

## FSH Society welcomes Nancy Van Zant, new executive director

By Daniel Paul Perez

I am pleased to announce that we have appointed Nancy Van Zant as our new executive director. Nancy holds a BA from Earlham College, Richmond, IN; and an M.S., Library Science, from the University of Illinois. She lives with her husband, Kent, in Brookline, MA, on the edge of Boston. She is a regular hiker in the Rockies in the summer and a cross-country skier in the winter.



Nancy Van Zant

Nancy started with the FSH Society on June 11th. She comes to the Society from a career of leading fundraising at academic medical centers including the National Jewish Center for Medicine and Research (Denver), the Kennedy Krieger Institute (Baltimore), and Beth Israel Deaconess Medical Center (Boston). She has raised funds for many initiatives in biomedical research as well as capital projects, clinical programs, endowed chairs and fellowships.

During her early weeks and months at the Society, Nancy has focused her attention on organizing a more disciplined development program. Specifically, she is looking at our processes and systems, our case for support and our constituency. At our July board of directors meeting, Nancy presented a draft plan for growth in philanthropy.

During the course of this FSH Society survey, Nancy has spoken with many of you about your experience with the Society and your desire to see us grow to a new level of achievement and service. I'm sure she will continue to reach out to you to learn more. In the meantime, if you want to speak with her directly, please do so. Nancy works in the Society's new office in Watertown, MA:

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## Current trends in FSHD research

By Sara Winokur, Ph.D.

The pace of FSHD research has accelerated significantly over the past year. Several key findings have shed light on the molecular mechanism of the disease. Many dedicated laboratories across the globe continue to collaborate with the shared goal of understanding and eventually treating FSHD. In this review, I present an overview of the recent progress in FSHD research and our current understanding of the molecular basis of the disease.

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## Society compiles strategic research plan

The FSH Society SAB assembled key researchers, funding agencies and industry to formulate a detailed plan to rapidly accelerate FSHD research. The **Tactical and Strategic Research Plan** is the result of the hard work and collaboration of those involved. Please see article on page 41 for the details of this important step forward for the Society.

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## From the President & CEO

By Daniel Paul Perez

We have been making steady progress for those affected with facioscapulohumeral muscular dystrophy (FSHD). I am pleased to present this issue of the *FSH Watch* to our members and those interested and involved with FSHD. The FSH Society continues to make remarkable progress on a budget that is 1/500 the size of the next largest funding agency working on muscular dystrophy.

This newsletter describes the FSH

Society, who we are, and our organization and mission. It has educational information that you need to know about living with FSHD. It details the incredible inroads the Society has made through research and the Society's research programs in the last nine years in understanding FSHD. It calls for the scientific resources that are

needed to continue making progress and lets you how you can provide research materials and resources.

We proudly display the faces of patients with FSHD and detail how the Society makes progress by building community and support. This edition also describes ways that you and your friends and family can contribute financially to keep the Society's office open and running.

Major developments are underway with new staff, new offices and new board members. Nancy Van Zant, our new executive director, brings substantial and unparalleled experience in developing and running non-profits — the FSHD community is exceptionally fortunate to have her on our side. Our former executive director, Carol A. Perez has joined the executive board of directors and will continue to work one-on-one with patients and outreach in a voluntary capacity. Nancy will handle the executive and development functions, I will have more time to devote

to research programs and issues and Carol will serve as a resource for patients.

The Society has subleased space in a world-class research facility called Boston Biomedical Research Institute and we are engaged in active day-to-day discussions on accelerating research. See article on page 7.

Since our last newsletter we have lost more than our share of dear friends to FSHD, including Stephen J. Jacobsen, former chairman of the board and co-founder

of the Society. I am pleased to say the Society remains in good and secure hands with its new chairman, William R. Lewis, Sr., M.D., who is a renowned neurosurgeon.

The Society's Scientific Advisory Board (SAB) and a team of dedicated FSHD researchers under the skilled direction of SAB

chair, Prof. David Housman of M.I.T., have compiled short- and long-range research plans to help solve FSHD. Our fellowship program and fellows are unmatched by any in the world and our seed grants are yielding rapid growth and funding for FSHD research. The Society's peer-reviewed grants and respect for scientific discipline are the keys to our success. As you read the research update you will see how rapidly we are moving towards a solution to FSHD. The Society has its finger on the pulse of the current research and direction of future research.

The FSH Society is about "possible things" and having a vision and compass to achieve what others may consider "impossible things." Missing are the funds to run and execute the research programs needed. We need money, we need bequests, we need generous gifts to help fund promising young scientists and ideas, and to help implement the Society's research plan and infrastructure. I ask you to take just a moment of your time after

*continued on page 5*



(L-R): Dr. Bill Lewis Sr., FSH Society Chairman of the Board & SAB Member, Prof. David Housman, Chairman of the Society SAB, Charles Perez, Daniel Paul Perez, President & CEO

## The purpose of the FSH Society

The FSH Society is a world leader in combating muscular dystrophy. It has provided nearly two million dollars in seed grants to pioneering FSHD research and education worldwide and created an international collaborative network of patients and researchers. The Society relies entirely on private grants, donations and grass roots philanthropy. Its purpose is to increase public awareness, understanding and education, and to foster research on FSHD, the second most prevalent muscular dystrophy in adults and third most prevalent muscular dystrophy overall.

The FSH Society has brought together — through education, patient network meetings, support groups, peer-support, and advocacy — more than 3,600 FSHD-affected families committed to working cooperatively. Through the FSH Society, its electronic bulletin board, chat room and quarterly newsletter, the *FSH Watch*, FSHD patients have found ways to be useful to medical and clinical researchers working on their disease. The support patients receive from one another through sharing their common experiences is invaluable and immeasurable.

The FSH Society offers basic research grants and research and postdoctoral fellowships to support research on the molecular genetics and cause of FSHD on an on-going and ad-hoc basis. The SAB diligently carries out its mission of providing strategies for FSHD research, recruiting and attracting qualified researchers, selecting and evaluating research proposals, and monitoring ongoing projects and research opportunities.

Since 1997, the FSH Society has funded over \$1.75 million dollars in \$30,000- to \$45,000-a-year grant fellowships to more than two dozen researchers, leading to well over a hundred publications acknowledging Society support in top-tier scientific journals. The Society also organizes an annual symposium for researchers

worldwide that yields immeasurable gains in our understanding of FSHD.

The FSH Society acts as a clearing-house for information on FSHD and on potential drugs and devices designed to alleviate the effects of the disease. It fosters

communication among FSHD patients, their families and caregivers, charitable organizations, government agencies, industry, scientific researchers, and academic institutions.

### A guide to acronyms

In the interest of readability and space, we would like to offer a list of acronyms used in this newsletter.

AFM	Association Française Contre les Myopathies
AFO	Ankle Foot Orthotic
AHRQ	Agency for Health Care Research and Quality
CDCP	Centers for Disease Control and Prevention
BMD	Becker Muscular Dystrophy
CFC	Combined Federal Campaign
CIRM	California Institute for Regenerative Medicine
CRISP	NIH Computer Retrieval of Information on Scientific Projects
DHHS	Department of Health and Human Services
DM	Myotonic Muscular Dystrophy
DMD	Duchenne Muscular Dystrophy
EDMD	Emery-Dreifuss MD
FDA	Food and Drug Administration
FSHD	Facioscapulohumeral Muscular Dystrophy
GDF	Growth and Differentiation Factors
IFSHD	Infantile Facioscapulohumeral Muscular Dystrophy
INSERM	French National Institute for Health and Medical Research
LGMD	Limb Girdle Muscular Dystrophy
MD	Muscular Dystrophy
MD-CARE	Muscular Dystrophy Community Assistance, Research and Education Act of 2001
MDA-USA	Muscular Dystrophy Association United States of America
MDCC	Muscular Dystrophy Coordinating Committee
MDCRC	Muscular Dystrophy Cooperative Research Centers
MYO-29	Myostatin-inhibitor
NIAMS	DHHS NIH National Institute of Arthritis & Musculoskeletal & Skin Diseases
NICHD	DHHS NIH 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
OPMD	Oculopharyngeal MD
PGD IVF	Pre-implantation Genetic Diagnosis In Vitro Fertilization
PITX1	Paired-like homeodomain transcription factor 1
P.T.	Physical Therapy
R01	NIH Basic research track grants
R21	NIH High risk research track grants
RFA	Request for Applications
SAB	FSH Society Scientific Advisory Board
SAMHSA	Substance Abuse and Mental Health Services

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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.

## FSH SOCIETY WELCOMES NEW BOARD MEMBERS

### *New FSH Society board members*

#### **JAMES A. CHIN, SR.**

**J**ames A. Chin Sr. is a native New Yorker who graduated from the Baruch School of the City College of New York in 1970 with a BBA in Economics and Marketing. After a successful seventeen year career in broadcasting sales, predominantly with the CBS television stations, Jim changed directions and made his hobby his new career. In 1987, he joined Shearson Lehman Bros. as a financial consultant. In 1992, he moved his practice to Merrill Lynch. He is currently the Senior Managing Partner of the Chin-Meador Team at Merrill Lynch in White Plains, New York.



*James A. Chin, Sr.*

He is active in his church and has been a former volunteer firefighter, baseball coach, umpire and regional director for the Fresh Air Fund. He enjoys financial lecturing, golf and traveling with his wife, Barbara.

Jim joins the board as a director and chair of the FSH Society Development Committee.

#### **JOANN FORANCE**

**J**oAnn is a graduate of Kent State University and has experienced a well-rounded career life. Her most important jobs were mother, school teacher, accountant, and later, as a hobby, selling real estate in affluent suburbs of Boston. Though successful in all of these jobs, her best accomplishments were starting and/or building multi-million dollar companies. As original founder, manager and owner she propelled two businesses into very successful concerns. Later, she married a man from Hudson, MA who owned a local ambulance company and over the next five years helped that company double in size and profits.



*JoAnn Forance*

JoAnn is a creative and innovative

thinker who has excellent planning and organizational skills and the ability to execute. She understands people and is able to work with all kinds of individuals to motivate and persuade them to contribute one hundred per cent. She joins the Society knowing that it has accelerated research and is getting very close to finding a cure and welcomes the opportunity to serve in any way she can.

