Industry Collaborative for Therapy Development in FSHD

March 12, 2019

Tommy Douglas Conference Center
Silver Spring, Maryland

Workshop Report

Workshop organized by the FSHD Society with sponsorship from the Geraldi Norton Foundation

FSHD Society
Industry Collaborative for Therapy Development in FSHD
March 12, 2019
Workshop Report

The FSHD Society is focused on obtaining approved and marketed therapies that have a meaningful impact for patients living with FSHD, by 2025. Since the development of a testable molecular genetics model of FSHD in 2010, there are now multiple molecular targets that may yield effective treatments. A variety of therapeutic strategies for disease intervention are soon to enter clinical trials.

The Society plans to help leverage the expanding clinical research enterprise worldwide and the increased interest of biotechnology/pharmaceutical firms in FSHD. The formation of the FSHD Clinical Trial Research Network, in particular, has resulted in improvements in clinical trial readiness. This Workshop, "Industry Collaborative for Therapy Development in FSHD," was designed to critically evaluate the current status of clinical trial readiness and identify opportunities and gaps that could be addressed through a collaboration among key stakeholders in the field – academics, industry, regulators, patient advocates, and the Society. Presentations and discussion sessions focused on the current status of and efforts needed to advance the identification and validation of pharmacodynamic and imaging biomarkers, and clinical outcome assessment measures. This Report summarizes the proceedings and key outcomes of the Workshop.

I. Underlying Issues

1. Diagnostics

The genetic tests for FSHD1 (<10 D4Z4 repeats) and FSHD2 (SMCHD or DNMT3B mutations) are specific and sensitive, and a decision tree is in place to guide genetic testing (University of Iowa decision model) and facilitate the inclusion of genetically confirmed patients in clinical studies and trials. Rare FSHD alleles are still being discovered, and these raise

some as-yet unresolved questions, but it is notable that the first comprehensive molecular genetics model of FSHD was informed by such genetic outliers. Overall, discovery of new outliers has not challenged fundamental models of the disease, and such discoveries are likely to continue to refine understanding of genetic mechanisms for FSHD.

An estimated 80% of FSHD patients who have been clinically diagnosed will have developed symptoms by age 20. Others are subclinical/asymptomatic (estimated 25% of people who genetically have FSHD) or non-manifesting carriers (estimated 15%), and many do not have a prior family history (i.e., de novo mutations; estimated 10%-20% of all patients diagnosed). FSHD patients often suffer from the diagnostic odyssey common to nearly all rare diseases – accurate diagnosis is typically obtained only after a long journey, involving multiple practitioners. Estimates of the percentage of patients with a molecular diagnosis are very low (40% in the University of Rochester registry), in part because of cost and testing refusals by payers. Thus, for a variety of reasons, it is likely that many FSHD patients will not be detected outside of a population screening program. This problem will need to be addressed as candidate therapeutics advance toward approval and marketing.

2. Symptomatology

Clinical features of FSHD1 and FSHD2 are strikingly similar and have been described elsewhere. The slowly progressive nature of FSHD has been held up as a potential difficulty in establishing efficacy during the course of a typical (six months to one year) interventional clinical trial. Any clinical outcome assessment measure effort must include a patient-focused drug development approach to ensure that symptoms important to patients and caregivers are targeted in therapeutic development efforts. Since sporadic DUX4 expression and sporadic and asymmetric clinical manifestation are cardinal features of FSHD, these must be accounted for in the discovery and implementation of biomarkers and clinical outcome measures addressing disease activity and progression.

3. Natural history

Well-powered, longitudinal natural history studies are the primary means to catalog disease progression and establish a path for sound clinical outcome measures. Study adherence to the core FSHD data elements, established through a 2016 European Neuromuscular Center workshop, is an essential step to facilitate subsequent sharing, aggregation, and meta-analyses of natural history study data. A lack of data sharing has hindered progress in other neuromuscular diseases – this cannot be allowed to become a problem for patients living with FSHD.

A prospective natural history study documented a slow but significant functional decline (2%-4% per year) in FSHD subjects during the timeframe of a typical clinical trial (one year), and established criteria for powering clinical trials based on either halting progression or achieving improvement in quantitative and/or manual muscle testing endpoints. Subsequent natural history studies have built upon this base (with sometimes conflicting results) to establish that disease severity and progression rates are influenced by age at onset, size of the residual repeats, gender, and as-yet unknown epigenetic factors – understanding the interaction of these and other factors with disease progression will improve patient selection/stratification in clinical trials. The temporal pattern of involvement of skeletal muscles is not always predictive of severity and progression, as earlier affected shoulder muscles may be better preserved than lower extremity muscles at later disease stages.

Strength measures haven't held up particularly well in subsequent natural history studies, due to higher variability – by contrast MRI endpoint measures have shown much lower standard deviations. As the natural history studies work through evaluation of batteries of biomarkers and functional measures, direct comparisons with the responsiveness of patient-reported outcome measures (PROMs) are essential in determining meaningful benefit of changes. Some PROMs (Dutch PRO and FSHD-HI) are nearing validation and will benefit from inclusion in upcoming clinical trials; investigators at Radboud University will soon complete Rasch analysis of several PROMs.

The ongoing FSHD Clinical Trial Research Network ReSOLVE study will report on 220 subjects assessed over 18 months (interim data to be shared

at 12 months). There's a need for increased attention to the natural history of FSHD cohorts with early onset (prior to age 10) and/or more rapid progression, as these could be the most relevant for some therapeutic strategies (although see caveats later in this Report).

