FSHD Advocate

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FSHD SOCIETY
LIGHTING THE WAY TO A CURE

GLOBAL LEADERSHIP SPECIAL REPORT

UNITE FOR A CURE

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FSHD Advocate

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CEO Letter

A Global Problem Demands a Global Solution

"You must change with the times unless you are big enough to change the times." — ANONYMOUS

When I ponder the scale of the tasks before us, I think of several things.

First, I think of you – our families – and the millions that live with FSHD every day. I think of the fact that there is currently no treatment to stop the degradation of muscle. I think of the challenges of FSHD, such as the unpredictability of disease progression, which make designing clinical trials enormously problematic. This is a global problem that requires us to "change with the times."

But I also think of the initiatives that, together, we are putting into motion. While no one of us alone can change the world, the Society is bringing all stakeholders and resources to the table to focus efforts on one goal: delivering disease-modifying therapies to our families by 2025.

The stories in this issue describe some of the initiatives we have launched, the leadership we're providing, and the collaborations we are forming – all aimed at achieving a global solution to a global problem.

For instance, along with Friends of FSH Research, the Chris Carrino Foundation, and the Muscular Dystrophy Association, the Society hosted the first-ever Industry Collaborative on Drug Development for FSHD in March. Eight biopharmaceutical companies, members of the FDA and NIH, and leading researchers spent the day examining the challenges of taking promising therapeutics through the clinical trial and approval process. One pharma executive noted, "You certainly had the right people in the room." To conclude the meeting, our chief science officer Jamshid Arjomand outlined the next steps, including the formation of an industry coalition led by the FSHD Society to overcome the challenges over the next three years.

In June, the FSHD Society hosted the International Research Congress (IRC) in Marseille, France. Nearly 200 of the world's leading scientists, clinicians, pharmaceutical partners, and global patient group leaders (representing 11 countries) convened to discuss the latest in research advances and ways to "go further faster" by working together. Representing the largest gathering of its kind, this congress served as a catalyst to accelerate the development of solutions for our families.

Mark A. Stone

I want to highlight one more example: our amazing national chapter program. As of this writing, we have 24 chapters providing a local presence, yet facilitating our global impact. Through educational and community-building meetings, our dedicated volunteer chapter directors, along with the hands and hearts of local volunteers, are ensuring that no one has to make this journey alone, and we are stronger together. Our chapters also offer an outlet to serve through fundraising events that raise awareness, build community, and procure necessary funding for programs such as our Therapeutic Accelerator Initiative.

I believe you're beginning to get the picture. With the FSHD Society's work and leadership, all of us – families, companies, regulatory agencies, researchers, and clinicians from around the world – do not have to settle for "changing with the times," because collectively we are "big enough to change the times."

Mark

Mark Stone
President and CEO
FSHD Society

UNITE FOR A CURE

BY JUNE KINOSHITA, FSHD SOCIETY

Researchers and advocates from around the world gathered in Marseille this summer.

Intensive discussions occurred at the Industry Collaborative Workshop in March.

Sheila Hawkins of Muscular Dystrophy UK asks a q uestion at the International Patient Advocacy Summit.

The International Research Congress is the premier platform for sharing the latest data.

FSH muscular dystrophy has been found in every part of the world. It wouldn't surprise us to learn that someone on Antarctica has it, given the number of accomplished scientists and explorers we have in our community! FSHD is everywhere, and so the FSHD Society must be, too, working with patients and families around the globe to speak with "one voice" that will be heard, loud and clear, by all who have the power and resources to bring effective treatments to the market.

This is an imperative, not only because we seek to empower patients to achieve well-being wherever they live, but also because, given the relative rarity of the condition, clinical trials will have to draw on international communities in order to recruit the volunteers they need. In this issue of *FSHD Advocate*, we report on how the Society is accelerating treatment discovery and drug development through our global leadership in research, advocacy, and engagement with industry and drug regulators.

Katherine Mathews, MD, describes FSHD symptoms to biopharma and FDA representatives at the Industry Collaborative Workshop.

Industry Collaborative on FSHD Drug Development

Preparing the way for clinical trial success

BY JAMSHID ARJOMAND, PhD, FSHD SOCIETY

Getting a new drug approved by the Food and Drug Administration is a tall challenge, one that requires convincing regulators that the data on the drug meet the highest scientific standards. The ideal time to begin persuading the FDA on the merits of a clinical trial design is well *before* the trial is launched.

This is why, on March 12 of this year, the FSHD Society convened a landmark meeting with FDA representatives to discuss clinical trial readiness in FSHD. The meeting was moderated by John Porter, PhD, former program director for neuromuscular disease at the National Institute of Neurological Disorders and Stroke. Along with the FDA, this meeting brought together companies developing FSHD treatments and academic leaders forging the standards for clinical trial outcomes.

The meeting opened with a powerful testimonial by Lexi Papas, who provided her personal account of living with FSHD (viewable on YouTube). Katherine Mathews, MD, of the University of Iowa followed up with a review of the pathogenic mechanisms and clinical manifestations of FSHD.

Stephen J. Tapscott, MD PhD, of the Fred Hutchinson Cancer Research Center and Angela Cacace, PhD, of Arvinas gave academic and industry views, respectively, on FSHD as a "tractable" condition. This means that FSHD is well enough understood biologically to identify possible treatment strategies, has sensitive tools to monitor disease progression, and has sufficient patient volunteers for clinical trials in order for the pharmaceutical industry to forge ahead.

In the next sessions, the speakers provided a detailed synopsis on the state of progress in their areas of expertise. Their presentations were followed by a discussion with industry and FDA scientists to determine what was still needed to move therapeutics forward.

Rabi Tawil, MD, from the University of Rochester described the status of patient registries in the US. These long-term studies track the "natural history," or natural course, of symptom progression and provide a fundamental understanding of FSHD and its impact on daily living. These studies provide insights on how to develop methods to measure whether a drug can dampen, halt, or reverse the course of FSHD.