Today, in retirement, she lives in Fort Myers, Florida. She finds herself very busy and on top of current events while staying involved in many diverse activities and ventures.

JoAnn joins the board as a director and is a member of the FSH Society Development Committee.



#### **BILL HERZBERG, M.D.**

**D**r. William Herzberg joins the board of the FSH Society to be of service to patients with FSHD and the organization. Bill has personal and professional connections with FSHD. He fervently hopes that there will be something available in the near term for those suffering from FSHD. Bill wishes to be part of the process that will bring about a treatment and someday a cure. "At 17, I was most impressed by a neurologist who had a strong interest in FSHD," he said.



*Bill Herzberg*

Bill is a graduate of Harvard College and pursued a medical degree at Stanford Medical School, a neurology residency, then did a neuromuscular fellowship with Dr. Robert G. Miller. He is a clinical neurologist with expertise in clinical neurophysiology. He has staffed MDA clinics in San Francisco and Portland where he has met many patients with FSHD and other neuromuscular disorders. It is his sincere intention to do more than label the next FSHD patient who comes to his office; he wants to be able to treat him or her.

Bill joins the board as a director and is a member of the FSH Society Development Committee.

#### **CHRISTOPHER P. STENMON, C.P.A., M.S.T.**

**C**hris Stenmon was born and raised in Quincy, MA and resides there with his wife, Ellen, and daughter Lauren. Chris is a Certified Public Accountant for O'Connor & Drew, P.C. and has been working for the firm for ten years. He graduated from Boston College with a Bachelor of Science in management



*Chris Stenmon*

and graduated from Northeastern University with a Masters of Science in Taxation.

Chris was diagnosed with FSH muscular dystrophy in 1989 at age sixteen. He discovered he had muscle weakness while wrestling at Boston College High School. Chris has been involved with the FSH Society since his diagnosis.

Chris has organized an annual fundraiser for the FSH Society for several years. This year Chris and Ellen will be holding the "Ninth Annual End of Tax Season Bar Crawl." Each year they design and sell t-shirts for the event and hold a raffle with prizes donated by friends, family and local businesses.

The night consists of visiting local restaurants and bars in and around Quincy Center and meeting up with friends and former co-workers to socialize. Approximately 100-150 people attend the event during the course of the evening, therefore, all of the bars and restaurants also make donations. This year's event raised approximately \$8,500. Next year the goal is to hit the \$10,000 mark. Chris met his wife Ellen at this event four years ago, so it has played a very important role in his and his family's life.

Chris was recently appointed to the board of directors of the FSH Society where he hopes to use his past experiences in financial management and fundraising to benefit the long-term goals of the Society.

Chris joins the board as a director and is a member of the FSH Society Development and Finance Committees.

## FSH SOCIETY WELCOMES NEW STAFF

### Goodbye & hello to Carol Perez

Carol A. Perez, M.Ed., C.R.C., experienced administrator and counselor in rehabilitation, has served as Coordinator and Executive Director of the FSH Society since 1992. Initiating the New England FSHD Support Group in 1989, her dual role as both service provider and consumer served to fuel her activism to advocate for the FSHD community in all arenas.



Carol A. Perez with friends and donors, (L-R) Eileen Luttmann, Bill Luttmann & Cyrina Wolf

Carol officially submitted her resignation as executive director effective May 31, 2007. In her note to the Board she wrote:

"I want you to know how much pleasure it has been to work with all of you for the last fifteen years. My deepest gratitude goes to you for making this Society grow and letting me be part of that process. I have had an exciting fifteen years full of highs and lows as we make progress towards achieving our mission. Thank you.

"It is also my unique pleasure to see the new executive director, Nancy Van Zant, join us to propel the Society into the next level of growth. I know that Nancy Van Zant is the consummate professional to work with the Society. I look forward to working with Nancy as she transitions into our organization.

"Having submitted my resignation, it is with absolute delight that I accept the honor of nomination to your Board of Directors effective immediately. I thank you for the opportunity to join you on the Board of Directors to continue to make the FSH Society a leader and be the force behind finding the treatment and cure for this devastating disease. I know that we are so close now and that Daniel's dream in 1989 is coming to fruition.

"This has been an amazing fifteen years. I look forward to joining the board of directors so that I may continue to work with all of you.

"Goodbye and hello."

Carol joins the executive board as secretary. We thank and congratulate her.

### Board of Directors

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### Letter from the new executive director

Dear Friends of the FSH Society,

I am pleased and honored to be writing to you today to introduce myself as your new executive director of the FSH Society. I follow in the footsteps of a great leader and one whom you love and respect. Carol Perez is still available to all of us, but she has earned her new life in retirement while serving as a volunteer board member and continuing to help FSHD patients daily on a one-on-one basis.

The Society has a strong foundation of individuals and families concerned about FSHD. We have a distinguished Scientific Advisory Board and an outstanding group of researchers around the world. Together we can solve facioscapulohumeral disease, but we need generous gifts from as many as can give them. I look forward to working with all of you as we seek to increase philanthropy for the Society — each giving more and reaching out to others to give.

Sincerely,  
 Nancy Van Zant Executive Director,  
 FSH Society, Inc.

### From the President,

*continued from page 2*

reading this newsletter to consider the undeniable and clear impact the Society has had on FSHD research and clinical solutions, and to make a donation at this time. Please give generously, ask your friends and family to give, and include the FSH Society in your regular and ongoing philanthropic giving. *Your help is needed and make no mistake — every penny counts!*

After many years of hard work, the staff and board members of the FSH Society are seeing remarkable progress. I want to thank you for your ongoing support and invite you to be an even bigger part of finding a cure for FSHD.



### The Kellys — One family, one hope

By Julie A. Kelly

For every family impacted with FSHD, every day comes with a challenge. My family is no different. Several family members live with FSHD but all of us are faced with the challenges brought on by FSHD. In 2006, several family members attended the annual FSH Society conference held at the Charles Hotel in Cambridge, MA. We were all impressed by the speakers and in awe of the families that raised money. We were left wondering, What can we do to help in the FSHD fight?

As we were exiting the conference, my sister, Pauline, noticed the FSH Society envelopes. Being the successful fundraiser that she is for the high school attended by her boys, Pauline asked one of the volunteers at the conference if she could take some envelopes. Pauline knew we could use the envelopes some how in fund raising. We had no plan of action; Pauline just reacted on her impulse to take home some envelopes. So in 2006, we decided to have our own Kelly Family FSHD Fund Raiser.

We were approaching the end of

*continued on page 6*

## Organization & mission

The FSH Society, Inc. is a 501(c)(3) non-profit tax-exempt U.S. corporation organized in 1991 to fund, encourage and promote scientific and clinical research on FSHD. Papers certifying its incorporation, bylaws and tax-exempt status are deposited at the corporation's east coast office.

The FSH Society is a world leader in combating muscular dystrophy. It has provided millions of dollars in seed grants to pioneering research worldwide and it has created an international collaborative network of patients and researchers. The Society relies entirely on private grants and donations so grass roots philanthropy is leading the way here, and if you want to go with a leader, here is your opportunity. Contributions are acknowledged for tax purposes.

FSHD is the second most prevalent adult muscular dystrophy. FSHD affects men, women and children. It occurs with a frequency of 1/20,000 in the population and may be three times higher due to misdiagnosed cases. The majority of cases of FSHD are caused by a genetic defect, a deletion on chromosome 4. FSHD is genetically autosomal dominant meaning that a child of either sex has a fifty percent chance of inheriting the genetic defect from an affected parent. Once present, FSHD is genetically transmissible. Genetic diagnostic and prenatal diagnostic tests are available as well as pre-implantation genetic diagnosis (PGD). Thirty percent of new FSHD patients have no prior family history and are a result of a congenital spontaneous genetic mutation.

FSHD causes a progressive loss of all skeletal muscle, with weakness usually noticeable starting with facial, scapular/back and upper arm muscles. The prognosis includes both a loss of muscular strength that limits personal and occupational activities of most FSHD individuals and a loss of mobility in perhaps twenty percent of the cases. Early facial involvement is a hallmark of FSHD.

The age of onset is variable as is the eventual extent and degree of muscle loss but noticeable muscle weaknesses are usually present by the age of twenty in ninety-five percent of patients. Hearing loss and retinal abnormalities associated with

FSHD have been reported, but the frequency of these effects and their relationship, if any, to the causative gene for the muscle defect are uncertain.

The FSH Society was created because of a need for a comprehensive resource for FSHD individuals and families. Purposes of the organization are:

- ◆ to encourage and promote scientific and clinical research and development on the causes, alleviation of suffering, treatment and cure of FSHD;
- ◆ to support such research and development through solicitation of grants and contributions from individuals, corporations, private foundations, the pharmaceutical industry and others to support such research and development;
- ◆ to make grants and awards to qualified applicants so that such applicants may accomplish such research and development;
- ◆ to accumulate, disseminate and encourage the exchange of information about FSHD, including educating the general public, relevant governmental bodies, and the medical and scientific professions about the existence, diagnosis and treatment of FSHD;
- ◆ to actively cooperate with related organizations and foster communication among all interested parties; and
- ◆ to serve as a resource for individuals and families with FSHD and represent them and advocate on their behalf.

The Society invites contact from any interested individuals, families, physicians, caregivers, charitable organizations, government agencies, industry, scientific researchers and academic institutions. Any inquiries regarding membership, charitable donations, purposes and goals or other issues pertaining to the Society and FSHD, should be addressed to the east coast office.

## The Kellys

*continued from page 5*

summer so we thought it would be best to reach out to friends and family coincident with the MDA Labor Day Telethon. Our friends and family give to MDA each Labor Day because of our family fight with muscular dystrophy. We recognized that friends and family cannot give to every cause and didn't want to ask for a donation to both the MDA telethon and the FSH Society.

Therefore, last Labor Day weekend, September 2006, our family joined efforts from Boston to Florida in raising contributions for the FSH Society. Labor Day was a little over a week away when we started this effort. We knew that every contribution counted so we set forth to get a fundraiser done. It was a family effort: from our 80-year-old mother down to our six- and nine-year-old nieces.

We decided to use those envelopes Pauline took home from the summer FSH Society conference. Our family gathered over pizza and soda to formulate our fund raising letter and to create our list of contacts. We set our goal high — to raise \$10,000. This was an aggressive goal with such little time.