Accessibility of the existing natural history data sets was discussed at the Workshop, but answers here seem to be that access is variable. Every effort should be made to ensure that there is transparent exchange of natural history data, and that the resulting biomarkers and clinical outcome assessment measures enter the public domain. Finally, as noted above, the percentage of FSHD patients with a molecular diagnosis is unacceptably low – eligibility and recruitment for clinical studies and trials can be improved by increasing the percentage of genetically confirmed patients in national registries.

4. Standard of care

Site-to-site differences in standard of care represent a potential barrier for the conduct of clinical trials, as efficacy assessments may be influenced by baseline level of care to an extent that trial results are confounded. FSHD care guidelines have been developed in 2008 and 2015, but are likely out of date. Continuing efforts to improve, update, and disseminate care standards are essential in optimizing patient management and feasibility of interventional clinical trials.

5. Regulatory considerations

The slow progression of FSHD has thus far created difficulties in developing clinical outcome assessment measures that are feasible for the duration of a typical clinical trial. By no means should the field abandon the search for drug development tools that allow standard regulatory approval based on an evidentiary standard of clinically meaningful benefit shown in adequate and well-controlled trials. The field should work toward defining "meaningful change" in the context of an FSHD drug registration trial. For now, one step that was discussed at the Workshop was potentially using FDA's Accelerated Approval Program to achieve initial marketing approval.

Regulatory guidance is that accelerated approval relies upon a surrogate endpoint that is thought to be reasonably predictive of long-term clinical benefit. The FDA states that "accelerated approval is a stepping stone to [the] full approval process" and post-marketing studies within a specific timeframe are necessary to establish efficacy. The overall goal should be full approval of candidate therapeutics, and FDA staff indicated that any readout used for accelerated approval needs to have been well characterized – shown reasonably likely to predict clinical benefit. Finally, the FDA did comment at the end of the Workshop that accelerated approval "may not be unreasonable for a disease like this, where you have a long latency period … ideally, that's what accelerated approval is supposed to be for."

The recent Center for Biologics Evaluation and Research (CBER) guidance for genetic therapies in rare diseases places considerable reliance upon the accelerated approval path – policies at the FDA should be monitored for any softening of the "artificial separations" between drugs and biologics and further considerations given for any candidate therapy program in a serious and rare disease like FSHD.

There is no apparent regulatory approval precedent at the FDA based upon a mechanism of action of deactivating a transcription factor. The FDA's perspective is that if a PD biomarker panel and MRI measures are to be relied upon to initially pursue accelerated approval, understanding has to move beyond simple *correlations* with functional outcomes to a point where it can be demonstrated that biomarkers supporting approval are *predictive* of functional outcomes. In the context of an accelerated approval process, it may be reasonable to consider evaluating drug response in specific skeletal muscles, but to obtain full approval in a post-market clinical trial, the field will need to demonstrate overall patient response and meaningful clinical outcomes. The FDA will want to see data from carefully conducted natural history studies to establish the predictive value of any drug development tools used for FSHD.

Critical Path Innovation Meetings (CPIMs) provide disease fields with a means for soliciting non-binding FDA input into a range of drug development tools – according to the FDA, CPIMs can provide input on: 1)

biomarkers in the early phase of development and not yet ready for the Biomarker Qualification Program; 2) clinical outcome assessments in the early phase of development and not yet ready for the Clinical Outcome Assessment Qualification Program; 3) natural history study design and implementation; 4) emerging technologies or new uses of existing technologies; and 5) innovative conceptual approaches to clinical trial design and analysis.

6. Tractability for therapy development

There is a compelling case that FSHD is tractable for biopharmaceutical company interest in this disease indication. This case includes: 1) well-defined genetics and downstream disease mechanisms; 2) a validated, disease-modifying target, DUX4 toxic gain-of-function, with restricted/sporadic protein expression in adult patients (plus other putative upstream and downstream targets); 3) availability and expanding selection of more realistic/relevant preclinical models and endpoints (including phenotypic and target-specific screens and assays for general effectors of immune response and muscle regeneration) to establish proof of concept; 4) an ability to stratify patients in clinical studies and trials based on genetics (and, potentially, skeletal muscle imaging); 5) established standards of care to minimize differences in patient management as a variable in interventional clinical trials; 6) continuing evolution of candidate clinical outcome assessment measures; 7) the presence of an expanding international clinical trials infrastructure; 8) organized and effective patient advocacy groups to assist with improvement of patient management and therapeutic development efforts.

While the preclinical resources are certainly important in attracting drug discovery and development efforts, the Industry Consortium's focus will be on components of clinical trial readiness, and that is the focus of this Report.

II. Pharmacodynamic Biomarkers

1. DUX4 and DUX4-regulated genes

Based upon a broad array of evidence, DUX4 is regarded as a validated target for therapy development in FSHD. Although this target is deemed a developmental transcription factor, both FSHD1 and FSHD2 involve upregulated expression of DUX4 and aberrant activation of its normally early, developmentally regulated transcriptional program. More recent evidence of target validity comes from the positive correlation between local DUX4 activation and muscle pathology detected by MRI. Yet activation of DUX4 in affected skeletal muscles appears to occur in difficult-to-capture transient bursts, raising issues of its potential biomarker value and directing efforts toward targets up- or downstream of DUX4. In the final analysis, DUX4 likely may prove to be a key therapeutic target, with quantifiable PD biomarkers best found downstream. It has been established that 4q35 DNA methylation levels correlate with disease presentation and severity – these findings can provide insights into the level of knockdown necessary to achieve a meaningful clinical benefit and thus into the spatial and temporal responsiveness of DUX4 to an effective intervention.

