



# FSH Watch

A publication of the Facioscapulohumeral Muscular Dystrophy Society

Connecting the community of patients, families, clinicians and investigators

## FSH Society facilitates proposal for new Boston FSHD Wellstone Research Center

The FSH Society proudly announces that it facilitated and helped organize the submission of a grant application to the National Institutes of Health (NIH) to establish a Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Center to study facioscapulohumeral muscular dystrophy (FSHD). The center involves a group of distinguished researchers/clinicians and the FSH Society to advance our understanding of how FSHD works and can be treated. The new center will be the first and only Wellstone Center focused solely on FSHD. The center will receive \$1.73 million per year for five years, for a total of \$8.64 million.

The MD-CARE Act of 2001 mandated the creation of centers of excel-

lence to accelerate muscular dystrophy research. These centers, named after the late **Senator Paul D. Wellstone**, are supported by close collaboration between program staff at institutes of the NIH and the centers' scientific staff. To date, eight Wellstone Centers have been established by NIH, with only six in operation at a given time.

Shortly after the FSH Society moved its headquarters to the Boston Biomedical Research Institute (BBRI) in June 2007, **Daniel Paul Perez** discussed the Society's 2006 research plan with Drs. **Charles Emerson** and **Henry Paulus**, the Director and Deputy Director of BBRI, respectively. Based on the recommendations of the international FSHD research community, the plan is a blueprint for developing a large center for FSHD research.

Mr. Perez suggested using the plan as the basis for a grant application for a NIH Wellstone Center.

The most recent call for applications for Wellstone Centers represents a paradigm shift with an increased emphasis on collaboration and a new mandate to include patient advocate organizations as full partners in the research process. After several months of planning between BBRI principals and scientists, Mr. Perez and the FSH Society's Scientific Advisory Board (SAB) members **Louis Kunkel, Ph.D.**, and **David Housman, Ph.D.**, a proposal was submitted to the NIH. The proposal received dozens of letters of

*continued on page 6*

## FSHD International Research Consortium

On Tuesday, October 23, 2007, the FSH Society held the FSHD International Research Consortium (FSHD IRC) 2007, in San Diego, California as severe fires raged to the north and east of the city. The meeting was sponsored by the FSH Society, the Association Française Contre les Myopathies (AFM), the Muscular Dystrophy Association (MDA) and Athena Diagnostics.

The meeting was organized by **Daniel Paul Perez, Silvère van der Maarel, Ph.D.**, and **Rabi Tawil, M.D.**

The latest developments in FSHD research were well reflected in the program which featured 16 platform presentations and five poster presentations. Presentations covered a wide range of new and exciting developments. Notable areas were the re-emergence of DUX4 as a candidate gene for FSHD; research on the function of the FSHD Region Gene 1 (FRG1) candidate gene; clinical research studies; added evidence that FSHD may be considered a "chromatin disease;" and genetic developments in chromosome-4q-linked FSHD (FSHMD1A) and non-chromosome-4q-linked FSHD (FSHMD1B).

The meeting has been expanding nicely from year to year, with a broad audience of clinicians, scientists, biotechnology companies, pharmaceutical companies, government research funding agencies, nonprofit funding agencies, and patients themselves, highlighting the translational character of the workshop.

Initial remarks were given by **William R. Lewis, Sr., M.D.**, and **Silvère van der Maarel, Ph.D.** This was followed by a keynote speech by **John D. Porter, Ph.D.** titled "*Translational Research in Muscular Dystrophy: NIH Activities from Target Identification to Trials.*"

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## From the president & CEO, and the research programs office

On behalf of the FSH Society staff, Board of Directors, Scientific Advisory Board (SAB) and volunteers, I sincerely thank you for your continued contributions and support of the Society and its research programs and efforts. The last two years have brought remarkable progress in gaining



Daniel Paul Perez,  
President & CEO,  
FSH Society

additional insight into the biological mechanism of facioscapulohumeral muscular dystrophy (FSHD), as well as rapid developments in beginning to consider how to treat FSHD using:

- ◆ small molecules;
- ◆ gene therapy;
- ◆ RNAi;
- ◆ morpholinos (“molecule used to modify gene expression. Morpholino oligonucleotides (oligos) are an antisense technology used to block access of other molecules to specific sequences within nucleic acid. Morpholinos block small [~25 base] regions of the base-pairing surfaces of ribonucleic acid [RNA]”);
- ◆ adult iPS (“Induced pluripotent stem cells — a type of pluripotent stem cell artificially derived from a non-pluripotent cell, typically an adult somatic cell, by inducing a ‘forced’ expression of certain genes”);
- ◆ stem cells;
- ◆ embryonic stem cells;
- ◆ and other approaches.

In July 2006, at the FSH Society research planning meeting, we asked the Society’s SAB and an international group of FSHD researchers and experts to consider:

- ◆ What do we know about FSHD?

- ◆ What do we not know about FSHD?
- ◆ What do we need to know about FSHD?
- ◆ What are the obstacles to complete understanding?
- ◆ What must we — the FSH Society, as well as the FSHD patient and professional community at large — do next to accelerate progress toward solving FSHD?

What did come out of the meeting was a clear statement on obstacles to our understanding and ideas to move FSHD forward.

We’ve taken this consensus and blueprint of ideas and transformed it into a large-scale center of research excellence known as a U.S. National Institutes of Health Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Center. The proposed center will be solely dedicated to FSHD and funded for nearly \$9 million over a five year period. The new center is based in Boston at the Boston Biomedical Research Institute (BBRI) and will be led by **Charles Emerson, Ph.D.**, and **Louis Kunkel, Ph.D.** The center’s network of collaborators includes **Kathryn Wagner, M.D., Ph.D.**, **Mayana Zatz, M.Sc., Ph.D.**, **Robert J. Bloch, Ph.D.**, **Jeffery B. Miller, Ph.D.**, **Woodring Wright, M.D., Ph.D.** and **Daniel Paul Perez.**

After the center is awarded and operational, the next steps will be for scientists and staff from the FSH Society, the NIH, the Boston FSHD Wellstone MD CRC, the Fields Center for FSHD & NMD research, and the MDA to meet later in the year to coordinate efforts and resources and create the massive infrastructure needed to begin to answer the above questions about FSHD. The Society will continue to do what it does well in advocating, coordinating and promoting FSHD research efforts.

## President

It is equally important for us to continue the vital Society research and fellowships program to continue the education and training of new generations of scientists and clinicians working on FSHD. This program is extremely high impact and FSHD experts credit the Society for bringing FSHD research as far as it is today.

Through these programs and others at the Society, we fund FSHD research, educate the community about FSHD, advocate for federal research in Washington, D.C., and provide peer support to patients and their families.

Thanks to continuing support from committed donors like you, we are working to eliminate FSHD through treatment and a cure. Because of contributions like yours, remarkable progress has been made in understanding and treating FSHD since 1991. With continued efforts, we hope to arrive at a treatment for FSHD soon and continue to improve the quality of life for people living with FSHD.

To learn more about how we are doing that, how to get involved with research, or how we can help you and your family, call (617) 658-7878 or visit our new website:

[www.fshsociety.org](http://www.fshsociety.org)

Thank you again for your ongoing generosity at this most critical time. Please consider making a donation online or by using the enclosed envelope or by contacting any of us at the Society.

Sincerely,

Daniel Paul Perez  
President & CEO  
FSH Society

## In Memoriam

**Judge William E. Hall, Jr.**, a long-time FSH Society board member, passed away on July 4, 2008. Judge Hall and his wife, Lady Williams Hall, were at the very first meeting of the Society and were founding members. For those of us who had the honor of knowing both Will and Lady, they were uncommonly generous, kind, caring and deeply committed to making a difference for those living with facioscapulohumeral dystrophy. We will miss Judge Hall and his insight, wisdom, humor and his steadfast and unwavering support. Will always posed the question, "How can we help?" and answered with unswerving generosity of spirit. Both Will and Lady inspired us with their words of support to stay the course to become a great Society and to make the difference for FSHD.

We shall miss the Judge deeply and extend our condolences to the family members.

### William E. Hall, Jr. 1920-2008

William E. Hall, Jr. passed away peacefully at his home surrounded by family and his faithful dog, Lola, on Friday, July 4, 2008, in DeRidder following a lengthy illness. He was born on January 1, 1920, in Shreveport to W.E. Hall and Virgil Jeter Hall. A graduate of Byrd High School in Shreveport, Will attended Virginia Military Institute and received his law degree from Louisiana

State University. He was admitted to the Louisiana State Bar in 1942 and enlisted in the Army the day after graduation from law school. He was one of the 90-day wonders. Will served as Captain of Battery "C," 748th Field Artillery Battalion, 9th Army. He was stationed at Burton on the Trent, England before going into Germany. He was discharged as a Captain in the Field Artillery in 1946. Will married



*It is the editorial policy to report on developments regarding FacioScapuloHumeral Muscular Dystrophy (FSHD), but not to endorse any of the drugs or treatments discussed. We urge you to consult with your own physician about the procedures mentioned.*



Judge William Hall

Lady Van Beth Williams of Jefferson, Texas on November 13, 1943, and they moved to DeRidder in 1946. He became a partner in the law firm of LeCompte and Hall. In 1953, the firm became LeCompte, Hall, and Coltharp, and finally Hall, Lestage, and Landreneau. In addition to his law practice, Will served as City Judge in 1954 and retired October 31, 1983 after serving 29 years.

Will was a member of the First United Methodist Church, where he taught Sunday school for 25 years beginning in 1947 and served on many church committees. He served for many years on the Board of Directors of City Saving Bank and the Board of Directors of the FSH Society, Inc. Active in civic affairs, Will was a past president of the Chamber of Commerce, Lions Club, the 30th Judicial Bar Association, and the Beauregard Country Club.

He was preceded in death by his loving wife, Lady Williams Hall, and his daughter, Lady Beth Hall. He is survived by two daughters, Dabney Richey and her husband, Lanier Richey, and Jill Hall and her husband Sterling Smith of Austin, Texas, and two grandchildren, Will and Molly Richey of Tyler, Texas. Will is also survived by his brother, Frank J. Hall and his wife, Dorothy of Shreveport, Louisiana, and a nephew and three nieces.

—Leesville Daily Leader, Leesville LA

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## A guide to acronyms

In the interest of readability and space, we would like to offer a list of acronyms for your reference. We will use these acronyms throughout the newsletter.

|         |  |
|---------|--|
| AFM     | Association Française Contre les Myopathies  |
| AHRQ    | Agency for Health Care Research and Quality  |
| BBRI    | Boston Biomedical Research Institute   |
| CDCP    | Centers for Disease Control and Prevention   |
| CFC     | Combined Federal Campaign  |
| CRISP   | NIH Computer Retrieval of Information on Scientific Projects                             |
| CSR     | NIH Center for Scientific Review   |
| DHHS    | Department of Health and Human Services  |
| DM      | Myotonic Muscular Dystrophy  |
| DMD     | Duchenne Muscular Dystrophy  |
| EDMD    | Emery-Dreifuss Muscular Dystrophy  |
| FDA     | Food and Drug Administration   |
| FSHD    | Facioscapulohumeral Muscular Dystrophy   |
| LGMD    | Limb-Girdle Muscular Dystrophy   |
| MD      | Muscular Dystrophy   |
| MD-CARE | Muscular Dystrophy Community Assistance, Research and Education                          |
| MDA     | Muscular Dystrophy Association   |
| MDCC    | Muscular Dystrophy Coordinating Committee  |
| MDCRC   | Muscular Dystrophy Cooperative Research Center   |
| MRC     | Medical Research Council of the United Kingdom   |
| NIAMS   | DHHS NIH National Institute of Arthritis & Musculoskeletal & Skin Diseases               |
| NICHD   | DHHS NIH Eunice Kennedy Shriver National Institute of Child Health and Human Development |
| NIH     | DHHS National Institutes of Health   |
| NINDS   | DHHS NIH National Institute of Neurological Disorders and Stroke                         |
| OASH    | Office of Assistant Secretary of Health  |
| OPM     | Office of Personnel Management   |
| PPMD    | Parent Project Muscular Dystrophy  |
| R01     | U.S. NIH Basic research track grants   |
| R21     | U.S. NIH High risk research track grants   |
| SAB     | FSH Society Scientific Advisory Board  |
| SAMHSA  | Substance Abuse and Mental Health Services   |
| TRC     | Translational Research Center  |
| WMS     | World Muscle Society   |

## Please make a contribution to the FSH Society, Inc.

Your donation makes a difference in the lives of those affected by facioscapulohumeral muscular dystrophy (FSHD). Thank you for considering a gift to the FSH Society. Your support for the FSH Society helps us every day to accomplish the work of solving, treating and curing FSH muscular dystrophy.