The US FSHD registry has about 900 participants and has been collecting data for 15 years. The registry has already generated several reliable tests highlighting the progression and impact of FSHD. However, there is limited information on early and milder stages of the disease. Greater participation in studies by early and mildly affected patients could help better define earlier changes and improve upon methods to measure them, so that clinical trials can be designed for the earliest disease stages. (For information on joining, contact *study@fshsociety.org*.)

Peter Jones, PhD, from the University of Nevada, Reno, reviewed the status of molecular markers in FSHD. These include genetic testing, as well as tests that can shed light on disease activity (also known as biomarkers). Biomarker tests performed on muscle biopsies are currently being validated for regulatory approval. Ideally, tests that can be done on blood samples rather than on muscle would be preferable, as they would be much easier on patients.

To advance enrollment in clinical trials, it will be imperative to have a more efficient and reliable genetic test so that all patients wishing to volunteer for studies can have their diagnosis confirmed genetically. Such a test would also help pharmaceutical companies by providing insight on the

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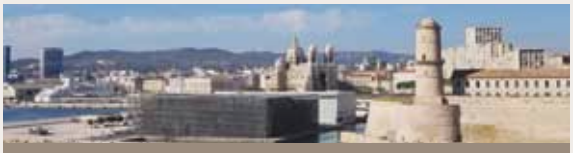
2019 FSHD International Research Congress

A growing presence for clinical research and disease triggers

BY JAMSHID ARJOMAND, PhD, AND JUNE KINOSHITA, FSHD SOCIETY

At the 26th annual FSHD International Research Congress (IRC) this June 19-20, held in a 19th-century palace overlooking the harbor of Marseille, the 180 attendees were treated to a spectacular panorama of France's second-largest city. From the massive 17th-century stone ramparts of Fort St. Jean to the cutting-edge architecture of the Museum of European and Mediterranean Civilisations, the view encompassed the ancient and the modern in this bustling Mediterranean port.

Similarly, the congress itself spanned the past and future of the FSHD field. In the first keynote, Michel Fardeau, the "father of muscle research in France" who founded what became the Institute of Myology in Paris, reflected on the historic work of Louis Landouzy and Joseph Dejerine, the neurologists who identified the hereditary muscle condition that was named for them (Landouzy-Dejerine disease) and came to be called facioscapulohumeral muscular dystrophy.



The congress itself spanned the past and future of the FSHD field.

On the second day, keynote speaker Brad Cairns of the University of Utah School of Medicine described ground-breaking findings by his group and others of DUX4's role as a "zygotic activator" gene that switches on the genetic program that launches the transformation of a four-cell zygote into an embryo and eventually a fully formed human being. DUX4 expression in adult skeletal muscle is implicated in the damage to muscle in FSHD, but the gene's role in normal development is still being worked out; the connection, if any, between DUX4's developmental and FSHD roles remains a mystery for future investigation.

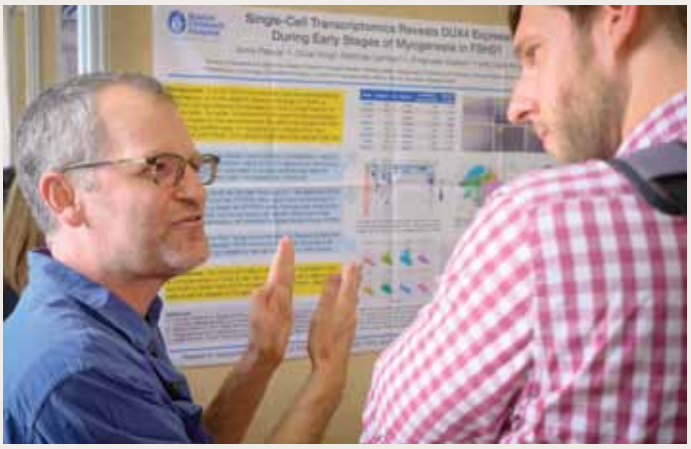
Cairns described still-unpublished research indicating that in human development, DUX4 is switched on by the cell's response to DNA damage that is "common" throughout the genome during fertilization, he said. Untangling the cause and effect of DUX4 activity during development could yield insights into the gene's role in FSHD and new strategies to treat the condition.

One notable theme of this year's IRC was the number of talks that discussed nongenetic triggers of FSHD, including hormones, oxidative stress, and, in particular, the immune response – something that just a few years ago was not considered to play a significant role. Talks given by Stephen Tapscott, Joel Chamberlain, and Anna Panamarova, among others, discussed evidence for the immune response in driving FSHD.

One intriguing manifestation of autoimmune mechanisms at work in FSHD was suggested by Sabrina Sacconi, MD, of Nice University Hospital. She reported that FSHD patients had an increased incidence of skin conditions such as atopic dermatitis, actinic keratosis, seborrheic dermatitis, and rosacea. Utilizing the French patient registry and social media, her team collected photos of 88 patients and analyzed them for skin conditions. "I initially doubted that there was a connection, but it seems to be prevalent," Sacconi said. The prevalence of skin conditions among FSHD1 patients was 16 percent, while among patients with FSHD2 and FSHD1 combined with FSHD2, it was closer to 60 percent. She noted that the D4Z4-2.5 mouse model of FSHD develops skin lesions and that autoimmune mechanisms may be associated with the abnormal proliferation of keratinocytes (a type of skin cell).

Not surprisingly, there was keen interest in the talks about treatments that are getting closer to the clinic. Jeffrey Statland of the University of Kansas spoke about Acceleron's ACE-083 clinical trial and reported that the drug, which is given through multiple muscle injections every three weeks, is "well tolerated over three months." MRI data on the percentage of fat in muscle (a measurement of muscle loss) showed a linear correlation with muscle strength, function tests, and patient reports (collected through the FSHD-HI questionnaire). The placebo-controlled Phase 2b trial has recruited all of the patients needed, and the collection of data from these patients is expected to be completed over this summer.

