DHHS National Institutes of Health (NIH) FY2017 Budget Appropriations Request
For research on facioscapulohumeral muscular dystrophy (FSHD)
Witness appearing before the
Senate Appropriations Subcommittee on Labor, HHS, Education and Related Agencies
Daniel Paul Perez, President & CEO, FSH Society April 15, 2016

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 2017 Report Language: *The Committee strongly encourages the NIH to accelerate research efforts and significantly increase projects and funding on facioscapulohumeral muscular dystrophy (FSHD). The Committee hopes and recognizes that scientific opportunities and recent epigenetic breakthroughs in FSHD will help NIH access therapies for this and many other grave diseases such as Cancer.*

Honorable Chairman Blunt, Ranking Member Murray, and distinguished Members of the Subcommittee, thank you for the opportunity to submit this testimony. It is an honor to have the opportunity to present the (FY) 2017 request for NIH funding for research on facioscapulohumeral muscular dystrophy (FSHD) and update you on scientific opportunities. We thank this subcommittee for making research funding a national priority and for its strong investment in the NIH with the $2 billion funding increase in the FY 2016 Omnibus Appropriation bill.

About FSHD, about our disease, my disease. FSHD, a heritable disease, is among the most common forms of muscular dystrophy with a prevalence of 1:8,000 [1], affecting approximately 870,000 children and adults of both sexes worldwide. It can affect multiple generations and entire families. FSHD is characterized by the progressive loss of muscle strength. Muscle weakness typically starts at the face, shoulder girdle and upper arms, often progressing to the legs, torso and other muscles. The symptoms can develop at any age. The progression of FSHD is highly variable. FSHD has a high burden of disease and can cause significant disability and, in severely affected individuals, premature death, mainly through respiratory failure. Around 20% of affected individuals use a wheelchair or scooter. Besides muscle weakness, FSHD can also have the following manifestations: high-frequency sensorineural hearing loss, respiratory insufficiency, abnormalities of blood vessels in the back of the eye, and non-symptomatic cardiac arrhythmias.

The National Institutes of Health (NIH) is the principal worldwide source of funding of research on FSHD currently at the $8.398 million level FY2015 actual (and $12.616 million FY2016 current), a fraction of the $77 million FY2015 actual it spent on all of the muscular dystrophies. For two decades, this Subcommittee has supported the incremental growth in funding for FSHD research. I am pleased to report that this investment has produced remarkable results and remarkable advances in scientific understanding of human diseases.

A partnership of Congress, NIH, patients and scientists has made truly outstanding progress in identifying areas in need of funding and in communicating these objectives to the public. Congress is responsible for this success by its sustaining support of the 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). Several days ago, NIH leadership and staff that oversees muscular dystrophy published an editorial in *Muscle & Nerve* describing the work of the truly collaborative Muscular Dystrophy Coordinating Committee (MDCC), mandated by the MD CARE Act, which publicizes the 2015 NIH Action Plan for the Muscular Dystrophies as the roadmap for all funding, patient, family, and research communities. [2] The eighty-one objectives of the Action Plan, released in November, are organized within six sections: mechanism, screening, treatments, trial readiness, access to care, infrastructure including workforce. I have been very involved in creating the MD CARE Act, remain of service to the MDCC, and helped draft, write and edit the first and revised Action Plans. NIH leadership, program and grant review staff have our highest respect and I echo Stephen

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I. Katz, M.D., Ph.D., chair of the MDCC, director of the NIAMS at the NIH when he says we can all use this plan "to guide research, collaborations and strategies to extend and improve the quality of life of people suffering from these disorders." We are aware that MD Care Act does not set the amount of spending on FSHD or the other dystrophies at the NIH and we recognize that funding levels are determined in the appropriations process and the numbers of grant applications received and funded by the NIH on FSHD. We hope there are additional efforts and pathways that Congress can request and the NIH can enact to increase the amount of research funding on FSHD in the NIH portfolio that neither increases the NIH budget required nor takes money from another area of research and achieves more efficiency out of a non-growing research budget.

As tiny as it is, the FSH Society continues to deliver huge results in improving our understanding of FSHD -- and in turn helping scientists be more competitive at NIH with respect to the grant application and review process. As the nation's most expert and largest FSHD research funding non-profit, the FSH Society's mission is to conduct research, increase awareness, understanding and education on FSHD. While we remain ever curious about how FSHD works, our goal is to improve health, reduce disability and illness and lengthen life for those living with FSHD. As of April 13, 2016, the FSH Society has provided approximately $6.97 million, since the inception of its research fellowships and grants program, in seed funds and grants to pioneering FSHD research areas and education worldwide and created an international collaborative network of patients and researchers. Recent advances in understanding the molecular genetics and cellular biology of FSHD have led to the identification of potential therapeutic targets. Impressive scientific progress was again achieved in 2015 in the basic molecular and clinical understanding of the disease largely due to cumulative Society funding of research. In 2015, the Society issued twelve new grants and fellowships, continued funding five ongoing grants, and issued three travel grants to facilitate travel for professionals working on FSHD. The Society also works with various research institutions doing clinical research on FSHD to help facilitate patient travel for evaluation and tissue and blood donation by covering patient travel and lodging expenses. Dollar for dollar the Society is one of the best investments one can make in FSHD research funding outside of NIH funding and we have been effective and successful stewards of the resources we have been given by our donors to provide individuals, data and new hypotheses of extraordinary quality that the NIH can fund research on FSHD.

