This new program will focus on optimizing small molecule drug candidates which increase the SMA back-up gene in order to make them ready for human clinical trials. It is well demonstrated that increasing production from the back-up gene can lead to improvement in mouse models of SMA. Small molecule drug candidates have particular advantages: mainly ease of use by oral dosing and the ability to clear the drug quickly from the body. Dr. Peter Schultz, a renowned chemist and successful biotech leader, will be leading this new research effort.

In addition to founding the California Institute for Biomedical Research where the Families of SMA funded project will take place. Dr. Schultz also was Institute Director at the Genomics Institute of the Novartis Research Foundation (GNF) from 1999 to 2010. Dr. Schultz has founded multiple biotech companies, including Affymetrix Research Institute, Syrrx, Kalypsys, Phenomix, Symyx Technologies, Ilypsa, Ambix and Wildcat Technologies. Dr. Schultz has published over 500 scientific publications, and received numerous awards for his work including: the Waterman Award of the National Science Foundation, the 1994 Wolf Prize in Chemistry, the 2003 Paul Ehrlich Prize, and the 2005 Arthur C. Cope Award of the American Chemical Society. He is a member of the National Academy of Sciences and the Institute of Medicine.

“Dr. Schultz is greatly respected in the research community, both as an academic scientist and in the biotech industry. He has successfully led many drug programs that continued on to clinical development”, said Jill Jarecki, Ph.D., FSMA Research Director. “FSMA is very pleased to have a chemist and drug developer of Dr. Schultz’s experience spearheading a program for Spinal Muscular Atrophy. We are also excited that Spinal Muscular Atrophy is one of the initial drug programs at the newly formed California Institute for Biomedical Research.”

This new institute will focus on innovative new approaches to unmet medical needs, including neglected and rare diseases. Their expertise will be in translating basic research discoveries from bench to bedside. Therefore, this group will be ideally poised to move newly identified SMN enhancing compounds through all the preclinical steps of drug development towards first-in-human clinical trials.

In early March, Merck announced that it will invest $90 million the California Institute for Biomedical Research (CALIBR, www.calibr.org), a private, nonprofit center to be led by Peter Schultz, a renowned chemist at The Scripps Research Institute. The goal of the new institute is to bridge the gap to promote translational research and early drug development. The roughly 25,000-square-foot research center will be equipped for programs in immunology, autoimmune and metabolic disorders, cardiovascular disease, regenerative medicine, cancer biology and neurodegenerative disease.
Importance of FSMA Funding in Building the SMA 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 drug development research, funding the most successful and innovative scientists and organizations. See Figure 1 for the current SMA drug pipeline.

Several key details demonstrate the progress being made in the SMA drug pipeline:

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.

2) There is a broad diversity of approaches in development. This breadth is important in case one particular approach to treatment turns out not to have benefit in patients.

3) The total number of programs is growing. There are now 13 novel SMA therapeutic programs in various stages of preclinical and clinical research, up from just 2 ten years ago. This volume is necessary to balance the low odds of only 1 in 10 programs successfully advancing through clinical trials to final FDA approval.

4) Funding and resources from industry are increasing. There are now 9 companies actively investing in the SMA drug pipeline, which is essential to advance programs through the expensive and complicated later clinical stages.

New Increased Funding.

Families of SMA invests in broad research initiatives. A major goal at FSMA has been to help build the SMA drug pipeline. 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. 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.

The new SMA drug discovery funding is significant, as FSMA will now begin to fund several programs simultaneously, using different biological approaches to developing SMA therapies. This will both enhance our overall chances of success and also accelerate the timeline to approved SMA drugs. With this new funding, FSMA will have been involved in funding half of all the ongoing novel drug programs for SMA.
The goal of drug research is to find a new chemical or an existing drug that will work as an effective treatment or cure for SMA. Drug research includes many stages and phases (see Figure 2). A drug candidate needs to pass each stage before it can move on to the next. Pre-clinical drug discovery typically refers to the early stage of this process when drugs are discovered and designed. This phase tests raw chemical compounds and turns the most promising chemicals into SMA drug candidates. Once a chemical compound passes the early tests, it moves into the clinical development process which involves human clinical testing.

Pre-Clinical Drug Discovery includes the following major steps:

- Identification of chemicals that could potentially work as SMA drugs (completed already in the Schultz project). Often researchers screen hundreds of thousands of chemical compounds just to find one candidate that has the potential to be an SMA drug. This is called high throughput screening.
- Medicinal chemistry to turn these compounds into drugs (being funding in the FSMA grant to Dr. Schultz). Medicinal chemistry occurs to make many different versions of a chemical in a reiterative manner, each time trying to improve its properties as a drug.
- Efficacy and safety studies in animals on the newly identified compounds (animal efficacy studies, are being funded in the current grant to Dr. Schultz). Here, scientists test the optimized candidate drugs in animals for both efficacy and safety to make sure it is worthy of human testing.

After these steps are complete, the FDA reviews all the data, collected in the form of an Investigational New Drug Application.

Once these features are optimized, the compounds will be tested in mouse models of SMA as the final milestone in the current funding agreement. Good efficacy in these models could trigger the studies required by the FDA before human trials can begin.

The Schultz program was chosen by the FSMA Translational Advisory Committee (TAC) for funding, after reviewing ten total programs. The TAC is comprised of experts in both drug discovery and SMA. Please see the website below for short biographies of each. (http://www.fsma.org/AboutFSMA/Board/TranslationalAdvisoryCouncil/) A project-specific Steering Committee will also be put in place. This Committee will help manage the project and ensure it progresses in an efficient and well-run manner. Project funding will be awarded upon meeting pre-determined milestones, decided on by the Steering Committee.
**Project Summary:** Optimization of Small Molecules that Increase SMN2 Levels for the Treatment of Spinal Muscular Atrophy

Discovery of a disease modifying therapy for SMA will be facilitated by the development of small molecules that increase SMN protein levels. To this end, the Schultz group has previously screened a large library of chemical compounds using an SMN2 expression reporter. When doing so, they discovered several different compound classes that enhance SMN protein levels.

The current focus of the program is to optimize the drug-like properties of the new compounds through further chemical modification in a process called “medicinal chemistry” (see section below for more details).

**The goals of the project are:**

- To make optimized compounds with increased amounts of drug reaching the brain (pharmacokinetics),
- To make compounds needing less drug to enhance SMN levels (potency),
- To ensure the compounds are safe in preliminary tests (in vitro toxicology), and
- To test the compounds in mouse models of SMA.

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**Figure 3. How a Therapy Targets the SMA Back-up Gene.**