

# DRAFT

## Priorities as Stated by FSHD Research Community For FSHD Research: 2012 and Beyond

The international FSHD clinical and research community recently came together at the DHHS NIH NICHD Boston Biomedical Research Institute Senator Paul D. Wellstone MD CRC for FSHD. Almost 95 scientists working on FSHD globally met at the 2011 FSH Society FSHD International Research Consortium, held November 7-8, 2011.

The summary and recommendations of the group state that given the recent developments in our definition of FSHD and the potential that within one to two (1-2) years, evidence-based intervention strategies, therapeutics, and trials being planned and conducted. Our immediate priorities should be to confirm the DUX4 hypothesis, if valid then understand normal DUX4 function, and finally, understanding the naturally occurring variability should allow us to manipulate the disease in our favor. We need to be prepared for this new era in the science of FSHD, by accelerating efforts in the following four areas:

### 1. Genetics / epigenetics

It is now broadly accepted that the dysregulation of the expression of D4Z4 / DUX4 plays a major role in FSHD1 and FSHD2. Additional FSHD (modifier) loci are likely to exist.

**FSHD molecular networks.** The relaxation of the chromatin structure on permissive chromosome 4 haplotypes leads to activation of downstream molecular networks. Importantly, the upstream processes – triggering of activation – are equally important. Detailed studies on these processes are crucial for insight in the molecular mechanisms of FSHD pathogenesis and may contribute to explaining the large intra- and interfamily clinical variability. Importantly such work may lead to intervention (possibly also prevention) targets.

**Additional FSHD genes.** FSHD2 is characterized by hypomethylation of D4Z4 on chromosome 4 as well as chromosome 10. This also leads to bursts of DUX4 expression. Identification of the responsible factor (gene) and molecular mechanisms is of utmost importance. This work will be facilitated by the recruitment of additional families. Also other genes need to be considered that may give rise to FSHD-like phenotypes. These include, but are not limited to, CAPN3 and the FAT1 gene that was recently suggested to be involved in FSHD.

### 2. Clinical trial readiness

It is now broadly accepted that dysregulation of the expression of D4Z4 / DUX4 is at the heart of FSHD1 and FSHD2. This finding opens perspectives for intervention along different avenues.

**Clinical Trial Readiness.** Intervention trials are envisaged within the next several years. The FSHD field needs to be prepared for this crucial step. To design and coordinate this important translational process, it was envisaged to install an international task force Clinical Trial Readiness (FSHD-CTR), with Dr Rabi Tawil as leader. The FSHD-CTR needs to be a multidisciplinary group, including members with expertise, not only in FSHD but also, in trial design and execution, statistics, (non-invasive) biomarkers etc. Important issues are:  
Natural history

Homogeneous clinical criteria  
BioBanks, biomarkers, etc.  
Reliable outcome measures  
Patient registries

**Biomarkers.** Sensitive biomarkers are needed to monitor intervention: they might also improve diagnosis. Important to consider biomarkers established from easily accessible sources like blood. Non-invasive methods like imaging needs further attention. Quantitative muscle function methods are instrumental as are patient-reported indicators.

### 3. Model systems

There are a plethora of cellular and models, based on different pathogenic (candidate gene) hypotheses. Moreover, the phenotypes are very diverse and often difficult to compare with the human FSHD phenotype.

**FSHD Model Data Base.** The importance of a systematic database was recognized. This data base should contain detailed information on the molecular characteristics of the model (design and phenotype). Particular emphasis should be paid to the muscle pathology. Non-muscle phenotypes – described also in FSHD patients deserves attention.

**Human pathology and bio-banking.** Importantly, this data base should also contain well-documented muscle pathology data of patients – astonishingly difficult to find in the literature.

Human cellular resources continuously deserve attention. Recent progress in ES-cell technology, including iPS lines, allows for inter-group distribution and dedicated molecular (epi)genetic studies.

### 4. Sharing

Timely sharing of information and resources remains a critical contributor to the progress in the field. There are several initiatives that create large repositories of data and resources, e.g. Wellstone and Fields Center. Their websites should be used for sharing of information (e.g. protocols, guide to FSHD muscle pathology (images), model systems, contact information), reagents, and resources.



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