A Publication of the Facioscapulohumeral Muscular Dystrophy Society

FSH Watch

ISSUE 2 • 2017

FSH SOCIETY
FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

CONNECTING THE COMMUNITY OF PATIENTS, FAMILIES, CLINICIANS, AND INVESTIGATORS

Social media was filled with hundreds of images and messages as advocates around the world flashed their orange slice smiles to raise awareness on June 20. Thanks to all who participated!

RESEARCH

Clinical Trial Research Network receives major award from NIH

Leveraging the FSH Society's investment

by JUNE KINOSHITA
FSH Society

The FSHD Clinical Trial Research Network (CTRN), which was launched last year with a $121,000 grant from the FSH Society, has received a UO1 award from the National Institutes of Health. The project will receive $469,642 for the first year. Additional funds, up to a total of nearly $2.7 million, will be

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ADVOCACY

World FSHD Day 2017

#OrangeSlice selfies everywhere

by JUNE KINOSHITA
FSH Society

The goal was to create attention-grabbing images that would splash the official orange color of World FSHD Day across social media while educating the public about FSHD. And it had to be cheap, fast, and fun. That's how our marketing team at SHIFT Communications came up with the genius idea of orange slice selfies—photos of people holding half an orange slice over their mouths—to raise awareness of FSH muscular dystrophy and how it can affect your smile.

The campaign was embraced by advocates around the world and received media attention from *Huffington Post* (with 450 shares and 87 Facebook reactions), *Muscular Dystrophy News*, and *Rare Disease Report*.

Our Facebook post encouraging supporters to participate in our Spring Campaign's $50,000 matching gift challenge by the June 20 deadline made 27,678 impressions and received 239 engagements.

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Chief Science Officer
Daniel Paul Perez
daniel.perez@fshsociety.org

Executive Director & Chief Operating Officer
June Kinoshita
june.kinoshita@fshsociety.org

Director of Finance and Administration
Lisa Schimmel
lisa.schimmel@fshsociety.org

Development Officer
Beth Johnston
beth.johnston@fshsociety.org

Executive Assistant
Robyn O'Leary
robyn.oleary@fshsociety.org

Gifts and Membership
Kathryn Puzzanghera
kathryn.puzzanghera@fshsociety.org

Washington, DC Counsel
Morgan Downey

FSH Society
450 Bedford Street
Lexington, MA 02420 USA
(781) 301-6060
info@fshsociety.org

www.fshsociety.org

Prescription for a cure

Be as persistent as Dan Perez

Dear Friends,

June Kinoshita

Those of you who have met Daniel Perez, the co-founder of the FSH Society, know he is a trove of stories from his multi-decade crusade to shed light on FSH muscular dystrophy and find treatments. One that sticks with me is a story about his visit in the early 1990s to Dr. David L. Coulter at Boston University Medical Center. Dr. Coulter had only the usual discouraging news that there was no effective treatment. But while there was nothing medically to be done, he said the most important thing Dan could do was to lobby Congress to fund research on FSHD.

Doctors are accustomed to patients not complying with their advice, but in this case, Dan followed the prescription. He began making regular trips to the nation's capital and submitting detailed testimony to both houses of Congress on the needs of the FSHD community, and he has never let up.

In 2001, his efforts ensured that the MD-CARE Act would cover all muscular dystrophies including FSHD. He has served on the presidential Muscular Dystrophy Coordinating Committee and submitted to extreme vetting that makes electromyography (electric currents applied to muscles) seem like a walk in the park.

Dan has been relentless in demanding more attention and more funds for FSHD. Slowly but surely, the efforts have paid off. From less than $250,000 granted by the National Institutes of Health (NIH) for FSHD research in 2001, the federal investment has grown to almost $13 million a year. The Society's grants have seeded much of the work that is now receiving those NIH awards. We have a genetic cause and drug targets. Seven research centers have joined forces to form the FSHD Clinical Trial Research Network. There have been two clinical trials in the past three years, and we can expect more very soon.

We have been just as dogged in our efforts to raise FSHD's profile with the public. This year, orange slice selfies took over social media on World FSHD Day, June 20, while Team FSHD Cycling put the spotlight on FSHD by competing in the grueling, 3,000-mile Race Across America, accompanied by support vehicles covered with photos of FSHD patients from around the world. A group of committed benefactors powered our Spring Campaign through a matching gift challenge of $50,000, and you, our grassroots supporters, met and exceeded the challenge! Altogether, our Spring Campaign and Team FSHD Cycling raised more than $200,000!

It makes me smile to imagine how astonished Dr. Coulter would have been if he could have foreseen how his sage advice has grown into a worldwide movement. We are so grateful to the FSH Society staff, Board of Directors, Scientific Advisory Board, incredible volunteers, and donors for propelling us toward our collective prize.

With sincere appreciation,

June Kinoshita
Executive Director & Chief Operating Officer

FSH Society's FY2018 testimony to congressional committees

$28 million requested for FSHD research

by DAN PEREZ, PRESIDENT, CEO, & CSO
FSH Society

The FSH Society successfully launched its 2017 Washington agenda on March 7 with the submission of written testimonies to the U.S. House of Representatives Appropriations Committee; Senate Appropriations Committee; and Subcommittees on Labor, Health and Human Services, Education and Related Agencies, which sets the funding for biomedical research. The testimonies request $28 million FY2018 appropriations for NIH research on FSHD.

The Society expressed its concern with the overall level of annual FSHD research funding by the National Institutes of Health (NIH), given the opportunities and quality of science at present. There are 28 active projects NIH-wide totaling just over $13 million as of May 27, 2017.

The U.S. House testimony was submitted March 7 directly to Tom Cole (R-OK), chairman of the Subcommittee on Labor, HHS and Education. In it, I asked the subcommittee to strongly encourage "the NIH to significantly accelerate basic and exploratory research efforts and increase clinical trial readiness funding to provide access to treatment of facioscapulohumeral muscular dystrophy (FSHD) and other epigenetic diseases," given recent breakthroughs and community-defined priorities in FSHD.

In the U.S. Senate testimony submitted May 28 directly to Roy Blunt (R-MO), chairman of the Subcommittee on Labor, HHS and Education, I testified that "looking at the current portfolio against the backdrop of scientific understanding and opportunity in FSHD, the NIH needs to expand its portfolio." I also stated that additional NIH funding in building blocks of workforce training, exploratory/developmental research grants (parent R21s), and research project grants (parent R01s) are sought.

I emphatically expressed the need to increase R21-, R01-style research project grants together and "with purpose address the acute shortage on the supply side of researchers and clinicians entering the FSHD research and clinical and dystrophy field by actively engaging the best and brightest minds through 'K series' career development awards and 'T & F series' research training grants and fellowships. We ask NIH to consider a proactive pilot program for five years whereby between six K awardees and six F,T awardees are brought online each year."

Many of the priorities as specified by the community call for more basic grants and exploratory research awards, and expansion of postdoctoral and clinical training fellowships. Now that the NIH has conveyed to researchers that it has a revised plan and an interest in funding research in FSHD, these funds will be needed to fill the demand.

I am also a member of the federal advisory Muscular Dystrophy Coordinating Committee, which was created by the Muscular Dystrophy Community Assistance, Research and Education Amendments of 2001 (MD-CARE Act, Public Law 107-84). The MDCC, along with working groups of experts in the field, presented the 2015 NIH Action Plan for the Muscular Dystrophies to Congress. It specifies 81 objectives organized in six sections (mechanisms, screening, treatments, trial readiness, access to care, and infrastructure, including workforce) in need of immediate and further development.

See full versions of testimony at: *https://www.fshsociety.org/advocacy-2/*. FSH Watch

Reference:

Rieff HI, Katz SI et al. The Muscular Dystrophy Coordinating Committee Action Plan for the Muscular Dystrophies. I. 2016 Mar 21.

FSHD Family Day Conference in Ohio

Strengthening our network in the Midwest

by JUNE KINOSHITA
FSH Society

The FSHD Family Day Conference, hosted by Nationwide Children's Hospital and the FSH Society on June 11, 2017, drew about 70 patients, families, researchers, and clinicians to Columbus, Ohio. The half-day meeting provided an opportunity for two of the nation's leading FSHD research centers to share expertise and research advances with patients and families in the region. Patients and caregivers shared their observations and experiences of living with FSHD.

The opening talk by Kevin Flanigan, MD, speaking via Skype, laid out the background of FSH muscular dystrophy, from its earliest description by French physicians Duchenne, Landouzy, and Dejerine, to the pioneering studies by Frank Tyler, who first described a Utah family of 1,249 individuals descended from an individual born in England in 1775, who emigrated to America, converted to Mormonism, had four wives, and produced numerous progeny. Flanigan identified an additional 971 descendants.

Typical symptoms, Flanigan noted, include the curious fact that muscles are affected asymmetrically, and some muscles more than others. A bicep may be quite affected, while the deltoid is fine. He also reviewed the genetic model of FSHD, with the location of the FSHD1 region isolated to the tip of chromosome 4, where a loss of repetitive genetic units called D4Z4 leads to increased expression of the DUX4 gene, which is thought to be toxic to muscle cells.

This introductory talk was followed by Scott Harper, PhD, who provided an excellent primer on the central dogma of molecular biology, explaining how information encoded in DNA is first copied into RNA, which provides instructions to build a protein. He noted that our genome contains the code for approximately 20,000 proteins, but that these proteins are further modified to give rise to 100,000 functionally distinct molecules. A mind-bending fact that Harper shared is that the total DNA in a single human body weighs about 23 pennies. Uncoiled, that DNA would extend 67 billion miles, enough to make 150,000 round trips to the moon.

Harper explained that the central dogma allows us to identify disease genes, clone them, create animal models, and develop gene therapy. With FSHD, he noted that the DUX4 gene is next to a PolyA signal, which is needed to stabilize the gene. He also explained that every gene requires a "promoter" to turn on gene expression. "We don't understand what turns the DUX4 promoter on and off in FSHD," Harper said. "What we do know is that the gene is transcribed, undergoes splicing, and is translated. If we disrupt any of these steps, we could interfere with the production of DUX4."

