Dear Families and Friends

Why is a Drug Pipeline so Important?

Although there are a number of promising drug avenues for SMA emerging right now, we are cognizant of the fact that only 10% of therapies reaching clinical trials typically receive FDA approval. Therefore, we believe a critical role for FSMA is to help build the size of our SMA drug pipeline, which simply means increasing the number of viable SMA candidate therapies in pre-clinical or clinical drug development. To date we have been involved in five such ventures:

1) The Quinazoline compounds to increase production of the back-up SMN2 gene, which was licensed to Repligen in 2009.

2) The Tetracycline compounds at Paratek Pharmaceuticals to correct SMN2 splicing, which is now being funded in part from a multi-million dollar award by NINDS.

3) Cellular Therapy at California Stem Cell, which recently received orphan disease designation from the FDA.

4) The Gene Therapy project at Nationwide Children’s Hospital in Ohio, to replace the entire SMN1 gene.

5) The Oligonucleotide program at UMASS, recently licensed to Isis Pharmaceuticals, which uses genetic material to modify the back-up SMN2 gene.

The SMA pipeline should be diverse in nature, using multiple distinct approaches to treat SMA. Once pre-clinical safety studies are started on a drug candidate to enable an Investigational New Drug (IND) application to the FDA to begin clinical trials, there is still 18 to 24 months of work ahead, and several significant scientific hurdles to jump over. These typically include: 1) understanding where the drug is going and for how long in several animals species 2) formal toxicology and safety assessment in several animal species, and 3) a viable and well-controlled manufacturing process. Once this data is collected and deemed acceptable by the FDA, clinical trials can begin, sometimes on healthy adult volunteers and sometimes in patients, depending on the risk / benefit profile of the drug under consideration.

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The Importance of Independent Scientific Oversight in SMA Research Projects

Who are the FSMA Advisors?
FSMA has three key advisory teams, which include:
- Scientific Advisory Board (SAB) who govern basic research funding.
- Translational Advisory Council (TAC) who govern drug discovery and development projects.
- Medical Advisory Council (MAC) who govern patient care and support services.

What are the Main Functions of our Advisors in Research Funding?
- Advise on the best scientific strategy for our research programs.
- Generate the annual requests for proposals.
- Review grant applications, resulting in a rank order of all grants received.
- Review requests for presentations at the Annual SMA Research Group Meeting.
- Develop criteria for successful benchmarks of FSMA funded projects.
- Serve on management teams for funded projects, representing FSMA.

What is the FSMA Funding Model?
The Families of SMA research funding model is firmly based on the philosophy of expert and independent review and oversight of research projects. The FSMA strategy consists of having expert advisors review, prioritize, select, and then oversee the research projects that we fund. This system has many advantages. Primarily, it ensures that FSMA funds only the most promising research, and that the funded projects are run in a professional and efficient manner under the guidance of world-class experts. This type of system is the gold standard for effective scientific funding worldwide and is used extensively by both governments and non-profit groups. It is often referred to as “peer review”, which means scientists working in similar areas judge each other’s work.

Jill Jarecki, Ph.D.
Research Director, Families of SMA

Families of SMA Announces Launch of New Translational Advisory Council (TAC) to Select and Govern New Drug Discovery Projects for SMA

The ultimate research goal at Families of SMA is to develop safe and effective therapies for SMA. In the drug discovery area, our strategy has been to provide incentives for industry to invest in SMA drug discovery to build a growing and diverse therapeutic pipeline. Families of SMA has been funding drug discovery translational research since 2000. We now plan to increase our efforts in the translation area.

In order to build on recent successes and rapidly create a growing SMA therapeutic pipeline, Families of SMA is starting and will fund several new translational research projects. To achieve this goal effectively, Families of SMA has launched a formal translational research program that will provide funding and direction to new and diverse SMA drug discovery projects.

To govern this new program, FSMA is launching a new Translational Advisory Council (TAC). Our immediate goals for the TAC will be to:
1) Assess feasible strategies for SMA drug discovery and development,
2) Release a request for proposals focusing on those strategies,
3) Evaluate the submitted proposals, and then
4) Fund and then manage the best new translational projects.

This new advisory group will fill a critical position in the step between early academic research that creates seed ideas for new therapies and later clinical and medical stages. Translational research is the critical middle step that takes research ideas and makes them into practical solutions for patients.

The new members of the TAC are:
Brian Pollok, Ph.D., Chief Scientific Officer, LIFE Technologies Assay Development.
Lee Rubin, Ph.D., Director of Translational Medicine, Harvard Stem Cell Institute, Neuronal Assay Development and High-Throughput Screening.
Christine Brideau Ph.D., Director of In Vitro Sciences, Merck Frost Canada, Preclinical Drug Development.
Jim Inglese, Ph.D., Deputy Director, NIH Chemical Genomics Center, Assay Development.
Peter Hodder, Ph.D., Senior Director, Lead Identification, The Scripps Research Institute, Scripps Florida, Assay Development and High-Throughput Screening.

How Does Basic Research Impact the Drug Pipeline?

The oligonucleotide work discussed in this issue of Compass is a great illustration of how basic research can lead to new therapeutic avenues for SMA. Our grant awards to Dr. Singh were intended to gain understanding of how the splicing of the SMN2 is regulated and controlled in cells. The immediate aim of gaining greater understanding of a biological process led to a new therapeutic avenue. As Dr. Bennett of ISIS Pharmaceuticals, the company progressing the anti-sense oligo approach forward, nicely phrased it nearby: “basic research often is the ‘road map’ leading to new therapeutic directions”.

