



FAMILIES OF SPINAL MUSCULAR ATROPHY

COMPASS

A Publication Dedicated To Research Updates

First Novel Clinical Candidate for SMA

*By Mark Gurney, PhD, MBA, Senior VP Drug Discovery and Development
deCODE Chemistry*

FSMA has had the vision to pursue drug discovery for spinal muscular atrophy. We now are beginning to see the outcome of that leadership vision. The goal of the FSMA-deCODE drug discovery effort has been to find chemicals that increase the amount of full-length SMN protein produced from the SMN2 gene. Excitingly, the FSMA-deCODE drug discovery effort has identified drug-like compounds that act on SMA patient cells in culture to increase SMN2 gene activity and thereby the amount of functional, SMN protein. The same compounds also have now demonstrated therapeutic benefit in a mouse model of a severe form of SMA. The FSMA compounds have been shown to improve lifespan in the SMA mice and to improve their movement and bodyweight. It has not been an easy task to reach this point. Having shown potential therapeutic benefit, the goal for the FSMA-deCODE collaboration now is to evaluate the potential safety of the lead compound in animal tests prior to beginning human clinical trials.

In 1999 this project began at Aurora Biosciences where a large SMA screening campaign was completed. An initial compound was identified. At deCODE a

medicinal chemistry team began improving the drug-like properties of the original compound in 2003.

Every drug discovery project has its own unique challenges. In the case of the project undertaken for FSMA, very potent compounds were synthesized within the first year of work. These initial compounds were promising as they increased activity of the SMN2 gene leading to an increase in full-length SMN protein in cells exposed to the compounds. However, toxicity was observed at higher concentrations due to off-target activity on an enzyme unrelated to SMN activity. Through the efforts of the chemistry team, the undesired off-target activity was removed while maintaining SMN2 promoter activity. While this was possible, it was not a simple challenge.

Also challenging was the task of optimizing compounds for the ability to cross the blood-brain-barrier. Unlike blood vessels elsewhere in the body, blood vessels in the brain have a unique seal to prevent the free movement of small chemicals from the blood into the brain. The focus of the deCODE chemistry effort over the last year has been to identify and develop a lead compound that satisfies these many criteria.

Having passed those tests, and with the demonstration of therapeutic benefit of the lead compound in the SMA mouse model, the next goal of the FSMA-deCODE project is to show that the compound is safe for use in human clinical trials. To date, only small amounts of the lead compound have been produced. The project now needs to transfer to a manufacturing team to produce larger quantities of the compound for further animal studies and then for human clinical trials. Generally, safety evaluation and manufacturing require 9-12 months. Results of safety testing in cells and mice have been positive to date, but there is the real possibility that unexpected safety issues could still be identified as more comprehensive tests are performed.

This next phase of the FSMA-deCODE project will determine if the lead compound has adequate safety to allow entry into clinical trials. It has been a long road, but within one year our lead compound will enter human clinical trials, if adequate safety is established.



First Round of Lead Optimization Successful in Development for SMA Treatment at Paratek Pharmaceuticals