Researchers from Fulcrum Therapeutics, which is launching a Phase 2b trial of losmapimod this summer, presented



Clockwise from upper left: FSHD Society CEO Mark Stone welcomes banquet attendees. At the poster session, Oliver King, PhD, from UMass Medical School, explains his data. The audience listens closely to a research talk. Angela Roch (right) translates for French patient advocate Vincent Tronel.

multiple talks and posters that described the data that led the company to select the drug as its lead candidate. The drug inhibits p38 mitogen-activated protein kinase, which is involved in cells' response to stress. Fulcrum's studies showed that losmapimod reduced DUX4 protein as well as the genes that are activated by DUX4, and reduced cell death. At the same time, the drug has minimal negative effects on the formation of muscle tissue from muscle stem cells.

In separate talks, Robert Bloch of the University of Maryland and Fran Sverdrup at St. Louis University presented data supporting the efficacy of p38 inhibitors in knocking down DUX4, providing independent validation of Fulcrum's findings.

Joris De Maeyer of Facio Therapies presented a high-content screening platform that identified casein kinase I (CK1) as a novel drug target. An inhibitor of CK1 was demonstrated to suppress DUX4 expression in FSHD myotubes and in a xenograft model of FSHD. Others, including Lindsay Wallace of Nationwide Children's Hospital and Rika Maruyama of the University of Alberta, described methods for silencing DUX4 using various antisense approaches.

At this year's IRC, for the first time, a prize was given for best poster. The program committee reviewed the 35 poster talks and awarded the prize to Gholamhossein Amini Chermahini, Afrooz Rashnonejad, MD, and Scott Q. Harper, PhD, from Nationwide Children's Hospital in Columbus, Ohio. The researchers had invented a super-sensitive method for detecting DUX4 messenger RNA (mRNA) in muscle tissue. They noted that this task was "challenging, due to the low level of DUX4 expression." Their technique, called an RNAscope assay, "was highly sensitive for tracking reductions in DUX4 mRNA following treatment with our therapeutic mi405 microRNA, suggesting that RNAscope-based DUX4 expression assays could be developed as a prospective outcome measure in therapy trials."

Also, for the first time this year, the congress was opened by patients. Pierre Laurian and Marie-Martine Fleck spoke movingly about the lifelong impact of their condition. Afterward, congress attendees responding to a survey said this was one of the highlights of the meeting, a timely and powerful reminder, as one attendee said, that "for every researcher, whether they are working with cells or with patients, our main goal is to improve the life of the patients."

PHOTO: JEAN MARIE HURON

After a full day of getting to know one another and beginning discussions about how to advance our common goals, attendees posed for this historic photograph.

International FSHD Patient Advocacy Summit

Marseille meeting convenes delegates from 11 nations

BY SHEILA HAWKINS, TRUSTEE, MUSCULAR DYSTROPHY UK

FSH muscular dystrophy affects people of every nation and ethnicity, and the effort to develop treatments will undoubtedly require the participation of patients from multiple countries. With international clinical trials already under way and more on the horizon, it was more than timely this June 18 when leaders from 13 organizations and 11 nations gathered in Marseille for the first-ever International FSHD Patient Advocacy Summit to discuss global collaboration and coordination.

The summit was sponsored by the FSHD Society and jointly organized with FSHD Europe. It was attended by 38 delegates from Brazil, China, France, Germany, Israel, Italy, Japan, the Netherlands, Spain, the UK, and the US. More than half of the delegates were patients and family members, some of whom are also doctors or researchers in the FSHD field, and the others were scientists or representatives of the FSHD Society.

It was important for the attendees to make connections, so we got to talking to one another early in the day. Hearing about patient groups in the different countries was fascinating. It was sobering to learn that in some countries genetic testing was either unavailable or so expensive that few people could afford it.

We heard about the latest research from Jeffrey Statland, Doris Leung, and Scott Harper, and looked at how we could develop strategies for patient engagement, working with scientists and industry, and fundraising.

We also discussed the concept of a global "contact registry" or patient database so that people around the world could be educated about FSHD research studies and drug trials, and be contacted when a study is enrolling patients in specific geographic regions. A key benefit of such a database is that it enables the advocacy groups to work more effectively with companies to coordinate study recruitment campaigns globally.

One issue that will need to be solved is how such a contact registry would comply with Europe's General Data Protection Regulation, which governs how individuals consent to provide and share their personal information. Even

From left to right: Listening intently are delegates from Brazil, Israel, and China.

Annette Menheere from the Netherlands facilitates a workshop discussion.

when this is resolved, some may feel they already receive enough information to participate in trials in their own countries, and might not see the need to join a global list.

What was most exciting about this event was the opportunity to meet people from all over the world with FSHD, to see that although their symptoms might be similar, the healthcare systems and cultural attitudes toward disability make such a difference as to how they are able to get on with their lives.

Building an international FSHD patient community will mean understanding and recognizing these differences and developing local approaches to patient engagement.

NOTE:

It has been 30 years since Sheila Hawkins was diagnosed with FSHD. She has found it very helpful to be part of the FSH-MD Support Group in the UK. Hawkins is a trustee of Muscular Dystrophy UK and represents the UK FSH-MD Support Group in FSHD Europe, a collaboration of patient groups from six different countries across Europe.

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Industry Collaborative on FSHD Drug Development

study participants and help guide the design of clinical trials. Currently, tests for FSHD can be complicated, and only a few specialized labs perform them. New technologies, along with better scientific understanding of FSHD biology, should lead to more efficient and sensitive genetic tests.

Imaging biomarkers are based on methods such as MRI and X-ray, which can measure the condition of muscles in a patient. Doris Leung, MD PhD, of the Kennedy Krieger Institute presented advances in this area. Current studies suggest that disease progression might be tracked by imaging modes that detect signs of possible muscle inflammation and the replacement of healthy muscle by scar tissue (fibrosis) and fat. However, most studies to date have been of patients with varying degrees of disease progression who were scanned on only one occasion. Several "longitudinal studies," which measure changes in the same volunteers over time, are under way, and their results should provide more information on disease progression.

