

FACIOSCAPULOHUMERAL (FSH) SOCIETY RESEARCH GRANT AND FELLOWSHIP APPLICATIONS

The Facioscapulohumeral (FSH) Society offers postdoctoral fellowships, research fellowships, and basic research and clinical-research grants to support research relevant to understanding the molecular genetics, pathophysiology, cause, and treatments of facioscapulohumeral muscular dystrophy (FSHD).

To obtain an application, please submit a letter of intent. The letter of intent should contain a single page introductory cover letter plus a one or two-page descriptive summary of the proposed – enough for a decision from the Scientific Advisory Board. In addition, please provide a highly intelligible lay summary of several paragraphs for presentation to non-scientists and prospective and current donors. A well thought out and tight rationale for a research project can easily lend itself to one page. The letter of intent may be submitted at any time to the FSH Society, attention: Dr. David Housman, Scientific Advisory Board Chairman. Please e-mail letter of intent to both David Housman (dhousman@mit.edu) and Daniel Paul Perez (daniel.perez@fshsociety.org) or fax or mail to address below.

Indirect costs are not allowed but fringe benefits are considered a part of personnel costs and are allowed.

Deadlines for receipt of both research grant, clinical grant, research- and post-doctoral- fellowship applications are: **February 28, 2019 and August 31, 2019.**

Payment if awarded, is made in two equal installments. The first payment is executed on the activation date. The second payment is executed six months after the beginning of the award period. A progress-to-date package will be sent to the FSH Society at the end of six months. The subsequent year of funding will not be activated prior to a review of the six-month progress reports and an explanation of changes that the work necessitates or changes in specific aims for the next year. The progress report is required at 6 months after the start of each award period.

Propagatable materials (including monoclonal antibodies, recombinant DNAs, animal models, cell lines, and any propagatable cells) should be freely available to other investigators following publication. The Society's position is that there be no restriction or proprietary rights in materials produced with our support.

+

RESEARCH GRANT APPLICATIONS

The Society's focus is on facioscapulohumeral muscular dystrophy (FSHD).

Support will be for research projects that will contribute to identify and understanding the basic defect in FSHD and preclinical, translational and clinical/therapeutic research related to FSHD.

The range of awards for grants is between \$7,500 and \$125,000 per year with an average award being about \$57,500. Grants are usually for one year, with the possibility of funding or renewal for up to three years.

General areas of interest include -- tissue, cell and molecular biology studies of FSHD, the development of animal models for FSHD, biomarkers and outcomes measurements and clinical trials readiness. Proposals are sought for research that helps with understanding of the genetic, pathophysiological, neuromuscular and developmental mechanisms of the disease. Further, there is interest in the development of cell, small-molecule and gene therapy, genomic engineering technologies and other therapeutic programs that may arise from that understanding.

Specific areas of interest, as highlighted in the FSH Society's 2018 Annual International Research Consortium meeting in Las Vegas, include --

1. Therapeutics

Trial Tool Kit. While drug development pipelines are beginning to produce candidate drugs, the trial tool kit needs to be completed. Evidence was presented that MRI STIR positivity correlates well with DUX4 target gene expression but this needs further refinement and to be reproduced. MRI directs to active disease processes but longitudinal studies are needed. Uniform definitions for (interpretation of) MRI imaging need to be established by the community. In the cardiac field stress tests are informative, which may also be explored in FSHD. Ultrasound is not a priority as it is hard to standardize between users, although does have the advantage of being lower cost and higher throughput, and may be useful earlier in the disease process. Electrical impedance myography may correlate to changes in muscle structure but its sensitivity to changes in muscle over time still needs to be determined. The tool kit comprises biological and non-invasive biomarkers and clinical outcome assessments which will be important for drug approvals.

Biological Biomarkers. The search for biological biomarkers need to be continued. While DUX4 target genes in the muscle may be better targets than DUX4 itself, several efforts are ongoing including RNAseq and proteomics studies, which also point towards suppression of PAX7 target genes as a potential FSHD biomarker. Peripheral serum markers for FSHD are preferred due to their easy assessment from blood samples. Caution should be taken to avoid as many potential confounders as possible.

Clinical Outcome Assessments. Strength, function and functional tests are relevant outcome measures, likely for later phase clinical trials. Non-invasive or peripheral serum markers may also facilitate trial recruitment. Studies into these COAs preferably need to be done in multi-center context such as the FSHD clinical trial research network, or through international partnerships. Video measures are experimental and need further studies. Home devices, such as activity monitors, allow to follow patients longitudinally, for example in training trials. Patient reported outcomes are in development and will be important ultimately for clinical trials.

Alternative/complementary therapies. Focus is currently on reducing DUX4 expression/function by various means, but therapies that also ameliorate some of the major pathological drivers in FSHD, and/or augment muscle repair, may be quicker to clinic and improve quality of life, while DUX4-targeted therapies are being developed.

2. Pathophysiology

DUX4 With Regard to Fibrosis, Inflammatory Infiltrates and Fatty Infiltration. There is a gap between basic (DUX4) knowledge and clinical observations that need to be filled. It is unclear how assumingly sporadic, barely detectable expression of DUX4 results in generalized muscle weakness and wasting. Investigations in downstream consequences such as fibrosis, inflammatory infiltrates, oxidative stress, repair/regenerative response and fatty infiltration are warranted as these are often targets of therapy in other MDs as well. Studies in animal models may accelerate studies into these downstream pathways.

Temporal Analyses of Models. A number of animal models have been generated and there are more in development. All models have their utility and limitations. It is likely that these models may give us clues into what happens in patients and studies should focus on temporal analyses of these models to capture aspects of the disease over time. The models are also important for therapeutic studies. Imaging may aid temporal studies to define the order of events. Non-human primate models are not considered a priority due to cost and ethical issues?

