FSHD Advocate

2019 • ISSUE 1

FSH SOCIETY
FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

SPECIAL SECTION

How we accelerate therapies

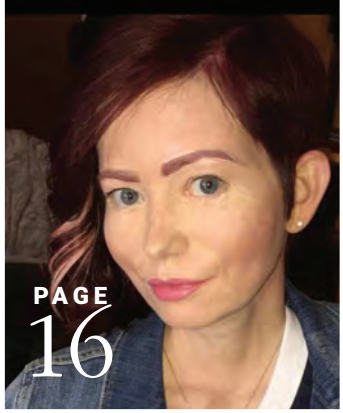
See page 4

MOUNTAINS TO CLIMB

Achieving my dream, one step at a time

See page 17

Neenah Williams poses proudly on Uhuru Peak.



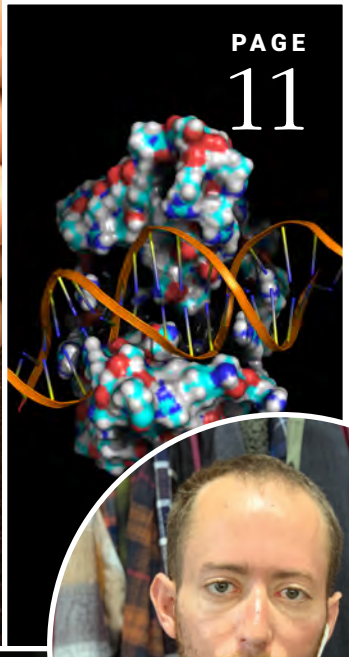


Table of Contents

Special Section

THERAPEUTIC ACCELERATOR

RESEARCH NEWS

FSH SOCIETY NEWS

LIVING WITH FSHD

NOTEWORTHY

UPCOMING EVENTS

FSHD Advocate

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CEO Letter

Carpe diem

This Latin phrase "seize the day" seems apropos as we consider the drug development process for FSHD. Never have there been so many pharmaceutical companies working on therapies to stop the muscle decline and restore function for those with FSHD. I believe that some of the dozen or so therapies currently in the pipeline *will work* to stop disease progression.

But as Charles Dickens penned in *A Tale of Two Cities,* "It was the best of times, it was the worst of times." While the pipeline is robust, obstacles to the advancement of therapies loom large. Some clinical trials are being delayed due to the unique challenges of the disease. FSHD affects individuals differently, changes are hard to measure over the brief weeks or months of a trial, and the FDA requirement to show functional change (such as in strength) may unfairly weed out drugs that actually stop the underlying disease process. These delays could drag out a decade or longer if we don't act now.

The good news is that with the FSH Society operating as the "general contractor" to bring together companies, academic researchers, the FDA, and patients, we can eliminate these obstacles.

We intend to have therapies to our families by 2025, an aspirational but attainable goal – if we act now to shorten the drug development timeline. Leaders in the field have said this is a realistic goal, but reaching it will require the best in us and the best from us.

Mark A. Stone

As you read this issue, you will gain a better understanding of the opportunities and challenges inherent in the drug development process. But we are up for the challenge. Recently, I saw a quote that to me embodies the FSHD community: *Never let weaknesses convince you that you lack strength.*

Together, we are strong enough to ensure that no one on this journey travels alone.

Together, we are strong enough to catalyze a global community to get treatments and a cure to our families faster.

Together, we are strong enough to positively influence regulatory agencies and verify that safe, effective therapies get through the approval process unhindered.

I am honored to be a partner in this noble endeavor with you. Together, we will change the world for all those with FSHD.

Seizing the day,

Mark Stone
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A Golden Age for FSHD

WILL WE RISE TO THE CHALLENGE?

BY JUNE KINOSHITA, FSH SOCIETY

In a world awash with billion-dollar profits for drugs to treat the most common ailments – hypertension, acid reflux, diabetes, high cholesterol, and so on – patients with FSH muscular dystrophy may believe that rare conditions like theirs will never get the time of day from the pharmaceutical industry.

In fact, this is no longer true. With the passage of the Orphan Drug Act (ODA) in 1983, new incentives were created to attract companies to take on rare diseases (defined as having fewer than 200,000 patients in the US). These include tax breaks, market exclusivity, and millions of dollars in waived fees.

In many respects, the law has been a resounding success. Prior to the Act's passage, the Food and Drug Administration (FDA) had approved only 34 drugs for orphan diseases. Since then, more than 600 orphan disease indications have been approved.

Apart from a few trials of drugs intended to increase muscle size, however, drug developers showed little interest in FSHD, even in the decades following the ODA. This changed dramatically with the publication in 2010 of a "unified model" for the genetic basis of FSHD. This hypothesis, from an international research team led by Silvère van der Maarel (the first recipient of an FSH Society grant), proposed that the genetic alteration in FSHD activated a gene called DUX4 to damage muscles.

About the same time, researchers equipped with better genetic tests and patient data began to realize that FSHD is more common than previously thought. Estimates of its prevalence rose from one in 20,000 to as high as one in 5,000. Once believed to be ultra-rare, FSHD is now viewed as one of the most common forms of muscular dystrophy.

As researchers unraveled how DUX4 expression leads to FSHD, they began to think about ways to intervene. The drug industry took notice. Our phones at the FSH Society started receiving calls from companies asking, What are the symptoms, and what is the impact on people's lives? How many have it? Where are they? Are there doctors who see many patients? How hard would it be to conduct a clinical trial? If a treatment was developed, would people want to take it?

Fortunately, we could tell companies what they needed to know, thanks to years of work by the pioneering researchers and leaders at the FSH Society. We have a good understanding of the disease and the variable ways in which it affects people. The Society had funded research

to develop "FSHD in a dish" cell-based and animal models, early-stage drug and gene therapy work, and clinical measurement tools. We had compiled the largest global database of patients and families, and are able to contact them on behalf of researchers and companies seeking volunteers for their studies.

It is remarkable to see all of this painstaking work converging around a collective goal – to get a treatment onto the market by the year 2025. This March 12, the FSH Society convened industry researchers, academic leaders, advocacy groups, and FDA representatives to assess how ready the FSHD field is for clinical trials. We discussed gaps in the data and tools – natural history studies, biomarkers, imaging methods, clinical measurements – and developed a plan to fill those gaps as quickly and efficiently as possible.