The vital FSHD advocacy, education, research, networking and patient resources provided by the Society would not be possible if it were not for the generous donations from people like you. Whether you choose to make a one time donation, a recurring monthly gift, a tribute gift in memory of/in honor of someone special, or a planned gift, your generosity will allow the FSH Society to continue to work to find effective treatments and a cure for FSHD. All gifts are tax-deductible.

Together we can improve the quality of life for those living with FSHD. We have a variety of options for charitable donations. Please use the enclosed contribution envelop, or visit us online at <http://www.fshsociety.org/pages/conMembership.html>, or

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## What is CRISP?

CRISP (Computer Retrieval of Information on Scientific Projects) is a searchable database of federally funded biomedical research projects conducted at universities, hospitals and other research institutions. The database, maintained by the Office of Extramural Research at the NIH, includes projects funded by the NIH, SAMHSA, FDA, CDCP, AHRQ and OASH. Users, including the public, can use the CRISP interface to search for scientific concepts, emerging trends and techniques, or to identify specific projects and/or investigators. See: <http://crisp.cit.nih.gov/>

## *FSHD Wellstone Center, continued from front page*

support from throughout the international FSHD research community.

The proposed new Boston FSHD Wellstone Center is based at BBRI and will be led by **Charles Emerson, Ph.D.**, and **Louis Kunkel, Ph.D.** The Center's network of collaborators includes **Kathryn Wagner, M.D., Ph.D.**, **Mayana Zatz, M.Sc., Ph.D.**, **Robert J. Bloch, Ph.D.**, **Jeffrey B. Miller, Ph.D.**, **Woodring Wright, M.D., Ph.D.**, and **Daniel Paul Perez.**

The goals of the Boston FSHD Wellstone Center are to identify and test biomarkers for the development of new therapies; assess myostatin inhibitors as a potential FSHD treatment; establish a repository of FSHD and normal cells and tissues that will be made available to FSHD researchers internationally; and create an outstanding environment for training young scientists.

The Center will focus on identifying biomarkers to evaluate outcomes of clinical trials for FSHD through four research projects and three support cores. The first project focuses on clinical trials and biomarkers of myostatin inhibition and involves a clinical trial with Acceleron Pharma using the myostatin inhibitor ACE-031 to assess effects on healthy human subjects preparatory to assessing its use in FSHD. The project has excellent access to patients due to collaborating clinical centers and the involvement of the FSH Society.

The second project involves biomarker discovery in muscles from FSHD patients and will focus on identifying key proteins and key miRNAs and their targets which are specifically upregulated in FSHD muscle. Finding biomarkers will lead to insights into the downstream pathophysiology in FSHD and help build a library of markers to assess trials in patients.

The third project focuses on myogenesis studies for FSHD biomarkers, examines the impaired myogenesis and regeneration of both, and FSHD biopsies and cell cultures to be developed and housed at the Center. This will help to understand and to generate data on cellular pathogenesis of FSHD.

The fourth project involves model

studies for FSHD biomarkers and exploring currently available and future animal models of FSHD including: mice over-expressing FRG1, PITX1, DUX4 and mu-crystallin, using histology, muscle force generation and proteomics. Data and markers developed in other projects will be used to compare the mouse models and human cells to evaluate the consistency of findings between animal models and human FSHD.

The Boston FSHD Wellstone Center will include three cores: a national research resource cell core; an education and training core; and an administrative core. The cell core will collect and maintain a bank of biopsies from FSHD patients and unaffected individuals and establish primary myogenic cultures. It will be at the heart of the center and will be a tremendous resource for the FSHD research community, which has repeatedly expressed an urgent need for this resource. This core will help achieve priorities outlined by the FSHD research community at the 2006 FSH Society Research Planning meeting and will provide important and long-awaited consistent reagents for researchers around the world.

The education and training core is designed to provide a pathway for young scientists to enter independent careers in skeletal muscle biology and muscular dystrophy, with emphasis on FSHD, and to deepen their research skills through mentoring and other assistance.

The administrative core will provide the Center's administrative, financial and communications functions. Close communication with researchers throughout the US and internationally, NIH, other Wellstone Centers and the patient advocate community will be an integral part of the Center's mission. The administrative core will also organize and promote the Center's resources for the entire FSHD community.

The Center will have a local executive committee, an education and training committee, and an advisory committee of external scientific advisors. Mr. Perez is a member of the

local executive committee, serving and donating time as the Office of Patient Communication and Liaison (OPCL). The FSH Society and the Center will co-organize and co-fund biennial patient meetings, the annual FSH Society FSHD research workshops held in conjunction with the American Society of Human Genetics meetings, annual research planning meetings and training efforts, and will assist with website development and patient recruitment.

The FSH Society is optimistic that the new Boston FSHD Wellstone Center will bring FSHD research to the next level leading to deeper understanding, treatments and, ultimately, a cure for FSHD!

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*The FSH Society would like its members and supporters to know that it will not be receiving funds from the NIH via the Boston FSHD Wellstone Center when funded — other than for meetings and the website — despite its major role in organizing, and ongoing role in consulting with the Center. We chose to do this to maximize the already stretched federal dollars invested in the Center. As the Center is based on the FSH Society research plan, and the maximum allowable NIH funding is \$1 million for direct costs, or \$1.8 million including indirect costs, per year for five years, we were only able to cover 50% of the items in the plan. The Society is supporting the mouse work within the Center, enabled by a generous gift from Mr. Stuart Lai. This gift, along with additional money and resources from institutions that will be participating in the Center and from corporations — donations for mouse work, fellowships, a clinical trial, cell and telomere development — made the application very attractive to the NIH. The Center will continue to require an additional \$1 million to \$2 million annually to meet the full compliment of research. The FSH Society needs your help in supporting this work as we set out to raise these and other funds for the mission of the Society!*

## FSHD International Research Consortium, *continued from front page*

The set of presentations on **D4Z4 DUX4 Expression** was moderated by Silvère van der Maarel, Ph.D. Five talks were given: **Darko Bosnakovski, D.V.M., Ph.D.**, on “A small molecule screen identifies inhibitors of DUX4-mediated toxicity in myoblasts;” **Jane E. Hewitt, Ph.D.**, on “Evolutionary conservation of D4Z4 and implications for understanding facioscapulohumeral muscular dystrophy;” **Michael Kyba, Ph.D.**, on “Genetic interactions between DUX4 and Pax3/Pax7 suggests a stem cell etiology for FSHD;” **Yi-Wen Chen, D.V.M., Ph.D.**, on “Characterization of a tet-repressible muscle-specific Pitx1 transgenic mouse;” and **Alexandra Belayew, Ph.D.**, on “Further studies on the DUX4, DUX4c and PITX1 genes in FSHD.”

The set of presentations on **D4Z4 Chromatin** was moderated by Sara T. Winokur, Ph.D. Four talks were given: **Frédérique Magdinier, Ph.D.**, on “CTCF as a new regulator of D4Z4 function;” **Kyoko Yokomori, Ph.D.**, on “Specific loss of histone H3 lysine 9 trimethylation and HP1(gamma)/cohesin binding at D4Z4 repeats in facioscapulohumeral dystrophy (FSHD);” **Melanie Ehrlich, Ph.D.**, on “Special DNA and chromatin structures in and adjacent to D4Z4 may contribute to its biological effects;” and **Galina N. Filippova, Ph.D.**, on the “Role of CTCF and chromatin structure in FSHD.”

The set of presentations on **Clinical and Genetic Studies** was moderated by William R. Lewis, Sr., M.D. Three talks were given: **R. Ted Abresch, M.S.**, on “Chronic pain in persons with FSHD and other neuromuscular disorders;” **Richard J.L.F. Lemmers, Ph.D.**, on “Specific sequence variations within the 4q35 region are associated with FSHD;” and **Meena Upadhyaya, Ph.D.**, on “A clinically well-characterised FSHD family not linked to 4q35.”

The set of presentations on **FRG1 Gene Function and Gene Expression in FSHD** was moderated by Jane E. Hewitt, Ph.D. Four talks were given: **Meredith L. Hanel, Ph.D.**, on the “Analysis of FRG1 in *Xenopus laevis* during development;” **Joseph G.**

**Marx, Ph.D.**, on “Characterization of FRG1’s RNA associated activity and its implications in FSHD pathogenesis;” **Rossella Tupler, M.D., Ph.D.**, on “Selective muscle involvement in facioscapulohumeral muscular dystrophy: the role of 4q35 gene expression;” and **Peter Masny, Ph.D.**, and **Sara T. Winokur, Ph.D.**, on the “Allele specific detection of FSHD gene expression in single nuclei.”

A session with **Posters** was held and moderated by presenters and Silvère van der Maarel, Ph.D. Five posters were presented: **Patrick Reed, Ph.D.**, and **Robert Bloch, Ph.D.**, on “Abnormal expression of mu-crystallin in facioscapulohumeral muscular dystrophy;” **Valery M. Kazakov, M.D., Ph.D., D.Sc.**, on “Lower limb muscles MRI findings in patients with 4q35-linked facio-scapulo-limb, type 2 muscular dystrophy (FSLD2) (or a facioscapuloperoneal dystrophy [FSPD]);” **Kyle T. Siebenthal, Ph.D.**, and **Barbara J. Trask, Ph.D.**, on the “Study of aberrant nuclear organization in facioscapulohumeral dystrophy (FSHD) using circular chromosome conformation capture (4C);” **Hermien E. Kan, M.D.**, and **Arend Heerschap, M.D.**, on “MR imaging in FSHD at 3T – initial experience;” and **Graham J Kemp, M.D.**, and **Malcolm J Jackson, M.D.**, on “Oral creatine supplementation does not change muscle strength, body composition or muscle biochemistry in patients with FSH dystrophy.”

The presentation by Ted Abresch included an interesting piece of information — that the optimal exercise for FSHD patients is at about 70% of capacity; more is harmful. However, he did not indicate how to determine patients’ capacity for exercise.

Dr. Meredith Hanel’s presentation about studying FRG1 in the African clawed frog was interesting and well-received, as this was the first time the frog as an animal model was presented in an FSHD forum. Dr. Joe Marx of the NIH presented his work on the FRG1 mouse using mice given to him by Dr. Rossella Tupler. His results are very preliminary and from a limited sample size, but he says that FRG1 is expressed in muscle precursors and

vascular tissue in the mice. Dr. Rossella Tupler’s lab stated that the amount of FRG1 expression varies with the age of the FSHD subject.

Dr. Sara Winokur, University of California, Irvine, is beginning to use human embryonic stem cells in FSHD research, according to Peter Masny who is collaborating with Winokur. Yokomori, also at UC, Irvine, recently got a grant from the California Institute of Regenerative Medicine for an FSHD study involving human embryonic stem cells. There is a belief in the strong likelihood that the FSHD pathology begins very early when the embryonic cells start to differentiate. We can expect more embryonic stem cell research in FSHD in California, where there is strong public and state governmental support for embryonic stem cell research.

A group discussion followed at the end of the day moderated by the panel of Silvère van der Maarel, Ph.D., Rune R. Frants, Ph.D., (member of the FSH Society Scientific Advisory Board and professor at LUMC, Leiden, The Netherlands), William R. Lewis, Sr., M.D., and John Porter, Ph.D., to identify the top five to ten priorities for 2008 FSHD research directions and collaborations

The panel made observations — in general the FSHD field has advanced light-years in the past two years and a coherent scientific conceptual framework for the disease is coming together.

