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Summary of Priorities Discussion, November 10-11, 2016
2016 FSHD International Research Consortium and Research Planning meetings

The 2016 FSHD International Research Consortium and Research Planning meetings were held in Boston on November 10-11, 2016 to update each other and to discuss their latest findings 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 Kathryn Wagner, MD, PhD (Kennedy Krieger Institute & Johns Hopkins SOM, Baltimore, Maryland). Daniel Paul Perez, FSH Society, Lexington, Massachusetts served as the organizational chair.

This meeting is organized by the FSH Society and sponsored by Acceleron, Association Française contre les Myopathies (AFM), aTyr Pharma, BioMarin, Cytokinetics, Facio Therapies BV, FSH Society, Fulcrum Therapeutics, Genea Biocells, Genomic Vision, Genzyme / Sanofi, Idera Pharma, Mouse Specifics, Muscular Dystrophy Association, Muscular Dystrophy Campaign (UK), NIH NICHD UMass Senator Paul Wellstone MD Cooperative Research for FSHD, Quintiles, Sarepta, Ultragenyx. We thank our sponsors for their generous financial support.

The following is the final listing of items, areas and priorities generated by consensus of the 2016 FSHD International Research Consortium.

Statement of FSHD Scientific/Research Priorities 2016-2017

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.

Highlighted excerpts from group discussion:

"A lot of consensus that the 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. So there's consensus if you knew how to epigenetically silence it, silence the RNA, silence the transcriptional activity that's a good process."

"Need to open big black box in terms of what the real pathophysiology is, is it transcriptional toxicity from inducing apoptosis, is it RNA toxicity, protein toxicity -- that box really intellectually needs to be filled in. It may not need to be filled in to continue at present with developing therapies – but none-the-less this understanding is critical and essential."

"Relationship to other markers. The next priority is to really start to correlate between the expression and activity, transcriptional activity of DUX4 with some of the markers that we have, how do the molecular markers correlate with disease muscle, how does the MRI correlate with the markers, and how can we measure disease progression in a mechanism that does not require years long functional assays, but might be focused to a specific marker or a specific muscle group."

IV. Models.

- There is no ideal model; each model will serve its own needs.
- 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.
- Need for further development, characterization and use of variety of animal models.
- Xenograft models -- real human muscle represents the true disease state either patients or grafts
- More emphasis on cellular models (e.g. iPSC) -- all aspects of all models.

Highlighted excerpts from group discussion:

"Need to create a nucleating focus to ensure that we are measuring the same kinds of things, that it does translate into a usable tool for our therapeutic industry brethren to ensure that these things can move as quickly as possible into testing paradigms in that way."

"We need to consider 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 high throughput assays using a variety of cells. If stem cells, either induced or embryonic, were useful in this. 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, but I do think those models might actually provide some insight into that as well."

"Meetings of the consortium of laboratories that are working on mouse models I believe is very valuable and almost essential and I would argue that the various commercial entities that are attempting to enter the FSHD therapeutics space should be involved in attendance and I would argue support at least the meetings of the consortium if nothing else, because I think this is a very simple way in which the therapeutic development can (a) be accelerated, and (b) to some extent, de-risk or lower the risk."

V. Therapeutic studies.

- Clinical trials are on the horizon, meaning that the community needs to be prepared (clinical trial preparedness).
- FSHD models need to be available to address drug delivery and efficacy in preclinical trials.
- For clinical trial preparedness registries need to be assembled and harmonized.
- For clinical trial preparedness registries biomarkers (e.g. MRI or molecular markers) need to be identified and validated.
- For clinical trial readiness validated patient relevant functional outcome measures need to be available.

Highlighted excerpts from group discussion:

"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."

"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. Now even Need to address formulation and delivery issues and half life issue, PK, PD, all that stuff. You can do some of that in normal animals, but it really 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, let's say, in the muscular dystrophies we know some of the issues in delivery to Duchenne muscle and that's been an issue, I think, in some of this clinical work that's been done. So I agree with you completely, we have to think about and have ready thoughtful understanding of how we're going to develop both understanding of delivery modalities and understand PK and PD and everything else about the use of a therapeutic intervention, whatever it is."

VI. Workshops.

Ideas for workshops that came up during parts of the discussion (no specific ranking).

- Workshop 1 -- Mouse models consortia/meeting powered by industry.
- Workshop 2 -- Uniformity in the genetic testing as so far as that is possible (the establishment of a central equivalent of WADA for the Olympics or something like that where, done under uniform conditions).
- Workshop 3 -- The subgrouping of patients (a further understanding of the epigenetic regulation of the repeats helps us to better understand the disease process and the disease mechanism).
- Workshop 4 -- Surrogate outcome biomarkers.

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