

### Dream On: The Pursuit to Cure Myotubular Myopathy Born out of a Mother's Vision

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“MYOTUBULAR MYOPATHY”—those words leaped off the page at me. “What is myotubular myopathy (MTM)?” What could this diagnosis possibly mean, and how did centronuclear myopathy (CNM) fit into the equation?” I stared at the three pages copied from a medical textbook for a moment before flipping to a couple of published medical articles, one from early 1966 written by Dr. Alfred Spiro, describing MTM.<sup>1</sup> It was my first time reading a published medical article and the text was completely foreign to me. As I read through these pages I learned of MTM and its effects on the skeletal muscles in infants. Difficulties feeding and the frequent need for mechanical ventilation were troubling descriptions of this disorder. Though my son did not require mechanical ventilation, the prognosis of a short life span, and the medical complications expected, were devastating. Strangely, amidst the confusion and painful realization of my son's future, there was a bit of relief. After three months of rigorous searching, my son finally had a diagnosis.

Three months earlier when Joshua was born, he came into the world “floppy,” a term used to describe a baby with extremely low muscle tone. His muscles were so weak that he was unable to breathe on his own and subsequently failed his Apgar test miserably. Doctors rushed him to the NICU, which is where he stayed for the first 24 days of his life. While he was there, we worked with teams of doctors trying to figure out the root cause of his hypotonia, but it was to no avail. Nobody had a clue what was wrong with him, and when they discharged us on day 24, it was their belief that it would be better for him to pass away at home. We left the hospital with our son on an NG (nasal gastric) feeding tube and a suction machine, and nothing else.

Those pieces of paper, delivered to our family while on vacation in Maine, held the answer to our question. X-linked MTM, or XLMTM, is a rare orphan disorder that almost exclusively affects males.<sup>2</sup> The *MTM1* gene provides instructions for producing a small enzymatic protein called myotubularin. Myotubularin is thought to be involved in the development and maintenance of muscle cells. The absence of this protein also results in a malfunction of calcium transfer responsible for muscle contraction.<sup>3</sup> XLMTM brings with it a very high mortality rate, as 50% of children born with this disorder do not live to see their second birthday. At the time of Joshua's birth, he was 1 of 55 known cases worldwide, making the term “rare orphan disorder” a massive understatement. The term “ultra-rare” was coined for disorders as rare as Joshua's.

My sole responsibility the first year of Joshua's life was to keep him alive. That alone was an all-consuming task. 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. I knew that I would need money to find answers, and I knew enough about the world of philanthropy to know that a foundation would be the best way to raise the money. One afternoon, I looked over at my husband, Paul, a defensive lineman in the NFL, and said, “I'm starting a foundation. I'm using your platform and I'm going to do it. I've got to do it.” Three weeks after Joshua turned one, the Joshua Frase Foundation for Congenital Myopathy Research, Inc. (Joshua Frase Foundation, or JFF), was officially registered with the IRS as a 501C3 and could begin accepting donations.

Everything in the beginning was a learning curve. During the first year, we didn't have a

marketing plan in place, but sports writers from across the country shared our story and donations began flowing in. Being fully aware that there was no road map for us to follow, we knew we would have to forge ahead and make one for ourselves. But how do two parents with no scientific background do that? To start, we began looking into cutting-edge research.

In 1997, we approached our first researcher, Dr. Anthony Atala. Dr. Atala was a rising star in the field of regenerative medicine and, at the time, was practicing at Boston Children's Hospital and Harvard Medical School. He was gaining attention for growing a bladder *in vitro* in just 8 weeks. My mom watched a piece on CNN about Dr. Atala and his work, stating that within 60 days he could take a cell line the size of half a postage stamp and create enough new cells to cover an area the size of a football field. She called him, and within days he returned her phone call. Amazed by Dr. Atala's callback to a concerned grandmother, my mother shared Joshua's story and what we were trying to accomplish.

Our goal was to support research to find answers. Before he hung up, Dr. Atala offered to help. Even though we did not know where we were going, it felt great to take the first step.