At the DNA level, DUX4 production can be disrupted by turning off the DUX4 promoter, which has been done in cultured cells, but this is "not viable right now" in humans, Harper said. DUX4 expression could also be blocked by genome editing, for example, by removing the PolyA signal, an approach now being

The FSH Society's first FSHD Family Day conference in Columbus, Ohio, gave patients and families a chance to hear featured researchers from Nationwide Children's Hospital.


Kevin Flanigan, MD


Miriam Freimer, MD


Richard Shell, MD


Jennifer Roggenbuck, MS, CGC


Scott Harper, PhD

investigated by several labs.

At the RNA level, one can disrupt splicing so that full-length DUX4 mRNA is not made and instead results in a short form of DUX4, which is not toxic. Another tactic is to destroy RNA before it can be translated into protein using a method called RNA interference. Harper's lab has successfully used RNA interference to knock down DUX4 in human cells and in mice. "It's our lead strategy now," Harper said. Lindsay Wallace, PhD, in Harper's lab is now testing the safety of this strategy.

The Harper lab is also tackling DUX4 at the protein level. Jocelyn Eidahl, PhD, is analyzing the details of how DUX4 protein is modified, to determine which form is responsible for toxicity to muscle cells. Understanding this could point the way to drugs that interfere with the formation of toxic forms of the DUX4 protein. (Research in the Harper lab by Drs. Saad, Eidahl, and Wallace, has been supported by the FSH Society.)

The next speaker, Miriam Freimer, MD, professor of neurology at Ohio State University (OSU), spoke about two clinical trials for FSHD that have been conducted at OSU. The first trial was for Resolaris, by the biotech aTyr Pharma. "aTyr's drug is designed to reduce the T cell immune response," she explained. "Even though FSHD is not considered a disease of immune cells, in the images Dr. Harper showed you, there are immune cells in FSHD muscles." The Phase 1B/2 trial was able to show that Resolaris is safe and, as dosage was increased, "fairly well tolerated." The study is "on hold," but volunteers who want to continue are in long-term extension studies. "We are hoping to get some important data out of that," Freimer said.

OSU is also involved with the ongoing trial of ACE-083, a drug from Acceleron Pharma. "In healthy volunteers, ACE-083 was associated with a 14.5 percent increase in muscle volume," Freimer said. "Now, in a two-part Phase 2 trial, we are asking whether ACE-083 increases muscle volume in the tibialis anterior or biceps of FSHD patients."

There are a few other clinical trials at other research institutes investigating such approaches as electrical stimulation of muscle and testosterone, Freimer noted. "I don't have more to tell you right now, but in the next three to five years," she said, "I hope there will be an explosion in clinical trials," thanks to the identification of DUX4 as a therapeutic target.

The next set of talks focused on best practices in managing FSHD. Wendy King, PT, spoke about physical therapy and exercise for FSHD patients and the need for individualized approaches. "Light exercise is helpful, and moderate-intensity exercise is safe and likely to be beneficial," she said.

An OSU study of ankle-foot orthoses (AFOs) showed that the vast majority of patients were very pleased with carbon fiber-based ones. She also mentioned that Alignmed's S3 posture brace can be helpful for correcting scapular protraction ("winging" of the shoulder blade).

Richard Shell, MD, spoke on "The Art of Respiratory Care in FSHD." He noted that abdominal muscles, which play an important role in breathing and coughing, are often weakened in FSHD patients. "You have normal lungs, but the weakened muscles can compromise your breathing," he explained. He advised FSHD patients to be assessed with spirometry, which measures how much air they can push out of their lungs. Shell also noted that "we use cough assist equipment a lot," and he recommended pulmonary function testing at least once a year. "If you are experiencing decline, you might want to test more frequently," he said.

Sleep issues in FSHD patients involve hypoventilation, or shallow breathing, which can cause carbon dioxide to build up in the bloodstream (known as hypercarbia). "You may wake up more tired," he said. Risk factors for hypercarbia include early age of onset of FSHD symptoms and wheelchair use, but Shell said there is weak evidence of correlation with larger D4Z4 deletion size.

"We should be proactive about screening for any respiratory symptoms," Shell advised. This includes yearly pulmonary function testing and screening for sleep-disordered breathing.

Genetic testing is one of the more complicated aspects of FSHD, and genetic counselor Jennifer Roggenbuck, MS CGC, masterfully explained the key points. While FSHD Type 1 (FSHD1) is inherited in a classic "autosomal dominant" manner (one copy is sufficient to cause disease, so each child has a 50 percent chance of inheriting FSHD1 from an affected parent), FSHD Type 2 (FSHD2) is passed on with a lower probability because it requires two distinct genetic changes to cause disease symptoms.

With FSHD there is also a phenomenon called germline mosaic, in which the mutation occurs in the egg or sperm of an unaffected parent. In such cases, even if both parents test negative for FSHD genes based on a blood test, each of their children faces a risk of inheriting FSHD through the carrier parent's egg or sperm.

To get a genetic test for FSHD, Roggenbuck advised individuals to begin by asking a neurologist. They may need a referral to a genetic counselor, and should be prepared to provide details of their family history and genetic test results from family members.

One question family members often ask is whether to be tested if you don't have symptoms but have an affected parent or sibling. Roggenbuck recommended discussing this with a genetic counselor. She noted that a genetic test by itself cannot predict if or when an individual will develop symptoms. Because currently there are no medical interventions to prevent or delay the onset of symptoms, "what you will do with this information is a very individual decision." She noted that non-symptomatic children are not tested.

The conference concluded with two patients, Maureen Eye and Nicky Dexter, sharing their thoughts about living with FSHD, advocacy, and volunteering for research studies. June Kinoshita, executive director of the FSH Society, reminded patients and families that they are the ultimate experts of FSHD, and by actively engaging in advocacy, making their voices heard, and collaborating with researchers, they will ensure that meaningful, effective treatments will be developed. FSH Watch

Why donating biospecimens is so important

Scientist Angela Lek explains in this Q&A

by JIM ALBERT
Eldersburg, Maryland

Editor's note: While interviewing researchers about their work on FSHD, Jim Albert, a member of the FSH Society and volunteer contributor to the *FSH Watch*, became interested in learning more about donating biospecimens for research. He interviewed Angela Lek, PhD, a scientist working at Harvard Medical School in the laboratory of Louis Kunkel. Dr. Lek is currently conducting an FSH Society-funded study, "A genome-wide CRISPR knock-out strategy to identify modifiers of FSHD." Here is their interview.

Angela Lek, PhD

Q: What repositories serve as a source for your samples?
Lek: Our main source of patient samples is the repository established by the Wellstone Center for FSHD Research based at University of Massachusetts Medical School in Worcester. These samples were collected by Dr. Kathryn Wagner in her clinic at Johns Hopkins and sent to Dr. Charles Emerson's lab for storage.

Q: For your research, are you finding that sufficient samples exist of families of FSHD patients and their genetically positive but asymptomatic family members?
Lek: No. We can never have too many samples! We suspect that there is a different underlying genetic variant unique to each family that causes individuals to be asymptomatic. The more samples we get, the more we can verify if our theory is correct, and we can catalogue these genetic variants.

Q: What patient material is being used in the gene modifications? Muscle tissue (open muscle biopsy), muscle cells (needle muscle biopsy), or blood?
Lek: We are currently doing gene modifications on non-patient samples because patient samples are a very valuable resource, and we want to be careful not to exhaust our supply. I believe Dr. Wagner has collected patient muscle biopsies, cells, and blood—all of which we have access to through the Wellstone initiative. I will move on to gene-editing patient cells when it comes time to validate my hypothesis as to which gene may be involved in causing resistance to DUX4 toxicity in a particular family.

Q: Are there other types of samples that FSHD patients can donate which are important for your research?
Lek: For my specific area of research, it's not so much a question of what other types of samples I need. I think what would help me a lot is to get the whole family involved in sample donation. I would love to get more cases of family members who theoretically should have FSHD (according to their genetics) but are walking around just fine. If we can understand why this is the case, then we may be able to approach treatment from that perspective.

The gene scan

Q: Given my understanding that the number of genes in the human genome is about 20,000, and your plan is to selectively turn on each gene separately and individually, this indicates the type of work suitable and even necessary for computers or some other means of automation. What kind of automation assists you in performing genetic edits of this magnitude?
Lek: So, computers are involved only in the last stage of the experimental process—the sequencing and data analysis to identify the gene edits that allow for DUX4 resistance. Unfortunately, the first part (growing cells, turning genes on and off) involves a lot of manual labor and cannot be automated.

Q: How much effort and time are required to complete each loop of examining a single gene?
Lek: I do the gene edits all at once in a pool of cells. There are approximately 20,000 human genes, and we have six different gene-editing constructs that target each gene, so in total we have 6 x 20,000 or 120,000 constructs in the gene-editing construct library. We also want to perform each gene edit about 300 times to make sure that what we are observing is an actual effect and not a fluke, so 120,000 x 300 equals 36 million cells required for each experimental run. Each run takes about one month from start to finish. Dr. Monkol Lek (my husband) helps me with the data analysis, as he is really good with computers. (He also has muscular dystrophy, a limb-girdle type.)

Q: Are you required to first turn off all or most genes prior to individually turning on each gene?
Lek: No, I think this would be too difficult to achieve, not to mention an endless combination. The turning off part is easy. Currently, I'm finding that the turning on is not as straightforward because the levels of being "on" are variable. Off is off, but on can be at multiple intensities.

Q: Are there genes you will consistently leave on during this research (e.g., DUX4 gene or D4Z4 region)?
Lek: DUX4 levels are very difficult to control inside cells—it is not homogenously expressed in every cell, and we don't yet understand why this is the case. Some people express it in one out of every

1,000 cells (others less). In my screen, I am introducing DUX4 from an outside source (using a virus to turn on DUX4 at very high levels to induce cell death).

Q: Do the genes you will individually turn on include only protein-encoding genes?
Lek: Most of the gene edits only target protein-coding genes, but there are also constructs that target microRNAs that are known to regulate the expression of protein-coding genes.

