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Summary of Priorities and General Discussion, October 5-6, 2015
2015 FSHD International Research Consortium and Research Planning meetings

More than 100 scientists, patients, advocates, biotech and pharmaceutical companies, and clinicians from throughout the world gathered at the 2015 FSHD International Research Consortium and Research Planning meetings in Boston on October 5-6, 2015 to share and discuss their latest progress and ideas on facioscapulohumeral muscular dystrophy (FSHD) research. The meeting was co-chaired by David E. Housman, PhD (FSH Society Scientific Advisory Board Chairman & 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), and Michael Altherr, PhD (FSH Society Scientific Advisory Board & Los Alamos National Laboratory, Los Alamos, New Mexico). 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. This meeting is organized by the FSH Society and sponsored by Acceleron Pharma, Association Française contre les Myopathies (AFM), aTyr Pharma, BioMarin Pharmaceutical, Facio-Therapies, FSHD Canada, FSH Society, FSHD Global Research Foundation, Genomic Vision, Genzyme, a Sanofi Company, Idera Pharma, Muscular Dystrophy Association United States (MDAUSA), Muscular Dystrophy Campaign United Kingdom, NIH Eunice Kennedy Shriver NICHD Senator Paul D. Wellstone MDCRC for FSHD at University of Massachusetts Medical School, Sarepta, and, Regeneron Pharmaceuticals.

After a brief welcome by the organizers including an overview of last years' priorities and the follow up on these priorities as defined by the FSHD community in the calendar year 2014. There was a general consensus that, based on the publications that have appeared in the past year, there had been an impressive response to the priorities formulated during the 2014 meeting.

The overview was followed by a series platform sessions reviewing the latest advancements in 1.) clinical studies; genetics & epigenetics, 2.) molecular mechanisms, 3.) models, and 4.) therapeutic studies. Each platform session included presentations selected from pre-submitted abstracts. Sufficient time was allowed after each of the four platform sessions, each moderated by two distinguished scientists, whose role was to provide a stimulating overview of the topic and facilitated discussion. There was ample time to review and further

discuss the latest developments at the posters. The meeting was a working meeting with experts, developing future plans in the context of what we know now. 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.

Tuesday, October 6 was solely dedicated to the discussion and planning session, and included several sessions chaired and moderated by Drs. Housman, Tapscott, Van der Maarel, and Altherr. From these discussions and analysis of transcripts of the meeting the following conclusions were made and priorities were defined.

The second day, October 6, was in actuality an International "lab meeting" with planning and problem solving sessions. Three moderated discussion sessions were conducted with the entire group of attendees based on data presented at the first day with the goals to: help identify and troubleshoot bottlenecks; and, define the research/clinical priorities for the next year 2015 to 2016. One discussion was aimed at educating FSHD community on issues important to industry. Issued suggested for discussion were: Important points to consider in academic-industry collaborations; drug targets and validating drug targets; importance (or lack thereof) of animal models; clinical trial design: measures of efficacy, Phase 2 vs. Phase 3; natural history; therapeutic index; opportunity to restore muscle health (in addition to disease stabilization) and ways to know in a clinical trial; biomarkers; and, Uniform Clinical Assessment. Another discussion was an introduction on FSHD Champions Initiative of FSHD funding agencies. And the last discussion was to identify and troubleshoot bottlenecks; and, define the research/clinical priorities going forward

Priorities Part I. Identifying and Troubleshooting Bottlenecks for FSHD 2015-2016
As defined by the FSHD clinical and research community

The 2015-2016 IRC for FSHD brought together active members of the research community as well as members of the drug development industry. This was a powerful assemblage that is helping to define the parameters for success moving forward. A number of specific issues were called out that need support both in terms of dollars, as well as consensus of the research community and potential mandates from funding organizations.

The meeting represented a catalyst to move from fundamental studies of genetics and molecular mechanisms (while remaining important) to defining parameters necessary for successful clinical trials. Toward that end an often cited refrain by the industrial participants was the requirement for the development of therapeutics that have measurable biological outcomes.

A significant priority should, therefore, be the establishment of standards across the community in a variety of areas partially described below. These standards could be

required, if demanded, by the organizations, both private and governmental, supporting FSHD research.