We call this enterprise our Therapeutic Accelerator Project. Our goal is to complete the work over the next three years. We will do so by acting as the "general contractor" to coordinate all of the stakeholders to collaborate on these projects. We intend to enlist the most capable labs, eliminate redundancy, and shorten the timelines to get the work done.

Substantial funds – $15 million over three years – are needed to complete this monumental task on schedule. This February, the FSH Society launched a campaign to raise the needed funds from a combination of industry partners and philanthropists.

In addition to funding, we will need a substantial investment of something equally valuable and even scarcer – the time and effort of patients willing to volunteer for the pivotal Therapeutic Accelerator studies. Did you know that across all medical research, 85 percent of trials face delays and 30 percent never get off the ground due to a lack of volunteers? We cannot let this happen in FSHD.

Our patients and families are waiting.

Our inaugural Volunteer Leadership Summit

Activating our community is essential to our mission

BY BETH JOHNSTON, FSH SOCIETY

On the last week of January, a force descended upon the Chicago O'Hare Airport. And we're not talking about the polar vortex.

Twenty-nine chapter directors and Walk & Roll leaders convened for the FSH Society's inaugural Volunteer Leadership Summit for two days of intensive learning, sharing, and networking to train them to become effective, impactful leaders within their local communities.

The weekend's agenda included sessions on the history and evolution of the FSH Society and our mission, working with volunteers and different communication styles, local patient advocacy, hosting educational and support meetings, and fundraising – just to name a few topics.

While we were all there to learn, the most powerful part of the meeting was the relationships that were formed among the leaders who attended. Everyone has the same goal, which is to bring hearts and hands closer to the FSHD families we serve. Educating, empowering, and activating our communities across the nation – and the world – are essential to achieving our mission to improve the lives of patients and accelerate the development of treatments. Together, we are an unstoppable force!

To learn more about the Chapter Program or join a local chapter, please visit *www.fshsociety.org/connect-locally/fsh-society-chapters/*.

Questions? Contact Beth Johnston, our chief community development officer, at *beth.johnston@fshsociety.org*.

Keep an eye on our Event Calendar for upcoming local meetings and fundraisers in your area.

Chapter directors and Walk & Roll leaders gather in Chicago for the first Volunteer Leadership Summit. Front row (seated): Bill Maclean, Virginia Wyckoff, Carden Wyckoff. Front row (standing): Jane Pollock, Jann Maclean, Laurie Heyman, Karen Dunkerly, Kristin Zwickau, Katie Ruekert, Sue Aumiller, Beth Johnston, Susie Kanewske, Anna Gilmore, Adam Warren. Back row: George Pollock, Jack Gerblick, Marsha Sverdrup, Paul Senecal, Kathy Senecal, Bob Aumiller, Amanda Hill, Landon Morrell, Marie Morrell, Tim Hollenback, Meredith Huml, Allison Calder, Mark Stone, Manuel Gomez, Dave Lukas, Sue Drescher, Kent Drescher.

2019 International Research Congress

The FSH Society's flagship conference crosses the Atlantic

The Pharo Palace in Marseille, France, is the site of the 2019 IRC. Researchers working on FSHD therapies speaking at the 2018 FSH Society conference (inset).

This year, the FSH Society's International Research Congress (IRC) will be held for the first time outside the US. On June 19-20, researchers and clinicians will gather in the marbled halls of the Pharo Palace, an imposing structure overlooking the harbor of Marseille, France.

The IRC will bring together world-leading clinicians and scientists to present the latest developments, reinforce collaborative efforts, facilitate new initiatives, and coordinate research and clinical activities. With the growth of the FSHD field, the meeting has been extended from one full day to two, and will include more sessions on clinical research and clinical trial readiness. The meeting also hopes to attract researchers and clinicians who previously have not attended the IRC, especially those from centers in Europe.

Frédérique Magdinier, PhD, and George Padberg, MD, are co-chairs of the IRC. Program committee members are Alexandra Belayew, PhD; Sabrina Sacconi, MD PhD; Stephen Tapscott, MD PhD; Rabi Tawil, MD; Rossella Tupler, MD PhD; and Peter Zammit, PhD.

The local host institutions are Marseille Medical Genetics; Aix Marseille Université, INSERM; GIPTIS (Genetics Institute for Patients, Therapies, Innovation and Science); and the Department of Medical Genetics, Timone Children's Hospital, Marseille.

In addition, the FSH Society is partnering with FSHD Europe, an alliance of European patient advocacy groups, to organize an international patient advocacy summit on June 18, the day before the IRC.

Questions about the 2019 IRC and patient advocacy summit can be addressed to organizer June Kinoshita at the FSH Society (*june.kinoshita@fshsociety.org*).

MRI-guided biopsy shows promise for clinical trials

BY JUNE KINOSHITA, FSH SOCIETY

A central tenet of modern FSH muscular dystrophy research is that the muscle damage in this disease is caused by a gene called DUX4. Normally silent in adult skeletal muscle, DUX4 is expressed through a genetic aberration and triggers a shower of toxic molecular events. This idea lies behind efforts to treat FSHD with drugs and gene therapies designed to repress DUX4.

But proving that DUX4 causes damage in actual patients has been no easy task. In a major step forward, researchers from the University of Washington and the University of Rochester reported that pathologic changes in patients' muscles are correlated with patterns of genes that are switched on when DUX4 is expressed.

The transcontinental team accomplished this discovery by collecting tiny bits of patients' muscles guided by magnetic resonance imaging (MRI). Prior studies had suggested that MRI can detect various stages of the disease process. "Dystrophic" muscles were filled with fat and scar tissue, which showed up as bright spots when the MRI was tuned to detect fat. On the other hand, some healthy-looking muscles looked abnormal when the MRI was tuned to detect water. Researchers had suspected that the excess water in these muscles resulted from inflammation.

These prior MRI studies hinted that inflamed muscles might have DUX4 activity leading to dystrophy. Data from the new study are consistent with this idea and point the way to designing clinical trials. MRI-guided muscle biopsy could, in theory, show that a drug is actually repressing DUX4 in patients, while a sequence of MRI images taken after treatment might reveal whether the drug is slowing the damage to muscles.

The researchers would like to study the same group of patients over time to gain a fuller understanding of how the disease progresses.

Most importantly, scientists need to show this method is reliable over repeated use in diverse groups of patients before the approach can be considered ready to use in a clinical trial. Those studies are now going on, with results expected in about a year.

