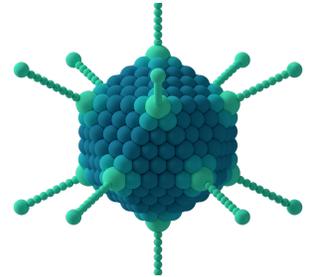




Gene Replacement Therapy

A Boy With the Will to Live

From the moment of Joshua Frase's birth, doctors were saying that the odds were he wouldn't live through the day. How could he? None of the striated muscles in his body functioned normally, including the frail diaphragm muscles surrounding his lungs. But, there was something about Joshua present in that delivery room that the doctors couldn't see; *Joshua had the will to live.*



Joshua would spend his almost 16 years on earth battling with Myotubular Myopathy, a debilitating and mortal disease that stole normalcy from his life. His life consisted of hospital visits that were too numerous to count, and middle of the night conversations with his parents after near death experiences the previous day. But, through it all, Joshua's tenacious spirit gave him the courage to

dream of the future. He dreamed of becoming a scientist who would help find a cure for his disorder, so that he could help his peers. MTM kept his body frail, but he never let it touch his mind or his spirit, and while he lived on this earth with severe physical limitations, he never let that slow him down. For nearly sixteen years, Joshua lived life to the fullest and his legacy lives on as scientists are closing in on a cure.

A Mom Who Would Stop at Nothing

Vision, Fortitude, Resolve – those words have been at the bottom of every email that Alison Frase has sent for the past two decades, and they describe her character well. The day after Joshua was born, amidst every bad report the doctors gave her concerning how long her son had to live, she looked at her newborn son on a ventilator and said, ***“Let's give him a chance to live.”*** Those words changed her life, and at that moment, she became her son's advocate. With shoulders squared, she faced the world of MTM and all the unknowns, which surrounded an orphan disease.



A Father in the NFL

Paul Frase sat in the living room with his wife one afternoon and joked that he was 'just the muscle' behind the Joshua Frase Foundation, but the truth is, as the Joshua Frase Foundation wouldn't be where it is today without Alison's tenacity and 'never quit' attitude, the Joshua Frase Foundation also wouldn't be where it is today without Paul's muscle. Paul's job as an NFL lineman was more than just a dream job; it was the vehicle the Frase's would use to start their foundation. Every Sunday when Paul put on his team uniform, he was using his muscles to build a platform to raise awareness and funding for research for this deadly disorder, as his son, whose muscles failed him on a daily basis, fought for his life.



Paul carried Joshua through the playground of life one activity at a time, hiking through the woods, on a tour of the White House, on a scavenger hunt, and to all night church lock-ins, all so his son could experience what 'normal' kids did. Carrying Joshua through life created a bond that most fathers and sons never experience. When Paul won the Ed Block Courage Award an unprecedented second time in his eleven year NFL career, he knew it was because his son showed him every day what it meant to be courageous, to stand firm in the face of adversity, and to keep getting back up time and time again when life knocks you down.

GENE REPLACEMENT THERAPY



Gene replacement therapy progress over the last 10 years has shown great promise for therapeutic potential. Of 31 countries, 65% of gene therapy trials have been approved in the US, a substantially higher percentage than the rest of the world. Since 1990, there have been nearly 2,000 human gene therapy trials, close to 100 clinical trials annually.

"My son Joshua's journey was a struggle between life and death. His perseverance and character gave us guarded hope that he would live and not die. He inspired us to raise awareness and forge a path to find a cure for he and his peers. Although he succumbed to the mortality of this deadly disorder, his legacy will blossom from that small seed of hope to a therapy or cure for his peers "

- Alison Rockett-Frase

What is Gene Replacement Therapy?

Gene replacement therapy is the process of identifying a faulty gene, applying a piece of DNA in its correct form through a viral vector (known as the carrier molecule) to the gene, thus overriding the faulty gene with the correct copy. The success of gene replacement therapy is contingent upon directing a gene to the correct cells.

While the current delivery models and strategies continue to be intensely investigated, the most common approach is through viral vectors. Viral vectors are carrier molecules derived originally from viruses. Scientists have been able to engineer viral vectors to render them safe for human medicine application. These vectors are able to carry normal copies of genes to replace defective genes in tissues (like muscle). In patients with genetic diseases, these viral vectors offer a way to address the root cause of the patient's illness.

Why is Gene Replacement Therapy The Perfect Model for MTM?

