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PATIENTS

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Together, we move toward a cure	
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Advocate

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Look for us on the Internet at *fsbdsociety.org*. We thank the FSHD Society staff for their editorial assistance.

Special Section UNITING THE WORLD

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One week in June

Bringing the world together to cure FSHD

1 WEEK • 3 CONFERENCES • 14 COUNTRIES • 100 ORGANIZATIONS • 700 PARTICIPANTS • 1 GOAL - A CURE FOR FSHD!

CEO

here are two factors that have been identified as catalysts in expediting development and delivery of effective therapies to families: collective intent, which is the fusion of thought that comes from a shared sense of urgency, and patient advocates, which are active and engaged groups of individuals, coming together, speaking with one voice, and focused on one purpose. These two factors were fully activated when we brought the global FSHD community together this past June for a full week in Orlando.

Researchers, clinicians, regulators, biopharmaceutical companies, and families living with FSHD from all over the world gathered to engage, be challenged, inspired, ignited, and to develop friendships and partnerships, all with a singular focus – to accelerate the development and delivery of effective therapies for FSHD.

The week was anchored by three main events. The first was the FSHD Society-hosted Industry Collaborative for Drug Development in FSHD, where 70 people representing 14 pharmaceutical and biotech companies, the FDA, the National Institutes of Health, clinicians, and patients worked together to solve problems in the clinical trial and regulatory pathway. In our second event, more than 230 scientists attended our 29th Annual International Research Congress, which received high marks for presentations as well as the stimulating collaborative environment. And the grand finale occurred when the FSHD community gathered over the weekend. With 400 participants in breakout groups and plenary sessions, it was a hope-filled, community-enriched atmosphere that words fail to adequately express. As one individual said, "You just had to be there!"



Mark A. Stone

In these pages, you will read about the meetings, insights, and innovations, as well as the purpose behind the programs.

And I hope you will also "feel" the presence of genuine community – a whole that was far greater than the sum of its components. Everyone had a sense that they were a part of influencing the future – literally putting the pieces in place to stop FSHD in its tracks.

I want to express my personal appreciation to the researchers, patients, and family members who served on the planning committees. In large part, our week was a success because of their work. To everyone, enjoy this special conference edition of the *FSHD Advocate*. It was prepared with you in mind.

Forward together!

Wale

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WE ARE bringing the world together FIRING UP THE WILL TO CURE FSHD

BY JUNE KINOSHITA, FSHD SOCIETY

ver six days during the month of June, the FSHD Society convened a series of workshops and conferences that brought together all the stakeholders in our world, the patients and families, scientists, clinicians, government agencies, biopharmaceutical companies, and funding organizations that are working to improve the well-being of our community and deliver effective treatments for FSH muscular dystrophy.



It was a huge lift for the Society – major kudos to our brilliant staff and volunteers – and we succeeded, thanks to our supporters who invested in the Society over many years. Because of you, we were able to grow the talent and capacity to organize a highly impactful series of events involving more than 700 individuals, in-person and virtually.

Our meetings were designed to communicate our strategy and every stakeholder's role. Our aim was to tell the bigger story.

The week began with our Industry Collaborative workshop, where academic leaders and industry scientists from more than a dozen companies discussed the current tools available for clinical trials in FSHD. Representatives from the FDA listened in to gain the background that would help them evaluate clinical trial applications and data that will be coming before them soon. The workshop opened with a heartfelt testimonial by Heloise Hoffmann, who at 18 is our youngest chapter director. Her plea for a treatment hit hard and reminded everyone in the room about our purpose.

Over the next two days, researchers from around the world gathered to share their latest findings at our International Research Congress (IRC). Convening for the 29th year, the meeting was both a celebration of how far the field has come as well as a reminder of the uncharted territory ahead, including, excitingly, new approaches to treating FSHD. The congress concluded with a lively reception, sponsored by Fulcrum Therapeutics, where IRC attendees and patients and families arriving for the FSHD Connect conference mingled over wine and appetizers. There were many joyous reunions.

FSHD Connect unrolled over the weekend, starting with breakout sessions that attracted large groups who engaged in conversations and hands-on experiences. Plenary sessions covered the fascinating history of FSHD research, frontiers of physical therapy, supplements, and mental health. Sunday sessions focused on drug development, with several companies answering questions about their FSHD therapies and clinical trials.

The conference culminated with the unveiling of our newest initiative, PACT, Patients Accelerating Clinical Trials, a set of programs and calls to action – steps every person can take to help the FSHD community be trial-ready. By the time the conference adjourned, it felt as though we had lit fires everywhere – of friendship, understanding, and commitment to join the fight!

On facing page, clockwise from upper left: International Research Congress (IRC) banquet; IRC attendees celebrate World FSHD Day in their orange hats, courtesy of Avidity Biosciences; Anthony Saleh and Carlo Serra at the IRC poster session; Lucienne Ronco asks a question; Nam Nguyen, Mitsuru Honda (back view), and Nao Sasaki; Mark Stone; Susan and Ian Rhys; Leigh Reynolds talks to FSHD Radio host Tim Hollenback; Jeremy Gawryluk and Kelsie Miller; Richard Lemmers and Yi-wen Chen. Center: IRC in session at the Waldorf Astoria Bonnet Creek, Orlando, Florida.