REFERENCE

Wang LH, Friedman SD, Shaw D, Snider L, Wong CJ, Budech CB, Poliachik SL, Gove NE, Lewis LM, Campbell AE, Lemmers RJFL, Maarel SM, Tapscott SJ, Tawil RN. MRI-informed muscle biopsies correlate MRI with pathology and DUX4 target gene expression in FSHD. *Hum Mol Genet*. 2019 Feb 1;28(3):476-486.

Jamshid Arjomand, PhD, is our new CSO

Brings biotech expertise to the Society

BY JUNE KINOSHITA, FSH SOCIETY

Jamshid Arjomand, PhD, has joined the FSH Society as its chief science officer. "Dr. Arjomand will be the driving force behind our Therapeutic Accelerator Project," said Mark Stone, president and CEO of the FSH Society. The project aims to speed up the development of treatments for FSHD by focusing on gaps in the preclinical and early drug development space.

Jamshid Arjomand, PhD, chief science officer

Arjomand comes to the FSH Society from Genea Biocells, a San Diego-based biotechnology company where he served for five years as vice president of business development. Genea's pipeline included FSHD, for which their lead asset, GBC0905, received orphan drug designation by the Food and Drug Administration in May 2018.

From 2005 to 2013, Arjomand served as director of basic research at CHDI Foundation, where he oversaw a complex portfolio of projects related to biomarker discovery, stem cell development, and target discovery and validation efforts for Huntington's disease.

"Jamshid is an experienced leader," said Stone. "His expertise will be a valuable asset to the FSHD community as well as to the FSH Society's goal of bringing therapies to our families by the year 2025."

Newly funded grants

BY DANIEL PAUL PEREZ AND JUNE KINOSHITA, FSH SOCIETY

The FSH Society's board of directors voted to approve $332,906 in funding for three grant applications submitted for the August 2018 cycle. The first project investigates a novel hypothesis based on evidence that DUX4 damages muscle cells by disrupting internal quality-control processes. The other projects aim to advance candidate therapies to shut down expression of the DUX4 gene, considered to be the root cause of muscle damage in FSHD.

- **Investigating the Molecular Consequences of Reduced NMD in FSHD Skeletal Muscle Myoblasts**
  Michael Dyle, PhD, postdoctoral fellow in the laboratory of Sujatha Jagannathan, PhD, University of Colorado Denver, USA
  $115,937 for two years


Michael Dyle, PhD

This project focuses on better understanding a molecular pathway that contributes to skeletal muscle deterioration in FSHD. Previous studies have found that DUX4 expression in skeletal muscle cells leads to severe perturbation of an important cellular quality-control pathway: nonsense-mediated decay (NMD). In healthy skeletal muscles, NMD plays a beneficial role in eliminating RNA molecules that give rise to deleterious, muscle cell-killing proteins (as a reminder, RNA is a cell's "instructions" to build proteins). In FSHD skeletal muscle, the NMD pathway is severely repressed, which leads to the accumulation of destructive muscle proteins. The research team is focused on pinpointing those proteins that cause muscle cells to die when the NMD pathway breaks down. The team is also exploring the idea that restoring NMD function may slow or prevent skeletal muscle deterioration in FSHD. The results may lead to the development of diagnostic tools and new therapeutic strategies for FSHD.

- **Optimizing Gapmer Therapy for Facioscapulohumeral Muscular Dystrophy**
  Yi-Wen Chen, PhD DVM, associate professor of genomics and precision medicine, George Washington School of Medicine, and Children's National Health System, Washington, DC, USA
  $125,969 for one year


Yi-Wen Chen, PhD DVM

Antisense oligonucleotide (AON) therapy is a promising approach to treating FSHD (see article in *FSH Watch* 2017, Issue 3). However, several issues arise with AONs including: difficulty in delivering the drug into the muscles; harmful side effects and toxicities; rapid degradation in the body so that the AON can't provide its beneficial function; and immune responses induced by the AONs. To address these issues, one can chemically manipulate the AON. One method uses 2'-O-methoxyethyl (2'MOE), and the other is called locked nucleic acids (LNAs). The 2'MOE chemistry was used in the FDA-approved treatment for spinal muscular atrophy.

In a previous study supported by the FSH Society, Chen and her collaborator Toshifumi Yokota, PhD, at the University of Alberta, showed that an "LNA gapmer" was effective in knocking down DUX4 in cell culture and improved muscle strength in an FSHD mouse model. In this proposal, the Chen lab will test 2'MOE gapmers targeting DUX4. This construct may be less potent but safer than the LNA gapmer. Yokota has shown that the 2'MOE gapmers effectively knocked down DUX4 transcripts in the test tube. Chen will compare the efficacy and safety of the 2'MOE gapmers in mice. The goal is to carefully characterize and identify the most promising candidate to develop as a therapy.

- **Identification of Natural Human DUX4-Targeted miRNAs and Development of a Novel DUX4-Targeted miRNA-Based Gene Therapy for FSHD**
  Nizar Y. Saad, PhD, postdoctoral fellow in the laboratory of Scott Harper, PhD, Center for Gene Therapy, Nationwide Children's Hospital, Columbus, Ohio, USA
  $91,000 for one year


Nizar Y. Saad, PhD

The FSH Society has funded Dr. Saad for past two years to investigate endogenous microRNAs (miRNAs) that could reduce DUX4 expression. So far, he has found that H19 and miR-675 reduce DUX4 expression and toxicity. This project aims to develop a potential new gene therapy based on miR-675.

My journey continues

BY IAN RYS, PORT ST. JOHN, FLORIDA

When I turned 50, I began to feel I was moving and walking differently. I won't lie: That scared me.

I've always tried to have a positive outlook, but FSHD was starting to break me. I have great support from family and friends, but I needed something more. I didn't know what it was. One thing was for sure – I needed to know where others afflicted with this disease were getting their medical care and information.

Then last year I decided to go to the FSHD Connect Conference in Las Vegas. There, I discovered what I had been hoping to find. Not only did I meet others like me for the first time, but I was also among patients and doctors from around the world gathered to hear and tell of all the latest findings on FSHD.

I learned of different therapies being developed and got information on trials and studies. I also learned that one of the best ways I could contribute was to participate in the research. I'm all in!

After the conference, I called Dr. Rabi Tawil's office at the University of Rochester in upstate New York and was guided through the process of becoming his patient. My son Josh, a nurse anesthetist, CRNA, accompanied me on my visit. I was so excited!

