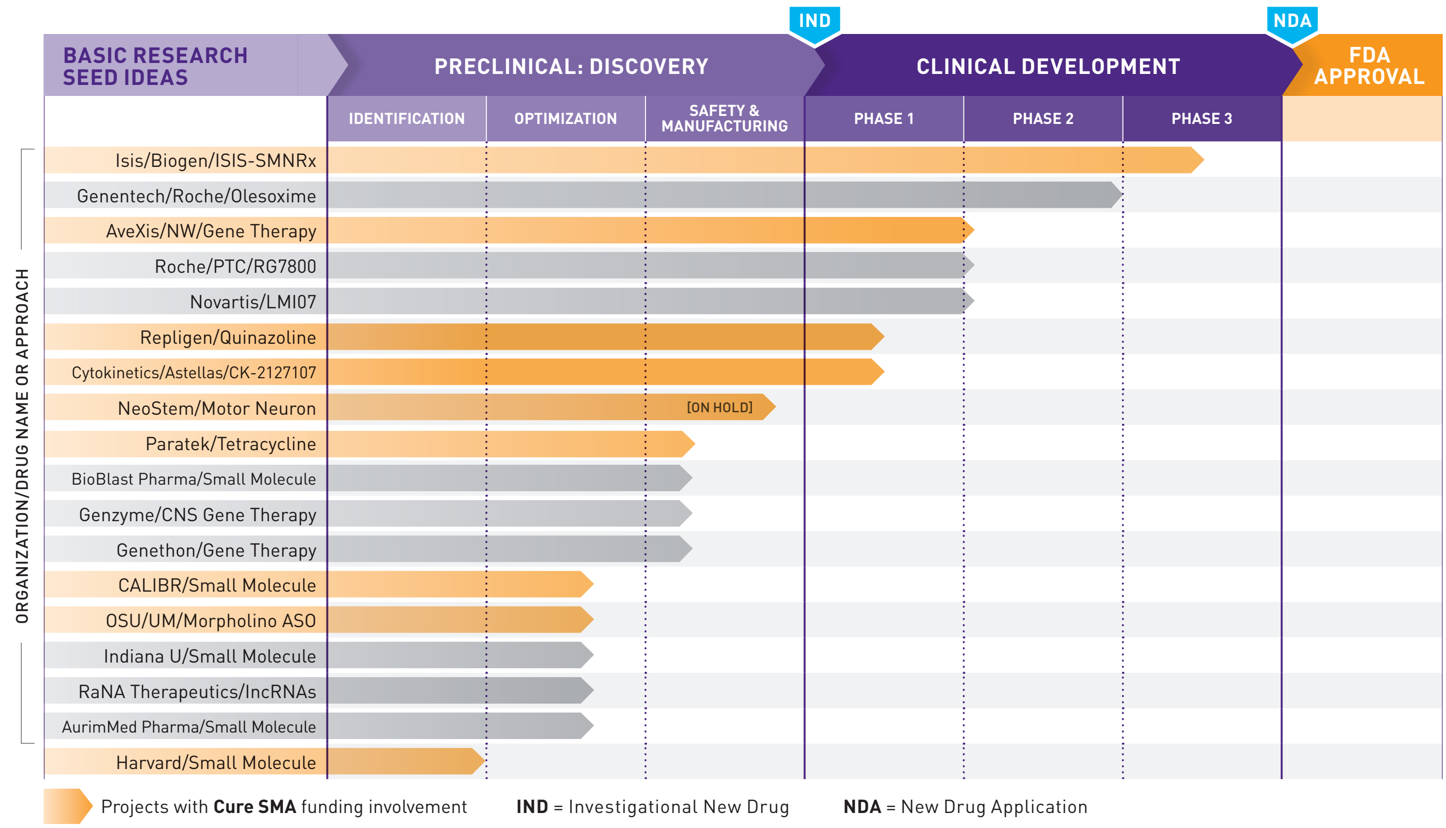
SMA DRUG PIPELINE: JUNE 2015



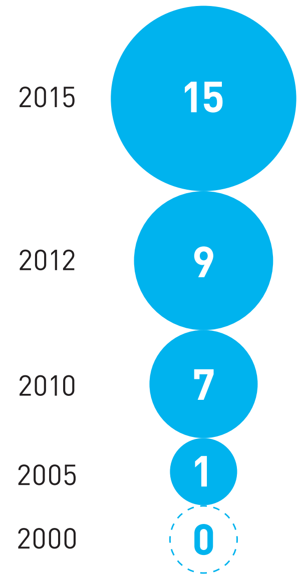
Our approach to research is focused on continually expanding the pipeline of potential drugs and therapies for SMA, cultivating new approaches and advancing promising ideas. The drug candidates shown represent all of our therapeutic approaches. Every year, the pipeline gets broader and deeper. We've seen enormous growth over the past decade, and we expect that growth to continue in the coming years as more projects approach potential FDA approval.

This newest update to the pipeline includes 18 programs in development, and seven of those 18 now in clinical trials. Both of these are the highest totals we've reached so far.

It can take upwards of 15 years for a drug to reach FDA approval, a process that starts with thousands of potential compounds before narrowing to a single drug candidate for testing in clinical trials. And even then, an estimated 90% of drug candidates will fail in clinical trials. While much work has already been accomplished, we know that much more remains to be done:

- **We're aiming to increase the cumulative number of drugs in the pipeline to over 30**—a key tipping point at which we'll have a realistic chance of finding a treatment and cure.
- **We're continuing to pursue a breadth of options** that will ultimately lead to a treatment and cure for every person affected by SMA.
- **We're looking at how researchers are treating related diseases,** to see if their discoveries can tell us anything new about how we can develop new approaches for SMA.

NUMBER OF COMPANIES INVESTING IN SMA DRUG PROGRAMS



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Progress to Date

Beginning in 2010, Cure SMA made a series of grants to Dr. Kaspar to study gene transfer. Dr. Kaspar and his team have studied two approaches for SMA gene therapy: an injection into a vein, a process known as systemic delivery which is currently in clinical trials, and delivery directly into the cerebrospinal spinal fluid (CSF), a process known as CSF-delivered gene therapy.