Q: Is DUX4-fl considered a protein-coding gene, given that in most people it is repressed?
Lek: Yes, it is a protein-coding gene in individuals who harbor the 4qA haplotype and can add a polyadenylation signal to the DUX4 RNA (this later allows for the RNA to be translated into a protein).

Q: How do you measure a reduction in FSHD-related cell toxicity to define a "hit" in terms of a gene being classified as a "modifier"?
Lek: The readout is simple—if cells are able to survive the DUX4 virus I introduce, then it is said to be able to resist DUX4 toxicity. The majority of cells will die within 48 hours.

Q: Based on resulting hits, will you expand your research to turning on combinations of hits as potential modifiers of increased ability to ameliorate disease?
Lek: Yes. This is a good idea!

Q: How deep are you into this project in terms of the number of genes you have examined (turned on)?
Lek: So far I am pretty confident in the genes I have turned off, but not so much the genes that I have turned on. I will need to repeat the experiments several more times.

Male/female research

Q: The FSHD severity in my family very much favors females who remain very mildly affected to asymptomatic, while males experience some level of obvious symptoms from mild to moderate. Assuming my family is not an anomaly, and my understanding is accurate that FSHD disease penetrance in genetically positive females in general is only about 60 percent, is there any particular attention in your research (or perhaps other research that you are aware of) to either the X or Y chromosome?
Lek: I actually haven't thought of specifically looking for sex chromosome genes. This is a very good idea you are proposing, and I will make a note to categorize my gene "hits" for sex-specific expression.

Q: Is the male/female genetic difference being examined anywhere with respect to FSHD?
Lek: Yes, I think some French, Argentine* and Italian* groups are investigating the effect of estrogen, testosterone, and progesterone in modulating DUX4 cytotoxicity. (*Funded by FSH Society.)

Protection against DUX4 toxicity

Q: What attributes of the zebrafish model make it well suited for the rescue portion [finding genes or chemicals that protect against DUX4] of your research?
Lek: We can recapitulate some human features of FSHD in zebrafish—muscle abnormality, and eye and ear defects.

Q: With the anticipation that one of the resulting hit genes might not be part of the zebrafish genome, how difficult is it to produce a transgenic zebrafish for both DUX4 and your hit gene(s)?
Lek: It may take some months, but it's doable.

Q: Have you found or do you expect to find that muscle cells of people who have FSHD-permissive genetics but are asymptomatic express no DUX4-fl protein, or that DUX4-fl is in lesser amounts, than in those who are genetically positive and symptomatic?
Lek: In our Wellstone cohort, these asymptomatic individuals do express DUX4-fl but I believe in lesser amounts.

Q: Is there any correlation between the amount of DUX4-fl expressed and disease severity?
Lek: No, there is currently no known correlation, which makes things confusing.

Q: Given that FSHD patients "make" everything necessary for healthy muscle and produce something extra, DUX4, which is toxic to muscle and is presumed to set off disease, and assuming DUX4 levels are consistent between symptomatic and asymptomatic genetically positive people, is it reasonable, albeit an oversimplification, that some people simply react differently to the toxin that is DUX4? Maybe similar to toxins like salmonella? Maybe 100 people eat the same tainted potato salad, but only a dozen or so get seriously sick. I guess my point here is, How sure are we that there is some unresolved genetic element that leads to disease severity?
Lek: These differences in how individuals are susceptible to process X (X being a Mendelian genetic condition) can be attributed to variants, called "genetic modifiers," in the genome. For example, an ex-colleague of mine just released a publication about a genetic modifier he discovered for Duchenne muscular dystrophy: *http://www.nature.com/articles/ncomms14143*.

Genetic modifiers are a big area of research, not just in muscular dystrophy but all Mendelian disorders, as they ultimately determine the disease penetrance (or how an individual manifests the disease, i.e., disease severity). FSH Watch

FSH muscular dystrophy at annual MDA conference

Several FSH Society grant recipients highlighted

by JUNE KINOSHITA
FSH Society

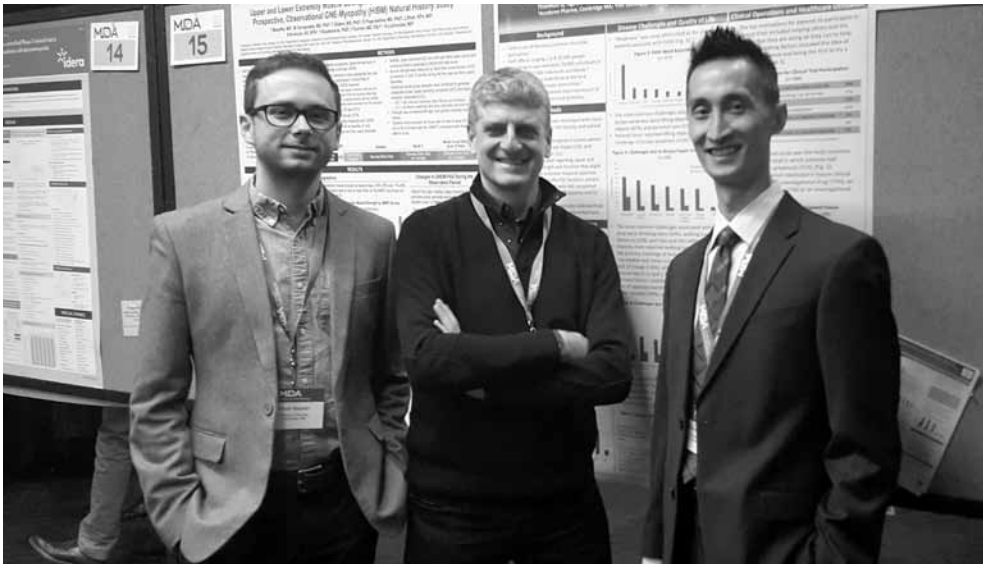
At the Muscular Dystrophy Association's biennial scientific conference, held in Washington, DC, on March 19-22, 2017, FSH muscular dystrophy received the spotlight in several podium talks by FSH Society-funded scientists.

Peter L. Jones, PhD, of the University of Nevada Reno delivered an energetic crash-course in epigenetic disorders and FSHD. Advances in gene therapy approaches using RNA-interference technology to silence the DUX4 gene were described by Lindsay Wallace, PhD, of Nationwide Children's Hospital. Stephen Tapscott, MD PhD, of the Fred Hutchinson Cancer Research Center gave an overview of treatment strategies being developed based on current hypotheses about the biological mechanisms of the disease.

The FSH Society—including many of you, our members—had a direct hand in a poster talk presented by Acceleron Pharma about the most prominent symptoms and daily life impact of FSHD, as reported by patients and caregivers. The report was based on results from a survey developed by Acceleron in collaboration with Dr. Jeffrey Statland of the University of Kansas Medical Center and June Kinoshita from the FSH Society. Researchers at aTyr Pharma also contributed comments on the survey questions.

The survey was sent to FSH Society members in December 2016, and 388 individuals responded. The most highly reported regions of muscle weakness were the scapula and abdominals, followed by biceps, ankle, and face. Leg, arm, and core weakness were considered to have the greatest impact on patients' quality of life.

The survey respondents showed a high level of engagement, with 31 percent saying they had previously participated in a clinical research study. They are an altruistic group, too. Some 69 percent said they would volunteer for a clinical trial even if it might not help them, because it might help others in the future. Kinoshita noted, "It's really motivating to work alongside such a committed and selfless community of patients."



Chad Glasser, Ken Attie, and Thienhuu Nguyen pose in front of Acceleron's poster presentation.

In addition, FSHD was well represented among poster abstracts. Since most of the data are not yet published, we provide only titles and authors below.

Vital research continues on how muscle damage occurs in FSHD and on the search for genes that modify the expression of the disease:

- Protein chemistry of myotoxic DUX4 (Eidahl et al.)
- Using genome-wide CRISPR libraries to identify modifiers of FSHD (Lek)

Several labs reported on studies of diverse treatment strategies using cell and animal models of FSHD:

- Local administration of ACE-083 increases muscle mass in mouse model of FSHD (Pearsall et al.)
- In vivo delivery of third generation oligonucleotides targeting DUX4 using a new mouse model of FSHD (Murphy et al.)
- Identification of three independent, novel small molecular classes for regulation of DUX4 in hESC-derived skeletal muscle (Schmidt et al.)
- miR-675 reduces DUX4 expression and confers resistance to DUX4 toxicity in FSHD myoblasts: a framework to define the DUX4-targeted miRNome (Saad et al.)
- Translating DUX4-targeted RNAi therapy for facioscapulohumeral muscular dystrophy (Wallace et al.)

Many labs continue to improve cell and animal models so that they more accurately mimic essential features of FSHD, or to make them more reliable or controllable for experiments:

- iPSC Modeling of FSHD (Emerson et al.)
- Generation of a new, inducible model of FSHD that develops overt myopathic phenotypes (Giesige et al.)
- Comparison of DUX4 protein expression in FSHD muscle biopsies and an AAV-DUX4 mouse model (Hall et al.)
- A tunable phenotypic FSHD-like mouse model (Takako Jones and Peter Jones)
- Methods for improving quality of xenografts in mice (Llac-Martinez et al.)
- A transgenic zebrafish model for FSHD (Pakula et al.)

The majority of these projects have received support from the FSH Society. Your donations have been game-changing, for which all of us in the FSHD community are sincerely grateful! FSHWatch

2017 Event Calendar

Save the date

Additional meetings in Baltimore, Chicago, Dallas, New York City, and other locations are being planned. Check our website at *www.fshsociety.org/events* for updates, details, and maps.