Dr. Tawil was gracious, kind, and respectful. We went through quite a bit of range-of-motion and strength testing, far more than I ever had before. Next, we talked about why I was there, various trials, and what I hoped to accomplish. The best news came when Dr. Tawil told me I would be a very good candidate for the trials we had discussed. We talked about my battle so far and how to be proactive in my fight.

By the time I left, I had also met with another neurologist, Dr. Phillip Mongiovi; Katy Eichinger, a physical therapist who gave me a prescription for an ankle-foot brace; and a representative from the local Muscular Dystrophy Association. I couldn't believe all of this took place on my very first visit!

Now I have a plan. I will be genetically tested and then, toward the end of this year, I will be eligible for the trial I'm interested in. Dr. Tawil is now my FSHD doctor as well! I'll be heading back to see him in six months.

I'm happy to say I'm no longer scared. In fact, I feel as if I'm back on the winning side. I'm not naïve. I know there is no "cure" that will restore me to my physical condition prior to the FSHD progression, but I'm doing all I can to help myself be the strongest I can be.

I will conduct my journey with grace and gratitude, and I will continue sharing my experiences in the hope of helping others. We are all in this together, and we are all worthy of the best medical treatment available.

Before leaving the University of Rochester, I got a bit emotional as I thanked Dr. Tawil for taking me on as a patient. He said, "It's not a privilege to have this disease." That was when I told him I agree, but it is a privilege to be treated by him.

I am forever grateful for my rock star doctor!

"Dr. Tawil was gracious, kind, and respectful. We went through quite a bit of range-of-motion and strength testing, far more than I ever had before. We talked about why I was there, various trials, and what I hoped to accomplish. The best news came when Dr. Tawil told me I would be a very good candidate for the trials."

— IAN RYS

Follistatin gene therapy for FSHD?

Muscles get stronger in a mouse model

BY JUNE KINOSHITA, FSH SOCIETY

An experimental gene therapy has been shown to enlarge and strengthen muscles in a mouse model of FSH muscular dystrophy.

The study by Scott Harper, PhD, and his team at Nationwide Children's Hospital in Columbus, Ohio, involved mice that are genetically engineered to express the DUX4 gene, which is implicated in FSHD. When DUX4 is switched on, "these animals develop progressive muscular dystrophy," Harper said. Called TIC-DUX4, this mouse model was developed with funding from the FSH Society (see story in *FSH Watch* 2017, Issue 1).

Harper said the new study was designed to determine whether the TIC-DUX4 mouse could provide useful insights into the development of FSHD treatments. The lab engineered adeno-associated virus (AAV) to carry the gene for follistatin into muscle cells. There, the gene integrates into the mouse DNA and the cells produce follistatin, a protein that blocks another protein, myostatin, which inhibits muscle growth. Follistatin's action is similar to that of ACE-083, an experimental therapy that is currently in a clinical trial in FSHD patients.

When the follistatin-carrying AAV was injected into the leg muscles of the TIC-DUX4 mice, the researchers observed increased muscle size and "improved overall strength," Harper said.

Harper noted it would "be interesting to test the impact of combining AAV1-follistatin treatment with DUX4-inhibitory strategies, which could work to both suppress DUX4-associated damage and improve muscle mass and strength."

"This proof-of-principle study provided encouraging evidence that DUX4-expressing muscle can be treated with AAV-delivered myostatin inhibition approaches to improve muscle function," the study stated. "We conclude that TIC-DUX4 mice are a relevant model to study DUX4 pathogenicity and disease progression. Moreover, the TIC-DUX4 mouse develops numerous molecular, histological, and functional outcomes that can be used as powerful tools to test gene therapies and other therapeutic strategies for FSHD."

Harper said the TIC-DUX4 mice are available through the Jackson Laboratory (*www.jax.org*), stock number 032779.

Funding for this research was provided by the FSH Society, Muscular Dystrophy Association, Chris Carrino Foundation, Friends of FSH Research, and the National Institutes of Health.

REFERENCE

Giesige CR, Wallace LM, Heller KN, Eidahl JO, Saad NY, Fowler AM, Pyne NK, Al-Kharsan M, Rashnonejad A, Chermahini GA, Domire JS, Mukweyi D, Garwick-Coppens SE, Guckes SM, McLaughlin KJ, Meyer K, Rodino-Klapac LR, Harper SQ. AAV-mediated follistatin gene therapy improves functional outcomes in the TIC-DUX4 mouse model of FSHD. *JCI Insight*. 2018;3(22):e123538.

