Testimony of Daniel Paul Perez, President & CEO, FSH Society phone: (781) 275-7781, e-mail: daniel.perez@fshsociety.org before the United States House Appropriations Committee, Subcommittee on Labor, Health and Human Services, and Education on the subject of $18 million FY2015 Appropriations for U.S. DHHS National Institutes of Health (NIH) Research Programs on Facioscapulohumeral Muscular dystrophy (FSHD) March 28, 2014

Honorable Chairmen Rogers and Ranking Member Lowey, thank you for the opportunity to submit this testimony. Facioscapulohumeral muscular dystrophy (FSHD), is one of the most common adult muscular dystrophies with a prevalence of 1:15,000–1:20,000[1,2]. For a half-million men, women, and children worldwide the major consequence of inheriting this genetic form of muscular dystrophy is a lifelong progressive loss of all skeletal muscles. FSHD is a crippling and life shortening disease. No one is immune. It is both genetically and spontaneously transmitted to children. It can affect multiple generations and entire families.

With FSHD there is a loss of muscle strength that ranges between one and four percent a year during a lifetime. In terms of functional impairment, 20 percent of FSHD-affected individuals over age fifty will require the use of a wheelchair. FSHD also has very specific non-muscular manifestations; hearing-loss, restrictive lung disease, supraventricular arrhythmias (rare), and retinal vasculopathy. 95% of individuals with FSHD have the FSHD1 (FSHD1A) genetic variation -- caused by the contraction of DNA macrosatellite repeat units, termed D4Z4 repeats, on chromosome 4, leading to the release of transcriptional repression of a retrogene (DUX4) believed to be associated with the cause of disease. Of the 5% of FSHD individuals remaining, 80% of those are the FSHD2 (FSHD1B) genetic variation -- caused by mutations in the SMCHD1 gene on chromosome 18 that helps to maintain the structure of the D4Z4 repeats on the long arm of chromosome 4.

The National Institutes of Health (NIH) is the principal source of funding of research on FSHD currently at the $5 million level. For nearly two decades, this Committee has supported the incremental growth in funding for FSHD research. I am pleased to report that this modest

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investment has produced huge scientific returns.

1. Congress has made a major difference in muscular dystrophy. I have testified many times before Congress, nearly fifty. When I first testified, we did not know the mechanism of this disease. Now we do. When I first testified, we assumed that FSHD was a rare form of muscular dystrophy. Now we understand it to be one of the most prevalent forms of muscle disease, if not the most prevalent muscle disease based on new ways of evaluating the disease clinically within families. Congress is responsible for this success, through its sustaining support of the NIH and the enactment of the Muscular Dystrophy CARE Act. 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. Even though it is a technically separate legislative process, the reauthorization of the MD Care Act does raise the visibility of all the muscular dystrophies which can be of help in the appropriations process – and we thank you for your support of the MD Care Act. Further, we recognize and feel at this time in FSHD research that 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.

2. Quantum leaps in our understanding of FSHD have occurred in past three and a half years. The past three and a half years have seen remarkable contributions made by researchers funded by NIH.

- On August 19, 2010, American and Dutch researchers published a paper which dramatically expanded our understanding of the mechanism of FSHD.[3] A front page story in the New York Times quoted the NIH Director Dr. Francis Collins saying, "If we were thinking of a collection of the genome's greatest hits, this would go on the list."[4]
- Two months later, another paper was published that made a second critical advance in determining the cause of FSHD.[5] The research shows that FSHD is caused by the inefficient suppression of a gene that may be normally expressed only in early development.

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- On January 17, 2012, an international team of researchers based out of Seattle discovered a stabilized form of a normally suppressed gene called DUX4 required to develop chromosome 4 linked FSHD.[6]
- Six months later, another high profile paper produced by a Senator Paul A. Wellstone Cooperative Research Center of the NIH, used sufficiently "powered" large collections of genetically matched FSHD cell lines generated by the NIH center that are both unique in scope and shared with all researchers worldwide, to improve on the Seattle group's finding by postulating that DUX4-fl expression is necessary but not sufficient by itself for FSHD muscle pathology.[7] This work was also supported by a NIH cooperative research center grant mandated by MD CARE Act.
- On July 13, 2012, a team of researchers from the, United States, Netherlands and France identified mutations in a gene causing 80% of another form of FSHD. This paper furthers our understanding of the molecular pathophysiology of FSHD. This work too was supported in part by a program project grant from NIH.[8]
- In 2013 and continuing into 2014, papers have been published clearly documenting functional impairment in FSHD, clinical and genetic features of hearing loss FSHD, restrictive lung disease and respiratory insufficiency, Coats syndrome and vision loss in FSHD, high-throughput screening that identify inhibitors of DUX4-induced myoblast toxicity, better definition of epigenetic features of FSHD, Pain and FSHD, MRI/MRS studies, biomarkers for FSHD, the demonstration that although the transcription of the toxic protein DUX4 occurs in only a limited number of nuclei, the resulting protein diffuses into nearby nuclei within the myotubes, thus spreading aberrant gene expression throughout a muscle, to name a few.

