Fiscal Year 2020 written testimony of Daniel Paul Perez, Co-founder, FSH Society before U.S. House Appropriations Subcommittee on Labor, HHS, Education and Related Agencies for U.S. DHHS National Institutes of Health (NIH) funds for $40 million towards research grants and programs on facioscapulohumeral muscular dystrophy (FSHD) April 8, 2019

Agency: ***National Institutes of Health (NIH) and other federal agencies as appropriate.*** *FY2020 report language: Scientific opportunities alongside community research defined priorities in facioscapulohumeral disease (FSHD) call for far more funding on the disorder. The Committee strongly encourages the* ***NIH to increase its FSHD grant portfolio to at least $40 million for basic and exploratory research and clinical trials readiness efforts.***

Honorable Chairman DeLauro, Ranking Member Cole, and distinguished members of the Subcommittee, thank you for the opportunity to testify.

Facioscapulohumeral Disease (FSHD) is a heritable disease and one of the most common neuromuscular disorders with a prevalence of 1:8,000.[1] It affects 934,000 children and adults of both sexes worldwide. FSHD is characterized by 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. In addition to affecting muscle it can bring with it breathing issues, hearing loss, eye problems and cardiac arrhythmias. FSHD causes significant disability and death.

FSHD is associated with epigenetic changes at chromosome 4q35 in the D4Z4 DNA macrosatellite repeat array region leading to an inappropriate gain of expression (function) of the D4Z4-embedded double homeobox 4 (DUX4) gene [2]. DUX4 is a transcription factor that kick starts the embryonic genome during the 2- to 8-cell stage of development [3 - 5]. Ectopic expression of DUX4 in skeletal muscle leads to muscle death. DUX4 is never expressed in 'healthy' muscle. FSHD has had few clinical trials [6 7 8 9 10], and currently there is no cure or therapeutic option available to patients. DUX4 requires and needs to activate its direct transcriptional targets for DUX4-induced gene aberration and muscle toxicity [11 - 24]. Blocking DUX4's ability to activate its targets has profound therapeutic relevance [25].

NIH-supported basic research on muscle disease and muscular dystrophy over the past 25

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years has improved health outcomes. Small molecule and genetically engineered therapies are now in the works for FSHD and on the market for several neuromuscular diseases! [26 - 32] Each year, the non-profit, private and public investment in research yields critical advances in FSHD. Together we foster new treatments, diagnostics, and intervention strategies that affect the health of our nation. Meticulous efforts by FSHD researchers/clinicians working with funding from FSH Society, the NIH and others have brought forth significant advancements in epigenetic diseases. FSHD is the only human disease known to be caused by the contraction of repetitive "junk" DNA. The Society has funded approximately $11 million in seed grants for research.

Let me now turn your attention to how together we can contain health care costs and improve outcomes via three initiatives: the FSH Society Industry Collaborative Workshop (hereafter called *'FSHS NIH/FDA Collaborative'*), the NIH supported FSH Society annual International Research Congress (hereafter called *'FSHS NIH IRC'*) and the *NIH Action Plan for the Muscular Dystrophies* (hereafter called *'DHHS NIH MD Plan') (See https://mdcc.nih.gov/Action_Plan*).

On March 12, 2019, in Silver Spring, the *FSHS NIH/FDA Collaborative* assembled 10 academic thought leaders, 17 industry representatives (8 companies), 5 NIH officers and scientists (EP/IP: NCATS, NIAMS, NINDS), 6 FDA scientists and regulators (CDER, CBER, DNP), and 9 patient advocates and organizations to discuss clinical trial readiness and accelerated approval process for therapies. We assessed disease tractability in four directions: natural history, pharmacodynamic biomarkers, imaging biomarkers, and clinical trial design/readiness. A journal publication/manuscript (in process) will detail roadblocks that need rapid mitigation in seven areas: diagnostics, molecular biomarkers, imaging biomarkers, functional outcome measures, patient reported outcomes, biorepository and animal models.

