Muscular Dystrophy Coordinating Committee Meeting
September 17, 2018
NIH via WebEx

2018 FSHD International Research Congress and 2018 FSHD Patient Connect

Daniel Perez, Co-founder & CSO, FSH Society

FSH SOCIETY
FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

FSH Society
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Day 1 [1.0 day]

Review/Data dump

Review of **previous year's priorities** as stated by FSHD workshop

5 **platform sessions** (30+ presentations)

poster sessions (25+ posters)

Recap

Day 2 [0.5 day]

International "lab meeting"

Discussion/Planning **Planning and problem solving session(s)**

Moderated discussion sessions with entire group focusing on data presented at day 1. Identify and troubleshoot bottlenecks; and, define the research/clinical **priorities for the next year 2018/2019**

https://www.fshsociety.org/wp-content/uploads/2018/06/2018ResearchConferenceProgramFINAL.pdf

SCHEDULE

Friday, June 8, 2018—El Dorado Ballroom

BREAKFAST
7:00–7:55 a.m
El Dorado Ballroom Foyer & Carson City Ballroom

WELCOME
7:55 8:00 a.m.
Opening remarks
James Chin, Mark Stone, *2018 IRC Meeting Organizing Committee*

REVIEW OF 2017
8:00–8:10 a.m.
Review 2017/2018 priorities stated by FSHD workshop in 2016
Moderators: Michael Altherr, Stephen Tapscott, others TBD

PLATFORM SESSION 1—8:10–9:25 a.m.
Genetics, epigenetics, and related syndromes and diseases, cancers, and BOSMA Arhinia)
Moderators: Silvère van der Maarel and Marnie Blewitt

8:10–8:25 a.m.
Brand (presenter)/Talkowski: **Lessons in oligogenetics and pleiotropy: identical SMCHD1 alleles can be associated with arhinia, Bosma syndrome, FSHD2, comorbidities, or no phenotype at all**

8:25–8:40 a.m.
Mohassel/Shaw (presenter): **Deep neuromuscular phenotyping of arhinia patients with SMCHD1 mutations reveals a mild myopathy distinct from FSHD2**

8:40–8:55 a.m.
Jansz/Blewitt (presenter): **The epigenetic repressor, FSHD2 gene and FSHD1 modifier SMCHD1 functions by mediating long range chromatin interactions**

8:55–9:05 a.m.
Nguyen/Magdinier (presenter): **Genetic variability and identification of complex genotypes in FSHD patients by molecular combing**

9:05–9:15 a.m.
Lemmers (presenter)/van der Maarel: **Cis D4Z4 repeat duplications associated with FSHD2**

9:15–9:25 a.m.
Campbell (presenter)/Tapscott: **Identifying mechanisms that regulate DUX4 and the D4Z4 macrosatellite repeats**

9:25–9:35 a.m.
Discussion

PLATFORM SESSION 2– 9:35 11:00 a.m.
The role of DUX4 in development and disease
Moderators: Peter Zammit and Stephen Tapscott

9:35–9:45 a.m.
de Morrée (presenter)/Rando: **U1 snRNA controls alternative polyadenylation of Pax3 in muscle stem cells**

9:45–10:00 a.m.
Banerji (presenter)/Zammit: **Dynamic transcriptomic and morphological analysis of FSHD atrophic myogenesis reveals a correctable defect in mitochondrial biogenesis**

10:00–10:15 a.m.
Kyba (presenter)/Aihara: **Structural and functional studies on DUX4 in human myogenesis**

10:15–10:30 a.m.
Eidahl (presenter)/Harper: **Regulation of facioscapulohumeral muscular dystrophy candidate protein DUX4**

10:30–10:40 a.m.
DeSimone (presenter)/Emerson: **Identification of a DUX4-intercting protein and the hyaluronic acid pathway as novel therapeutic targets for FSHD**

10:40 10:50 a.m.
Mariot/Dumonceaux (presenter): **Myostatin expression in neuromuscular diseases: challenges and hopes**

10:50–11:00 a.m.
Saad (presenter)/Harper: **The natural microRNA miR-675 reduces DUX4 expression and toxicity in vitro**