The field generally regards upstream modifiers and downstream regulatory targets of DUX4 as putative therapeutic targets. If a dominant pathogenic cascade emanating from DUX4 expression can be fully validated, and shown to be persistent enough to facilitate capture in biomarker assays, the downstream signaling pathways may serve as both a target of and a readout for therapy development efforts.

Various deficiencies in existing preclinical model organisms, and the hundreds of DUX4-regulated genes, mean that answers for PD biomarker discovery and validation may only come from incorporation of exploratory biomarkers into all current and future natural history studies and interventional clinical trials. A key knowledge gap is that many of the PD biomarker studies to date have been exploratory and have not yet produced the longitudinal data that will be essential to understanding their potential.

2. General muscle effector engagement

Evidence is emerging that at least some DUX4-regulated genes may be immunogenic – many are normally expressed only during the privileged immune environment of early development, and their aberrant expression in adults with FSHD triggers a response. Moreover, immune cell infiltration into pre-symptomatic FSHD skeletal muscle has been observed – it remains to be determined whether these events are predictive of subsequent pathology.

A key question is: Does a DUX4-driven immune response have a dominant role in the pathogenesis of FSHD? RNA signature analysis of FSHD-affected skeletal muscles supports the notion that inflammation plays a meaningful role in the disease and should be pursued as a therapeutic target. Muscle atrophy and regeneration targets also have validity in mitigating the impact of FSHD.

The question of plasma/serum biomarkers capable of tracking progression or intervention efficacy has received little attention – data from studies done thus far (including using the SomaLogic SOMAscan platform) may have cross-site reproducibility problems and do not appear to correlate with DUX4-regulated genes.

Finally, it will be important to understand the association between hypomethylation at the D4Z4 locus and disease pathology, including whether methylation status changes with disease progression or is responsive to intervention. This knowledge may provide insights into additional pharmacodynamic biomarkers.

III. Imaging Biomarkers

Evidence is building in support of MRI as a measure of FSHD disease activity and progression. While the heterogeneity of FSHD is potentially problematic for clinical trials, data from recent studies help establish the molecular correlates of an abnormal MRI signal. Specifically, MRI-informed muscle biopsies show a correlation between MRI signal and DUX4 expression. Further studies have supported a model with an initially normal MRI signal, followed by an abnormal STIR signal that progresses to T1-positive fatty infiltration. The temporal properties of MRI signal

progression and reversibility at different stages of progression are not yet worked out. The muscle-specific nature of FSHD (differing onset times and progression rates) means measures will be muscle specific, not averaged across entire muscle compartments. MRI protocols used in imaging studies internationally currently lack the standardization essential to meta-analysis – that unique pathologic profile of FSHD may benefit from recruitment of expertise to develop FSHD-specific sequences and analytical packages.

Imaging studies to date in FSHD have been primarily small and cross-sectional. That approach will not yield the information needed to improve clinical trial readiness. Instead, studies must be sufficiently powered and longitudinal to give a better idea of the progression and potential reversibility of imaging signals.

NMR imaging provides an opportunity for assessing muscle metabolites – such studies still appear to be at an exploratory stage for FSHD. A variety of new MRI technologies – new sequences to detect fibrosis, diffusion tensor imaging, texture analysis, and machine-learning algorithms and automated tracing of muscle outlines – also appear to be at an exploratory stage and require further analysis; it is unclear whether the FDA yet has experience with these new MRI methodologies. DEXA (lean muscle mass potentially important in FSHD; a DEXA caveat is lack of individual muscle data), ultrasound, and electrical impedance myography also may have potential use in FSHD – current validation status, costs, and feasibility for multisite studies need to be examined.

Taken together, these data indicate a solid rationale that imaging biomarkers may provide a bridge between the molecular mechanism of FSHD and clinically meaningful functional consequences of the disease. Use of imaging in an adaptive trial measure – i.e., intermediate outcome without breaking trial blind – may be worth exploring. Overall, it's likely that intensive, longitudinal studies in a cohort sufficiently powered to account for disease heterogeneity will be needed to fully validate and establish predictive value of this molecular biology-to-patient functional phenotype link.

IV. Clinical Trial Endpoints and Design

The established FSHD Clinical Trial Research Network has launched a study to address the critical goals of: 1) determining the multisite validity of the clinical outcome assessments (COAs); 2) comparing the responsiveness of new COAs to other FSHD outcomes; 3) determining the minimal clinically meaningful changes; and 4) establishing FSHD cohort characteristics to determine clinical trial eligibility criteria. The ReSOLVE study will run 18 months with an optional extension to 24 months, although the investigators plan an initial analysis at 12 months. An industry perspective was that studies such as this should include more functional outcome measures in preparation for Phase 3 trials. There also are concerns regarding the lack of inclusion of MRI measures. Straightforward functional measures that clearly demonstrate the "meaningful benefit" standard, such as reachable workspace, should be pursued.

Patient selection will be key to whether or not safety and efficacy of a candidate therapeutic can be established in an interventional clinical trial. A key question of cohort selection involves consideration of a strategy used in other neurological disorders (e.g., LSDs), i.e., choosing the most uniform cohort of predictably progressing patients based on a solid understanding of disease progression trajectories.

V. Recommended Actions

The Merck "Translational Medicine Guide" was presented at the Workshop to model when a biopharmaceutical company should invest in a particular disease indication. The key tenets of this perspective are: 1) "Trust in Target" – have the right biological target and understand its role in disease (including being able to quantify the patient response/efficacy); 2) "Trust in Therapeutic Window" – have the right therapeutic window (including optimizing the molecule, dose, and treatment regimen during clinical proof of concept; and 3) "Trust in Targeted Patient Population" – have the right patient group (stratification factors considered). The Guide underscores the importance to success of validating biomarkers, demonstrating clinical utility, tracking natural disease history, and biobanking. The activities of the Industry Consortium should focus on this or other models that define tractability in industry terms in order to optimize clinical trial readiness for

FSHD while making "choosing FSHD" an easy decision for venture capital and industry.