DUX4 structure revealed

Could guide the design of drugs to block the FSHD gene

BY JUNE KINOSHITA, FSH SOCIETY

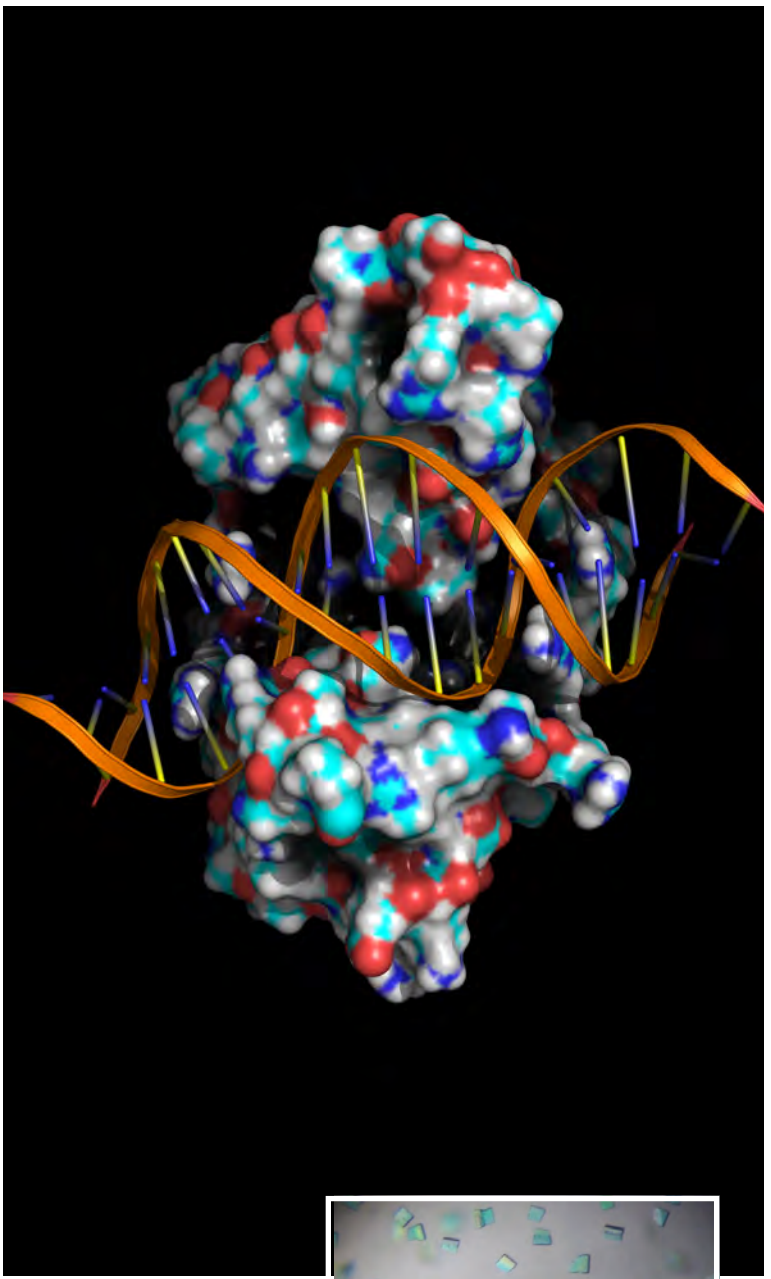
When James Watson and Francis Crick famously deciphered the structure of the DNA molecule in 1953, they based their epoch-making discovery on the work of Rosalind Franklin, who had crystalized the DNA molecule, aimed a beam of X-rays through it, and obtained a diffraction pattern that, through much painstaking calculation, revealed the underlying double helix structure. A similar method has now been used to obtain the structure of DUX4, the molecule at the center of FSH muscular dystrophy (FSHD). This work was published in December by Michael Kyba, PhD, Hideki Aihara, PhD, and their colleagues at the University of Minnesota.

Individuals with FSHD have a genetic change that leads to the expression of the DUX4 gene, which is normally repressed in mature skeletal muscles. The resulting DUX4 protein binds to other pieces of DNA like a key inserting into a lock, triggering many other genes to "turn on" and causing damage to muscle.

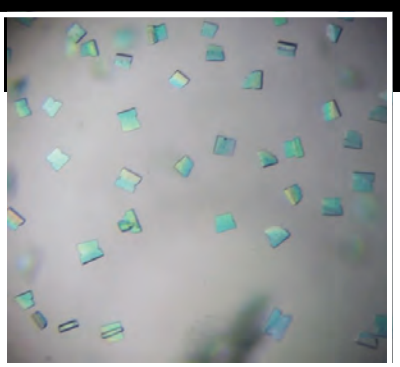
Figuring out the shape of the DUX4 "key" can help scientists design a drug that can block the key precisely (and not glom up other molecules). If the drug sticks to the DUX4 protein, the key will not be able to turn in the lock, and the damaging effects of DUX4 ought to be stopped.

"Although we have known for many years that DUX4 causes FSHD, we have not had a good explanation for how it damages muscle," said Kyba. "Seeing for the first time what this protein actually looks like when it binds to DNA, and knowing that this is the act that is responsible for so much suffering, was both remarkable and sobering."

This research was funded by the Friends of FSH Research, the National Institute of General Medical Sciences (NIGMS), and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS).



Computer-generated structure of the DUX4-DNA binding site.



Crystals of DUX4 protein.

REFERENCE

Lee JK, Bosnakovski D, Toso EA, Dinh T, Banerjee S, Bohl TE, Shi K, Orellana K, Kyba M, Aihara H. Crystal Structure of the Double Homeodomain of DUX4 in Complex with DNA. *Cell Rep.* 2018 Dec 11;25(11):2955-2962.e3. doi: 10.1016/j.celrep.2018.11.060.

FINDING FSHD:
The story of DUX4 in a zebrafish

BY AMANDA HILL, HIGHLANDS RANCH, COLORADO

When studying human disease and working to develop treatments, researchers typically perform experiments on animal models that represent the disease in a controlled laboratory setting. However, in the case of FSHD, creating an animal model which accurately represents the human disease has proven difficult.

One reason is that FSHD is highly variable from person to person. Another is that the specific form of the DUX4 gene found in humans only exists in other primates, not in common laboratory animals such as mice or fish. So in order to use these common lab animals, scientists must first *artificially* express the DUX4 gene in them. This can be a difficult and delicate process to get just right.

Now, add to that the fact that scientists are learning about DUX4 every day. They are still trying to understand exactly how, where, and when DUX4 is expressed in FSHD, so artificially re-creating the gene's behavior in laboratory animals is no easy task. It's like building a house of cards – with a blindfold on.

For a number of years, FSHD scientists have been diligently working to create animal models of FSHD using fruit flies, frogs, zebrafish, and mice. To date, no single model fully recapitulates all the clinical realities of the human disease. However, each model provides unique pros and cons for scientific studies and has taught researchers how to improve their strategies for the next model.

Recently, Louis Kunkel, PhD, and his team in Boston published the results of their work establishing and characterizing a new model of FSHD in zebrafish. Zebrafish are handy creatures for studying muscle diseases because their translucent bodies offer relative ease in seeing and assessing muscle abnormalities. The FSHD zebrafish was engineered so that the researchers can turn on expression of DUX4 in muscle cells by adding a specific chemical to their water. This is a widely accepted strategy in the field and is simple in theory, but not in practice.

You see, the amount of drug that is added to the water affects how much DUX4 will be expressed. And there's the question of *when* to express DUX4 – when the fish is an adult, or a young hatchling, or immediately after an egg is fertilized? And finally, you have to know *for how long* to express DUX4. An hour? A day? A week? Answering these questions is where that blindfold comes in. Scientists can't yet fully answer all these questions about how DUX4 behaves in human FSHD, let alone know how to translate that to zebrafish.

Nevertheless, Dr. Kunkel and his team succeeded in creating a model that has led us one step closer to accurately representing FSHD in the laboratory and better understanding the underlying pathophysiology. The team decided to turn on expression of DUX4 in the zebrafish one day after fertilization of an egg and for only 24 hours, representing a scenario in humans where DUX4 would be expressed only briefly during early development, and its levels would decrease over time to be largely undetectable later in life. Remarkably, this strategy produced zebrafish FSHD that behaved a lot like human FSHD.