11:00–11:15 a.m.
Discussion

Last year's FSHD research priorities are reviewed at the outset of the International Research Congress IRC Workshop. Additionally and subsequently, **presenters are asked to indicate in talks/posters which priorities they have addressed**

Priorities as stated by FSHD Research Community for FSHD Research in 2017/2018 at the 2016 FSH Society FSHD International Research Consortium, held November 10-11, 2016 in Boston, Massachusetts

Statement of FSHD Scientific/Research Priorities 2017
By consensus of the 2016 FSHD International Research Consortium

I. Clinical and therapeutic studies.

- There is a need for surrogate outcome biomarkers now that trials are becoming reality.
- Need for validated outcome measures - preferably internationally standardized.
- Additional natural history studies are required.

Highlighted comments from the group:

"Think a little bit about the issues that are posed by when therapeutic 'A' is actually in use how it might impact on the design and implantation of clinical trials. For Huntington's Disease, clinical studies which use the UHDRS, the Universal Huntington's Disease Rating Scale, rely heavily on movement. So that in fact if the use of tetrabenazine, which inhibits movement, is now allowed into the clinical trial, which may have to be, because it's an approved therapeutic which has become the standard of care, now what you've done is to dramatically diminish the dynamic range that is available to your therapeutic."

"So all of these outcomes discussed are going to become increasingly important as we move through the clinical development process, we need good data from them, as we can't really convince regulators that these are good outcome measures in the clinic that are clinically meaningful and should be approvable. The more people that start using these measures, the better, and, obviously, in a nicely longitudinal way, that's even better."

II. Genetics and epigenetics.

- Need to focus on the uniformity in the genetic testing and the subgrouping of patients as so far as that is possible for trial readiness.
- Further understanding of the epigenetic regulation of the repeats helps us to better understand the disease process and the disease mechanism and to identify therapeutic targets.
- The search for modifiers of the disease mechanism needs to be continued as this can explain variability and identify new therapeutic targets.
- Consistent measures of (epi)genetic changes are needed.

Highlighted excerpts from group discussion:

"Consider Request for Applications (RFA) from funding agencies related to one or more these priorities. Consider Sub-meeting(s) that certainly addresses each of these areas, sometime in the next 7 or 8 months. Essentially the establishment of a central equivalent of World Anti-Doping Agency (WADA) for the Olympics or something like that so that uniformity in the genetic testing is achieved and the sub grouping of FSHD patients can be done, done under uniform conditions."

III. Molecular mechanisms.

- Need to understand genetic toxicity in FSHD. There is a gap in our knowledge between DUX4 cellular toxicity and pathophysiological processes in FSHD.
- We need to understand the regulation and identity of DUX4. We need to know how to silence it, and how much to silence it.
- Refine relationship to other markers and correlation between the expression and activity, transcriptional activity of DUX4 with some of the markers that we currently have.