We crafted the letter, printed up mailing labels and set up an assembly line. We printed, folded, stuffed and sealed envelopes. Our two youngest nieces placed a frog sticker on every envelope. This sticker identified to Carol Perez that the donation sent in was related to the Kelly Family FSH Society Fund Raiser.

Carol tracked our progress. Although we didn't meet our financial goal, we were pleased with the effort. We were very grateful to the friends and family who made donations and we sent personal thank you notes to those who contributed. We're planning to have the Kelly Family Fund Raiser again this Labor Day, 2007. We plan to expand our list of family, friends, and co-workers and to start our effort sooner. We want to raise more money than last year and shoot for the \$10,000 mark. You, too, can have a family fundraiser. Think about the impact we could all have for the effort of the FSH Society. It doesn't matter if each family raised \$500 or \$5,000 — the collective effort would be great!

## ***Boston Biomedical Research Institute welcomes FSH Society***

**B**oston Biomedical Research Institute (BBRI) welcomed the FSH Society to its Watertown laboratories on June 1, 2007 to partner on innovative research initiatives to develop research that helps to understand the mechanism and to develop more effective therapies for FSHD.

The Society is subleasing office space in the Watertown facilities of BBRI; this is not a merger of two non-profits. The FSH Society and BBRI are separate non-profits co-located at BBRI's world class research facility. Please note that all donations made to the FSH Society are not subject to BBRI overhead.

Boston Biomedical is renowned for its research on muscle pathophysiology and muscular dystrophy as well as other diseases including cancer, Alzheimer's and cardiovascular disease. Scientists in the Degenerative Disease and Regenerative Biology group at Boston Biomedical investigate how muscles develop, grow and regenerate, and how they deteriorate in response to disease, injury and aging.

This exciting new collaboration between the FSH Society and the Institute has been established as a dynamic partnership between a non-profit volunteer health agency and non-profit research institute to help build the foundation of FSHD research locally and internationally. This partnership is designed to bring together government, non-profit, private and industry agencies to focus efforts on facioscapulothoracic muscular dystrophy. The knowledge and information gained by understanding FSHD as a unique human disease will help accelerate discoveries and treatments for other muscular dystrophies as we study muscle regeneration pathways, and will provide insights into more prevalent diseases such as cancer.

The FSH Society, formerly based in Lexington MA, funds, encourages and promotes scientific and clinical research on FSHD and is a world leader in combating FSHD. The Society has established a seed grant program to support pioneering muscle research worldwide and an international collaborative network of patients and researchers. FSHD is the second most prevalent adult muscular dystrophy and causes a progressive loss of all skeletal

muscle, with weakness usually noticeable starting with facial, scapular/back and upper arm muscles.

"We are delighted to be welcoming the FSH Society to our laboratories and are very optimistic that our combined expertise will lead to important new advances in promoting regeneration and repair of diseased muscles," says Boston Biomedical Director, Dr. Charles Emerson. FSH Society President & CEO, Daniel Paul Perez, adds "The FSH Society is excited about establishing our office at BBRI, a world-class research institution with a strong emphasis on muscle research. The synergy created by patients, researchers, and clinicians working side by side will bring rapid understanding and tangible treatments for FSHD and many other diseases."

### ◆ **About the Boston Biomedical Research Institute**

Founded in 1968, Boston Biomedical Research Institute is a not-for-profit basic research institute dedicated to the understanding, treatment and prevention of a wide range of human diseases and conditions including cancer, cardiovascular diseases and degenerative diseases. For more information visit [www.bbri.org](http://www.bbri.org)

### **Media Contacts:**

**Virginia Sullivan, BBRI**  
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or

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***The FSH Society  
would like to thank you  
for your support as we  
carry on the fight  
for excellent research,  
treatment and a cure.  
We can't do it without you!***

## ***Making the case for more effective research***

By Daniel Paul Perez

**T**he power of the FSH Society resides in its scientific advisory- and patient-driven board. In the span of nine years, the FSH Society has transformed the face of FSHD research and we are on the verge of a series of significant breakthroughs. It is essential to fund new ideas and give support to new investigators and new lines of investigation when tackling a disease as complex as FSHD.

For scientific progress, it is essential to have the most qualified panel of experts who are not only judging the merits of funding new proposals before them, but are also actively engaged in thinking about the scientific problem. Peer reviewed science is key to research success and peer review means just that — reviewed by scientists and doctors who have comprehensive command of the grants and science being judged.

We know that FSHD research proposals reviewed by the SAB will be absolutely top rate and necessary science. The NIH has a peer review system that prides itself on funding the "best science." I am often surprised at the number of missed opportunities by the NIH to fund first rate and progressive FSHD projects. Unfortunately with NIH, the study sections do not have panels entirely comprised of experts in FSHD science.

Respect for the scientific review process and discipline in the scientific method and critical thinking are required. The Society enforces and abides by this principle. It is easy to reason that making a direct donation to a researcher at a university is a simpler transaction and that major progress is forthcoming. However, when not run through the litmus of experts judging the science and listening to the pulse of the research, this is not in the best interest of the FSHD research community as a whole. Donations that are not made through the Society may not be working as hard or efficiently as they could to solve FSHD.

## *On the passing of Stephen J. Jacobsen*

With sorrow, we inform you that Dr. Stephen J. Jacobsen, co-founder and chairman of the board of the FSH Society, passed away suddenly on Saturday night, January 21, 2006 surrounded by his family. We mourn the loss of a beloved friend, co-worker and fellow patient who was dedicated to seeing a cure for FSHD. We know that Stephen touched the lives, and continues to touch the lives, of so many people in a positive way. He was a great researcher and an extraordinarily compassionate man.

A memorial service was held at one of Stephen's favorite places — the San Dieguito County Park, Del Mar, California. Stephen is survived by his wife, Jan, his children, Natasha, Laurel, Nathan and Jared, and his brother Robert.



### *In memory of Stephen J. Jacobsen* *May 3, 1945 - January 21, 2006*

*Letter sent to Jacobsen family by Daniel Paul Perez  
January 26, 2006, Lexington, MA*

Please accept my condolences on the loss of your husband, father, a dear friend, the chairman of the board and co-founder of the FSH Society, and a great leader in the field of facioscapulo-humeral muscular dystrophy research – Dr. Stephen J. Jacobsen.

In life, there are a few rare individuals that have a remarkable impact on others — and I know Stephen was one of those people. Stephen was a true pioneer in the field of facioscapulo-humeral muscular dystrophy research. I knew Stephen as an older, wiser, fellow sufferer of FSHD. He was the first person I ever met outside of my family with FSHD and I traveled from Boston to San Diego in May 1989 simply to meet him. He was an infinitely compassionate man who provided assurance and faith that life could be lived fully in no uncertain terms, despite the crippling effects and ravages of FSHD. To me, he always represented a certain sureness, correctness, a fine intellect, sharp thinking and good feeling.

In our comings and goings he was always gentle, loving, thoughtful, patient and kind. I hear in my memory his deep resonant voice, his addressing himself as “Stephen” and not “Steve,” and his laugh coming back through the past. I hear the music of the Eagles song, *Hotel California*, playing in the background as we spoke of science, research and trail-blazing research projects and proposals. He was an imposing man though I only knew him seated, with direct eye contact and strong constitution — as though he never outgrew the boy from southern Utah. He loved his wife, his children, and his family without question and wanted to see the best for them and a future without the burden of FSHD for any of them. To the end

he strived to solve FSHD and he knew we were getting close to a solution.

My connection to Stephen and to the true and shared experience of FSHD grew over the years. We worked against enormous odds to cure and solve FSHD. I am proud to say I know the man who took unprecedented and great risks as a patient with FSHD to research his own disease and to establish the bedrock of FSHD research as we know it today. Stephen is one of the bravest men that I ever knew. I tell you the FSH Society is today a world leader in combating muscular dystrophy. It has provided millions of dollars in seed grants to pioneering research worldwide and it has created an international collaborative network of patients and researchers.

Speaking for myself, I am truly a richer person knowing Stephen and hope that I can emulate those things that I admired and loved in him. I'll miss his physiognomy, voice, humor, uncommon strength and ever engaging eye in life. I am happy to know that the image is colorfully and more than three dimensionally indelibly etched in my psyche. I regret we did not have more time together and the opportunity to see the cure, treatment and dream of solutions for FSHD together. The Board of Director's, Scientific Advisory Board and I are infinitely grateful for those things that Stephen helped us build in the FSH Society that have made all the difference. I am certain he sensed this as well.

I know this is a most difficult time for you. Our thoughts are with you and we wish you strength and healing in this time of adversity. We will miss him terribly.

With deep affection, sorrow and condolences,  
Daniel Paul Perez, President & CEO,  
FSH Society



*Stephen J. Jacobsen  
photo: Laurel Jacobsen*

## Obit: Dr. Marcy Carlson Speer

It is with great sorrow and sadness that we inform you that Dr. Marcy C. Speer died on Saturday night August 4, 2007. Dr. Speer was an FSH Society Delta Railroad and FSH Society Tides foundation fellow in the years 2001 to 2003 and made extraordinary contributions to our understanding of FSHD and FSHD non-4 chromosome linked families. With Dr. Speer's passing we lose an extraordinary and irreplaceable resource for FSHD families suffering from unique genotypes. We know that her colleagues and students will continue to honor her endeavor and interests in these special cases of FSHD. The Society will establish a memorial fund in Dr. Speer's memory dedicated to research on unusual FSHD families and genotypes.

Dr. Speer was warm, caring and supportive, never lost sight of the patients with FSHD, and was always resourceful and affirming. She took the time during FSHD research consortium meetings to explain with levity and humor how the Society connected patients and researchers through a sometimes elaborate series of steps. Dr. Speer understood the value in harnessing the power of volunteer health agencies and took time to explain why this is so. Her letters always had a "voice" and began with a spark of energy and had the most positive approach.

FSHD research has lost one of its most intelligent and talented researchers. Society as a whole has lost a fine human being and a wonderfully caring and engaged spirit. We are very grateful that we had the opportunity to know and work with Marcy. We have lost a dear friend and a dedicated scientist.

Our condolences go to Dr. Speer's husband, daughters and family. Our condolences go to all of you who have lost a dear friend and a good colleague.

