



FAMILIES OF SPINAL MUSCULAR ATROPHY

COMPASS

A Publication Dedicated To Research Updates

This issue was produced based on transcripts from the 2007 FSMA Family and Professional Conference in Chicago.

Dear Families and Friends

Hopefully, everyone now should have read about the exciting announcement that we have a clinical candidate for our SMN enhancing drug discovery program. With a lot of work and effort, and making many related molecules to our original hit that came out of the Aurora screen, we have been able to optimize a drug candidate so that it is available in the brain, it stays in the human body for a long enough time, and it has efficacious activity. We are now beginning to embark on the studies that are needed to go into an IND application to the FDA which will allow us to do first in human testing.

So, now that we have heard the punch line to this entire talk, I'll just start at the beginning and give you a more comprehensive overview of the Families of SMA research programs for the last year.

In the last year, Families of SMA funded \$4,000,000 in research. We funded 28 different basic research grants to academic laboratories and universities. We funded two different drug discovery programs: The one that I mentioned above, which are Quinazoline compounds to enhance SMN expression, and the other at Paratek Pharmaceuticals, which is a much earlier stage program to look at Tetracyclines to correct SMN2 splicing defects. We have also been funding the Project Cure SMA Clinical Trials Network. There are about 30 people now in

Project Cure SMA at 7 sites; 5 in the US, 1 in Argentina, and 1 in Montreal. The Project Cure SMA Network has been working on a Phase II trial for the last several years to look at the combined regimen of Valproic Acid and Carnitine in children with Type II and Type III SMA. We heard at a Project Cure SMA meeting this week that 91% of study visits have been completed and the trial will end in November of 2007. We are expecting data from the trial by the time of this conference next year. Also, the Ohio State site, under the direction of Dr. John Kissel, started an adult SMA ambulatory trial. We have also been funding the Indiana SMA Registry to help patient recruitment into clinical trials. This is a registry that all of you can join and then be contacted to enter clinical trials. This registry, which we started 20 years ago, is open for use by all researchers around the world.

Now I would like to go into a bit more detail about the three areas of research that Families of SMA funds. For the last couple of years, we have been funding basic research, drug discovery, and clinical testing about at equal levels. Therefore, our research funding is basically divided into thirds, with a third of our money going to each of those areas. The reason we allocate our funds like this is that we feel these three areas are very interconnected and essential to developing SMA therapies. The basic research allows us to understand

how SMA is working in motor neurons and in cells. Understanding this is critical to designing effective drug discovery strategies. The drug discovery strategies then lead to compounds to be tested in humans in clinical trials. So, all of these activities must go on simultaneously to be effective and efficient. In addition, we also fund alternative therapies like stem cells and some gene therapy work.

I now want to talk a little bit on why basic research remains so important to SMA. Even though we have now gotten to the point that we are testing drugs in the clinic, there is still a lot we do not understand about the basic mechanisms of SMA and how the protein SMN works. Understanding these mechanisms is going to be critical to designing new drugs and making them better and more effective. So what we do know is that SMN protein is required for motor neuron function. We know that motor neurons are very specialized cell types. They have cell bodies which are in the spinal cord and they expand very long axons out to the muscles in your body. This can be a very long distance from your spinal cord to your foot say. SMN is found in two places in this cell. First, in the main cell body, and second way down in the axon. We still do not know whether or not the critical function of SMN in SMA is up in this cell body or in the distinct function down in the axon, or it may be both. But basic research is

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the path to answering this question. Knowing the function of SMN is critical to help us really focus in and develop drugs in a better way. There are also a number of other questions that basic research can answer, such as how far into SMA disease progression can SMN levels be increased and still have a therapeutic benefit? We do not know very much about how SMN expression or levels are controlled and regulated? Knowing these things, and having a greater understanding about the way that SMN functions, will also allow us to intervene at different points in this pathway. If SMN requires other proteins A, B, and C to do its job, you may be able to do drug discovery projects directly on proteins A, B, and C – and not just focus on SMN. This could really help us move forward.

There are also other questions that we can ask in our basic research such as can we replace SMN protein with gene therapy? Can we directly replace motor neurons with stem cell therapy? All of these questions are really important and they are mostly looked at in the academic labs in the universities. They are funded through our basic research program.