https://www.fshsociety.org/wp-content/uploads/2018/06/2018IRCAbstractBook.pdf

First Author	Presenting Author	Title
Banerji	Banerji	Dynamic transcriptomic and morphological analysis of FSHD atrophic myogenesis reveals a correctable defect in mitochondrial biogenesis
Brand	Brand	Lessons in Oligogenetics and Pleiotropy: Identical SMCHD1 Alleles can be Associated with Arhinia, Bosma Syndrome, FSHD2, Comorbidities, or No Phenotype at All
Calandra	Deidda	Large-scale methylation analysis in facioscapulohumeral muscular dystrophy (FSHD)
Cammish	Orrell	The UK FSHD Patient Registry: A Key Tool in the Facilitation of Clinical Research
Campbell	Campbell	Identifying mechanisms that regulate DUX4 and the D4Z4 macrosatellite repeats
Chang	Chang	Testing the potential for comorbidity of FSHD with arhinia using inducibility of DUX4 expression in dermal fibroblasts
Chen	Hayward	Single-cell Transcriptome Heterogeneity in Myogenic Cells from Individuals with FSHD
Chen	Chen	Systemic delivery of LNA gapmers targeting DUX4 improved muscle function in FLExDUX4 mice
Choi	Choi	Establishment of FSHD-PAX7 genetic reporter lines to study function of muscle stem cells in FSHD
Choi	Lim	Modular platform for the myogenesis of human embryonic stem cells by using multiple genetic reporter lines
Ciskewski	Popplewell	Novel epigenetic mechanisms regulating DUX4 expression
Claus	Claus	Direct interaction of DUX4/4c with the multifunctional protein C1QBP
Coulis	Coulis	Overexpression of DUX-4 induces muscle Tregs: A potential role for the immune system in FSHD
Cruz	Clarke	Protein kinase A activation inhibits DUX4 gene expression in myotubes from patients with FSHD
Daman	Daman	An FSHD cell xenograft assay for drug development
de Morrée	de Morrée	U1 snRNA controls alternative polyadenylation of Pax3 in muscle stem cells
Denny	Denny	High-Density Lipoproteins protect against DUX4-mediated damage in a lentiviral model of FSHD
DeSimone	DeSimone	Identification of a DUX4-intercting protein and the hyaluronic acid pathway as novel therapeutic targets for FSHD
Dion	Robin	Implication of SMCHD1 in D4Z4 epigenetic dynamics: lesson from IPSCs
Eidahl	Eidahl	Regulation of Facioscapulohumeral muscular dystrophy candidate protein DUX4
Giesige	Giesige	AAV.RNAi and follistatin gene therapy development in the TIC-DUX4 Mouse Model of FSHD
Hamel	Hamel	MRI Correlates to Electrical Impedance Myography in Facioscapulohumeral Muscular Dystrophy
Han	Han	Longitudinal study of Kinect-based upper extremity reachable workspace in FSHD
Hiramuki	Hiramuki	A mapping study of SMCHD1 identifies the region of nuclear localization, dimerization, and protein cleavage
Homma	Homma	DUX4 alters mRNA splicing of TDP-43 target genes
Horlings	Horlings	Clinical outcome measures, muscle imaging and (epi)genetic testing in a large cohort of FSHD patients
Hupper	Clarke	A low molecular weight compound screen in FSHD patient myotubes identifies modulators of Dux4 activity and novel mechanisms of action
Jansz	Blewitt	The epigenetic repressor, FSHD2 gene and FSHD1 modifier SMCHD1 functions by mediating long range chromatin interactions
Jones T	Jones T	The FLExDUX4 transgenic mouse can be used to develop FSHD-like mouse models with pathophysiology ranging in severity

First Author	Presenting Author	Title
Kazakov	Kazakov	Some problems connected with AD FSHD classification
Kyba	Kyba	Structural and functional studies on DUX4 in human myogenesis
Lemmers	Lemmers	Cis D4Z4 repeat duplications associated with FSHD2
Lopez	Lopez	Autologous stem cell treatment in FSHD. Preliminary report
Lu-Nguyen	Lu-Nguyen	In vivo assessment of antisense therapy for Facioscapulohumeral muscular dystrophy
Lunt	Lunt	No evidence for altered incidence of cancer in FSHD
Mariot	Dumonceaux	Myostatin expression in neuromuscular diseases: challenges and hopes
Maruyama	Maruyama	Development of LNA and 2'-MOE Gapmers to Treat Facioscapulohumeral Muscular Dystrophy
Mohassel	Shaw	Deep neuromuscular phenotyping of arhinia patients with SMCHD1 mutations reveals a mild myopathy distinct from FSHD2
Mueller	Mueller	Xenografting Human Muscle Stem Cells into Mice to Study FSHD
Nguyen	Magdinier	Genetic variability and identification of complex genotypes in FSHD patients by Molecular Combing
Pakula	Pakula	The role of estrogen regulation in FSHD-1
Rashnonejad	Rashnonejad	AAV.U7-snRNA-mediated exon skipping of the toxic DUX4 gene as a promising therapeutic approach for facioscapulohumeral muscular dystrophy
Rickard	Schmidt	GBC0905: A Novel Targeted Therapeutic Agent to Treat Facioscapulohumeral Muscular Dystrophy
Robertson	Robertson	Measurement of evidence of DUX4 as a proof of concept biomarker for FSHD clinical trials
Rojas	Rojas	Pharmacological inhibition of DUX4 expression rescues FSHD pathophysiology in FSHD skeletal muscle myotubes
Saad	Saad	The natural microRNA miR-675 reduces DUX4 expression and toxicity in vitro
Sacconi	Sacconi	FSHD1 and FSHD2 form a disease continuum
Sanson	Sacconi	Self-report questionnaire vs. clinical evaluation form in the French National FSHD Registry: a statistical comparison
Statland	Statland	Preliminary Results from a Dose-Escalation Phase 2 Study to Evaluate ACE-083, a Local Muscle Therapeutic, in Patients with Facioscapulohumeral Muscular Dystrophy
Teveroni	Moretti	Set-up of an in vivo model of facioscapulohumeral muscular dystrophy (FSHD) based on human perivascular cells
van den Heuvel	van den Heuvel	Single-cell RNA-sequencing in Facioscapulohumeral muscular dystrophy disease etiology and development
van der Stoep	van der Stoep	Evaluation of FSHD1 testing in diagnostics using FiberVision Molecular Combing technology
Zhang, VW	Zhang, C	Accurate molecular diagnosis of Facioscapulohumeral muscular dystrophy in a cohort of 37 Chinese patients
Zheng	Zheng, Y	A case of first trimester prenatal diagnosis for FSHD1 using Karyomapping and single-molecule optical mapping