Thursday, July 13, 2017
7 p.m. – 9 p.m.
Lexi's Charity Bartending @ McGreevys
McGreevy's, Boston, MA

Saturday, July 15, 2017
Noon – 4 p.m.
2017 FSH Society Family Day
Jewish Community Center of San Francisco, CA

Saturday, July 15, 2017
6 p.m. – 10 p.m.
4th Annual Songs in the Key of Steven Blier
Jewish Community Center of San Francisco, CA

Saturday, July 22, 2017
10 a.m. – 12 p.m.
FSH Society Dallas meeting
Irving, TX

Saturday, July 22, 2017
2:30 p.m. – 5:30 p.m.
Western Washington FSH Community
Skype

Saturday, July 22, 2017
11 a.m. – 2 p.m.
Charlotte FSH Society Meeting
Myers Park Country Club
Charlotte, NC

Thursday, August 3, 2017
6:30 a.m. – 8:30 p.m.
FSHD Connecticut Connections
First Church in Wethersfield, CT

Saturday, August 5, 2017
2 p.m. – 4 p.m.
Tulsa FSH Society Meeting
Tulsa Country Club, OK

Saturday, August 26, 2017
10 a.m. – 12 p.m.
Western Washington FSH Community
Skype

Thursday, September 7, 2017
6:30 p.m. – 8:30 p.m.
FSHD Connecticut Connections
First Church, Wethersfield, CT

Saturday, September 9, 2017
9 a.m. – 2 p.m.
Walk & Roll to Cure FSHD 2017
Phillip S. Miller Park, Castle Rock, CO

Saturday, September 23, 2017
10 a.m. – 12 p.m.
Western Washington FSH Community
Skype

Thursday, October 5, 2017
6:30 p.m. – 8:30 p.m.
FSHD Connecticut Connections
First Church, Wethersfield, CT

Saturday, October 21, 2017
Noon – 5 p.m.
FSHD Family Day Conference
Los Angeles, CA

Saturday, October 28, 2017
10 a.m. – 12 p.m.
Western Washington FSH Community
Skype

Saturday, October 28, 2017
Noon – 5 p.m.
2017 Inherited Neuromuscular Disorders Family Conference
University Park Marriott
Salt Lake City, UT

Thursday, November 2, 2017
6:30 p.m. – 8:30 p.m.
FSHD Connecticut Connections
First Church, Wethersfield, CT

Saturday, November 25, 2017
10 a.m. – 12 p.m.
Western Washington FSH Community
Skype

Connecticut Connections

First-time meeting

by SARAH PASHE and KATHY SENECAL
Broad Brook and Cromwell, Connecticut

At our Connecticut Connections inaugural meeting on May 4, we were pleased to welcome 11 attendees: seven individuals with FSHD, three spouses, and one family member. We gathered on an early Thursday evening at First Church in Wethersfield. Nearly every attendee had heard about the meeting through the FSH Society mailing.

During our time together, we briefly described the FSH Society and handed out information about World FSHD Day (June 20). Participants introduced themselves to one another, sharing their connection to FSHD, talking about ideas to improve accessibility, and describing their challenges, careers, communities, and something they enjoy doing.

Kathy Senecal gave a brief program about bed yoga, including ways to adapt poses to specific abilities. Bed yoga includes four poses to release the spine and provide the body and mind with the benefits of a yoga practice. The poses are done on your back with mindful breathing. They include: knees to chest, knee-down twists, crossed ankle to opposite bent knee, and a hamstring/foot flexion stretch called hand-to-big toe. Modifications include pillows, straps, and a partner to help achieve the positions.

We decided to continue to meet at this location on the first Thursday of each month and extend our time together to two hours. We agreed to coordinate speakers for our meetings and plan to have someone from the FSH Society attend our September meeting. We'll evaluate meeting frequency in six months.

The general response for this new group was extremely positive, with many contributing ideas and suggestions for the direction and future of the group. There was a consensus regarding the value and benefits of meeting together in a physical space, and an interest in exploring options for when the weather makes it difficult to travel.

This get-together came about because the two of us independently reached out to the FSH Society to ask about helping to organize a meeting. Robyn O'Leary from the Society put us in touch with each other. Kathy arranged for the meeting space at the church, and once we had a date and location, the FSH Society posted the information on its website and sent out postal and email announcements. If you would like to start a meeting in your area, just contact *robyn.oleary@fshsociety.org*. FSH Watch

Bone health and FSHD

New study points the way to better managing of risk

by JUNE KINOSHITA
FSH Society

Muscle plays an important role in bone health, and diseases such as Duchenne muscular dystrophy have been linked to low bone mineral density (BMD), abnormal bone turnover, and increased risk of fractures. It was not known whether FSH muscular dystrophy also affects bone health, and a new study published in *Muscle & Nerve* begins to address this question.

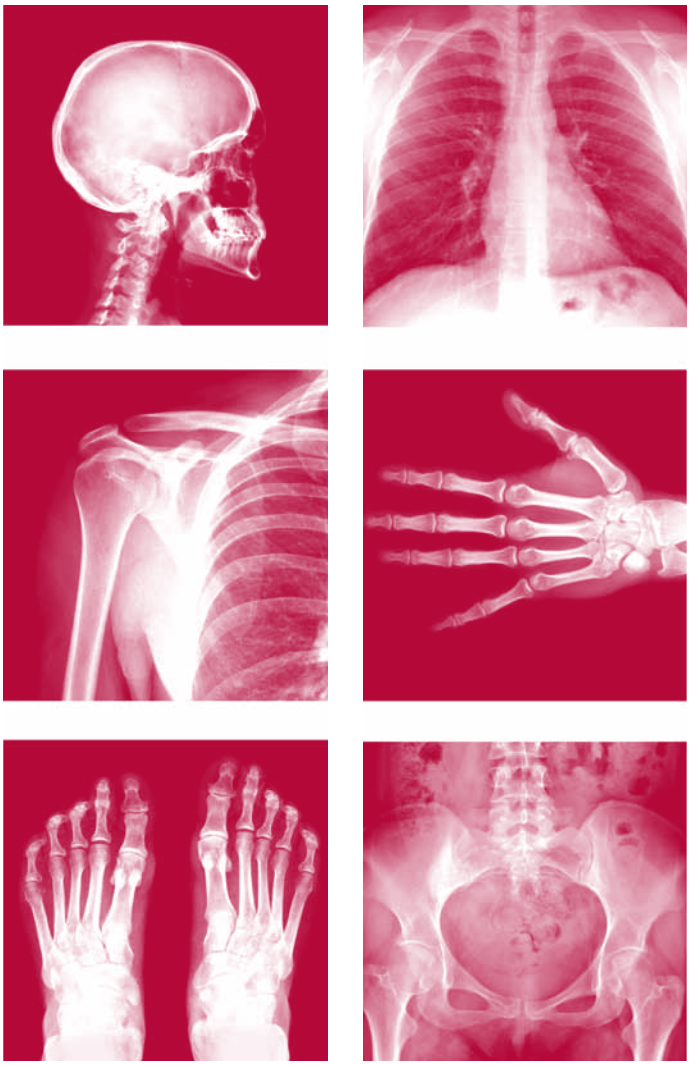
This is a topic that many FSHD patients worry about, because weaker muscles lead to more falls, and fractured bones take long recovery times. Reduced mobility, in turn, can further weaken muscles.

The study, led by Kathryn Wagner, MD PhD, of the Kennedy Krieger Institute in Baltimore, Maryland, examined 94 FSHD patients, half in Australia and half in the U.S. The volunteers had genetically confirmed FSHD Type 1 and were examined for correlations among disease severity score, BMD, blood biomarkers (molecules associated with bone turnover and health), strength tests, and function.

Overall, the study reported that a diagnosis of FSHD was not predictive of decreased BMD or increased bone fractures. However, the researchers found that declines in whole-body and regional BMD were moderately correlated with reduced strength and function. These patients had a higher prevalence of traumatic fractures, as well as abnormally low levels of vitamin D3.

"Given the considerable variability of bone health in the FSHD population, strength and function can serve as predictors of BMD," the study concluded. The authors suggested that periodic bone-density scans be done in FSHD patients whose strength and functional tests indicate a higher risk of lower BMD. This will assist doctors in developing effective treatment plans tailored to individuals to help prevent fractures and promote bone health.

The study was funded by a grant from FSHD Global Research Foundation and the U.S. National Institutes of Health.



Reference:

Chagarlamudi H, Corbett A, Stoll M, Bibat G, Grosmann C, Matichak Stock C, Stinson N, Shapiro J, Wagner KR. Bone health in facioscapulohumeral muscular dystrophy: A cross-sectional study. *Muscle Nerve*. 2017 Feb 18. doi: 10.1002/mus.25619. FSH Watch

Minneapolis TV news channel features FSHD

MICHAEL KYBA AND MARGE BRCHAN SHARE THEIR STORY

Over the weekend of March 25-26, FSH Society grant awardee Michael Kyba, PhD, of the University of Minnesota and Society member Marge Brchan shared their amazing story with Leah Beno of FOX 9 Minneapolis.

Since being diagnosed at age 19, Brchan has battled the effects of FSHD most of her life. "It was very hopeless," said Brchan. "They knew very little about the disease.

Leah Beno interviews Marge Brchan about FSHD.

There wasn't anyone focusing on the disease. Basically, each year you find you lose more and more ability to lift, to walk."

"[For] patients with this disease, one of the saddest things that happens [is that] they are robbed of their ability to smile," said Kyba. Along with his staff at the University of Minnesota, Kyba is focusing his research on finding treatments by targeting the DUX4 gene, thought to be a key cause of

Why I donated tissue

Providing hope to the community

by MAUREEN EYE
Centerport, New York

In November of 2016, I underwent scapula fusion surgery in Baltimore, Maryland. During that surgery I had the privilege to donate muscle tissue for FSHD research.

The donation itself was relatively simple. The paperwork prior to the surgery was minimal and mainly taken care of by the doctor's office. The procedure itself was included as part of my overall surgery, and did not cause any further pain or loss of mobility.

Liam and Maureen Eye

Several months prior to the surgery, June Kinoshita from the FSH Society reached out to me to ask if I would be interested in donating muscle tissue taken from my surgery. It wasn't even a question in my mind. Without hesitation I committed to donating muscle.