In the final session, Jeffrey Statland, MD, from the University of Kansas Medical Center reviewed the types of clinical tests and trial designs pharmaceutical companies need in order to obtain regulatory approval. No single clinical outcome measure nor any single clinical trial design can serve the diverse therapeutic approaches being developed. The FSHD Clinical Trial Research Network (CTRN), with eight sites in the US and three in Europe, is conducting a longitudinal, NIH-sponsored observational study to validate a variety of outcome measures. Called ReSOLVE (Clinical Trial Readiness to Solve Barriers to Drug Development in FSHD), it is a four-year study that began in 2018.

As the initial sponsor of the CTRN, the FSHD Society realized the opportunity such a network approach could have on helping validate promising clinical outcome measures. Without these, pharmaceutical companies would be reluctant to launch clinical trials, and regulatory agencies wouldn't have benchmarks from which they could determine if a therapy is safe and effective.

Over the course of 2019, we will work closely with our industry partners, academic leaders, regulatory agencies, and the global patient community to accelerate each of these important areas of research.

We are grateful to the Geraldi Norton Foundation for its generous support of the workshop.

Workshop proceedings are posted at *fshsociety.org*.

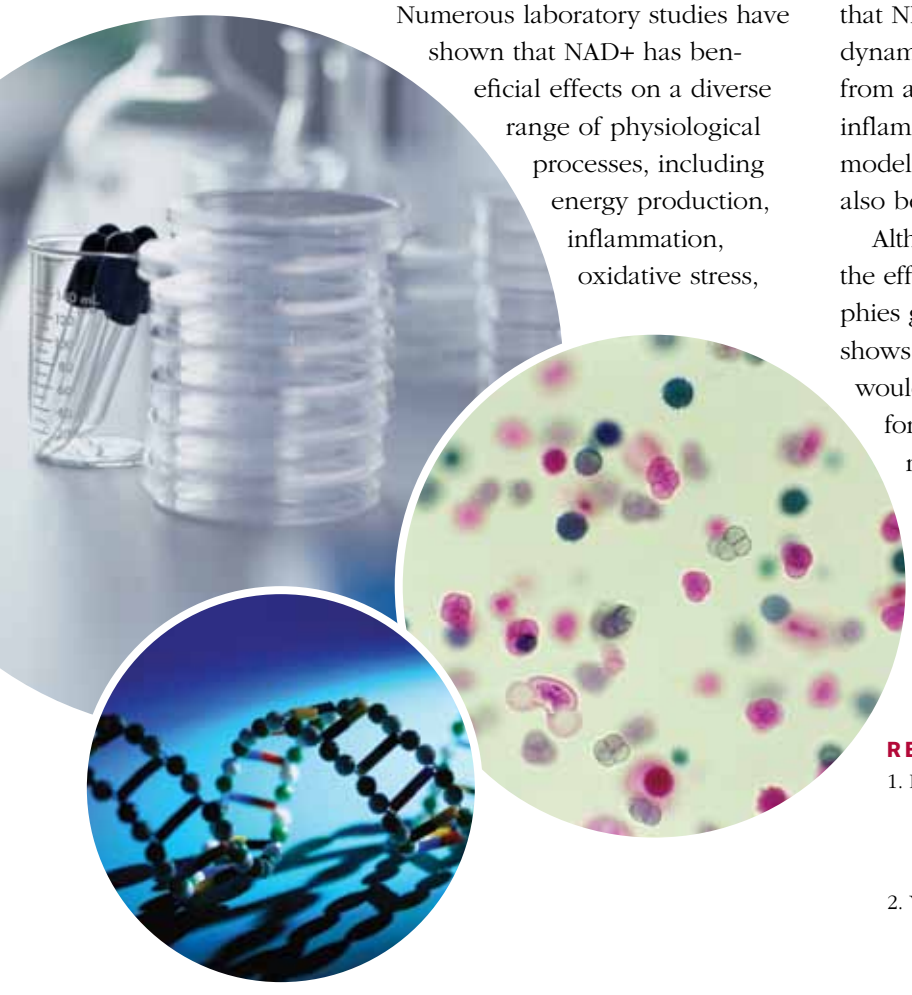
NAD+ supplementation may help aging muscle

Could it be helpful for FSHD?

BY AMANDA HILL, HIGHLANDS RANCH, COLORADO

In the current absence of a treatment for FSHD, many patients experiment with a variety of lifestyle or diet changes, supplements, naturopathic medicine, or other types of treatments to help alleviate and cope with disease symptoms. In recent years, several laboratory studies have shed light on one such supplement that may have a variety of positive effects across multiple types of muscular dystrophies: nicotinamide adenine dinucleotide (NAD+) or one of its precursors, nicotinamide riboside (NR) or nicotinamide mononucleotide (NMN).

You may have seen NAD+ supplements touted as anti-aging molecules in mainstream media channels, and there is a significant body of science supporting this idea. NAD+ plays an important role in the generation of mitochondria, the cellular machinery responsible for producing your body's energy supply from the nutrients you eat.



Numerous laboratory studies have shown that NAD+ has beneficial effects on a diverse range of physiological processes, including energy production, inflammation, oxidative stress, insulin resistance and weight gain, memory and cognition in Alzheimer's disease, cardiac function, and more. Interestically, it is fairly well established that NAD+ levels decline with age.

In the case of muscular dystrophies in general, one study looked at gene expression patterns across multiple mouse models of different types of muscular dystrophies, including FSHD. The researchers found that as expression of genes involved in the pathogenesis of disease went up, expression of genes involved in the generation of mitochondria and NAD+ synthesis went down. Although we must be careful to understand that *correlation* does not show *causation*, this is an interesting result to explore further.

The same group then went on to evaluate the therapeutic impact of supplementation with NR in a mouse model of Duchenne muscular dystrophy (DMD). They found that NR supplementation improved mitochondrial energy dynamics, increased running capacity, protected animals from and reversed muscle damage, and decreased muscle inflammation. These results were obtained in a mouse model of DMD, but all of these effects would theoretically also be beneficial in FSHD.

Although more studies are needed to better understand the effects of NAD+ supplementation in muscular dystrophies generally, and in FSHD specifically, the early evidence shows some therapeutic potential. NAD+ supplementation would not cure FSHD, but there is a scientific rationale for thinking it may improve some symptoms, such as muscle damage, muscle pain, and fatigue.