Now I want to return to the subject of drug discovery and drug development and give you an update on where the two drug discovery programs that we fund are in this process. Before I do that, I am going to give you an overview of how drug development works so you have some kind of context to put all this information into.

Drug development is divided into two main steps. One is preclinical drug discovery and the other is clinical development. They are very distinct steps. Preclinical is the stage before you test in humans, and then clinical development is when you begin testing drugs in humans. Getting to this milestone of testing in humans is a huge step in the process. You probably have all heard statistics about this process taking about 10 to 15 years and costing about 1 billion dollars. As SMA is an orphan disease the FDA has different guidelines to help expedite orphan disease drug develop-

ment, so luckily these statistics do not directly apply to our situation.

When we started our first drug discovery program at Aurora BioSciences, which was seven years ago now, we began at the start of this whole process where we knew that there was a target: the SMN2 gene whose expression could potentially be increased to have therapeutic benefit. At Aurora, they developed an assay to see whether SMN2 expression could be increased. They used this assay to test thousands of compounds to look for some that could increase SMN protein levels. At the point where you find compounds that do this, they are called hits. A hit is then shown in cellular models of SMA to increase SMN levels. When you have a compound that does something desirable in a Petri dish it does not mean it can act as a human drug however. A huge amount of effort has to go into turning that hit into a real drug. That process is called lead optimization.

In order to turn a hit into a drug, many relatives of this original hit compound are made - usually several thousand - until you have one that looks good enough to be considered a clinical candidate. When your clinical candidate is selected you then run through a pre-clinical package of safety studies, which takes about 9 to 12 months to complete. When we do pre-clinical safety studies we are looking to see if this compound is safe enough to be tested in human beings. Once you have that data, you can file an application to the FDA, and they will review it and let you know if you can begin testing in humans in phase I clinical trials.

For the Families of SMA Quinazoline collaboration with deCODE chemistry, we have just selected a clinical candidate for the program and are now beginning pre-clinical safety tests. In our second drug discovery program, with Paratek Pharmaceuticals, we are currently working on compounds to correct SMN2 splicing. This is a much earlier stage project where we have a hit that we are beginning to optimize into a drug.

This process of lead optimization, mak-

ing thousands of versions of that compound, is essential because a drug needs to do many things at once. It does not only have to increase SMN levels, but it needs to be present in the blood stream, and in our case, cross the blood-brain barrier. This is something that has to be engineered into our compound. In addition, the compound has to be safe and selective. It can't be toxic. Many compounds will have a few of these characteristics but not all, and that means they are not going to be a human drug. This is what makes drug discovery a long, complex, expensive and high-risk process.

Just to give you a quick update on the status of the Paratek program: Paratek is focusing on a tetracycline compound that can directly correct SMN2 splicing. It causes exon 7 to be included in the SMN protein, so making it fully functional. As I said, this project is in very early stages of lead optimization. We are just starting to understand what parts of the compound are required for activity. Over the next year, we are going to make hundreds of analogs of our hit and look for one that can cross the blood-brain barrier.

Note: More details on our clinical programs will be included in the next edition of Compass which should be available in a few months. Some quick notes from Dr. Sandra Reyna on the current clinical trials we are funding are opposite. Also, to learn more about the status of the Quinazoline project, I encourage you to read the remarks given by Dr. Mark Gurney from deCODE Genetics.

Sincerely,

Jill Jarecki, Ph.D.

Research Director, Families of SMA.

In the spring 2007 issue of Compass was a transcript of a clinical trials chat with Dr. John Kissel. During the chat Dr. Kissel referred to a study of hydroxyurea. The study which he referred to was conducted in Taiwan and was not the study currently underway at Stanford University. The Stanford Study is still blinded and the results entirely unknown.

Quinazoline Project Update

Given by Dr. Mark Gurney at the 2007 FSMA Conference

I am pleased to report that the compound that we have created for you is showing benefit in a genetic model of the disease, the SMA mouse model. Also, the data that is emerging is showing that the compound is quite tolerable in baby mice and also in adult rats. These are the two main things that are needed to now advance towards the clinic: the first is that our compound works and then second, that the compound looks as if it has the potential to be safe. The next step is to show, in fact, that it is safe enough to advance into human clinical trials. That is a fairly straightforward process. The FDA works with drug companies and has clearly articulated what are the safety studies that need to be done.