### Marcy Carlson Speer

Marcy Carlson Speer, 47, died Saturday in Duke Hospital following a valiant battle with breast cancer. She was born October 1, 1959 in Indianapolis, and raised in Indiana and Illinois. Marcy graduated from Indiana University and received a Master's degree in genetic counseling from Sarah Lawrence College. She obtained her Ph.D. in genetics from Duke University. A Durham resident since 1985, Marcy was a long-term faculty member at Duke in the Center for Human Genetics. She was named director of the center just this past year. While Marcy Speer was an accomplished researcher with international acclaim, she was also a devoted mother, whose energies were always primarily directed toward her children.

Marcy is survived by her husband of 24 years, Kevin P. Speer, M.D.; her daughters, Kira Carlson Speer and Casey Carlson Speer; her mother, Marsha Carlson; and brothers, Ned Carlson of Washington, DC; and Eric and Kris Carlson of Chicago. She is predeceased by her father, Milton Carlson, this year.



Marcy Carlson Speer

### Dedication to three dear friends

The FSH Society 2006 International Patient Researcher Network and Contact Day (see article on page 20), held on July 16, 2006, was dedicated to the memory of Stephen J. Jacobsen, Karen Johnsen and William "Billy" Michael, three dear friends of the Society and many of its members. They lived fully with FSHD, helped countless others understand, accept and cope with FSHD, and were devoted to solving its mystery. This was the Society's first Patient Network day since they passed away, and it was fitting and proper that we honored their memory. They lived with grace, wisdom, kindness and courage, and used their experience of having FSHD to help others, both by specific contributions and by personal example.

#### STEPHEN J. JACOBSEN

Stephen J. Jacobsen co-founded the FSH Society in 1991, serving as its chairman of the board from its inception until his death. A pioneer of FSHD research, Stephen methodically, creatively and patiently researched his own disease. At a time when few others shared his belief, Stephen was convinced that the FSHD puzzle could be solved and eventually treated and cured. Stephen was an optimist who never wavered in this conviction and an advocate who believed that FSHD is unique and merits specialized research.

FSHD research and the FSH Society wouldn't be where they are today without him. He earned a Ph.D. in biochemistry and virology from Brigham Young University and did post-doctorate work at Harvard University's Massachusetts General Hospital. Stephen died on January 21, 2006 in San Diego and is survived by his wife, Jan; sons, Jared and Nathan; daughters, Laurel and Natasha; and son-in-law, Kevin. The FSH Society has established the Stephen J. Jacobsen Excellence in Research Award Fund to recognize outstanding work in the field of FSHD research and as a memorial to Stephen's life's work.

The lecture by Dr. Noah Lechtzin on "Respiratory Therapy and Issues in FSHD" was dedicated to Stephen. During the several years before his death, Stephen had become especially interested in respiratory issues in FSHD.

#### KAREN L. JOHNSEN

Karen L. Johnsen was a founding member of the FSH Society and served as a board member from the Society's inception until her death. Karen was director of Beltsville Agriculture Day Care, Miss Wheelchair Maryland two years in a row and an effective disability rights advocate who was present at the signing of the Americans with Disabilities Act. She testi-

*continued on page 10*

## **Dedication**, continued from page 9

fied before Congress many times advocating disability rights and funding for muscular dystrophy research. Together with her husband, Dean, she formed one of the first support groups for people with FSHD. Through the support group, phone and email, Karen touched the lives of hundreds of people with FSHD in the United States and abroad, giving them hope, love and counsel. Karen died on December 14, 2004 in Maryland and is survived by her husband, Dean; son, Jeremy; and mother, Doris Olds Eck. Mrs. Olds Eck established the "Karen's Dream for a Cure" research fund at the FSH Society.

The lecture by Dr. Kathryn Wagner on "Therapies, Compounds and Strategies to Treat FSHD" was dedicated to Karen. Karen was instrumental in educating and recruiting FSHD patients for Dr. Wagner's clinical trials of myostatin inhibitors.

### **WILLIAM T. "BILLY" MICHAEL**

William T. "Billy" Michael attended the initial meetings that led to the formation of the FSH Society. Billy was diagnosed with infantile FSHD at age four, after having had weakness for several years and, although he was able to participate in Little League as a young boy, he needed to use a wheelchair by age 10. The severity of his FSHD tested Billy's courage, faith, ability to love, maturity, resourcefulness and wisdom early in life and in a way that few people ever are tested. He loved life and loved his family who were devoted to him and ensured that he continued to live with them instead of an institution. Billy was strong, selfless, uncomplaining, compassionate and brave. He was accomplished in computers, an avid collector of sports and other memorabilia and interested in current events. Billy's father, Bill, is the treasurer and a board member of the FSH Society, serving in both roles since the Society's inception. Billy died at age 35 on December 7, 2004 in West Bridgewater, MA and is survived by his father, William; mother, Ginny; sister, Beth; both grandmothers and a very loving and supportive extended family.

The lecture by Dr. Katherine Mathews on "Clinical Medicine and Research Advances in Adult and Early-Onset FSHD" was dedicated to Billy.

## **HEALTH INFORMATION**

### **FSHD P.T. brochure an overwhelming success!**

The FSH Society is a leader in developing materials to help patients and professionals with FSHD. Several years ago we recognized an unmet need in training for physical therapists on FSHD and materials for patients to help them understand the process and benefits of physical therapy on FSHD. The FSH Society contacted two of the leading physical therapists with knowledge of FSHD in the United States, Shree Pandya and Wendy King, to enlist their help in creating an informative, knowledgeable and educational project.

The exclusive FSH Society publication, "Physical Therapy & FSHD: A Guide for Patients & Physical Therapists" is the result of several years work and has been reviewed by physical therapy professionals, doctors and the FSH Society SAB. This was the last project that FSH Society co-founders Daniel Paul Perez and Stephen J. Jacobsen worked on together, and the brochure is dedicated to the memory of Dr. Stephen J. Jacobsen, a great pioneer and a wonderfully caring man.

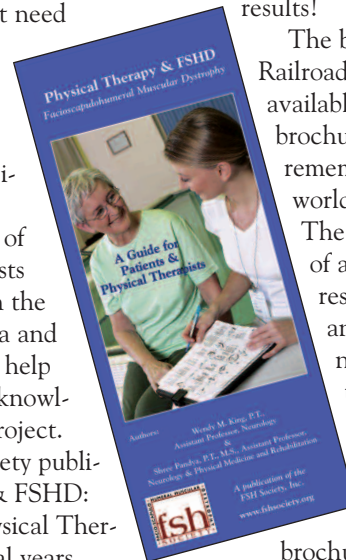
We are pleased to have started distributing the FSHD P.T. brochure and know it is the most complete report of its kind ever offered outside the professional community. We are very pleased with this comprehensive guide written by leading experts in the field of physical therapy for FSHD. It has been a long time coming and will be a great value to patients and professionals.

This brochure has been edited to provide concise, direct and simple-to-understand information about FSHD. You will find answers to questions you have asked yourself or of your medical professional such as: How does FSHD progress? What about respiratory insufficiency? What exercises can help me with FSHD? Is hydrotherapy (water therapy) helpful? What helps manage the pain? How can a physical therapist help and what can I expect? How can physical therapy treat and manage pain? These and many more

questions are answered, along with information that will help you and your physical therapists produce more successful results!

The brochure was funded by a Delta Railroad Construction grant and is available in printed format. The P.T. brochure is free upon request. Please remember that the FSH Society is a world leader in combating FSHD. The Society was created because of a need for a comprehensive resource for FSHD individuals and families. Of course, as a non-profit charitable organization, the Society relies entirely on individual contributions, grants and philanthropy. We certainly appreciate your request for the P.T.

brochure and your help.



### **GRANT INFORMATION**

Grant: FSHS-DR-006B Honoraria  
 Researcher1: Wendy M. King, PT  
 Institution1: Ohio State University  
 389 McCampbell Hall  
 1581 Dodd Drive  
 Columbus, Ohio 43210-1205 USA  
 Researcher2: Shree Pandya, MS, PT  
 Institution2: University of Rochester  
 School of Medicine  
 Physical Medicine and Rehabilitation  
 University of Rochester  
 Rochester, NY, 14642 USA  
 Project Title: "Fascioscapulohumeral muscular dystrophy Physical Therapy Booklet/Brochure and Article for Physical Therapy Journal."  
 \$15,000 5/1/2004-4/30/2005 Year 1

**Goal:** Gather and review literature and information related to FSHD natural history, surgical options, orthotics, rehabilitation, physical therapy interventions, role of exercise, hydrotherapy, pain, etc. Review scientific literature, brochures and web sites of various organizations from English speaking countries to assess the type and format of information already available. Draft, peer-review and publish booklet/brochure on FSHD and Physical Therapy and submit journal article to Physical Therapy journal on P.T. and FSHD.

## HEALTH INFORMATION

### *Making the case to Acceleron Pharma for FSHD clinical trials*

In August 2006, the FSH Society received a call from Dr. Matthew Sherman, Chief Medical Officer of Acceleron Pharma, Cambridge, MA, regarding the FSH Society and FSHD. On August 28, 2006 Daniel Paul Perez met with Dr. Sherman, founders and key staff of Acceleron to listen to a presentation on a novel set of compounds being tested for clinical trials.

During the presentation, Daniel answered questions about FSHD and access to patients with FSHD. He discussed the work of the Society and ways that Acceleron and the Society could work together to have clinical trials on FSHD. Daniel explained the rationale for FSHD being an excellent candidate for a clinical trial focused on harnessing the capabilities of the anti-myostatin compounds, and the TGF-beta super-family of growth and differentiation factors. He explained that FSHD is a dystrophy that involves documented and published problems in the differentiation of muscle, and that the rationale and hypothesis for conducting a trial on FSHD using myostatin-

inhibiting compounds is quite compelling and sound.

As in the early stages of the Wyeth myostatin inhibitor trial with MYO-029, Daniel provided numerous contacts, advice and networks to the professionals involved. He suggested contact with two colleagues: Kathryn Wagner, M.D., Ph.D. and Rabi Tawil, M.D. Both are leading clinicians in FSHD and familiar with running and conducting clinical trials for FSHD.

