Gene therapy for myotubular myopathy—early signs of success

June 8 2018, by Ricki Lewis, Phd

Nibs founded the dog colony that led to gene therapy for MTM. Allison went to Canada to get him. Credit: Allison Frase

Parents cherish developmental milestones, from a newborn's grip of an offered finger; to an infant's holding her head up the first time; to rolling over, creeping, and crawling; then to standing, cruising, and finally walking. Even kicking during a diaper change or yowling requires muscle strength and coordination. But a boy with X-linked myotubular myopathy (MTM) is so weak that even breathing is a huge struggle. If a baby survives the initial hospital stay, care at home becomes a full-time job and is only supportive, delaying the inevitable. That grim picture may be changing.

Thanks to the efforts of parents, geneticists, physicians, and veterinarians, a gene therapy for MTM has had early encouraging results as a few treated boys are maxing out on standard tests of neuromuscular function (CHOP INTEND) and breathing (maximal inspiratory pressure or MIP). One boy who'd only received nutrition through a stomach tube is now feeding himself; another can pick up and throw a ball.

The story of gene therapy for MTM begins with Alison Rockett Frase and Paul Frase, and their son Joshua. She was an assistant personnel manager for Guns'N'Roses, he a linebacker for the NFL. More importantly, they're what I call catalyst parents – moms and dads who refuse to listen to the refrain of "bring your baby home to die" and "there's nothing we can do." These parents push for progress, even if it comes too late for their own children.

Alison's pregnancy had been mostly uneventful. An ultrasound at 22 weeks showed a fetal body a bit small for the head, and by 38 weeks the baby-to-be had settled into a breech position. A physician could

maneuver him head-down, but he'd soon flip back. When Joshua was born by C-section a few days later, on February 2, 1995, everyone in the delivery room could see that something was wrong.

Joshua was small, skinny, dusky, and eerily silent. Alison and Paul heard the word "floppy" to describe his absent muscle tone. The APGAR score was zero, and nurses began to prepare the young couple for their newborn's imminent demise. But Joshua Frase had other ideas.

On Joshua's 24th day of life, Alison and Paul took him home and began the complex care required to help him to eat and breathe that would sustain him for nearly 16 years. Diagnosis came rather quickly for the rare disease world circa mid-1990s: after 3 months of testing, a muscle biopsy revealed MTM, inherited from Alison's X chromosome. (Rarely, girls who are carriers can get MTM if many of their muscle cells have the X chromosome bearing the working copy of the gene turned off. Cells of female mammals inactivate one X, a normal way of genetically evening out the sexes called dosage compensation.)

Joshua's prognosis couldn't have been much worse: 75% of boys with MTM die in weeks or months of respiratory failure, and the average life expectancy is 29 months. The weak muscles affect development of the skeletal system, and scoliosis and a large head result.

In MTM the protein myotubularin 1 is absent or abnormal, stemming from a missing or mutant MTM1 gene. All cells make the protein, but it's especially critical for skeletal muscle cells, which remain in a fetal-like state. MTM is a "centronuclear myopathy," which means that skeletal muscle cell nuclei are centrally located, rather than crowded to the sides of the abundant contractile proteins that fill the long, spindly cells. The unusual structure prevents calcium from entering the muscle cells and they can't contract, like a cell phone unable to receive incoming signals.

Assembling the Team

Joshua Frase didn't die in those first few weeks. Or months. Again and again he would astound caregivers with his will to live. But time was running out.

"As we approached his first birthday, a milestone we never truly expected to make, we began to realize that if we didn't do something for our son, nobody else would," Alison recalls.

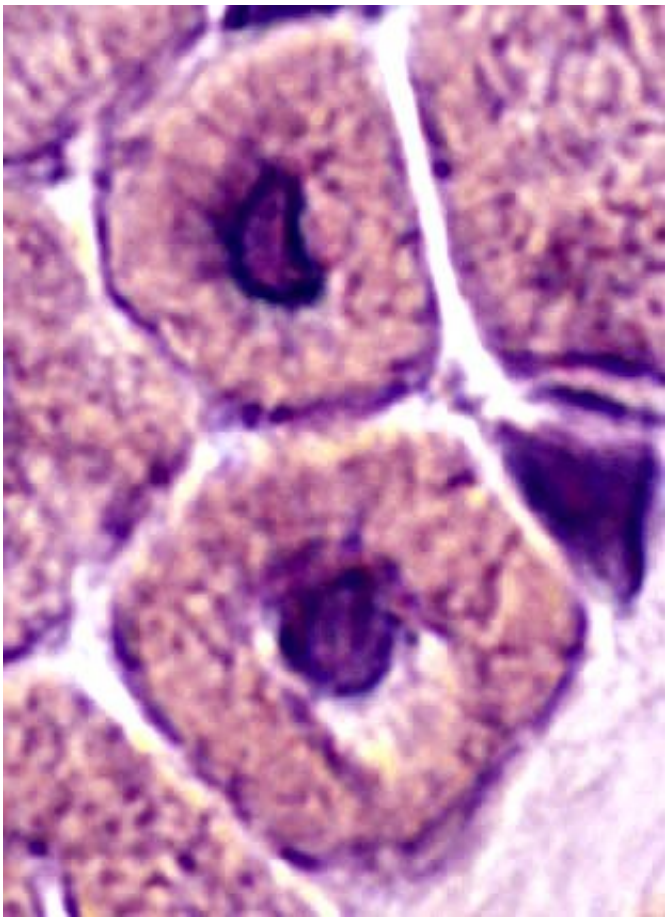
That meant forming a research foundation, fundraising (helped by celebrity connections), assembling a team of investigators, and, of course, learning the science. The Joshua Frase Foundation for Congenital Myopathy Research was born three weeks after the boy's first birthday. Only 55 cases were known in the world then. MTM affects 1 in 50,000 live male births.