In this zebrafish model, not every muscle cell ended up expressing DUX4. Instead, the expression pattern was mosaic, similar to what has been observed in FSHD patient biopsies. At a young age, about 30 percent of zebrafish had abnormal muscle fiber formation and could not swim as far as their non-FSHD counterparts, while the remaining 70 percent appeared unaffected. This is not unlike the percentage of people with FSHD who have earlier onset of symptoms. A bit later in development, all the FSHD zebrafish, on average, generated less force with their muscle contractions than the non-FSHD controls.

As adults, all the FSHD zebrafish exhibited varying levels of abnormal muscle structure, mild inflammation, and asymmetric replacement of muscle with fat or collagen – much like in humans. Some of these fish tended to swim more slowly than regular zebrafish, while others were just as fast, again representing the spectrum of disability in human FSHD, even as adults.

Overall, Dr. Kunkel and his team deemed this particular zebrafish model to represent a relatively mild form of FSHD. They went on to compare this artificially expressed DUX4 model to another zebrafish model they had previously established using a different technique (with FSH Society funding, Mitsuhashi, et al., Hum Mol Genet. 2013). That model had many similarities, but the disease symptoms tended to be more severe. Importantly, the team noted that in both models, *temporary expression of DUX4 during early development was sufficient to spawn FSHD later in life.*

This observation could be of paramount importance, and suggests that the presence of DUX4 in an adult may not be the sole cause of FSHD. Instead, it could be that DUX4 expression in a fetus or a young child is responsible for setting off a chain of events that eventually leads to the development of FSHD later in life. In that case, one would have some degree of FSHD symptoms regardless of whether DUX4 was still expressed in an adult. Dr. Kunkel and his team are the first to suggest such a theory, and if their hypothesis is correct, it would have important implications for how to treat FSHD.

Much work must still be done to determine whether this observation holds true in humans, and to what extent DUX4 expression during development versus adulthood contributes to disease progression and severity. Moving forward, Dr. Kunkel's team plans to use these zebrafish models to test potential therapeutic compounds and their ability to correct the FSHD symptoms exhibited by the fish. This will be an important precursor to moving into mouse models, and eventually into humans.

REFERENCES

Pakula A, Lek A, Widrick J, Mitsuhashi H, Bugda Gwilt KM, Gupta VA, Rahimov F, Criscione J, Zhang Y, Gibbs D, Murphy Q, Manglik A, Mead L, Kunkel L. Transgenic zebrafish model of DUX4 misexpression reveals a developmental role in FSHD pathogenesis. *Hum Mol Genet*. 2019 Jan 15;28(2):320-331. doi: 10.1093/hmg/ddy348.

Lek A, Rahimov F, Jones PL, Kunkel LM. Emerging preclinical animal models for FSHD. *Trends Mol Med*. 2015 May;21(5):295-306. doi: 10.1016/j.molmed.2015.02.011. Epub 2015 Mar 20. Review. PubMed PMID: 25801126; PubMed Central PMCID: PMC4424175.

Danny Kurtzman designs for life

BY JUNE KINOSHITA, FSH SOCIETY

The headquarters of Ezekiel Clothing is tucked in a bland office park in Irvine, California, but inside it's anything but bland, with its too-cool-for-school interior of concrete, charred timber, and smoky steel. When I arrived there, tapping tentatively on an unmarked, tinted glass door, I wondered if I had come to the right place. Soon, a shadow darted up behind the dark glass, and the door swung open to reveal Danny Kurtzman, perched on a red scooter.

Kurtzman, 31, is co-owner of the company. With his russet hair, trim beard, and piercing gaze, he is an undeniable presence. Although FSH muscular dystrophy has taken a toll on his muscles, his mind is constantly on the move, twirling and swooping like the surfers and skateboarders to whom his clothing line appeals.

Kurtzman and his younger brother (who passed away in 2008 from FSHD) were diagnosed in childhood. "My parents told me and my brother that you're going to public school. You're playing baseball. You're not made out of glass," he said matter-of-factly. That can-do attitude shaped how his friends saw him. "They never looked at me like 'you have a disability.'"

After graduating in 2009 from Loyola Marymount University in Los Angeles, where he studied business administration in entrepreneurship and marketing, Kurtzman went into the family's garment manufacturing business. The company bought Ezekiel Clothing, which does private label for retailers like Nordstrom Rack and Stitch Fix, and Kurtzman mastered the complexities of running the enterprise.

On the day of my visit, Kurtzman was excited about his latest brand, ALDAY Denim, a line of knit denim men's pants that combines the comfort of sweatpants with the swagger of denim. His team was about to launch a Kickstarter, which would raise $67,000 to jump-start the brand.

Kurtzman is passionate about great design, particularly universally accessible design. He invested in WHILL, a company that makes wheelchairs with the sleek appeal of an iPhone, and offered advice to improve the design. He recently flew to San Francisco for a two-day hackathon at Google, putting together a wheelchair that can be controlled by an Android app.

> *"My parents told me and my brother that you're going to public school. You're going to play baseball. You're not made of glass."*
>
> — DANNY KURTZMAN

Outspoken in his belief that "FSHD doesn't define me," Kurtzman is an avid supporter of Life Rolls On, a California nonprofit dedicated to improving the quality of life for people with disabilities through adaptive skateboarding and surfing.

Right now, Kurtzman is completing an extensive renovation of his new home in Costa Mesa. The house embodies universal design, he said proudly, with all smart home features, zero steps or thresholds, wide doorways, and accessible bathrooms.

Asked about his philosophy for living, Kurtzman replied, "Giving up isn't a choice I give myself. I do whatever I put my mind to, regardless of how big the obstacle is, but that's what makes overcoming them that much sweeter.

"It's been amazing meeting more people that share the same mentality, and I hope to meet many more through this Society," he said. "And to those who share this disease but not my mindset of never giving up, feel free to contact me. Sometimes you need a friend or a brother like the one I was very lucky to have to kick you in the butt."

Danny Kurtzman can be reached through his Instagram account *@heavydk*.

Organizing a Walk & Roll – if I can do it, so can you!

BY SUSAN AUMILLER, POWELL, OHIO

Scenes from 2018 Walk & Rolls, blazing the way for growth and even greater success in 2019. Lower photo: Mark Stone and Sue Aumiller.