5

Platforms

Genetics, epigenetics, and related syndromes and diseases, cancers, and BOSMA Arhinia)

The role of DUX4 in development and disease

Preclinical studies in FSHD, including cellular (myoblasts/ iPS) and animal models

Clinical studies and clinical trial

Industry aspects and therapy development (screens)

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New and current FSHD research priorities were defined by the "core" global FSHD research community at the 2018 International Research Congress IRC Workshop June 8, 9 in Las Vegas, Nevada

Drs. Nuckolls and Carifi sent to MDCC members via e-mail on 9/11/2018

FSHD research priorities stated by the FSHD research community at the **2018 International Research Congress IRC Workshop June 8, 9 in LVNV**

More than 135 scientists, patients, advocates, biotech and pharmaceutical company representatives, and clinicians from throughout the world gathered at the 2018 FSHD International Research Congress (IRC) and Research Planning meetings in Las Vegas, Nevada on June 8-9, 2018 to share and discuss their latest progress and ideas on facioscapulohumeral muscular dystrophy (FSHD) research since the last IRC meeting in 2016. The meeting was co-chaired by Michael Altherr PhD (FSH Society Scientific Advisory Board &Los Alamos National Laboratory, Los Alamos, New Mexico), Marnie Blewitt PhD (Walter and Eliza Hall Institute, Melbourne, AUS), Peter Jones PhD (University of Nevada, Reno), Michael Kyba PhD (Lillehei Heart Institute, University of Minnesota), Jeffrey Statland MD (University of Kansas, Kansas City, Kansas), Stephen Tapscott MD, PhD (Fred Hutchinson Cancer Research Center, Seattle, Washington), Silvère van der Maarel, PhD (Leiden University Medical Center, Leiden, Netherlands), Baziel van Engelen MD, PhD (Radboud University Nijmegen Medical Center, Nijmegen, Netherlands) and Peter Zammit, PhD (King's College London, London, United Kingdom). Daniel Paul Perez (FSH Society, Lexington, Massachusetts) served as the organizational chair.

The goal of this meeting was to integrate clinical and basic FSHD research, explore and verify the complex disease mechanism and various features of FSHD, and to follow up on considerations to move into the development of potential treatments for FSHD. All volunteer agencies working on FSHD were invited by the organizers and encouraged to attend. After a brief welcome by the organizers an overview was presented of previous IRC's priorities and their follow up as defined by the FSHD community in the calendar year 2016. Based on the publications that have appeared in the past year, it was again clear that there had been an exceptionally impressive response to the priorities formulated during the 2016 meeting.

The overview was followed by a full day of 29 platform presentations, combined with poster sessions, reviewing the latest advancements in 1.) genetics, epigenetics and related syndromes and diseases, 2.) the role of DUX4 in development and disease 3.) preclinical studies, including cellular and animal models, 4.) clinical studies and clinical trials, and 5.) Industry aspects and therapy development. Each platform session included presentations selected from pre-submitted abstracts. Group discussion followed each platform session, each moderated by two distinguished scientists, whose role was to facilitate discussion and active and candid debate of the topic. There was time to review and further discuss the latest developments at the posters. The IRC is a working meeting with experts, developing future plans in the context of what we know now and what we need to know. It was a very successful workshop with a positive, constructive and collaborative atmosphere where new and unpublished findings were communicated to the audience, and with excellent interaction between all participants. For the first time, we had presentations from industry with insightful and deep details about their drug development programs.

