COMPASS

A Publication Dedicated to Research Updates SUMMER 2016

Cure SMA Announces $704,000 in New Drug Discovery Grants

As the SMA drug pipeline has grown in breadth, depth, and sophistication, the need for combination therapies has become increasingly apparent.

Individuals with SMA don't produce survival motor neuron (SMN) protein at high enough levels due to a mutation in the survival motor neuron 1 (*SMN1*) gene. Much of the early research into SMA has focused on increasing SMN production, either by replacing or correcting *SMN1* or by modulating *SMN2*, the low-functioning SMA "backup gene." Many of these SMN-based approaches (also called "SMN-enhancing" approaches), such as gene therapy and antisense oligonucleotides, are already being tested in clinical trials.

Furthermore, research has also revealed that a number of systems, pathways, and processes are affected in SMA, and there may be additional ways to treat SMA that work on these other areas. These types of treatments are often referred to as "non-SMN" treatments or approaches.

And perhaps most crucially, these non-SMN approaches could be used in combination with SMN-enhancing approaches, allowing us to attack SMA from all sides and giving us the best chance of a comprehensive, effective treatment. This is particularly important as we seek to develop treatments for all ages, stages, and types of SMA.

How We're Working to Advance Treatments for All Ages, Stages, and Types of SMA

This current round of drug discovery funding reflects the importance of combination therapies. Grants totaling $604,000—$300,000 to Dr. Charlotte Sumner, in collaboration with Imago Pharmaceuticals, and $304,000 to Dr. Livio Pellizzoni—will support investigation into non-SMN treatments that could eventually be used in combination with SMN-enhancing treatments.

The remaining $100,000—$50,000 each to Dr. Barrington Burnett and Dr. Kevin Hodgetts—will support investigation into SMN-enhancing treatments that work in different ways than the SMN-enhancing treatments already being studied. This could provide yet another avenue for potential combination therapies: the use of two different SMN-enhancing approaches together to provide a stronger overall effect.

About the Sumner/Imago Project

Jun N-terminal kinase (JNK) is a stress-activated enzyme (an enzyme is a special kind of protein capable of producing specific chemical changes in cell) that is known to be activated in many neurodegenerative diseases, perhaps including SMA. When activated, JNK may cause motor neurons to function improperly and die. It may also cause muscles to atrophy in SMA.

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

www.cureSMA.org

cure SMA

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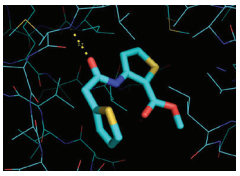
IMAGO PHARMACEUTICALS

Dr. Sumner



Inhibitor compounds binding the JNK Kinase

Imago Pharmaceuticals has developed compounds that inhibit JNK and therefore protect neurons and muscle. The goal of this project is to test these compounds in SMA animal models to see if they improve survival, motor function, reduce neuron loss, and/or improve muscle function, both alone and in combination with SMN enhancers. The safety of these compounds will then be tested.

If these JNK inhibitors are safe and work in SMA animal models to protect either neurons and/or muscle, they will progress into studies required by the FDA to support human clinical trials.

About the Pellizzoni Project

Dr. Pellizzoni

Dr. Pellizzoni and his colleagues at Northwestern University have identified a novel cellular pathway, called p38αMAPK, that is altered in SMA and may directly contribute to how the disease develops. For instance, SMN deficiency results in activation of p38αMAPK in mouse models of SMA.

The goal of this project is to evaluate whether inhibiting this pathway may help treat SMA. An orally available p38αMAPK inhibitor is currently in advanced clinical trials for the treatment of Alzheimer's disease and other neurological disorders. Researchers will be testing this compound in a mouse model of SMA, to see if it might also be useful in treating SMA.

The results of this project may be used to support further pre-clinical and clinical development of this drug for use in SMA.

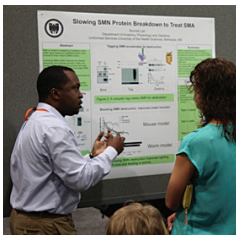
About the Hodgetts Project

Dr. Hodgetts

Another potential way of increasing SMN levels is to increase transcription of the *SMN2* gene. *Transcription* is the process by which the information in DNA is copied into messenger RNA (mRNA) for protein production. This process can be thought of in terms of an engine, where increasing or decreasing transcription is akin to turning a gene on or off. Dr. Hodgetts and his team are investigating two distinct series of chemical platforms, to see if they might be used to increase *SMN2* transcription.