Quantum leaps in our understanding of FSHD. The past year and one-half has brought forth exceptional if not remarkable contributions made by a very small but extremely dedicated tribe of researchers funded by the Society, NIH and other non-profits.

- On September 25, 2014, researchers from United States, France, Spain, Netherlands and United Kingdom narrow the focus mechanistically opening the possibility of all types of FSHD having an epigenetic basis.[3]
- On March 29, 2015, different researchers involved with the NIH Senator Paul A. Wellstone Cooperative Research Center using its large collection of different FSHD patient samples and different techniques arrive at the same answer that there is an underlying principle of epigenetics defining asymptomatic or non-manifesting and playing a role in disease severity.[4]
- On September 1, 2015, researchers from Fred Hutchinson Cancer Research Center, Seattle, Rochester, New York and the Netherlands funded by a NIH P01 program project describe the role of siRNA-directed AGO/DICER-dependent epigenetic repression (silencing the DUX4 retrogene with the D4Z4 region) showing a pathway to therapeutically target FSHD.[5]
- On November 3, 2015, researchers at the University of Massachusetts Medical School (UMMS) successfully used a derivation of the CRISPR-based gene-editing method known as dCas9 to target and silence the DNA sequence implicated in FSHD. For the very first time a CRISPR-based system was been used to ameliorate pathogenic gene expression in FSHD successfully in primary human muscle cells.[6]
- On March 6, 2016 researchers at the University of Minnesota define an important function of the C-terminal domain of DUX4, namely to recruit the acetyltransferases p300 and CBP, which modify chromatin in the vicinity of DUX4 binding.[7]

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Many of these findings have their origins in seed funding from the FSH Society to researchers who have then used preliminary data to secure funding from the NIH. We are thrilled that our grantees and colleagues have data and publications that prove that the FSHD-causing DUX4-fl and cascading events can be turned off. Also in this last year in clinical and preclinical research multiple groundbreaking papers have emerged in whole body MRI, xenograph and transgenic/Cre-lox mouse models, improved diagnostic testing, biomarkers and clinical aspects of FSHD and the very first evidenced based evaluation, diagnosis, and management clinical care guideline was written, compiled and distributed by the Centers for Disease Control, American Academy of Neurology and FSH Society.[3, 8, 9, 10, 11] Despite this, the FSHD research and clinical enterprise is still starved for federal funding from NIH!

We must keep moving forward. In October 2015 the FSH Society held its annual FSHD 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 100 researchers from around the world gathered to present latest data and discuss research strategies. Areas defined by the FSHD clinical and research community as priority areas are as follows:

Table 1.

Genetics and epigenetics

Priority 1: Continued identification of the parameters that determine disease severity and progression, including identification of additional modifier and disease loci.

Priority 2: Improved diagnostic tests and tests to better predict onset and severity.

Mechanisms and targets

Priority 3: Determine the major mechanism(s) of muscle damage caused by DUX4 expression. DUX4 in muscle activates a diverse panel of pathways and mechanisms, which individually, or combined lead to muscle pathology.

Priority 4: Determine the relationship between DUX4 expression and disease onset and progression.

Priority 5: Determine how the expression of DUX4 in one muscle cell nucleus results in the spread of the pathology throughout the muscle.

Models

Priority 6: Continued development and validation of pre-clinical models to test specific pre-clinical goals.

Clinical and therapeutic studies

Priority 7: Validation of subjective and objective measurements of disease onset and progression. Quality of life, muscle function measurements and other physical biomarkers, molecular biomarkers, and imaging biomarkers all show tremendous promise. Individual and cooperative studies to identify, validate, and determine the best standard measurements are critical for trial preparedness in FSHD.

The detailed priorities stated for 2016, at the October 5-6, 2015, FSH Society FSHD IRC meetings can be found at: http://www.fshsociety.org/international-research-consortium/ . We need to be prepared for this new era in the science of FSHD. Many leading experts are now turning to work on FSHD because it represents the potential for great discoveries, insights into stem cells, transcriptional processes, new ways of thinking about disease of epigenetic etiology, and for treating diseases with epigenetic origin.