United in our fight against FSHD

BY EMMA WEATHERLEY, FSHD GLOBAL RESEARCH FOUNDATION, AUSTRALIA

he 2022 FSHD Industry Collaborative, International Research Congress, and FSHD Connect meetings were held in Orlando, Florida, June 15-19, hosted



Emma Weatherley

by the FSHD Society and attended by 700 participants, including many worldwide FSHD organizations, more than 20 pharmaceutical companies and biotechs, as well as clinicians, scientists, and patients - a truly global collaboration. I attended, along with FSHD Global Research Foundation chairperson Natalie Cooney, to represent Australians with FSHD. We had the opportunity to contribute to the valuable Industry Collaborative, where we discussed our goal to bring clinical trials to Australia, including our diagnostics drive and recent investments into diagnostic technology and clinical trial readiness.

A common theme connected all three events - the commitment across all organizations, all countries, and all participants to find treatments and a cure for FSHD. Spirits and hopes were high as advances in science were presented, and even with challenges in front of us, there was overall confidence that we are getting closer, particularly with the progression of Fulcrum Therapeutics into Phase 3 trials and the welcome announcement made by Avidity Pharmaceuticals that their drug to target DUX4 mRNA for degradation is on track to be in clinic by the end of 2022, as well as other therapeutics expected to progress to clinical trials sometime over the next few years.

It was wonderful to celebrate the advancements made in FSHD research over the last five years, with many of FSHD Global's grant programs having funded essential work performed to better understand FSHD disease mechanisms - work that has led to the exciting phase we are entering now, with therapeutic clinical trials emerging. The room was full of many scientists we have supported over the last 15 years. It was also wonderful to see so many new researchers joining the fight against FSHD, and pharmaceutical companies and biotechs working hard on therapeutics and potential treatments. The next five to 10 years will see some amazing advancements,

Uniting the World

> serve special recognition and thanks from my family and from my fellow Australians with FSHD.

First is Alexandra Belayew, PhD, who discovered *DUX4*, the gene that causes muscle loss in FSHD. Her discovery was the breakthrough this disease needed to enable scientists to start solving the puzzle. Meeting her was like meeting the Queen of FSHD. Quite an extraordinary experience, and wonderful to be able to personally thank her for her contributions.

The next amazing scientists were the reason we were able to get to the bottom of the four-year diagnostic journey of my 12-year-old daughter, Hannah, and eventually discover she



Alexandra Belayew, PhD

Peter Jones, PhD

Silvère van der Maarel, PhD

"I met some extraordinary people, but three in particular deserve special recognition and thanks from my family and from my fellow Australians with FSHD."

- EMMA WEATHERLEY

and we are hopeful that sometime soon we will welcome initial therapies – something that only 15 years ago seemed an impossible dream.

Attending the 2022 International Research Congress and the FSHD Patient Connect was a memorable experience. I met some extraordinary people, but three in particular dedoes not have FSHD. Peter Jones, PhD, who runs MyFSHD and the Peter Jones Lab at the University of Nevada, ran the saliva test that first indicated that Hannah didn't have FSHD. His hard work and perseverance in establishing free screening for FSHD worldwide has changed the patient *Continued on page 18*...

Stakeholders convene to chart future priorities

The FSHD Society's 2022 Industry Collaborative workshop

BY LUCIENNE RONCO, PHD, WELLESLEY, MASSACHUSETTS

eventy-three researchers, industry representatives, FDA officials, and patient advocacy leaders gathered on June 15, 2022, to review and discuss the current state of tools and methods available to study the efficacy of drugs to treat FSH muscular dystrophy. The workshop is the second one convened by the Society and aims to update the 2019 workshop.



Lucienne Ronco, PhD

The day began with 18-year-old Heloise Hoffmann bravely speaking to the group about her life-changing FSHD diagnosis. She opened the eyes of all in attendance as she described the profound physical and mental impact of her diagnosis while setting the stage for a very productive meeting by grounding attendees in empathy and commitment to action.

Fourteen biopharmaceutical companies along with 60 members from the regulatory, clinical, and patient communities listened as Doris Leung, MD PhD, of the Kennedy Krieger Institute introduced FSHD and highlighted the limitations of traditional medical training, which fails to capture the full and telling signs of FSHD. She emphasized the need for better education of doctors and those in medical schools.

While updating the group on clinical trial advances, Jeffrey Statland, MD, of the University of Kansas Medical Center noted that clinical trial inclusion criteria have evolved from the requirement for ambulatory walking to new criteria which now select muscles for biopsy by magnetic resonance imaging (MRI). He reported that whole-body MRI to track diseased muscles over time is a real revelation for

the field, and that functional endpoints like Reachable Work Space (RWS) may bring new insights to changes in patients' function during clinical trials. RWS is a novel measurement using a camera originally found in Xbox.

Jay Han, MD, the inventor of RWS, spoke of his hope to one day have RWS in patients' homes so upper body function can be monitored in a real-life, continuous manner. One major question Han hopes to answer is: Does RWS correlate with an individual's ability to remain independent?

While the field is still seeking the best tools to measure novel therapeutic efficacy, Katy Eichinger, DPT, talked the group through the performance-based outcomes being evaluated by the Clinical Trial Research Network (CTRN).

Per Widholm, MD, of AMRA Medical described a new publication of whole-body MRI and related how the new imaging technique correlates with a patient's functional change in muscle over time.

Lucienne Ronco, PhD, presented the FSHD Society's initiative to use a highly sensitive method to find *DUX4*-related biomarkers in blood which, if successful, may reduce the need for biopsies in FSHD clinical trials.