Last year, soon after my son and husband were diagnosed with FSHD, I called the FSH Society and said I'd like to organize a fundraiser. Within weeks, I found myself launching the first Walk & Roll to Cure FSHD in the state of Ohio. I had never done anything like that before.

I'm no party planner. It seemed overwhelming to consider putting on an event like this. Would anyone show up? How would we make it educational and fun so that those who did show up would want to come back next year? Where do I begin?

Great news! You're not alone. There's a team at the FSH Society waiting to help you get started and guide you every step of the way. Let me introduce them to you.

Anna Gilmore pulls it all together. She is ready to give you all the tools you need to put on a successful event, from a donation website to checklists. Anna will order your marketing materials – posters, postcards, signage, T-shirts – and keep you up to speed on any loose ends. She is responsive to every request and anticipates needs that may arise.

Beth Johnston will guide you throughout the entire process. She and Anna schedule web conference calls for all of the Walk & Roll leaders. The calls are informative and break down the tasks into manageable chunks to keep you on track. They make possible what seems like an insurmountable undertaking. It would be difficult not to be successful if you commit to participating in all of the training calls and studying the written materials provided in the Society's Walk Manual. The training calls are recorded and available to listen to at any time, and to share with your committee members.

Once you've chosen a date and location, Anna can work her magic and put together pre-event marketing materials so you can start advertising and soliciting for your event. It's at that point where you can see a light at the end of the tunnel. Once you have postcards and posters in-hand, it's *real*. That's when things get exciting!

I have always enjoyed participating in fundraising events, but I never imagined I'd be the person behind the curtain organizing one. It takes dedication and desire. One thing we all share is our commitment to keeping our eye on the ball and raising those much-needed funds. Brilliant researchers and scientists – and all the FSHD patients and families – are counting on us.

What are you waiting for? Contact Beth Johnston today at *beth.johnston@fshsociety.org.*

WALK & ROLL TO CURE FSHD

Surgery fixed my eye problems

BY NIKKI YOUNG, CLARKSBURG, MARYLAND

Like many others with FSHD, I have suffered from dry eyes. Weakness in the muscles around my eyes prevented me from closing my eyelids fully, even in my sleep, so my eyes would become dry, itch, burn, and tear up. It got so bad at times that people would ask me if I was crying.

I consulted Nicholas R. Mahoney, MD, at the Wilmer Eye Institute in Baltimore, Maryland, an ophthalmologist who is familiar with FSHD. I told Dr. Mahoney that I had tried lubricants and gels, to no avail. I had also had punctum plugs put into my tear ducts to keep tears from draining from my eye, but I had no luck with those, either.

Dr. Mahoney and I talked at length about eye surgery and the various risks involved. The muscle loss in my eyelids affected my ability to keep my eyes opened properly. With the surgery, there was a risk that even more muscle could be lost. The procedure would be a simple one, though. A small incision in my upper eyelid would allow for a tiny prosthetic to be implanted into the lid, and the lower eyelid muscles would be tightened surgically. The expected result was that the eyelids would fit closely together.

I decided to proceed and scheduled separate surgeries for each eye so that I would still have the use of one eye while the other recovered.

On the day of the surgery, the kind staff at the Wilmer Eye Institute prepared me for the operation and administered local anesthesia to the surgical field. I would be completely conscious and sitting straight up through the whole procedure.

It all took less than two hours. I left with very few stitches, which would later fall out on their own, and an eye patch and bandages to wear for a few days. I had bruising, but other than that everything was perfect, I was able to see clearly from my left eye, and the irritation and tearing were gone. About six weeks later, the same procedure was performed on my right eye. Two weeks after that, my right eye was healed, and I was symptom-free and able to see better.

While the procedure had its risks, I've experienced quite the improvement to my quality of life. I no longer have to deal with constant pain and tears, and my vision has improved so that I no longer need glasses. The only ones I wear now are a pair of designer sunglasses to enhance my good looks!

Nikki Young before surgery

Nikki Young after surgery

Mountains to climb

BY NEENAH WILLIAMS, COLORADO SPRINGS, COLORADO

Neenah Williams poses proudly on Uhuru Peak.

I was diagnosed with FSH muscular dystrophy at the age of 16. I am now 27 years old and have started to feel more of its effects. From an early age, I began to lose the ability to lift my arms higher than 90 degrees. That never stopped me from doing the things I enjoy, most of all dancing.

Fast forward to Christmas 2017. I was driving back home from visiting my family, and I had a thought – that I should do something wild and spontaneous in 2018. Life is too short, and I hadn't been on a real vacation in a long time. I had a truly random idea that it would be awesome to climb Mt. Kilimanjaro.

I wasn't sure what country Mt. Kilimanjaro is in or what type of climb it would be. I honestly decided to go on a whim. However, I believe that everything happens for a reason. So I researched the climb and, a couple of weeks later, I booked my trip to Tanzania.

At the time, I had never experienced weakness in my legs. But sometime last spring or summer, I noticed that my thighs were beginning to get the hollow feeling that I have come to associate with rapid muscle deterioration.

About a month before my trip, I realized that I could no longer walk on my heels, and when hiking in preparation for my trip, I began to fall a lot more.

A couple of weeks before I left for Tanzania, I scaled Pikes Peak in Colorado, 14,115 feet in one day. Three weeks later, I successfully summitted Mt. Kilimanjaro, the highest mountain in Africa, at 19,341 feet. It was one of the proudest days of my life.

The ascent took six days, and I carried my 15-pound daypack the whole time. It was more weight than I had ever carried on a hike, and was a challenge both mentally and physically. Also, altitude sickness was a concern. We were required to walk very slowly to keep our heart rate down.

The hikes each day ranged anywhere from four to seven hours. On summit day, the trek took about 11 hours, because we climbed to the summit from base camp and then returned to a camp at a lower altitude all in the same day.

On the day we reached the summit, I stood on top of Mt. Kilimanjaro with about 400 other hikers, unfurled my "Stronger than FSHD" sign, which I had made months earlier, and took my summit photo. I wanted to show this to all my friends who are struggling with FSHD. I doubt anyone else on the summit that day had FSHD, and for that I am proud. I had just begun to notice new weaknesses in my body, but did not allow that to stand in my way.

Many times, it feels like we stand alone against FSHD. My advice is to take things one step at a time, push your limits whenever you can, and soon you'll be standing on top of the world.