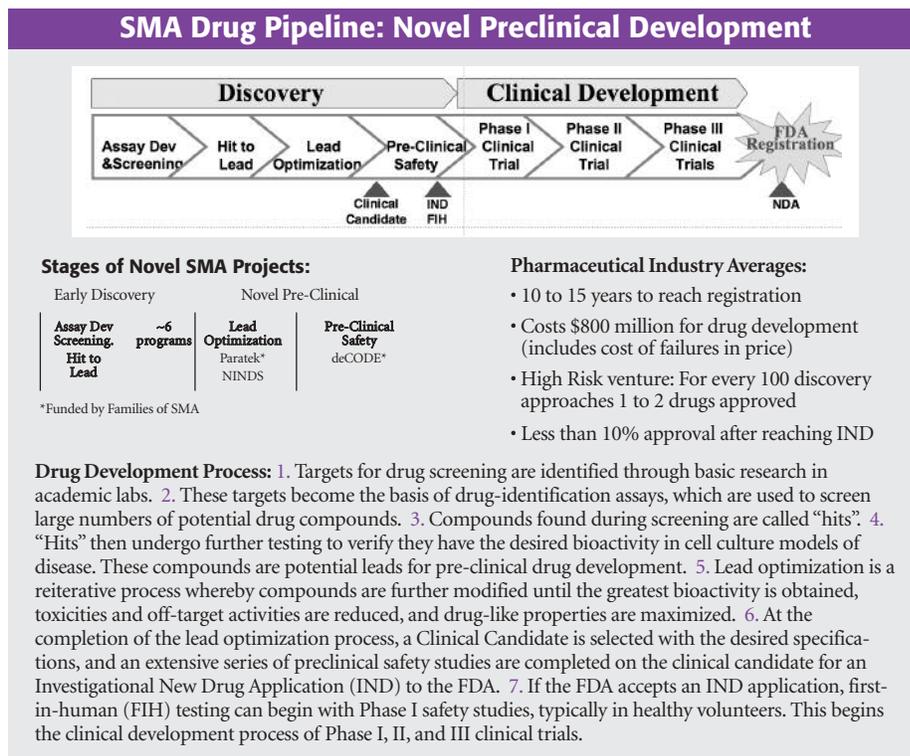
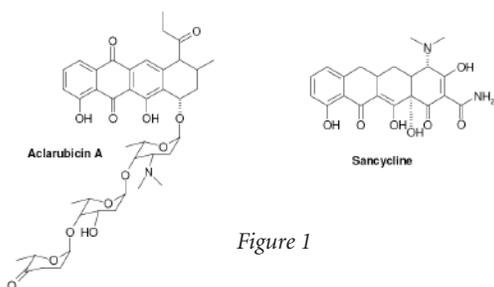
By Joel A. Berniac, Ph.D., M.B.A., Principal Scientist and SMA Project Leader
Paratek Pharmaceuticals

Paratek Pharmaceuticals' interest in developing a small molecule drug discovery program in the Spinal Muscular Atrophy (SMA) therapeutic area started back in 2002 when a portion of Paratek's library of over 2,000 modified Tetracycline (TC) derivatives were screened in an SMA relevant *in vitro* assay. The initial concept of screening tetracycline (TC) derivatives for SMA came from their structural similarity with Aclarubicin A (see Figure 1). This chemotherapeutic drug was reported in 2001 to be active in cellular assays relevant to SMA:

- (1) it enhanced the inclusion of exon 7 in the splicing of SMN2 pre-messenger RNA (pre-mRNA); and
- (2) it restored normal SMN protein levels in an SMA patient-derived cell line.

However, Aclarubicin is toxic and not suitable for clinical development. Paratek surmised that nontoxic TC derivatives could potentially increase full-length mRNA production and SMN protein synthesis from the SMN2 gene. The discovery of a nontoxic TC derivative would be an important finding leading to a potential treatment for SMA.

SMN2 fails to compensate for the SMN1 mutation, and thus to protect from development of SMA, because its mRNA undergoes alternative splicing to encode for an unstable SMN protein, known as $\Delta 7$ SMN. After transcription of a gene into its corresponding pre-messenger RNA (pre-mRNA), the nuclear splicing machinery is responsible for processing that pre-mRNA into its corresponding messenger RNA (mRNA) by eliminating introns (bits of pre-mRNA unnecessary for protein synthesis) and joining together exons (bits of pre-mRNA coding for protein synthesis). The aberrant production of the truncated $\Delta 7$ SMN is due to exon 7 being skipped during splicing of the SMN2 pre-mRNA, resulting in insufficient amounts of full length



SMN protein and consequently in decreased motor functions in SMA patients. Therefore the SMN2 gene is an ideal target for drug intervention to induce the synthesis of normal SMN protein in SMA patients.