NAD+, NR, and NMN supplements are all available for purchase over the counter and without a prescription. Although laboratory studies sound promising, it's important to emphasize that there is no clinical data yet that these supplements provide patients with any benefits.

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Fulcrum plans to launch Phase 2b clinical trial in mid-2019

Their drug is the first to target DUX4

BY JUNE KINOSHITA, FSHD SOCIETY

This April, Fulcrum Therapeutics announced that it is planning a Phase 2b clinical trial in facioscapulohumeral muscular dystrophy (FSHD) of the drug losmapimod. The company, which has focused on FSHD since its founding in 2015, identified losmapimod as a powerful inhibitor of the expression of DUX4, the gene that is seen as the root cause of FSHD. In laboratory systems developed from FSHD patients' muscle cells, losmapimod reduced DUX4 expression and restored a healthy appearance to muscle cells.

Robert J. Gould, PhD

The drug was developed by GlaxoSmithKline (GSK) and previously tested in more than 3,500 healthy volunteers and patients in 24 clinical trials across multiple indications, including in Phase 2 and 3 clinical trials in acute coronary syndrome. The drug was well tolerated by patients but was shelved after it failed to show sufficient efficacy in those trials. Losmapimod has never been tested in muscular dystrophies.

"Losmapimod is a foundational clinical asset for Fulcrum that has the potential to become the first approved therapy that targets the root cause of FSHD," said Robert J. Gould, PhD, Fulcrum's president and chief executive officer. "Fulcrum believes losmapimod has the potential to slow or halt the progressive muscle weakness that characterizes the condition, which would significantly improve patients' quality of life. We will work urgently to advance the compound through the clinic."

Fulcrum expects to initiate a Phase 2b clinical trial of losmapimod in patients with FSHD at multiple clinical sites in the US and Europe in mid-2019.

NOTE:

To receive alerts about volunteering in your area for Fulcrum's clinical trial, please make sure the FSHD Society has your name, address, and email contact.

Self-healing from muscular dystrophy

BY BEATRIZ NASCIMENTO, SAO PAOLO, BRAZIL

I had some mild muscle weakness since childhood, but in my 20s everything was getting harder. I was constantly fatigued and stressed. By my early 30s, fast decline in muscle functions due to FSH muscular dystrophy was making me believe that the rest of my life would be a painful downhill trip toward more weakness, limitations, and paralysis.

As a full-time professor of occupational therapy at Federal University of San Carlos, Brazil, I had already explored what conventional medicine and mainstream rehabilitation had to offer, and it was not nearly enough. When I read Meir Schneider's *Movement for Self-Healing,* it became clear that I had to try it. Meir had overcome his blindness by working incredibly hard on his eyes, and he applied those principles to serious diseases, including muscular dystrophy. I promised my department to bring back the technique if they gave me a grant to study with Meir. That is how I ended up in San Francisco in 1989.

Throughout nine months at the School for Self-Healing I lived entirely from my body's perspective. In addition to classes, I averaged four hours daily of gentle movements, self-massage, stretches, breathing, and visualization. I rested and enjoyed myself with music and inspirational media. I also received massage, which prepared the muscles to repeat the movements many times. There was emphasis on body awareness and on activating muscles that were not being used. My body felt that it was finally receiving what it needed.

Feed the mind, move the body

I experienced remarkable progress in my overall health, movement patterns, and flexibility, and estimated that I was about 40 percent better after only nine months of work.

Here are some of the improvements I experienced:

- Raising my arms up about 150 degrees; previously I could not pass 90 (shoulder level).
- Walking for longer distances without stumbling or feeling fatigued and achy.
- More control of my arms and hands, no more dropping objects.
- Straighter posture, shoulders no longer protruded and lower back less arched.
- Chewing and smiling easier.
- Lighter and more graceful movements.

I was no longer stressed out and physically exhausted like I had been in the previous years. Instead, I was relaxed, happy, and full of enthusiasm to spread this work not only in Brazil, but to the world. People need to know that options for a higher quality of life are available now! This has been my purpose for the past 30 years.

Maintaining benefits in daily life

Being back at a very demanding job, armed with my new life's mission, brought less improvement and new challenges. My position at the university allowed the work

to spread quickly. I traveled giving lectures, workshops, and trainings, translated materials, and worked with clients. In 2001 we created the Brazilian Self-Healing Association, with more than a hundred members spreading the good word.

Like every adult, I had to face many other life crises, which caused the disease to advance faster. Literature corroborates my experience that stress is very damaging for people with degenerative conditions because it weakens the body. We must learn how to alleviate the stress and constantly adjust the delicate balance among the needs of the body, daily exercises, family, social life, and attacks from the disease.

I was not always successful in doing that, but from time to time did short intensives of bodywork. It is remarkable that during all these intensives I experienced a shift between "going downhill" to "feeling healthy and fresh" again, while regaining some of the losses. It works like a reset button, proving that every time we do the work, we gain the results.

It is very empowering to know that we can bring comfort and pleasure to our bodies, even as the disease progresses and the body changes.

Some examples of what I do when I am fatigued and stressed are:

- floating and moving very gently in warm water;
- receiving a supportive self-healing massage;
- gently stretching and moving in all directions to give the joints more freedom;
- deepening my breathing with movement, massage, and awareness
- self-massage; and
- visualizations and meditation.

I also exercise more vigorously the areas that are not very affected, but this can be tricky! I believe it is safer and more productive to do more repetition with less resistance, using our full range of motion, moving in different angles and planes. Water allows for endless adjustment in resistance, and it is fun. Water is my all-time favorite!

All of this works synergistically to replenish the body's energy

Self-healing is not a magic bullet, and muscular dystrophy is not an easy condition to treat. It takes dedication and commitment on a daily basis, and this may not be feasible for many. It is like practicing to become a piano virtuoso, and not everyone can do it, but for those who wish to try, I share my story as a way to offer encouragement and alternatives.