The Senator Paul Wellstone MD CRC are NIH/government funded centers for the study of dystrophy. There are currently six centers. The two centers that offer the most synergy, in Daniel's opinion, are Hopkins and Rochester.

The Hopkins Wellstone's primary focus is looking at compounds that affect muscle cell differentiation and growth. This Wellstone is set up to identify new compounds for dystrophy treatment, expedite them to trials and facilitate clinical trials on new drugs.

Acceleron Pharma is a privately held biotechnology company in Cambridge,

MA that was recently profiled in the Boston Globe. You can find the article at this link:

[http://www.boston.com/business/technology/biotechnology/articles/2007/0716/super\\_buff\\_cattle\\_may\\_hold\\_key\\_to\\_treating\\_muscular\\_diseases/](http://www.boston.com/business/technology/biotechnology/articles/2007/0716/super_buff_cattle_may_hold_key_to_treating_muscular_diseases/)

Of particular interest to readers of the *FSH Watch* is that Acceleron has a research and development program for treatments of diseases involving loss of muscle mass, strength and function. ACE-031 is the lead drug candidate in the program and is currently in pre-clinical safety studies as Acceleron prepares to begin clinical development.

ACE-031 is a "protein therapeutic" based on the activin receptor type IIB (ActRIIB) that binds to myostatin and other negative regulators of muscle mass and strength. Over-expression of myostatin has been shown to cause a loss in muscle mass and strength whereas inhibition of myostatin results in the selective increase in skeletal muscle mass and strength.

Acceleron is planning to submit an IND (Investigational New Drug application) to the FDA later this year with the intent of starting the first clinical study with ACE-031 by early 2008. While the indication or disease focus of the trial has not been announced, we are certain that muscular dystrophy is on the short list of diseases to be considered for the clinical trial with, hopefully, FSHD included as well.

Acceleron scientists presented data at the Gordon Research Conference on Myogenesis in May 2007. The presentation, "Treatment with a Soluble Activin Receptor IIB Causes Increased Muscle Mass and Strength in mdx Mice," included data from preclinical studies in normal mice and in the mdx mouse model of muscular dystrophy. These studies showed a substantial increase in muscle mass and a dose-dependent increase in lean body mass in ACE-031-treated animals.

The effects were significant in just two weeks following start of therapy and increased further as treatment continued. In the mdx murine model of muscular dys-

### *Update on Wyeth Pharmaceuticals clinical trial*

In the last issue of the *FSH Watch* we included an article titled "The Myostatin Inhibitor Story" introducing how the FSH Society helped facilitate the Wyeth study evaluating anti-myostatin inhibitor MYO-029 in adult muscular dystrophy.

The clinical trial began in February, 2005 and enrolled 108 patients with the purpose of being a phase I/II, multi-center, safety trial to study MYO-029 in adult patients with confirmed clinical and molecular diagnosis of BMD, FSHD or LGMD.

An enormous amount of effort has gone into this trial. Regarding Wyeth's commitment to the trial and infrastructure, FSHD patients have reported to the Society a significantly positive experience gained by being in this trial and from the clinicians involved.

The clinical trial of anti-myostatin in adult muscular dystrophy has completed and is not enrolling new patients. This phase I/II safety trial had some measures of efficacy. It was a multiple ascending dose at three levels with 36 patients per cohort.

While the FSH Society is very optimistic about the trial, it is being very cautious not to lead on FSHD patients with preliminary results or anecdotal evidence from patients in the trials. We are waiting for word from Wyeth Pharmaceuticals on the outcome of their trial.

As of today, Wyeth Pharmaceutical is still analyzing the data and could have an announcement soon. We are hopeful for news and/or a publication by the fourth quarter of 2007.

The FSH Society is most appreciative of the FSHD patients who took the initiative and showed the courage and conviction to participate in the trial and put FSHD on the radar for large pharmaceutical and biotechnology companies. The Society and patients with FSHD also thank Wyeth!

## ADVOCACY

### *Broadening the clinical research horizons for FSHD*

In 2005, the U.S. Congress mandated the NIH to conduct a workshop on the current status of therapeutic development efforts in Duchenne muscular dystrophy.

The NIH workshop on Translational Research in Muscular Dystrophy was held on June 25-27, 2007. The workshop was held contiguously to the Muscular Dystrophy Coordinating Committee meeting on June 25, 2007.

Daniel Paul Perez, FSH Society, was asked to serve on the organizing committee of the workshop. The organizing committee also included Kathy Mathews, M.D., Ph.D., Workshop Chair; John Porter, Ph.D.; Cristina Csimma, Pharm.D., M.H.P., Clarus Ventures; Sharon Hesterlee, Ph.D., MDA-USA; Jerry Mendell, M.D., Columbus Children's Research Institute; Lee Sweeney, Ph.D.; and Peter Wald, M.D., M.P.H., DM.

Given the emerging opportunities for new therapies, the committee felt that it was an important time for the entire field and that a thorough review and analysis of ongoing efforts was critical to help expedite the movement of new therapies to the clinic for all of the muscular dystrophies and not just DMD. NINDS, NIAMS, NICHD, and NHLBI were involved as well as patient advocacy groups.

The organizing committee worked out the meeting scope, agenda and participant list. An independent advisory committee, drawn from academic and corporate leaders with substantial therapy development experience (oncology, inflammation biology, etc.), examined and offered advice on the current efforts and directions for therapeutic development in muscular dystrophy. The goal of the organizing committee was to represent all stages of therapeutic development and all major efforts in the program.

Excellent keynote speeches were given by Francesco Marincola, M.D. (NCI/NIH): "Identifying and Managing Obstacles to Translational Research" and Francesco Muntoni, M.D. (Imperial College): "Specific Challenges in Therapy Development for Muscular Dystrophy."

Panels of experts in their respective areas presented summaries and consensus in the following areas:

#### ◆ **Therapeutic Development**

**Processes:** Case Study in Therapeutic Development: Genzyme Pompe Myozyme, Milestone-Driven Translational Research Model, Challenges of Target Identification and Development Decisions Working Group, Animal Models and Preclinical Endpoints Working Group, Regulatory Issues and Ethics Working Group;

◆ **Therapeutic Development Collaborations:** Keys to Establishing Academic-Corporate Partnerships in Drug Development, Building International Collaboration in Translational Research: TREAT-NMD and Beyond;

◆ **Therapeutic Development Strategies:** Gene Therapy & Repair/RNA Targeted Therapies Working Group, Cell Based Therapies Working Group, Muscle Regeneration Therapies Working Group, Anti-Inflammation/Fibrosis Therapies Working Group, Membrane Repair/Compensatory Membrane Proteins Therapies Working Group; and

◆ **Panel Discussion:** Status Report and the Way Forward.

There was excellent representation

from clinical researchers, venture capital, biotechnology, pharmaceutical, four institutes of the NIH and two branches of the FDA. The meeting was quite successful and all dystrophies were recognized. The efforts of the FSH Society to promote FSHD and all other dystrophies (in addition to DMD) to lead candidates for clinical trials and clinical research was recognized at the meeting. It was striking to note that despite all of the dollars invested in clinical trials for DMD, DMD is no further along than the other eight dystrophies.

Members of the FSH Society and Daniel discussed the scientific and clinical opportunities available in FSHD. Also noted by presenters was the enthusiasm and willingness of the FSHD constituency to volunteer to participate and help in clinical trials research. This is another way that your support of the FSH Society brings treatments and solutions for FSHD closer to reality through advocacy.

The meeting minutes, transcript and summary will be posted by the NIH on its website when available.

### *Acceleron Pharma clinical trials, continued from page 11*

trophy, ACE-031-treated animals showed increased muscle mass which translated into significantly increased muscle strength. Acceleron has also demonstrated that ACE-031 increases muscle mass and strength in animal disease models of amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease), glucocorticoid-induced muscle loss and age-related muscle loss (sarcopenia).

Acceleron is unique because its founders are leading experts in the field of growth and differentiation factors (GDFs), which includes myostatin and related compounds, and because they have an organization with full drug development capabilities. Though Acceleron was only founded several years ago, they are equipped and staffed to conduct discovery research, animal pharmacology, GMP manufacturing and clinical development. Through their understanding of GDF biology, they have development programs focusing on the modulation of growth and repair of a variety of tissues including muscle, bone, fat and vasculature.

*Have you ever thought about leaving a bequest to the FSH Society in your will? Please see "Estate planning" on page 47 for more information on just one way you can support the Society.*

## ADVOCACY

### *Perez submits three testimonies before Congress*

FSH Society President & CEO, Daniel Paul Perez, submitted three congressional testimonies in early 2007 on behalf of the FSH Society and its members. On March 30, 2007, Daniel submitted testimony to the U.S. Senate Committee on Appropriations, Subcommittee on Labor, Health and Human Services, Education and Related Agencies regarding FY2008 appropriations for the NIH programs on FSHD research. On March 27, 2007, he gave testimony both in writing and in person to the U.S. House Committee on Appropriations, Subcommittee on Labor, Health and Human Services, Education and Related Agencies regarding FY2008 appropriations for the NIH programs on FSHD research.

Daniel submitted a summary statement to both houses of Congress explaining that

"he is a patient who has suffered from facioscapulohumeral muscular dystrophy (FSHD), the second most common form of muscular dystrophy, for the last 45 years. He is a graduate of Harvard College and an internationally renowned patient advocate for muscular dystrophy. He has given 36 congressional testimonies over the last 15 years resulting in a dozen sections of report language instructing the NIH to increase the portfolio in FSHD. His non-profit FSH Society is known worldwide for its highly successful research program yielding many new insights into FSHD and for its work with patients and families.

"Mr. Perez is known by the director of NIH and well known by the directors of various institutes of NIH and worldwide research agencies involved with muscular dystrophy. He serves at the behest of Secretary Leavitt and Dr. Zerhouni on the Muscular Dystrophy Coordinating Committee as mandated by the MD-CARE Act 2001 and has been intimately involved with this federal advisory committee.

"He will convey the shock and outrage

that comes with the knowledge that after all this time and effort, only one out of the twelve NIH institutes responsible for muscular dystrophy research has grants on FSHD and that the lead institute of NIH for dystrophy, NIAMS, has no research grants for FSHD.