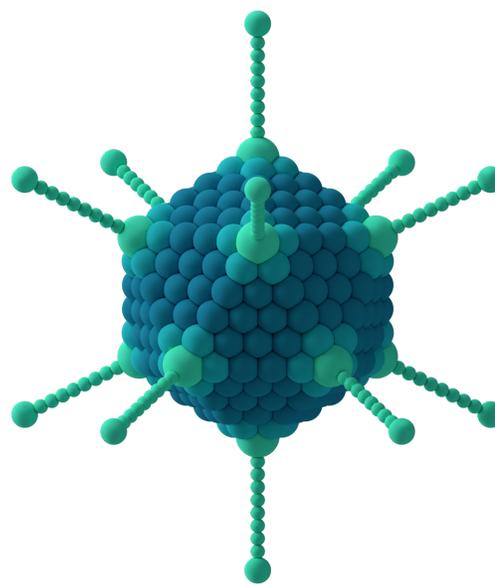
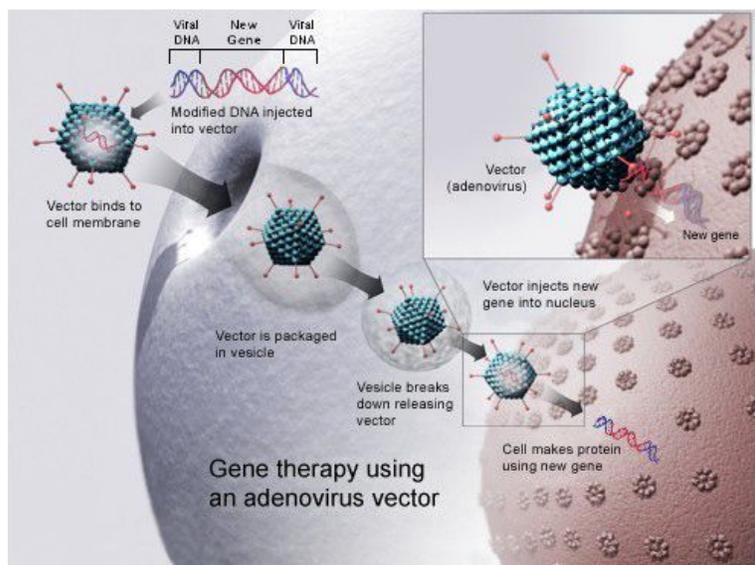
As in the case of Myotubular Myopathy, gene replacement therapy may offer a once-in-a-lifetime solution that not only potentially saves lives, but may also reduce the development of risk going forward.

Fortunately, MTM presents as the perfect model for gene replacement therapy in that the viral vector carrying the healthy gene does not require placement in a defined area since myotubularin (a protein produced during normal muscle development) is able to produce and be replaced rather quickly.

Because myotubularin is a very small enzymatic protein, unlike other diseases such as Duchene Muscular Dystrophy which contain very large proteins, the process of gene replacement therapy using myotubularin is “like replacing windows or doors as opposed to Duchene where it is more like replacing the steel girders of a building,” says Alan Beggs, PhD, Boston Children’s Hospital ⁽¹⁾

⁽¹⁾ [Dr. Beggs](#) is internationally recognized as an expert in the genetics of congenital myopathies.

How Gene Therapy Works



Viral Vector

The Research

Recent research may prove gene replacement therapy can be an effective treatment option for MTM. In 2008, scientists funded by the Joshua Frase Foundation identified the first canine model carrying an MTM gene mutation. This discovery, and creation of a colony of MTM-mutant dogs led researchers and scientists to test gene replacement therapy in this model. These pre-clinical “proof of concept” gene therapy trials ultimately led to clinical patient trials, now beginning in the US. Dr. Martin Childers oversees the care and research of the MTM canine colony at the University of Washington.

Our Partners



The Joshua Frase Foundation, Boston Children's Hospital, Wake Forest Institute of Regenerative Medicine, and University of Washington Over Sixteen Years of Partnership and Progress

With the help of all Joshua's friends and benefactors, JFF has supported many discoveries that have been published and disseminated to the greater medical and scientific community.

Highlights of this JFF-sponsored research in Genetics at Boston Children's Hospital and Wake Forest include:

Past Accomplishments

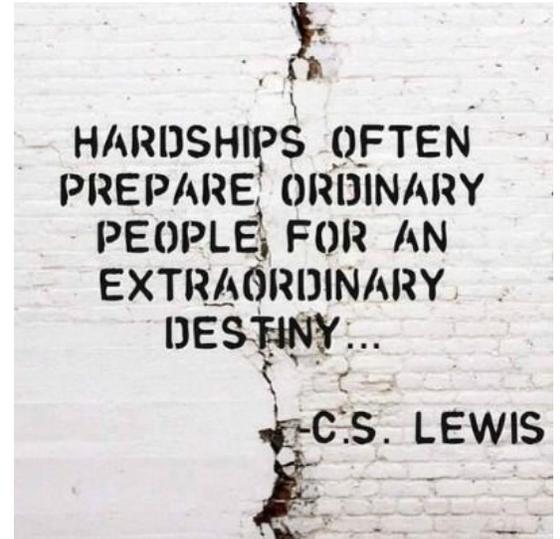
- 1996 - Creation of the Joshua Frase Foundation and the start of funding of research on X-linked myotubular myopathy (XLMTM) and related neuromuscular disease.
- 2001 - [NIH funding of the Program Project at Children's Hospital Boston, supporting research on XLMTM and related neuromuscular diseases.](#)
- 1999 – 2004 - Discovery and analysis of several new muscle genes and investigation of their relationship to congenital myopathies.
- Analysis of muscle defects in X-linked myotubular and centronuclear myopathies.
- 2002 – 2003 - Analysis of gene expression patterns in normal and diseased muscles to understand how the effects of weakness might be reversed.
- 2004 - Development of a cell-based model of normal muscle development used to study the effects of myotubularin loss in XLMTM.
- 2005 - [Discovery of DNM2, a new gene for centronuclear myopathy.](#)
- 2005 - Identification and characterization of muscle stem cells, which are a potential therapy option for muscle disease.
- 2005 - Establishment of the first colony of "MTM mice" in the United States to test new treatments for congenital myopathy.
- 2007 - [Discovery that boys with XLMTM who have larger muscle fibers survive longer.](#)
- 2008 – [Proved that gene therapy is an effective treatment for XLMTM in mice.](#)
- 2009 – [Discovered that weakness in XLMTM is caused by abnormal calcium flow in muscle.](#)
- 2010 – [Identification of the first large animal model for XLMTM, the Labrador retriever.](#)