From that point on, we were moving toward our ultimate goal of finding a treatment or cure for our son. Our team of researchers grew organically, because of the altruistic views of Dr. Atala and the team he chose. Dr. Atala introduced us to Alan Beggs, PhD, and Louis Kunkel, PhD, also a part of the Harvard team. Their work surrounding XLMTM encompassed genetics and regenerative medicine. The team began collaborating immediately, sharing their discoveries among one another as well as other scientists abroad. Dr. Beggs established collaboration with a scientist in France named Anna Buj Bello, PhD, who had developed a mouse model of XLMTM.<sup>4</sup> When I speak of "we" and "our" throughout this piece, I am referring to the group of collaborative researchers working on MTM. Together, they agreed to establish a colony of these mice here in the United States.

At times, research in the field moved at a turtle's pace—creeping ever so slowly toward a breakthrough. At other times, we moved at warp speed and could hardly keep up with the advancements being made. But, we were always—ALWAYS—pushing science past its known limitations. It needs to be said that this would have never happened without the collaboration of many scientists. Each piece of the puzzle was hidden in different fields of research, and had our scientists not been so

altruistic we would not be where we are today. I have often said that we are where we are today because our team of researchers cared more about the betterment of humankind than their independent success.

My part, in the beginning, was to raise money through private entities in order to keep the science moving forward. Several years and a few million dollars into our research, the success of our science captivated the attention of the NIH and for the first time, the NIH supported the potential of our promising results in the area of congenital myopathies. The first commitment was \$5 million over 5 years. This was the first large financial backing outside of our JFF donor pool, but it couldn't be the last. We began to realize that we needed proof-of-concept for our science to extend from bench to bedside. Once we achieved that, we would need substantial investments from the venture capital world to carry the therapy through clinical trials into commercialization.

By the spring of 2008, we were experiencing success using gene therapy with our mouse model. Multiple groups around the world, including the discoverer of the *MTM1* gene, Dr. Jocelyn Laporte,<sup>5</sup> as well as Drs. Buj Bello and Beggs, made significant strides understanding the pathology of XLMTM and we walked into a perfect storm for research. This is where the tables turned even more so in our favor.

There was a veterinarian in Canada who had tissue samples from several puppies who had been euthanized because of what they called "wasting puppy syndrome." The tissue samples made their way to a university in San Diego, where Diane Shelton, DVM, PhD, is a clinical specialist with neuromuscular diseases of companion animals. Dr. Shelton's analysis suggested that these dogs had a form of congenital myopathy analogous to human XLMTM.<sup>6</sup> Through neuromuscular disease conferences, Dr. Shelton knew of Dr. Beggs's work and contacted him to share her findings. At the end of one of our foundation's million-dollar fundraisers, Dr. Beggs found me in the hallway and shared that there was a researcher in California who might be able to connect us with a large-animal model. I asked Dr. Beggs to make the introduction.

We all knew that, although the mice were responding beautifully to gene therapy,<sup>7</sup> the FDA wouldn't even consider our science without a large-animal model. When Dr. Beggs told me that he might have connections to one, it was as if new life had been given to our quest. There were so many moving pieces to the puzzle that we lost our opportunity to retrieve the first dog. We went from a

potential large-animal model to starting over, and that was a crushing blow. My husband told me I was to get on a plane and retrieve the next XLMTM dog we found.

In the fall of 2008, shortly after the debacle of losing our first possible canine XLMTM carrier, Dr. Shelton introduced me to Dr. Elizabeth Snead, the veterinarian in Canada who had located the first dog.<sup>6</sup> I shared with Dr. Snead the success of our work in a mouse model and that we would never make it to clinical trials without a large-animal model. Dr. Snead vowed to help us, and immediately began tracing the lineage of the affected puppies she had treated. She even called random owners around Canada leaving messages hoping to find someone who also might own a female dog giving birth to affected puppies. It took a few weeks before somebody called her back. Vic Wagman, a horse rancher in Leader, Saskatchewan, thought his chocolate Labrador retriever fit her description.