Recently, meditation has also been a big part of my life, giving me the tools to calm the mind, rest more deeply, and live fully in the present, instead of comparing things to the past or worrying about the future. Whenever exhaustion and hopelessness kick in, meditation dissipates it, allowing peace and happiness to enter. I highly recommend it.

Now at 60, I want to focus on creating materials that will outlive me, giving people with debilitating diseases inspiration and empowerment to move easier, feel better, and live life to its fullest.

More than meets the eye (and ear)

BY JENNY HASENJAEGER, BENNET, NEBRASKA

Since the time he performed his first childhood song, "I Love My Lips," made famous by *VeggieTales'* Larry the Cucumber, Levi Benson's lips have been crooning tunes, and those on the listening end have been loving every note.

Accentuating his singing talent are his skills on the piano, violin (wife, Jaime, also plays), and guitar, which he began nurturing when he was nine years old.

"My parents said I could learn to play rock if I also studied classical, so I learned to play both while growing up in Grand Island, Nebraska," Benson said.

Today, his Johnny Cash-like bass voice is as deep as the passion he has for the gift of music and sharing it with others. If given the choice to do anything, he said being a country music singer would top the list.

"I love getting the chance to tell stories through songs, …"

— LEVI BENSON

"I love getting the chance to tell stories through songs, whether they are mine or someone else's. I would love to give people music to unite over – music that celebrates life's successes and challenges."

In December 2017, Benson came face to face with a challenge that wasn't music to his ears. Following a series of tests ordered when his body started having difficulty adapting to the physical stresses of an active military life, he was diagnosed with FSHD Type 1.

"I never imagined being medically retired from the military due to FSHD or being diagnosed with FSHD in the first place," he said.

Benson said FSHD challenges him in ways he has never been challenged before.

"When your body decides it's done doing something and you don't have a choice, it's hard to accept right away," he said. "But the adaptive challenges are always uplifting, and when I overcome through adaptation, I feel a surge of victory and confidence that I can do whatever task is set in front of me."

While he still has lower-extremity strength, Benson's greatest weakness is in his upper back muscles, which causes a lot of fatigue when he doesn't adapt movements to accommodate daily tasks. And Benson's tasks are many as he is a full-time student in the Doctor of Chiropractic program at Cleveland University-Kansas City.

"My father is a chiropractor, so it is something I grew up around and knew I wanted to do. In light of my FSHD, I have a passion for researching the effects and benefits that chiropractic care could have on patients with neuromuscular conditions," he said.

Benson is emphatic that FSHD is not going to define who he is. "I have moments of apprehension about the future but know that God will use this in my life for His glory," he said. "I don't know what tomorrow will bring, but I know that I will keep fighting, pushing forward, and enjoying life because every day is a gift."

He encourages others with FSHD never to give up on their passions. "The days when a hobby or dream seems impossible, it may just be a sidetrack that takes you the long way around," he says. "Enjoy the ride, show kindness, and love yourself, so you can then turn around and spread that love to the people you meet along the way."

NOTE:

Levi Benson (stage name, Levi James) participates in FSHD studies conducted in the Kansas City area and is involved in FSHD Facebook groups.

Art lets me grow

BY TIFFANY ZIMMERMAN, DELTONA, FLORIDA

I don't think any of my work as an artist really focuses on my having FSHD. I do feel, however, that my art and creativity are among the major things in my life that keep me mentally balanced and uplifted.

One of the hardest things about dealing with FSHD is the unpredictability of my future health. Yet whenever I'm creating something, I'm able to gain a sense of control that I lack elsewhere. My paintings are chaotic and messy, but that's my choice. My resin work can be unpredictable, and it requires patience, but I'm still creating something beautiful out of nothing. I may not be able to build a stronger body, but these outlets definitely allow me to grow and compensate in other ways.

There's always some extra thought that goes into creating when you have a disability. I'm in a wheelchair, so I've had to adapt how I paint over the years. I have to arrange things a certain way around me so I can reach them. I'm right-handed, but that is my weak hand, so I have to brace my wrist and elbow with my other hand. Slowly, I've learned to paint with my left hand as well. Now I can change hands when my right hand becomes fatigued.

When I build dioramas, I use a lot of tools that most people wouldn't necessarily need. I've cut my hands a bunch of times with a rogue knife and burned my fingers with the hot glue gun, but that's just part of it. For my work with resin, I have to lay out my space so that I'm not constantly knocking stuff over. I also purchase resin in quantities I know I can lift.

Finding happiness can be a struggle when you also have FSHD. Creating art makes me happy, but it doesn't do the dishes. I only have a certain amount of energy every day, and when it's gone, it's gone. On most days, choices are made. The stack of dishes in the sink will tell you what I most often pick.

Resin art by Tiffany Zimmerman

***Autumn*, painting by Tiffany Zimmerman**

The disappearing bomb

How DUX4 could cause FSHD without actually being there

BY AMANDA HILL, HIGHLANDS RANCH, COLORADO

In the FSHD research field, there is an emerging idea that the damage caused by DUX4 may linger on long after DUX4 is no longer present. But how can this be? To illustrate, imagine DUX4 as one of those trendy bath bombs that dissolve in your bathwater – drop in a bomb and it goes absolutely crazy! But only for a short time; soon the bomb dissolves and disappears. You wouldn't know it was ever there, except that its earlier presence has now fundamentally changed the makeup of your bathwater, leaving behind a host of scents, salts, oils, fizz, and even colors.

DUX4 may act similarly in the muscle tissue of people with FSHD. It gets expressed, goes crazy doing all sorts of activities, then disappears. And it's possible that what gets left behind is just as important as the initial presence of DUX4 in causing disease.