In the afternoon session, several impactful activities by the FSHD Society were discussed. Important work on a patient registry, health economics, and a new international clinical care guideline were reviewed. The very exciting TestFSHD pilot program, whose goal is to lower barriers to genetic testing for FSHD, was presented by Jamshid Arjomand, chief science officer of the FSHD Society. The new initiative presents an opportunity to prepare FSHD patients to participate in clinical trials, as one of the eligibility criteria for volunteering in an FSHD clinical trial is positive confir-



The 2022 Industry Collaborative workshop

mation of the disease by a clinically approved genetic test. TestFSHD offers an opportunity to 150 individuals to secure a genetic test at no cost to patients. More information can be found at *fshdsociety.org/testfshd/*.

The Society's 2019 workshop resulted in a white paper that was used as the foundational document for the Society's Therapeutic Accelerator programs. This year's workshop will offer updated guidance for future priorities and strategies. the World

29th FSHD International Research Congress

More companies and greater focus on trial outcomes

BY ALEXANDRA BELAYEW, PHD, MONS, BELGIUM



his year's congress opened with a keynote presentation by Lexi Pappas, who gave a very moving testimony of what it can be like to live with FSHD. She noted that the image of FSHD as a slowly progressing disease for older adults is not true for many. At 28 she has already experienced a rapid decline, as



Alexandra Belayew, PhD

seen in videos taken now and five years ago. Developing effective therapies is an urgent matter for patients since they lose strength and independence with every passing year.

I then gave a talk to provide a historical perspective for the many researchers who recently joined the FSHD field. I described the issues encountered by the pioneers who discovered and characterized the *DUX4* gene: the conditions in which FSHD muscle cell cultures express very low amounts of *DUX4* mRNA and protein, the high toxicity of DUX4 protein, hundreds of similar genes that proved not to be linked to FSHD ... and the then-widely accepted concept that repeat-DNA was "junk DNA" and could not harbor a functional gene like *DUX4*.

The other keynotes also engaged the audience around broader topics. Eva Chin, PhD, executive director of Solve FSHD, a new Canadian venture philanthropy with a \$100 million budget, described the organization's aims to facilitate the transition from fundamental research to drug development. Jane Larkindale, PhD, of Pepgen, pleaded for scientific and clinical data sharing in rare-disease research and presented an FDA-funded project, the RDC-DAPP, to standardize data from diverse sources and facilitate investigators' navigation through such datasets.

Discovery research

DUX4 protein is normally only expressed for 24 hours in the four-cell human embryo and wakes up a large gene set to initiate its development. We already knew that in FSHD muscles, inappropriate *DUX4* expression was activating the same gene set, as if to convert muscle to early embryo. Danielle Hamm, PhD, from the Stephen Tapscott lab at Fred Hutchinson Cancer Center, presented an additional *DUX4* property: It only allows protein synthesis of the mRNAs expressed from the genes it activates and prevents protein synthesis from other mRNAs normally present in muscle (and needed for healthy muscle function).

Christopher Brennan and collaborators from several pharmaceutical companies (Pfizer, Entrada, Kymera, Sanofi) searched for ways in which DUX4 protein could convey toxic signals inside the muscle cell. They found it activates enzymes including p38 MAPK, which activates *DUX4* expression which in turn further activates p38 MAPK, driving more *DUX4*. Losmapimod, the Fulcrum Therapeutics drug that is in a Phase 3 clinical trial for FSHD, appears to interfere with this vicious cycle.

Researchers of Davide Gabellini's group at San Raffaele Scientific Institute, Milan, Italy, are developing new therapeutic strategies. Paola Ghezzi found a protein called MATRIN3 which prevents *DUX4* from binding to its target genes. She cut MATRIN3 into pieces and identified the smallest fragment capable of inhibiting *DUX4*. This frag-



ment has been synthesized by a collaborating biotech to be evaluated as a putative drug in mouse models. Emanuele Mocciario focuses on the mechanism by which the DBET long RNA, found several years ago by the group, activates *DUX4*. He has identified a protein that binds to DBET and is required for this activation, and is now developing molecules to inhibit this process.

Genetics and epigenetics

Epigenetics refers to the way DNA is packed with proteins to form chromatin. Small chemical marks called methylations can decorate the DNA. DNA hypermethylation causes compact chromatin and prevents gene activation, while hypomethylation is linked with open chromatin allowing for gene expression.

Anna Karpukhina from Yegor Vassetzky's group (Institut Gustave Roussy, Villejuif, and Koltzov Institute, Moscow) presented her complex strategy to restore normal DNA/ chromatin loop organization in the nuclei of FSHD muscle cells with the aim of decreasing *DUX4* gene expression.

Russell Butterfield (University of Utah) studies the large FSHD kindred with more than 2,000 descendants of a single gene carrier who arrived in Utah in the 19th century. Using Nanopore sequencing technology, he studied methylation of long DNA stretches with up to 12 D4Z4 repeats and found lower methylation of the last D4Z4 unit, which favors activation of its *DUX4* gene.

Mitsuru Sasaki-Honda (Kyoto University) received the Best Poster prize for his project of "hit and run" D4Z4 methylation to prevent *DUX4* gene expression. With a modified CRISPR/Cas9 system he targeted the *DUX4* gene with KRAB, a potent transcription inhibitor (similarly to C. Himeda and P. Jones, University of Nevada), combined with a DNA methylating enzyme to form compact chromatin. The inhibitor combination strongly decreased *DUX4* expression. His therapeutic strategy is to use an engineered virus to administer these inhibitors multiple times as needed by patients.