It felt as if I was clinging to the last bit of hope my son had when I picked up the phone to call him on that mid-December day. There was no way to know his willingness to be involved, but I had nothing to lose and everything to gain. Five minutes into sharing our story, Vic gave us our ultimate hope when he said, "I want you to have our dog. I want to help your son." I was so overwhelmed by his generosity that I could barely utter the words "Thank you."

Seven days later I was on a plane to pick up their beautiful lab named Nibs, who might possibly carry the same gene that I did. (At this point, everything surrounding Nibs being a carrier was still speculation. We would need to isolate the gene to speak definitively.) I arrived in Saskatoon on December 27, 2008, to meet Vic and his wife, Karen, and very uncharacteristic of Nibs she approached me and stood by my side. I believe wholeheartedly that Nibs knew what she came to do for me. I left Canada trying to outrun a blizzard, and 4 airlines and 10 ticket changes later I arrived back in the United States to meet my researcher and his wife.

During those several months prior, the researchers and I had to put together a plan for the housing of a large-animal model. If the first dog gave us anything, it was a connection via Dr. Atala with a new researcher named Martin Childers, DO, PhD, whose career before Wake Forest Institute of Regenerative Medicine (WFIRM) revolved around working with canine models affected with Duchenne muscular dystrophy. We knew that with Dr. Childers on our team we could bring Nibs to Wake Forest, but I made a last-minute decision to rent space at a breeder's farm so that Nibs could run the hills of Virginia like she was used to back in

Canada. Four days after Nibs's arrival, both our team in the Beggs Lab here and a group led by Jocelyn Laporte in France found a mutation in the *MTM1* gene carried by Nibs, which was passed on affecting her puppies.<sup>8</sup> We knew right then and there what this would do for our research efforts. I was cc'd on several e-mails with researchers from around the globe and you could feel the excitement in their text.

The promise of this advancement was immense. That spring, Nibs produced her last litter—an exceptionally large litter—and our dog colony was established. Five out of the eight females were carriers and one out of the four males was affected like my son. What we were seeing with both the mouse and canine model were the same (with the calcium uptake), and we knew we were headed toward great discoveries.

Building on the foundation that Dr. Beggs and Dr. Buj Bello had developed over the 13 years prior, Dr. Childers joined the collaboration and began testing in affected dogs the gene therapy vectors that Dr. Buj Bello had developed for the mouse studies in France. Success was immediate and a cure seemed closer than ever before. However, because of the nature of the research world, our success would have to be held in tight confidence for over a year as it underwent rigorous testing and multiple peer reviews before being published.<sup>9</sup> Paul and I wanted to yell it from the rooftops, but we could only discuss these positive and promising results with our scientists, and among ourselves.

At this point in our journey it was 2010; we'd existed as a foundation for 14 years, and we were no longer singularly focused on research alone. When Joshua was first born, knowing he was 1 of 55 known cases across the globe spurred us to search out other families afflicted with MTM. I found Pam and Gary Scoggins, the parents of another boy with XLMTM, when Joshua was a toddler. They were passionate about finding families like theirs, and had taken full advantage of the newly formed Internet. Pam became a mentor to me and helped me navigate the murky waters of those early years. Later on, we joined forces to locate families new to the disorder, and shared our resources for patient advocacy. We used the Internet to list symptoms of XLMTM and other centronuclear myopathies, and parents started finding us. Today, I spend hours every week talking to families all over the globe, providing patient advocacy, lending support, and sharing care guidelines for these critical children with parents and clinicians. This support is desperately needed in the early days after birth in order for survival.

Over the years, my relationship with both the researchers and the community has created a valuable vehicle for JFF to operate as the bridge between the two. It is vital for our researchers to have community participation in their research efforts. From an early stage, I saw the need to vocally support their efforts in the community we were building. Dr. Beggs and I have worked in tandem for nearly 19 years encouraging research participation and providing day-to-day support for our critical children. I can say with certainty that if it weren't JFF, it would have had to be another patient-led foundation that forged these ties—because this task alone requires a central network to bring together and coordinate activities across a widespread group of stakeholders focused on a single rare disease such as XLMTM.