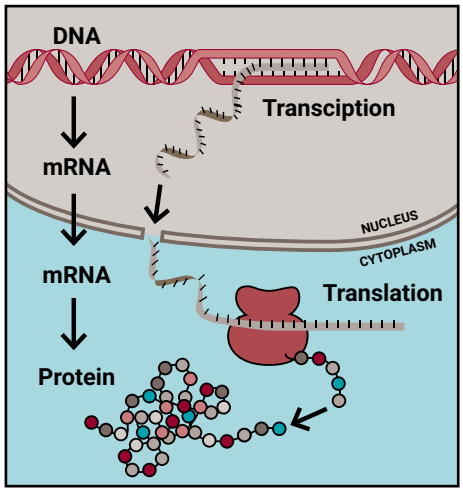
To explain how this works biologically, I first want to explain a molecular biology concept often referred to as the Central Dogma. The Central Dogma describes the most common flow of genetic information. Simply put, genetic information flows from DNA to RNA to protein. The first step employs a process called *transcription* to read a strand of DNA and synthesize a corresponding piece of RNA; the second step employs a process called *translation* to read that piece of RNA and build a corresponding protein. Proteins are the basic building blocks of all cells in the body and work together to perform biological processes.

Molecular biologists trying to understand how DUX4 causes FSHD have largely focused their efforts on understanding how the first step of the Central Dogma is altered. FSHD is the result of genetic changes that allow DUX4 DNA to be erroneously available for transcrip-

Suja Jagannathan (third from left) and her team at the University of Colorado.

tion to RNA. Then, once made into a protein, DUX4 interacts with DNA to regulate transcription for many other genes and cause all sorts of disruptions that lead to FSHD. These disruptions happen within the first step of the Central Dogma. But what about the second step?

This question was recently addressed by Sujatha Jagannathan, PhD, then a postdoctoral fellow at the Fred Hutchinson Cancer Research Center, working with a team of scientists including Robert Bradley, PhD, and Stephen Tapscott, MD PhD.



This diagram illustrates the Central Dogma of molecular biology.

Jagannathan explains the team's thinking: "The field has long held the view that FSHD biology is all about the RNA molecules induced by DUX4. It made sense, because DUX4 is a transcription factor, whose main function is to induce the synthesis of hundreds of RNA molecules. However, … [recent] results opened up the new possibility that DUX4's effect on protein molecules might play an important role in FSHD. Therefore, systematically measuring the level of all protein molecules in DUX4-expressing cells was a key piece of the puzzle that we needed to understand FSHD pathogenesis, and that is what we set out to do in this project."

Jagannathan used two different models of FSHD in which she had engineered normal muscle cells to express DUX4 protein. She then performed mass spectrometry to measure the levels of proteins, and at the same time, also sequenced all the RNA. With these new datasets, she was able to, for the first time ever, directly compare RNA levels and protein levels for thousands of unique genes in a model of FSHD.

One of the most important findings was that several genes that would normally respond to cellular stress had hugely elevated levels of RNA in the presence of DUX4, but their protein levels were only minimally changed.

Jagannathan explains, "We were surprised to find that many of the stress response genes that were transcriptionally upregulated when DUX4 is expressed (due to the stress it causes to cells) are not actually translated into proteins that can help the cells combat the stress. In other words, the cells are stressed but unable to cope with it. This could very well be one of the reasons that DUX4 is toxic to cells."

Her analysis also validated a notable previous finding in the field: that DUX4 inhibits an important RNA quality-control pathway. Similar to the stress response example above, some genes that are required to maintain this quality-control pathway were being upregulated at the RNA level, but not translated into proteins that can actually do the needed work.

These findings are examples of post-transcriptional regulation – biological processes that affect the second step of the Central Dogma – and demonstrate why it is important for scientists to look at both steps to gain a better understanding of how DUX4 causes FSHD. As a result of this work, Jagannathan formed an important hypothesis that has the potential to change how we understand FSHD.

"Cells that are exposed to DUX4 proceed to undergo cell death even after they cease to express DUX4," she said. "Our paper indicates at least two reasons for this: 1) the complete shutdown of RNA quality control can wreak havoc on the cells by generating faulty proteins, and 2) the inability to mount an effective stress response prevents the cells from coping with the loss in quality control and commits them to a path of inevitable cell death. Hence, therapeutic interventions that can reverse the downstream consequences of DUX4 expression should be an integral part of our strategy to combat FSHD."

Jagannathan uses her team's findings to propose two synergistic mechanisms that could contribute to the prolonged negative effects of DUX4. These are like the salts, oils, and fizz left behind by the bath bomb. She notes that effective therapies for FSHD may need to not only shut down DUX4, but also reverse these lingering effects that could otherwise still lead to the death of muscle cells.

Jagannathan is now an assistant professor at the University of Colorado Anschutz Medical Campus and leads a team of scientists working to better understand how changes occurring at the second step of the Central Dogma contribute to the DUX4 "bath bomb." In fact, earlier this year, postdoctoral fellow in Jagannathan's lab, Michael Dyle, PhD, received funding from the FSHD Society to study the consequences of the reduced RNA quality-control pathway in FSHD.

You can learn more about Dr. Jagannathan's lab and research at *Jagannathan-lab.org*.

REFERENCES

1. Jagannathan S et al. Model systems of DUX4 expression recapitulate the transcriptional profile of FSHD cells. *Human Molecular Genetics.* 2016;25(20):4419-4431.
2. Jagannathan S et al. Quantitative proteomics reveals key roles for post-transcriptional gene regulation in the molecular pathology of facioscapulohumeral muscular dystrophy. *eLife.* 2019;8:e41740.

A surprise $50K gift from a simple act of kindness

From left to right: Kevin Blake, Hilary Roberts, and Ann Blake at the Red Songbird Foundation gala in Beverly Hills.

When Jim Chin, chair of the FSHD Society board of directors, donated funds for travel scholarships so that 20 patients could attend our 2018 FSHD Connect conference in Las Vegas, he had no inkling of the dividends his gift would yield: $50,000, to be exact. That's the amount of the check that the Red Songbird Foundation presented to the FSHD Society on May 11 in honor of Ann and Kevin Blake, close friends of the foundation's founder, Hilary Roberts. Roberts had been impressed by the Society's kindness to the Blakes. A full-circle moment.

The Blakes had no clue as to what their friend had in store when they traveled from their home in England to Los Angeles to celebrate Roberts' birthday and official launch of her foundation, which supports survivors of trauma caused by sexual, physical, and verbal abuse. Roberts, herself a survivor, is a singer-songwriter who has reached number one on the Billboard Dance Club charts.