Pathology and disease mechanism

Although the role of aberrant *DUX4* expression in the pathophysiology of FSHD is undisputed, the mechanism by which *DUX4* exhibits toxicity to muscles remains elusive. This session focused on the various mechanisms by which *DUX4* can elicit toxicity in muscles. Philipp Heher (King's College London, Prof. P. Zammit) focused on mitochondria, the small, energy-producing units in our cells. *DUX4* causes oxidative stress by disturbing mitochondrial function, resulting in less effective metabolism. Use of antioxidants that enter mitochondria proved more efficient in rescuing cell metabolism.

Michael Kyba (University of Minnesota) discovered a new mechanism of *DUX4* toxicity causing cell suicide. This process is normally counteracted by the FAIM2 protein, but *DUX4* interferes in two ways: by inducing an enzyme that destroys FAIM2 and by miR-3202 microRNA, which blocks FAIM2 synthesis. Suppression of miR-3202 rescues FAIM2 and could constitute a new therapeutic strategy.

Prakash Kharel (Harvard Medical School, Prof. Pavel Ivanov) described his investigation of *DUX4* mRNA toxicity linked to unusual G-rich structures (G-quadruplexes) it harbors that favor interaction with various proteins.

Tessa Arends (Fred Hutchinson Cancer Center, Prof. S. Tapscott) followed previous studies on *DUX4* target genes in repeated DNA (satellite repeats) located in the central part of chromosomes. Accumulation of these repeated RNAs in muscle cells contributes to *DUX4* toxicity by disturbing chromatin structure and DNA repair pathways.

Interventional strategies

These strategies address either *DUX4* repression or improvement of muscle regeneration. Several groups are investigating mesenchymal stem cells (MSCs), usually derived from bone marrow, that can be injected to help muscle regeneration.

Nizar Saad (The Ohio State University) studies tiny bubbles (extracellular vesicles) which MSCs produce in the test tube and naturally contain therapeutic substances. He has optimized their purification and shown that injecting them into mouse models of FSHD strongly reduced *DUX4*induced damage to muscles.

Barbora Malecova (Avidity Biosciences) presented very encouraging preclinical data about a small inhibitory RNA (siRNA) targeting the *DUX4* mRNA for destruction. This agent is coupled to an antibody that recognizes transferrin receptor 1, which is found mostly on muscle membrane. The antibody delivers the siRNA to the muscle. Full muscle protection occurred when the drug was injected in mouse blood two weeks before *DUX4* expression. However, additional mouse tests should now target muscles already expressing *DUX4*, which better mimics the situation in patients.

Afrooz Rashnonejad (The Ohio State University) is in the early stages of developing an AAV virus that expresses a CRISPR/Cas13 system to cut *DUX4* mRNA, which would prevent *DUX4* from being translated into the toxic protein.

Karim Azzag (University of Minnesota, Profs. R Per-

lingeiro and M. Kyba) proposes to graft muscle progenitors to help mouse muscle regeneration. Interestingly, these cells engrafted more efficiently in *DUX4*-expressing muscles and formed new fibers that improved contraction.

Clinical studies and outcome measures

A major issue for clinical trials is the availability of biomarkers and imaging markers to evaluate disease progression and treatment efficacy despite the heterogeneity in FSHD presentation. A study named ReSolve has been following the evolution (natural history) and muscle strength/function of 240 patients over two years at nine US and two EU centers.

Sjan Teeselink (University Hospital Nijmegen, Prof. Baziel van Engelen) shared data on muscle imaging by easy and cheap ultrasound analysis to distinguish FSHD from healthy muscles.

Mauro Monforte (University Hospital A. Gemelli, Rome, Profs. E. Ricci and G. Tasca) received the Best Young Investigator award for his use of artificial intelligence to improve the accuracy of diagnosis with MRI (magnetic resonance imaging) by retrospective analysis of 300 patients with and without FSHD, and evaluation of 15 image parameters.

Jeffrey Statland (University of Kansas) presented on the reachable workspace measure (RWS), which was used for the losmapimod (Fulcrum Therapeutics) Phase 3 clinical trial. RWS correlates with patients' everyday functions (see story on page 17). The test is easy to perform, with the person sitting on a chair and moving the arms as shown on a video screen, with automated movement measures.

I have attended every FSHD International Research Congress since 1997, and this year I was really impressed by the number of companies that joined the search for drugs against FSHD, and by the efficiency of researchers and clinicians networking in the quest for biomarkers that could reliably detect changes in disease progression or drug efficacy in the many clinical trials that are about to start.



A long journey but worth it

Through the World FSHD Alliance, we work together

BY RICARDO GERPE, FSHD SPAIN

had decided to go to Orlando for the FSHD Connect conference, although due to my work responsibilities, I could only attend the Sunday session. It was a 20-hour journey from my home in Spain, and by the time I arrived at the Waldorf Astoria, I was asking myself if coming for just one day was worth such an exhausting trip.

The moment I walked into the conference ballroom, I knew I had made the right decision. I was in a room with hundreds of other people with FSHD, and I immediately felt connected, deeply so, with all of them. I knew several people from previous virtual meetings like the Wellness Hour, and this was the perfect occasion to see them all in three dimensions, which was great.

Virtual meetings provide the unbeatable benefit of allowing people from anywhere to participate, regardless of location and time. It is convenient for planning and executing activities or for sharing information. But face-to-face meetings add an extra layer of feelings and motivation.

Additionally, having the option to talk to the pharmaceutical industry representatives and researchers was truly amazing. All of them said that meeting the individuals who would benefit from their work was inspiring and energizing.

Just these two things I've mentioned made the trip worthwhile.