Therapies that specifically increase inclusion of exon 7 into the SMN2 mRNA are likely to be effective treatments for even severe SMA type I patients. With the support of Families of SMA and in collaboration with Professor Adrian Krainer's team at Cold Spring Harbor Laboratory (CSHL) in NY for *in vitro* screening, several TC derivatives from Paratek's compound library were screened. Among several "hit compounds", PTK-SMA1 emerged as the most promising. When incubated in nuclear extracts from HeLa cells, PTK-SMA1 showed an increase in the percentage of exon 7 inclusion during mRNA splicing of SMN2 by 2.6-fold.

The same screening compounds were evaluated collaboration with Professor Arthur Burghes at Ohio State University in a whole cell "Gems" assay which looks at the concentration of full length SMN protein in nuclear studies called "Gems." PTK-SMA1 showed

promising results in that assay with an increase of SMN protein levels in a Type I SMA patient fibroblast cell line of 8.3-fold increase. In addition, PTK-SMA1 again increased SMN protein levels in the same fibroblast patient cell line when visualized by Western Blot analysis instead of gems count.

While further *in vivo* evaluation of PTK-SMA1 is currently underway in an animal model of SMA with adult heterozygote transgenic mice expressing the human SMN2 gene, Paratek's medicinal chemists were able to synthesize more than 30 derivatives, 13 of which showed activities similar to PTK-SMA1's in the exon 7 splicing assay. Paratek Pharmaceuticals, armed with its expertise and intellectual property coverage in chemical modifications of the Tetracycline class of molecules, is perfectly positioned to implement a drug discovery project for the treatment of SMA. *In addition to demonstrating sufficient increase of SMN protein levels in an *in vivo* model of SMA, Paratek's objectives also include the optimization of the pharmacokinetic profile and of all other drug-like properties of the selected lead compound in order to develop a small molecule candidate for the treatment of SMA within the next few years.*

Dear Families and Friends,

Since 2000 FSMA has invested substantial funds in SMA therapeutics development. The ultimate goal of our investment in pre-clinical drug development is to find an effective treatment for SMA. One strategy we have actively pursued to reach this goal is to encourage biotech and pharmaceutical partners to engage in pre-clinical SMA drug research by providing direct funding. Traditionally, it has been difficult to attract companies to conduct research in orphan disease therapeutic

The goal of the deCODE collaboration was to generate a final optimized compound with the required properties of an effective SMA drug, called a "Clinical Candidate". **Now in May of 2007 this goal has been met.** As will be reported at the upcoming 11th Annual International SMA Group Meeting (sponsored by FSMA), our compounds prolong survival in mouse models of SMA and are very effective at crossing the blood brain barrier to reach motor neurons in the spinal cord.

areas, such as SMA that have small patient populations. Therefore, our best option has been to provide financial incentive for companies to pursue early stage SMA drug discovery, as well as providing the tools, academic expertise, and SMA advisors to help make these projects successful.

Our first venture in drug discovery began in 2000 as a collaboration with **Aurora Biosciences**, since acquired by **Vertex Pharmaceuticals**. The goal of that collaboration was to develop screening tools to search for chemical compounds that could increase SMN levels specifically from the SMN2 gene. Several compounds with the capability of doing this were discovered, and one of these compound classes (called **Quinazolines**) has since been chemically modified at **deCODE Chemistry** to optimize and generate drug-like properties. **FSMA is now enter-**

ing into a new agreement with deCODE to generate the data package for an "Investigational New Drug" application to the FDA, which is required to initiate human testing. This package of data will require approximately one year to generate and cost \$2.5M.

Our ultimate goal for this project is to find an industrial partner to progress this compound through human clinical testing and development. Therefore, FSMA hopes to advance the project with our own funding to the point where the risk to industrial partners is effectively reduced to allow their own financial investment in the program. Overall, we are trying to provide incentives to industry partners to enter the SMA drug development arena, by reducing risks and simultaneously

supplying them with resources such as research tools, scientific expertise, and established clinical networks. The costs of drug development increase substantially as we are successful and reach later stages. For example, a late-stage clinical development project for SMA, consisting of a full set of Phase I, II, and III trials, can cost between \$25M to \$50M over 5 years.