The FSHD Clinical Trial Research Network adds one US and three European sites

The FSHD Clinical Trial Research Network (CTRN) has expanded to eight sites in the US with the addition of Virginia Commonwealth University (VCU) in Richmond. Three European centers have also been added to collaborate with the CTRN on its US National Institutes of Health UO1 grant-funded projects.

Funding sources for the network and the studies running on the network include: the FSH Society, Muscular Dystrophy Association, private philanthropy, National Institute of Neurological Disorders and Stroke, Friends of FSH Research, Institute of Myology Association, and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS).

Here are the FSHD CTRN and collaborating sites, with the site principal investigators:

- University of California, Los Angeles – Perry Shieh, MD PhD
- University of Kansas Medical Center, Kansas City – Jeffrey Statland, MD
- Kennedy Krieger Institute, Baltimore – Kathryn Wagner, MD PhD
- University of Rochester Medical Center, Rochester, NY – Rabi Tawil, MD
- The Ohio State University, Columbus – Samantha LoRusso, MD
- University of Utah, Salt Lake City – Russell Butterfield, MD PhD
- Virginia Commonwealth University, Richmond – Nicholas Johnson, MD MS-CI
- University of Washington, Seattle – Leo H. Wang, MD PhD
- Radboud University, Nijmegen, The Netherlands – Karlien Mul, MD PhD, and Baziel van Engelen, MD PhD
- University of Milan, Italy – Valeria Sansone, MD
- University of Nice, France – Sabrina Sacconi, MD PhD

Virginia Commonwealth University in Richmond, VA.

Team FSHD Cycling rides again

Two years ago, more than 400 people joined me in raising $107,000 for our first Race Across America (RAAM) campaign to support research and bring awareness for FSH muscular dystrophy, which affects me along with nearly one million others around the world.

Riding 3,000 miles across 12 states and 170,000 feet of climbing was life changing for me and my teammates. But our personal victory was dwarfed by the impact we together had on FSHD research.

This coming June, I will once again lead an eight-person team in the RAAM, as we race from Oceanside, California, to Annapolis, Maryland. We are teaming up with Skyland Trail, an Atlanta, Georgia, mental health organization.

Team FSHD Skyland Trail expects to cover more than 450 miles each day and complete the race in fewer than seven days. I hope many people will be excited about our effort and join us in supporting our fundraising campaign.

There may come a time when I cannot pedal a bicycle. Until then, I will continue to ride, and I encourage everyone to enjoy their passions and be ambassadors for our efforts to find a cure.

We will win this fight.

Support Team FSHD Cycling and the FSH Society here: *teamfshd.fshsociety.org/RAAM.*

by George Pollock
Lithia, Florida

From left to right: George and Jane Pollock; George valiantly pedaling in the 2017 RAAM; a happy family at the finish line.

Balloon art

Our New England Chapter's Kristin Zwickau sent this photo to us and said it was okay to share. Too cute not to! This is a picture of Kristin's daughter Katelyn (left) with her little friend. Her friend's mom, Dr. Marianne Lindahl Allen, has been running private "this is how muscles work" classes for the girls so that Katelyn can understand her FSHD muscles better. They had a session on how the muscle is created and how it functions in the body. Then they made these arms.

Commit to the future

Take your support to the next level by including the FSH Society in your will. Your bequest sustains our work for future generations. Questions? Please contact June Kinoshita at (781) 301-6649 or *june.kinoshita@fshsociety.org*.

Always check with your financial advisor when making a change in your will or estate plans and learn how current tax laws and other legislation may affect your plans.

Get social

Find our Facebook and Twitter groups by visiting *www.fshsociety.org* and clicking on the logos at the foot of the page. Our online communities are great sources of news, advice, and social support.

Upcoming

Visit *www.fshsociety.org/events/events-calendar/* for updates.

CONFERENCES

April 28: Stanford, CA
Bay Area FSHD Family Day Conference

June 19-20: Marseille, France
FSHD International Research Congress

WALK & ROLL TO CURE FSHD

September 7: Castle Rock, CO
Colorado Walk & Roll

September 14: Barrington, IL
Chicagoland Walk & Roll

September 14: Dublin, OH
Columbus Walk & Roll

October 6: Madison, CT
Connecticut Walk & Roll

W·E·B·I·N·A·R

All webinars begin at noon EST unless otherwise indicated. They will be recorded and posted on the FSH Society YouTube channel.

March 27: How to Launch a Chapter and Host a Walk & Roll
with Beth Johnston, Anna Gilmore, and guests

June 5: Stance-Control Braces
with Abbey Downing, certified prosthetist/orthotist

August 7: CRISPR Strategy to Treat FSHD
with Charis Himeda, PhD

CHAPTER AND LOCAL MEETINGS

April 6: Gilbert, AZ
Arizona chapter meeting

April 13: Bellevue, WA
Pacific Northwest chapter launch

April 27: Los Angeles, CA
LA Connects chapter meeting

May 18: Malvern, PA
Greater Philadelphia chapter meeting

May 18: St. Petersburg, FL
Tampa-area member meeting & Team FSHD Skyland Trail send-off party

FSH SOCIETY RADIO

VIRTUAL MEETINGS

FSH Society Talk Radio
Broadcasts on Facebook Live on the last Wednesday of every month at 9 p.m. EST (8 p.m. CST). Podcasts are recorded and available in the video section of the FSH Society Facebook page. 2019 dates: March 27, April 24, May 29, June 26, July 31, August 28, September 25, October 30, November 27.

Connecticut Connections
Meets via webinar on the first Thursday of each month (except in summer), 7-8:30 p.m. EST. 2018 dates: April 4, May 2, June 6, September 5, October 3, November 7, December 5.

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THE TIME TO ACT IS NOW

$100,000 matching gift challenge

If we deliver on our promise to have therapies to our families by 2025, it will be because of your donation today. Your continued support will help us:

- begin our Therapeutic Accelerator Project to clear the path to clinical trials and FDA approval of new treatments;
- expand our national chapter program, because a community of patients and families united around a collective goal is the only thing that has ever made a difference in the outcome of drug discovery and development.

The clock is ticking! This is why a group of visionary benefactors has pledged to **match up to $100,000 in gifts made by May 31, 2019.** By donating now, you will empower all of us to move forward with the urgency demanded.

Take action:

- Donate at *www.fshsociety.org*.
- Mail a check to FSH Society, 450 Bedford Street, Lexington, MA 02420.
- Call (781) 301-7301.