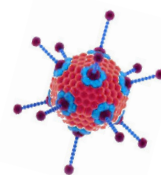




# Gene Replacement Therapy



## 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

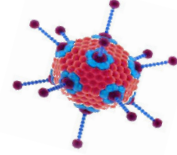
**Vision, Fortitude, Resolve** – those words have been at the bottom of every email that Alison Frase has sent for the past 13 years, and they describe her character well. The day after Joshua was born, amidst every bad report the doctors gave her concerning how long her son had to live, she looked at 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.





## Gene Replacement Therapy



**Vision, Fortitude, Resolve** - Showing tremendous fortitude, she taught herself how to keep her son alive, and more times than any mother should ever have to, she resuscitated him after his lungs had collapsed yet again. Before Joshua had his first birthday, Alison and her husband Paul decided that they would start a foundation that would one day find the cure for their son, and with Alison's tenacious flare for attacking problems head on, the foundation was formed. Knowing nothing about scientific research for a rare orphan disease, she educated herself and she trusted her instincts, and when she received a vision of handing a large check to a renowned researcher, she chased that vision with relentless passion until its fruition.

Joshua's death only served to strengthen her and her husband's resolve to find a cure so that one day, no parent would have to experience the tremendous sorrow of losing a child with MTM.

### A Father in the NFL

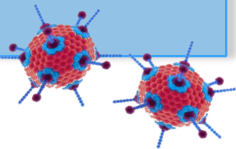
Paul Frase sat in the living room with his wife one afternoon and joked that he was 'just the muscle' behind the Joshua Frase Foundation, but the truth is, as the Joshua Frase Foundation wouldn't be where it is today without Alison's tenacity and 'never quit' attitude, the Joshua Frase Foundation also 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.



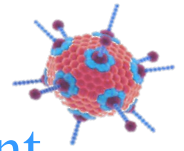
Paul carried Joshua through the playground of life one activity at a time, hiking through the woods, on a tour of the White House, on a scavenger hunt, and to all night church lock-ins, all so his son could experience what 'normal' kids did. Carrying Joshua through life created a bond that most fathers 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.

"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, his peers will live and not die. "

Alison  
Rockett-Frase



## 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.

### 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 containing a virus. Because viruses are able to attach or enfold to healthy cells, viral vectors are genetically altered to represent normal DNA and re-injected to compromised cells, which in turn generates restoration to the cell to a healthy or normal state.

### 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.

## Gene Replacement Therapy The Perfect Model for MTM - Continued

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, it would be like replacing the steel girders of the infrastructure of a building,” says Alan Beggs, PhD, Boston Children’s Hospital <sup>(1)</sup>

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

### How Gene Therapy Works

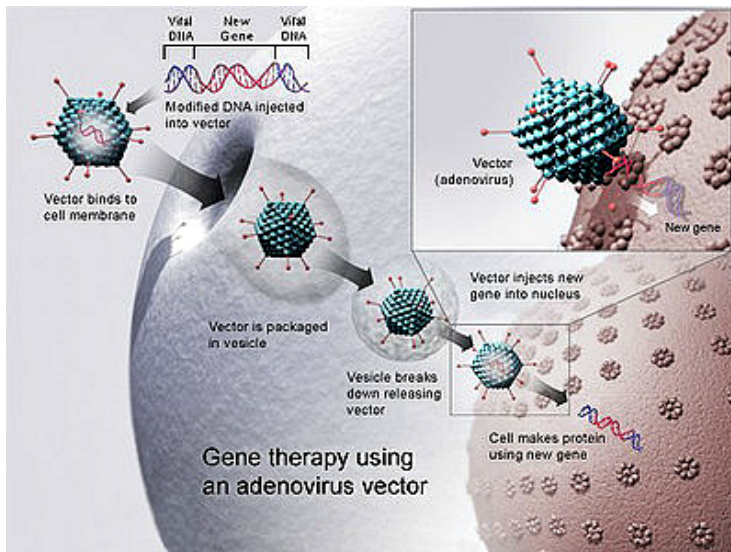


Image Credit: National Library of Medicine

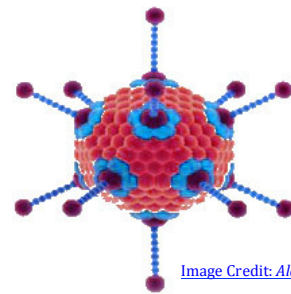


Image Credit: Alan J. Cann

### Viral Vector

### The Research

[Recent research](#) may prove gene replacement therapy can be an effective treatment option for MTM. In 2008, the first (large) animal in the world to have symptoms and the same gene as MTM was discovered by researchers. This discovery has led researchers and scientists to introduce gene replacement therapy, by verifying and validating proof of concept by way of final preclinical end-stage trials. This validation has spurred initial talks with the FDA for clinical trials, of which are now being designed. For more information, please contact:

### Our Partners:



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Until every child is well™



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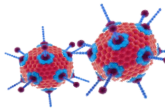
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## The Joshua Frase Foundation, Boston Children's Hospital & Wake Forest Institute of Regenerative Medicine

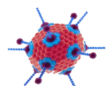
### Over Sixteen Years of Partnership and Progress

*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.*

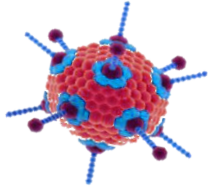
*Highlights of this JFF-sponsored research in Genetics at Boston Children's Hospital and Wake Forest include:*

### 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.](#)
- **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** - [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.



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



*"Hardships often prepare ordinary people  
for extraordinary destiny." ~ C. S. Lewis*

**Past Accomplishments (continued):**

- 2012 – Reported establishment of the first colony of dogs with XLMTM and determination of their natural history and disease progression
- 2012 – First report of defective growth and survival of XLMTM cells
- 2012 – Comprehensive review and publication of the largest series of DNM2-related centronuclear myopathy to date
- 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 – Studies on the interactions between myotubularin and its partner MTMR12 in zebrafish, and in mouse and human cells.
- 2013 – Discovery of a new gene, Titin, as a cause of centronuclear myopathy.

**Future Goals:**

- Creation of a Registry for all the boys with XLMTM and their families to prepare for future clinical trials.
- Expansion of the XLMTM dog colony for use in pre-clinical development of gene and other therapies.
- Develop gene replacement therapy for XLMTM.
- 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.



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 904 607 1358 phone /fax 904 273 9818  
[info@joshuafrase.org](mailto:info@joshuafrase.org)  
<http://www.joshuafrase.org>

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