(PAST ACCOMPLISHMENTS cont'd)

- 2010 - Establishment of a colony of XLMTM dogs to better understand the disease and develop treatments.
- 2011 – [Publication of first pre-clinical trial of Myostatin inhibition to increase muscle size in mice with XLMTM.](#)
- 2011 – [Discovery of new functions for myotubularin, including control of muscle skeleton and energy production by mitochondria.](#)
- 2012 – [Announced creation of the “Mtm1 R69C” mouse, a new milder model of XLMTM.](#)
- 2012- [Abnormal muscle function identified in dog model of XLMTM.](#)
- 2012 – [NIH funds a collaborative grant to study the dog model of XLMTM.](#)
- 2012 – [Demonstration of abnormal neuromuscular transmission in XLMTM and first preclinical trial of a drug to enhance transmission in mice with XLMTM.](#)
- 2012 – Publication of a [“Clinical Utility Gene Card”](#) to establish diagnostic standards for XLMTM and centronuclear myopathy.
- 2013 – [NIH renews funding for centronuclear myopathy research](#) at Boston Children’s Hospital.
- 2013 – [Report of a new type of mutation - duplications in the *MTM1* gene](#) and establishment of a [clinical test](#) at the [University of Chicago Genetic Services Laboratory.](#)
- 2013 – Studies on the [interactions between myotubularin and its partner *MTMR12* in zebrafish](#), and in mouse and human cells.
- 2013 – [First report of a successful preclinical therapeutic trial of protein replacement therapy for XLMTM.](#)
- 2013 – [Discovery of a new gene, Titin, as a cause of centronuclear myopathy.](#)
- 2014 – [Created Registry for all XLMTM children and their families to prepare for future clinical trials](#)
- 2014 – [Gene therapy prolongs survival and restores function in murine and canine models of myotubular myopathy.](#)
- 2014 – [Syngeneic myoblast transplantation improves muscle function in a murine model of X-linked myotubular myopathy.](#)
- 2014 – [Respiratory assessment in centronuclear myopathies.](#)
- 2014 – [Ultrasound assessment of the diaphragm: Preliminary study of a canine model of X-linked myotubular myopathy.](#)
- 2014 – [Gait characteristics in a canine model of X-linked myotubular myopathy.](#)
- 2014 – [Regenerative rehabilitation: a new future?](#)
- 2014 – [Gene therapy for inherited muscle diseases: where genetics meets rehabilitation medicine.](#)
- 2014 – Discovery of a new gene, [SPEG](#), as a cause of centronuclear myopathy.
- 2015 – [Guiding intramuscular diaphragm injections](#) using real-time ultrasound and electromyography.
- 2015 – Discovery of [X-linked myotubular myopathy in Rottweiler dogs.](#)
- 2015– [Neurological Scoring System for canine X-linked myotubular myopathy](#)
- 2015 – Comprehensive assessment of [disease progression in canine X-linked myotubular myopathy.](#)
- 2016 – Cross-species analysis of [muscle defects in X-linked myotubular myopathy.](#)
- 2017 – Demonstration that [gene therapy for XLMTM corrects muscles throughout the whole body.](#)
- 2017 – Long term follow-up of [MTM1 gene therapy shows benefits lasting for at least 4 years.](#)

Current and Future Objectives

- Development of late onset gene therapy studies.
- Continued patient advocacy as well as clinical and institutional education.
- Develop protein replacement therapy for XLMTM.
- Partner with biotechnology companies and the patient community to develop the “natural history” data that the FDA will require for clinical trials of new therapies.
- Develop zebrafish models of other centronuclear myopathies.
- Screen drug libraries for new therapies using zebrafish with centronuclear myopathy.



CONTACT INFO



If you would like to make a donation, learn more about the Joshua Frase Foundation or for event information please contact:

Alison Rockett Frase
c/o Joshua Frase Foundation
PO Box 2041
Ponte Vedra Beach, FL 32004

PHONE 904 607-1358 **FAX** 904 273- 9818

info@joshuafrase.org
<http://www.joshuafrase.org>