I.A. In establishing these standards the following considerations should be weighed:

1. What is being measured?
    a. How might the measure be used?
    b. Can it be measured with accuracy and reliably in different locations / facilities?
2. How is the measure related to FSHD?
3. How does the measure impact those afflicted
4. How would modifying the measured phenomena look to the patient

Examples of measurements that might be included are:

1. Quantitative measures of muscle strength
2. Definitive measure of DUX4
3. Other biomarkers

I.B. What's needed:

1. The community should agree on a "robust" model that involves multiple facets of disease for which reliable assays are in hand.
    a. DUX4/Dux4 readouts
    b. Other Biomarkers?
    c. Genetic characterization
    d. Epigenetic characterization
    e. Phenotypic measures
        i. muscle strength
        ii. quantitative walk test
        iii. ophthalmology
        iv. hearing
    f. Cell models
    g. Xenografts
    h. Animal models
        i. Sufficient animal models may already be in hand to support safety studies and phase I trials
        ii. A primate model would be an expensive endeavor. Marmosets are small, known to contain structurally relevant copies of Dux4, and 'relatively' inexpensive primates. This is a recurring theme and should be seriously evaluated

2. Natural history studies are accumulating, but support for longitudinal assessments are lacking. These studies should be linked to and similar imaging analyses should be supported in a longitudinal analysis.
    a. These measurements need to be moved from the laboratory to the clinic

b. Certainly a collection of routine measurements can be identified on routine visits
c. If necessary legislation needs to require payers to support these measurements as part of primary care
d. These features will likely be critical to long range studies of therapeutic impact

3. Unifying features need to be established between registries so that all groups are including the same or clearly translatable measurements
    a. Sustaining support for these repositories is critical!
    b. Phenotypic measures
    c. 4q genetic description
    d. Epigenetic profile
    e. Cell lines from individuals with measured phenotypic data

It is imperative that the FSHD research community move to a better position in the approach to the problem, and into a highly organized assessment of therapeutic leads. To do so, will require better coordination of widely distribute and often distinct efforts. This could be accomplished through the establishment of defined processes associated with the 'robust model', and used by all members of the research community. These processes could be established by the sharing of protocols and defined substrates made available to the community from laboratories across the world. A defined process could be validated by the sharing of data produced by distributed groups within the boundaries of experimental norms and agreed on by FSH IRC and supporting organizations. Once established new and improved processes could be benchmarked to established processes, and subsequently agreed to replace or add to the processes defining the model. Funding organizations, both public and private, could and should demand, through their support mechanisms, that established processes be used as benchmarks in all of their supported studies.

Priorities Part II. Research/Clinical Priorities Defined 2015-2016
As defined by the FSHD clinical and research community

II.A Genetics and epigenetics.

Priority 1: Continued identification of the parameters that determine disease severity and progression, including identification of additional modifier and disease loci. FSHD1 and FSHD2 were initially identified as two distinct genetic pathways that cause FSHD. Work published over the last year and presented at this year's meeting showed that FSHD was the result of the interaction of at least two genetic variables: the number of D4Z4 units on a 4qA permissive haplotype and variations in genes, such as SMCHD1, that modify the epigenetic repression of the D4Z4. Although a subtle change in how we think of the disease, it is possibly profound in understanding disease penetrance and developing models that predict disease progression, the latter being critical for future

clinical studies. Additional efforts in identifying disease genes in unexplained FSHD2 cases may further strengthen this process.

Priority 2: Improved diagnostic tests and tests to better predict onset and severity. The advances described in Priority 1 gives guidance on how to develop assays of D4Z4 repression that can be tested for correlation with disease onset and severity. The most obvious is DNA methylation at certain sites or particular D4Z4 repeats, but additional approaches, either allele-specific or based on chromosome or genome averaging, can be envisioned.

II.B. Mechanisms and targets.

Priority 3: Determine the major mechanism(s) of muscle damage caused by DUX4 expression. DUX4 in muscle activates a diverse panel of pathways and mechanisms, which individually, or combined lead to muscle pathology. However, our understanding of the primary mechanism and the resulting pathological processes is still limited. A better understanding between cause and consequence will aid biomarker discoveries and therapy development.

Priority 4: Determine the relationship between DUX4 expression and disease onset and progression. The asymmetric onset of disease could be due to different propensities to express DUX4, or DUX4 could be expressed in all muscles and a second event is necessary for the disease pathology. Distinguishing these two models is critical for guiding therapeutic development.

Priority 5: Determine how the expression of DUX4 in one muscle cell nucleus results in the spread of the pathology throughout the muscle. DUX4 protein to spread to adjacent nuclei in a muscle fiber, but a major goal will be to determine how regional expression of DUX4 spreads both through the entire length of the fiber and to adjacent muscle fibers.

II.C. Models.

Priority 6: Continued development and validation of pre-clinical models to test specific pre-clinical goals. A healthy number of pre-clinical models have been developed over the last few years. Further development should focus on validating existing models and developing new models that are needed to test specific interventions and determine successful targeting of specific aspects of the molecular pathogenesis.