Novel Models for Other Aspects. Novel models are likely necessary to capture other aspects of the disease. One example is to express mouse Dux in mice, as, although DUX4 and mDux have diverged considerably, there is large functional overlap between both proteins. Other examples are to continue investing in cellular models such as stem cells, iPSC cells, organoids / organs-on-a-chip.

3. Molecular Mechanisms

Mechanisms of DUX4 Pathology. While expression of DUX4 is considered the cause for FSHD, the exact molecular mechanisms of DUX4 pathology are only partly understood. Studies of DUX4 and mDux in cellular and animal models are also necessary to understand why cells die from DUX4. Temporal studies are necessary to capture the heterogeneity and order of events. Caution should be taken with respect to endogenous versus overexpression, primary versus immortalized cells, and origin of the muscle biopsies need consideration.

DUX4 Functionality. Posttranslational modifications of DUX4 may affect its function, co-factors need to be identified and studied and its cellular localization and functionality should be further explored in the context of FSHD pathophysiology. Its role as transcription factor, also in relation to PAX3/PAX7, warrants further investigation. Most studies have focused on pathways that are activated by DUX4, and relatively few studies have addressed those genes and pathways that are suppressed. Roles of DUX4, in addition to being a transcription factor, are relatively understudied.

DUX4 Native and Conserved Function. The natural distribution and regulation of DUX4 expression should be studied. DUX4 is expressed at cleavage stage embryos but little is known about the regulation of DUX4 during development and which tissues express DUX4, as well as its (lack of) toxicity in those tissues. The distribution of DUX4 in FSHD muscle is not known, nor how it correlates with clinical and pathological aspects of FSHD muscle, nor at the preclinical level.

4. Genetics and Epigenetics

Harmonization of Genetic Testing. New diagnostic techniques are available, including those for prenatal or preimplantation diagnostics. While current DNA diagnostics is accurate, there remains a continuous need for harmonization and improvement, also in view of future trials. New technologies may aid this effort and allow for identification of new disease mechanisms, although it remains to be determined if new strategies are as cost- and time-efficient as current standards.

Disease Continuum and Genotype Classification. While for trial participation genetic confirmation is mandatory, the terms FSHD1 and FSHD2 need to be reconsidered as to prevent potential exclusion of FSHD2 patients from future therapies. The terms FSHD1 and FSHD2 have an historical basis but recent studies show that both are 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.

Understanding Drivers of Clinical Variability. Continuous efforts are necessary to increase our understanding of (the genetic and epigenetic basis) of clinical variability. Data presented at the workshop suggest that 50% of variance is familial, but that this differs between muscle groups varying from 30% in the facial muscles to 1% for upper extremity. Suggests different vulnerability to DUX4 e.g. there is 50% familial contribution to clinical variability of which 1-30% comes from D4Z4 repeat size. Genome wide studies in large patient cohorts may facilitate identification of modifiers, such as SMCHD1.

Role and Effects of Modifiers. The role of modifiers need to be better understood. We need to increase our ability to type the function of variants of these modifiers such as SMCHD1 and DNMT3B. Mutations in both disease genes can result in very discordant phenotypes (SMCHD1: FSHD and BAMS; DNMT3B: FSHD and ICF), but the cause for this discordance is not understood. Other modifiers are likely to exist and additional efforts are necessary to identify these genetic, epigenetic and non-genetic modifiers.

As the Society has limited funds, grants that are funded are considered "seed money." If the project shows promise, it is hoped that other institutions will fund it thereafter. Generally the Society does not include salaries of the principal investigator. Indirect costs are not allowed, but fringe benefits are considered part of the personnel costs and are acceptable. Grant applications should be completed and forwarded in electronic form (pdf/Word) to the FSH Society. Grant applications and reference letters should be e-mailed to Daniel Paul Perez (daniel.perez@fshsociety.org) or faxed and/or mailed to address below.

If reprints are to be considered as part of the application, please provide in electronic format (pdf/Word).

One to three letters of support are optional and may be from your own institution.

Applications are reviewed by two primary reviewers as well as by the FSH Society's Scientific Advisory Board. The Society will notify the applicant about the funding decision by letter only.

+

(POST-DOCTORAL-, PRE-DOCTORAL- and GRADUATE-), FELLOWSHIP APPLICATIONS

Support will be for research fellowship projects that contribute to identifying and understanding the basic defect of FSHD and preclinical and translational research related to FSHD.

Indirect costs are not allowed but fringe benefits are considered part of personnel costs and are acceptable.

The range of awards for grants is between \$7,500 and \$80,000 per year with an average award being about \$55,000. Funded fellowships may be requested for one, two or three years, subject to satisfactory progress reports at 6 months intervals.

A reference sheet is enclosed with each fellowship application for use by three or more applicant-selected personnel acquainted with the applicant's relevant experience. **Three (3) references are required** and may be from your own institution.

Applications should be completed to include the applicant's curriculum vitae, plus that of the research sponsor, and forwarded in electronic form (pdf/Word) to the FSH Society. If reprints are to be considered as part of the application, please provide in electronic format (pdf/Word) for distribution.

The Society will notify the applicant about the funding decision by letter only.

If any questions, please contact:

Daniel Paul Perez
Co-founder & CSO
FSH Society
Research Programs
450 Bedford Street
Lexington, MA 02420 USA
Phone: (781) 275-7781 Bedford, (781) 301-6650
Fax: (781) 275-7789
Internet: www.fshsociety.org
e-mail: daniel.perez@fshsociety.org