Furthermore, neuromuscular disease drug development has benefited from advice from the TREAT-NMD Advisory Committee on Therapeutics (TACT) as an expert, confidential, and independent review body to provide guidance on the translation and development path of therapeutics programs in rare neuromuscular diseases. Sponsors are strongly encouraged to take advantage of the TACT review process to assess their programs at an early stage of candidate therapeutic development for FSHD.

Specific recommended actions for the Industry Consortium are shown below in italics.

1. Support multisite, large cohort, longitudinal natural history studies

A central challenge for development and regulatory approval of a therapeutic for FSHD is the considerable variability in age of onset, symptoms, and severity. Effort needs to be devoted toward discovery, development, and validation of pharmacodynamic and imaging biomarkers and clinical outcome assessment measures. In developing FSHD biomarkers, attention needs to be paid to the "context of use" of the putative biomarker, as defined by the FDA. PD biomarkers that can rapidly read out target engagement and modulation are critically important for decision making in early-stage clinical trials, as well as in dose-ranging studies. Achieving a biologic response context of use for a PD biomarker is both valuable and more easily achieved, but the field also needs to plan to meet the bar for surrogate biomarkers in order to leverage the Accelerated Approval Program, an important consideration given the slow rate of progression of FSHD. In addition, data linking PD biomarkers to imaging changes and, in turn, to functional clinical endpoints of importance to patients will be compelling for drug developers and regulators. Data must be sufficient to establish predictive value of the biomarker, not simply correlations; thus, the PROMs included must be adequate for regulatory purposes.

Many biomarker and endpoint studies in the FSHD field have involved small cohorts, often at single or few sites. Cohort size limitations are particularly problematic in grant-funded imaging studies. As these transition into studies sufficiently large for powering in a heterogeneous disorder, data sharing mechanisms and cross-site standard operating procedures need to be implemented to ensure validation of PD and imaging biomarkers and clinical outcome assessment measures. Adherence to FDA and EMA expectations for such studies is critical. To avoid approved therapeutic labeling constraints, leadership of large natural history studies should be encouraged to refine outcome measures to reflect milder FSHD patients.

The NIH U01-supported Clinical Trials Network in the US is a model to build upon, including further expansion of the range of patients studied and an international focus essential to trials in this rare disease. As an academic-driven effort, it can benefit from regulatory and biopharmaceutical industry guidance. *Given the heterogeneity of the disease, support for multisite, large cohort, longitudinal natural history studies that combine pharmacodynamic, imaging, and clinical outcome measure assessments (using standard operating procedures informed by academia, regulatory, and industry best practices) is essential to achieve validated predictive biomarkers for FSHD.*

2. Establish a molecular signature biomarker panel

Establishment of biomarkers that identify and track the DUX4 molecular signature is critical for candidate therapeutic programs directed toward DUX4 and/or its upstream modulators or downstream targets. A PD biomarker panel can evaluate muscle integrity (does biomarker address pathophysiology or drug mechanism of action?), muscle function (does the biomarker correlate, or better, predict changes in function?), and/or patient function (does the biomarker predict an impact on patient quality of life?). Biopharma engaging in FSHD will need to be able to get basic information for their program – clear evidence that their candidate therapeutic engages and modulates a validated target in early-stage clinical trials. The molecular signature biomarker panel that is identified

will only begin to be validated as a drug development tool if shown to be modulated by a candidate therapeutic.

While considerable progress has been made, the linkage between DUX4 gene signature and disease activity/progression is largely based on small, cross-sectional studies and requires additional supportive data. Given the large number of downstream events, there's a need to establish a standard, focused PD biomarker panel of DUX4-regulated genes (i.e., selecting a panel of genes from the hundreds identified downstream of DUX4) that are most sensitive to change and show reproducible responsiveness to both disease progression and therapeutic interventions. Parallel assessments of biomarkers for muscle breakdown, especially if obtained non-invasively, may prove complementary to the DUX4 downstream gene panel.

Longitudinal assessments of the molecular signatures in FSHD patient biopsies must be done in order to establish PD biomarkers, but it will be important to know the frequency with which muscle biopsies can be repeated without a residual inflammatory response confounding signal. From there, standard operating procedures, quality controls, and GLP compliance must be incorporated into studies to allow for subsequent regulatory use of a molecular signature biomarker panel. Available regulatory guidance must be used in designing biomarker studies, whether or not qualification is ultimately sought. *Efforts should be directed toward ensuring sufficient validation of an FSHD molecular signature biomarker panel for industry to use to establish preclinical and clinical pharmacokinetic (PK)/pharmacodynamic (PD) parameters and for the FDA to recognize as valid for Investigational New Drug (IND) and/or Accelerated Approval, New Drug Application (NDA)/Biological License Agreement (BLA) decision making in the disease. Use of MRI-guided muscle biopsies likely is essential to this goal.*

3. Validate the MRI signals

Being able to measure and account for the heterogeneity of FSHD (asymmetry as well as patient-to-patient variability) will help control for a critical variable in interventional clinical trials. Imaging has shown promise

as that potential control as well as a biomarker for FSHD. Initial findings support a correlation between MRI signal and DUX4 expression – that linkage must be fully validated.