In June 2018, over 135 researchers from around the world gathered at the *FSHS NIH IRC*

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meeting, co-funded by the U.S. DHHS NIH, in Las Vegas to present the latest data and discuss research strategies. The FSHD scientific community listed 2019-2020 priorities as:

Table II. 2019 IRC Research Priorities *(Source: https://www.fshsociety.org/events/international-research-conference/ for full version)*

1. Therapeutics

Therapeutics Trial Toolkit, including biological biomarkers, imaging markers, and clinical outcome assessments;
Non-DUX4-centric therapies that ameliorate some of the major pathological drivers in FSHD, and/or augment muscle repair;

2. Pathophysiology

Pathophysiology, such as the role of DUX4 in fibrosis, inflammatory infiltrates, and fatty infiltration; temporal analysis of disease models; and novel model systems;

3. Molecular Mechanisms

Molecular mechanisms of DUX4 pathology and function;

4. Genetics and Epigenetics

Genetics and epigenetics around harmonizing diagnostics, disease continuum and genotyping, and understanding genetic modifiers and drivers of genetic variability.

Last, but not least, this Subcommittee and **Congress in partnership with NIH, patients and scientists have made truly outstanding progress in understanding and treating the nine major types of muscular dystrophy through the** Muscular Dystrophy Community Assistance, Research and Education Amendments of 2001 (MD-CARE Act, Public Law 107-84). The federal advisory committee mandated by MD CARE Act, called the MDCC, along with working groups of outside scientific experts in the field assembled the '*2015 NIH Action Plan for the Muscular Dystrophies.'* It was presented by the Director of NIH to Congress. It specifies 81 objectives, in six sections (mechanism, screening, treatments, trial readiness, access to care, infrastructure including workforce) in need of funding and further development.[33] The genetics that give rise to FSHD are so remarkable, NIH Director Dr. Francis Collins emphasized its significance 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." [34] We understand this Subcommittee seeks evidence of translating research spending into tangible improvement in health status and patient care. The *FSHS NIH/FDA Collaborative, 'FSHS NIH IRC'* and the *'DHHS NIH MD Plan'* demonstrate the solid gains and show the rate of change in care.

Madam Chairman, these advances in scientific understanding and epidemiological

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surveillance come at a significant cost. Since passing the MD CARE Act in 2001, NIH funding for FSHD has been unbalanced given the growth in discoveries and needs to be set right.

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, a=actual)

Fiscal Year	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**
All MD ($ millions)	$47.2	$56	$83	$86	$75	$75	$76	$78	$77	$79	$81	$85ea	$80e
FSHD ($ millions)	$3	$3	$5	$6	$6	$5	$5	$7	$8	$9	$12.8	$13.7a	$17a
FSHD (% total MD)	5%	5%	6%	7%	8%	7%	7%	9%	10%	11%	16%	16%	21%

The NIH is the principal worldwide source of funding of research on FSHD. Currently active projects are $17.037 million FY2019 (actual), a portion of the estimated $80 million spent on all muscular dystrophies. FY2019 projects cover 1 F31, 1 K22, 1 K23, 13 R01, 1 R13, 4 R21, 1 P01, 4 P50, 3 U01, 1 ZIC grants. There are 30 active projects NIH-wide totaling $17.037 million as of March 21, 2019, versus 28 active projects NIH-wide totaling $13.654 million as of April 18, 2018; and 28 active projects NIH-wide totaling $12.751 million as of March 3, 2017. (source: NIH Research Portfolio Online Reporting Tools (RePORT) keyword ‘FSHD or facioscapulohumeral or landouzy-dejerine’).

Without research on muscle disease, supported by the FSHD patient-advocacy groups in concert with the NIH biomedical research funding -- families with FSHD would be living shorter, less productive, and far less hopeful lives. Nearly 41,000 Americans have FSHD, a disease that can cause damage to skeletal muscle, hearing, vision, breathing and lead to death.

What we need. Viewing at the current portfolio alongside the areas in need of bolstering in FSHD the NIH needs to fast expand its portfolio. Specifically, NIH needs to increase funding by adding R01 and R21 style grants in areas outlined by hundreds of experts in the *FSHS NIH/FDA Collaborative, the FSHS NIH IRC* and the *DHHS NIH MD Plan*. The engine of federal research runs on the basic building blocks of workforce training, exploratory/developmental research grants (parent R21) and research project grants (parent R01). NIH can issue targeted funding announcements covering FSHD. A request for applications (RFA) on FSHD will yield results. These

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efforts will help convey to FSHD patients and allied researchers that NIH encourages more grant applications coming through its front door.