Using the data generated with Cure SMA funding on the CSF-delivery of the drug, Dr. Kaspar and his team were able to secure a $4 million grant from NINDS in 2013, to develop this delivery approach for human clinical trials in SMA.

In a November 2014 article in *Molecular Therapy*, Dr. Kaspar and his team reported that, after a one-time delivery of the *AAV9* carrying the human SMN gene, SMA animals, which typically die at 15 days of age, surpassed 280 days median survival, with many animals surviving past 400 days. This is a remarkable extension in survival with normal motor function. Furthermore, the group tested this delivery approach in larger species and found significant targeting of motor neurons throughout the brain and spinal cord.

"We were able to demonstrate remarkable survival rates with normal motor functions in our SMA animal models, and found significant targeting of motor neurons throughout the brain and spinal cord," Dr. Kaspar explained. "We are excited about our progress to advance a CSF route of delivery to human clinical trials for SMA and we are grateful for the continued support from Cure SMA."

Next Steps for New Funding

The new funding will now support regulatory filings with the FDA to begin a new clinical trial, studies to define dosing levels for a clinical trial focused on CSF-delivered gene therapy, and support screening potential patients for the trial and evaluating their responses to the therapy.

A critical long-term goal of the Cure SMA drug discovery approach is to help identify treatments for SMA patients of every age, disease type, and stage. One of the most compelling aspects of CSF-delivered gene therapy is the promise it shows for reducing the amount of drug required for larger and older patients. This could eventually make the treatment accessible to a wider population.

The technology for both systemic and CSF-delivered gene therapy has been licensed to AveXis, a clinical stage biotechnology company.

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