Other key issues yet to be resolved include whether quantifying fat fraction is *predictive* of disease activity/progression and whether pathology detected by MRI can be mitigated or reversed by interventions (e.g., there are open questions regarding duration/progression of STIR+ status and whether STIR positivity in FSHD muscle is reversible) – thereby allowing imaging to viably serve as a biomarker. Physical activity can impact a variety of parameters, including fat fraction, and must be controlled for in the design of protocols for clinical studies and trials.

Using imaging in multisite studies will require consensus on standard operating procedures for signal acquisition and analysis – there is no need to reinvent the wheel, as biopharma has confronted these problems in other diseases (consult Biogen and Novartis for starters). Incorporating automation into imaging (see use of VirtualScopics by Acceleron) would solve some key issues facing FSHD.

Ongoing longitudinal natural history studies should be enhanced or additional studies launched: 1) to better establish the molecular correlates of abnormal MRI signal; 2) to further evaluate and establish predictive value between abnormal MRI signals and functional measures important to the patient; and 3) to ultimately determine whether the pattern of MRI changes can be halted and/or reversed, and thus used as a sensitive efficacy measure for therapeutic interventions. Standardized protocols and analytical tools will be essential here.

4. Organize and hold a Critical Path Innovation Meeting to inform biomarker efforts

The design of biomarker studies should have the desired context of use and regulatory outcome in mind at the start. Achieving full regulatory qualification of or official Letter of Support for any one biomarker may or may not be necessary (there was debate on this point at the Workshop). Regulatory agency policies should ensure that all validated biomarkers

reside in the public domain and thereby be available as precompetitive tools to any drug developer targeting FSHD. Based upon the importance of linking focal DUX4 expression and MRI evaluations of muscle-specific pathology, it's likely that these two putative biomarkers should be viewed in combination. *A Critical Path Innovation Meeting (CPIM) should be organized with the FDA in order to gain regulatory insights into how best to validate biomarkers appropriate for the intended context of use. Feedback from the CPIM, then, should guide further biomarker efforts in FSHD.*

5. Establish care considerations for FSHD

Clinical trials can be confounded by differences in baseline care across study sites. This is evident in the differences that implementation of recommendations from prior care consideration efforts has had for patients living with FSHD. In rare diseases, available data on patient care may not always be sufficient to support evidence-based standards, but this should be the overall goal. *To ensure that clinical outcome measures are not compromised by site-to-site differences in study subject care, efforts should be made to establish, disseminate, and monitor uptake of best practice-based (if not evidence-based) care considerations for FSHD patients.*

6. Advance clinical trial feasibility and design

Improving the percentage of patients with genetic confirmation of FSHD1 and FSHD2 mutations will be important to establish clinical trial feasibility and accelerate recruitment. There is no one database that lists all genetically confirmed patients, and national registries can have rather low percentages with genetic diagnosis. Moreover, current means of obtaining genetic confirmation for FSHD are expensive and slow. Partnerships between advocacy and drug developers addressing this genetic diagnosis issue in Duchenne and limb-girdle muscular dystrophy (LGMD) can serve as models. Identifying and being able to enroll the right population for a given trial are central elements to trial success or failure. Another consideration is that once an effective therapeutic is available, molecular diagnosis is likely to be required by payers; thus, population diagnostic solutions should be sought now. *To avoid barriers to patient recruitment and*

stratification, partnerships should be sought to establish adequate laboratory resources for genetic testing and to ensure that all patients with phenotypic FSHD internationally receive a molecular genetics diagnosis.

Understanding interactions among genetics, PD biomarkers, and disease activity/progression is essential for patient cohort selection and, in return, the potential for success in interventional clinical trials. The critical need (and an apparent gap for FSHD) is to be able to identify the patients who will progress predictably and thus are amenable to improvement during the course of an interventional clinical trial. It's recognized that rate of progression in a natural history study and rate of response in a clinical trial are not one and the same – their relationship will likely not be recognized until the first proof-of-concept trial with a positive outcome. For now, molecular diagnostics and other assessment measures (e.g., quantitative MRI for identification of potentially responsive muscles) need to be in place to stratify patients in clinical trials, so as to select cohorts that are most likely to progress during the timeframe of a clinical trial, and thus are potentially responsive to a given intervention.

Given the clinical heterogeneity of FSHD, it is unlikely that confidence in outcomes from proof-of-concept and registration trials can be achieved with clinical outcome assessment measures alone (variability making it difficult to power a study). A more likely scenario is that PD biomarkers are used to establish target engagement and modulation and/or MRI measures will provide both guidance on muscle group selection for functional analyses and an efficacy endpoint adequate to meet criteria for accelerated approval. A variety of issues around MRI data collection and analysis will need to be resolved before incorporating imaging into multisite trials. Another view is that composite measures may be required to overcome the weakness of strength and functional measures in FSHD. Patient reported outcome measures may support accelerated approval and, if validated, will have a key role in subsequent confirmatory studies.

A major gap in achieving this trial design goal is the absence of MRI measures in the FSHD Clinical Trial Research Network study (a large cohort study centered at Radboud University Medical Center will have a five-year MRI follow-up later this year, but shorter readout intervals are necessary

to inform trials). Such comprehensive studies may begin to answer questions about potential outcomes for clinical trials – specifically whether skeletal muscle damage can be either mitigated or reversed. *Every effort should be made to support inclusion of key MRI measures in the Clinical Trial Research Network natural history studies and in other appropriately powered and comprehensive natural history studies.*

7. Organize and hold a Patient-Focused Drug Development meeting with the FDA

Perhaps most important is the need to ensure that the patient perspective informs clinical trial design and conduct. An externally led Patient Focused Drug Development (PFDD) meeting with the FDA serves the dual purposes of patient inclusion in study design and education of FDA staff. Multiple groups have gone before FSHD for PFDD meetings, and guidance can be solicited from them (e.g., Myotonic Dystrophy Foundation and Cure SMA). Another resource: James Valentine/Hyman, Phelps & McNamara, P.C., have extensive FDA experience and have facilitated multiple externally led PFDD meetings.