II.D. Clinical and therapeutic studies.

Priority 7: Validation of subjective and objective measurements of disease onset and progression. Quality of life, muscle function measurements and other physical biomarkers, molecular biomarkers, and imaging biomarkers all show tremendous

promise for monitoring disease onset and progression. Individual and cooperative studies to identify, validate, and determine the best standard measurements are critical for trial preparedness in FSHD.

Part III. "FSHD Champions" Initiative Considerations

Additional considerations from discussion session on the introduction (to industry, researchers and clinicians) of "FSHD Champions Initiative of FSHD Funding Agencies."

III.A. FSHD Champions can help with Clinical Trial Preparedness

The Tuesday, October 6 discussion session on Industry Relations underscored the need for FSHD foundations and groups such as the Champions collective of funding stakeholders to lead in the area of FSHD clinical trials preparedness. Each company will commit resources necessary for its clinical program, but is not likely to commit significant resources prior to having a treatment to move forward, which will be later than ideal and might delay clinical testing. However, each company is interested in "risk management" and might be willing to contribute to a foundation-sponsored effort in return for access to the process and results. The Champions have already taken a lead in this area by sponsoring the second international workshop on FSHD Clinical Trials Preparedness held in Rochester, New York in May 2016. The discussion during the October 6 session on Industry Relations suggested that the Champions leverage their demonstrated ability to make progress in this area by soliciting support from interested companies in exchange for participation in the process.

III.B. FSHD Champions: might help accelerate efforts in increased targeted approach based on overall assessment of research

There has been a huge change in FSHD research over the last several years. Several years ago there was little agreement on the genetic mechanism and pathophysiology of FSHD and no consensus on the most important drug targets or areas of investigation. Now, there is general consensus on the pathophysiology of FSHD and general agreement on the path forward. This "sea change" alters the landscape of FSHD research and has several important implications for the role of FSHD foundations.

1. Achieving a consensus on the genetics and pathophysiology of FSHD increased the participation of major funding agencies. Previously, the fundamental disagreements among the reviewers on NIH or MDA panels regarding the pathophysiology of FSHD prevented the consensus needed for any individual grant to be funded, and might have resulted in low funding success rates for FSHD grants. Funding from these agencies has dramatically increased following a general agreement in the field on the cause of FSHD. Therefore, while the past objective of FSHD foundations was to broadly support the FSHD research community, this role is rapidly being fulfilled by NIH and other major funding groups, providing the opportunity for foundations to begin a re-assessment to determine their most valuable role.

2. Achieving consensus on the pathophysiology of FSHD focuses the field on a common path. The near-term opportunities in FSHD research are relatively clear and many different research groups will be seeking support for similar studies. FSHD foundations might be quickly overwhelmed by trying to support all qualified studies, or might have significant difficulties, or conflicts of interest, in deciding which of the competing studies or approaches to fund. In this regard, the success of the prior FSHD foundation support that led to the consensus model of FSHD is also a major new opportunity for the foundations because it requires a shift in the funding goals to ensure that the foundations continue to drive FSHD research and therapeutic development faster than would be achieved by conventional funding mechanisms. Because the peer-review process of conventional funding mechanisms is now appropriate for the majority of research proposals on FSHD, the FSHD foundations might need to consider mechanisms to identify and fund efforts that have high impact or that make major advances to the fields of FSHD pathophysiology and FSHD therapeutics.

3. Foundations need to support clinical trials preparedness. This is a critical area for therapeutic development that will not be pro-actively addressed by industry nor adequately funded by NIH. Foundations can lead in this area and gain financial support from industry by offering a mechanism of risk-management for industry participants.

4. Foundations can reward research that accomplishes goals critical for FSHD therapeutic development. Previously foundations needed to provide seed money to keep investigators working on FSHD because it was nearly impossible to get grants from the major funding sources. Now major funding sources are supporting FSHD research and the opportunity for foundations to have a major impact on therapeutic development is shifting from funding discovery-oriented research toward rewarding research that solves major obstacles to developing successful FSHD therapies. Although premature to implement, it is not too soon to discuss FSHD PRIZES based on overcoming specific barriers toward therapeutic development. This could be as simple as a small monetary prize (designated for future FSHD research, such as the further development or implementation of the advance) based on improving diagnostic procedures, finding new modifier loci, prioritizing mechanisms of pathogenesis, advances in pre-clinical models, or identifying new targets for drug development. It might also still be a bit premature to consider a “moon-shot” prize for a cure, but intermediate small prizes might further motivate current FSHD researchers and might recruit new researchers to the field.