### *Other priorities were:*

1. Myoblasts and the quality of the myoblast tissues need to be identified; it was suggested that all papers indicate what percentage of the cells are myoblasts and what procedures the lab has done to them;
2. An appeal was made for open-mindedness in reviewing grant proposals, particularly for colleagues/peer-reviewers to be open minded about projects not involving the candidate gene FRG1;
3. Given the emergence of muscle and protein research in FSHD,

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## *FSHD International Research Consortium, continued from page 7*

the research community should also consider participating in a muscle organization conference in addition to the ASHG conference;

4. Since retinal and hearing vasculature are common in FSHD (although typically at subclinical levels), researchers should be studying not only muscle but also these changes in vasculature. The vascular effects typically cluster in families;
5. A need to figure out how to measure and define success in pre-clinical terms;
6. The need to standardize research protocols;
7. The need to have a sufficient number of patients ready for trials;
8. Patient population natural history is critical for trials; in particular, a natural history would allow grouping of patients with similar characteristics;
9. A need to define (and, to the extent possible, quantify) the endpoints, the goals of any therapy or treatment, and include input from patients in defining these goals;
10. Consider requesting advice from the NIH early on when designing a trial;
11. The FSH Society should have comprehensive information on its website about what resources are available for what types of research.

Researchers were energized by the enthusiasm, excitement and collegiality in the room, and agreed the conference was one of the most successful to date. We are continually impressed by the increasingly international composition of the researchers—among the presenters were researchers from the United States, France, Italy, Belgium, the UK, South Africa, The Netherlands, Australia and Argentina. Several of the researchers from US institutions are from abroad. Also, there were nonscientist observers from the US, France and Australia. It was impressive to see the increasing generational span of the researchers. There were three generations — senior, mid-career, and junior

researchers. This is a testament to the success of the FSH Society fellowship and grants program and other programs that enable and facilitate young people entering the field and to allow them to envision a career in FSHD research. It's also a testament to the success of the senior scientists in recruiting and mentoring a new generation. The group remarked that it is especially valuable to have clinicians, clinical trials and clinical perspectives at the meeting

### *Key points, findings and hypotheses of presentations*

- ◆ DUX4 is an FSHD candidate gene located within the chromosome 4q D4Z4 repeats, and there is evidence that DUX4 is toxic to myoblasts and induces several FSHD-associated transcriptional changes.
- ◆ The DUX4 ORF is conserved in primates (Apes, Old and New World Monkeys and Lemurs) and in Afrotheria (elephants and related species), and analysis of the primate sequences indicates evidence of selection at the codon level, which is indicative of a protein-coding function. Exogenous expression of mouse DUX protein results in a nuclear localization pattern that is consistent with its expected function as a transcription factor.
- ◆ There is competition between DUX4 and Pax3/Pax7: when either Pax3 or Pax7 is expressed at high levels, DUX4 is no longer toxic. As Pax7 is required for maintenance of the myogenic stem cell pool, it is proposed that DUX4 interferes with muscle regeneration at two levels – by limiting self-renewal of the myogenic stem cell pool leading to premature loss of regenerative ability, and (2) impairing regeneration.
- ◆ Paired-like homeodomain transcription factor 1 (PITX1) is a homeobox transcription factor, which plays a critical role in hind-limb specification during embryonic development, and in FSHD there is up-regulation of Pitx1 in muscles-activated molecular pathways involved in muscle atrophy. Tet-repressible muscle-specific Pitx1 transgenic mice were generated by crossing Pitx1 transgenic mice (TRE-Pitx1) with

transgenic mice expressing tetracycline activator driven by mouse creatine kinase promoter (mCK-tTA).

- ◆ The DUX4 gene is within each unit of the D4Z4 repeat array and is expressed at the mRNA and protein levels in FSHD myoblasts but not in controls. Additionally, the homologous DUX4c gene mapped 42 kb of the D4Z4 array was expressed in control and FSHD myoblasts. The DUX4c protein was found at higher levels in biopsies of patients with FSHD and low D4Z4 copy number. That DUX4c specifically induced the Myf5 transcription factor, suggesting a role in the maintenance of the satellite cell pool and its expression could affect muscle regeneration and contribute to the FSHD pathology.
- ◆ The D4Z4 subtelomeric element is a bona fide insulator element protecting from TPE and able to block enhancer-promoter communication. As the number of repeated elements increases, the D4Z4 array facilitates telomeric position effect having a repressive effect upon gene expression. CTCF participates in D4Z4 insulation mechanisms.
- ◆ FSHD is an “epigenetic abnormality” disease in which the loss of H3K9 heterochromatin at D4Z4 plays a critical role in pathogenesis. Similarities were observed in Emery-Dreifuss (EDMD) and limb-girdle muscular dystrophies (LGMD), suggesting a common pathway.
- ◆ Chromatin immediately proximal to D4Z4 arrays (including the p13E-11 region) showed an unexpectedly large difference in DNase I sensitivity relative to D4Z4 chromatin in both FSHD and control myoblasts and lymphoblastoid cells. That unusual chromatin structure at the proximal end of the array, and atypical DNA secondary structures within each 3.3-kb repeat unit, contribute to topological constraints that confer pathogenicity on short 4q D4Z4 arrays and make long ones phenotypically neutral.
- ◆ The chromatin structure of the 4q D4Z4 region, including DNA methylation and chromatin loop organization, is affected in FSHD alleles. Several other findings, including

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## FSHD International Research Consortium, *continued from page 8*

upregulation of 10q genes in FSHD and hypomethylation of both 4q alleles in phenotypic FSHD, also point to the role of complex epigenetic interactions — including trans-allelic and inter-chromosomal interactions — in the pathogenesis of FSHD.

The known chromatin insulator protein, CTCF, has been recently implicated in mediating long-range intra- and inter-chromosomal interactions. Researchers identified two clusters of CTCF binding sites within the D4Z4 repeat unit and demonstrated that CTCF binds to the 4qD4Z4 region *in vivo*.

◆ Since CTCF binding is regulated by methylation, this suggests that epigenetic changes at the 4qD4Z4 repeats in FSHD alleles, including loss of DNA methylation, make these repeats accessible for CTCF binding, providing chromatin insulation in the region and altering long-range chromatin interactions that could account for both cis- and trans-effects in deregulation of gene expression observed in FSHD.

◆ Muscles from patients with FSHD showed large increases over controls in a single soluble, 34 kDa protein called mu-crystallin. Mu-crystallin has thyroid hormone and NADPH binding activity and so may influence differentiation and oxidative stress responses, reported to be altered in FSHD. It is also linked to retinal and inner ear defects, common in FSHD, suggesting that its up-regulation may play a specific and important role in pathogenesis of FSHD.

◆ 4q35 consistently resides at the nuclear periphery and is physically tethered to the nuclear lamina in both FSHD and normal cells; FSHD locus comes into contact with other genomic loci and impacts their regulation. A strategy to use the FRR-MAR and first proximal D4Z4 unit as ‘bait’ in Circular Chromosome Conformation Capture (4C) assays, to create a complete picture of the potential interaction space of the FSHD locus in normal and FSHD myoblasts was presented.

◆ Dedicated imaging of muscular edema and imaging at a field strength of 3T, allowing increased resolution, has, to our knowledge, never been applied. The aim of the present study

was to apply different MRI methods to detect lower leg muscle involvement in patients with FSHD at a field strength of 3T.

◆ Creatine supplementation had no significant effect except to increase plasma creatinine by 7%. No significant change in muscle strength or muscle cross-sectional area, in spirometry, bio-impedance measurements and quality of life or in ROS measures. There was no significant change in muscle creatine content. Of interest is the strong correlation between aggregate MRI measures of muscle cross-sectional area and average isometric strength, which both correlate less well with fat-free mass by bio-impedance.

◆ Pain is a common problem in FSHD, with the majority of adults reporting pain. The universal pain sites were lower back and legs. Additionally, FSHD differed from the other dystrophies in the study, with patients reporting pain often in their shoulders and hips. Findings highlight the need to identify and provide effective pain treatments for patients with FSHD.

◆ Upon examining additional sequence variations in the FSHD locus, including a relatively stable simple sequence-length polymorphism (SSLP) proximal to D4Z4; a single-nucleotide

polymorphism (SNP) within D4Z4; and the A/B variation distal to D4Z4 was observed. The sub-telomeric domain of chromosome 4q can be subdivided into nine distinct haplotypes, of which three carry the distal 4qA variation. Repeat contractions in two of the nine haplotypes, one of which is a 4qA haplotype, are not associated with FSHD. Each of these haplotypes has its unique sequence signature and it is proposed that specific SNPs in the disease haplotype are essential for the development of FSHD.

◆ After thorough molecular analysis, a family has been identified with a second FSHD-associated locus unlinked to 4q35. A genome-wide linkage analysis may identify the location of a potential second FSHD locus in this family and may help to further define the molecular pathogenesis of FSHD.

◆ The expression of the FRG1 homolog was cloned and analyzed in the African clawed frog *Xenopus laevis*, a model organism that is well suited for studying muscle development. This provides insight into the role of FRG1 in a developing vertebrate organism and suggests that disruption of normal FRG1 expression may, in fact, lead to the muscle deterioration seen in FSHD that is possibly a

*continued on page 10*



## ***New FSH Society website now online!***

We are pleased to announce the new, much improved, FSH Society website. With resources for researchers as well as patients and families, we are confident it will become a much-bookmarked site for all things concerning FSHD. Please see articles on page 18 for more information.

## Continued FSHD advocacy efforts on the federal muscular dystrophy advisory committee

In the previous edition of the FSH Watch, we highlighted the FSH Society's role and history in the MD-CARE Act and **Daniel Paul Perez's** role on the federal advisory committee mandated in the Act, the MDCC.

"The Muscular Dystrophy Community Assistance, Research, and Education Amendments of 2001 (MD-CARE Act) authorized the establishment of

the Muscular Dystrophy Coordinating Committee (MDCC) to coordinate activities across NIH and with other Federal health programs and activities relevant to the various forms of muscular dystrophy. The MD-CARE Act directed the Committee to develop a plan for conducting and supporting research and education on muscular dystrophy through the national

research institutes, and to submit this plan to Congress within the first year of the establishment of the MDCC. The MDCC has conducted two stages of planning. The first stage led to the Muscular Dystrophy Research and Education Plan for NIH, which was submitted to Congress in August 2004. This formed the basis for a subsequent, more intensive planning process that produced the MDCC Action Plan for the Muscular Dystrophies (approved by the MDCC in December 2005). The Action Plan contains specific research objectives that are appropriate to the missions of all MDCC member agencies and organizations and thus serves as a central focus for coordination of research in muscular dystrophy."

[source: NIH NINDS MDCC internet home page]

The FSH Society was instrumental in rewriting the MD-CARE ACT 2001 to meet the needs of the entire community — people with all nine major types of muscular dystrophy — not just one type of muscular dystrophy. On December 18, 2001, Congress passed the MD-CARE Act, an unprecedented law mandating research, study and education on each type of muscular dystrophy. The law established the MDCC oversight committee to coordinate activities across the NIH, national research institutes and federal health programs relating to all forms of muscular dystrophy. The MDCC is responsible for developing and implementing a plan for conducting and supporting research and education on muscular dystrophy, measuring progress and periodically reviewing and revising the plan. The Society is currently working to improve the MD-CARE Act in the 2008 reauthorization process.

Daniel Paul Perez, President & CEO of the FSH Society, was appointed to the MDCC at its inception in 2003, one of only five patient advocates appointed to the committee. The MDCC has developed a research and education plan for muscular dystrophies for the NIH and other federal agencies involved with muscular dystrophy.

The MDCC met again on June 23, 2008 in Washington, D.C. for the

## Observations on PubMed and FSHD

It is heartening to see the excellent research and increasing body of publications on Entrez Pubmed. In the 91 year period between January 1, 1900 and July 15, 1991, when the Society was founded, 157 papers including seven reviews were published on FSHD. Since the Society began its efforts, 477 papers — including 62 reviews — were published on FSHD. Search on Pubmed was done using key words [FSHD or facioscapulohumeral or DUX4 or D4Z4 or landouzy-dejerine].

The last five years demonstrate steady progress:

|      | Journal Articles | Reviews |  | Journal Articles | Reviews |
|------|------------------|---------|--|------------------|---------|
| 2003 | 27               | 5       |  | 2006             | 6       |
| 2004 | 38               | 5       |  | 2007             | 5       |
| 2005 | 47               | 8       |  | 2008             | 3       |

Over the years 2007 and 2008 it is very interesting to see the emergence of research papers covering treating and working with FSHD patients in addition to cellular and molecular biology. Noteworthy are papers on hormonal and testosterone differences in FSHD patients, scapular surgery, exercise, pain, spirometry and breathing measurements, anesthesia, hearing, vision, compounds for clinical trials, results of clinical trials of myo-029 myostatin inhibitor and folic acid, cardiac involvement, respiratory insufficiency, orthopaedics/orthotics, fatigue and physical therapy. It is excellent to see the emergence of research on treating the disease and elucidation of clinical aspects of the whole-body syndrome of FSHD.