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 Congress passed the MD CARE Act in 2001, research funding at NIH for muscular dystrophy has increased 4-fold (from $21M). While FSHD research funding has increased 16-fold FY2015 (from $0.5M) during this period, the level of funding is still too underpowered for FSHD given the remarkable discoveries in the past six 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%

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Despite the great success of the past six years in the science of FSHD brought about by Congress, NIH, non-profit funding agencies, patients, families and researchers we are gravely concerned that FSHD research is too under-represented in the NIH portfolio. Though in our story DUX4 is inappropriately expressed in the context of muscle only and is harmful in FSHD; there now are several papers in the last month showing DUX4 at work in other diseases and conditions -- in the out layer of skin it is harmful to keratinocytes in another context of gene fusions it causes cells to divide uncontrollably and cause cancer (B cell acute lymphoblastic leukemia).[12, 13] The extraordinary depth and impact of discovery should soon allow a flood of new talent and higher quality and completive proposals to help NIH redress the imbalance of funding in the FSH muscular dystrophy portfolio by fostering opportunities for multidisciplinary research on FSHD commensurate with its prevalence and disease burden. We are concerned, very concerned that economy of scale is so different in particular for FSHD within the muscular dystrophy funding group. There are no quotas on peer-reviewed research above pay line at the NIH and given now that all the requisites are in place –funding for FSHD should increase rapidly at this time.

There are 32 active projects NIH-wide totaling $12.616 million as of April 14, 2016 versus 26 on March 12, 2015 (source: NIH Research Portfolio Online Reporting Tools (RePORT) http://report.nih.gov keyword 'FSHD or facioscapulohumeral or DUX4') the 32 projects cover 2 F32, 1 K22, 1 K23, 1 R03, 4 R21, 15 R01, 1 P01, and 2 U54 grants. It was back in 2010, that the NIH Director Dr. Francis Collins said "If we were thinking of a collection of the genome's greatest hits, this [FSHD] would go on the list."[14] In the last year alone, incredible opportunities for public, private and non-profit entities engaged in FSHD research and clinical research have emerged. Oddly these discoveries clearly belonging to the leading edge of human genetics and our understanding the epigenome and treating epigenetic diseases are sitting somewhat idle. NIH needs to maximize research funding by capitalizing on the low hanging fruit that FSHD presents as a gateway to treating human epigenetic disease.

We request for FY2017, a doubling of the NIH FSHD research portfolio to at least $24 million. This will allow an expansion of basic research awards, expansion of post-doctoral and clinical training fellowships, dedicated centers to design and conduct clinical trials on FSHD and more U.S. DHHS NIH Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers. Now that NIH has conveyed to researchers that it has a revised plan and an interest in funding research in FSHD and muscular dystrophy these funds will be needed to fill the demand. Mr. Chairman, thank you for this opportunity to testify before your committee.

Footnotes:

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3. Lemmers RJ, et al. Inter-individual differences in CpG methylation at D4Z4 correlate with clinical variability in FSHD1 and FSHD2. Hum Mol Genet. 2015 Feb 1;24(3):659-69. Epub 2014 Sep 25.
4. Jones, TI, et al. Individual epigenetic status of the pathogenic D4Z4 macrosatellite correlates with disease in facioscapulohumeral muscular dystrophy. Clinical Epigenetics 2015, 72-6, 29 March 2015
5. Lim JW, et al. DICER/AGO-dependent epigenetic silencing of D4Z4 repeats enhanced by exogenous siRNA suggests mechanisms and therapies for FSHD. Hum Mol Genet. 2015 Sep 1;24(17):4817-28.
6. 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.
7. Choi SH, et al. DUX4 recruits p300/CBP through its C-terminus and induces global H3K27 acetylation changes. Nucleic Acids Res. 2016 6 Mar [Epub ahead of print]
8. Tawil R, et al. Evidence-based guideline summary: Evaluation, diagnosis, and management of FSHD: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the Practice Issues Review Panel of the American Association of Neuromuscular & Electrodiagnostic Medicine. Neurology. 2015 Jul 28;85(4):357-64.
9. Leung DG, et al. Whole-body magnetic resonance imaging evaluation of FSHD. Muscle Nerve. 2015 Oct;52(4):512-20. Epub 2015 Mar 31.
10. Sakellariou P, Bloch R, et al. Neuromuscular electrical stimulation promotes development in mice of mature human muscle from immortalized human myoblasts. Skelet Muscle. 2016 Feb 27;6:4. eCollection 2015.
11. Calandra P, et al. Allele-specific DNA hypomethylation characterises FSHD1 and FSHD2. J Med Genet. 2016 Feb 1. pii: jmedgenet-2015-103436. [Epub ahead of print]
12. Gannon OM, et al. DUX4 Is Derepressed in Late-Differentiating Keratinocytes in Conjunction with Loss of H3K9me3 Epigenetic Repression. J Invest Dermatol. 2016 Feb 9. pii: S0022-202X(16)00464-4. [Epub ahead of print]
13. Yasuda T, et al. Recurrent DUX4 fusions in B cell acute lymphoblastic leukemia of adolescents and young adults. Nat Genet. 2016 Mar 28. doi: 10.1038/ng.3535. [Epub ahead of print]
14. 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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