

# Tackling a rare disease: Working toward a treatment for SMA

Most people have never heard of spinal muscular atrophy (SMA), a rare genetic disease that affects approximately 1 in 6,000 babies born worldwide each year. Innovative research may produce treatments for patients suffering from SMA and other rare diseases.

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It's a tragedy that Brian Tseng, a pediatric neurologist, has witnessed too often.

"You look at an infant in the newborn nursery and he or she may look perfectly well," says Tseng, who is also a translational medicine specialist (someone who figures out how to move drugs from the lab to early clinical trials) in musculoskeletal disease research at the Novartis Institutes for BioMedical Research (NIBR) in Cambridge, Mass. "Then you come back at 2 or 4 months for a well-child checkup and all of a sudden you say, 'Wow, the baby appears a bit floppy or hypotonic.' Then at 6 months the baby is falling off the growth charts, and the red flags go up."

## SMA: A devastating diagnosis

What raises the flags are symptoms of an inherited condition called spinal muscular atrophy, or SMA. The disease is characterized by accelerated, irreversible death of motor neurons, leading to progressive loss of muscle function. Few patients with the most severe form of SMA, called type I, live past their second birthday unless families elect for aggressive interventions that involve life-support equipment. Unfortunately, this medical equipment cannot halt the loss of motor neurons.

SMA is the number one killer of infants and toddlers.

(adapted from the SMA foundation website)

The disease is so devastating that Tseng's medical school adviser warned him against specializing in pediatric neuromuscular disease. "He told me, 'They're all going to die,' " Tseng recalls. " 'You can't do anything to help, aside from getting patients wheelchairs. You're going to be attending a lot of funerals.' "

Instead of heeding the grim advice, Tseng turned his passion toward finding effective treatments for pediatric neuromuscular disorders such as SMA. He's part of an SMA research team at NIBR that includes chemist Natalie Dales and biologist Rajeev Sivasankaran, who lead crucial components of the project. Together, they're on a quest to improve and extend the lives of SMA patients.

## Clear genetic roots

SMA is caused by a defect in a single gene and — like many other rare diseases — it's well characterized at a molecular level, making it an ideal candidate for rational drug discovery. At NIBR, researchers follow the science, focusing on diseases with defined mechanisms. The idea is to develop targeted therapies and address unmet medical needs. NIBR scientists are currently investigating treatments for more than 40 rare

diseases.

In the case of SMA, the mutated gene codes for a protein called survival motor neuron (SMN). Without it, cells in the spinal cord and nervous system wither and die. Luckily, people have a second, backup gene that generates SMN at low levels. In fact, the backup gene is what enables SMA patients — who don't have any functional copies of the first SMN gene — to survive in the first place.

The number of copies of the backup gene varies from one person to the next, so some children produce more SMN while others produce less. They're diagnosed as type I, II or III, based on symptom severity and age at onset. The Novartis team hopes to stop the progression of the disease in all SMA types by boosting production of SMN from the backup gene.

"The exciting thing about SMA is that a lot is known about the underlying biology, and there is a clear therapeutic hypothesis to pursue," says Sivasankaran.

We are getting closer. This is the most compelling and important work I've ever done.

**Natalie Dales**, organic chemist on the Novartis SMA Research Team

The backup gene produces a draft template for SMN that can be read two different ways, a process known as alternative splicing. Only the second, less common interpretation leads to a functional protein. The goal is to force cells to read the template the second way more often and thereby increase SMN levels. This requires finding compounds called "splicing modulators."

## Early progress is positive

During the early stages of the project, partnerships with academic researchers and the SMA Foundation provided a springboard for the team's drug discovery efforts. These collaborators supplied key tools and a deep understanding of the disease biology, accelerating NIBR's SMA program, explains Sivasankaran. His group leveraged the existing network of experts to design initial experiments.

"We started by screening a library of compounds and found a few potent splicing modulators, which gave us the confidence to continue our work," he says.

Approximately 10 million Americans (1:40 – 1:50) carry the defective SMA gene.

(adapted from the SMA foundation website)

The team expanded its screening effort to identify additional splicing modulators. The most promising compounds entered an optimization phase led by Dales and Sivasankaran. The team then selected the best molecules to advance to animal studies.

"The goal is to find compounds that will work in the right way at the right time, and in a safe manner," says Dales.

The team recently tested one of the investigational compounds in mice with a severe form of SMA. After receiving the substance, the mice — which typically die by 15 days of age — regained use of their muscles and lived longer than expected.

"We are getting closer," says Dales. "This is the most compelling and important work I've ever done. We face many challenges, but I'm still optimistic.

Tseng is collaborating with the biologists and chemists to map a path to the clinic. Several hurdles remain. The

team hopes to overcome them to help bring a safe, effective treatment forward. Any new drug needs to be proved in clinical trials, and success is not guaranteed. But the Novartis SMA team is motivated to keep working toward a solution. Tseng says, “SMA patients and families have little hope for the future except to know that research is being done now and that smart people on dynamic teams are working really hard trying to develop new SMA treatments. We must keep pushing the cutting edge forward.”

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