## FSHD Research Consortium, *continued from page 9*

result of an inability of muscle precursors to repair and regenerate normal muscle.

◆ FRG1 interacts with heterologous ribonucleoprotein U (hnRNP-U). hnRNP-U is involved in a wide range of activities ranging from transcription to mRNA stability and splicing. FRG1 manifests itself in muscular dystrophy by altering key RNA processing events in muscle.

◆ Myoblasts obtained from clinically and histologically affected territories are more susceptible to the alteration control of gene expression associated with D4Z4 contraction when compared to myoblasts issued from unaffected territories.

◆ Regulatory models include a cis effect on proximal gene transcription (position effect), DNA looping, and nuclear localization/trans effects. An experiment was proposed to directly test whether deletions of D4Z4 affect gene expression in cis, investigated nascent RNA transcription in single nuclei so that expression from each allele could be measured independently.

For a complete copy of program and abstracts, please see:

<http://www.fshsociety.org/pages/sciConsortium.html>

## FSHD advocacy

seventh time and continued to implement a **Muscular Dystrophy Research and Education Plan** for NIH that was submitted to Congress in August 2004. The topics of *“Therapy Development and Living with Muscular Dystrophy”* were covered.

The meeting began with welcome and introductions by the new Chair of the MDCC, **Story Landis, Ph.D.**, Director, NINDS, and Executive Secretary of the MDCC, **John Porter, Ph.D.** NINDS. As a reminder to everyone why the work needs to continue and to help set the tone, three parents were invited to give their perspectives on living with muscular dystrophy as caregivers of Duchenne and myotonic dystrophy children.

The morning presentations were *“MDCC Member Action Plan Reports”* from respective agencies on the committee. These included the NIH Overview and NINDS report, the Wellstone Centers Program and NIAMS report, the NICHD, the NHLBI, the DoD, the CDC, the FSH Society, the PPMD, and the MDA.

The afternoon sessions and talks focused on opportunities for “MDCC Partnering” and defragmenting efforts in muscular dystrophy research. Presentations included the need for more training and education resources for professionals — MDCC Partnering Opportunity — Muscular Dystrophy Workforce Needs NIAMS; Fields Center for FSHD and Nemaline Myopathy (N-M) Disease; and the Translational Research in Europe — Assessment and Treatment of Neuromuscular Disease (TREAT-NMD) and the MRC Centre for Neuromuscular Disease.

The last presentation of the day was coding schemas and rules for tracking diseases and research areas — changes in “NIH Disease-Coding Procedures by the NIH.”

For more information on the MDCC plans, staff, rosters, meeting agendas and minutes please see the FSH Society website at:

<http://www.fshsociety.org/pages/resPNIHMDCC.html>

## FSHD representation at “New Directions in Skeletal Muscle Biology” meeting

The third New Directions in Skeletal Muscle Biology meeting was held April 27-30, 2008, in New Orleans, Louisiana. All information on the meeting and full program books and abstracts can be found at

<http://www.med.upenn.edu/muscle/program.shtml>

The origins of this meeting are from early discussions and behests by **Daniel Paul Perez**, the FSH Society and other patient advocates with the NIH at planning meetings and at the federal MDCC. We asked for a domestic U.S. meeting where researchers, clinicians and new investigators working on muscle biology could interact with those working on muscle disease/dystrophy in a forum similar to international meetings of the European Neuromuscular Coalition (ENMC), World Muscle Society (WMS), etc. These types of interdisciplinary meetings facilitate attracting new researchers, clinicians, perspectives and disciplines not found within the muscular dystrophy community. Many of the research meetings at that time were research focused or clinically focused but rarely a mix of the two. The goal of this meeting is “to facilitate research progress and information exchange in basic biology of muscle and therapeutics for muscular diseases.”

This was an excellent meeting whose scope has broadened very nicely since its inception. We thank the NIH for organizing this important meeting. We especially thank FSHD researchers and past and present FSH Society research fellows and grantees, for presenting on FSHD to demonstrate an extremely strong and timely representation on behalf of FSHD.

## 13th International World Muscle Society will highlight FSHD research advances

Information on the 13th International World Muscle Society (WMS) Congress to be held from 29 September 2008 – 2 October 2008 at Newcastle upon Tyne, UK, can now be found at [www.wms2008.com](http://www.wms2008.com)

FSHD is prominently represented in the 2008 WMS Congress details: *“New Insights into the pathogenesis of FSHD, myotonic dystrophy and other dominant muscular dystrophies”* and *“Therapeutic advances in neuromuscular disorders.”*

We thank Drs. Straub and Bushby for the timely and considerate emphasis on FSHD at this meeting. The FSH Society is a special sponsor of the World Muscle Society’s 13th International Congress meeting. We will be designating speakers who are giving FSHD plenary lectures, **Silvère van der Maarel, Ph.D.**, **Alexandra Belayew, Ph.D.**, and **Rossella Tupler, M.D., Ph.D.** as the *“Stephen J. Jacobsen, Ph.D., Memorial”* lectures.

Scientific information questions should be addressed to professors

**Volker Straub**, [volker.straub@ncl.ac.uk](mailto:volker.straub@ncl.ac.uk), and

**Kate Bushby**, [kate.bushby@ncl.ac.uk](mailto:kate.bushby@ncl.ac.uk)

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## What is Entrez?

Entrez is the integrated, text-based search and retrieval system used at NCBI for the major databases including PubMed, Nucleotide and Protein Sequences, Protein Structures, Complete Genomes, Taxonomy and others. See:

<http://www.ncbi.nlm.nih.gov/sites/gquery>

## *Perez represents FSH Society and FSHD at Wellstone center director's meeting*

Each year the Wellstone Muscular Dystrophy Cooperative Research Centers hold an annual meeting to discuss research progress and collaboration. The fifth meeting was held on May 12th - 14th at the University of Rochester, Rochester, New York. The NIH, along with the directors of the Wellstone centers, recognized the increasing need to improve coordination and synergy among centers and patient advocacy groups to avoid fragmentation of efforts. Additionally the role of advocacy groups in passage of the MD-CARE Act was recognized as being responsible for the formation of the Wellstone centers.

The format of this year's meeting was modified to allow extensive interaction of advocacy groups, to help researchers in Centers and other stakeholders in the endeavor to find treatments and solutions for muscular dystrophy. As the data presented included unpublished and preliminary data, the information discussed remains confidential. The theme of the

meeting as presented by the organizers was "to discuss opportunities for partnership – between Wellstone Centers, between these Centers and other researchers, and between Wellstone Centers and groups that promote research on muscular dystrophy.... [and for the NIH] to highlight specific examples of successful partnerships."

May 13th was a meeting with oral and poster presentations from each Wellstone center: University of Washington, University of Rochester, University of Pittsburgh, University of Iowa, Children's National Medical Center D.C., and University of Pennsylvania/Johns Hopkins University. Researchers from each center presented research progress, impediments, and the opportunities for collaboration. On May 14th there was a series of presentations from patient advocacy groups, and key personnel on strategies to combine efforts to maximize the effectiveness of the centers, and opportunities to leverage projects and resources.

The FSH Society and **Daniel Paul Perez** attended to present, ask questions and to give perspective on FSHD as well as thoughts on the role of the non-profit working together with the Wellstone centers, and on Wellstone centers working with one another. Overall, there were very positive developments presented on FSHD research and therapy. Since the Boston BBRI FSHD Wellstone center has not been awarded, we could not detail the great progress the FSH Society has made in working to coordinate FSHD by working with other non-profits, NIH, multiple Wellstone centers including the one it is attached to, academic institutions, hospitals and pharma and biotechnology companies. We hope to promote this model of coordination and materials sharing at the next meeting, and add to our combined team other organizations and centers working on FSHD.

## *FSHD muscle biopsies needed for research repositories*

FSHD researchers are in constant need of muscle biopsies from FSHD patients. Muscle biopsies play a crucial role in FSHD research. When considering how many researchers use muscle biopsies, the need is clear.

A muscle biopsy is a surgical procedure in which a small sample of muscle is removed for diagnostic and research purposes. The biopsy procedure is a minor surgery that is usually done as outpatient day surgery under local or general anesthetic. FSHD clinicians and researchers need two types of biopsies, depending on the requirements of their work. One is called a needle biopsy and the other is an open biopsy. A needle biopsy involves inserting a needle into the muscle to a certain depth and capturing the sample of muscle inside the needle. The incision is usually five millimeters deep and a few millimeters in length. An open biopsy requires making an incision or a cut that is a few centimeters in length; a sample of muscle about the size of a pea is removed and stitching is required to close the incision. Both types of biopsies are needed and are in high demand to help researchers and clinicians quicken the pace of their work.

Please consider making a valuable gift to research by contacting the FSH Society to let us know you are willing to donate tissues. Contact **Daniel Paul Perez** at the Research Office of the Society or e-mail [biopsy@fshsociety.org](mailto:biopsy@fshsociety.org) if you are interested in making a contribution to the science that could ultimately find treatments and a cure for FSHD.

## *FSH Society FSHD ASHG meeting planned*

The FSH Society invites research professionals and clinicians to the annual FSHD International Research Consortium (IRC) workshop. The workshop will be held as an ancillary/satellite event just preceding the 2008 Annual Meeting of the American Society of Human Genetics (ASHG). IRC workshop attendees will meet on Tuesday, November 11, 2008 from 8 a.m. - 5 p.m. at the ASHG headquarters' hotel in Philadelphia, Pennsylvania. **Silvère van der Maarel, Ph.D.**, and **Kathryn Wagner, M.D., Ph.D.**, will be the scientific co-chairs for this important and unique meeting. 2008 is shaping up to be one of the most significant years in basic and clinical research for FSHD. Research professionals, please contact **Daniel Paul Perez** if interested in presenting or attending the meeting.

## Finding genes where you did not expect them

By Melanie Ehrlich, Ph.D., Hayward Human Genetics Center and Department of Biochemistry, Tulane Medical School, New Orleans, LA 70112

What's a gene? Where are the DNA elements that turn genes on and off? These issues, which many thought were well on their way to being understood, are now wide open again with the increasing demonstration of DNA being copied into RNA from unexpected places in the human genome. Sometimes this means the "wrong" strand of double-stranded DNA being copied in addition to the correct strand that codes for a protein. The product of wrong-strand copying, logically enough, is called antisense RNA, as compared to the sense RNA that codes for proteins.

In addition, many other types of new genes are being discovered in human DNA. One of the biggest surprises is that many of these new genes don't code for proteins but only make RNA, which usually is just the intermediate for making protein. These genes are called non-coding RNA genes because they make RNA but not proteins. The RNAs that they make come in a variety of categories in terms of sizes, shapes and functions. One of the most actively studied of these categories is a very small type of RNA, called microRNA. However, there are other biologically important and new types of non-coding RNAs in addition to microRNAs and antisense RNAs. The variety of genes that make non-coding RNA makes it difficult to predict where most of them are in the genome. It is clear that many of their product RNAs are involved in normal functions and in diseases.<sup>1</sup>

This could be important for FSHD research. There are many uncertainties about the genes involved in FSHD. For example, some hypotheses about how a short D4Z4 array on chromosome 4 leads to FSHD involve a gene outside the array that is rather far, but not too far, away and gets turned on when it should not. However, there are very few known genes within two million base-pairs of D4Z4, so few that we call this region a gene desert. Maybe the gene on chromosome 4 that gets activated in FSHD so as to start the whole series of pathological events is one of these new non-coding RNA genes that has not yet been discovered.

In collaboration with **Greg Crawford, Ph.D.**, at Duke University, we are examining virtually all the four million base-pairs at the end of chromosome 4 in FSHD and control muscle cells with his lab's new technique that looks for genes in a different way.<sup>2</sup> This method, DNase-chip, identifies tiny sites on the chromosome that are very uncondensed so that they are susceptible to cutting with an enzyme, DNaseI, after a brief incubation. It seems that the very beginnings of all active genes (and some other regulatory elements) have these uncondensed chromosome sites. Therefore, DNase-chip can lead us to the beginnings of all kinds of active genes, including genes that no one has described before. DNase-chip involves trapping the free ends of DNA created by DNaseI from the very uncondensed sites in chromosomes, amplifying them, and then detecting them with microarrays that have up to 2 million tiny DNA probes (oligonucleotides).