A PFDD will help ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation. Patient-FDA staff interactions will also help regulators understand the challenges and severity of FSHD. *Key stakeholders in the FSHD field should band together to submit a Letter of Intent and conduct an externally led PFDD meeting on FSHD to produce a PFDD Voice of the Patient report that will inform drug developers and the FDA.*

Synopsis

An overall understanding emerged from the Workshop of the need to establish predictive value rather than simply correlations, from the molecular events initiated by DUX4 expression and its downstream PD biomarkers to the imaging signals indicative of muscle pathology to clinical outcome measures and PROMs that reflect meaningful, functional changes

for the patient. Too often we are limited by the available data to using variants of the word “correlation” in speaking about FSHD data, when we need to get the evidence to say “has predictive value.” Nearly all of the recommendations from the Workshop ultimately revolve around establishing predictive value – an accomplishment that would establish a clear regulatory pathway for therapeutic development in FSHD.

Appendices

Appendix 1: Workshop Participants

- Jamshid Arjomand, PhD, Chief Science Officer, FSHD Society
- Ken Attie, MD, Vice President Medical Research, Acceleron Pharma
- Abbas Bandukwala, LCDR, USPHS, Program Coordinator, Office of Medical Products and Tobacco/CDER/FDA
- Camille Bedrosian, MD, Chief Medical Officer, Ultragenyx,
- Carsten Bonnemann, MD, Senior Investigator and Chief of the Neuromuscular and Neurogenetic Disorders of Childhood Section, NINDS/NIH
- Teresa Buracchio, MD, Clinical Team Lead, Division of Neurology Products/CDER/FDA
- Angela Cacace, PhD, Vice President of Neuroscience and Platform Biology, Arvinas, Inc.
- Diego Cadavid, MD, Senior Vice President, Clinical Development, Fulcrum Therapeutics
- Larry Charnas, MD PhD, Executive Director, Clinical Research, Rare Neurologic Diseases, Rare Disease Unit, Pfizer
- Tom Cheever, PhD, Program Director, Muscle Disorders and Therapies Program, NIAMS/NIH
- Terry Colella, President, Friends of FSH Research
- Rick Colella, Board member, Friends of FSH Research,
- Joris De Maeyer, PhD, Research and Development Director, Facio Therapies
- Gersham Dent, PhD MBA, Director, Clinical Research, Biogen
- Chris Eklund, Patient Advocate FSHD Clinical Trial Research Network Advisory Committee
- Kurt Fischbeck, MD, Chief, Neurogenetics Branch, NINDS/NIH
- Scott Galasinski, PhD, Senior Director, Translational Research, Ultragenyx
- Jack Gerblick, Patient Advocate and Atlanta Chapter Director, FSHD Society
- Laura Hagerty, PhD, Scientific Program Director, Muscular Dystrophy Association

- Sarabeth Hahn, PharmD, Associate Director, Regulatory Affairs, Acceleron Pharma
- Jay Han, MD, Professor and Vice Chair, Physical Medicine & Rehabilitation, University of California Irvine
- Scott Harper, PhD, Associate Professor, Department of Pediatrics, Nationwide Children's Hospital and The Ohio State University
- Chris Hughes, Board member, Chris Carrino Foundation
- Peter Jones, PhD, Mick Hitchcock Endowed Chair, Medical Biochemistry & Associate Professor of Pharmacology, University of Nevada Reno
- Ameet Khara, PharmD, Sr. Director, Global Patient Advocacy, Acceleron Pharma
- June Kinoshita, Chief Strategic Programs Officer, FSHD Society
- Frank Kolakowski, PhD, Patient advocate and Board member, FSHD Society
- Mehmet Kosoglu, Regulatory Information Specialist, Biomarker Qualification Program/CDER/FDA
- Doris Leung, MD PhD, Assistant Professor of Neurology, Kennedy Krieger Institute
- Erin MacSweeney, Patient advocate
- Hank Mansbach, Vice President, Global Clinical Development, Ultragenyx
- Katherine Mathews, MD, Professor and Vice Chair for Clinical Investigation, Department of Pediatrics, University of Iowa
- Michelle Mellion, MD, Medical Director, Clinical Development, Fulcrum Therapeutics
- Karlien Mul, MD PhD, Neurology Resident/Postdoctoral Researcher, Department of Neurology, Raboud University Medical Centre
- Thienhuu Nguyen, MBA, Global Commercial Lead, Acceleron Pharma
- Glen Nuckolls, PhD, Program Director, Neurogenetics Cluster, NINDS/NIH
- Bronwyn Owens, PhD, Director of Program Management, Acceleron Pharma
- Rainer Paine, MD PhD, Medical Officer, Division of Neurology Products/CDER/FDA
- Lexi Pappas, Patient advocate

