Testimony of Daniel Paul Perez, Co-Founder & Director Emeritus, FSHD Society before
U.S. Senate Appropriations Subcommittee on Labor, HHS, Education and Related Agencies
May 18, 2023

Honorable Chairman Baldwin, Ranking Member Moore Capito, and distinguished members of the Subcommittee, thank you. We are requesting a FY2024 appropriation of **$32.5 million** to the *agency* U.S. DHHS National Institutes of Health (**NIH**) for facioscapulohumeral muscular dystrophy (*hereafter called* **FSHD**) research *programs*.

I am co-founder, Director emeritus, past -Chairman, -President & CEO, and -CSO of the FSHD Society. As a patient with FSHD, my life's work on FSHD disease and its funding spans nearly every research lab, biotechnology and pharma company working today on FSHD globally. My efforts through the FSHD Society have led to understanding how FSHD1[1] and FSHD2[2,3] work. I was a key architect of the Muscular Dystrophy Community Assistance, Research and Education Amendments of 2001 (MD-CARE Act, Public Law 107-84). I have served on the Muscular Dystrophy Coordinating Committee (MDCC) since its inception and am the longest serving member. MDCC is a Federal Advisory Committee designed to coordinate activities relating to the various forms of muscular dystrophy across the NIH and with other Federal health agencies.

FSHD is a heritable disease and one of the most common neuromuscular disorders with a prevalence of 1:8,000.[4] It affects nearly one million children and adults of both sexes worldwide. FSHD is characterized by progressive loss of skeletal muscle strength that is asymmetric in pattern and widely variable. Muscle weakness typically starts at the face, shoulder girdle and upper arms, often progressing to the legs, torso and other muscles. In addition to affecting any skeletal muscle, it can bring with it respiratory failure and breathing issues[5-7], mild-profound hearing loss[8], eye problems and cardiac bundle blockage and arrhythmias[9,10]. FSHD causes significant disability and death according the U.S. Centers for Disease Control and Prevention (CDC), National Center on Birth Defects and Developmental Disabilities, Atlanta, and others[11,12].

FSHD is associated with epigenetic changes on the tip of human chromosome 4q35, in the D4Z4 DNA macrosatellite repeat array region, leading to an inappropriate gain of expression (function) of the D4Z4-embedded **d**o**u**ble homeobo**x 4** (DUX4) gene[13-16]. DUX4 is a transcription factor that kick starts the embryonic genome during the 2- to 8-cell stage of development[17-19]. Ectopic expression of DUX4 in skeletal muscle is associated with the disease and the disease's pathophysiology that leads to muscle death. DUX4 is never expressed in 'healthy' muscle. FSHD has had few clinical trials[20-26,27,28], there is no cure or therapeutic options. DUX4 requires and needs to activate direct transcriptional targets for DUX4-induced gene aberration and muscle toxicity[29-41].

Our patient community through its fundraising efforts and intensive research-integration has pioneered inroads to treating FSHD using genomic sequencing, genomic medicine, gene editing and next generation diagnostics. All with the goal of reducing DUX4 in its DNA or RNA or protein state, or the effects of DUX4-driven toxicity e.g. modulating DUX4 repressive pathways, targeting DUX4 mRNA, DUX4 protein, or cellular downstream effects of DUX4 expression[44-47].

Currently active projects listed in NIH RePORT as being applicable to FSHD are $16.961 million FY2023 (18May2023) vs. $17.507 million year-ago FY2022 (source: NIH Research Portfolio Online Reporting Tools (RePORT) 'FSHD or facioscapulohumeral or landouzy-dejerine'). The NIH is

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p: (781) 275-7781, f: (781) 275-7789, e: daniel.perez@fshdsociety.org. Full testimony with footnotes references at http://www.fshdsociety.org

currently the principal worldwide source of funding of basic biomedical research on FSHD. Currently annual funding directly dedicated for FSHD listed in NIH RCDC is $10 million.

Table 1. **FSHD Research Dollars (millions) & FSHD Percentage of Total NIH Muscular Dystrophy Funding**
Sources: NIH/OD Budget Office & NIH OCPL & NIH RePORT / RCDC (e=estimate, a=actual vers=March 31, 2023)

Fiscal Year	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**	**2023e**	**2024e**
All MD ($ millions)	$75	$76	$78	$77	$79	$81	$81	$83	$95	$82	$78	$81	83
FSHD ($ millions)	$5	$5	$7	$8	$9	$11	$11	$10	$9	$9	$10	$10	10
FSHD (% total MD)	7%	7%	9%	10%	11%	14%	14%	12%	9%	11%	13%	12%	12%