DNase-chip might also lead to discovery of a regulatory region on chromosome 4 that is moderately far from

D4Z4 but controls the array so as to make FSHD a chromosome 4-specific disease and to genes on other chromosomes important in FSHD further down the gene pathways. DNase-chip is starting to give us new insights into the district of the chromosome 4 where D4Z4 resides. We hope that it will lead to a better understanding of the molecular genetics of FSHD. It might thereby aid in development of effective therapies, especially because there is much excitement in the field of non-coding RNA therapies.<sup>3</sup>

### References

- <sup>1</sup> Boyd, S.D. (2008) Everything you wanted to know about small RNA but were afraid to ask. *Lab Invest* **88**, 569-578.
- <sup>2</sup> Boyle, A.P., Davis, S., Shulha, H.P., Meltzer, P., Margulies, E.H., Weng, Z., Furey, T.S. and Crawford, G.E. (2008) High-resolution mapping and characterization of open chromatin across the genome. *Cell* **132**, 311-322.
- <sup>3</sup> Couzin, J. (2008) MicroRNAs make big impression in disease after disease. *Science* **319**, 1782-1784.

## Marjorie Bronfman grant for research on FSHD for 2008

The generosity and commitment of Mrs. **Marjorie Bronfman** to FSHD research started in 1997. Mrs. Bronfman renewed her commitment through 2008 of one hundred-thirty thousand dollars per year. Through a review and recommendation of our SAB, grants are awarded for two-year research fellowships (US\$30,000-US\$35,000/year) for research projects that show extraordinary promise to find the cause of FSHD. This foresighted contribution significantly aids progress in FSHD research and has already created advances worldwide. The FSH Society is deeply indebted to Mrs. Bronfman and the Marjorie and Gerald Bronfman Foundation for this significant opportunity to advance FSHD research.

## CFC #10239 & United Way

Federal employees and military personnel can donate to the FSH Society through the Combined Federal Campaign (CFC). Please consider making a contribution to the FSH Society through the CFC. The CFC is operated by the United States Government Office of Personnel Management. The FSH Society CFC code is #10239. For more information about the CFC, you may visit the OPM website at:

<http://www.opm.gov/cfc/index.htm>



## FSH SOCIETY

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

HOME THE FSH SOCIETY CONTRIBUTE ABOUT FSHD FOR PATIENTS **FOR SCIENTISTS** FSH SOCIETY RESEARCH COMMUNITY & REFERENCE



### FSH Society Contacts, Information and Resources For Scientists

## *New FSH Society website for scientists, clinicians, researchers and patients*

The FSH Society recently upgraded and expanded its website. We invite the scientific, research, clinical and translational research community to make contributions, use the site and to send materials, information, research data and research plans you wish to convey to colleagues working on FSHD.

As part of the 2006 FSH Society research plan for FSHD, the collective FSHD research community and the Society's SAB called for the creation and implementation of a web research resource for FSHD. It was requested that the FSH Society create an "FSHD Research Resource" on its web site. In an effort to build communication among the Society-funded researchers, access should be limited to funded investigators and SAB board members via a Wiki. A system to expand membership (and revoke access when necessary) should be developed that provides a "voting" privilege to each FSH Society-funded investigator. A greater level of collegiality and willingness to share needs to evolve to build an environment which will come to understand the significance of disparate results arising in this effort.

The site was requested to include (at a minimum) the following information:

1. detailed research protocols;
2. available research materials (also see below);
3. research progress reports;
4. "apparent" negative research results, the importance of which was most telling in the discussion of some proposed experiments that could build on a past strategy. An online "Journal of Negative Results" for FSHD;
5. a "blog-like" forum for discussions by active researchers;
6. a dynamic listing of the three to five most important experiments needing execution. Something similar might be offered on the FSH Society's open site;
7. FSH Society tactical and strategic plans; and
8. a parallel open site was requested that contains more limited but less sensitive information to help those interested in entering FSHD research and controversial areas in FSHD research. For example, the open site might include the list of high research priorities or funds available for specific activities, but would not include recent unpublished observations or active research reports.

To move the field ahead, the Society has implemented a modified version of the above specifications with a website containing two navigation trees or channels — one dedicated

#### Research Contacts

FSH Society International Research Consortium

#### Resources

Accessing FSHD Patients

Grant Opportunities

Training Opportunities

Meeting Reports

Special Interest Research Groups

FSHD Wiki Investigator Login  
(Restricted Access)

*The FSH Society Research website navigation channel highlights the Society's research and fellowship efforts, its Scientific Advisory Board, research milestones, fellows and grantees, details on the fellowship and grants program, compiled research plans and road maps . . .*

## New FSH Society website

to scientists and another to FSH Society research and planning efforts. The “For Scientist” channel contains contacts, research workshop information, a place for resources to be listed (e.g. cells, antibodies, tissues, biomaterials, animal models, and materials found in Wellstone MD CRC cores), ways to request access to patients, grant and training opportunities, meeting reports, special focus groups and the FSHD Wiki (under development).

### For Scientists

- Research Contacts
- FSH Society International Research Consortium
- Resources
  - Cell Repositories
  - Tissue Banks
  - Biomaterials
  - Animal Models
  - NIH Wellstone Cores
- Accessing FSHD Patients
- Grant Opportunities

- Training Opportunities
- Meeting Reports
- Special Interest Research Groups
- FSHD Wiki Investigator Login (Restricted Access)

The FSH Society Research website navigation channel highlights the Society’s research and fellowship efforts, it’s Scientific Advisory Board, research milestones, fellows and grantees, details on the fellowship and grants program, compiled research plans and road maps, biomaterials, resources the community wishes to post, ways to request the Society to help find patients for your research, books and online materials and datasets that the community wishes to post online.

### FSH Society Research

- Scientific Advisory Board
- Research Milestones
- Research Fellows & Grantees

- Fellowship & Grants Program
  - Overview
  - Applications
  - Policy
  - Questions of Grants
- FSHD Research Plans
  - FSH Society Research Plan
  - U.S. NIH Action Plan
  - U.S. NIH MDCC
- Biomaterials & Resources
- Requests for Patient Involvement
- Books About FSHD
- Bioinformatics & Online Resources

We hope the website is more user friendly, a richer experience and, as recommended by researchers in the 2006 FSH Society research planning meeting, a valuable resource for researchers. The web address remains the same: [www.fshsociety.org](http://www.fshsociety.org). Check it out!

### *www.fshsociety.org is for patients & families*

The new FSH Society website offers extensive information designed to educate and assist those with FSHD and their families. On the home page you will find links to the Patient and Physical Therapy brochures. From the “For Patients” link you can access an explanation of the different health care professionals you may encounter, a page about the genetics of FSHD, patient registries and research trials and how you can help donate to research.

In addition, the “Health Information” link will give you valuable information about pain, cardiac involvement, pulmonary and respiratory health, exercise and surgical treatments. From the “Community & Reference” link at the top of each page, you can access online groups, bulletin boards and chat for FSHD. We hope this expanded site will be a great resource for those with FSHD and the community as a whole!

## FSH Society Sam E. and Mary F. Roberts Foundation grant for nutrition research

**Grant:** FSHS-SMRF-003

**Researcher:** Hermien Kan, Ph.D./Arend Heerschap, Ph.D.

**Institution:** Head Biomedical Magnetic Resonance group

- Department of Radiology
- Radboud University Nijmegen Medical Center
- Nijmegen, The Netherlands

**Project Title:** “Assessment of the metabolic inter-muscular heterogeneity, and muscular creatine uptake and turnover in FSH patients *vivo*.”

## FSH Society Helen Younger and David Younger research fellowship

**Grant:** FSHS-HDY-001

**Researcher:** Kyoko Yokomori, Ph.D.

**Institution:** University of California, Irvine

- Department of Biological Chemistry
- College of Medicine
- Irvine, CA

**Project Title:** “The Molecular characterization of the chromatin structure of the D4Z4 repeat associated with FSHD.”

## Research planning – helping to solve FSHD

Since the identification of the FSHD locus on chromosome 4 in the early 1990's, FSHD research has made quantum leaps in understanding the mechanism and function of the molecular, cellular and evolutionary biology of the disease. Today there is a much better understanding of the underlying biology of FSHD — so much so that FSHD research has begun to enter the area between basic research and clinical trials known as translational research.

Researchers and clinicians have begun to identify major biochemical pathways in muscle control and growth and high priority drug targets for the disease. FSHD cell and animal models have begun to be developed that help build and accelerate the rationale for preclinical testing of candidate drugs.

Despite these achievements, the precise and complete genetic, biological, chemical and physical mechanism of FSHD is still unknown, and there are no effective treatments or cures.

We continually ask ourselves: What do we know about FSHD? What do we not know about FSHD? What do we need to know about FSHD? What are the obstacles to complete understanding? What must we — the FSH Society — as well as the FSHD patient and professional community at large do next to accelerate progress toward solving FSHD?

These questions are addressed by generating plans and strategies that come from the consensus of researchers, clinicians, patients, funding agencies and industry.

In Cambridge, Massachusetts in 2006, the FSH Society addressed these questions at a planning meeting of its SAB and other members of the FSHD research community. We developed the *FSH Society FSHD Tactical and Strategic Research Plan*, a review of FSH Society grant funding, how it has been spent and what it has accomplished, and an assessment of how to go forward to find treatments and a cure for FSHD.

This plan and related recommendations will guide the direction of the

FSH Society's research programs and help optimize FSHD research funding by federal agencies, non-profits and private funding sources.

One of the answers to these questions was that it is a priority to undertake the production of a series of uniform reagents for the purpose of providing consistent experimental materials. This will allow the research community to access similar starting materials across multiple laboratories and experiments. Section 2 of the short-term objectives of the Society research plan outlines the need for the creation of uniform research reagents and materials in three broad areas: antibodies, cell lines and animal models. The third section focuses on animal and mouse models.

The FSH Society has funded multiple research and fellowship projects to help generate mouse and animal models. Several of these projects have continued on to be supported by a three year grant of the MDA, or by five year grants from the NIH. These are fine examples of how seed funds and grants of the Society are instrumental in generating follow-up grants. Many of the animal models developed under FSH Society funds have never been published simply because they have no outward visible signs of disease (also known as a phenotype). However, it is realized that they will be very instrumental for epigenetic studies of the FSHD locus.

The Society research plan calls for providing ways for rapid access to potential animal models of FSHD to confirm the validity of the models and to begin to develop therapeutic strategies to cure or ameliorate the consequences of the disease. The FRG1 gene mouse model produced by Dr. **Rossella Tupler** and Dr. **Davide Gabellini** is the first mouse model created and published. Though the phenotype of the mouse is not completely concordant with the human form of FSHD, and few animal models are, having a mouse model rapidly expands the number of potential experiments to the point where the amount of work to be done

is quite formidable for two research groups. A mechanism to share the model would help distribute the work load and expand the potential of this model, or any other model, to contribute to finding therapeutic interventions for FSHD.

It is suggested that the Society should consider hosting a meeting on how best to exploit animal models to maximize these types of models while working with the scientists to insure that their intellectual property and patent position are protected. The FSH Society has a policy that encourages our grantees to make these types of resources (animal models) available to other FSH Society funded researchers and members of the broader research community. The Society plan calls for experiments and projects proposed by those who develop the models and by other teams to provide independent evaluations.

### *Projects and experiments might include:*

- ◆ silencing expression of the trans-gene and evaluating its effect;
- ◆ evaluating the pattern of aberrant muscle development in the model;
- ◆ generating cell lines for study from embryonic stem cells;
- ◆ attempting to correct the defect in embryonic stem cells and restore a 'normal' muscle program in affected tissues in the model;
- ◆ using expression profiling and proteomics to compare the model to the syngeneic strain to identify other genes and proteins that respond to the mis-expression of FRG1 (or other FSHD candidate gene);
- ◆ evaluating the significance of responding target genes;
- ◆ establishing the chromatin environment of the trans-gene(s); and
- ◆ evaluating the effect of modifying the chromatin environment on the trans-gene(s) using chemicals, drugs or other mechanisms.