Hosted by actor Terry Crews, the gala took place at the Beverly Hilton. Later on, Ann posted on her Facebook page, "I just had the most amazing night of my life thanks to Hilary Roberts. I got diagnosed with muscular dystrophy two years ago. Whilst staying with us in our house, we talked about life and what it throws at us."

Ann's conversation inspired Roberts to write a song, "Fight to the Other Side," which she debuted at the gala. It was "heartfelt and so beautiful," Ann said. "The video [of the song] was played for the first time last night, and we were called to the stage where the CEO of the FSHD Society was presented with a check for $50,000. I feel privileged, blessed, and hugely grateful to everyone involved in making that happen."

So do we!

Universal design is smart design and makes living easier

I am 66 years old, with FSH muscular dystrophy, and live with my 82-year-old husband, Tony Earl, in a high-rise condominium in downtown Madison, Wisconsin. I anticipate having to transition from a walker and scooter to an automated wheelchair in the future. So when another unit became available in our building, we decided to purchase it and apply "universal design" principles to remodeling it so that we could age in place, in our own space.

Enjoy the before and after photos on the FSHD Society website at *www.fshsociety.org/2019/06/universal-design/*.

— Jane Earl, Madison, Wisconsin

The condo is both functionally and aesthetically altered. It is a beautiful, colorful, accessible home customized to our needs. The well-appointed kitchen is filled with universal design elements that make meal preparation no longer a challenge. The master suite is open and accessible. We can move effortlessly from room to room.

World FSHD Day 2019

Members of the St. Louis chapter celebrated the day with #OrangeSliceSelfies.

We're now the FSHD Society

Discerning readers will notice that, with this issue of the *FSHD Advocate,* we have changed our name to align with how the rest of the world abbreviates facioscapulohumeral muscular dystrophy. This is not simply an exercise in trendiness. When we were the FSH Society, we led the charge for using "FSHD," providing a single, consistent name for doctors, patients, and researchers to call the condition.

In the Internet era, having one common name makes FSHD more searchable. And, as it happens, searching for "FSH" pulls up an unrelated medical term: follicle stimulating hormone! Today, it is critically important that patients and families be able to find us at the top of the search results page, hence the name change. Because we have already done the hard work of getting the world to adopt the term FSHD, we hope the transition will be barely noticeable!

What's at *www.fshsociety.org*?

HELPFUL TOOLS AND RESOURCES:

- Medical alert card
- Letters for requesting insurance coverage for genetic testing
- Medicare coverage for ongoing physical therapy

GREAT INFORMATION FROM OUR RECORDED WEBINARS:

- FSHD 101, with Samantha LoRusso, MD
- Stance-control braces, with Abbey Downing
- How to launch a chapter and host a Walk & Roll
- Swallowing and speech in FSHD, with Kiera Berggren
- FSHD research advances, with Stephen Tapscott, MD PhD
- Insights from MRI, with Doris Leung, MD PhD
- Pulmonary health, with John Bach, MD

Upcoming

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

CONFERENCES

October 20, Chicago, IL
Chicagoland FSHD Family Day Conference

November 16, New York, NY
New York City FSHD Family Day Conference

FUNDRAISERS

September 7, Castle Rock, CO
Colorado Walk & Roll

September 7, Salt Lake City, UT
Utah Walk & Roll

September 14, Barrington, IL
Chicagoland Walk & Roll

September 14, Dublin, OH
Columbus Walk & Roll

September 14, Chesterfield, MO
St. Louis Walk & Roll

September 15, Alameda, CA
Bay Area Walk & Roll

September 29, Roswell, GA
Atlanta Walk & Roll

October 5, Raleigh, NC
North Carolina Walk & Roll

October 6, Bellevue, WA
Pacific Northwest Walk & Roll

October 6, Madison, CT
Connecticut Walk & Roll

October 27, Torrance, CA
Los Angeles Walk & Roll

November 16, Greeneville, SC
Fundraiser in Honor of Zachary

CHAPTER AND LOCAL MEETINGS

August 3, Fairway, KS
Kansas City Support Group Meeting

August 6, Austin, TX
Austin Support Group Meeting

August 10, Minneapolis, MN
Dr. Perlingeiro Presentation at the University of Minnesota

September 21, Knoxville, TN
East TN Meeting and Social Gathering

WEBINARS

August 10, CRISPR Strategy to Treat FSHD
With Charis Himeda, PhD, University of Nevada, Reno

September 11, CBD and Medical Marijuana
With Jen Bernstein, CEO of World Help Awards

December 7, The ABC's of Clinical Trials
With Rabi Tawil, MD, University of Rochester

VIRTUAL MEETINGS

FSHD Society 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 FSHD Society Facebook page. 2019 dates: 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. 2019 dates: August 1, September 5, October 3, November 7, December 5.

Western Washington FSH Community
Meets via webinar on the fourth Saturday of each month except in December, 10:00 a.m. PST. 2019 dates: August 24, September 28, October 26, November 23.

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ACCELERATING TREATMENTS

What can you do?

1 **Go to *FSHsociety.org/JoinUs* and provide your current contact information.** We won't ever share your data. Our purpose is to keep you informed about current research, clinical trials, events, and resources.

2 **Volunteer for the ReSOLVE study, listed at *FSHsociety.org/ClinicalTrials*.** This major observational study is imperative for designing future clinical trials for FSHD therapies.

3 **Go to *FSHsociety.org/Rochester* to join the national registry.** Registry data are shared with researchers to better understand the biology, progression, and other important issues in FSHD. If you haven't had a genetic test, the registry can provide it.

4 **Get an annual check-up at one of the Clinical Trial Research Network sites listed at *FSHsociety.org/CTRN*.** These centers offer high-quality care. Getting seen by a clinician at one of these centers can also open up opportunities to volunteer for research and learn about clinical trials and the latest treatment options.

5 **Get involved with your local FSHD Society chapter and encourage affected family members to do the same at *FSHsociety.org/Chapters*.** Help us build a powerful, active community that serves families where they live while advocating nationally and globally for better care and effective treatments.