I was wearing two hats (actually three if we count the orange one for World FSHD Day!). One hat was as a patient, interested in all the new



"The moment I walked into the conference ballroom, I knew I had made the right decision. I was in a room with hundreds of other people with FSHD, and I immediately felt connected, deeply so."

- RICARDO GERPE

things presented here and in all the people I could meet. The second hat was as a representative of FSHD Spain, the patient advocacy group in my country, so I kept an eye open for what is relevant to our organization and how we can both benefit from and contribute to common goals. In that sense, the actions we take in the World FSHD Alliance, which encompasses two dozen FSHD associations from around the globe, are aimed at common objectives. There are no borders for this illness. We come from different degrees of

organizational development, but we share similar obstacles and the same ultimate goal – to help patients and support finding a cure.

I returned back home energized by what I had seen, full of hope that there will be a cure at some moment, and with work to do for the World FSHD Alliance, aiming to reach our objectives and optimize our resources.

I would like to thank the FSHD Society for having made this possible, and for the continuous help to all of us. I wish I could put into words how grateful I am to all of its staff.

Walk & Roll 2022

"The most powerful weapon on Earth is the human soul on fire." - Ferdinand Foch

BY JUNE KINOSHITA, FSHD SOCIETY

he FSHD Society's Therapeutic Accelerator program is about research – and so much more. Patient involvement in all aspects of our activities is every bit as essential and vital to speeding up the development of treatments. Through our chapters, virtual meetings, and conferences, we are building an educated, empowered, and activated community. Nothing embodies this spirit better than our flagship international fundraising event, the Walk & Roll to Cure FSHD.

Launched in 2018, this annual event is an incredible example of how individuals, working at the grassroots, can build a huge movement simply by showing up, connecting, and joining together around a single purpose.

I experienced the power of the Walk & Roll viscerally when I joined Ally Roets, her son Sam Ray, and their friends and supporters in Tucson last September 18. We met in a lovely municipal park, and about a dozen of us walked and rolled on a nicely paved circuit. While we walked, Tim Hollenback from FSHD Radio connected with us via smartphone, and we all waved at the online audience and shared what we were doing. As we did so, I had a powerful sense that we were far more than a scrappy little band out in the Arizona desert. We were participating with more than a thousand others. This was a huge Walk & Roll! We just happened to be in different places, but we were together in spirit. And the impact was just as



huge - more than \$820,000 raised.

FSHD may be a rare disease that most people have never heard of, but we are smart, nimble, determined, and effective. Join a team this fall, virtually or in person, and feel the awesome power of human souls on fire.



Clockwise from upper left: Heloise Hoffmann and Lucca's Beard band; Cassidy Dunn in Idaho; Ontario, Canada, Walk & Roll team; Arizona Walk & Roll team; Amy Bekier (right) with "Amy's Army" in San Diego; sidewalk chalk message from the Minnesota Walk & Roll.

Therapeutic Accelerator update

Trial Readiness

Bringing us closer to treatments by 2025

BY JAMSHID ARJOMAND, PHD; JUNE KINOSHITA AND LEIGH REYNOLDS, FSHD SOCIETY

S ince the genetic disease mechanism of FSHD was discovered in 2010, our field has gained tremendous momentum. While the FSHD Society continues to invest strongly in discovery research, it has also taken on many additional essential projects to pave the way for successful clinical trials and the approval of effective therapies.

Nearly two dozen companies have or are exploring drug development programs in FSHD. We listen to their challenges and map out a responsive strategy for overcoming obstacles. On the following pages, you'll read about some of our projects that are designed to bring all companies that are developing treatments closer to our shared goal – therapies for our families by 2025.

Artificial intelligence to mine FSHD datasets

Seeking evidence to help design future clinical trials

The FSHD Society has launched a collaboration involving the FSHD Clinical Trial Research Network (CTRN) and BullFrog AI, an innovator in artificial intelligence based

in Gaithersburg, Maryland, to analyze the largest-yet natural history dataset collected from patients with FSHD.

"We hope these studies will help with clinical trial design and patient stratification to accelerate clinical trials for our community," said Jamshid Arjomand, PhD, chief science officer at the FSHD Society.

BullFrog AI will be using the bfLEAP[™] platform to analyze a large and multidimensional clinical dataset of FSHD collected by the FSHD CTRN in the National Institutes of Health (NIH)-funded Clinical Trial Readiness to Solve Barriers to Drug Development in FSHD (ReSolve) study. The study enrolled 220 patients at eight US and three European CTRN sites, and used multiple motor outcome instruments to track disease progression over 24 months, including an FSHD Functional Composite, the Motor Function Measure



Domain 1, Reachable Workspace, and electrical impedance myography.

The AI analysis is aimed at assessing which outcome measures, or combination

of measures, are most sensitive to changes associated with disease progression. Additionally, as FSHD is known to have variable rates of progression among individuals, the investigators hope to identify other factors or medical conditions that correlate with different rates of progression.

Individuals who have factors correlating with faster progression would be good candidates for inclusion in a clinical trial, because they would be more likely to demonstrate whether an experimental therapy is able to slow disease progression.

Jeffrey Statland, MD, the co-director of the FSHD CTRN, said, "This collaboration can set the stage for more efficient clinical trial design, and can serve as a model for collaborations with AI companies to evaluate large clinical trial preparedness datasets."

Data, data everywhere...

Collecting it for analysis can unlock insights

The FSHD Society has partnered with the Critical Path Institute (C-Path) in Tucson, Arizona, to help aggregate clinical trial data from the placebo arm of various FSHD-related clinical

studies into C-Path's Rare Diseases Cures Accelerator Data and Analytics Platform (RDCA-DAP). As part of this collaboration, several companies that have sponsored clinical trial studies in FSHD agreed to share data to this repository.

