COMPASS

A Publication Dedicated to Research Updates | Winter 2019

Cure SMA is pleased to announce $600,000 in grant funding to help build programs focused on novel targets in the SMA drug pipeline.

Drug discovery, also called translational research, is the second step in the drug development process. Drug discovery takes the seed ideas discovered in basic research, the first stage, and converts them into usable drugs that can then be tested in the third stage, clinical trials.

Our unique approach minimizes the most common challenges of drug discovery by building a diverse "pipeline" of drug candidates.

- **We invest in a number of projects at a time,** which means that if a drug candidate fails, several others can take its place.
- **We fund projects that represent a variety of therapeutic approaches,** attacking SMA from all sides.
- **We provide seed funding for new projects.** Traditionally, it has been difficult to get pharmaceutical companies to invest in research for rare diseases like SMA. By providing early-stage funding, we lower the risk and attract larger investments from industry and government as drug candidates move through the process.
- **We are unbiased as we evaluate all possible treatment opportunities,** and we prioritize, select, and manage our drug discovery projects through a Translational Advisory Committee, comprised of industry experts.

This current round of funding reflects this diverse, unbiased strategy. The grants given represent the two of the most significant and promising avenues for SMA treatment.

Currently, there are two major ways of treating SMA that researchers are studying. Due to a mutation in the survival motor neuron 1 gene, individuals with SMA don't produce survival motor neuron protein at high enough levels. One way of treating SMA is to address this directly, by increasing the amount of survival motor neuron protein in the body. These approaches are called "SMN-based" or "SMN-enhancing" approaches.

Our grant to Dr. Kevin Hodgetts will help develop this therapeutic approach, by exploring ways to increase the amount of SMN protein in the body.

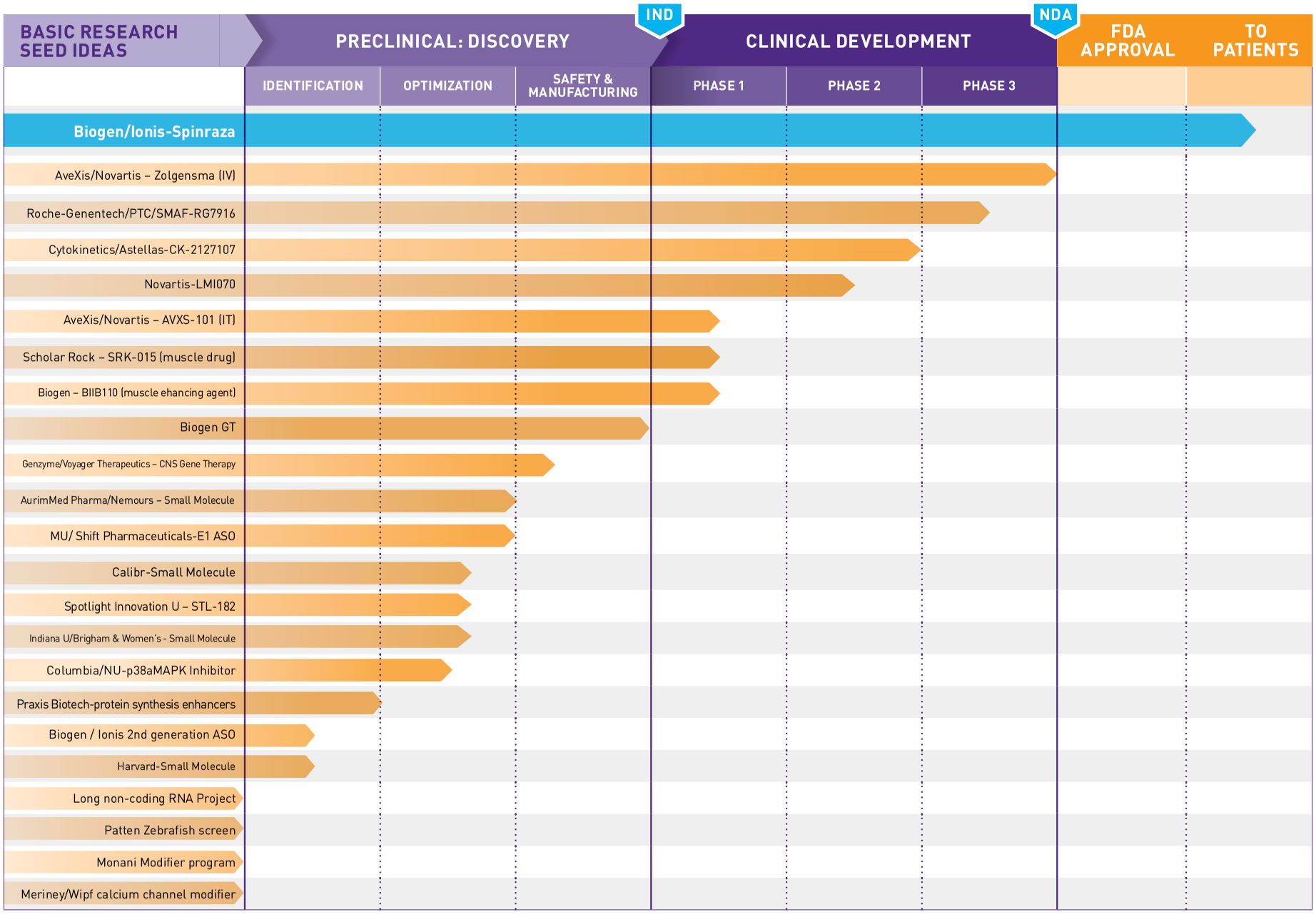
This loss of survival motor neuron protein also impacts a number of other systems, pathways and processes in the body. A second way of treating SMA is to address these other systems, pathways and processes directly. These approaches are often called "non-SMN" approaches. New research is required to identify and validate these new drug targets.

