Interview with Jill Jarecki, PhD

Research Director, Families of SMA, Elk Grove Village, Illinois.

Jill Jarecki, PhD, has served as the research director at Families of Spinal Muscular Atrophy (FSMA) since 2004. In this capacity she has managed over $35 million in FSMA research investments, including for basic research, preclinical drug development, and clinical research. During her tenure at FSMA she has driven a preclinical drug program and taken a drug development project through a pre-investigational new drug meeting at the U.S. Food and Drug Administration (FDA), designation of orphan disease status from the Orphan Products Office of the FDA, and finally through successful out-licensing of the program for clinical development to an industry partner—all of which were firsts for the SMA field. Dr. Jarecki received her PhD in genetics from Yale University and completed her postdoctoral fellowship at Stanford University. Prior to working at FSMA, she spent 5 years working in the biotech industry at both Vertex Pharmaceuticals and Invitrogen Corporation, where she led project teams developing high-throughput screening assays, conducting high-throughput screens, and validating the bioactivity of small molecules.

Dr. Jarecki, please tell our readers about FSMA and whom it represents. How and when did the organization get started and what are its mission and main activities?

FSMA is a nonprofit organization started in 1984 by a group of parents of children with SMA. The overarching mission of FSMA is a world without SMA, and we do a number of activities to support that all-encompassing goal. The two main ones are supporting families by providing materials, access to experts, and packages for newly diagnosed children (such as a care package with toys that we give to families when they first contact us) and offering an annual conference to help families, both those with a child who is newly diagnosed and those already in the community, to learn more about SMA and find support from those in a similar situation. We also have 31 chapters across the United States that families can join to access similar services and events.

The second part of our mission is the research mission, which is under my primary oversight. We support research to help find a cure and new treatments for SMA. FSMA has funded $55 million in its history, with $35 million of that since 2004. We fund research in three primary areas: basic research, applied drug discovery research, and the development of clinical trial infrastructure, which was previously referred to as clinical trials.

When FSMA began in 1984, the landscape was very different for SMA parents. The gene responsible for SMA had not been identified as the SMN1 gene, and there was little active research on the disease. This has dramatically changed over the past 30 years. In 1996, Judith Melki, MD, PhD, at INSERM in France, discovered that the causal gene of SMA is the SMN1 gene. This changed the research field dramatically, and research rapidly progressed from that point.

Beginning in about 2000, more formal drug discovery efforts began, and we currently have five clinical trials enrolling patients, some in healthy volunteers and others in SMA patients. There are also about 10 programs at earlier preclinical stages, and we now have 12 companies investing in the SMA field. Thirty years ago, SMA patients really had nowhere to go for help, and it was very hard for them to find a physician who knew much about SMA. Now we have a robust research community and drugs in the clinical trials process.

What is the biological basis of spinal muscular atrophy, and how clearly is the pathology understood? How many patients are affected in the United States and worldwide?

Some things about SMA are quite clear, and some things are not. The genetic basis of the disease is now very clear, with the discovery that the SMN1 gene is deleted in about 95% of SMA patients. Other patients have missense mutations in the SMN1 gene. The interesting thing about SMA is that there is a back-up gene to SMN1 called SMN2. This is a somewhat unique situation. SMN2 is almost identical to SMN1 in the coding region. However, it has one critical nucleic acid change—a C to T transition in exon 7. This causes the SMN2 gene to undergo the mRNA splicing process incorrectly; as a result, exon 7 is deleted from the SMN2 transcript about 80% of the time. Therefore, only a little bit of SMN protein is made from the SMN2 gene, but this protein is essential for patient survival. The SMN protein is required for cell viability, so all SMA patients who are lacking the SMN1 gene have a copy of the SMN2 gene (see Figure 1).

Interestingly, there is a wide clinical severity in SMA. Patients who are severely affected tend to die by 2 years of age unless they receive respiratory and nutritional support. About 60% of patients have this type of SMA, called SMA type 1. In the intermediate form of the disease, called SMA type 2, the diagnosis is made after 6 months of age and patients have the ability to sit, but they never walk. The
The genetics of SMA are well understood. What is not as well understood is exactly which tissues are affected when the SMN protein is missing. We know that the affected motor neurons represent a primary manifestation of the disease, but other tissues are probably involved as well; those involved may differ by SMA type and severity. Another thing not well known in SMA is what the protein actually does to cause the disease. There is a canonical function for the SMN protein, which is assembly of the small nuclear ribonucleoparticles (snRNP) that are involved in mRNA processing. This is well established; however, whether or not that is the function that goes awry in SMA is not clear. We have a variety of different philosophical camps in the SMA research field on these two positions, and we talk about this debate in a review article published in this issue of the journal (page 315).1

A recent article by Sugarman et al.2 suggests that the incidence of SMA is about 1 in 11,000 patients. Lifespan in the different types of SMA is not well tracked, but by making a best estimate of the lifespan for each type it is possible to calculate the number of people living with SMA in the United States, which we estimate to be about 15,000, with about the same number in Europe. Of course, a disease-modifying therapy could prolong lifespan in the most common form of SMA—type 1 SMA, which affects children from birth—and this would change the disease prevalence.

