



Families of SMA *Research. Support. Hope.*

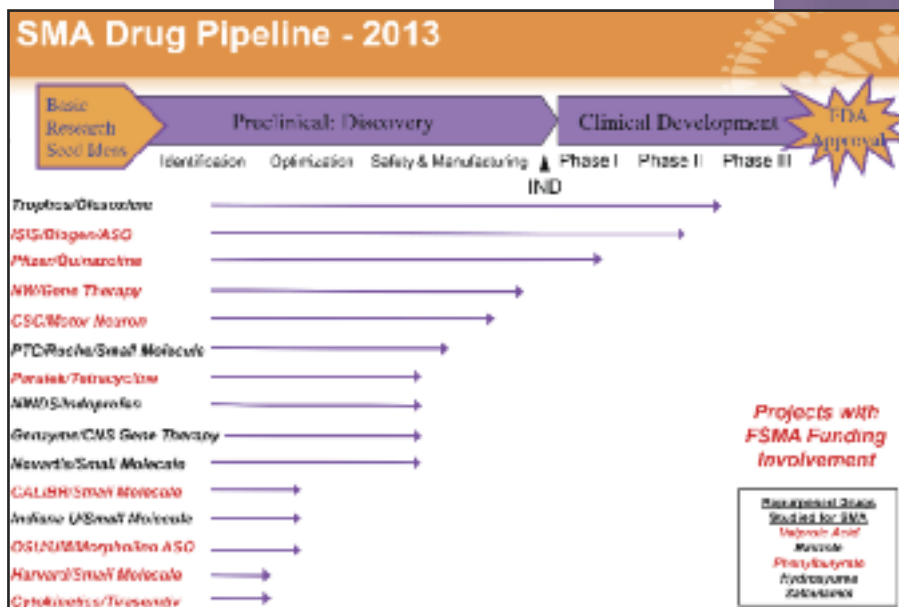
COMPASS

A Publication Dedicated To Research Updates

2013 Update on The Spinal Muscular Atrophy Drug Pipeline

Developing new therapies to treat and ultimately cure SMA is the driving force behind Families of SMA. To achieve this goal, Families of SMA aggressively invests in basic research to identify therapeutic approaches and applied drug development research to make drugs, funding promising and innovative scientists and organizations around the world. Clear evidence of progress is being seen:

- 1) Programs are advancing into the clinical trial stage of testing.** There are now 3 novel programs actively being testing in clinical trials for SMA. We expect two more to file investigational new drug applications (IND) to the FDA to begin early Phase I trials over the next year.
- 2) There is a broad diversity of approaches in development.** Diversity is important in case one particular treatment approach turns out not to have benefit in patients. Currently there are six drug strategies being advanced for SMA:
 - 1) Small Molecule SMN Enhancers,
 - 2) Neuroprotectants, 3) ASOs to Correct SMN2 Splicing, 4) Stem Cell Therapy, 5) Gene Therapy, and 6) Regulators of Muscle Function.
- 3) The total number of programs is growing.** There are now 15 novel SMA therapeutic programs in various stages of preclinical and clinical research, up from just 1 a decade ago. Three programs newly funded by FSMA have been added to the pipeline in just the past few months. These include assessing second-generation ASO sequences for SMA, using a patient derived motor neuron screen to identify novel SMA Therapeutics, and testing in SMA mice a drug that enhances muscle function now in Phase II trials for ALS. This volume is needed to balance the very low odds of only 1 in 10 programs successfully advancing through clinical trials to final FDA approval.
- 4) Funding and resources from government and industry are increasing.** There are now



11 companies actively investing in the SMA drug pipeline. Industry expertise and resources are essential to advance programs through the expensive and complicated later clinical stages of development. For example, in 2013 Pfizer began a SMA drug program after licensing the FSMA Quinazoline drug candidate. Also, the NINDS in collaboration with Families of SMA and Nationwide funded a \$3.8M project to advance a CNS directed gene therapy for SMA.

Overview of Clinical Programs:

Our community has seen success over recent years in advancing basic research discoveries from the bench to the clinic. There are now 3 novel programs testing drugs in human clinical trials for SMA with more anticipated to begin in 2013. These include:

- Trophos with Olesxime currently in Phase II/III clinical trials.
- Isis Pharmaceuticals and Biogen Idec with Antisense in Phase II clinical trials.
- Pfizer with Quinazoline currently in Phase I clinical trials.

FSMA Announces Grant to Cytokinetics for Preclinical Development of Tirasemtiv for SMA

Families of SMA awarded a grant to Cytokinetics to support preclinical research on muscle function in a mouse model of spinal muscular atrophy (SMA) to be conducted with the company's fast skeletal muscle troponin activator, tirasemtiv.

Tirasemtiv, the lead drug candidate from Cytokinetics' skeletal muscle contractility program, selectively activates the fast skeletal muscle troponin complex by increasing its sensitivity to calcium, thereby increasing skeletal muscle force in response to neuronal input and delaying the onset and reducing the degree of muscle fatigue. Cytokinetics is evaluating tirasemtiv as a potential treatment for amyotrophic lateral sclerosis (ALS) in BENEFIT-ALS (Blinded Evaluation of Neuromuscular Effects and Functional Improvement with Tirasemtiv in ALS), an international Phase IIb clinical trial that is now enrolling patients.