Many of these researchers have started their efforts in FSHD with seed funding from the FSH Society and have received continued support from the FSH Society, the NIH, and the Muscular Dystrophy Association and other partners.

3. Remarkable progress in FSHD research and the need to keep moving forward. Last October, nearly 100 researchers from around the world gathered under the direction of Massachusetts Institute of Technology professor, David Housman, PhD, Chair of the FSH Society's Scientific Advisory Board, at the David H. Koch Center for Integrative Cancer Research on the campus of M.I.T. for the annual FSH Society International Research Consortium meeting; there was a palpable feeling of FSHD research having "arrived" in the big time. The general discussion of day two covered four major areas. With respect to the first area, called **DUX4**, the unanimous conclusion of the general discussion was that over-expression of the toxic transcription factor Dux4 is at the root of FSHD1 and FSHD2 and that DUX4 expression is necessary but not always sufficient to cause FSHD. Research should focus on upstream and downstream molecular pathways and mechanisms as they form the most plausible intervention targets. The group also discussed needs and priorities in three additional areas: **disease models**,

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intervention, clinical studies and trial readiness. The priorities stated for 2014, at the October 21-22, 2013, FSH Society FSHD IRC meetings are as follows: [9]

- The DUX4 interactome
- Understanding DUX4 manifestation and variation
- Additional genetic heterogeneity; non-FSHD1 and FSHD2
- Disease models
- Well documented Natural history with reliable endpoints; modulating mechanisms/genes
- Increasing data depth of patient databases with extensive (follow-up) clinical data
- Prepare for clinical trials: reliable and meaningful outcome measures; with access to discreet patient populations and disease mechanism of action classes.
- Therapy; proof-of-principle experiments
- Focus on translational research; from clinic to bench and back
- Understanding pathophysiology of FSHD: connection to DUX4, heterogeneity, asymmetry, role of inflammation; infiltrates and etiology

Given the recent developments, there is a need to ramp up the preclinical enterprise and build/organize infrastructure needed to conduct clinical trials. Our immediate priorities should be to confirm the new hypotheses and targets. We need to be prepared for this new era in the science of FSHD. Many leading experts are now turning to work on FSHD not only because it is one of the most complicated and challenging problems seen in science, but because it represents the potential for great discoveries, insights into stem cells and transcriptional processes and new ways of thinking about and treating human disease.

4. 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, research funding at NIH for muscular dystrophy has increased 4-fold. While FSHD research funding has increased 12-fold during this period, the level of funding is still anemic and, for FSHD, has been astonishingly flat for 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 RCDC RePORT
(e = estimate)

Fiscal Year	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014e**	**2015e**
All MD ($ millions)	$39.1	$38.7	$39.5	$39.9	$47.2	$56	$83	$86	$75	$75	$76	$78	$78
FSHD ($ millions)	$1.5	$2.2	$2.0	$1.7	$3	$3	$5	$6	$6	$5	$5	$6	$6
FSHD (% total MD)	4%	6%	5%	4%	5%	5%	6%	7%	8%	7%	7%	8%	8%

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Despite the great success of the past three and a half years in the science of FSHD brought about by Congress we are concerned that under the current funding environment that new research projects will not be funded or existing programs will not be renewed. We have conveyed to the NIH leadership at the Office of the Director, NIAMS, NINDS, NICHD, NHLBI and the Executive Secretary of the MDCC our grave concern that FSHD research is way too under-represented in the NIH portfolio and needs a proactive effort on the part of NIH.

We request for FY2015, a tripling of the NIH FSHD research portfolio to $18 million or a level of approximately 20% of the total muscular dystrophy funding at NIH. 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.

We are aware of the great pressures on the federal budget, but NIH can easily help increase its portfolio on FSHD by issuing one or more of the following on FSHD: Program Announcement (PA), Program Announcement (PA) with set-aside (PAS), PA with special review (PAR), or PA with set-aside special review (PAR/S). A request for applications (RFA) on FSHD would certainly help for the very short-term given the breakneck speed of discovery in FSHD, and the case can be made to NIH leadership . These are easy ways for NIH to convey to researchers that it has an interest in funding research in FSHD. Additionally, NIH could issue announcements with special receipt dates – this too would send a positive signal to the research community. There are no quotas on peer-reviewed research above pay line at the NIH, and NIH can help by issuing written announcements that efforts invested in writing FSHD grant applications will be met with interest. This is the time to fully and expeditiously exploit the advances for which the American taxpayer has paid. Thank you for this opportunity to testify before your committee.

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9. 2013 FSH Society *FSHD International Research Consortium*, held October 22-23, 2013 co-sponsored by DHHS NIH NICHD University of Massachusetts School of Medicine Senator Paul D. Wellstone MD CRC for FSHD. To read the expanded summary and recommendations of the group see: http://www.fshsociety.org/pages/sciConsortium.html

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