"Mr. Perez is asking for an appropriation of \$100 million for the MD-CARE Act 2001 for FY2008 to bring muscular dystrophy in line with other diseases with similar cost burden (based on diseases with similar burden listed on NIH Office of the

Director disease spending figures). He is requesting \$250 million in the five years after that. Mr. Perez is also asking for a readjustment of muscular dystrophy funding to make FSHD funding proportional. Right now

FSHD receives 4 percent or \$1.7 million of the total NIH dystrophy budget. He is asking for \$20 million to be appropriated for NIH FSHD research as required under the MD-CARE Act 2001 and by the Muscular Dystrophy Research Action Plan submitted to the Congress."

Daniel went before Hon. Rep. David Obey (D-WI) in person to remind the Congress that FSHD is still taking its toll on Americans. FSHD is the second most common dystrophy, a crippling disease causing loss of all skeletal muscle, and it affects at least 20,000 Americans. He asked for three things:

"One.

"Please resume the five year doubling of the NIH budget. Appropriate \$32.8 billion as required in the NIH Health Reform Act 2006. At minimum, appropriate the 6.7% annual increase to restore funding. Only America has the ability to solve FSHD. Only NIH can do this. The question is — does America have the will? Small non-profits such as the FSH Society can not shoulder the burden year after year for new research funding. This is what NIH is designed to do. Congress needs to fund it.

"Two.

"Tell the director of NIH to make the Dystrophy Research Action plan viable. The MD-CARE ACT authorization needs an appropriation with it. The NIH portion requires \$100 million and \$250 million over the next five years. Tell the director that the 'Pioneer' and 'Roadmap' programs have taken funding away from peoples' diseases. Tell the Director to spend the 'Common Fund' on research that will have a direct effect on patients' lives.

"Three.

"\$1.7 million for FSHD research does not cut it. It is absolutely clear that individuals with FSHD have suffered greatly due to NIH's failure to act. Funding for dystrophy research is not equitable. The funding for FSHD is abysmal. FSHD research and its novel mechanism will help solve other diseases such as cancer, autism and diabetes. Tell the Director to assign \$20 million for FSHD research.

"Congress has asked NIH many times for a comprehensive portfolio on FSHD. I have served for six years on the Muscular Dystrophy Coordinating Committee. I have done everything that the administration and NIH has asked of me. I implore you to ask the Director, why, after all this time and effort, only one of twelve NIH institutes covering dystrophy has funded grants for FSHD?

"You know, I know and the American public knows that we have fallen behind when it comes to health care and biomedical research.

"We are waiting.

"While we wait, our quality of life diminishes.

"Research must be funded and hope rekindled.

"I ask you to fund NIH, fund muscular dystrophy, fund FSHD."

Mr. Obey thanked Mr. Perez for his compelling and moving testimony.

For those interested in reading the full text of the testimony, or in sending the FSH Society testimony to your congressman or congresswoman, please see online versions at [www.fshsociety.org](http://www.fshsociety.org).

*Daniel Paul Perez, President and CEO of the FSH Society, has given 36 congressional testimonies over the last 15 years resulting in a dozen sections of report language instructing the NIH to increase the portfolio in FSHD.*

## POLICY ISSUES

### *Perez advocates for FSHD on MDCC 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 mandate in the act called the Muscular Dystrophy Coordinating Committee (MDCC).

The MD-CARE Act mandated the establishment of the MDCC to coordinate activities across the DHHS, NIH, NINDS, NIAMS, NICHD, and other national research institutes as appropriate and with other federal health programs and activities relating to the various forms of MD. The act charges the MDCC with responsibility to develop a plan for conducting and supporting research and education on MD through the national research institutes and periodically to review and revise the plan.

MD-CARE Act is an act: "To amend the Public Health Service Act to provide for research with respect to various forms of MD, including DMD, Becker (BMD), Limb Girdle (LGMD), congenital, FSHD, DM, oculopharyngeal OPMD, distal, and Emery-Dreifuss (EDMD) muscular dystrophies.

In the MD-CARE Act, Congress requested the director, Elias Zerhouni, M.D. of the NIH, to further initiatives and progress in MD research. The act calls for "expansion, intensification and coordination of activities. In general, the director of NIH, in coordination with the directors of the NINDS, NIAMS, NICHD and other national research institutes as appropriate to expand and intensify programs of such Institutes with respect to research and related activities concerning various forms of MD, including Duchenne, DM, FSHD and other forms of MD."

The MDCC has now met six times and continues to implement the Muscular Dystrophy Research and Education Plan for NIH that was submitted to Congress in August 2004.

On November 9, 2005 the fourth meeting of the MDCC was convened. This meeting was the first of two MDCC meetings held in the federal fiscal year 2006.

Rune Frants, Ph.D. presented a scientific update to the U.S. president's committee titled "Scientific Update: Facioscapulo-humeral Muscular Dystrophy."

Dr. Frants outlined the strategies, mission, materials and methods needed within the five sections of the NIH action plan for the dystrophies to rectify the unmet research needs and research funding in FSHD. Daniel Perez presented a talk on "FSH Society Strategies: Research Grants and Meeting Programs" highlighting the tremendous success and track record of the Society's research projects and grantees. He was also very vocal and adamant that the NIH and other government funding agencies address the enormous funding disparity between DMD and all the other dystrophies including FSHD, as well as the anemic and thin presence of FSHD in the Wellstone MD CRC network.

On May 10, 2006 the fifth meeting of the MDCC was convened. This meeting was the second of two MDCC meetings held in federal fiscal year 2006. Daniel was asked by the committee to update the FSH Society's activities as they relate to the MD Action Plan. He again highlighted the exciting and rapid science breakthroughs and several missed opportunities by the NIH to fund needed and cutting edge research when FSHD research applications were turned away.

On June 25, 2007 the sixth meeting of the MDCC was convened. This was the first meeting held in federal fiscal year 2007. Daniel Perez was asked by the committee to update the FSH Society's activities as they relate to the MD Action Plan. He again highlighted the exciting and rapid scientific breakthroughs and several missed opportunities by the NIH to fund needed and cutting edge research when FSHD research applications were turned

away by NIH

Daniel Perez also presented the FSH Society Short- and Long-Range Research Plan including six of the components (see article on page 41). He asked the MDCC to look at the wide gap in funding between DMD and all the other dystrophies including FSHD.

The NIH announced the results of the RFAs specifically focused on FSHD, EDMD and OPMD with three of six grants being funded for FSHD. FSHD received two R21 and one R01 style grant; the R21's are several hundred thousand dollars per year for two years and the R01 is approximately \$1 to \$1.5 million total for five years.

The NIH also announced the award of several interesting Wellstone collaborative grants that facilitate interactions between the Seattle and Rochester Wellstones and outside investigators e.g. Stephen Tapscott (Seattle), Rabi Tawil (Rochester) and Silvere van der Maarel (Leiden). This will help greatly to introduce and grow the FSHD research presence within the Wellstone MD CRC centers.

The Society is doing this as well by providing funding for FSHD researchers to travel and study within established Wellstone MD CRC centers. FSH Society Marjorie Bronfman grantee Yvonne Meijer-Krom, Ph.D., based at Leiden University but working at the University of Washington, Seattle with Dr. Tapscott to create the best preliminary data on both sides to allow for larger and future NIH grant submissions.

For more information on the MDCC plans, staff, rosters, meeting agendas and minutes please see "The NIH Home Page of the Muscular Dystrophy Coordinating Committee (MDCC)" Internet link on the FSH Society's home page,

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

***The FSH Society depends on  
YOUR contributions to continue its work!  
Please consider a tax-deductible contribution today.***

## EDUCATION

### About FSHD... Important information for medical professionals

**F**acioscapulohumeral muscular dystrophy (Landouzy-Déjérine disease) is an inheritable muscle disease commonly called FSH or FSHD. FSHD is the second most prevalent inheritable adult dystrophy. Progressive weakening and loss of skeletal muscle are its major effects. It has significant medical and health impacts on individuals, families and society. Details about the nature of the disease and some basic knowledge of inheritance of genetic diseases are important to better understand FSHD.

Since its inception, the FSH Society has offered its FSHD patient brochure in English and Spanish. We have printed and distributed close to 35,000 hard copies worldwide based on request and demand. We review the information periodically and update the literature to provide FSHD patients and families with the latest and best advice on FSHD.

The FSH Society knows that its brochure circulates understanding of FSHD more widely, and that better understanding will help those who are living with, and concerned about, this unique disease. The text and PDF version of the brochure can be found at:

<http://www.fshsociety.org/fsh/PatientBrochure.html>

or

<http://www.fshsociety.org/fsh/PatientBrochure.pdf>

### For Medical Professionals

Will you assist us by making your patients aware that:

◆ Facioscapulohumeral muscular dystrophy (FSHD [MIM 158900]) is the third most common inherited muscular dystrophy, with an estimated frequency of at least 1 in 20,000.<sup>1</sup>

◆ FSHD affects men, women and children. "Males are typically more severely affected than females and there is a wide clinical inter- and intra-familial variability of the disease, with approximately 20% of patients eventually becoming wheelchair-bound and with an equal frequency of non-penetrant gene carriers."<sup>1</sup>

◆ "The disease displays an autosomal dominant mode of inheritance with the vast majority of familial cases linked to a genetic lesion in the sub-telomere of chromosome 4q (4qter)."<sup>1</sup> Genetic and prenatal testing is available.

◆ "There is a rough and inverse relationship between clinical severity and the residual repeat size, with the smallest repeats causing the most severe phenotypes."<sup>1</sup> At a minimum, 70 percent of FSHD patients inherit the disease from a parent and, at maximum, 30 percent of FSHD is caused by a spontaneous genetic deletion that had not previously existed in the family. Offspring of a FSHD patient have a 50 percent chance of inheriting the disease.

◆ "Generally, FSHD displays a characteristic gradual spread of muscle involvement, starting in the face and slowly progressing to the shoulder and upper-arm musculature and to the abdominal and foot-extensor muscles."<sup>1</sup> "Foot dorsiflexion weakness leading to footdrop is an early manifestation of FSHD and one amenable to the use of molded ankle-foot orthoses (AFO)."<sup>2</sup>

◆ "The most common initial symptom is difficulty reaching above shoulder level. Less common presentations include foot drop (such patients, however, almost invariably have compensated), asymptomatic scapular fixator, and facial weakness on examination. Truncal weakness is an early and frequent manifestation that is easily overlooked during examination of these patients. Weak abdominal muscles result in a protuberant abdomen and contribute to the lumbar lordosis. Lower abdominal muscles are weaker than the upper abdominal muscles, causing a strikingly positive Beevor's sign, a physical finding fairly specific for FSHD."<sup>2</sup>

◆ FSHD can or may affect all skeletal muscles.

