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## Muscular Dystrophy Coordinating Committee Meeting

November 29, 2016

Neuroscience Center, Conference Room C/D

6001 Executive Blvd., Bethesda, Maryland 20892

## 2016 FSHD International Research Consortium

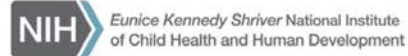
Daniel Perez, CEO & CSO, FSH Society



FSH Society  
450 Bedford Street  
Lexington, MA 02420 USA  
(781) 301-6060  
[www.fshsociety.org](http://www.fshsociety.org)

**FSH Society Facioscapulohumeral Muscular Dystrophy [FSHD]  
2016 International Research Consortium & Research Planning Meetings**

Sponsored by:



**FSH Society Facioscapulohumeral Muscular Dystrophy [FSHD]  
2016 International Research Consortium & Research Planning Meetings**

Thursday, November 10, 2016

8:30 a.m. – 6:00 p.m.

[Registration and breakfast begins 7:30 a.m.-]

Friday, November 11, 2016

8:30 a.m. – 12:45 p.m.

[Registration and breakfast begins 7:30 a.m.-]

**The Westin Copley Place Hotel, Staffordshire & Essex Rooms  
10 Huntington Ave, Boston, MA 02116 USA**

Co-Chairs: **David E. Housman, PhD**  
Massachusetts Institute of Technology, Cambridge, Massachusetts  
**Stephen J. Tapscott, MD, PhD**  
Fred Hutchinson Cancer Research Center, Seattle, Washington  
**Silvère van der Maarel, PhD**  
Leiden University Medical Center, Leiden, the Netherlands  
**Kathryn Wagner, MD, PhD**  
Kennedy Krieger Institute & Johns Hopkins SOM, Baltimore, Maryland

Organizer: **Daniel Paul Perez**  
FSH Society, Lexington, Massachusetts

Sponsored By:

Accelaron  
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Mouse Specifics  
Muscular Dystrophy Association  
Muscular Dystrophy Campaign (UK)  
NIH NICHD UMass Senator Paul Wellstone MD Cooperative Research for FSHD  
Quintiles  
Sarepta  
Ultragenyx

**NOTES ON TALKS AND POSTERS**

	<b>First/Last Author</b>	<b>Presenting Author</b>	<b>Topic</b>
* = 10 minute talk; others 15 minute			
Platform Session 1			
<b>Clinical Studies &amp; Genetics and Epigenetics</b> <b>Moderators: Rabi Tawil, Kathryn Wagner</b>			
9:00 – 9:15 a.m.	Capet/Sacconi	Sacconi	18p deletion
9:15 – 9:30 a.m.	Eichinger/Statland	Eichinger	composite outcome: 1 year find
9:30 – 9:45 a.m.	Gershman/Ashlock	Shukla	ATYR1940
*9:45 – 9:55 a.m.	Gordon/Reversade	Xue	SMCHD1 congenital arhinia
*9:55 – 10:05 a.m.	Lassche/van Englen	Lassche	Muscle weakness in FSHD
*10:05 – 10:15 a.m.	Shaw/Talkowski	Shaw	SMCHD1 congenital arhinia
*10:15 – 10:25 a.m.	Vercelli/ Tupler	Tupler	Disease progression and natural history
10:25 – 10:55 a.m.	<b>Discussion</b>		
10:55 – 11:10 a.m.	<b>Break</b>		
Platform Session 2			
<b>Molecular mechanisms</b> <b>Moderators: Scott Harper, Michael Kyba</b>			
11:10 – 11:25 a.m.	Casa/Gabellini	Gabellini	PRC1
*11:25 – 11:35 a.m.	Eidahl/Harper	Eidahl	DUX4 modifications and interactors
*11:35 – 11:45 a.m.	Jagannathan/Bradley	Jagannathan	RNA and Protein Toxicity
11:45 – noon	Lemmers/van der Maarel	Lemmers	bi-allelic expression of DUX4
noon – 12:15 p.m.	Whiddon/Tapscott	Whiddon	DUX4 network
12:15 – 12:45 p.m.	<b>Discussion</b>		
12:45 – 2:00 p.m.	<b>Lunch and Posters</b> (lunch located in Essex Ballroom Foyer)		
Platform Session 3			
<b>Models</b> <b>Moderators: Yi-Wen Chen, Louis Kunkel</b>			
2:00 – 2:15 p.m.	Bloch/Jones	Bloch	Mouse xenograft model
2:15 – 2:30 p.m.	Chal/Pourquie	Chal	iPS modeling
2:30 – 2:45 p.m.	Giesige/Harper	Giesige	inducible mouse model
2:45 – 3:00 p.m.	Kyba	Kyba	Cell and animal models
3:00 – 3:15 p.m.	Shi/Emerson	Emerson	iPS models
3:15 – 3:45 p.m.	<b>Discussion</b>		
3:45 – 4:00 p.m.	<b>Break</b>		
Platform Session 4			
<b>Therapeutic Studies</b> <b>Moderators: Charles Emerson, Jr., Davide Gabellini</b>			
4:00– 4:15 p.m.	Jubert/Dumoncaux	Dumoncaux	Talen mutation of DUX4 pA
4:15 – 4:30 p.m.	Murphy/Chen	Chen, YW	3 <sup>rd</sup> generation antisense
*4:30 – 4:40 p.m.	Rickard/Schmidt	Rickard	hESC chemical screen
*4:40 – 4:50 p.m.	Saad/Harper	Saad	mir-675 and FSHD
4:50 – 5:05 p.m.	Teveroni/Moretti	Moretti	estrogens suppress DUX4 activity
*5:05 – 5:15 p.m.	Wallace/Harper	Wallace	siRNA therapies for FSHD
5:15 – 5:45 p.m.	<b>Discussion</b>		
<b>Posters</b>	[	Anseau	Transcription DUX4 and DUX4c
		Chagarlamudi	Bone Health Cross-sectional Study
		Chen, J	Third Generation Oligonucleotide
		Choi	FSHD myogenic cell model and transcriptome
		DeSimone	C1QBP Inhibits DUX4 targeted with 4MU
		Gershman	ATYR1940
		Glasser	ACE-083