These new models are absolutely one of the most promising areas of endeavor to emerge in FSHD-focused research in recent years and every



## Research planning – helping to solve FSHD

effort should be made to exploit them as expeditiously as possible. A number of animal models have been constructed with Society funds in recent years. Those projects will be described, summarized, and posted on the Society's new web-based research resource. Mammalian and non-mammalian models will be requested.

Last, the plan calls for ways to

encourage investigators to insure the survival and long-term viability of these expensive and important resources by deposition of viable animal models and animal model embryos in established repositories — such as the Jackson Laboratories — and other mouse/animal model repositories for all animals produced with the Society's funds. Sharing plans and project sun-

setting provisions should be required in funded proposals.

This is a compilation of animal and mouse models of facioscapulohumeral muscular dystrophy. As part of the short term objectives we've generated a partial list of researchers involved with the development of animal models.

### Mouse/Rat/Murine FSHD Models

- ◆ **Alexandra Belayew, Ph.D., and Hao Ding, Ph.D.**  
Group has worked with DUX4 transgenics and has experience with establishing mice expressing DUX4 in their skeletal muscles. Expression vector for DUX4 followed by an IRES and a DNA coding for GFP.
- ◆ **Robert Bloch, Ph.D., and Patrick Reed, Ph.D.**  
Group has published studies of the myd mouse. Studying technology called IVGT (in vivo gene transfer), also called in vivo electroporation to generate animal models for FSHD.
- ◆ **Darko Bosnakovski, D.V.M., Ph.D., and Michael Kyba, Ph.D.**  
Group has Tet-on DUX4 and other mouse models for FSHD.
- ◆ **Joel Chamberlain, Ph.D.**  
Group is focusing on reducing mRNA in muscle as a potential therapeutic and is in process of generating mouse models [FRG1/DUX4]
- ◆ **Yi-Wen Chen, D.V.M., Ph.D.**  
Group is running experiments using Tet-repressible muscle-specific PITX1 transgenic mouse models for FSHD.
- ◆ **Davide Gabellini, Ph.D.**  
Group is currently using transgenic mice over-expressing the 4q35 genes FRG1, FRG2 or ANT1 selectively in the skeletal muscle and other models.
- ◆ **Scott Q. Harper, Ph.D.**  
Group is experimenting with DUX4/AAV8 using TRE-FRG1 mice crossed with mCK-tTA mice to create Tet-on double transgenic mice.
- ◆ **Stephen D. Hauschka, Ph.D., and Joseph G. Marx, Ph.D.**  
Group is using medium- and high-expressing FRG1 mouse constructs from Tupler lab.

- ◆ **Jane E. Hewitt, Ph.D.**  
Group has done extensive mouse work. Published on the myd mouse and expert on comparative genomics. Generating mouse models with deletions of the mouse DUX array.
- ◆ **Peter Jones, Ph.D.**  
Group is conducting research on developmental biology of FSHD in mice.
- ◆ **Katherine Mathews, M.D.**  
Group has researched myd mouse, mouse models and drosophila models for FSHD.
- ◆ **Jeffrey B. Miller, Ph.D.**  
Group is studying models for FSHD biomarkers, exploring available and future animal models of FSHD, including mice over-expressing FRG1, PITX1 as well as over-expressors of DUX4 and mu-crystallin.
- ◆ **Rossella Tupler, M.D., Ph.D.**  
Group has FRG1 model from Cell paper that has three constructs: low-, medium-, and high-expressing FRG1. High expressing model has phenotype. Has mice that express FRG1 ubiquitously, express FRG1 specifically to muscle and mice with conditional knock-out of FRG1 as well as double and triple crosses of the 4q35 genes.
- ◆ **Silvère van der Maarel, Ph.D., and Tonnie Rijkers, Ph.D.**  
Group has various transgenics with different D4Z4 number copies and/or FSHD candidate genes. Has investigated the expression of the different transgenes in adult mice — concludes that these mice are bona fide animal models to study transgene gene regulation and function.
- ◆ **Kyoko Yokomori, Ph.D.**  
Group is working on transgenic mouse over-expressing PITX2.

### Frog/Tadpole/Xenopus FSHD Models

- ◆ **Peter Jones, Ph.D., and Meredith Hanel, Ph.D.**  
Group has animal model exhibiting FSHD using *Xenopus laevis* frogs (manuscript in preparation), supporting the assertion that FSHD pathology is due to the over-expression of FRG1.

### Fruit Fly/Drosophila FSHD Models

- ◆ **Peter Jones, Ph.D.**  
Group is conducting research on developmental biology in fruit fly.
- ◆ **William W. Mattox, Ph.D.**  
Group is focusing on RNA splicing defects and has model in which FRG1 expression causes degeneration of the flight muscle rendering the fly flightless.

### Worm/c. elegans FSHD Models

- ◆ **Rossella Tupler, M.D., Ph.D.**  
Tupler lab has generated FSHD models using *c. elegans*.
- ◆ **Peter Jones, Ph.D.**  
Group is conducting research on developmental biology of FSHD in worm.

The FSH Society has funded fellowships to develop mouse and animal models. The following researchers have been funded to develop models for FSHD: **Silvère van der Maarel, Tonnie Rijkers, Rossella Tupler, Davide Gabellini, Yi-Wen Chen, Scott Q. Harper, and Jane Hewitt**. Progress reports are on file with the FSH Society and we encourage researchers to contact these researchers to see what they are willing to share.

For more information on research plans compiled by the FSH Society and other entities working on FSHD please see:

<http://www.fshsociety.org/pages/resPlans.html>

## FSH Society research

The FSH Society has played a key role in driving the understanding of the underlying biology of FSHD, advocating, educating, coordinating, networking, planning, and organizing and funding research. We have awarded over \$2 million in research grants since 1997, supporting innovative ideas and recruiting and supporting scientists and clinical researchers.

When the Society started, there were only a handful of scientists and clinical researchers working on FSHD. It was not customary for institutions to fund salaries for FSHD research, and researchers were reluctant to enter the field. Early on the Society recognized the need to attract promising young researchers to the field and to support the relatively few established FSHD researchers, both financially and by fostering the exchange of information.

Our seed funding has paid off by fostering a community of more than 300 FSHD researchers worldwide who have successfully secured over \$40 million of government funding since 1999. The FSH Society research program is responsible for the rapid growth in publications over the last decade resulting in more than 200 peer-reviewed journal articles acknowledging the support of the FSH Society.

The FSH Society's research funding allows innovative and entrepreneurial research to develop and ultimately to be able to attract funding from large funding sources such as the NIH, MDA and AFM. The FSH Society helps move the field forward with critical seed funds to develop data and bring novel ideas to the next stage of development.

The Society's Scientific Advisory Board is critical to this work. Chaired by Professor David Housman of MIT, an internationally renowned geneticist, the SAB is composed of international experts whose knowledge of FSHD research ensures both that new research is complementary, not

duplicative, and that it holds promise to fill gaps in existing knowledge. The SAB provides strategy for FSHD research, recruits researchers, evaluates and approves research proposals, and monitors projects and research opportunities. Several SAB members are also advisors to the NIH, the MDA and the Association Francais contre les Myopathies (AFM - the French Muscular Dystrophy Association) on FSHD and other muscular dystrophies. SAB members are in close contact with NIH, MDA and AFM, which fosters collaboration and helps avoid funding overlap and duplication.

Despite these achievements, the precise and complete genetic, biological, chemical and physical mechanism of FSHD is still unknown and there are no effective treatments or cures. It is, therefore, critical to expand FSHD research through philanthropy. The methods for expanding research are threefold.

First, the pool of researchers must be increased. Expanding the pool of researchers requires donations to the FSH Society of both size and quantity to support increasing the number of fellows. It is also important to improve the experience of the current fellows by providing opportunities for fellows in U.S. laboratories to work for a time abroad, and for fellows based in foreign labs to work in the United States.

Second, additional resources, materials and tools must be acquired. There is a great need for financial help to

support programs to develop vital and identifiable research resources. For example, there has been a problem in obtaining and preserving muscle biopsies and cell lines from affected families in the United States; we need to help develop permanent repositories for these materials. Another area in need of funding is efforts to map and sequence allele- and repeat-specific segments of the genome for both conventional and non-conventional genes believed to be implicated in the development of FSHD. The SAB will identify needed resources, and the Society will develop specific proposals and submit them to agencies for funding.

Third, innovative approaches must be supported and given an opportunity to be tested. As resources are developed to maximize current avenues of investigation, we need to continue to appreciate the complexity and difficulties which have been the experience of FSHD research. Innovative approaches, capitalizing on the experience of the best researchers on FSHD, with contributions from other areas of biomedical investigation, are needed to keep the field intellectually challenged and stimulate additional research. One productive way to do this would be to hold an annual retreat of a small number of distinguished researchers from within and without FSHD research to discuss new approaches to investigating FSHD. This retreat would be separate from the FSH Society International Research Consortium Workshop because it would not reflect current experimental models and data, but rather would be more open-ended, with the goal being the development of new conceptual approaches.

**“We have awarded over \$2 million in research grants since 1997, supporting innovative ideas and recruiting and supporting scientists and clinical researchers.”**

## What is PubMed?

PubMed is a service of the U.S. National Library of Medicine that includes over 18 million citations from Medline and other life science journals for biomedical articles back to the 1950s. PubMed includes links to full text articles and other related resources. See: <http://www.ncbi.nlm.nih.gov/sites/entrez>



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### Participate in FSHD Clinical Trials, Research and Tissue Donation

Medical Professionals

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Genetics

Diagnostic Testing

Patient & Disease Registries

FAQs on Trials & Research

**FSHD Studies & Tissue Donation**

Please consider the valuable gift to research of tissue and organ donation while living and at death. Please sign up to be a tissue donor. Also, please be aware that valuable tissues such as muscle can be obtained from certain types of surgery such as scapular fixation.

## *Wanted in life and in death – FSHD tissue donation*

*As more tissue becomes available and more researchers dedicate their life's work to this disorder, new discoveries can lead to new treatments and, eventually, to a cure. It is only through the study of donated tissue that important answers will be found.*

The NIH NICHD Brain and Tissue Bank for Developmental Disorders at the University of Maryland in Baltimore is a tissue resource center established by the NIH NICHD to further research aimed at improving the understanding, care and treatment of developmental disorders.

The NICHD Brain and Tissue Bank serves as an intermediary between the research community and people who wish to donate tissue for research at their death. The bank safely stores the tissue until qualified researchers request the tissue for research which has been approved by their Institutional Review Board. Both people with developmental disorders and people free of disorders are encouraged to register and donate tissue. Often it is the comparison of the unaffected with the affected that unlocks the medical mystery of a disorder.

FSHD is the second most prevalent adult muscular dystrophy. FSHD affects men, women and children. The availability of tissue from donors with this disorder is especially limited. As more tissue becomes available and more researchers dedicate their life's work to this disorder, new discoveries can lead to new treatments and, eventually, to a cure. It is only through the study of donated tissue that important answers will be found.

If you are interested in becoming a registered donor, or if you have any questions or concerns regarding the donation process, please contact **Melissa Larkins-Davis**, Project Coordinator of the NICHD Brain and Tissue Bank, at (800) 847-1539 during normal business hours (9 a.m.-5 p.m. EST Monday through Friday). Ms. Larkins-Davis can be reached any time in an emergency.

Thank you for taking the time to consider tissue donation.

Please visit their website [www.btbank.org](http://www.btbank.org) or contact:

Melissa Larkins-Davis, Project Coordinator  
NICHD Brain and Tissue Bank  
for Developmental Disorders  
University of Maryland  
655 W. Baltimore St., 13-013 BRB  
Baltimore, MD 21201-1559

Toll free: (800) 847-1539  
Local: (410) 706-1755  
Fax: (410) 706-2128  
e-mail: [btbumab@umaryland.edu](mailto:btbumab@umaryland.edu)  
or [mlark001@umaryland.edu](mailto:mlark001@umaryland.edu)

## Sixteenth and Seventeenth FSH Society Marjorie Bronfman fellowships

The FSH Society is pleased to announce the commencement of two new exciting research projects and the recipients of the sixteenth and seventeenth FSH Society Marjorie Bronfman Post-doctoral Research Fellowship awards. The FSH Society is deeply indebted to the generosity of **Mrs. Marjorie Bronfman** for enabling FSHD research to flourish. This unique program, offered by the FSH Society and through the efforts of its peer review and SAB, has rapidly accelerated the understanding of FSHD.