Our grant to Dr. Umrao Monani will focus on validating a non-SMN genetic target that could be used along with an SMN-enhancing therapy.

Most importantly, many researchers believe the best possible effect may come from using an SMN-enhancing approach together with one or more non-SMN approaches.

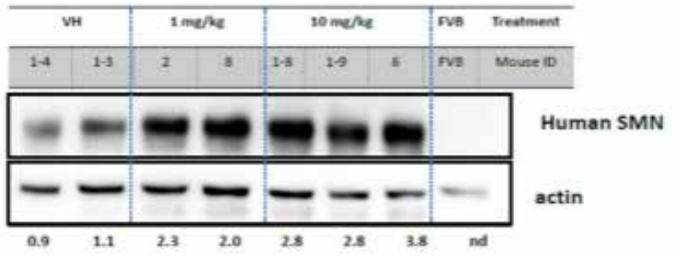
SMA DRUG PIPELINE

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 for everyone affected, and eventually lead to a cure.



IND = Investigational New Drug **NDA** = New Drug Application Last updated: February 2019

Cure SMA Awards $300,000 Grant to Kevin Hodgetts, PhD, The Brigham and Women's Hospital



The above protein blot demonstrates an increase in SMN protein following drug treatment.

Cure SMA has awarded a $300,000 preclinical drug discovery grant to Kevin Hodgetts, PhD, at the Brigham and Women's Hospital, for his project, " Pre-Clinical Development of LDN-5178 for the Treatment of SMA."

This grant will be conducted by two academic research teams working together to identify new treatments for SMA. The two teams are led by Prof. Kevin Hodgetts at the Laboratory for Drug Discovery in Neurodegeneration (LDDN) at Brigham and Women's Hospital, an affiliate of the Harvard Medical School, and Prof. Elliot Androphy at Indiana University.

The two academic research teams work together on the optimization of novel small molecules as activators of SMN2 protein. With this funding, they will continue the development of their lead series of compounds that increase the half-life and accumulation of normal SMN protein. These lead compounds have been shown to increase SMN protein in brain and extend survival and motor function in a mouse model of SMA.

In this proposal, the research teams will perform pre-clinical safety and toxicity studies on their lead molecules to ready them for Investigational New Drug (IND) submission.