The carrier rate for the SMA gene is 1 in 50. There is literature that points to a 1 in 37 or 1 in 40 carrier rate, but the most recent paper that had the largest number of people sampled gives a carrier rate of 1 in 50.2 Unlike a disease such as cystic fibrosis, SMA does not differ dramatically between different races. There are small differences in carrier rates between races, but not greater than twofold.

What types of therapeutic targets would drugs act on to modify the underlying basis of SMA and its symptoms?

The therapies in development today are primarily approaches that would either replace the missing SMN1 gene or modulate expression from the SMN2 gene such that more full-length protein would be produced. Those are the two main disease-modulating strategies being pursued that will hopefully benefit patients if given early enough in disease progression. I think timing is one of the big questions in SMA therapeutics development: When in disease progression can you deliver back SMN protein and still realize benefits? In mouse models of severe disease, the answer is in the first week of life. We do not have good data on when that would be in mouse models of milder disease, and we certainly do not know how that would extrapolate to human disease. Because of those mouse data, FSMA and many others in the field are advocates of newborn screening and hope eventually to get SMA recommended by the federal Advisory Committee on Heritable Disorders in Newborns and Children, which recommends to the states which diseases should be screened for in newborns. The SMA test would be a DNA test, whereas all of the other disorders now on the newborn screening panel are detected using mass spectrometry, so there are some technical hurdles to overcome before SMA could be added to the list. It is clear that earlier is better for delivering higher levels of SMN protein to intervene in the disease.

Overall, the disease-modifying approach aims to increase SMN protein levels, either by replacing the faulty SMN1 gene through gene therapy or by using various methods to modulate SMN2 expression to lead to additional SMN protein. One way to turn the gene on is by increasing promoter activity. Another approach would be to correct the splicing defect in the SMN2 gene to promote inclusion of exon 7. Another approach could be to stabilize the SMN protein, both the delta7 form (primarily produced by the SMN2 gene) or the full-length form, so they would not be degraded as quickly, thereby increasing SMN protein levels.

Other therapeutic strategies that are not disease modifying include a neuroprotectant approach. A pivotal trial has been completed by
Trophos, a French company, with a molecule (olesoxime) that can protect motor neurons from cell death in SMA. In a similar vein, other researchers are looking at muscle protectants, but that work is at a much earlier stage.

At present, five drugs are either in or entering clinical trials. The furthest along is the Trophos neuroprotectant drug, for which a placebo-controlled trial has been completed in 165 patients. Other small molecule compounds from Pfizer and Roche, which are intended to increase SMN protein levels, are in phase 1 safety trials in healthy volunteers. Additionally, Isis and Biogen have a partnership for an antisense oligonucleotide therapeutic called ISIS-SMN\textsubscript{exo}, which targets a sequence in exon 7, allowing exon 7 to be included in the SMN2 transcript; in this way, it corrects the splicing defect. The Biogen/Isis compound is supposed to begin several placebo-controlled registration trials in 2014. It is currently in multiple safety trials, including in infants and children. The fifth therapy in clinical development recently began enrollment of a small safety trial in nine type 1 infants ages 0 to 9 months. It is a gene therapy trial intended to replace the faulty SMN\textsubscript{1} gene. It uses an adeno-associated virus 9 (AAV9) vector and involves a partnership between Nationwide Children's Hospital and a new start-up company, AveXis (see Figure 2).

How would you describe the scope of the research effort focused on SMA? Where is most of this work being done and how is it funded?

In 2000, FSMA began funding its first drug discovery project, at Aurora Biosciences, which was later acquired by Vertex Pharmaceuticals. With the acquisition of Aurora, the project came back to FSMA, and we continued to pursue it through a number of contract research organizations (CROs). It was then out-licensed to Repligen, which then licensed it to Pfizer. This reflects a pattern in SMA drug development. Today, a number of large pharmaceutical companies are interested in SMA. In another example, one of the small molecules now in clinical development started out at PTC Therapeutics with funding from the SMA Foundation and was later licensed to Roche, so Roche now has an active SMA program too. Novartis also has an active SMA program, but it is at an earlier stage. The antisense program involving Isis is partnered with Biogen. At present, there is a good mix of biotech and pharma companies active in SMA.