NOTES ON TALKS AND POSTERS (continued)

	First/Last Author	Presenting Author	Topic
<b>Posters</b>	Goselink	Goselink	Characterizing early onset FSHD
	Goselink	Goselink	FSHD biomarker: focus on the face
	Hall	Chamberlain	Mouse model of FSHD
	Hamanaka	Hamanaka	FSHD1 carrying 5-10 D4Z4 repeats and FSHD2
	Homma	Homma	Nuclear bodies
	Jones	Jones	Large family cohorts of LCLs
	Kazakov	Kazakov	Erb and Landouzy-Dejerine concerning
	Lek	Lek	Genome-wide gain- and loss-of-function
	Lemmers	Lemmers	SSLP-converter tool to enable
	Llach-Martinez	Llach-Martinez	Quality of Xenografts in Mice
	Moore	Moore	FSHD Diagnostic Testing at Iowa
	Pakula	Pakula	transgenic zebrafish model
	Statland	Statland	The FSHD Clinical Trial Research Network
	Sverdrup	Sverdrup	A High Throughput Xenograft Model
	Tasca	Tasca	Muscle microdialysis
	Tidwell	Tidwell	FSHD Tissue Donation Registry
	Udaka	Udaka	Physiological charact. Early Stage Disease
Wang	Wang	Smchd1 regulating gene expression ]	

**Day 1**

**Review**                      **Review of 2015/2016 priorities** as stated by FSHD workshop in 2015  
**Moderators:** Michael Altherr, Stephen Tapscott

**Platform 1**                      **Clinical Studies; Genetics & epigenetics** (3x15 mins & 4x10 minutes)  
**Rabi Tawil, Kathryn Wagner**

**Platform 2**                      **Molecular mechanisms** (3x15 minutes & 2x10 minutes)  
**Scott Harper, Michael Kyba**

**Posters & Lunch**

**Platform 3**                      **Models** (5x15 minutes)  
**Yi-Wen Chen, Louis Kunkel**

**Platform 4**                      **Therapeutic studies** (3x15 minutes & 3x10 minutes)  
**Charles Emerson, Jr., Davide Gabellini**

## Day 2

### **International “lab meeting”** Discussion/Planning

#### **Planning and problem solving session(s)**

Moderated discussion sessions with entire group of attendees based on data presented at day. The goals are to help identify and troubleshoot bottlenecks; and, define the research/clinical priorities for the next year 2016/2017.

#### **Identify/troubleshoot bottlenecks; and, define the research/clinical priorities going forward**

**Moderators: David Housman, Daniel Perez, Stephen Tapscott, Silvere van der Maarel and Kathryn Wagner**

#### **Finalizing listing of items, areas and priorities**

## I. Clinical studies

- There is a need for surrogate outcome biomarkers. Of the greatest need.
- Need for validated outcome measures.
- Additional natural history studies are required.

Validation of subjective and objective measurements of disease onset and progression. Quality of life, muscle function measurements and other physical-, molecular-, and imaging-, biomarkers all show promise for monitoring disease onset and progression.

Need to think about issues posed when therapeutic A is actually in use how it might impact on the design and implantation of clinical trials

- Individual and cooperative studies to identify, validate, and determine the best standard measurements are critical for trial preparedness in FSHD.

Moving 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. More people using measures, the better, and, in a longitudinal way, that's even better.