Those safety studies basically fall into three types. First, we have to show that the compound does not have an effect on the functioning of any organ systems: so that it does not adversely affect the brain, the lungs, or the heart. Second, we need to show that on repeat dosing, the compound has no toxicity, or at least if we dose up, we can show that the window between toxicity and the efficacious dose is wide enough to enable the compound to go in to the clinic. Third, for a pediatric disease such as SMA, we need to show that the compound does not affect either prenatal development, or postnatal development.

So, this is a big hurdle. It was a big hurdle to get this far to show that we could make a compound that was drug like; that had efficacy in the animal model; and that had pharmacokinetics that would support treatment for a disease that affects primarily the brain.

The time required at deCODE to conduct pre-IND studies is generally on the order of 9 months. This data generated from these studies allows us to file the Investigational New Drug application, the IND. At that point in time, we begin conducting preliminary studies

of the compound in healthy adults, and we ask: when we give a single dose of the drug, is it absorbed, does it appear into the blood, and then is there any indication that it is acting via the mechanism of action that we designed? If we find that in the single dose that the compound is behaving properly, then we would do a second study in healthy adult subjects which is called multiple dose tolerability. From that study, we obtain information as to whether the drug accumulates in the body on repeat dosing, and again check that it is exerting the mechanism that we desired.

At that point in time we would have preliminary data on tolerability that allows us to move into actual patient clinical trials. From our experience, this has usually taken about eight months with the first dose in a human, to a completion of Phase I.

So I think from where we are standing now, if everything goes smoothly, and this is not an easy industry to be working in, but if everything goes smoothly, we could see maybe 9 months to an IND and then another 8 months in Phase I that you would need to begin your initial studies in SMA patients.

I think we have come a long way. FSMA has been one of the very first disease foundations to try and undertake drug discovery. You have shown that you can conduct a high throughput screening campaign, that you can identify hits, that you can work with a chemistry company to turn those hits into leads, and now show that those lead compounds have benefited animal models of SMA. So that has been quite a long road, a very difficult one, and now we will see as we progress, do we have a compound that is safe enough to take into human clinical trials, and we should know that on the order of months rather than years!

Current Clinical Trials in Project Cure SMA

By Dr. Sandra Reyna

CARNI-VAL. Project Cure SMA's first randomized, placebo-controlled trial tested valproic acid (VPA) and carnitine in children with SMA type II. When the remaining dozen study visits are completed by Thanksgiving CARNI-VAL will meet its ambitious goal of taking a full 90 participants through the entire trial. So what's the upshot? First, achieving that participation goal is scientifically crucial. It allows us determine the safety and efficacy of VPA in treating the symptoms of SMA. Second, having produced a rigorous study by requiring random assignments of drug and placebo arms in the larger cohort of type II children, we meet the FDA requirements for a well defined study of efficacy. In other words, if analysis of the data shows that VPA does improve the motor function of SMA children, we could move closer to possible FDA approval of this promising treatment.

In mid-November 2007, Project Cure SMA researchers begin the final step in the process -- data collection and entry will be completed and sophisticated biostatistical analysis will take place. Results will be ready by mid-2008. Currently our investigators remain blinded to the drug and placebo assignments, as required. Project Cure SMA owes much to Families of SMA, who funded this trial in its entirety and to Abbott Laboratories, who donated the VPA in the form of study drug and placebo, and to Sigma-Tau

Pharmaceuticals, who donated the carnitine in the form of study drug elixir and placebo.

VALIANT. The preliminary data of the Utah pilot trial on VPA also led to the decision to embark on an adult trial of VPAs. Thus VALIANT was conceived. In late November, 2006, FDA approval was sought for this trial of adults with Type III SMA. To focus the research and give VPA its optimum chance at showing efficacy in adults, only those adults who are still able to walk unaided were included between the ages of 18-60 years.

The Project Cure SMA adult trial is conducted under the direction of John Kissel, M.D., of The Ohio State University. Families of SMA has provided full funding, while Abbott has donated study drug and placebo. Following the design of CARNI-VAL, our adult trial is randomized and placebo-controlled. However, unlike CARNI-VAL, half of all 36 project participants will begin with placebo, half with study drug, and then switch after 6 months. Dr. Kissel received FDA approval for the trial at the end of 2006 and all institutional regulatory requirements have been met, allowing enrollment to begin in mid-summer 2007. To date, 4 participants have been screened and included. Each participant to complete the study will engage in study visits over a 13-month period.