I was diagnosed with FSHD in 2011. My son Liam, then only six years old, was also symptomatically diagnosed. Since that time I, like everyone else I have spoken to with FSHD, have been on a quest to learn everything I can about the disease and, most importantly, how to treat it, how to slow the symptoms, how to cure it.

As a mother, I have not encountered any obstacle as frustrating and upsetting as bringing my son to doctor after doctor, only to be told there is no treatment—there is no cure. My only choice is to sit idly by, watch and wait for progression, and pray that the wonderful doctors and scientists come up with a treatment before his disease progresses.

This is why I would not even call it a decision to donate; it was simply something I could finally do to be able to contribute to my son's health. In the past, I have donated money, which I know is of the utmost importance for the continuation of research.

Being able to donate tissue is something completely different. It was finally something positive I could provide from having this disease. The knowledge that perhaps the tissue from my body will help children not lose their smile, or the ability to raise their arms or keep them walking, fills me with such hope and gratitude.

This disease can take away so many physical things, but it can also make us stronger in ways we didn't know were possible. Helping others by donating tissue is a way to find strength in the midst of weakness. It is providing hope to our community. FSHWatch

TISSUE WANTED DEAD OR ALIVE!

Apologies for the macabre humor, but there's no way around this reality. FSH muscular dystrophy is a rare condition, and tissue from patients is the rarest and most precious resource for furthering our understanding of the disease. For some research, the muscle is best obtained from a recently deceased donor. But in other instances (such as growing muscle cells in a test tube), living tissue is required, and can be recovered through a biopsy or from a medically needed procedure such as scapular surgery.

For current research studies that need volunteers for biopsy samples, please visit "Find a Clinical Study" on our website: *https://www.fshsociety.org/find-a-clinical-study/.*

To become a tissue donor, you need to sign up in advance, similar to organ donation. Simply call NDRI at (800) 222-6374. Be sure to mention that you wish to join the "FSHD registry" when you call.

the disease.

"There is actual work being done to discover the drug. About 10 years ago, we didn't know what gene caused this disease," said Kyba. "That's our hope—that someday in the near future we'll have candidates that we take to clinical trials."

Brchan is currently volunteering to donate everything from blood samples to muscle biopsies and stem cells, anything she can to help Kyba's research. "I've participated in a few research studies over the years, but nothing that is this concerted effort that we see now internationally," said Brchan.

Two of Brchan's three children have FSHD, along with four of her eight grandchildren. From her view, the hope behind this research is for them. "I do have hope," she said. "I'm 72. The hope is not that I'm going to start running marathons or anything like that, but for my children and grandchildren." To watch the news clip, go to http://www.fox9.com/news/243798872-story. For more information about the research being done at the University of Minnesota, go to *https://www.mdcenter.umn.edu/.*

—SHIFT COMMUNICATIONS
Newton, Massachusetts

Ask the physical therapist (part 3)

Julie Hershberg answers your questions

The following is a transcript of a question-and-answer session, conducted over the FSH Society's Facebook page, with Julie Hershberg, PT DPT NCS. Hershberg is a physical therapist who is a Board Certified neurologic specialist. She practices at [re+active] physical therapy & wellness and is an instructor in the Doctor of Physical Therapy program at the University of Southern California.

Julie Hershberg (standing at left) guides and encourages a client.

Q: How can we know when we are overexerting ourselves? I cannot "feel the burn" until it's too late. Is this a normal response to exercise among FSHD patients? To preface my query: I have FSH muscular dystrophy but am what I call a "middle grounder" in the sense that I am not "normal" in appearance or walking, but don't yet require super heavy-duty artillery (i.e., full leg braces or chair) to move around. In my youth, I was a dancer and quite an active outdoors person (hiking, swimming, bungee, hang gliding, cycling). But as I have lost my abilities to move around, I also seem to have lost my sense of when too much is too much. My brain still thinks of my "old normative lifestyle," and my body just can't do it anymore. What cues do I need to pay attention to when working out so I do not overtax the affected muscles?

A: This is such a great question, and I think a common one for those with neuromuscular disorders. I have seen this commonly in my clinical practice as well—though it is not a universal problem for everyone with FSHD. I think this is especially hard for the very active person like yourself—we are so used to just pushing through for the ultimate goal instead of necessarily listening to our bodies (I am the same way).

I think all of us as we age need to generally improve our ability to be attuned to our bodies. Everyone experiences fatigue differently, so I cannot give a very specific way for you to read your body. But I generally recommend people to set goals based on time and check-in. For example, swimming for 10-20 minutes and resting for one to two minutes and doing a check-in with your body to see what you are feeling.

If the attunement part is difficult, I highly recommend some of the mindfulness practices to help. The Body Scan is a great way to work on awareness of the body. There is a short Body Scan meditation practice available through UCLA (and many others): *http://marc.ucla.edu/body.cfm?id=22*.

I don't recommend doing the Body Scan as you exercise, but doing it separately can help with overall attunement to and awareness of the body. Finally, I recommend having someone—a friend, trainer, PT—watch how you are exercising. There may be some ways you are moving that are not efficient and may set you up for more fatigue or injury, and they could provide you with recommendations to improve the way you move.

Q: I have slowly continuing loss in what I think are my paraspinal muscles. What specific exercises can I do to help me improve my "pitch forward" posture?

A: The paraspinal muscles are the muscles that run along either side of your spine and include either the superficial erector spinae muscle group or the deep multifidi muscles. There is a vast amount of research looking specifically at which exercises best isolate these muscle groups. For trunk and back stability, it has been indicated to train the deeper multifidi muscles. It is difficult to recommend one particular exercise without knowing your ability, but some of my favorite exercises include the bridge, exercises on hands and knees, and lying on your stomach and lifting your legs and/or back. I cannot overemphasize how important it is to have an individual evaluation to determine which of these types of exercises are best for you. It is easy to compensate and perform the exercises incorrectly and therefore injure yourself—so I recommend a PT evaluation to set up exercises specific for you.

The "pitch forward" posture can have several causes that I like to examine to determine the best intervention. Some of the common causes include tight hip flexors, hamstrings, or calves, and weakness in abdominals, hip extensors, legs, and back muscles. The position and the posture of the head and neck can also be implicated. Again, I recommend a thorough PT movement evaluation to determine the underlying problems and guide you to the best treatment.

Q: Would you explain myofascial release and where I can direct a PT to go for information and training? No one in my rural area is doing this.

A: Myofascial release is a special type of mas-

sage or soft-tissue mobilization. The most popular form has been developed and taught by physical therapist John F Barnes. However, there are other methods. Many PTs and massage therapists practice different types of myofascial release, and I do not subscribe to one particular method, but a common element is this idea of gentle, sustained pressure. A definition from the John Barnes website: "Myofascial release is defined as a safe and very effective hands-on technique that involves applying gentle sustained pressure into the myofascial connective tissue restrictions to eliminate pain and restore motion. This essential 'time element' has to do with the viscous flow and the piezoelectric phenomenon: a low load (gentle pressure) applied slowly will allow a viscoelastic medium (fascia) to elongate." You can find a therapist trained in his specific techniques at *https://www.myofascialrelease.com/find-a-therapist/*. He also has some resources in *Massage Magazine* on techniques: *http://www.massagemag.com/practice/technique-articles/*. Finally, there are a lot of videos on YouTube under myofascial techniques or release that may be a good resource for your PT.

Another thing to think about: Often, new graduates and even PT students have a good background in these techniques because they are newer. You may benefit from working with a student who is doing an internship at your local clinic.

Q: Sometimes, especially in my arms, I feel a "ping" like a guitar string breaking. Is this the striae of a muscle? Is it dying? What does it mean?

A: Well—this is an interesting question! Thank you for asking it! However, without seeing you, this is tough to know exactly what you may be experiencing in your arms. I have heard people describe "pings" to me in various circumstances that can be muscular twinges or tightness, nerve "tightness," or even joint related. A physical therapist evaluation would help to determine the cause.

In general, the muscle degeneration that occurs with FSHD does not occur with muscle fibers "dying" instantaneously, so my guess is that this in particular is not a sensation of a dying muscle fiber specifically. What the research shows is that muscle biopsies from people with FSHD show nonspecific myopathic changes, including rounding of muscle fibers, degenerating and regenerating fibers, increased internal nuclei, and, later in the disease course, increased fibrosis. I am not sure what these muscle fiber changes "feel" like to the person, but I often hear people say that they feel "tight" or "restricted" sometimes. Other people more predominantly notice the atrophy involved.

As far as the striae—the striations of muscle tissue are made by the repetitions of sarcomeres (made of the individual filaments of the muscles). These give the muscle the striated or striped appearance. FSH Watch

Ask Beth

HOW CAN I USE A PLANNED GIFT TO SUPPORT THE FSH SOCIETY?

Beth Johnston, Development Officer at the FSH Society

It's hard to think about a will or estate plan when you're a busy family consumed with day-to-day stresses and chauffeuring children around like an Uber driver.

Heck, my husband and I are just spring chickens—why do we need to think about a will?

As the AARP letters began to come in the mail (are you kidding me?), we realized it's probably time to think about these things.

We whole-heartedly believe in the FSH Society and its work, and have always given what was in our budget to do so. Now, we would like to ensure that the work at the Society to fight FSHD continues beyond our lifetime by leaving a legacy gift. How on earth do we do that?

First and foremost, speak to your attorney or financial/tax advisor(s). You'll need to discuss with them and decide what your goals are both during life and after you are gone. They can also help you to fully understand the tax implications of your decisions and decide which option or options best suit the needs of you and your family.

We have chosen to make a **bequest** to the FSH Society by making the Society a beneficiary in our will. It was an easy change for us to make. All we had to do was ask our attorney to add a simple "codicil" to our existing documents.

We explored other ways to leave a legacy gift as well, such as designating the FSH Society to receive a percentage of our **life insurance policy,** or make them a beneficiary of our **IRA** or **retirement account.** Since our financial planner handles both of these things for us, it would also be a simple change to make. Once we get the kids through college, we may revisit this option.

Please visit the FSH Society website at *https://www.fshsociety.org/planned-giving/* to learn more about all the different ways to leave a legacy gift. There are downloadable forms and information for you to start the discussion with your family and your advisors.