### I. Clinical studies.

- Natural history of the disease for the experience of patients -- need to get really deep understanding of what the data is. We have to do better than what we're currently doing in the world of medicine with the EMR. We need to do it in a way that captures effectively.

## 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, a key issue
- Further understanding of the epigenetic regulation of the repeats helps us to better understand the disease process and the disease mechanism

RFA related to these priorities. Sub-meeting in the next 7 or 8 months. Establishment of a central equivalent of WADA for the Olympics so that uniformity in FSHD genetic testing is achieved and the sub grouping of FSHD done under uniform conditions.

- Modifiers of the disease mechanism
- Consistent measures

### III. Molecular mechanisms

- Need to understand genetic toxicity in FSHD
- Understand Dux4. How to silence it. How to silence the RNA

Expression of DUX4 probably its activity in the nucleus mediated through binding of the DNA possibly through its transcriptional activity is really the major cause of the disease. If you knew how to epigenetically silence it, silence the RNA, silence the transcriptional activity that's a good process.

- Need to understand what real pathophysiology is in FSHD. (This real culprit may remain while this effort to silence DUX4 is ongoing)

Need to open big black box in terms of what the real pathophysiology is, this box really intellectually needs to be filled in. It may not need to be filled in in order to continue to develop therapies.

### III. Molecular mechanisms (continued)

- 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

Priority need is to correlate between the expression and activity, transcriptional activity of DUX4 with some of the markers that we have. Markers correlate with disease muscle? MRI correlates with the markers? How to measure disease progression in short time window if focused to a specific marker or a specific muscle group?

#### IV. Models

- Create a focus to ensure that we are measuring the same kinds of things, that it does translate into a usable tool for our therapeutic industry. Establish meetings of the consortium of laboratories that are working on mouse/animal models

Commercial entities that are attempting to enter the FSHD therapeutics space should be involved – is a way in which the therapeutic development can (a) be accelerated, and (b) to some extent, de-risk or lower the risk.

- Need for further development, characterization and use of animal models.  
Whole animal; mice; fish; pig and mammal
- Xenograft models -- real human muscle represents the true disease state either patients or grafts
- More emphasis on cellular models -- all aspects of all models

Cell-based, again, are the kinds of things that lend themselves to high throughput assays. Our therapeutic industrial partners might look to engage in those kinds of throughput assays using a variety of cell models and this may provide insights on developmental time lines.

#### IV. Models (continued)

- Need good representation of cell-based models
- Models that really recapitulate the disease in their progression
- Models to help develop precisely how you deliver, how you formulate, how you get the conceptual entity to the effective therapeutic use of the entity requires something that you can test
- Need to address formulation and delivery issues and half life issue, PK, PD, etc.

Can do in normal animals, but begs the question if the delivery to an affected tissue is different from the delivery to a normal tissue and that, for example, might be relevant.

#### IV. Models (continued)

Consideration of this potentially being a developmental phenomena with a later in life trigger after some sub-population of cells has been set up is disquieting, these models might actually provide some insight into that as well.

In addition to testing our compounds, though, some models that really recapitulate the disease in their progression can give us insight into when we might consider treating, how early in the course of the disease we may need to treat in order to see the changes that we like to drive into the clinic. The other information it might give us is the duration of treatment that may be required to impact the disease. So if you were to have a model that recapitulates the course of the disease relatively accurately, using the endogenous gene and potentially even using the endogenous locus regulation region, that could be highly valuable in understanding not just how much to treat with, the dose, but the duration, and the time of initiation.

#### IV. Models (continued)

Great discussions on models, use, characterization and availability!

One of the FSHD mouse models funded by FSH Society was announced at consortium by Dr. Jones for distribution by the **Jackson Laboratory Mouse Repository**. B6(Cg)-Gt(ROSA)26Sortm1.1(DUX4\*)Plj/J is also known as: **Dux4-fl, FLExDUX4**

“**Large family cohorts of lymphoblastoid cells provide a new cellular model for investigating FSHD.**” NIGMS Human Genetic Cell Repository at the **Coriell Institute** for Medical Research repository for culturing, maintaining, and distributing the cell lines.



# Details and Full Discussion Priorities

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- FSHD International Research Consortium Discussion and Priorities – full details with extended description and discussion
- FSHD International Research Consortium Program and Abstracts Book – program, abstracts and charge

<https://www.fshsociety.org/international-research-consortium/>



## Contact

FSH Society  
Daniel Paul Perez, CEO & CSO  
June Kinoshita, Executive Director & COO

FSH Society  
450 Bedford Street  
Lexington, MA 02420 USA

(781) 301-6650; (781) 275-7781  
fax: (617) 658-7879

**[www.fshsociety.org](http://www.fshsociety.org)**