The integration of these data makes it possible to analyze data from larger numbers of patients than would otherwise be possible, and provides a more robust and detailed understanding of the natural disease progression in FSHD. This is particularly important in rare diseases like FSHD that progress at slow and unpredictable rates.

"RDCA-DAP promotes the sharing of existing patient data and encourages the standardization of new data collection," said Alexandre Bétourné, PhD PharmD, scientific director of RDCA-DAP. "By integrating such data in a regulatory-grade format suitable for analytics, RDCA-DAP accelerates the understanding of disease progression, clinical outcome measures, and biomarkers, and facilitates the development of mathematical models of disease and innovative clinical trial designs."

CRITICAL PATH

Organizations participating to date in the FSHD Society's initiative include the University of Rochester and Acceleron Pharma, recently acquired by Merck & Co., Inc.

The University of Rochester trial enrolled 90 patients to assess the effectiveness of albuterol, a beta-adrenergic agonist, at increasing the strength of FSHD patients. The study concluded in 2015. The functional data collected in this study included quantitative voluntary isometric contraction testing and muscle mass assessments by dual energy X-ray absorptiometry (DEXA).

Acceleron, based in Cambridge, Massachusetts, is contributing placebo data from its Phase 2 randomized, placebo-controlled trial of ACE-083. This therapy was designed to increase the strength and function of specific muscles in FSHD patients. Ninety-five patients were enrolled in the study, which terminated in October of 2019. Acceleron has agreed to provide data collected from the placebo arm of the study, including total muscle volume (measured by MRI) and quantitative muscle strength.

"We are grateful for the generosity of Acceleron and the University of Rochester for their leadership in this *Continued on page 19...*

True Cost of FSHD

Part of our battle plan to ensure patients will have access to treatments

The FSHD Society is undertaking a major study of the full socioeconomic

burden of FSHD. This is one of the most important and urgent studies we have ever done, and is the first of its kind in the US. Our goal is to learn about the costs in medical care as well as the unreimbursed and hidden costs that patients and families bear in out-of-pocket spending, unpaid caregiver hours, and lost educational and work opportunities.

Why is this so important? Our study will bolster the socioeconomic case, or "value proposition," for treatments for FSHD. This, in turn, influences the price of treatments and how much government healthcare systems and private insurance are willing to pay for it. We will publish our findings in key journals to make sure decision makers understand the true costs of living with FSHD and the difference that treatments can make in people's lives.

True Cost of FSHD Here's the plan. Part 1 is a collaboration with companies that own huge insurance claims databases to analyze how people with FSHD use the healthcare system and what the costs are. Part 2 is our True Cost of FSHD survey, which has just been sent out to hundreds of patients and family members who volunteered to take the survey. This study would literally not be possible without the help of our community, and for this we are incredibly grateful.

> We know that the lifetime costs of FSHD are significant, but there has been very little research done to date on the broad socioeconomic impact of FSHD. Yet it's imperative to understand the true costs, especially as we get closer to treatments. Our vision extends beyond North America. We are encouraging patient advocates in the World FSHD Alliance to undertake health economics research in their countries.



Will you join us in our PACT?

Patients Accelerating Clinical Trials

When newly diagnosed individuals contact the FSHD Society, they have two main concerns: What can I do to ensure I am living the fullest life possible? And when will there be treatments and a cure for FSHD?

The FSHD Society is doing all we can to ensure these needs are met. We are one of the few organizations in the world with a sole focus on FSHD that is engaged in patient education and support, and leading the way on a broad spectrum of research initiatives.

In 2018, we set an extraordinary goal to see the first-ever FSH muscular dystrophy therapy approved by the year 2025. That's just three years away. Currently, there are more than 20 companies with drug development programs in FSHD. Growing numbers of them are advancing from preclinical into clinical development. As we look ahead to multiple Phase 2 and Phase 3 clinical trials (in patients), we know significantly more patients will need to be engaged in the process.

Because FSHD is rare, affecting an estimated one in 8,000 to 15,000 people, and patients are scattered around the world, it is imperative to have a unified database of individuals with FSHD who are willing to participate in research initiatives.

To respond to this need, the FSHD Society brings you PACT: Patients Accelerating Clinical Trials. PACT is your onramp to participating in all types of research – completing surveys, volunteering for a clinical trial, or joining the upcoming PACT FSHD Registry. This registry will be an online platform where you will be able to contribute your data and access all types of research, including clinical trials. We are aiming to launch the PACT FSHD Registry in early 2023. This will help researchers get the information they need faster, speed up trial enrollment, increase trial efficiency, and reduce drug development costs.

The PACT FSHD Registry fills a critical gap in the research ecosystem. Our current contact registry is a basic marketing database – a targeted email list. In addition, there are several natural history registries, and they have greatly added to our understanding of FSHD, but they have a narrower focus and are limited in their capacity to engage patients on a deep and ongoing basis.



The PACT FSHD Registry will:

- Collect the patient perspective. You are the expert on your disease experience, so this platform will be patient powered and patient centered.
- Gather information in a standardized format. This will tell us about the patient journey, identify unmet medical needs, articulate patient preferences, and reveal more about the disease burden on everyday lives.
- Be hosted on a secure software platform that follows comprehensive measures to protect your information.
- Be easy to access online and from the comfort of your own home on your computer, tablet, or cell phone.