**Grant:** FSHS-MB-016

**Researcher:** Darko Bosnakovski, D.V.M., Ph.D.

**Institution:** Perlingeiro lab (ND5.120)  
Center for Developmental Biology  
UT Southwestern Medical Center  
5323 Harry Hines Blvd.  
Dallas, TX 75390-9133

**Project Title:** "Molecular Analyses of DUX4 and Interaction with Myogenic Regulators in FSHD."

\$21,488 12/1/2007 – 11/30/2008 Year 1

**Goal:**

The prevailing model for FSHD is that deletion of D4Z4 repeats at 4q35.2 causes local modification of heterochromatin resulting in deregulation of nearby genes. Which gene(s) may be directly responsible for FSHD is controversial. In preliminary studies in which I used an inducible gene expression system to screen FSHD candidate genes, I found that only DUX4, a candidate located within each D4Z4 repeat, has structural and toxic effects at a variety of expression levels in C2C12 mouse myoblasts. Furthermore, C2C12 cells induced to express DUX4 showed striking gene expression similarities to myoblasts from FSHD patients. Both display deregulation of MyoD and oxidative stress related genes. In addition, I show that DUX4 protein is expressed in cultured myoblasts from FSHD patients. We hypothesize that DUX4 plays a role in the pathogenesis of FSHD.

Aim 1 is to understand the mechanism of action of DUX4.

Aim 2 is to test the hypothesis that DUX4 interferes with the function of

myogenic regulators

The goals of this proposal are to understand the mechanism of the toxicity of DUX4 and to explore possible therapeutic interventions. Because DUX4 is extremely toxic to myoblasts, a conditional gene expression system needs to be used to study its effects (Aim 1). In the preliminary study, by using a doxycycline-inducible DUX4 expression system, I found that several crucial myogenic genes (MyoD, Myf5) are targets of DUX4 (Aim 1). I propose to study the underlying mechanism of the toxicity of DUX4 in myoblasts as well as in other cell types. I postulate that appropriate intervention of the deregulated genes (by over-expression or RNAi knockdown) in DUX4 affected cells should rescue the toxic phenotype (Aim 1). Furthermore I will test the hypothesis that DUX4 interferes with the function of myogenic regulators by competitive binding to the same target sites (Aim 2). In support of this, over-expression of Pax3, a crucial gene in myogenesis and whose homeodomain is most similar to DUX4, renders C2C12 cells resistant to DUX4-mediated toxicity. The aims of this proposed study target the most crucial and unknown aspects (both mechanism and therapy) of FSHD.

**Significance:**

The pathogenic mechanism of FSHD is controversial and largely unknown, which is the major hurdle in developing a rational therapy. Therefore it is extremely important to find the gene(s) involved in FSHD, and to understand their action, from which therapeutic strategies will arise. My proposed study is designed to answer these crucial questions. Using uniform gain of function approach, I will look closely on the effects of the FSHD candidate gene, DUX4 on myoblast phenotype, analyze the underlying mechanism in detail (Aim 1) and identify potential targets in the cascade of pathogenesis (Aim 2). Thus this study is directly relevant to progress towards a therapy for FSHD.

**Grant:** FSHS-MB-017

**Researcher:** Paola Picozzi, Ph.D.

**Institution:** Stem Cell Research Institute  
Milano, Italy

**Project Title:** "Functional characterization of D4Z4 in FSHD."

\$35,000 3/1/2008 – 2/28/2009 Year 1

**Goal:**

The long-term goal of our research is to identify and characterize the molecular pathways that become subverted in FSHD in order to develop therapeutic strategies. FSHD, the third most common myopathy, is an autosomal dominant neuromuscular disorder characterized by progressive weakness and atrophy affecting selective skeletal muscles. Unlike the majority of genetic diseases, FSHD is not caused by a classical mutation within a protein-coding gene but rather involves a complex cascade of epigenetic events following contraction of a 3.3 kb subtelomeric non-coding repeat (D4Z4) located on chromosome 4q35.

At present no treatment is available for FSHD. This has been also hindered by an incomplete knowledge of the disease pathogenesis and, until recently, by the lack of an animal model. Based upon recent experimental results, it has been proposed that deletion of D4Z4 leads to the inappropriate transcriptional de-repression of the 4q35 gene FRG1 resulting in disease. Understanding how deletion of D4Z4 causes up-regulation of 4q35 genes is important to develop therapeutic approaches aimed at preventing transcriptional de-regulation in FSHD.

**Our specific aims are:**

1. To characterize protein/DNA interactions at D4Z4. It has been shown that a transcriptional repressor complex composed of YY1, HMGB2 and nucleolin is associated with D4Z4 (Gabellini et al, 2002). In mammalian cells, transcriptional repression is the result of the cooperation between sequence specific repressors and general co-repressors such as histone deacetylases (HDACs) and DNA methylases. Notably, the activity of YY1 is regulated at the posttranslational level, possibly through interactions with other proteins. YY1 represses transcription by interacting with HDAC-1

## Marjorie Bronfman fellowships

and 2, and this interaction is regulated by HDAC phosphorylation. (Galasinski et al., 2002). Collectively, these observations suggest that other proteins may be associated with and regulate the activity of the DRC.

Our second aim is to elucidate the mechanism underlying control of gene expression at 4q35.

Our preliminary results suggest that non-coding RNAs and microRNAs generated by D4Z4 regulate chromatin structure and 4q35 genes expression. Our

analysis will generate novel insights into the biological role of repetitive DNA sequences in higher eukaryotes. The results of these studies will be very useful to identify effective therapeutic approaches for FSHD.

## Ongoing FSH Society Marjorie Bronfman fellowships

### Grant: FSHS-MB-010

**Researcher:** Richard Lemmers, M.Sc., Ph.D.

**Institution:** Leiden University Medical Center  
Department of Human Genetics  
Leiden, The Netherlands

**Project Title:** "Refinement of the FSHD critical region on 4qA chromosomes."

### Grant: FSHS-MB-013

**Researcher:** Melanie Ehrlich, Ph.D.

**Institution:** Tulane Medical School  
New Orleans, LA

**Project Title:** "Finding the 4q35 FSHD Gene."

### Grant: FSHS-MB-014

**Researcher:** Patrick Reed, Ph.D.

**Institution:** Department of Physiology  
University of Maryland School of Medicine  
Baltimore, MD

**Project Title:** "Analysis of Changes in the Proteome in FSHD."

### Grant: FSHS-MB-015

**Researcher:** Yvonne Meijer-Krom, Ph.D.

**Institution:** Leiden University Medical Center (LUMC)  
Department of Human Genetics  
Leiden, The Netherlands

**Project Title:** "Towards the Discovery of Early Developmental Defects in FSHD."

### Grant: FSHS-MB-016, see page 20

**Researcher:** Darko Bosnakovski, D.V.M., Ph.D.

**Institution:** Center for Developmental Biology  
UT Southwestern Medical Center  
Dallas, TX

**Project Title:** "Molecular Analyses of DUX4 and Interaction with Myogenic Regulators in FSHD."

### Grant: FSHS-MB-017, see page 20

**Researcher:** Paola Picozzi, Ph.D.

**Institution:** Stem Cell Research Institute  
Milano, Italy

**Project Title:** "Functional characterization of D4Z4 in FSHD."

## 2008 Delta Railroad Construction research fellowship grants established

The FSH Society Delta Railroad Construction Company fellowship program continues to help FSHD research efforts by awarding research grants that provide needed expansion of current work and innovative approaches in FSHD studies. The FSH Society is indebted to the Delta Railroad Construction Company of Ashtabula, Ohio, **Larry and Ida Laurello**, and their family for this groundbreaking effort on behalf of the FSHD community. Initiated in 1998, the Delta Railroad Research Fellowship Grants are yielding tremendous insights in new and novel areas of FSHD research and treatment. We hope this collaboration will continue and the members of the Society will consider matching this \$35,000 gift annually.

### FSH Society Delta Railroad Construction fellowship

#### Grant: FSHS-DR-008

**Researcher:** Jane Hewitt, Ph.D.

**Institution:** Institute of Genetics  
Queen's Medical Centre  
University of Nottingham  
Nottingham, UK

**Project Title:** "Development of Genomic Resources for Functional Studies of the Mouse DUX4 Array in Vivo."

## How is FSHD research at the NIH doing in 2008, seven years after the MD-CARE Act 2001 was passed?

We applaud **Dr. Story Landis**, Director, NINDS, and current Chair of the MDCC; **Dr. Stephen I. Katz**, Director, NIAMS and past-Chairman of the MDCC; **Dr. John Porter**, Program Director NINDS, and Executive Secretary of the MDCC; and **Dr. Glen Nuckolls**, Program Director, NIAMS, for their extraordinary comprehension, insight, accuracy and speed with which the NIH Action Plan for Muscular Dystrophy was researched, compiled, written and approved. The NIH is making significant investments to understand muscular dystrophy research needs and has made excellent choices in recruiting program staff with the ability to understand the extremely complex nature of each of the muscular dystrophies.

Between fiscal year 2006 and 2007, NIH overall funding for muscular dystrophy increased from \$39,913,000 to \$47,179,000, an 18-percent increase. Figures from the NIH Appropriations History for Muscular Dystrophy show that from the inception of the MD-CARE Act 2001 funding has doubled for muscular dystrophy.

Between fiscal year 2006 and 2007, NIH funding for FSHD increased from \$1,732,655 to \$4,108,555 a 137.1% increase. In 1988, a year after we started organizing the FSH Society, \$4.3 million was the overall NIH spending for all of the types of muscular dystrophy!

In fiscal 2007, FSHD was 8.7% of the total muscular dystrophy funding (\$4.109M/\$47.179M).

Between 2006 and 2007, the NINDS became the lead institute for funding in MD. Historically, the NIAMS, in its mission statement, has been primarily responsible for and has been the lead institute for muscle disease research. The CSR routes the majority of MD grant applications to NIAMS based on its mission. In fiscal year 2007, NIAMS was the second largest contributor, followed by the NICHD as third, and the NHLBI as fourth. It should be troubling that muscular dystrophy spending has declined significantly in several key institutes that could bring tremendous impact to these devastating diseases.

**NINDS:** In FY 2007, NINDS spent \$2,612,994 on FSHD and \$19,247,940 on MD. Forty-seven projects, including Well-

stone CRC components, were funded. FSHD was 13.6 percent of NINDS MD funding. NINDS funding for FSHD research was limited to three research grants, one research fellowship, one research contract, one-quarter of a Wellstone MDCRC and one-half of a TRC research grant for a total of six projects. NINDS funding for FSHD went up by \$1,191,398 or 83.8%. Total funding for MD by NINDS increased over the year by \$6,551,266 or 51.6%, overall.

**NIAMS:** In FY 2007, NIAMS spent \$1,495,561 on FSHD and \$17,734,317 on MD. MD research comprises 89 projects, including Wellstone MDCRC components. FSHD was 8.4 percent of NIAMS MD funding. NIAMS funding for FSHD research was limited to four research grants, one research contract, and 2% of a TRC for a total of six projects. NIAMS funding for FSHD went up by \$1,184,502

or 381%. Total funding for MD by NIAMS increased over the year by \$1,158,000 or 7%, overall.

**NICHD:** In FY 2007, NICHD spent \$0 on FSHD and \$4,591,826 on all MD. A total of 17 projects, including three Wellstone MDCRC centers were funded. Research for FSHD was zero percent of the budget for MD research at NICHD: total funding was \$0. Total funding for MD research by NICHD decreased over the previous year by \$225,756 or 4.7%, overall.

**NHLBI:** In FY 2007, NHLBI spent \$0 on FSHD and \$2.458 million on MD research in general. FSHD was zero percent of NHLBI FY 2007 MD funding. This should be of grave concern as respiratory insufficiency and failure is becoming increasingly recognized as a cause of poor quality of life and, even more significantly, of death in FSHD.