Jeff and I feel so good about this decision, and know we will be contributing to something that is so very important to us, long into the future.

Good luck with your planning!

New FSH Society grants

FSH Society awards $550,792 to six projects

by DANIEL PAUL PEREZ and JUNE KINOSHITA
FSH Society

The FSH Society, a world leader in combating facioscapulohumeral muscular dystrophy (FSHD), announced this spring that it has committed $550,792 in funding to six research projects that aim to break new ground in the search for a treatment and cure for FSHD. These grants follow the Society's record-breaking $1.36 million awarded for total research funding in 2016.

"These grants are a testament to the dedication of researchers within the FSHD community committed to understanding and solving how FSHD works through high-quality peer-reviewed research," said Daniel Perez, president, CEO & CSO of the FSH Society. "With these grants we look to further increase our understanding of the inner workings of FSHD and build upon our success in 2016, which would not have been possible without the generosity and sustained support of donors, Society management and staff, our Board members, and volunteers."

The Society's grants will come at a critically important time for the FSHD field this year, when other major funders of FSHD research are expected to invest significantly less than they have in the past. The National Institutes of Health may experience a 20 percent cut in its budget, and the Muscular Dystrophy Association has announced "a temporary pause in new grant funding for the RG mechanism for the 2017 Fall Review Cycle."

With these awards, the Society continues to significantly expand funding, and the search for treatments and a cure for FSHD, a disease that impacts more than 870,000 individuals worldwide. For full details and project summaries on the FSH Society's grant awards, please visit *http://www.fshsociety.org/funded-grants/*.

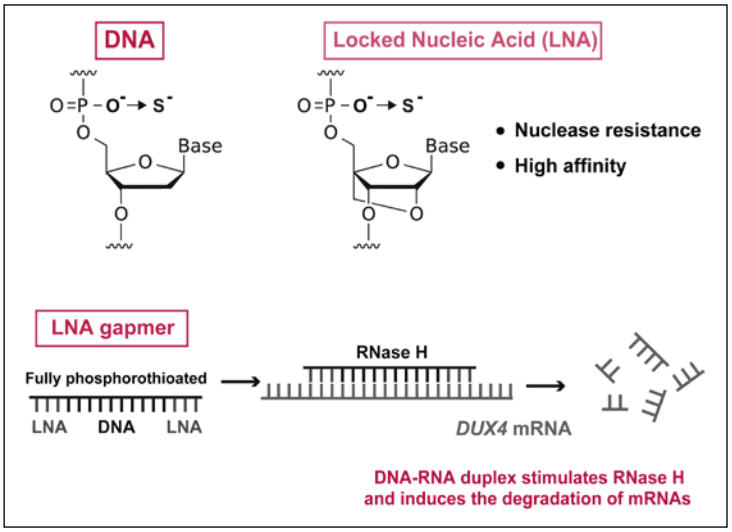
The following proposals submitted in August 2016 were reviewed in January and approved in February 2017:

▶ DEVELOPING LNA-BASED THERAPY FOR FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

Yi-Wen Chen, DVM PhD, Children's National Health System, Washington DC, and Toshifumi Yokota, PhD, University of Alberta Faculty of Medicine and Dentistry, Canada

$179,104 for two years

Summary: Yi-Wen Chen and Toshifumi Yokota are investigating one of the most promising antisense oligonucleotide (AON) compounds, called LNA (locked nucleic acid) gapmer, for its efficacy in reducing DUX4—the gene thought to cause FSHD—in cell culture and in a mouse model of FSHD. AONs are short, gene-like molecules that bind to and inactivate target genes. LNA gapmers are a "third-generation" AON designed to overcome some problems that made earlier AONs unsuitable for use as therapeutics. LNA gapmers are more stable, resistant to being degraded, and can penetrate the cell membrane and get into cell nuclei where the DUX4 gene resides. Dr. Yokota will continue to improve the anti-DUX4 LNA gapmers, testing them in FSHD cell lines, while Dr. Chen will test the safety and efficacy of the molecules in a mouse model of FSHD.



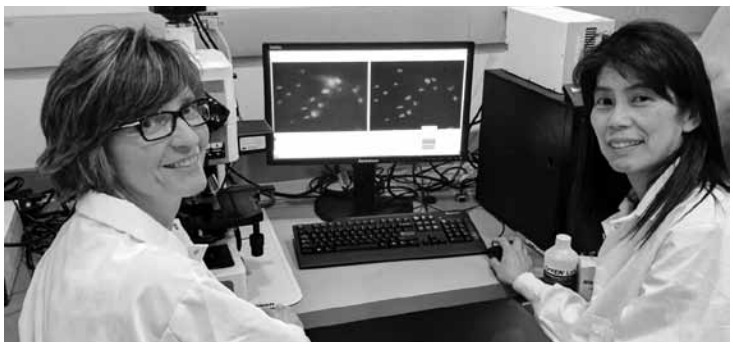
This diagram shows the chemical structure of an LNA gapmer (upper right) that makes it more resistant to degradation while having higher affinity to its target gene. The LNA-DNA complex stimulates the enzyme RNase H to degrade the DUX4 messenger RNA.

▶ INHIBITED PROTEIN TURNOVER AND TDP-43 AGGREGATION IN FSHD PATHOGENESIS

Sachiko Homma, PhD, and Jeffrey Miller, PhD, Boston University, Massachusetts

$58,920 for one year

Summary: Sachiko Homma and Jeffrey Miller discovered that DUX4-FL (full-length DUX4 protein) but not DUX4-S (shorter form of DUX4) inhibits the normal turnover of protein inside cells, and leads to abnormal expression of ubiquitin (involved in processing proteins for disposal) and nuclear aggregation of TDP-43 (TAR DNA-binding protein 43), one of the aggregation-prone RNA/DNA binding proteins previously associated with two other diseases, amyotrophic lateral sclerosis (ALS) and inclusion-body myositis (IBM). Homma has shown that TDP-43 aggregation and DUX4 toxicity can be lessened by treatments (e.g., forskolin or rolipram), which activate



Sachiko Homma (right) and Mary Lou Beermann (left) are examining images on the computer monitor of protein aggregations (bright spots) in DUX4-expressing human myogenic cells.

the proteasome. This result mechanistically links proteasome function with DUX4 cytotoxicity and TDP-43 aggregation. This research will work to identify mechanisms that underlie the DUX4-FL-induced dysregulation of proteostasis and protein aggregation as a step to understanding pathogenesis of FSHD and developing therapeutic strategies to treat the disease.

▶ ACTIVITY OF ESTROGEN ON FSHD MUSCLE DIFFERENTIATION

Fabiola Moretti, PhD, Institute of Cell Biology and Neurobiology National Research Council of Italy (CNR), Rome

$155,200 for two years

Summary: Recent data from this group showed that, in the lab dish, estrogens improve the ability of muscle precursor cells (myoblasts) derived from FSHD patients to mature without affecting cell proliferation or survival. Moretti's team aims to validate these results in vivo by measuring the activity of different estrogenic compounds on the regenerative potential of DUX4-expressing and FSHD-derived muscle precursor cells (perivascular cells, PVCs). The lab will confirm these data in live immunodeficient mice by analyzing the effect of estrogen on the ability of transplanted human muscle-derived cells (FSHD and unaffected) to participate in the regeneration of injured muscle in mice. This model will help with understanding in three areas: 1) the role of muscle differentiation defects in the pathophysiology of FSHD; 2) the ability of FSHD muscle-precursor cells to differentiate into skeletal muscle; and 3) the regenerative ability of FSHD muscle-precursor cells in mouse models relying on an innovative approach constituted by a hydrogel/growth factor scaffold.

▶ FSH SOCIETY NDRI TISSUE PROCUREMENT PROJECT

Tom Bell, MD PhD, and Denee Tidwell, National Disease Research Interchange, Philadelphia, Pennsylvania

$38,202 for one year, plus $26,500 tissue recovery costs

Summary: Tom Bell and Denee Tidwell are in the development and implementation phase of a resource to recover surgical and postmortem human biospecimens from individuals with FSHD and distribute them to approved investigators.

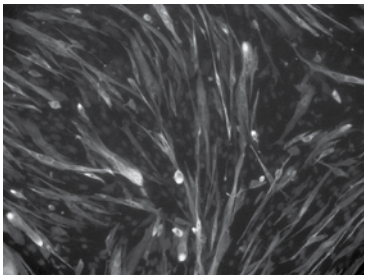
The FSH Society's brochure about the NDRI's tissue donation registry explains how to sign up.

▶ DYNAMIC MAPPING OF PERTURBED SIGNALING UNDERLYING FSHD

Peter Zammit, PhD, and Chris Banerji, PhD, King's College London, United Kingdom

$83,207.71 for one year

Summary: When muscle precursor cells (myoblasts) derived from FSHD patients differentiate, the resulting muscle fibers are often smaller and thinner than muscle fibers from unaffected individuals. To better understand this, Drs. Banerji and Zammit collected a huge dataset of changes in gene expression in muscle cells derived from FSHD patients. Using RNA-seq, they monitored and analyzed gene expression in cell culture during the differentiation of FSHD muscle cells from proliferating myoblasts through fusion into immature muscle fibers (myotubes) and maturation of muscle fibers. Their analysis has strongly implicated pathways involved in the generation of mitochondria (the energy-generating structures inside cells). By further analyzing modifiers of these pathways, Banerji and Zammit hope to improve understanding of the molecular defect in FSHD. Importantly, when these pathways controlling mitochondrial formation are activated by certain nutritional supplements in cell culture, the FSHD muscle fibers take on a more normal appearance. This focus on nutritional supplements is intended to rapidly translate findings to a clinical setting to maximize patient benefit.



Muscle fibers labeled with an antibody to reveal Myosin Heavy Chain, a protein important for muscle contraction. Such preparations show that muscle fibers formed from cells derived from FSHD patients are often thinner than those generated from the cells of unaffected individuals.