We request for FY2020, a doubling of the NIH FSHD research portfolio to $40 million. We are very appreciative of the slow but steady year-to-year increases and thank NIH and Congress. At this moment in time, FSHD needs an infusion of NIH grants both submitted and funded -- investments in centers, collaborative research grants – and, most importantly, a rapid ramp up of basic/exploratory, preclinical and therapeutic research awards along with moderate expansion of post-doctoral and clinical training fellowships. FSHD research calls for and needs this additional funding in order to succeed. Madam Chairman, thank you again for your help and efforts.

REFERENCES

1. Deenen, J. C. W. et al. Population-based incidence and prevalence of facioscapulohumeral dystrophy. Neurology 83, 1056–9 (2014).
2. Wang, L. H. & Tawil, R. Facioscapulohumeral Dystrophy. Curr. Neurol. Neurosci. Rep. 16, 66 (2016).
3. Hendrickson, P. G. et al. Conserved roles of mouse DUX and human DUX4 in activating cleavage-stage genes and MERVL/HERVL retrotransposons. Nat. Genet. 49, 925–934 (2017).
4. Whiddon, J. L., Langford, A. T., Wong, C.-J., Zhong, J. W. & Tapscott, S. J. Conservation and innovation in the DUX4-family gene network. Nat. Genet. 49, 935–940 (2017).
5. De Iaco, A. et al. DUX-family transcription factors regulate zygotic genome activation in placental mammals. Nat. Genet. 49, 941–945 (2017).
6. Tawil, R. et al. A pilot trial of prednisone in facioscapulohumeral muscular dystrophy. FSHDY Group. Neurology 48, 46–9 (1997).
7. Passerieux, E. et al. Effects of vitamin C, vitamin E, zinc gluconate, and selenomethionine supplementation on muscle function and oxidative stress biomarkers in patients with facioscapulohumeral dystrophy: a double-blind randomized controlled clinical trial. Free Radic. Biol. Med. 81, 158–69 (2015).
8. Kissel, J. T. et al. Randomized, double-blind, placebo-controlled trial of albuterol in facioscapulohumeral dystrophy. Neurology 57, 1434–40 (2001).
9. Elsheikh, B. H. et al. Pilot trial of diltiazem in facioscapulohumeral muscular dystrophy. Neurology 68, 1428–9 (2007).
10. Wagner, K. R. et al. A phase I/IItrial of MYO-029 in adult subjects with muscular dystrophy. Ann. Neurol. 63, 561–71 (2008).
11. Rickard, A. M., Petek, L. M. & Miller, D. G. Endogenous DUX4 expression in FSHD myotubes is sufficient to cause cell death and disrupts RNA splicing and cell migration pathways. Hum. Mol. Genet. 24, 5901–14 (2015).
12. Sandri, M. et al. Caspase 3 expression correlates with skeletal muscle apoptosis in Duchenne and facioscapulo human muscular dystrophy. A potential target for pharmacological treatment? J. Neuropathol. Exp. Neurol. 60, 302–12 (2001).
13. Block, G. J. et al. Wnt/β-catenin signaling suppresses DUX4 expression and prevents apoptosis of FSHD muscle cells. Hum. Mol. Genet. 22, 4661–72 (2013).
14. Statland, J. M. et al. Immunohistochemical Characterization of Facioscapulohumeral Muscular Dystrophy Muscle Biopsies. J. Neuromuscul. Dis. 2, 291–299 (2015).
15. Rickard, A. M., Petek, L. M. & Miller, D. G. Endogenous DUX4 expression in FSHD myotubes is sufficient to cause cell death and disrupts RNA splicing and cell migration pathways. Hum. Mol. Genet. 24, 5901–14 (2015).
16. Kowaljow, V. et al. The DUX4 gene at the FSHD1A locus encodes a pro-apoptotic protein. Neuromuscul. Disord. 17, 611–23 (2007).
17. Bosnakovski, D. et al. An isogenetic myoblast expression screen identifies DUX4-mediated FSHD-associated molecular pathologies. EMBO J. 27, 2766–79 (2008).
