DHHS National Institutes of Health (NIH) FY2018 Budget Appropriations Request for research on facioscapulohumeral muscular dystrophy (FSHD) witness appearing before the House Appropriations Subcommittee on Labor, HHS, Education and Related Agencies Daniel Paul Perez, President & CEO, CSO, FSH Society March 7, 2017

Agency: *National Institutes of Health (NIH).* ***Account:*** *National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute of Neurological Disorders and Stroke (NINDS), Eunice Kennedy Shriver National, Institute of Child Health and Human Development (NICHD), National Human Genome Research Institute (NHGRI) and other Institutes as appropriate.*
FY 2018 Report Language: *The Committee hopes and recognizes that scientific opportunities alongside recent breakthroughs and community defined priorities in facioscapulohumeral disease (FSHD) will help NIH call for more research proposals and modestly increase projects and funding. The Committee strongly encourages the NIH to significantly accelerate basic and exploratory research efforts and increase clinical trials readiness funding to provide access to treatment of facioscapulohumeral muscular dystrophy (FSHD) and other epigenetic diseases.*

Honorable Chairman Cole, Ranking Member DeLauro, and distinguished Members of the Subcommittee, thank you for the opportunity to submit testimony. We kindly request $26 million FY2018 for NIH funding for research on facioscapulohumeral disease (FSHD).

About FSHD, about our disease, my disease. FSHD, a heritable disease, is a most common form of muscular dystrophy with a prevalence of 1:8,000[1], affecting approximately 870,000 children and adults of both sexes worldwide. FSHD is characterized by the progressive loss of muscle strength that is asymmetric and widely variable. Muscle weakness typically starts at the face, shoulder girdle and upper arms, often progressing to the legs, torso and other muscles. FSHD has a high burden of disease and can cause significant disability and, in severely affected individuals, premature death, mainly through respiratory failure. In addition to affecting muscle it can bring with it respiratory insufficiency, hearing loss, eye problems and cardiac arrhythmias.

The National Institutes of Health (NIH) is the principal worldwide source of funding of research on FSHD currently active projects are $12.751 million FY2017, a portion of the estimated $80 million spent on all muscular dystrophies in FY2017.

This Subcommittee and **Congress in partnership with NIH, patients and scientists has made truly outstanding progress in identifying areas in need of funding in the nine types of muscular dystrophy.** Congress is responsible for this success by its sustaining support of the

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overall NIH budget, and specifically through the enactment of the Muscular Dystrophy Community Assistance, Research and Education Amendments of 2001 (MD-CARE Act, Public Law 107-84). The NIH leadership and staff published last year in *Muscle & Nerve* the '*2015 NIH Action Plan for the Muscular Dystrophies.'* This roadmap to increase efforts on dystrophy was assembled under the auspices of the federal advisory committee mandated by MD CARE Act, called the MDCC, along with working groups of experts in the field. It specifies eighty-one objectives organized in six sections (mechanism, screening, treatments, trial readiness, access to care, infrastructure including workforce) in need of immediate and further development.[2]

On our end, as tiny as it is, the FSH Society continues to deliver huge results in improving our understanding of FSHD. As of March 3, 2017, the FSH Society has provided approximately $8.165 million in seed funds and grants to pioneering FSHD research areas, education worldwide and created an international collaborative network of patients and researchers. Table I illustrates the rapid pace of discovery. Many of these breakthroughs have origins in seed funding from the FSH Society to researchers who have then used preliminary data to secure funding from the NIH. In the past few years, groundbreaking clinical and preclinical papers have emerged (MRI, biomarkers, surrogate outcome measures, cell and animal models, therapeutic studies in gene therapy, genetic engineering, CRISPR, antisense oligonucleotide (ASO), morpholino, LNA gapmers and small molecules). We are thrilled that our grantees have data and publications that prove that the FSHD-causing DUX4 toxicity can be turned off![3,4,5]