Q & A with Dr. Hodgetts

What do you hope to learn from this research project?

This funding will be used to continue the development of our lead series of compounds, performing pre-clinical pharmokinetics and toxicity studies, to ensure that they are as safe and effective as possible prior to entering clinical trials.

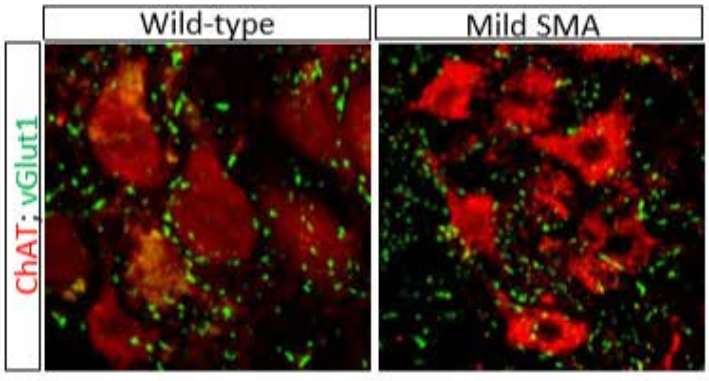
How will this project work?

We have identified lead compounds that increased SMN protein in brain and extended survival and motor function in a mouse model of SMA. In addition, we discovered in test tube experiments the use of our leading compounds, in combination with other SMN increasing agents (e.g., splicing modifiers), gave a synergistic increase in SMN protein. With this funding, we will perform pre-clinical pharmokinetics and toxicity studies on our lead molecules prior to IND submission.

What is the significance of your study?

If we can translate our test tube finding, that our compounds work synergistically with SMN increasing agents such as Spinraza, to first mice and then humans, it potentially would reduce the needed quantity and frequency of administration of Spinraza, resulting in greater therapeutic response and reduced occurrence of side effects.

Cure SMA Awards $300,000 Grant to Umrao Monani, PhD, Columbia University



The above image shows the equivalence in numbers of sensory synapses on motor neurons of mild SMA mutants overexpressing the gene of interest and healthy wild-type controls.

Cure SMA has awarded a $300,000 preclinical drug discovery grant to Umrao Monani, PhD, at Columbia University, for his project, " Restoring function at the NMJ: A novel means to treat SMA."

A drug directed at SMN enhancement, Spinraza, has recently become available but is unlikely to benefit all patients with maximal effectiveness. The objective of this project is to validate a novel genetic factor, besides SMN up-regulation, that could serve as a new target for complementary treatments for SMA.

Dr. Monani and his team will use viral vector technology (gene therapy), to determine if the genetic factor can be reliably delivered to SMA mice and attenuate severe disease. Secondly, the team will determine if the factor is equally potent in its effects across mouse models of differing SMA severity and at different points of time.

These experiments will serve as proof of concept studies to validate moving into IND enabling studies and human trials. The greater the number of ways one can combat SMA, the more likely the entire population of SMA patients will benefit.

Q & A with Dr. Monani

What do you hope to learn from this research project?

Spinal muscular atrophy is a devastating neuromuscular disorder caused by low SMN protein. SMN repletion as a treatment strategy has recently become available but is unlikely to benefit all patients. The objective of this project is to validate a novel genetic factor that could serve as a new target for complementary treatments for SMA.

How will this project work?

Two approaches are proposed here. Both involve SMA model mice. First, we will use viral vector technology to determine if the genetic factor can be reliably delivered to SMA mice and attenuate severe disease. Second, we will determine if the factor is equally potent in its effects across different mouse models of SMA.

What is the significance of your study?

It is absolutely essential that new approaches to treat SMA are developed. Currently only one strategy, SMN repletion, is being exploited as a means to a treatment. Furthermore, there is presently just one FDA-approved drug that accomplishes this objective. The greater the number of ways one can combat SMA, the more likely the entire population of SMA patients will benefit. A positive outcome to the project will serve as the springboard to another effective way to properly treat SMA.

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.

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