The objective of this new funded preclinical research is to examine whether tirasemtiv can improve muscle function in mouse models of SMA. Cytokinetics will examine the effects of tirasemtiv on leg and respiratory muscle function and the effects of tirasemtiv to reduce fatigue and improve muscle strength during exercise.

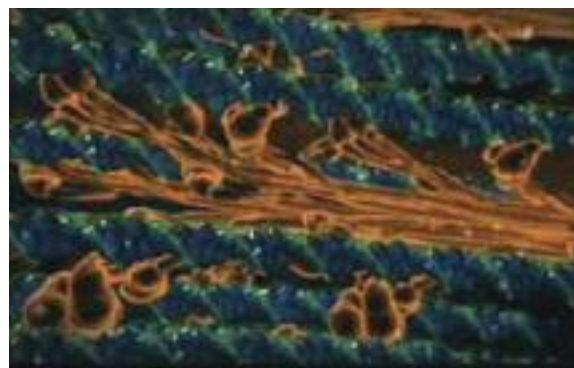
"There remains a significant unmet

medical need for a novel therapy that can improve muscle function, including respiratory muscle function, in patients with SMA," stated Jill Jarecki, Ph.D., Research Director of Families of Spinal Muscular Atrophy. "If tirasemtiv can improve muscle function in mouse models of SMA, it may also ameliorate muscle weakness in patients with SMA and thereby has the potential to improve quality of life for patients affected by this disease."

"We are pleased to be the recipient of this grant funding from Families of Spinal Muscular Atrophy which will enable us to investigate the potential of tirasemtiv to address some of the unmet needs of this grievous disease," stated Jeffrey Jasper, Ph.D., Cytokinetics' Head of Pharmacology. "We look forward to working with Families of Spinal Muscular Atrophy on this important project which may inform Cytokinetics' plans for future clinical development activities of tirasemtiv."

Development Status of Tirasemtiv

Tirasemtiv (formerly CK-2017357) is currently being evaluated in BENEFIT-



Skeletal Sarcomere Activators

ALS, an international, double-blind, randomized, placebo-controlled, Phase IIb clinical trial designed to evaluate the safety, tolerability and potential efficacy of this novel drug candidate in patients with ALS. BENEFIT-ALS is designed to enroll approximately 400 patients. Cytokinetics plans to conduct BENEFIT-ALS in over 70 sites across the United States, Canada, and several European countries. Data from prior Phase IIa clinical trials of tirasemtiv in patients with ALS were presented at the 2012 American Academy of Neurology Annual Meeting and the 2010 International Symposium on ALS and Motor Neurone Diseases.

Families of SMA has awarded 4 new drug discovery programs in 2013

Families of SMA is dedicated to creating a treatment and cure for SMA by funding and advancing a comprehensive research program, including drug discovery projects to make practical new therapies. In 2013, Families of SMA has awarded funding for four drug discovery projects for a total of \$550,000. In this issue of Compass, the first two of our four new drug discovery grants are described. They are to Dr. Lee Rubin at Harvard University to carry out novel drug screens directly in human motor neuron cells, and to Dr. Jeff Jasper at Cytokinetics to test an ALS drug in mouse models of SMA. The second two drug discovery awards focus on antisense oligonucleotides (ASOs) for the treatment of SMA. They will be described in an upcoming edition of Compass and have been awarded to:

- **Arthur Burghes, Ph.D. and Christian Lorson Ph.D.** to Assess the Potential of Novel ASO Sequences in Mouse Models of SMA.
- **Yimin Hua, Ph.D. in the Lab of Dr. Adrian Krainer** at Cold Spring Harbor Laboratory to Assess the Influence of Backbone Chemistry on Efficacy of ASO Sequence ISS-N1.

continued from front page

2013 Update on The SMA Drug Pipeline.

New Increased Funding to Build the SMA Drug Pipeline:

A major goal at FSMA has been to help build the SMA drug pipeline. FSMA has been investing in and advancing novel pre-clinical drug research since 2000. The goal for our drug discovery funding is to build a diverse therapeutic pipeline to maximize the chances for success in finding a treatment for SMA. Even with the community's current progress, FSMA believes it is critical to continue to grow the SMA drug pipeline. Statistics show that only 10% of all drugs initiating human clinical trials ultimately receive FDA approval.

Families of SMA has funded nearly two thirds of all the ongoing drug programs for SMA. In just the past 18 months, FSMA has funded five additional new drug programs. This new funding is significant as FSMA now funds several programs concurrently which have different approaches to developing a therapy for SMA. This will both enhance our overall chances of success and also accelerate the timeline to approved SMA drugs. **Families of SMA is attacking the disease from every angle possible, and there are now more new drug programs in development than at any other time.**

Failure is a normal part of the drug development process:

While we currently have 15 active new drug programs in development, over the previous decade six additional programs have failed, giving us a total cumulative SMA drug pipeline of 21. It is this overall volume and breadth that will lead us to our ultimate desired goal of approved treatments and a cure for SMA. In addition, failures teach us how to do SMA drug discovery better. The community learns which biological strategies won't work, and important new checkpoints to include in the drug development process.