◆ The FSH Society has developed a booklet on physical therapy for patients and professionals titled: "Guide for Patients and Physical Therapists."

◆ "Associated non-skeletal muscle manifestations include high-frequency hearing loss as well as retinal telangiectasias, both of which are rarely symptomatic."<sup>2</sup> "Approximately half of the patients present with subclinical high-tone hearing loss and retinovasculopathy."<sup>1</sup>

"Hearing loss is often more severe in infantile-onset FSHD and, if not detected and treated early, can interfere with learning and cognitive development. Audiograms should be performed on patients diagnosed with infantile FSHD."<sup>2</sup>

◆ "Respiratory involvement in FSHD is uncommon but can be seen. Thus, symptoms and signs of respiratory insufficiency should be sought during routine clinic visits in patients with severe FSHD and regular monitoring of respiratory function instituted. Symptomatic respiratory insufficiency can be initially managed with nighttime non-invasive pressure support (BiPAP) but may, in severe cases, require the use of a ventilator."<sup>2</sup>

The FSH Society continues to disseminate valuable and important information through its FSH Watch newsletter and online at [www.fshsociety.org](http://www.fshsociety.org)

The FSH Society website, international bulletin board and chat room continue as a unique and primary resource for those needing immediate advice and support from others coping with FSHD.

The FSH Society remains the watchdog for FSHD research worldwide by aggressively promoting research projects and treatments through collaboration with patients/families, researchers, doctors and funding agencies.

<sup>1</sup> van der Maarel SM, Frants RR. "The D4Z4 repeat-mediated pathogenesis of facioscapulohumeral muscular dystrophy." *Am J Hum Genet.* 2005 Mar; 76(3):375-86. Review. PMID: 15674778

<sup>2</sup> Taswil R, van der Maarel SM. "Facioscapulohumeral muscular dystrophy." *Muscle Nerve.* 2006 Jul; 34(1):1-15. Review. PMID: 16508966

## EDUCATION

### *Studying pregnancy and delivery in women with FSHD*

FSH Society-sponsored project entitled "The Course and Outcome of Pregnancy and Delivery in Women with FSH Muscular Dystrophy."

By Emma Ciafaloni

As of our last progress report, we have mailed out a total of 74 questionnaire packets and have received 55 completed questionnaires. All completed questionnaires have been reviewed and 50 have been entered into our database. The data collected from 48 of the participants has been analyzed and submitted for presentation at the American Academy of Neurology annual conference and for publication in the journal *Neurology*. Preliminary results indicated that pregnancy and birth outcomes were generally favorable in this group of women with FSHD. However, the rate of a certain obstetrical issue — most notably an increased number of cesarean sections and a significantly higher rate of infants with low birth weight — supports the need for additional research.

The project was recently re-approved by the University of Rochester IRB and will continue to recruit and enroll new participants. Annual updates were sent to the eleven women who were of child bearing age (18-40 years) from our first cohort of participants; six of these questionnaires were returned.

If you know someone who . . . would be interested in knowing about the FSH Society, who would like to support our efforts, or perhaps a physician who should be aware of FSHD, please call the Society at (617) 658-7878, give us their name and address, and we will be glad to send them the newsletter and other information about FSHD.

#### GRANT INFORMATION

Neurology. 2006 Nov 28;67(10):1887-9.

Pregnancy and birth outcomes in women with facioscapulohumeral muscular dystrophy.

Ciafaloni E, Pressman EK, Loi AM, Smirnow AM, Guntrum DJ, Dilek N, Tawil R.

Department of Neurology, University of Rochester, 601 Elmwood Avenue, Box 673

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Obstetric risk in FSHD is not known. We surveyed 38 women with FSHD reporting 105 gestations and 78 live births. Review of medical records showed that pregnancy outcomes were generally favorable. The rates for low birth weight and total operative deliveries were statistically higher than the national rates in the general population. Worsening of FSHD was reported in 24% of gestations and did not usually resolve after delivery.

Grant: FSHS-DR-006A & FSHS-LEWI-002

Researcher: Emma Ciafaloni, M.D  
Institution: University of Rochester School of Medicine  
Department of Neurology

601 Elmwood Avenue

P.O. Box 673

Rochester, New York 14642 USA

Project Title: "The Course and Outcome of Pregnancy and Delivery in Women with FSH Muscular Dystrophy."

\$13,074 1/1/2004-12/31/2004 Year 1

\$12,973 1/1/2005-12/31/2005 Year 2

\$13,363 1/1/2006-12/31/2006 Year 3

**Goal:** Very little is known about the course and outcome of pregnancy and delivery in women with muscular dystrophies. Our current ability to efficiently counsel women with muscular dystrophies when pregnant or planning a pregnancy is very limited due to the lack of studies addressing the issue of pregnancy and delivery outcome in this group. No specific attention has been paid to the possible interaction between gestation and progression of the myopathy. Objectives are: to increase our knowledge about the course and outcome of pregnancy and delivery in women with FSH muscular dystrophy; to assess the effect of pregnancy, delivery and post-partum on the progression of muscle weakness and muscle pain and on quality of life in women with FSH muscular dystrophy; and to ultimately improve counseling, family planning and obstetric management of women with FSH muscular dystrophy.

### *Can respiratory insufficiency occur in FSHD?*

Yes. Respiratory involvement can be seen. Evaluation of the symptoms and signs of respiratory insufficiency should be sought during routine clinic visits in patients with moderate to severe FSHD. Regular monitoring of respiratory function is suggested as one might experience insufficiency over a long period of time without presenting signs. Symptomatic respiratory insufficiency can be initially managed with nighttime non-invasive pressure support e.g. a BiPAP machine. In very severe cases, patients may require the use of a ventilator. In standard practice, trauma (ER,

ICU), surgery and anesthesiology settings, care should be taken not to suppress respiratory drive with narcotics unless it is a situation of palliative care. Oxygen supplementation can be detrimental to patients with hypercarbic (high CO<sub>2</sub>) respiratory failure and lead to worsening CO<sub>2</sub> levels. Oxygen should generally not be administered unless BiPAP or similar ventilatory support is also being used. Your physician and a pulmonologist can help you periodically monitor CO<sub>2</sub> levels in the office or pulmonary function lab in the hospital, or by nocturnal oxymetry study.

## GENETIC INFORMATION

### *FSHD molecular diagnosis flowchart now available*

An excellent paper published in the *Journal Chromosoma* and co-authored by FSH Society grantees Melanie Ehrlich, Ph.D. and Richard Lemmers, MSc., Ph.D., introduced improvements to genetic testing and education in genetic testing for FSHD. Their article contains one of the finest graphic depictions of a flowchart of recommended procedures for molecular diagnosis for FSHD.

The paper illustrates “the inherent complexity of FSHD molecular diagnosis due to the 4q and 10q homology between D4Z4 arrays and adjacent sequences, translocations between 4q and 10q D4Z4 arrays, mitotic D4Z4 contractions, deletions encompassing p13E-11, and the wide range of sizes of D4Z4 arrays combined with the need for high resolution of bands in the 30- to 45-kb range.” They also make an improvement to the genetic testing for FSHD. “An important advantage of using a D4Z4 probe for molecular diagnosis of FSHD in conjunction with the p13E-11 probe is that it permits the identification of about 3% of FSHD patients who have a deletion of the p13E-11 genomic sequence next to a short 4q D4Z4 array (Lemmers et al. 2003).”

The article is an excellent overview of the state-of-the-art complex genetics of FSHD. In particular, figure 6 on page 114 has a long-overdue flowchart for the molecular diagnosis of FSHD. It depicts testing scenarios for both confirmation of clinical FSHD as well as exclusion to prove no clinical FSHD.

Many thanks go to Drs. Ehrlich and Lemmers and co-authors for this significant improvement in both genetic tests for FSHD as well as providing materials and documentation of how FSHD genetic testing works for the un-indoctrinated genetic testing centers and counselors.

#### ABSTRACT

*Chromosoma*. 2007 Apr;116(2):107-16.

Hybridization analysis of D4Z4 repeat arrays linked to FSHD.

Ehrlich M, Jackson K, Tsumagari K,

Camaño P, Lemmers RJ.  
Program in Human Genetics and  
Department of Biochemistry,  
Tulane Medical School  
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FSHD is an autosomal dominant disease involving shortening of D4Z4, an array of tandem 3.3-kb repeat units on chromosome 4. These arrays are in subtelomeric regions of 4q and 10q and have 1-100 units. FSHD is associated with an

*continued on page 25*

### *Determining the number of D4Z4 repeats based on deletion size*

The FSH Society receives numerous inquiries about understanding genetic test results. The following excerpt is from a recent well-written book chapter by Peter Lunt, Ph.D. that defines the generally accepted correlation between clinical severity and D4Z4 repeat number calculation.

#### ABSTRACT

“Molecular Testing: Confirmation of Diagnosis”

“In 90-95% of cases of FSHD, as defined by meeting the diagnostic criteria, the diagnosis can effectively be confirmed by showing the presence of a shortened (<35 kb) DNA fragment at 4q35 (recognized by probe p13E-11), which arises from deletion of an integral number of copies of the 3.3-kb repeats from that region. The DNA probe used (p13E-11) also detects the closely homologous 3.3-kb repeat array from 10q26. However, each chromosome 10-type repeat has an additional BlnI restriction site. For the specific diagnostic test, a double digest with EcoRI/BlnI is employed on genomic DNA (obtained from peripheral blood), which removes chromosome 10-type repeats, but leaves chromosome 4-type repeats intact (albeit reduced by 3 kb in size compared to EcoRI single digest)

Chapter p 48-49 “Facioscapulohumeral Muscular Dystrophy: Diagnostic and Molecular Aspects,” by Peter Lunt, Ph.D.