One extremely important aspect of our research strategy for SMA drug discovery is to build a therapeutic pipeline, which will increase our chances of successfully developing a SMA therapy. In order to build a broader therapeutic pipeline, FSMA plans to invest in additional drug discovery programs. In March 2006 we began funding a program at **Paratek Pharmaceuticals** that involves assessing the ability of **Tetracycline** compounds to correct SMN2 splicing. This is a different approach from our Quinazoline program to increasing SMN levels. We recently renewed this collaboration for a second year – **please see attached WSJ article.**

Additional new drug discovery programs will be added to our portfolio over the next few years. We need to build a pipeline of candidates for treatment of SMA for a number of reasons:

- Individual patients may react differently to a drug, and so we must aim to have multiple treatment options available.
- A chronic treatment approach may require shifting between drugs over time to limit side-effects.
- The potential exists that two or more drugs could be used as a therapeutic cocktail to increase SMA levels even further than either one alone could.
- It is important that multiple approaches be taken as drug development is a very high risk venture for each individual program.

This is an exciting time in the SMA community. On multiple fronts, our basic research investments have allowed us to design rational therapeutic strategies for SMA. We are now beginning to see early results from the translational drug discovery programs that we and other groups have invested in.

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

FSMA Donation Form

FSMA will fund \$2.5M to move the deCODE drug discovery program to clinical trials over the next 12 months.

I want to help with a donation in the amount of \$

In honor/memory of

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Return form to **FSMA Donations**, PO Box 196,
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SMA Drug Discovery Program Reaches Stage of Clinical Candidate

Dear Supporters,

We are pleased to announce a major result for the SMA community in this Compass. Our general topic for this edition is Drug Discovery. This is the area of research where we take basic results and attempt to turn them into practical drugs. If successful in these programs we can then move into clinical trials.

The lead compounds in our program with deCODE have shown the ability to extend survival in a mouse model of SMA. Due to this successful result we have now been able to select a Clinical Candidate. This is the first time a novel compound specifically designed to treat SMA has reached this stage in drug development.

Families of SMA has been funding and directing this particular program for the last 7 years. Our total investment to date in this program alone is over \$10M. The collaboration has involved many partners: starting with Aurora/Vertex, then transitioning to deCODE, with assistance along the way from Ohio State University and Cold Spring Harbor Laboratory. So far we have been successful.

Selecting a Clinical Candidate means that we are now preparing to run the safety tests required to apply to the FDA to begin clinical trials. This work

will require funding of \$2.5M and take about 12 months to complete. If we are successful in this next stage we would then look to start phase I clinical trials.

Families of SMA has always focused the majority of our efforts and funds towards research to find a treatment and cure for this disease.

- We invested \$4.6M in research in our fiscal year 2006.
- We expect to fund over \$5M over the next year.

Our long term goal is to build a therapeutic pipeline for SMA that contains a number of drug candidates.

Thank you for your support which has enabled us to reach this point. Your backing has provided hope to many patients and families. Your help over the next few years will allow us to move forward to clinical trials with this particular program, and also to build the essential pipeline of treatments for SMA.

Kenneth Hobby
Executive Director, FSMA

The Patient Advocacy Group, consisting of representatives from FightSMA, MDA, SMA Foundation and Families of SMA is organizing and funding a "SMA Summit on Drug Development" to be held in September in Washington, DC.

In anticipation of major drug efficacy trials for SMA, the mission of this meeting is to identify and reduce or eliminate barriers to successful drug development.

FSMA FUNDED PROGRAM SELECTS CLINICAL CANDIDATE

- This is the first time a drug candidate specifically designed to treat Spinal Muscular Atrophy has reached this stage.
- FSMA is beginning work now to generate the application to the FDA which is needed to begin clinical trials.

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