An additional ad hoc request for funding was approved in April 2017:

▶ PATIENTS' STRATIFICATION AND ELIGIBILITY IN MYOSTATIN CLINICAL TRIALS

Julie Dumonceaux PhD, University College London, Institute of Child Health, United Kingdom

$9,659.43 for one year

Julie Dumonceaux

Summary: Muscle wasting is one of the biggest challenges in neuromuscular disorders. Myostatin being a negative regulator of muscle mass, blocking its activity has been seen as a promising tool to counterbalance this muscle wasting. At least six anti-myostatin molecules have been developed. However, so far, the clinical trials have been disappointing. These results are surprising, since during the Phase 1 trials in healthy volunteers, an improvement of muscle mass was observed. Dumonceaux will be investigating the role of several effectors of the myostatin pathway. The preliminary data indicate that the expression of these effectors in individual patients might be useful to predict whether a patient will be more (or less) responsive to anti-myostatin therapy. The funding provided by the FSH Society will help us to finish performing the experiments which may be of importance for neuromuscular patients—and FSHD patients, in particular—and may deeply impact future and current clinical trials using myostatin inhibitors. FSH Watch

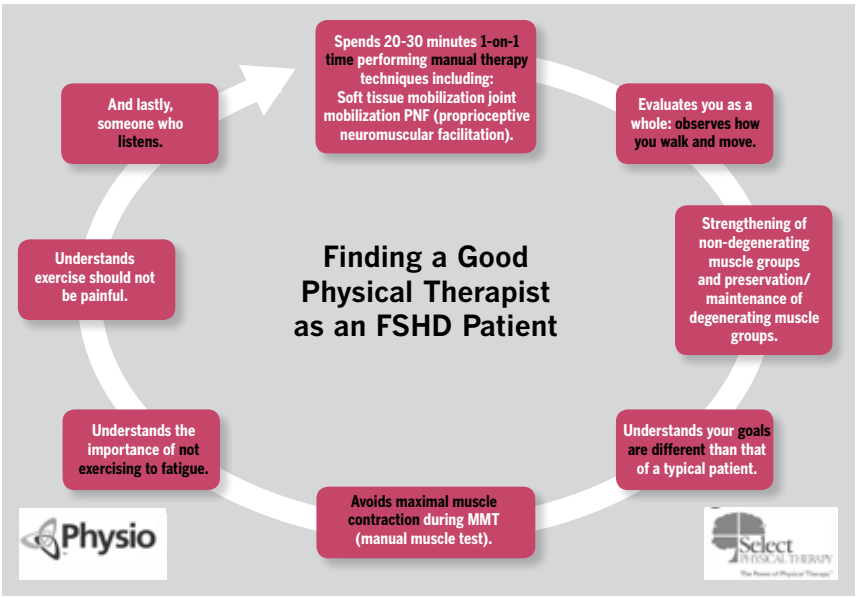
San Diego March meeting

Valuable tips on physical therapy

by AMY BEKIER, FSH SOCIETY BOARD OF DIRECTORS
San Diego, California

The March 4, 2017, San Diego FSH Society Member Support Group meeting was well attended by 23 enthusiastic patients and family members. Renee Stetkevich, PT OT DPS, of Physiotherapy Associates at the Mesa College Drive facility described proper hands-on manipulation and physical therapy utilizing muscle isolation and exercises for patients' healthier muscles to help them maintain function without injury.

Families attended from as far away as Baja, Mexico, Apple Valley, and Huntington Beach, with a bounty of questions and positive comments. The takeaway was that successful physical therapy and exercise very much depend upon the individual therapist who is working with the patient and that therapist's willingness to listen and adapt, not only to each patient, but to each session as that patient's condition continues to change and progress. FSH Watch



What to look for in a good physical therapist.

A Segway for mobility

INSTALLING A SEAT DID THE TRICK

The first time I ever saw a Segway I immediately recognized it as something that could possibly help my mobility. My FSHD had progressed to the point where I was having difficulty walking.

At my first opportunity I went to a Segway dealership to try one. It was an amazing machine, but I was disappointed that I couldn't ride it very far without getting tired due to the fact that it is designed to be operated only while standing. If only it had a seat!

I began to think about how I could make a seat that I could adapt to a Segway. I tried finding a local person or company that could help me fabricate one but without any success.

One day a thought came into my head: Maybe someone already has created a seat. I googled "seat for Segway" and was surprised to find three or four different seats. After some research and phone calls, I decided to purchase a Segway and order one of the seats.

The seat I ordered turned out to be the correct choice. I found that the way it works is

Tom Thompson on his Segway, with his wife Barbara (left) and FSH Society executive director June Kinoshita (right).

that it hacks the Segway control system, causing it to think a rider is standing on it. Over the next few months I was able to develop a system that allowed me to use the Segway safely.

I have now used my Segway for over 10 years, and it has allowed me to do things that I never would have been able to do otherwise. A Segway has much more maneuverability and versatility than a scooter or wheelchair, and the most amazing thing about it is the reaction it creates in those who see me on it. It diminishes the effects of my disability to a great extent.

I must caution anyone who may be interested to understand that there are some dangers in using a Segway in this way. The Segway company does not build seats or recommend that a Segway be used with one. Many professional medical personnel will see me riding it and say something like "That looks dangerous," but also many have reacted with "Wow! What a great idea!"

I choose to use it the way I do, knowing the potential hazards, because it is functional, exhilarating, and liberating in much the same way as riding a motorcycle or flying an airplane would be.

—TOM THOMPSON
Charlotte, North Carolina

Editor's note: The FSH Society does not endorse or recommend any specific inventions. Readers who choose to try these ideas out do so at their own risk.

Gimpy girl goes birding

A 2017 mid-Atlantic, physically accessible birding "Big Year"

by DEB CALHOUN
Frederick County, Maryland

Deb Calhoun

Midsummer last year, I became determined to fight back against FSH muscular dystrophy. Most of my friends and family know I have FSHD. This isn't a new diagnosis, and living fully with this disease has kept me determined and also sensitive to the challenges everyone faces throughout a lifetime. As my FSHD progressed rapidly the last few years, I allowed my world to become too small. I wanted to find ways of living a bit more boldly and pursuing (at least!) one more great passion.

I've been passionate about birds and birding since childhood. However, in recent years, birding has become an increasingly important part of my day and a constant source of great joy. Drawing inspiration from fellow birders, I decided to challenge myself to a 2017 mid-Atlantic, physically accessible birding "Big Year."

For those unfamiliar with the term, a birding "Big Year" is an informal competition birders have among themselves to see who can identify the most bird species in a specific geographic area in a calendar year.

My Big Year became a personal challenge. I wanted to make at least two birding trips per month outside of our family property—a tough challenge, since we have so many amazing birds right here at home! Of course, I wanted to see as many birds as possible. And as I set my goals for the year, I wondered if I could reach 100 different bird species.

I also wanted to make this Big Year about something bigger than me, so I set another goal of documenting physically accessible birding locations throughout the mid-Atlantic region, in the hopes that this information will benefit fellow birders (or anyone who loves the outdoors) who have some of the same physical challenges I do. Right now, whenever I am birding, I always have to have a cane or a walker for support, and sometimes a scooter.

I also wanted to raise awareness about FSHD and, for me—the most difficult goal—I wanted to seek donations for the FSH Society to fund ongoing research in the fight against this disease.

So far, I've found this experience amazing and am enjoying this challenge more than words can convey. In the first two months of the year alone, I completed six birding adventures and observed 104 different bird species. This achievement motivated me to set even more ambitious goals for the future!

I've joined a wonderful local birding club and have been encouraged by all the positive responses and support I've received for my goals. I've reached out to friends and family, those who have expressed any sort of interest in this journey I'm taking, or those who I just think love me enough to not be offended by my asking them to financially support a cause so personally important to me, and I've asked them to please donate to the FSH Society. I hope that part of my story will inspire them to support the Society.

If you'd like to learn more, you can follow my blog at *gimpygirlgoesbirding.com*. I can't wait to see where this year takes me. FSH Watch

Volunteers needed

OPPORTUNITY TO HELP WITH FSHD RESEARCH!

The University of Rochester is seeking volunteers for their study "Bioresources Core: Resources for FSHD Research and Clinical Trials." Recent genetic advances in the understanding of facioscapulohumeral muscular dystrophy (FSHD) have identified potential future targets for therapy. Consequently, it is important that we have appropriate tools in place for use in FSHD clinical trials.

Purpose: This study will help gain experience using multiple FSHD-related outcome measures for clinical trials via a blood sample only, serum sample only, or via a questionnaire, muscle strength and function testing, physical examination, blood testing, and skin and muscle biopsies.

Details: We are seeking one hundred fifty (150) subjects to participate in this research study. We will require subjects with FSHD1 and FSHD2, as well as control subjects who do not have FSHD or who are at risk of inheriting FSHD due to a positive family history. Subjects will be required to make one visit lasting approximately one to five hours, depending on the study activities in which you are eligible to participate. Subjects who are between the ages of 18 to 75 and are able to walk independently may qualify for this study. Subjects may be compensated $35.00 or $150.00 for their participation, depending on the study activities, as well as be reimbursed for reasonable transportation costs.

Location: University of Rochester Medical Center, 601 Elmwood Avenue, Rochester, NY 14642

Contact: If you're interested in participating in this study, please call research coordinator Leann Lewis at (585) 275-7680 or see our website for more details *(https://www.fshsociety.org/find-a-clinical-trial/)*. The IRB number is 59324.

Clinical trial updates

From Acceleron and aTyr

by JUNE KINOSHITA
FSH Society

The FSH Society has a long history of partnering with biotech and pharmaceutical companies to facilitate recruitment of patients and families for focus groups and provide patient input to clinical outcome measures and participation in clinical trials. The Society also assists companies by providing connections, insights, and scientific information in the research, therapeutic, and clinical areas. In response to the high degree of interest in the ACE-083 trial, Acceleron has worked with the FSH Society to provide an FAQ, available on the FSH Society website. We thank Acceleron for the company's commitment to patient education.