- John Porter, PhD, Neuromuscular Disease Consultant, FSHD Society
- Lucienne Ronco, PhD, Vice President, Translational Medicine, Fulcrum Therapeutics,
- Dennis Shaw, MD, Professor of Radiology, University of Washington
- Mike Singer, MD, Medical Officer, Office of Tissues and Advanced Therapies/CBER/FDA
- Ali Skrinar, MA MPH, Vice President, Clinical Outcomes Research, Ultragenyx
- Jeff Statland, MD, Co-PI of FSHD Clinical Trial Research Network and Assistant Professor of Neurology, University of Kansas Medical Center
- Mark Stone, President and CEO, FSHD Society
- Wouter Suurmond, Corporate Development Manager, Facio Therapies
- Veneeta Tandon, PhD, Pharmacologist, Division of Neurology Products/CDER/FDA
- Stephen Tapscott, MD PhD, Professor of Neurology, University of Washington
- Rabi Tawil, MD, Co-PI of FSHD Clinical Trial Research Network. Professor of Neurology and of Pathology and Laboratory Medicine, co-Director of the MDA Neuromuscular Disease Clinic, and Director of the Neuromuscular Pathology Laboratory, University of Rochester School of Medicine

Appendix 2: Workshop Agenda

Industry Collaborative for Therapy Development in FSHD
March 12, 2019
Tommy Douglas Conference Center
Silver Spring, MD

8:00 – 8:05 a.m. Welcome and Introductions
Mark Stone, CEO, FSHD Society

8:05 – 8:20 a.m. A Family's Journey
Lexi Pappas

8:20 – 8:35 a.m.	Introduction to FSHD Katherine Matthews, MD, University of Iowa
8:35 – 8:40 a.m.	Workshop Purpose and Plan John Porter, Ph.D., Consultant, FSHD Society
8:40 – 9:10 a.m.	Keynote: FSHD is Tractable for Therapy Development Stephen Tapscott, MD PhD, Fred Hutchinson Cancer Research Center
9:10 – 9:40 a.m.	Industry Perspective on Tractability of FSHD Angela Cacace, PhD, Arvinas, Inc.
9:40 – 9:45 a.m.	Break
9:45 – 10:15 a.m.	Current Status of Natural History Rabi Tawil, MD, University of Rochester
10:15 – 11:15 a.m.	Discussion #1: Status Assessment and Optimization of Natural History Studies/Data
11:15 – 11:45 a.m.	Current Status of Pharmacodynamic Biomarkers Peter Jones, PhD, University of Nevada Reno
11:45 – 12:45 p.m.	Discussion #2: Status Assessment and Optimization of Pharmacodynamic Biomarkers Studies/Data
12:45 – 1:20 p.m.	Lunch
1:20 – 1:50 p.m.	Current Status of Imaging Biomarkers Doris Leung, MD PhD, Kennedy Krieger Institute
1:50 – 2:50 p.m.	Discussion #3: Status Assessment and Optimization of Imaging Biomarkers
2:50 – 3:05 p.m.	Break

3:05 – 3:35 p.m. Current Status of Clinical Trial Design
Jeff Statland, MD, Kansas University

3:35 – 4:35 p.m. Discussion #4: Status Assessment and Optimization of Clinical Outcome Assessment Measures

4:35 – 5:15 p.m. Synthesis/Next Steps
Jamshid Ariomand, PhD, Chief Science Officer, June Kinoshita, Chief Strategic Program Officer, and John Porter, PhD, Consultant, FSHD Society

Appendix 3: Background Literature

A prospective, quantitative study of the natural history of facioscapulohumeral muscular dystrophy (FSHD): implications for therapeutic trials. The FSH-DY Group.
[No authors listed]
Neurology. 1997 Jan;48(1):38-46.

Relationship between muscle inflammation and fat replacement assessed by MRI in facioscapulohumeral muscular dystrophy.
Dahlqvist JR, Andersen G, Khawajazada T, Vissing C, Thomsen C, Vissing J.
J Neurol. 2019 Feb 18. doi: 10.1007/s00415-019-09242-y. [Epub ahead of print]

DUX4 activates germline genes, retroelements, and immune mediators: implications for facioscapulohumeral dystrophy.
Geng LN, Yao Z, Snider L, Fong AP, Cech JN, Young JM, van der Maarel SM, Ruzzo WL, Gentleman RC, Tawil R, Tapscott SJ.
Dev Cell. 2012 Jan 17;22(1):38-51. doi: 10.1016/j.devcel.2011.11.013. Epub 2011 Dec 29.

Early onset as a marker for disease severity in facioscapulohumeral muscular dystrophy.

Goselink RJM, Mul K, van Kernebeek CR, Lemmers RJLF, van der Maarel SM, Schreuder THA, Erasmus CE, Padberg GW, Statland JM, Voermans NC, van Engelen BGM.
Neurology. 2019 Jan 22;92(4):e378-e385. doi: 10.1212/WNL.0000000000006819. Epub 2018 Dec 19.

Distinct disease phases in muscles of facioscapulohumeral dystrophy patients identified by MR detected fat infiltration.
Janssen BH, Voet NB, Nabuurs CI, Kan HE, de Rooy JW, Geurts AC, Padberg GW, van Engelen BG, Heerschap A.
PLoS One. 2014 Jan 14;9(1):e85416. doi: 10.1371/journal.pone.0085416. eCollection 2014.

Individual epigenetic status of the pathogenic D4Z4 macrosatellite correlates with disease in facioscapulohumeral muscular dystrophy.
Jones TI, King OD, Himeda CL, Homma S, Chen JC, Beermann ML, Yan C, Emerson CP Jr, Miller JB, Wagner KR, Jones PL.
Clin Epigenetics. 2015 Mar 29;7:37. doi: 10.1186/s13148-015-0072-6. eCollection 2015.

Randomized, double-blind, placebo-controlled trial of albuterol in facioscapulohumeral dystrophy.
Kissel JT, McDermott MP, Mendell JR, King WM, Pandya S, Griggs RC, Tawil R; FSH-DY Group.
Neurology. 2001 Oct 23;57(8):1434-40.

