



Families of SMA *Research. Support. Hope.*

# COMPASS

A Publication Dedicated To Research Updates

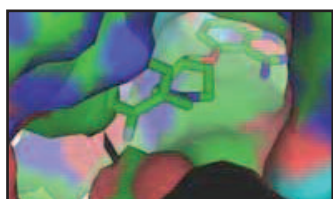
## FSMA Quinazoline Program Update: Preparations Now Underway for a pre-IND Meeting with the FDA.

By Jill Jarecki, Ph.D., Research Director FSMA

In June 2009, the IND-enabling safety studies were completed for the FSMA-directed Quinazoline program. This is the program previously worked on by Vertex Pharmaceuticals and deCODE genetics, and fully funded by Families of SMA.

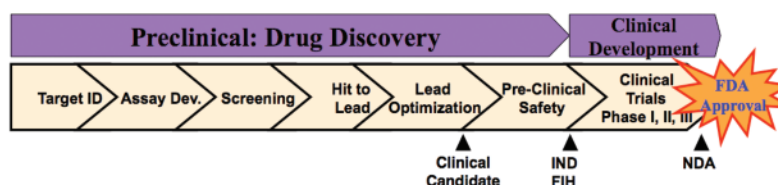
The next step for this program is to request a pre-IND meeting with the FDA and to prepare the required data package. Families of SMA will be working over the next several months with toxicology and regulatory experts to prepare for this meeting.

**This meeting will be an exciting milestone for the project, and an essential step in the path towards human clinical trials of the drug candidate.** During the pre-IND meeting, the FDA carefully assesses the existing data on the drug candidate, providing essential feedback on the feasibility of human clinical trials, and specific information on any additional experiments that may be required by the FDA for the Investigational New Drug (IND) Application.



X-ray crystallography reveals the nano-sized drug binding site of DcpS (Source: deCODE chemistry & biostructures)

### Drug Development Process



IND = Investigation New Drug Application needed for FIH  
FIH = First in Human  
NDA = New Drug Application for FDA approval

An IND application essentially seeks permission to begin human safety testing of a particular drug therapy. We anticipate our pre-IND meeting will occur in September of 2009.

An IND filing would be the culmination of almost 10 years of pre-clinical drug development work, which started at the earliest stage of drug discovery in assay development. This project has successfully progressed through each stage of the pre-clinical process shown in the figure above.

Many groups have collaborated with us to reach this point, including Vertex Pharmaceuticals, deCODE genetics, Invitrogen (Life Technologies), Paracelsus, the Burghes lab at Ohio State University, the Didonato lab at Northwestern University, the Kiledjian lab at Rutgers University, the Chung lab at Columbia University, and the SMA Project at NINDS.

**Families of SMA has invested over \$12 Million in this particular program to discover and develop a new drug treatment specifically designed for SMA.**

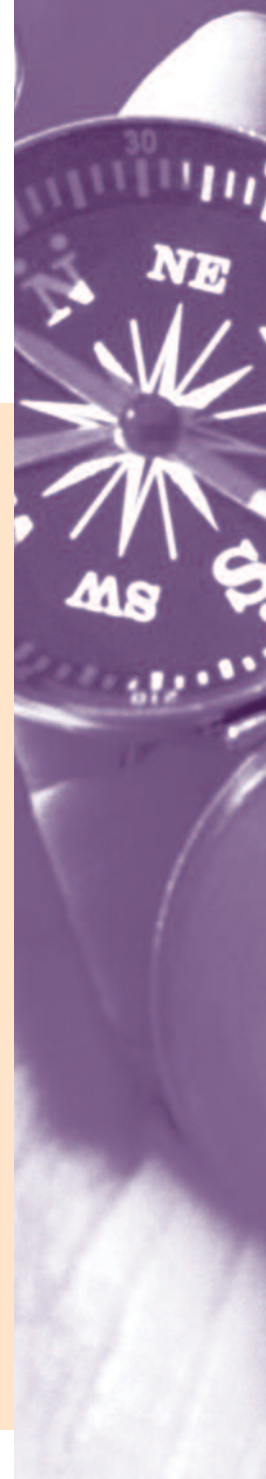
### Families of SMA Therapeutic Pipeline

FSMA is funding three distinct drug discovery programs:

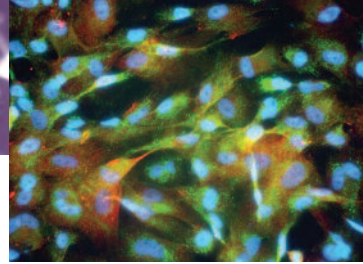
- 1) Quinazolines to boost SMN2 expression;
- 2) Tetracyclines at Paratek Pharmaceuticals to correct SMN2 splicing;
- 3) Motor neuron replacement program at California Stem Cell and UCI.

**These three programs represent an investment of over \$16 Million so far in our pursuit to build a SMA drug pipeline.**

FSMA plans to continue to invest and further expand the pipeline of drug programs. This pipeline will enable us to move multiple drugs forward at the same time. When one drug candidate drops out of consideration, another one will always be there. In addition, it allows us to tackle the treatment of SMA with several distinct approaches. Diversifying our approaches increases the chances of success.