### NIH appropriations history

Source: NIH/OD Budget Office & NIH OCPL (Dollars in millions)

| Fiscal Year | NIH Overall Dollars | MD Research Dollars | FSHD Research Dollars | FSHD % of MD |
|-------------|---------------------|---------------------|-----------------------|--------------|
| 2000        | \$17,821            | \$12.6              | \$0.4                 | 3%           |
| 2001        | \$20,458            | \$21.0              | \$0.5                 | 2%           |
| 2002        | \$23,296            | \$27.6              | \$1.3                 | 5%           |
| 2003        | \$27,067            | \$39.1              | \$1.5                 | 4%           |
| 2004        | \$27,887            | \$38.7              | \$2.2                 | 6%           |
| 2005        | \$28,494            | \$39.5              | \$2.0                 | 5%           |
| 2006        | \$28,587            | \$39.91             | \$1.7                 | 4%           |
| 2007        | \$28,899            | \$47.18             | \$4.11                | 8.7%         |
| 2008        | \$29,230 (Est)      | \$47.22 (Est)       | -                     | -            |

FSHD is the second most prevalent adult muscular dystrophy after DM. We are very concerned about the wide disparity in funding between the most widely recognized pediatric DMD and the entire group of the other eight types of MD. DMD has exclusive funding from the CDC, DoD and more than half (>50%) of NIH funding for MD. This is astounding considering FSHD and DM are each individually more prevalent than DMD and each received 5% and 15% respectively of total muscular dystrophy dollars as last reported by the NIH to Congress!

### NIH MD funding by institute FY 2007

Source: NIH/OD Budget Office (Dollars in millions)

| Participating ICs  | FY 2006 Actual | FY 2007 Actual | Change |
|--------------------|----------------|----------------|--------|
| NINDS              | 12.697         | 19.347         | +51.6% |
| NIAMS              | 16.576         | 17.734         | +7%    |
| NICHD              | 4.818          | 4.591          | -4.7%  |
| NHLBI              | 2.270          | 2.458          | +8.3%  |
| NIA                | 1.865          | 1.882          | +0.9%  |
| NCRR               | 0.770          | 0.679          | -11.8% |
| NCI                | 0.495          | 0.426          | -13.9% |
| NHGRI              | 0.391          | 0.161          | -58.8% |
| NINR               | 0.031          | -              | -      |
| NEI, NIMH, FIC, OD | 0.0            | 0.0            | 0%     |

## NIH NINDS FSHD research

*Special Emphasis Areas by Budget Category/Grant Number*  
**FSHD projects: 7 awards total for \$2,612,994**

### 2 RESEARCH CENTERS

1-U54-NS058572-01 **HUGH LEE SWEENEY**  
 Development of novel small molecules for delaying the progression of muscular dystrophy  
 \$1,317,078 Annually  
 [50% Costs Assigned to FSHD of \$2,634,156 total]

5-U54-NS048843-05 **RICHARD MOXLEY**  
 Muscular Dystrophy Cooperative Research Center  
 \$354,966 Annually 100% Costs Assigned

### 3 RESEARCH PROJECTS

5-R01-NS048859-04 **MELANIE EHRlich**  
 FSHD: Chromatin Structure, Looping, & Expression  
 \$293,050 Annually 100% Costs Assigned

5-R01-NS047584-05 **ROSSELLA TUPLER**  
 Investigating the Molecular Basis of FSHD  
 \$348,635 Annually 100% Costs Assigned

1-R21-NS059399-01 **WILLIAM MATTOX**  
 Genetic analysis of FRG1 function in Drosophila  
 \$168,438 Annually 100% Costs Assigned

### 1 RESEARCH CONTRACT

1-N01-AR-52274-001 **RICHARD MOXLEY**  
 National Registry for Myotonic Dystrophy & Facioscapulohumeral Muscular Dystrophy  
 \$100,000 Annually 100% Costs Assigned

### 1 FELLOWSHIP TRAINING AWARD

1-F31-NS058224-01A1 **AMANDA HAIDET**  
 Delivery of a Myostatin Inhibitor by AAV Gene Therapy for Muscular Dystrophy  
 \$30,827 Annually 100% Costs Assigned

## NIH NIAMS FSHD research

*Special Emphasis Areas by Budget Category/Grant Number*  
**FSHD projects: 6 awards total for \$1,495,561**

### 4 RESEARCH PROJECTS

1-R01-AR-52027-01-A2 **YI-WEN CHEN**  
 Molecular Pathophysiology of FSHD muscular dystrophy via genome-wide approach  
 \$356,900 Annually 100% Costs Assigned

1-R01-AR-55877-01 **PETER L. JONES**  
 Molecular mechanism of FSHD pathology  
 \$258,431 Annually 100% Costs Assigned

1-R01-AR-56129-01-A2 **ROSSELLA G. TUPLER**  
 An Animal model to develop therapeutic strategies for FSHD  
 \$355,180 Annually 100% Costs Assigned

1-R21-AR-55876-01 **SILVÈRE M. VAN DER MAAREL**  
 FSHD as a Disorder of Impaired RNA Biogenesis  
 \$116,100 Annually 100% Costs Assigned

### 1 RESEARCH CENTER

1-U54-NS-58572-01 **HUGH LEE SWEENEY**  
 Development of novel small molecules for delaying the progression of muscular dystrophy  
 \$60,000 Annually  
 [20% Costs Assigned to FSHD of \$300,000 total]

### 1 RESEARCH CONTRACT

1-N01-AR-52274-001 **RICHARD MOXLEY**  
 National Registry for Myotonic Dystrophy & Facioscapulohumeral Muscular Dystrophy  
 \$348,950 Annually 100% Costs Assigned

## 1st & 2nd FSH Society Landsman Charitable Trust fellowship

The FSH Society is pleased to announce the commencement of two new exciting research projects and the recipients of the first and second FSH Society Landsman Charitable Trust Fellowship. The FSH Society is deeply indebted to the generosity of Mr. **Emmanuel Landsman** and family and the Landsman Charitable Trust for enabling novel, innovative and high-risk FSHD research to develop.

**Grant:** FSHS-LCT-001

**Researcher:** Meredith Hanel, Ph.D.

**Institution:** Department of Cell and Developmental Biology University of Illinois at Urbana-Champaign, Urbana, IL

**Project Title:** "An *in vivo* *Xenopus* System for Studying D4Z4 Mediated Chromatin and Gene Expression."

\$30,000 03/01/2008 – 2/28/2009 Year 1

### Goal:

[Provided by applicant]: We have created a novel animal model exhibiting an FSHD phenotype using *Xenopus laevis* frogs, supporting the assertion that FSHD pathology is due to the over-expression of specific genes. This provides two therapeutic targets; 1) the mis-regulation of the gene by the mutated D4Z4 array and 2) the activity of the over-expressed gene product. This proposal addresses the former, seeking to understand the regulation mediated by the D4Z4 array and 4q sub-

telomere by systematically recapitulating the human FSHD region of chromosome 4q35 in the frog. Introducing these human sequences, and particularly the D4Z4 repeats, under controlled circumstances will allow us to determine the regulatory requirements lacking in the FSHD deletion

*Xenopus* transgenesis enables monitoring integrated genomic copies of engineered sequences in a developing animal in a high through-put method. The telomeric nature of the environment of the D4Z4 repeats will even be recapitulated in our system as we have recently engineered telomeres in *Xenopus* (Wuebbles and Jones, 2007). The

*continued on page 24*

## *Landsman Charitable Trust fellowship,* continued from page 23

*Xenopus* genome contains many of the same epigenetic characteristics as humans making potential findings applicable to humans. The goal of this proposal is to determine the cis and trans-regulatory requirements for normal gene repression in the 4q35 region and how this is disrupted in FSHD.

### **Our specific aims are:**

**Aim 1:** The impact of D4Z4 repeat number on the expression of FRG1 and neighbouring genes. D4Z4 repeats will be placed in cis with human and *Xenopus* FRG1 promoters driving the reporter GFP. Cis effects on gene expression will be visualized in a developing vertebrate and correlated with number of repeats. Subsequent analysis of DNA methylation and chromatin structure will determine the nature of repression or activation. Experiments will test the major hypotheses in the field that (1) D4Z4 repeat mediated gene repression is due to a local repressive effect of heterochromatin spreading, (2) A repressor bound to D4Z4 repeats associates with promoters, (3) An activator associated with the D4Z4 repeats activates transcription.

**Aim 2:** Regulatory roles of the sub-telomere region. The repetitive nature of CpG rich D4Z4 repeats and their sub-telomeric location suggest a structural role or maintenance of chromatin conformation. D4Z4 repeats have been proposed as an insulator from or propagator of telomere position effects. Since FSHD is strictly associated with the 4qA allele (containing a distal Beta satellite repeat), but not the 4qB allele (without beta satellites) telomeric transgenes containing D4Z4 arrays between the telomere and a reporter gene will test the influence of Beta-satellite DNA on gene expression as well as the insulator activity of the D4Z4. The number of D4Z4 repeats required to overcome telomeric position effect and the effect of the Beta-satellite DNA will be assayed. To test whether D4Z4 propagate heterochromatin we will assess the ability of D4Z4 repeats to override the effect of the Beta-globin HS4 insulators and result in gene repression.

**Aim 3:** D4Z4 repeats as transcriptional regulators with genome wide effects. If D4Z4 repeats regulate genes in trans, adding D4Z4 repeats to the *Xenopus laevis* genome may sequester proteins that bind D4Z4, and may ultimately manifest as a developmental phenotype. Since *Xenopus* development occurs externally, embryos at any stage of development are easily visualized and alterations in candidate myogenic markers and vasculature will be assayed.

*Xenopus* provides a unique opportunity to observe developmental stage and tissue specific differences in epigenetic and gene regulation. Combined with the intense research by numerous groups into pharmaceuticals targeting epigenetic regulators, elucidating the factors involved in gene regulation by the 4q35 region may make these treatments applicable to FSHD.

**Grant:** FSHS-LCT-002

**Researcher:** Scott Q. Harper, Ph.D.

**Institution:** Center for Gene Therapy  
Columbus Children's Research  
Institute and Department of Pediatrics  
The Ohio State University  
Columbus, OH

**Project Title:** "*In Vivo Investigation of DUX4 As A Candidate FSHD Gene*"  
\$10,000 03/1/2008 – 2/28/2009 Year 1

### **Goal:**

[Provided by applicant]: FSHD is an autosomal dominant disorder characterized by progressive and asymmetric weakness of facial, shoulder, and limb muscles. It is the third most common muscular dystrophy and no effective treatment exists. FSHD is caused by contraction of D4Z4 repeats on human chromosome 4q35. Though the causative mutation has been known for nearly 15 years, the underlying pathogenic mechanism for the disease remains unresolved. Current models suggest that normal chromatin structure at 4q35 is altered by pathogenic D4Z4 arrays (1-10 repeats) leading to aberrant up-regulation of nearby genes. To date, FRG1 is arguably the best candidate FSHD candidate gene; FRG1

over-expression in mice recapitulates some dystrophic changes associated with FSHD but the gene is not uniformly elevated in all patient biopsies. Thus, its uncertain role in FSHD pathogenesis justifies the search for other candidates. Recent evidence suggests DUX4 may play a role in FSHD development. DUX4 is the translated product of a transcript arising from D4Z4 which induces apoptosis of cultured myoblasts upon over-expression. However, the in vivo effects of DUX4 over-expression in muscle are unknown. The goal of this project is to determine whether viral vector-mediated DUX4 over-expression in mouse muscle causes histological changes associated with FSHD. This work will be an important step toward understanding the pathobiology of FSHD, which is necessary for ultimately developing effective therapies.

### **Specific aim:**

To investigate the in vivo effects of DUX4 over-expression in muscle. DUX4 is a candidate FSHD gene due to its chromosomal location (as a product of D4Z4 repeats) and because its over-expression induces apoptosis in cultured myoblasts. In vivo DUX4 over-expression in muscle is a logical next step toward investigating its potential role in FSHD pathogenesis. Adeno-associated viral (AAV) vectors are ideally suited for in vivo muscle gene delivery because they efficiently transduce muscle at high levels, produce no adverse effects on muscle histology/physiology, and allow cheap and rapid analysis compared to transgenic mouse methods. Here, we will use AAV serotype 8 (AAV8) vectors to deliver DUX4 or control genes to muscles preferentially or minimally affected in FSHD. We hypothesize that DUX4 over-expression will induce histological changes associated with muscular dystrophy in transduced animals. This study will be an important first step toward understanding the potential role of DUX4 in FSHD pathogenesis and may have future implications for developing FSHD therapies.