On Saturday, June 9, after being informed about the funding opportunities at the NIH by Glen Nuckolls (NINDS), a discussion and planning session ensued that included four session chaired and moderated by the scientific organizers. The following research priorities were selected for further discussion: (1) Therapeutics, (2) Pathophysiology, (3) Molecular Mechanisms and (4) Genetics and Epigenetics. From these discussions and analysis of transcripts of the meeting the following conclusions were made.

Priorities for FSHD research and funding in the coming year:

1. Therapeutics

Trial Tool Kit. While drug development pipelines are beginning to produce candidate drugs, the trial tool kit needs to be completed. Evidence was presented that MRI STIR positivity correlates well with DUX4 target gene expression but this needs further refinement and to be reproduced. MRI directs to active disease processes but longitudinal studies are needed. Uniform definitions for (interpretation of) MRI imaging

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https://www.fshsociety.org/wp-content/uploads/2018/08/2018-IRC-Priorities.pdf

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Current/new priority areas for FSHD

Therapeutics
Pathophysiology
Molecular Mechanisms
Genetics and Epigenetics

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1

Therapeutics

Trial Tool Kit.
Biological Biomarkers.
Clinical Outcome Assessments.
Alternative/complementary therapies.

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2

Pathophysiology

DUX4 With Regard to Fibrosis, Inflammatory Infiltrates and Fatty Infiltration.

Temporal Analyses of Models.

Novel Models for Other Aspects.

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3

Molecular Mechanisms

Mechanisms of DUX4 Pathology.
DUX4 Functionality.
DUX4 Native and Conserved Function.

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Genetics and Epigenetics

Harmonization of Genetic Testing.

Disease Continuum and Genotype Classification.

Understanding Drivers of Clinical Variability.

Role and Effects of Modifiers.

3c

Sample: Molecular Mechanisms

DUX4 Native and Conserved Function. The natural distribution and regulation of DUX4 expression should be studied. DUX4 is expressed at cleavage stage embryos but little is known about the regulation of DUX4 during development and which tissues express DUX4, as well as its (lack of) toxicity in those tissues. The distribution of DUX4 in FSHD muscle is not known, nor how it correlates with clinical and pathological aspects of FSHD muscle, nor at the preclinical level.

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4c

Sample: Genetics and Epigenetics

Understanding Drivers of Clinical Variability. Continuous efforts are necessary to increase our understanding of (the genetic and epigenetic basis) of clinical variability. Data presented at the workshop suggest that 50% of variance is familial, of which 10% comes from D4Z4 repeat size, but that this differs between muscle groups varying from facial muscles, upper and lower extremities approximately 30%, 15% and 3%, respectively. Suggests different vulnerability to DUX4 e.g. face is more sensitive to FSHD1 disease locus whereas leg depends on modifying factors. Genome wide studies in large patient coho may facilitate identification of modifiers, such as SMCHD1.

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Day 1 [0.5 day]

Understanding FSHD
- FSHD 101
- Care Guidelines
- Q&A

The Road to Treatments
- Trial Readiness
- Therapies 101
- Pipeline for Therapies

400 patients, family members, researchers, physicians, and health experts for a half-day and a day of intensive learning and community activism.

Day 2 [1.0 day]

Selected Presentations

- Sharing Our Stories
- Finding Our Voice
- Moving Well: P.T.
- Eating Safely
- Living Well With FSHD
- Loving Well
- Society's Chapter Pgm
- Respiratory Health

https://www.fshsociety.org/wp-content/uploads/2018/06/2018-FSHD-Connect-Program.pdf

FSHD Therapeutics

An Accelerator

Natural history and registry implementation
Biomarkers development and potential biomarkers
FDA/EMA requirements
Imaging, measurable markers and clinical outcome assessments
Innovative approaches to clinical trials and registration endpoints

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