Table I. Chronology of Developments

1886	FSHD was first described
1991	FSH Society formed
1991	FSHD genetic location found in the subtelomere of chromosome 4q35 in an area thought to be "junk DNA" (D4Z4 macrosatellite repeat array)
2001	MD CARE Act passed
2004	FSHD1 found to be caused by a contraction of repetitive D4Z4 array on chromosome 4
2007-2010	Critical role for DUX4 in FSHD1 pathophysiology established in FSHD1. De-repression of the D4Z4-encoded DUX4 retrogene coding for a transcription factor caused by a 1-10 unit D4Z4 repeat-array contraction and use of a polyadenylation signal distal to the D4Z4 repeat array to

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	create a stable RNA and toxic protein. NIH Director Dr. Francis Collins was quoted on the front page of the *New York Times*, saying **"If we were thinking of a collection of the genome's greatest hits, this [FSHD] would go on the list"** [6]
2012	Critical role for DUX4 in second type of FSHD called FSHD2 is established by the loss of D4Z4 silencing of DUX4 due to a chromatin repressor gene SMCHD1 on chromosome 18 having mutations responsible for maintaining the health of D4Z4
2014	Mechanism described for how disease modulates itself from non-manifesting to manifesting due to balance between genetic and epigenetic factors as relates to the notable inter- and intrafamilial variability in disease onset and progression
2016	A second type of FSHD2 found to be caused by mutations in DNA methyltransferase 3B (DNMT3B) causing D4Z4 de-repression yielding DUX4

The NIH now has increased clarity of genetic and epigenetic contributors to FSHD that control disease onset, progression and severity. With this data the NIH can presently increase the amount of research funding on FSHD with neither having to increase the NIH budget nor taking money from another area of research. Better data, higher quality science, and focus allows more efficiency out of a non-growing budget, while achieving the goals of the Plan.

We must keep moving forward. November 10-11, 2016, the FSH Society held its annual International Research Consortium meeting in Boston, Massachusetts. The meeting was funded in part by the NIH NICHD University of Massachusetts Medical School Wellstone Center for FSHD. Over 110 researchers from around the world gathered to present latest data and discuss research strategies. The FSHD clinical and research community listed 2017 priorities in Table II.

Table II. 2016/2017 Research Priorities

Molecular mechanisms

Priority 1: Understanding genetic toxicity in FSHD
Priority 2: Understanding Dux4 and how to silence it. How to silence the DUX4 RNA
Priority 3: Understanding what real pathophysiology is in FSHD
Priority 4: Studying relationship to other markers and correlation between the expression and activity, transcriptional activity of DUX4

Genetics and epigenetic

Priority 5: Studies that focus on the uniformity in genetic testing and subgrouping of patients
Priority 6: Understanding of the epigenetic regulation of the repeats helps us to better understand the disease process and the disease mechanism
Priority 7: Research on modifiers of the disease mechanism

Clinical and therapeutic studies

Priority 8: Generating and identifying surrogate outcome biomarkers
Priority 9: Establishing validated outcome measures
Priority 10: More research with natural history studies
Priority 11: Studies to identify, validate, and determine the best standard measurements are critical for trial preparedness in FSHD

Models

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Priority 12: Research that helps focus to ensure that we are measuring the same kinds of things, that translate into a usable tool for our therapeutic industry
Priority 13: Development, characterization and use of animal models: whole animal; mice; fish; pig mammal
Priority 14: Emphasis on development, characterization and use of FSHD human cellular models
Priority 15: Research on models to help develop 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
(Source: http://www.fshsociety.org/international-research-consortium/)

NIH funding for muscular dystrophy. Mr. Chairman, these major advances in scientific understanding and epidemiological surveillance are not free. They come at a cost. Since passing the MD CARE Act in 2001, funding at NIH for FSH muscular dystrophy is still too underpowered given the remarkable discoveries in the past five years.