Adding quantitative muscle MRI to the FSHD clinical trial toolbox.
Mul K, Vincenten SCC, Voermans NC, Lemmers RJLF, van der Vliet PJ, van der Maarel SM, Padberg GW, Horlings CGC, van Engelen BGM.
Neurology. 2017 Nov 14;89(20):2057-2065. doi: 10.1212/WNL.0000000000004647. Epub 2017 Oct 13.

Effects of vitamin C, vitamin E, zinc gluconate, and selenomethionine supplementation on muscle function and oxidative stress biomarkers in patients with facioscapulohumeral dystrophy: a double-blind randomized controlled clinical trial.

Passerieux E, Hayot M, Jaussent A, Carnac G, Gouzi F, Pillard F, Picot MC, Böcker K, Hugon G, Pincemail J, Defraigne JO, Verrips T, Mercier J, Laoudj-Chenivesse D.
Free Radic Biol Med. 2015 Apr;81:158-69. doi: 10.1016/j.freeradbiomed.2014.09.014. Epub 2014 Sep 20.

Low penetrance in facioscapulohumeral muscular dystrophy type 1 with large pathological D4Z4 alleles: a cross-sectional multicenter study.
Salort-Campana E, Nguyen K, Bernard R, Jouve E, Solé G, Nadaj-Pakleza A, Niederhauser J, Charles E, Ollagnon E, Bouhour F, Sacconi S, Echaniz-Laguna A, Desnuelle C, Tranchant C, Vial C, Magdinier F, Bartoli M, Arne-Bes MC, Ferrer X, Kuntzer T, Levy N, Pouget J, Attarian S.
Orphanet J Rare Dis. 2015 Jan 21;10:2. doi: 10.1186/s13023-014-0218-1.

Milder phenotype in facioscapulohumeral dystrophy with 7-10 residual D4Z4 repeats.
Statland JM, Donlin-Smith CM, Tapscott SJ, Lemmers RJ, van der Maarel SM, Tawil R.
Neurology. 2015 Dec 15;85(24):2147-50. doi: 10.1212/WNL.0000000000002217. Epub 2015 Nov 11.

Reevaluating measures of disease progression in facioscapulohumeral muscular dystrophy.
Statland JM, McDermott MP, Heatwole C, Martens WB, Pandya S, van der Kooi EL, Kissel JT, Wagner KR, Tawil R.
Neuromuscul Disord. 2013 Apr;23(4):306-12. doi: 10.1016/j.nmd.2013.01.008. Epub 2013 Feb 11.

Risk of functional impairment in Facioscapulohumeral muscular dystrophy.
Statland JM, Tawil R.
Muscle Nerve. 2014 Apr;49(4):520-7. doi: 10.1002/mus.23949. Epub 2014 Feb 10.

Facioscapulohumeral muscular dystrophy: a prospective study of weakness and functional impairment.
Stübgen JP, Stipp A.

J Neurol. 2010 Sep;257(9):1457-64. doi: 10.1007/s00415-010-5544-1. Epub 2010 Mar 30.

Magnetic resonance imaging in a large cohort of facioscapulohumeral muscular dystrophy patients: Pattern refinement and implications for clinical trials.
Tasca G, Monforte M, Ottaviani P, Pelliccioni M, Frusciante R, Laschena F, Ricci E.
Ann Neurol. 2016 May;79(5):854-864. doi: 10.1002/ana.24640. Epub 2016 Apr 4.

Strength training and albuterol in facioscapulohumeral muscular dystrophy.
van der Kooi EL, Vogels OJ, van Asseldonk RJ, Lindeman E, Hendriks JC, Wohlgemuth M, van der Maarel SM, Padberg GW.
Neurology. 2004 Aug 24;63(4):702-8.

Both aerobic exercise and cognitive-behavioral therapy reduce chronic fatigue in FSHD: an RCT.
Voet N, Bleijenberg G, Hendriks J, de Groot I, Padberg G, van Engelen B, Geurts A.
Neurology. 2014 Nov 18;83(21):1914-22. doi: 10.1212/WNL.0000000000001008. Epub 2014 Oct 22.

A phase I/IItrial of MYO-029 in adult subjects with muscular dystrophy.
Wagner KR, Fleckenstein JL, Amato AA, Barohn RJ, Bushby K, Escolar DM, Flanigan KM, Pestronk A, Tawil R, Wolfe GI, Eagle M, Florence JM, King WM, Pandya S, Straub V, Juneau P, Meyers K, Csimma C, Araujo T, Allen R, Parsons SA, Wozney JM, Lavallie ER, Mendell JR.
Ann Neurol. 2008 May;63(5):561-71. doi: 10.1002/ana.21338.

MRI-informed muscle biopsies correlate MRI with pathology and DUX4 target gene expression in FSHD.
Wang LH, Friedman SD, Shaw D, Snider L, Wong CJ, Budech CB, Poliachik SL, Gove NE, Lewis LM, Campbell AE, Lemmers RJFL, Maarel SM, Tapscott SJ, Tawil RN.
Hum Mol Genet. 2019 Feb 1;28(3):476-486. doi: 10.1093/hmg/ddy364.

DUX4-induced gene expression is the major molecular signature in FSHD skeletal muscle.
Yao Z, Snider L, Balog J, Lemmers RJ, Van Der Maarel SM, Tawil R, Tapscott SJ.
Hum Mol Genet. 2014 Oct 15;23(20):5342-52. doi: 10.1093/hmg/ddu251. Epub 2014 May 26.