The objective of this project is to optimize a compound that already increases transcription of *SMN2* to have more drug-like properties suitable for pre-clinical evaluation. They will develop acceptable formulations and improve solubility of the lead compounds to enable them to be administered more easily for mouse model efficacy studies. Dr. Hodgetts and his team are working in collaboration with Elliot Androphy's lab. Dr. Androphy was first to identify the compounds now being studied.

About the Burnett Project



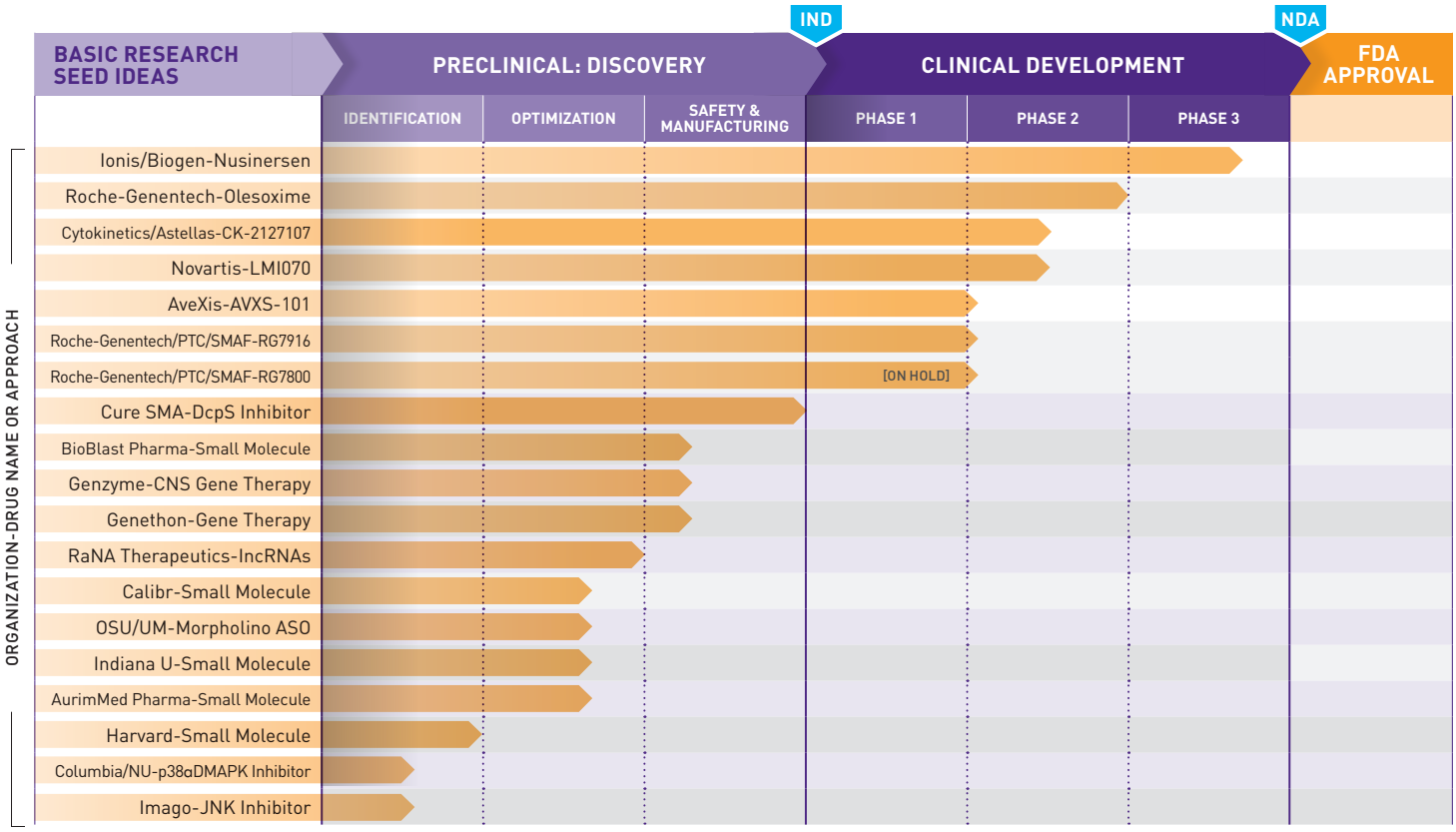
Dr. Burnett

Another potential way of increasing SMN levels is to target the SMN protein directly. Dr. Burnett and his team are investigating ways to slow the degradation of SMN protein, causing it to stay around for longer length of time and effectively increasing the overall levels of SMN protein in cells.