**SUPPORT OUR DRUG DISCOVERY  
AND DEVELOPMENT PROGRAMS:**  
Please visit [curesma.org](http://curesma.org) and  
make a donation.



## FSMA-Funded Project at Paratek Pharmaceuticals Moves into Next Phase with a Multi-Million Dollar NINDS Grant Award.

By Paul Higgins, Ph.D., Director, Inflammation Drug Discovery, Paratek Pharmaceuticals.

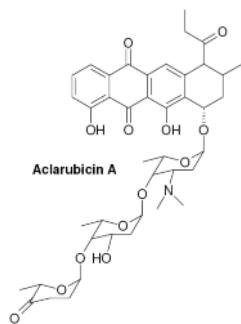
**F** SMA has supported the research at Paratek for the previous three years for our work on tetracycline derivatives as a potential treatment of SMA. These compounds are intended to correct SMN2 splicing and in turn increase SMN protein levels.

We have generated and tested many new tetracycline compounds for their ability to influence SMN2 splicing and to increase SMN levels. Importantly, several of the new compounds that can increase SMN protein levels have shown good capability to cross the blood-brain barrier (BBB) in mice, which will be a critical feature for a SMA drug. In addition, experiments were performed in SMA mice models to confirm compound ability in correcting SMN2 splicing in animals, not just in cells.

### Future Plans:

Using funding from FSMA to generate the preliminary data for a grant application, Paratek has been awarded a multi-million dollar U01 grant from the NINDS to continue our research that FSMA funded for the past 3 years.

With this funding, we will continue to synthesize new tetracycline derivatives, test them for SMN2 splicing modification and for BBB penetration in mice. Importantly, we will test additional compounds for efficacy in SMA mice. Two compounds



are particularly interesting candidates as both exhibit both splicing activity and BBB penetrability. In addition, we will test compound administration via the intrathecal route (the injection of a therapeutic agent into the sheath surrounding the spinal cord) in order to test brain-specific efficacy and to explore the possible clinical utility of this means of drug administration in humans.

Our overall goal for this project is to develop a drug candidate for SMA resulting in an Investigational New Drug (IND) application with the Food and Drug Administration (FDA) within 4 to 5 years.

For the past 3 years, FSMA has invested \$2 Million in research at Paratek Pharmaceuticals, and with collaborators in the Krainer Laboratory at Cold Spring Harbor, and in the Hastings Laboratory at Rosalind Franklin University, to discover new drugs for the treatment of SMA.

## High Purity Human Motor Neurons for Treatment of SMA Type I.

By Chris Airriess, Ph.D., Chief Operating Officer, California Stem Cell, Inc.

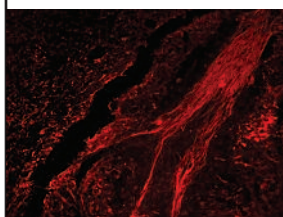
**C**alifornia Stem Cell (CSC) is preparing for a final FDA pre-IND meeting to take place in mid 2009. This is a critical step on the track to submitting a formal Investigational New Drug (IND) application to the FDA to begin clinical trials in SMA Type I.

CSC has developed methods for the manufacture of clinical grade human motor neurons from human embryonic stem cells. It is the intent of CSC to gain approval to begin FDA-approved clinical trials for the use of these cells in development of a cell replacement therapy for SMA Type I.

Numerous pre-clinical efficacy studies have been completed, demonstrating that the cells work. These include:

- 1) Correct localization of CSC motor neurons in the spinal cord;
- 2) Cell growth and extension out of the spinal cord toward the limbs;
- 3) Contact and synapse formation with target muscle;
- 4) Functional re-innervation of muscle, leading to restoration of limb function in animal models of motor neuron loss.

**The pivotal animal safety study, required to support an application to begin clinical trials, was completed in October 2008.** Data analysis is in the final stages and should be complete by the end of June 2009. There were no negative outcomes of this safety study, leading to the conclusion that motor neuron replacement should be a safe strategy in the treatment of diseases such as SMA characterized by motor neuron loss.



Numerous and comprehensive medical community focus groups have been held to develop the clinical strategy for SMA clinical trials. Topics included clinical site selection, inclusion criteria, route of administration, immunosuppression to prevent rejection after transplantation, and outcome measures to assess both benefit and safety of the treatment.

Manufacturing facilities and procedures have been audited for compliance with FDA guidelines for clinical manufacturing and the full Quality Assurance System is in place.

**CSC is now preparing for a final FDA pre-IND meeting to take place in mid 2009, keeping us on track for a formal IND application to begin a Phase I/IIA clinical trial in SMA Type I.** This stage of the project has included the hiring of a Medical Director and a Clinical Research Coordinator at CSC. The two new positions will be responsible for coordinating the preparation of the above IND application and for overseeing and monitoring the resulting clinical trials. The financial support for these positions came from a grant to CSC from Families of SMA through the generous support of the Dhont Family Foundation.

Families of SMA has invested over \$1.5 Million so far in a collaboration with the University of California, Irvine, California Stem Cell, Inc., and Johns Hopkins University to progress stem cell therapy for SMA to clinical trials.