18. Wallace, L. M. et al. DUX4, a candidate gene for facioscapulohumeral muscular dystrophy, causes p53-dependent myopathy in vivo. Ann. Neurol. 69, 540–52 (2011).
19. Geng, L. N. et al. DUX4 activates germline genes, retroelements, and immune mediators: implications for facioscapulohumeral dystrophy. Dev. Cell 22, 38–51 (2012).
20. Yao, Z. et al. DUX4-induced gene expression is the major molecular signature in FSHD skeletal muscle. Hum. Mol. Genet. 23, 5342–52 (2014).
21. Homma, S., Beermann, M. Lou, Boyce, F. M. & Miller, J. B. Expression of FSHD-related DUX4-FL alters proteostasis and induces TDP-43 aggregation. Ann. Clin. Transl. Neurol. 2, 151–66 (2015).
22. Jagannathan, S. et al. Model systems of DUX4 expression recapitulate the transcriptional profile of FSHD cells. Hum. Mol. Genet. 25, 4419–4431 (2016).
23. Jones, T. I. et al. Facioscapulohumeral muscular dystrophy family studies of DUX4 expression: evidence for disease modifiers and a quantitative model of pathogenesis. Hum. Mol. Genet. 21, 4419–30 (2012).
24. Campbell AE, Shadle SC, Jagannathan S, Lim JW, Resnick R, Tawil R, van der Maarel SM, Tapscott SJ. NuRD and CAF-1-mediated silencing of the D4Z4 array is modulated by DUX4-induced MBD3L proteins. Elife. 2018 Mar 13;7. pii: e31023. doi: 10.7554/eLife.31023. . (2018)
25. Jagannathan S1,2,3, Ogata Y4, Gafken PR4, Tapscott SJ3, Bradley RK1. Quantitative proteomics reveals key roles for post-transcriptional gene regulation in the molecular pathology of facioscapulohumeral muscular dystrophy. Elife. 2019 Jan 15;8. pii: e41740. doi: 10.7554/eLife.41740. (2019)
26. 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. (2016).
27. 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.2016.1118. (2016).
28. Himeda CL, Jones TI, Virbasius CM, Zhu LJ, Green MR, Jones PL. Identification of Epigenetic Regulators of DUX4-fl for Targeted Therapy of Facioscapulohumeral Muscular Dystrophy. Mol Ther. 2018 Jul 5;26(7):1797-1807. doi: 10.1016/j.ymthe.2018.04.019. Epub 2018 Apr 26. (2018)
29. Giesige CR, Wallace LM, Heller KN, Eidahl JO, Saad NY, Fowler AM, Pyne NK, Al-Kharsan M, Rashnonejad A, Chermahini GA, Domire JS, Mukweyi D, Garwick-Coppens SE, Guckes SM, McLaughlin KJ, Meyer K, Rodino-Klapac LR, Harper SQ. AAV-mediated follistatin gene therapy improves functional outcomes in the TIC-DUX4 mouse model of FSHD. JCI Insight. 2018 Nov 15;3(22). pii: 123538. doi: 10.1172/jci.insight.123538. (2018).
30. Lee JK, Bosnakovski D, Toso EA, Dinh T, Banerjee S, Bohl TE, Shi K, Orellana K, Kyba M, Aihara H. Crystal Structure of the Double Homeodomain of DUX4 in Complex with DNA. Cell Rep. 2018 Dec 11;25(11):2955-2962.e3. doi: 10.1016/j.celrep.2018.11.060. (2018).
31. Marsollier AC, Joubert R, Mariot V, Dumonceaux J. Targeting the Polyadenylation Signal of Pre-mRNA: A New Gene Silencing Approach for Facioscapulohumeral Dystrophy. Int J Mol Sci. 2018 May 3;19(5). pii: E1347. doi: 10.3390/ijms19051347. Review. (2018).
32. Dion C, Roche S, Laberthonnière C, Broucqsault N, Mariot V, Xue S, Gurzau AD, Nowak A, Gordon CT, Gaillard MC, El-Yazidi C, Thomas M, Schlupp-Robaglia A, Missirian C, Malan V, Ratbi L, Sefiani A, Wollnik B, Binetruy B, Salort Campana E, Attarian S, Bernard R, Nguyen K, Amiel J, Dumonceaux J, Murphy JM, Déjardin J, Blewitt ME, Reversade B, Robin JD, Magdinier F. SMCHD1 is involved in de novo methylation of the DUX4-encoding D4Z4 macrosatellite. Nucleic Acids Res. 2019 Jan 30. doi: 10.1093/nar/gkz005. [Epub ahead of print] (2019).
33. 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] (2016).
34. 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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