Partnering with Companies and Government:

Drug development in SMA has seen advances because of collaborative efforts between academic, government, pharmaceutical, and non-profit organizations. These collaborations are essential for effective drug development in orphan diseases. The FSMA strategy for drug discovery is to provide early seed funding for new projects with the goal of leveraging bigger funding from government and industry. There are now about a dozen companies involved in SMA drug development, including Pfizer, Roche, and Novartis. These companies have large resources and many decades of expertise to devote to SMA drug development. *FSMA is proud to have been involved in collaborations for many of the current programs in the SMA drug pipeline, including:*

- Licensing the Quinazoline program to Repligen Corporation, which is now being led by Pfizer, the largest pharmaceutical company in the world.
- Licensing the Antisense program to ISIS Pharmaceuticals. This program has initiated Phase IIB trials in Type II/III SMA patients and in Type I infants in 2013.
- Collaborating with NINDS and Dr. Brian Kaspar on an award support to CNS-directed gene therapy with potential funding of \$3.8 Million.

continued from back page

FSMA Awards \$150,000 to Dr. Lee Rubin at Harvard to Advance a New SMA Drug Discovery Program.

Dr. Rubin has worked both in academia and in industry, first as a Project Leader at Athena Neurosciences (now Elan Pharmaceuticals) and later as Chief Scientific Officer of Curis, a Cambridge biotechnology company. At Curis, he directed a project that identified the first small molecule hedgehog antagonists. One of these, Erivedge, was recently approved by the FDA to treat advanced basal cell carcinoma. Also, working on the project is Dr. Maureen Lynes in the Rubin laboratory. Dr. Lynes received her Ph.D. in Cellular and Molecular Physiology at Tufts Medical School, and joined the Rubin laboratory as a post-doctoral fellow in 2011. Since joining the lab, she has been interested in using SMA patient iPS cells as a tool for identifying SMA therapeutics as well as for studying SMA pathogenesis.

Project Goals:

Using disease relevant, patient-specific cells to screen for compounds that increase SMN should lead to the discovery of novel regulators of SMN expression in human motor neurons. This project aims to identify therapeutic candidates that can be moved into the clinic relatively quickly, and that will complement the existing therapeutic approaches.

The current FSMA award to the Rubin laboratory is for one year with the goal of conducting cell-based screening in human motor neurons for new SMN inducing drug candidates. Subsequent funding to advance any newly identified molecules towards an Investigational New Drug application to the FDA will be evaluated by our TAC through our planned 2014 Request for Proposals in Preclinical SMA Drug Development.

**PLEASE CONSIDER A
DONATION TO SUPPORT FSMA
RESEARCH PROGRAMS**

Families of SMA Awards \$150,000 to Dr. Lee Rubin at Harvard to Advance a New SMA Drug Discovery Program

In January 2013, Families of Spinal Muscular Atrophy awarded new drug discovery funding of \$150,000 to Dr. Lee Rubin at The Department of Stem Cell and Regenerative Biology at Harvard University. FSMA's Translational Advisory Committee (TAC) selected this program for funding after evaluating 14 total programs.

Project Description:

The overall objective of this project entitled "A patient-derived motor neuron screen to identify novel SMA therapeutics" is to identify novel SMA therapeutics by using patient-derived motor neurons for drug discovery and preclinical testing. To this end, the team has made induced pluripotent stem cells from Type I and Type II SMA patient skin biopsies, and produced large numbers of motor neurons

that can be used to model SMA. The team will use these motor neurons in a screen for drugs that increase SMN levels. They will test candidate drugs in a 35 cell line panel that includes motor neurons from different patients and different SMA types.

By using human motor neurons to screen for new SMA drugs, the Rubin laboratory hopes to identify compounds that can increase functional SMN levels in the cell type most affected by the disease. The group will prioritize compounds that are already approved for use so that they can move through the development pipeline more quickly. Candidate compounds will be tested across a panel of SMA patient-derived cells so that we can identify drugs that are effective across many genetic backgrounds and disease severities. This innovative approach will lead to the discovery of drugs that are mechanistically

unique so that they may be used in addition to the therapies that are currently being developed. These cell lines can also help assess existing SMA drug candidates.



Dr. Rubin received his PhD in Neuroscience from The Rockefeller University and completed postdoctoral fellowships in Pharmacology from Harvard Medical School and in Neurobiology from Stanford University School of Medicine.

continued on page 3



Families of Spinal Muscular Atrophy
925 Busse Road
Elk Grove Village, IL 60007
1-800-886-1762

Return Service Requested

**FSMA Awards 4 New
Drug Discovery Programs
\$550,000 in 2013**