Although the PACT FSHD Registry platform will launch in early 2023, you can engage now:

- Sign up at FSHDSociety.org/PACT.
- · Participate in our True Cost of FSHD survey.
- · Sign up for MOVE & MOVE+.
- Encourage other affected family members who have been on the sidelines to "get in the game."

Your participation in PACT is the single most important commitment you can make to accelerate research and find treatments and a cure. Will you join us in our PACT?





Trial Readiness

Fulcrum's Phase 3 clinical trial has launched

Losmapimod has the potential to be the first drug to treat FSHD

BY JUNE KINOSHITA, FSHD SOCIETY

he much-anticipated Phase 3 clinical trial of losmapimod, an experimental FSHD treatment being developed by Fulcrum Therapeutics, formally began this summer with the dosing of the first volunteer at the University of Massachusetts Medical School in Worcester.

In laboratory experiments, losmapimod reduces the expression of *DUX4*, the gene that is seen as the root cause of FSHD. Data from Fulcrum's Phase 2 trial of the drug, announced in June of 2021, demonstrated that losmapimod was superior to placebo across a number of clinically relevant endpoints. (See our story in *FSHD Advocate*, 2021, issue 2, page 14.)

The Cambridge, Massachusettsbased company designed the Phase 3 trial to show whether this drug is safe and effective in slowing the progression of FSH muscular dystrophy. The randomized, double-blind, placebo-controlled Phase 3 trial, called REACH, will enroll approximately 230 adults at more than 30 sites in the US, Canada, and Europe. The trial is designed to support the US FDA and European Medicines Agency (EMA) regulatory applications of losmapimod for the treatment of FSHD. If approved, losmapimod would be the first and only therapy for the disease.

The primary efficacy endpoint in the REACH study will be the change over the course of the trial in a measure called reachable workspace (RWS). RWS is a method using the Kinect game controller to track a person's arm movements in three



dimensions. FSHD-related changes, such as a worsening of scapular winging or loss of strength in upper body muscles, lead to a decrease in RWS. These decreases correlate with real-life changes that are meaningful to patients. For example, as RWS decreases, individuals have greater difficulty with dressing, self-care, and the ability to carry out daily tasks. The RWS was developed by Jay Han, MD, of the University of California, Irvine, with help from the FSHD Society and other funders.

Secondary endpoints in the trial include muscle fat infiltration (MFI), an indicator of muscle health that is measured using magnetic resonance imaging (MRI); Patient Global Impression of Change (PGIC); and Quality of Life in Neurological Disorders of the upper extremity (Neuro QoL UE), a measure of patient self-reported health-related quality of life. "The initiation of the REACH trial is a testament to our deep commitment to addressing the unmet medical needs of those living with genetically defined rare diseases, and exemplifies our leadership in FSHD," said Judy Dunn, PhD, Fulcrum's president of research and development.

Individuals who are interested in enrolling can visit *reachfshdstudy. com* to learn if they might be eligible. Thirty-two sites across the US, Canada, Europe, and the UK are listed as locations for the trial, according to *clinicaltrials.gov*, where you can find the latest updates.

Avidity Biosciences, Dyne Therapeutics, and Arrowhead Pharmaceuticals have announced plans to begin clinical trials of their FSHD therapies within the next 12 months. The issue of "clinical trial readiness" for the FSHD community is more urgent than ever.

Actor with FSHD returns to the stage

Madison Ferris made history in 2017 when she became the first wheelchair user to play a lead role on Broadway, where she portrayed Laura Wingfield in *The Glass Menagerie*. This fall, the actor, who has FSHD, will star in *All of Me* by Laura Winters. Here's the synopsis: "Boy meets girl. Boy uses wheelchair, girl uses wheelchair. Boy and girl use text-to-speech technology to connect to each other and the world around them. Love is holding them together even when



the people in their lives want to pull them apart. It's a romantic coming-ofage story that hasn't been seen before. *All of Me* is a hilarious and candid portrayal of disability and class in present-day America" (from Barrington Stage Company website).

The 2021 Burman New Play Award-winning play will have its world premiere with the Barrington Stage Company in Pittsfield, Massachusetts. The show will run from September 21 to October 9. Tickets are available online.

FSHD Radio podcast highlights

In our April 12 podcast, **Christel Rohrs,** who leads the FSHD South Africa support group on Zoom, shared her experience as a volunteer working with young victims of sex trafficking in Thailand.



On April 28, **David Younger** spoke about why

he has chosen to become one of our most active community members.

You can listen to FSHD Radio podcasts on the FSHD Society YouTube channel, Facebook page, and most podcast platforms.

Webinars to watch

All of these webinars are available for your viewing pleasure on the FSHD University page at *fshdsociety.org/fshd-university/*.



Fulcrum's Phase 3 Trial, with Judy Dunn, PhD, president of research and development, Fulcrum Therapeutics

Managing Pain in Individuals with FSHD, with neurologist Kathy Mathews, psychologist Krista Kohl, and physical therapist Shelley Mockler

Changing Our Mindset about Assistive Technologies, with Emma Weatherley, executive director, FSHD Global Foundation

The MOVE and MOVE+ Studies: All Ages Wanted! with Johanna Hamel, MD; Kate Eichinger, PhD; and Natalie Katz, MD

Exoskeleton provides a boost



At the FSHD Connect conference's breakout session on exoskeleton technology, Thomas Schratwieser from MyoMO lets a delighted Shandy Kawabata test out the company's upper body assist device, called the MyoPro.