FSMA has funded more than 145 basic research grants at 70 institutions around the world over the last 25 years.
Isis Pharmaceuticals Licenses Intellectual Property Created at the University of Massachusetts and Funded by Families of SMA, to Develop Drugs to Treat SMA.

Isis Pharmaceuticals, Inc (ISIS) has exclusively licensed certain intellectual property from the University of Massachusetts to develop a potential new therapy for Spinal Muscular Atrophy (SMA). Funding support for the University of Massachusetts’ research program responsible for creating this intellectual property was provided in part by Families of SMA.

ISIS is developing ISIS-SMNRx as part of its strategy to discover and develop antisense drugs against neurodegenerative diseases. ISIS’ SMA program is part of its collaboration in neurodegenerative disease with Dr. Adrian Kainer at Cold Spring Harbor Laboratory and Genzyme, pursuant to which Genzyme has an exclusive option to license ISIS-SMNRx from ISIS.

The antisense therapeutic approach for SMA involves the use of a short, chemical structure, called an antisense drug, to increase the production of the protein, SMN. SMN2 is a closely-related gene that normally produces a truncated and low-functioning form of SMN protein. Isis designed an antisense drug that binds to the SMN2 RNA and drives the production of SMN protein. Using this approach, ISIS hopes to provide therapeutic benefit to patients with SMA.

Families of SMA funded the early research for this program with three grant awards to Dr. Ravindra Singh and his colleagues between 2003 and 2006, originally in collaboration with Dr. Elliot Androphy at the University of Massachusetts. Dr. Singh is now at Iowa State University. The grants were given through the FSMa basic research program, which is governed by our Scientific Advisory Board. The FSMa funded projects were designed to gain a greater understanding of how the splicing of SMN2 is regulated and controlled in cells.

“SMA is a terrible disease and the leading genetic cause of infant mortality. The ability of our drugs to specifically target RNA and drive the production of SMN may be able to compensate for the underlying genetic defect and offer some therapeutic benefit to patients with SMA. We are grateful for the support provided by Families of SMA in funding early research on SMA, which has significantly expanded the basic science of SMA and provided a roadmap to developing the first targeted therapy to treat SMA,” said Frank C. Bennett, Ph.D., Senior Vice President of Research at Isis Pharmaceuticals.

“The strong commitment of Families of SMA to basic research has been very farsighted for finding novel drugs and drug targets for SMA. I began submitting transformative research proposals with apparent high risks. FSMA kept supporting my basic research that finally resulted in discovery of a novel drug target for antisense-based therapy of SMA. I take this moment to commend Families of SMA for its vision of promoting basic research, dividends of which have started to pay off”, said Ravindra Singh, Ph.D.

“This program is a perfect illustration of how basic research can directly lead to new therapeutic avenues to treat SMA. This idea is one of the main tenets of the FSMA research strategy”, said Jill Jarecki, Ph.D. Research Director of FSMA.

Both Isis and Genzyme were recent sponsors at The Annual SMA Conference in 2009.
Families of Spinal Muscular Atrophy is pleased to announce the approval of an exciting new grant to Dr. Brian Kaspar at The Ohio State University. This grant will support pre-clinical development of a Gene Therapy for Spinal Muscular Atrophy. With funding from FSM A, Dr. Kaspar’s team will begin the initial studies needed for an Investigational New Drug (IND) application to the Food and Drug Administration (FDA) to begin human clinical trials. This specific project will address which cells in the brain and spinal cord the therapy targets, at what stage of development this can occur, and how long this persists.

Gene therapy is an approach to treating diseases by replacing mutated genes, correcting abnormal genes, or modifying the expression of genes. Gene therapy works by administering genetic material, often through the use of a virus, rather than the use of a traditional small molecule drug. In this case it involves replacing the DNA for the SMN1 gene, which is mutated in SMA. This work appeared as an advanced online publication in Nature Biotechnology on February 28, 2010.

Dr. Kaspar’s group at Nationwide Children’s Hospital of The Ohio State University (OSU) has discovered that gene therapy can fully rescue SMA mice for normal function and lifespan. With funding from Families of Spinal Muscular Atrophy, Dr. Kaspar’s group, along with colleagues at OSU including Drs. John Kissel, Arthur Burghes, and Jerry Mendell will embark on moving this promising therapy forward towards clinical trials by conducting a number of key experiments needed for an IND application. This specific project will entail assessing the ability of the therapy to reach motor neurons in larger animal species, since most of the initial work has been in mice so far.

“Funding from FSM A provides crucial support for advancing our studies. We have assembled our translational team to move these exciting studies forward in a safe and rapid manner” states Dr. Brian Kaspar of Nationwide Children’s Hospital. Dr. Arthur Burghes of OSU states, “We are collecting the pertinent data that will be required by the FDA, which regulates therapy development in the US, to begin clinical trials in SMA patients”. “We are pleased to be partnering with FSM A to begin the process of moving this exciting and promising new therapeutic approach forward to clinical trials”, adds Dr. John Kissel of NCH/OSU.

This study is the first step in a series of experiments that will be needed to ready this therapy for human clinical trials. The full battery of IND-enabling studies is designed to establish both the potential benefit and risk to patients receiving the therapy.

See website for full article - http://www.curesma.org