FSHD Research Dollars (in millions) & FSHD as a Percentage of Total NIH Muscular Dystrophy Funding
Sources: NIH/OD Budget Office & NIH OCPL & NIH RePORT RCDC (e = estimate)

Fiscal Year	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016e**	**2017e**
All MD ($ millions)	$39.5	$39.9	$47.2	$56	$83	$86	$75	$75	$76	$78	$77	$80	$80
FSHD ($ millions)	$2.0	$1.7	$3	$3	$5	$6	$6	$5	$5	$7	$8	$9	$9
FSHD (% total MD)	5%	4%	5%	5%	6%	7%	8%	7%	7%	9%	10%	11%	11%

Despite the great success of the past five years in the science of FSHD brought about by Congress, NIH, non-profit funding agencies, patients, families and researchers we are gravely concerned with the overall level of FSHD research funding and its sideways trend. There are 28 active projects NIH-wide totaling $12.751 million as of March 3, 2017, versus 32 active projects NIH-wide totaling $12.616 million on April 14, 2016, and 26 projects on March 12, 2015 (source: NIH Research Portfolio Online Reporting Tools (RePORT) http://report.nih.gov keyword 'FSHD or facioscapulohumeral or DUX4'). NIH's 28 projects cover 1 F32, 1 K22, 1 K23, 1 R03, 3 R21, 12 R01, 1 P01, 1 P50, 2 U01, and 2 U54 grants. In the last year, there was a loss of one training grant F32, one exploratory/developmental research grant (R21), 3 research project grants (R01), offset by a gain of 1 research program project/center of research translation (P50) and 2 cooperative clinical research agreements (U01). The engine of the federal research runs on the basic building blocks of workforce training, exploratory/developmental research grants (parent R21) and research project grants (parent R01).

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What we need. Looking at the current portfolio against the backdrop of scientific understanding and opportunity in FSHD the NIH needs to expand its portfolio. Specifically, NINDS needs to increase its current portfolio of one R01 and no R21 grants by adding 12-15 R01s and R21s. And, the NICHD, NHLBI, NHGRI who also are heavily involved in MD CARE Act/MDCC each need to increase their current portfolios of zero R01 and zero R21 grants by adding 8-12 R01s and R21s each. NIH can easily help increase its portfolio on FSHD by issuing one or more of the following on FSHD: Program Announcement (PA), Program Announcement with set-aside (PAS), with special review (PAR), or with set-aside special review (PAR/S). A request for applications (RFA) on FSHD for R01 and R21 applications would certainly help given the breakneck speed of discovery in FSHD, and the need should be palpable to NIH leadership. These are easy ways for NIH to convey to researchers that it has an interest in funding research in FSHD and drawing in more applications.

What we are asking for. We request for FY2018, a doubling of the NIH FSHD research portfolio to $26 million. While in the past year NIH has invested in larger cooperative research centers and collaborative research grants – most of the priorities as specified by the community call for more basic grants and exploratory research awards, expansion of post-doctoral and clinical training fellowships. Now that NIH has conveyed to researchers that it has a revised plan and an interest in funding research in FSHD these funds will be needed to fill the demand. Mr. Chairman, thank you for this opportunity to testify before your committee.

1. Deenen JC, et al, Population-based incidence and prevalence of FSHD. *Neurology*. 2014 Sep 16;83(12):1056-9. Epub 2014 Aug 13.
2. Rieff HI, Katz SI et al. The Muscular Dystrophy Coordinating Committee Action Plan for the Muscular Dystrophies. *Muscle Nerve*. 2016 Mar 21. [Epub ahead of print]
3. Himeda CL, Jones, et al. CRISPR/dCas9-mediated Transcriptional Inhibition Ameliorates the Epigenetic Dysregulation at D4Z4 and Represses DUX4-fl in FSH Muscular Dystrophy. *Mol Ther.* 2016 Mar;24(3):527-35. epub 2015 Nov 3.
4. Chen JC, King OD, Zhang Y, et al. Morpholino-mediated Knockdown of DUX4 Toward Facioscapulohumeral Muscular Dystrophy Therapeutics. Molecular Therapy. 2016;24(8):1405-1411. doi:10.1038/mt.2016.111
5. Balog J, Thijssen PE, Shadle S, et al. Increased DUX4 expression during muscle differentiation correlates with decreased SMCHD1 protein levels at D4Z4 . Epigenetics. 2015;10(12):1133-1142. doi:10.1080/15592294.2015
6. Kolata, G., Reanimated 'Junk' DNA Is Found to Cause Disease. *New York Times*, Science. Published online: August 19, 2010 http://www.nytimes.com/2010/08/20/science/20gene.html

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