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United in our fight against FSHD

experience of diagnostics. We are thrilled to continue to work with Peter and facilitate screening in Australia.

It was also an honor to meet Silvère van der Maarel, PhD, whose laboratory at the University of Leiden in the Netherlands ran the genetic test that conclusively proved Hannah is clear of FSHD. He has worked with FSHD Global for a long time, and we are very grateful for his continued devotion to FSHD research.

At FSHD Global we know that taking these connections and experiences into our work with FSHD patients in Australia will be of significant benefit. Our clinical trial readiness program has gained momentum, and we were able to develop key relationships during this event.

We left the weeklong conference with renewed energy and determination to ensure that Australians with FSHD are able to join the global efforts against FSHD and be part of the solution. Our diagnostics and clinical trial readiness programs are critical, and we are working hard to build clinical trial infrastructure and connect Australia to the world. We would like to thank the FSHD Society for hosting such an amazing event, and we would encourage any patient or FSHD organization to join future events because, as we always say, "We are stronger together."

Upcoming

Visit our Events Calendar for updates and to register for events (fshdsociety.org/ fshd-events-calendar/).





October 22: University of Utah FSHD 360 conference (in-person and virtual)

November 12: Kansas City FSHD 360 conference (in-person and virtual)



Take part in the Walk & Roll to Cure FSHD this year! Visit FSHDSociety.org/Walk-Roll.

September 10: Pacific Northwest Walk & Roll to Cure FSHD September 10: San Diego Walk & Roll to Cure FSHD September 10: Southwest Florida Walk & Roll to Cure FSHD September 11: Colorado Walk & Roll to Cure FSHD September 17: Walk & Roll to

Cure FSHD in 19+ locations. Check calendar.

September 17: International FSHD Walk & Roll Livestream September 24: North Texas Walk & Roll to Cure FSHD September 24: Virginia Walk & Roll to Cure FSHD September 25: Minnesota Walk & Roll to Cure FSHD October 1: New England Walk & Roll to Cure FSHD October 15: Los Angeles Walk & Roll to Cure FSHD October 16: Atlanta Walk & Roll to Cure FSHD November 5: Central Texas Tacos and Tunes to Cure FSHD November 5: Western PA Drum & Roll

November 15: Magic for a Cure, Hoboken, NJ



Advance registration required.

August 18: Resilience and FSHD, Kent Drescher, PhD September 25: Exercise and Nutritional Interventions for the Treatment of FSHD, Mark Tarnopolsky, MD PhD October 20: Bowel and Urinary Issues in FSHD, Michael Cole, MD November 17: Drug Development Update, Jeffrey Statland, MD



Community Profiles, second Tuesday of each month, are indepth interviews with remarkable people in our community. Hot off the Press, fourth Thursday of each month, is short-form shows that will bring you the latest and greatest from the FSHD Society. All episodes premiere at 9 p.m. ET | 8 p.m. CT | 7 p.m. MT | 6 p.m. PT on the dates listed, and are available to stream on-demand on major streaming platforms.

August 9: Community Profiles August 25: Hot off the Press September 13: Community Profiles

September 22: Hot off the Press October 11: Community Profiles October 27: Hot off the Press November 8: Community Profiles November 24: Hot off the Press

CHAPTER MEETINGS

Our 30+ chapters are busy planning meetings for this fall so please visit our Events Calendar for updates. Many meetings are virtual or hybrid. All are welcome to join from anywhere. Please pay attention to the time zones.



Early-Onset Parent Roundtable

Third Tuesday of every month at 8 p.m. ET | 7 p.m. CT | 6 p.m. MT | 5 p.m. PT. One-time registration required.

August 16 September 20 October 18 November 15

GenZ of FSHD

Unless otherwise noted, second Sunday of every other month at 3 p.m. ET | 2 p.m. CT | 1 p.m. MT | noon PT. One-time registration required.

August 7: Fundraising Is Empowering September 18: Adaptive Sports November 20: TBD

CarePartner Hour

Last Tuesday of every month at 8 p.m. ET | 7 p.m. CT | 6 p.m. MT | 5 p.m. PT. One-time registration required.

August 30 September 27 October 25 November 29

Wellness Hour

Second Monday of every month at 5 p.m. ET | 4 p.m. CT | 3 p.m. MT | 2 p.m. PT. One-time registration required.

August 8 September 12 October 10 November 14

Women on Wellness

First Wednesday of every month at 5 p.m. ET | 4 p.m. CT | 3 p.m. MT | 2 p.m. PT. One-time registration required.

September 7 October 5 November 2

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Data, data, everywhere ...

effort, and for sharing meticulously collected clinical data to help advance the field of FSHD and clinical trial design," said Jamshid Arjomand, PhD, chief science officer of the FSHD Society. "We look forward to continuously augmenting these datasets as new studies generate additional clinical data. Over time, this project will lead to insights that will improve the design of clinical trials for FSHD."



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TOGETHER, WE MOVE TOWARD A CURE!







Join us for the Walk & Roll to Cure FSHD – fall 2022

In-person or online, in a small group or a large crowd, join us and Walk & Roll your way! Events are taking place this fall across the US and in Canada.

The Walk & Roll to Cure FSHD unites families, friends, neighbors, co-workers, and local businesses around one common goal. It has raised more than \$2 million for high-impact programs to move us faster toward the day when treatments will be available to our families.

Get involved

Join a Walk & Roll near you, or join the US or Canadian virtual campaigns (FSHDSociety.org/WalkRoll).

Ready to lead? Check out the Team Captain Toolkit (fshdsociety.org/walk-roll-teams/).