The road to gene therapy was long.

The team began to self-assemble in 1997, when Alison's mom saw a story on CNN about Anthony Atala, the superstar of regenerative medicine who famously grew a human bladder in 8 weeks at Boston Children's Hospital. Alison's mom contacted him and he not only responded, but put together a dream team that included Alan Beggs and Louis Kunkel at Boston Children's, Anna Bu Bello (who had a mouse model) from Genethon, Martin Childers and David Mack at the University of Washington, Jocelyn Laporte (who discovered the MTM1 gene) at the Institut de Génétique et de Biologie Moléculaire et Cellulaire in France, and others. Over the years, as Alison and Paul and other families raised millions, the NIH provided $5 million.

By early 2014 a gene therapy was working in mice and in dogs. In 2017 a report on body-wide delivery of the gene in dogs would prove critical

to the early success of the gene therapy in boys. "All readouts in the dog studies turned out to predict, with great accuracy, the outcome measures now being observed in the treated boys," Dr. Mack says. For example, the dog work revealed that myotubularin levels of 10% to 40% are enough to restore muscle structure and function, which helped greatly in determining dosages to test.



In MTM, skeletal muscle cells in crossection have unusual centrally located nuclei.

But I'm getting ahead of the story. My favorite part of this inspiring tale came in 2008, when the dogs entered the picture.

Labrador Retrievers Join the Team

At a scientific meeting, veterinarian Diane Shelton approached Beggs, who'd shown slides of MTM skeletal muscle. Shelton mentioned that she had skeletal muscle samples from animals with "wasting puppy syndrome" from a vet in Canada, and the cells with the central nuclei reminded her of those from the boys with MTM. That mention led to the discovery of MTM in Labrador retrievers; the puppies typically don't survive beyond 5 months. Such a natural dog model is a gift, both literally and figuratively. Canines were critical in developing gene-based treatments for Duchenne muscular dystrophy and a form of blindness (see the chapter "Kristina's dogs" in my gene therapy book).

In 2008 Alison and Paul learned, through their network of experts, of Nibs, a female chocolate lab living happily on a farm in Saskatoon, Saskatchewan. Nibs carried a dog myotubularin mutation. The farming couple generously offered Nibs to the couple when Alison explained that she could be bred to found a colony that could be used to develop and test a gene therapy for the lethal neuromuscular disease.

Alison flew out to collect Nibs, and the dog resettled on a farm near Wake Forest University, headquarters of the gene therapy research. Alison tells the astonishing tale in the journal Human Gene Therapy, and in the book that she and Paul are writing, "Game Changer," which opens with Alison's trip to fetch Nibs.

The very special chocolate lab went forth and multiplied, and the gene therapy begun on her descendants in 2013 worked. This paper assesses two of the treated dogs. Four years post-gene therapy, they had normal neuromuscular function, suggesting that the disease could be stopped in its tracks and maybe even reversed or prevented – not just slowed.

The gene therapy worked so well that one dog, Rocky, instead of dying

by 5 months, fathered a litter with a female carrier of MTM, giving rise to precious females who had a double dose of the mutation. Affected females, made well from the treatment, wouldn't exist in nature because a male dog couldn't survive to mate to produce them. More dogs became available, and soon the clinical trial was being planned. (The treated dogs didn't pass on the correction because it was delivered into muscle, not to sperm or eggs. And gene therapy adds a gene, it doesn't physically replace the mutant one.)

The Clinical Trial

In summer 2012, Paul Frase met with entrepreneur Matt Patterson, who would become CEO of Audentes Therapeutics, the company that has developed the gene therapy for MTM. The approval of Glybera, a gene therapy drug, in Europe that year helped to convince Patterson.