Knowing clinical trials were approaching, I anticipated the need for a registry to compile the demographics of our community and serve as a clearinghouse between families, researchers and the biotech entity to bring this science from bench to bedside. Where are our families located? Is their child alive? What is their genetic indication? To meet this need, I created the International Family Registry for Centronuclear and Myotubular Myopathies which is housed on a secure platform working in collaboration with The NIH/NCATS GRDR Program; Global Rare Diseases Patient Registry Data Repository. Families log on from all around the world, answer a series of questions, and then once the questions are completed they are assigned a de-identified number. When the researchers are looking for, let's say, a child younger than 10 with XLMTM not on a ventilator, I can find that in the database, contact the family, and with their permission connect them to the researcher.

All of our efforts would be in vain if they did not culminate in luring venture capital to the scene.

We needed outstanding proof-of-concept in the large-animal model with gene replacement therapy, which we got.

We needed a community of engaged families willing to take action and participate in moving research initiatives forward, which we have. We needed money to make it all happen, which we raised. But there is nothing that we could do to get this science to our children without venture capital thinking that we were a worthy investment.

In the summer of 2012, Paul had the opportunity to pitch our research to Matt Patterson, an entrepreneur-in-residence with Orbimed advisors. Matt was interested after the first phone call, but knew that the venture capital world was leery of gene replacement. Within weeks, a drug passed for approval in Europe and he quickly reached out to us and said, "We need to talk." Our science, years in the making, just became low-hanging fruit, and we were one of the first disorders in the modern era to attract attention for gene replacement therapy as a potential business model. Matt Patterson is now the CEO and co-founder of Audentes Therapeutics and has raised \$130 million for the gene therapy and XLMTM program.

The perfect ending to this story would be a cure for our children. We are very close to proving the efficacy of this treatment as we prepare to enter clinical trials. We have incredibly robust preclinical data, and we still dream that one day Joshua's peers will walk and run, and live long and healthy lives. Of course this day will be a bittersweet day for us, knowing that our Joshua is no longer with us, but we feel unfathomable joy as we dream about a cure. Believe it or not, some have chided us for letting our dreams grow so big, and for being excited about the possibilities ... we say big dreams give birth to big results, so dream on!

Here's to the Joshuas of the world, and the dream of a cure becoming a reality.

## REFERENCES

1. Spiro AJ, Shy GM, Gonatas NK. Myotubular myopathy. Persistence of fetal muscle in an adolescent boy. *Arch Neurol* 1966;14:1-14.
2. Pierson CR, Tomczak K, Agrawal P, et al. X-linked myotubular and centronuclear myopathies. *J Neuropathol Exp Neurol* 2005;64:555-564.
3. Al-Qusairi L, Weiss N, Toussaint A, et al. T-tubule disorganization and defective excitation-contraction coupling in muscle fibers lacking myotubularin lipid phosphatase. *Proc Natl Acad Sci U S A* 2009;106:18763-18768.
4. Buj-Bello A, Laugel V, Messaddeq N, et al. The lipid phosphatase myotubularin is essential for skeletal muscle maintenance but not for myogenesis in mice. *Proc Natl Acad Sci USA* 2002;99:15060-15065.
5. Laporte J, Hu LJ, Kretz C, et al. A gene mutated in X-linked myotubular myopathy defines a new putative tyrosine phosphatase family conserved in yeast. *Nat Genet* 1996;13:175-182.
6. Cosford KL, Taylor SM, Thompson L, Shelton GD. A possible new inherited myopathy in a young Labrador retriever. *Can Vet J* 2008;49:393-397.
7. Buj-Bello A, Fougerousse F, Schwab Y, et al. AAV-mediated intramuscular delivery of myotubularin corrects the myotubular myopathy phenotype in targeted murine muscle and suggests a function in plasma membrane homeostasis. *Hum Mol Genet* 2008;17:2132-2143.
8. Beggs AH, Böhm J, Snead E, et al. *MTM1* mutation associated with X-linked myotubular myopathy in Labrador Retrievers. *Proc Natl Acad Sci U S A* 2011;107:14697-14702.
9. Childers MK, Joubert R, Poulard K, et al. Gene therapy prolongs survival and restores function in murine and canine models of myotubular myopathy. *Sci Trans Med* 2014;6:220ra10.