ACCELERON

Acceleron Pharma has received a tremendous amount of interest in the Phase 2 study of its investigational drug, ACE-083, in patients with facioscapulohumeral muscular dystrophy (FSHD). In response to the robust interest in this clinical trial, we wanted to provide information for how best to inquire about participating.

The clinical trial consists of two parts. Part 1 of the study will include up to 36 patients at multiple sites in the United States. Part 2 will include up to 40 additional patients at sites in the United States, Canada, and Spain. There are currently twelve (12) U.S. sites and two (2) in Canada actively enrolling patients. The clinical trial listing at *www.clinicaltrials.gov,* with study identifier NCT02927080, will be updated when new sites are added and with information regarding whether or not each site is actively enrolling new patients. Please check *www.clinicaltrials.gov* to see if a site near you is enrolling patients in this clinical trial.

Please understand that, like most Phase 2 clinical studies, there is a limited number of patients to be enrolled, and therefore not every interested patient will be able to participate in this particular study. If you believe that you meet the eligibility criteria, which can be found on *www.clinicaltrials.gov,* and want to get involved in the study, please contact the site nearest to you directly. The individual study sites are responsible for all activities related to the execution of the study, including patient selection and administering therapy and tests. You should not contact Acceleron regarding eligibility and participation in the study, as the company is not allowed to interact directly with patients on these matters.

To learn more about the trial and to find contact information for the site nearest to you, please visit *www.clinicaltrials.gov.* In addition, a list of Frequently Asked Questions (FAQ) and answers is provided at *www.fshsociety.org/2017/04/ace083faq/.*

aTyr Pharma

Results from aTyr trial in early-onset FSHD

aTyr Pharma, Inc., a biotherapeutics company engaged in the discovery and development of Physiocrine-based therapeutics to address severe, rare diseases, announced promising clinical results from its Phase 1b/2 003 trial assessing the safety and potential activity of Resolaris™ in patients with early-onset facioscapulohumeral muscular dystrophy (FSHD).

- Sixty-three percent of patients (five of eight) had increases from baseline in their Manual Muscle Test (MMT), a validated assessment tool that measures muscle strength, with a mean change from baseline of +3.8 percent.
- Sixty-seven percent of patients measured (four of six) had improvement in

Ways to engage

SIGN UP FOR EMAIL NEWS!

Get our email alerts for the latest news, event notices, clinical trial info, and more. Sign up on our website by clicking "JOIN". If you are certain you are on our email list, please check your spam or junk folder.

GET SOCIAL!

Find our Facebook, Twitter and Yahoo! Groups by visiting *www.fshsociety.org* and clicking on the logos in the right-hand margin. Our online communities are great sources of news, advice, and social support. The FSH Society Yahoo! Groups forum, online since the 1990s, has tens of thousands of searchable posts. Bookmark these pages and come back often. Use your account privacy settings to limit who can see your posts.

HAVE YOU MADE A GIFT TO THE SOCIETY IN 2017?

Thanks to the support from members like you, the FSH Society is a world leader in combating muscular dystrophy. Your donations are tax deductible, and they make a real difference. Please send your gift in the enclosed envelope. Or contribute online at *www.fshsociety.org.* Thank you!

COMMIT TO THE FUTURE

Consider taking your gift to the next level by making a planned gift. A bequest or endowed fund helps to ensure that the FSH Society has the long-term support to sustain its mission. Questions? Please contact June Kinoshita at (781) 301-6649 or *june.kinoshita@fshsociety.org.* Always check with your advisors when making a change in your will or estate plans, and learn how current tax laws and other legislation may affect your plans.

their Individualized Neuromuscular Quality of Life (INQoL) score, a validated, patient-reported outcome measuring a patient's level of disease burden. On average, patients did not have a worsening of their disease burden as measured by INQoL.

"We are developing Resolaris, derived from a naturally occurring protein that we believe acts on a newly discovered immunological pathway to potentially treat patients with rare muscular dystrophies characterized by immune cell imbalance," said Sanjay Shukla, MD MS, chief medical officer of aTyr Pharma. "These results are important, as they reinforce previous clinical results (in adult FSHD and adult LGMD2B) with Resolaris in a younger patient population, with a potentially more aggressive progression of disease. We look forward to the advancement of Resolaris in the clinic in rare muscular dystrophies upon the identification of a pharmacodynamic assay and the successful execution of our pipeline partnering efforts."

For further details, visit our website at *www.fshsociety.org/2017/04/atyr-early-onset-fshd-trial/*. FSH Watch

WORLD FSHD DAY 2017

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The campaign also received strong engagement on Twitter:

- Total posts using either/both #WorldFSHDDay or @FSHSociety: 674
- Total Twitter users posting with either/both #WorldFSHDDay or #FSHSociety: 319
- Reach: 5,384,025
- Impressions: 10,632,475

In Boston, the landmark Zakim Bridge was illuminated orange in honor of the day. The date coincided with the visit of the Tall Ships to Boston Harbor, so the bridge was seen by thousands, including a dozen FSH Society guests who were treated by Shake-A-Leg Miami to a cruise aboard the accessible catamaran *Impossible Dream*.

Last year the Massachusetts legislature officially named June 20 FSHD Awareness Day. This year, the governor of Maryland issued a proclamation recognizing World FSHD Day. Next year, we'd like to shoot for proclamations in all 50 states. Let us know if you'd like to help.

Notable influencers participating in #WorldFSHDDay included Debby Ryan, Only in Boston, Acceleron Pharma, Muscular Dystrophy UK, Massachusetts Department of Transportation, and MDA News. FSH Watch

CLINICAL TRIAL RESEARCH NETWORK RECEIVES MAJOR AWARD FROM NIH

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released upon reaching annual milestones. The principal investigators are Rabi Tawil, MD, of the University of Rochester, and Jeffrey Statland, MD, of the University of Kansas.

"The support of the FSH Society and a private donor helped us establish the infrastructure necessary to propose such a study, and the continuing support will be essential not just for this study, but for future efforts toward creating new outcome measures, developing new therapies, and training the next generation of FSHD researchers," said Statland.

The study funded under the UO1 has the overall aim of speeding up drug development for facioscapulohumeral muscular dystrophy (FSHD). There are many drug companies actively working toward therapies for FSHD, but meetings with industry, FSHD researchers, and advocacy groups like the FSH Society have identified several gaps in the tools and infrastructure needed for currently planned and future clinical trials to test potential treatments.

The newly funded study aims to develop two novel "clinical outcome assessments" (COAs). The first is a composite functional outcome measure (FSH-COM), and the second is a method to measure disease-related changes in skeletal muscle using electrical impedance myography (EIM). Previous research funded by the FSH Society has shown these to be promising tools. They now need to be proven to work reliably across different clinical sites before they can be approved as validated measures to use in FSHD clinical trials.

In addition, the UO1-funded project will help researchers better understand how genetic and demographic features are related to disease progression. This is important to enable a researcher to identify a subset of patients who are likely to respond in a way that can be measured by the tools used over the timespan of a given trial. For example, patients who are likely to lose muscle strength in their legs within the next 18 months would be suitable candidates for a two-year trial that is using a walking test as a primary outcome measure.

To achieve these aims, the CTRN will carry out a multicenter, prospective, 18-month study involving 150 volunteers. The data from this study will be made available for any investigator or company pursuing treatments for patients with FSHD.

"Each advance that we make," Statland noted, "is a collaboration among people with FSHD, advocacy groups like the FSH Society, academic researchers, and industry." FSH Watch

FY2017 fundraising report card

Major gifts lift us to new heights

by **JUNE KINOSHITA**
FSH Society

This spring, the FSH Society was notified of two major gifts that will have far-reaching impact on our ability to fund important research. Board chairman William R. Lewis Sr. and his wife Duncan announced a gift of $1 million, most of which will be added to the Lewis Family Endowment, where it will generate significant annual revenue that will be invested in research grants for many years to come. We are immensely grateful to the Lewis family for establishing this sustainable source of funding for future FSHD research.

The Society also received a three-year grant from the Sylvia and Leonard Marx Foundation in the amount of $120,000 annually, or $360,000 in total, to support two postdoctoral fellowships per year. Our fellowship program has the most enduring impact on the FSHD research community because these grants invest in new talent. The Society's fellowships have launched the careers of many of today's research leaders. We thank the foundation for its generous, visionary support. FSH Watch

Duncan and William R. Lewis

FSH MUSCULAR DYSTROPHY KNOWS NO BOUNDARIES, AND NEITHER DOES OUR EDUCATIONAL BROCHURE!

The FSH Society's authoritative "About FSHD" brochure is now available in Spanish, in a downloadable version. We thank Manuel Gomez and Albert Rosa for their generous assistance. Download by visiting our website: *https://www.fshsociety.org/resources/*

BRINGING FSHD CONVERSATIONS TO OUR MEMBERS EVERYWHERE

The FSH Society has launched a monthly Internet radio talk show, which airs on the last Wednesday of each month at 9 p.m. EST/8 p.m. CST at *www.blogtalkradio.com/fshsociety.* Host Tim Hollenback interviews guests and invites questions from the listening audience. Past guests include FSH Society executive director June Kinoshita, Team FSHD Cycling leader George Pollock, and Brooklyn Nets announcer and FSHD advocate Chris Carrino.

FSH SOCIETY MEMBERS ENJOY AN ACCESSIBLE BOAT OUTING

Miami members of the FSH Society gathered on May 7, 2017, at Shake-A-Leg, a nonprofit dedicated to providing boating experiences to people of all abilities. The group enjoyed a scenic cruise on Biscayne Bay, courtesy of Shake-A-Leg. Attendees expressed great interest in mentoring young people to show them it's possible to enjoy a full life with physical disabilities.

HONORING THE MEMORY OF COSIE LAURELLO

On June 10, 2017, dozens of runners turned out for the Cosie Laurello Memorial 10K and 5K run and 1K Fun Run/Walk. They traversed a challenging course that wove through a forest at Fischer's Pine Lake in Jefferson, Ohio. An excellent time was had by all. Four generations of the Laurello family gathered for the occasion!