In 2000 it was difficult to get pharma companies interested in orphan diseases, and the only way was to have advocacy groups like FSMA sponsor the research. Fortunately, the landscape has dramatically changed. The fact that biotech and pharma companies are investing in SMA research is one of the most exciting changes in recent years for us at FSMA. This has been a long-term goal of our organization.

Today, funding comes from a variety of sources, including advocacy groups. FSMA has provided funding at differing levels to about 10 of the 15 programs that are currently in the drug pipeline. Government funding is also available. For example, the gene therapy drug in clinical trials has support from a $3.8 million grant from the National Institute of Neurological Disorders and Stroke. So, funding at present comes from a combination of industry, advocacy, and government sources.

How does a researcher obtain funding to work on a “rare disease” such as SMA?

One of the strategies we like to use for our limited resources is to provide seed funding, in which FSMA supports research projects or drug discovery programs at an early stage. This funding can then be leveraged through the use of preliminary results to obtain larger amounts of funding from industry or government.
Based on your experience working with FSMA, what do you feel are the best ways for rare disease foundations to make a difference in the way treatments and cures are being sought after and developed for patients?

Advocacy groups can impact research in a lot of different ways. As I mentioned, one strategy FSMA uses is to provide seed funding to support early stage research projects that will leverage bigger amounts of money. Another role of advocacy groups is to facilitate connections between researchers. For 18 years, FSMA has hosted its annual SMA research group meeting, which has grown from about 18 people to almost 250 people. We bring the SMA community together on an annual basis to provide a space for them to interact and develop collaborations, as well as to help quickly integrate companies into the community. For instance, many of the companies will hold advisory board meetings at the FSMA annual meeting.

Also along these lines, companies will often come to FSMA early on and ask us who they should talk to about different aspects of SMA research. We have developed a large network of researchers and clinicians that we have worked with for many years, and we can be very helpful in building connections and collaborations. Another aspect in which advocacy groups can play a role is in patient recruitment and providing information and education to patients. FSMA has a database of patients, and nearly 400 new SMA patients contact us every year. We can help connect these patients to clinical trials and to drug companies doing research on SMA.

Of course, government advocacy and gaining awareness of the disease is an important aspect of what we do; for example, advocating for more government research funding. One of the big advocacy issues that FSMA has supported, as I mentioned before, is newborn screening for SMA. In addition, we try to help raise awareness among drug developers and the FDA about the patient perspective on drug development. For instance, what kinds of things are important to patients; what types of clinical changes do they want to see from a drug treatment? Additionally, I think we can help identify gaps in the process and help galvanize people to start working on those. For example, when we recognize these gaps we may hold workshops or co-fund workshops with government or other advocacy groups.

Are there specific policy, regulatory, intellectual property, or other issues currently in place that either help or hinder drug discovery and rapid translation to the bedside of promising new therapies?

One of the biggest difficulties in translational research is moving things from the basic research arena where an idea is first identified to a bona fide drug program by getting the funding, expertise, and resources to make that happen. Sometimes this involves a transition from academia to industry. That transition can be difficult on all of those fronts. On the intellectual property front, there are always challenges in having people share things and making things accessible to the community, while still protecting the commercial incentive, but I don’t think this has been a huge problem in the SMA world so far.

The reality is that it is always a challenge to translate a really good idea that works well in a mouse model of SMA to an actual drug. That takes a lot of money and a lot of expertise, and those resources are not always easily available to an academic researcher. Making that transition happen efficiently is key in this process. FSMA has tried to facilitate that both with early seed funding and by promoting interactions between industry and academia.

How did you become involved with the FSMA?

I have been working with FSMA since early 2000. I began working in the SMA field when I was hired by Aurora Biosciences in San Diego to work on an SMA project; it was the first drug discovery project funded by FSMA and one of the very first projects in the SMA research community. It was a project to develop high-throughput assays and do high-throughput compound screening on these assays to identify candidates for lead optimization and a medicinal chemistry project.

I worked at Aurora for 3 years and then moved on to another biotech company. In early 2005, FSMA contacted me when it was transitioning from being primarily a volunteer organization with a few employees to becoming a more professionally oriented organization. At that time, FSMA was looking to hire a research director, and they offered that position to me.

What are the greatest challenges at present as researchers work toward developing new treatments and a cure for SMA? What are you most hopeful about as you envision the research progressing over the next several years?

Things are very hopeful in the SMA field because we now have drugs in clinical development. We all realize, though, that drug development is inherently risky, with a low success rate. I think one of the missions of FSMA is to not feel entirely comfortable with our situation and to continue to build a robust drug pipeline. Our mission at FSMA to treat every type and stage of SMA, and it is not clear that every treatment will be effective or viable for every patient. I think that is one of our challenges as we move into the future and a critical part of the mission at FSMA.

—Interview by Vicki Glaser

REFERENCES