The goal of this project is to characterize and validate a novel SMN protein modulator for possible treatment of spinal muscular atrophy. This modulator regulates the degradation of the SMA protein. The team will utilize cell-based assays and animal models to investigate safety, efficacy, and selectivity of a new compound identified using a high throughput screen that modulates SMN protein degradation. The project aims to help develop molecules that possess a unique mode of action to treat SMA.

We thank the following families and foundations for their generous contributions toward these grants: The Jacob Isaac Rappoport Foundation toward Dr. Burnett, and the Bugenske Family and Leo's Pride toward Imago Pharmaceuticals/Dr. Sumner.

SUMMER 2016 UPDATE TO THE SMA DRUG PIPELINE



IND = Investigational New Drug **NDA** = New Drug Application

SMA DRUG PIPELINE CONTINUES TO GROW

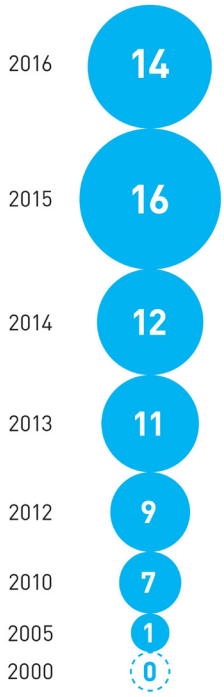
The most recent update to the drug pipeline also reflects our continuing progress toward new combination therapies. In just the last six months since the last pipeline update, two new Cure SMA-funded programs—the Jun N-terminal kinase (JNK) inhibitor and the p38αMAPK inhibitor program—have been added to the pipeline, both pursuing combination therapies.

With those additions, the latest version of the drug pipeline includes:

- 18 active programs
- 14 pharmaceutical partners
- 6 programs in clinical trials
- 28 programs in the cumulative pipeline total, including 10 failures to date
- An ever-increasing breadth of potential treatment approaches to SMA

The results give us cause for optimism, but we still have more work to do. Only 10% of the drugs that make it to clinical trials will ultimately receive FDA approval, so we need to keep building and growing the pipeline. Beyond funding the pipeline, Cure SMA is committed to advocating for the patient voice in drug development to ensure regulators understand the SMA community and its needs.

NUMBER OF COMPANIES INVESTING IN SMA DRUG PROGRAMS

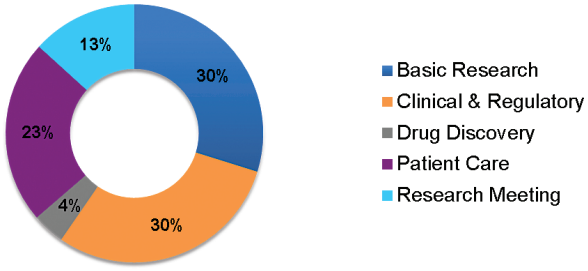


Cure SMA Announces $2.5 Million in New Planned Research Funding

As the SMA research landscape has developed and the drug pipeline has grown, we recently undertook a systematic review of our research funding priorities. Through conversations with independent SMA experts, our scientific advisory groups, and the newly formed Medicine and Science Committee in our Board of Directors, Cure SMA has created a strategic research plan to guide us into this next phase of SMA research. This strategic research plan identifies the areas of greatest need and where we are best positioned to make a significant difference:

- **Continued funding for basic research.** Funding for basic research, which investigates the causes and biology of SMA, will encourage further development of combination therapies. Basic research is the critical first step to identifying these non-SMN systems, pathways and processes that can be targeted for drug development.
- **Greater funding for clinical and regulatory research.** As more SMA drug programs progress through clinical trials, there is a need for us to address clinical and regulatory issues and bring the patient voice into the process.

$2.5 Million in New Research Funding



Many of the projects in this area will be carried out as part of a new a collaborative industry consortium. Through this group, seven companies working in SMA drug development will share information, ideas, and data, working together to benefit our community.

- **Greater funding for patient care initiatives.** Cure SMA has been working to collect data and information on the experiences of living with SMA. Funding for the coming year will be used to create a database that will demonstrate the impact of SMA over time. This information will help the scientific and research communities create answers that address these real-world concerns, and accelerate therapy development for SMA. The increased funding will also be used to help develop centers of excellence for SMA care.

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