Honorable Chairman, thanks to Congress' work in enacting the MD CARE Act, funding the NIH, and with communications with NIH-leadership and program/legislative staff -- several dystrophies now have FDA approved treatments. NIH has been especially thoughtful with its expenditure and approach to research on muscular dystrophy. In the past year, nearly one hundred peer reviewed publications on FSHD came online. Excellent gains made in expanding basic research, better understanding of natural history and disease heterogeneity, biomarkers and outcomes assessments, therapeutic compounds/interventions and clinical trial design[48-61]. Recent publications further underscore the need for broad and combinatorial therapeutic strategies as it is possible that any single approach may not be successful or not be enough e.g. immunomodulation plus DUX4 inhibition, DUX4 inhibition plus muscle regeneration, FSHD as a myodevelopmental disease ["satellite cell-opathy" a primary satellite cell disease] caused by specific stem cell epigenetically weakly repressed at the D4Z4 repeat needing early intervention[62-67]. The prospect of treating and curing FSHD in the next 12 to 24 months is very real and tangible. More than $1 billion from investment banks, venture capital, private/philanthropic investors across more than 25 companies recently flowed into companies working on FSHD therapies. Though target DUX4 completely black and white – all are still flying blind when it comes to measuring ectopic DUX4 in human muscle. What emerges -- is, on one end of the spectrum an overarching need for far more basic and mechanistic research e.g. better understanding of the fundamental mechanisms of FSHD disease, including muscle disease. Secondly, on the back-end with getting therapies to patients, is the need to eliminate projects that will never succeed in practice/clinic i.e. 'does this have a pathway to clinic?' Associated with our request for 32.5 million dollars in FY2024, we highlight top priorities, research questions in need of better answers and open-ended areas of investigation in tables 2 and 3 where NIH can improve on its FSHD research spending.

Table 2. FSHD1 and FSHD2 Broad NIH Cross-Cutting Thematic Areas

- **Better biomarkers**: we still need to improve on our non-invasive and invasive biomarkers for trial readiness;
- **Clinical variability and disease pattern**: our understanding of the causes for clinical variability in both FSHD1 and FSHD2 is too limited, let alone that we can predict progression;
- Studying the **normal function of DUX4** and how it causes muscle disease can focus design of future clinical trials;
- Investigating if muscle pathology can be reversed once DUX4 expression starts the **pathogenic cascade** in a particular muscle?;
- Exploring if there is a systemic effect of local DUX4 expression that leads to amplification of muscle decline, either **immune or some extracellular signaling**. Can we intercept and control the disease process?;
- Designing **new technologies and methods to track** biological, chemical, mechanical and electrical aspects of muscle function for improving or declining health of FSHD permissive genotype;
- Improving **registries**: need further international integration and sustainability;
- **Prioritizing pathways**: DUX4 activates many different pathways, we don't know if there is any hierarchy in contribution to disease, or different roles;
- **Genetic heterogeneity**: not all patients are explained, population differences, etc.;
- **Molecular/tissue heterogeneity**: do we sufficiently understand the muscle involvement? Other tissues/cell types?;
- **DUX4 dynamics**: what activates DUX4 as all nuclei are (epi)genetically sensitized but only few express DUX4. Is there active silencing (can we take advantage of the 8-cell stage mechanism of DUX4 silencing)? How are the DUX4 signals propagated within fibers, between fibers?;

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- **Therapy**: many different routes are being explored e.g. small molecule drugs, biologics, gene transfer/editing, cell/molecular therapies (including oligonucleotides), devices, nutritional and exercise, behavioral and combinatorial therapy. How do we handle this effort with the limited patient population that will be available for trials?;
- Improved **preclinical and large animal models** that accurately reflect mechanisms of disease onset and progression;
- **Genetic and environmental mechanisms** that determine timing of onset / rate of progression in genetically inherited disease;
- **Role of the adaptive and innate immune system** in disease onset and progression;
- **Uniform, reliable and scalable DNA diagnostics**, pre-implantation, prenatal and postnatal;
- Promoting research that helps to increase safety and efficacy of FSHD clinical trials, **addressing toxicity, immune response and efficiency of uptake.**

Table 3. FSHD1 and FSHD2 Inspirational Research Directions

- Individuals with FSHD1 and FSHD2 are born with DUX4 turned on from day one and it may be years/decades on non-symptomatic disease infiltrating the muscle – accelerate research efforts and ways of screening genetically and identifying and **tracking non-symptomatic disease progression and infiltration**;
- Developing **ways to assess, stop and reverse non-symptomatic disease progression** and infiltration in FSHD muscle e.g. outcome measures herein are strictly biological not clinical functional;
- Help accelerate movement of testable compounds toward clinical trials in FSHD, by the **discovery and generation of tractable markers of both symptomatic and non-symptomatic disease** to provide measurable outcomes;
- Understanding precisely **how FSHD skeletal muscle epigenome protects from FSHD or capitulates** to having active FSHD progression;
- Provide a platform for stakeholders [members of the FSHD research community, pharmaceutical and biotechnology companies interested in developing therapeutics for FSHD, and leading scientists who have successfully exploited model systems in understanding human disease writ large] to **identify viable biomarkers that could be exploited** in clinical trials;
- Identify and elucidate or **engineer specific biomarkers and models** associated with the onset, and progression of FSHD1 and FSHD2;

It is imperative to increase our efforts in the areas mentioned herein -- gains in these areas will help ascertain if therapies are effective, safe and not cost-prohibitive. We request for FY2024, increasing NIH FSHD research funding/appropriation of the standard portfolio to $32.5 million.

Honorable Chairman, thank you for this opportunity to update you with this testimony.

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Patients, professionals, and other parties interested in FSHD can contact us at FSHD Society, 450 Bedford Street, Lexington, MA 02420 USA
p: (781) 275-7781, f: (781) 275-7789, e: daniel.perez@fshdsociety.org. Full testimony with footnotes references at http://www.fshdsociety.org