"From day 1 we appreciated the severity of MTM and the unmet medical need. Our desire was to advance this product as rapidly as possible. MTM is extremely severe. Half of the boys don't live to their 2nd birthday. This is important and unique versus other programs where the goal is simply to slow the progression of the disease," Patterson told me.

Planning the gene therapy had three stages:

- RECENSUS reviewed medical records for 112 boys "so we could learn about the disease other than from the few publications," Patterson says. The records showed mortality in 64% of patients before 18 months and in 32% of patients older than 18 months.
- INCEPTUS is a natural history "run-in" study that collects information on the illness before treatment, using the same measures that will be used to evaluate response to gene therapy.

The findings provide a within-patient control because boys begin in INCEPTUS and transition to the treatment group.

- ASPIRO is the phase 1/2 clinical trial begun last fall.

Early Spellbinding Results

Alison and Joshua

The treatment, now called AT132, is delivered intravenously in an arm or leg using an adeno-associated virus (AAV) 8 vector. Twelve boys under age 5 will receive the treatment, at UCLA Medical Center, the University of Florida, and the Ann & Robert H. Lurie Children's Hospital of Chicago. The first treated boys received 100 trillion viruses per kilogram of body weight.

A news release from September 2017 announced dosing of the first patients. Each of the two dose cohorts includes one boy who is treated later, to continue to monitor untreated disease progression.

Results at 12 weeks, reported in a news release in January 2018, exceeded expectations. And Audentes presented even better news for the 24-week mark for 7 patients at the American Society of Gene and Cell Therapy annual meeting in May. The first two patients now have normal neuromuscular function, and one is off the respirator and the other just using it at night.

"We're thrilled to see early results of patients in whom we've removed reliance on mechanical vent support," says Patterson. Added Natalie Holles, president and COO at Audentes, when the company recently showed video of the first two boys to patient advocates, "Physicians and caregivers report really remarkable improvements in disease severity. The earliest treated patients are much more mobile, to the delight and maybe consternation of their parents … scooting and cruising around furniture."

The first boy, treated as a baby, couldn't lift his arms or control his head, and his mouth gaped open, a classic sign of profound hypotonia (lack of muscle tone). By week 24, he could lift his arms unaided. The second patient was just over 4 years old when treated. Before treatment he couldn't reach out to touch a baseball. "By week 24 not only does he want to throw it, he wants to go get it himself so he scoots his way off the mattress. A picture is worth 1000 words and a video, a million," said Holles.

The boys are doing so well that the researchers are replacing the CHOP INTEND tool with one that tracks more sophisticated movements during the first year of life.

Alison saw the videos and was astonished. "Watching this unfold before my eyes has been almost surreal. Am I really witnessing my son's dream, my vision before my eyes? The clinical trail is bringing 22 years of painstaking work to real tangible results some would consider miraculous."

Next will be analysis of muscle biopsies from the first treated children for myotubularin protein level and tissue structure, to see if the dose should be upped in other children.

Joshua's Legacy

As with any gene therapy for a disease so severe that children don't live long, it'll take time to see if effects are sustained, and whether symptoms never seen before because of the disease's lethality emerge. But for now, gene therapy for MTM is clearly on the trajectory towards regulatory approval. "The results are extremely encouraging, but they are still early and we have lots to learn. But it's a wonderful step forward in just 6 months. MTM provides yet another example of the exciting potential of gene therapy as a platform in rare diseases. We're glad to be part of the

ongoing story," says Patterson.

Gene therapy for MTM was too late for Joshua Frase, but it will be his legacy.

Alison and Paul made their son's short life as normal and meaningful as possible. "Some of my most cherished memories are blueberry picking on a hill in the Maine countyside while traveling in an RV on the eastern seaboard scouting dinosaurs. Those years he was strong, so full of life, a mind that was brilliant, he never asked why or complained. I miss his quick wit, his sense of humor. His line … "mom, don't sweat the small stuff." I miss his profound statements after life and death situations. That kid was one of a kind. I have no doubt Joshua is proud of our work, and he is orchestrating from above," says Alison.

I have no doubt that Joshua will, through his parents and their efforts and the investigators and biotech company that came on board, save lives. So I'll end with his wise words:

"The truth of the matter is nobody is perfectly normal. We all have various types of characteristics, but one thing is for sure; none of us are the same and none of us are completely different."—Joshua Miles Frase, 2009, 15 years of age

This story is republished courtesy of PLOS Blogs: blogs.plos.org.

Provided by Public Library of Science

Citation: Gene therapy for myotubular myopathy—early signs of success (2018, June 8) retrieved 6 May 2024 from https://medicalxpress.com/news/2018-06-gene-therapy-myotubular-myopathyearly-success.html

This document is subject to copyright. Apart from any fair dealing for the purpose of private

study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.