### *Test results and number of repeats*

A member of the FSH Society made an inquiry as to what the following genetic test results report meant in terms of numbers of repeats left e.g. these are my test results and how does this translate into number of repeats?

Enzymes	EcoRI	EcoRI/BlnI
Allele 1	>40kb	>40 kb
Allele 2	18 kb	15 kb

To make sense of the test results: each one of the inquirer’s chromosome 4’s is being tested for FSHD. First they are cut with an enzyme called EcoRI and then further checked to see if it is an unusual arrangement of DNA with another enzyme which further cuts the DNA called BlnI.

The results show the inquirer’s unaffected chromosome 4 and

affected chromosome 4. The unaffected chromosome (or allele 1) is the first when cut with enzymatic scissors. It is greater than forty or greater than the number of repeats needed to be affected or positive for FSHD.

The second number shows your affected chromosome (e.g. allele 2) is length at 18kb when cut with only one scissors. It is checked for special cases and to see if there are 10q repeats within the shortened fragment. It is 3kb less due to the test and is not a special case. The repeats are all from chromosome 4.

D4Z4 repeat numbers were calculated from EcoRI-fragment sizes as follows: number of repeats = (fragment size in kb - 5 kb flanking sequence) / 3.3 kb

This would appear to be  $(18-5)/3.3 = 3$  or 4 repeats.

## RESEARCH/DIAGNOSTIC TESTING

### FSHD: A molecular Cinderella

By Rune Frants, Ph.D., and Silvère van der Maarel, Ph.D., The Leiden University Medical Center

Elucidation of the molecular pathogenic pathways of FSHD is instrumental to improved patient diagnosis, counseling, management and treatment. During the past several years, important progress has been made with respect to insight in clinical, genetic and molecular aspects of FSHD. The variable clinical phenotype — ranging from practically asymptomatic gene carriers to wheelchair-bound patients or patients in need of respiratory support — is obvious in large families carrying the same mutation.

Next to the muscle involvement, the FSHD phenotype now includes retinopathy, hearing loss and mental retardation, underscoring the systemic and congenital nature of FSHD. An important step is the geno/phenotype correlation insight. It is well established that there is a rough inverse relationship between the residual length of the D4Z4 repeat cluster and the severity of the disease as defined by age-at-onset. The most severe symptoms like mental retardation and epilepsy are seen only in one repeat [Japanese] patients.

It is now generally accepted that FSHD is caused by a deletion (contraction) of D4Z4 repeats on 4q. New mutations are frequently encountered and approximately half of cases seem to be due to somatic rearrangements.

An interesting gender difference in disease expression in mosaic patients — males are more susceptible to disease — suggest a hormonal modulation of the phenotype.

Although FSHD is associated with a genomic rearrangement, it is unlikely that the D4Z4 deletion structurally compromises a putative FSHD gene. Available evidence strongly supports a model in which the D4Z4 contraction induces a change in the chromosomal environment, more specifically the chromatin structure, which in turn modulates the gene expression of gene(s) in cis or in trans. This may either occur by a spreading or looping mechanism, or more speculative, by a mechanism similar to transvection as chromosome

ends of 4q and 10q seem to exhibit a higher pairing frequency and other forms of cross talk. However, identification of the exact molecular mechanism and the crucial target gene(s) is still to be done.

Taken together there is increasing evidence for FSHD-specific changes in the chromatin structure and the histone code. Most arguments suggest a unique pathogenic mechanism behind FSHD. Elucidation of this intricate molecular network is instrumental to the development of evidence-based treatment (and preventive) strategies.

Below is a non-exhaustive list of research targets. The order is not intended to indicate priority rating.

1. Detailed characterization of individual candidate genes on #4q.
2. Identification of the difference between 4qA and 4qB; only short 4qA is causing FSHD.
3. The molecular causes and consequences of the exchange between 4q and 10q.
4. Chromatin structure and nuclear organization - histone code; methylation, acetylation etc.
5. Establishment of the gene expression modulation on:
  - a. #4q
  - b. Genome-wide
6. Development of functional models:
  - a. In vitro; cellular
  - b. In vivo; transgenic
7. Implementation of systems biology (integrated -omics and bioinformatics) to reveal molecular and metabolic pathways involved.
8. Harmonize molecular diagnostic procedures.
9. Systematic ascertainment and characterization of (homogenous) patient populations for clinical trials.
10. Generation of tools and reagents to monitor (pharmacological, training, or gene therapy) interventions.
11. Identification of additional FSHD loci and genes.

### FSHD molecular diagnostic & prenatal testing in Cardiff, UK

Cardiff has been providing molecular diagnostic service for FSHD for more than 10 years — ever since it was established that the D4Z4 repeat array deletion was associated with FSHD. For diagnosis, high molecular weight DNA samples are digested with EcoRI, EcoRI/BlnI and XapI and resolved on 1% agarose gels using pulsed-field gel electrophoresis (PFGE). Southern blots of these gels are hybridized with probe p13E-11. This protocol allows us to interpret complex DNA rearrangements including mosaicism. For the detection of 13E-11 deletion, DNA samples are digested with Hind III and southern blots hybridized with probe 4qA.

Diagnostic service is fully funded by the Wales NHS health service. The charge for the FSHD diagnostic test depends upon the exact nature of the diagnostic request. A large cohort of our FSHD patients and control individuals have been studied using probes 4qA and 4qB and have demonstrated that FSHD contracted allele is associated with the 4qA allele. Cardiff's aim is to develop the PCR-based assays to simplify FSHD molecular diagnosis.

Cardiff is offering both diagnostic and prenatal testing. For more information contact Drs. Ian Frayling and Meena Upadhyaya at (44) 2920 744081, Fax (44) 2920 747603.

### Finding a genetic testing clinic

See GeneTest at [www.GeneClinics.org](http://www.GeneClinics.org) for a list of well-known laboratories offering clinical testing for FSHD including deletion analysis, prenatal diagnosis and preimplantation genetic diagnosis. For those interested in locating a genetic testing facility, visit the FSH Society's home page and click on the "GeneTests: International Directory of Genetic Testing Laboratories for FSHD."

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## COMMUNITY AND SUPPORT

### 2006 International Patient Researcher Network and Contact Day

The 2006 International Patient Researcher Network and Contact Day for FSHD was held at the Charles Hotel in Cambridge, MA on Sunday, July 16, 2006. The meeting was an extraordinary success with more patients, researchers and doctors than ever attending. There were individuals from 22 states, the District of Columbia and six countries represented at the meeting.

The day began with keynote and welcome speeches from Daniel Paul Perez, FSH Society, John D. Porter, Ph.D., and William R. Lewis, M.D., Chairman, FSH Society.

The conference was dedicated to Stephen J. Jacobsen and a memorial tribute to three friends of FSH Society was distributed. Three lectures accordingly were named after three individuals who were involved in the Society and its work and who had made great contributions towards fighting and understanding the disease. See "Dedication to three friends" on page 9. Howard Chabner, Vice-Chairman distributed a comprehensive booklet on living with FSHD from the patient's perspective, essentially a survival guide to FSHD.

The day began with a panel of morning sessions titled "Health Information You Can Use Every Day!" Katherine Mathews, M.D., Ph.D. presented the "William T. 'Billy' Michael Memorial Lecture for Research on Infantile FSHD" titled "Clinical Medicine and Research Advances in Adult and Early-Onset FSHD." This lecture presented the state-of-the-art thinking on clinical research for adults and children with FSHD and had special emphasis on infantile FSHD.

Shree Pandya, P.T. gave a lecture on "Physical Therapy and FSHD" that generated a high level of discussion and excellent dialogue between patients and providers.

Noah Lechtzin, M.D. presented the "Stephen J. Jacobsen Memorial Lecture for the Stephen J. Jacobsen Excellence in Research Fund" titled "Respiratory Therapy and Issues in FSH Muscular Dystrophy." This lecture was full of useful information and an eye opener in terms of

raising awareness that respiratory insufficiency and compromise are of concern for those with FSHD and that vigilance needs to be maintained by patients and their families for symptoms of hyper-carbic respiratory failure either in day-to-day life or by physicians treating those with FSHD in the emergency room or trauma setting. Stephen Jacobsen passed away in January, 2006 from respiratory failure. Having the country's leading expert presenting on ways to help avoid respiratory failure and interventions was an extremely fitting tribute.

The morning panel/audience discussion and question and answers were moderated by Prof. David Housman, Ph.D.

After lunch, the afternoon sessions panel was titled "Helping to Solve FSHD!" This group of sessions was designed to focus more on current happening in research, clinical trials and genetic testing advances.

Sara Winokur, Ph.D. gave a lecture titled "New Insights in FSHD Research" that covered the current models, theories and approaches to understanding the molecular mechanism of FSHD. It was really great to see all of the remarkable progress made in the last few years.

Kathryn Wagner, M.D., Ph.D. gave the "Karen L. Johnsen Memorial Lecture for the 'Karen's Dream for a Cure' Research Fund" titled "Therapies, Compounds and Strategies to Treat FSHD." In a general manner, this lecture explained the current research happenings with a group of compounds that help with muscle growth called anti-myostatin inhibitors.

Dr. Wagner, who is involved with the Wyeth MYO-029 trials, fielded numerous questions regarding the clinical trials and prospects for the drug and treatments. Though not much was said specifically about the trial and results due to confidentiality reasons, this lecture generated a tremendous amount of enthusiasm and hope. Dr. Wagner had met with Karen Johnsen and her FSH Society support group at Karen's home in Bowie, MD to help recruit patients and get the word out about myostatin inhibition and thus this lecture was a fitting tribute to Karen.

Silvère van der Maarel, Ph.D. presented a lecture titled "FSHD Research and Genetic Testing Advances." At the outset, Dr. van der Maarel talked about a trial using folate to ameliorate FSHD thinking that nutritional supplements with folate would help restore the loss of methylation in FSHD. DNA methylation is a chemical modification of the DNA that is inheritable and important for many biological processes such as transcriptional regulation. It is reversible and can be manipulated with nutrition, supplements and drugs. Unfortunately, this small trial showed changes in DNA methylation in the subjects involved in the trial but not in the affected 4Q35 D4Z4 region.

The second half of the talk was on advances in genetic testing, and covered the new Japanese rapid diagnostic test for FSHD and its limitations. As well, Dr. van der Maarel presented a cautionary case of pre-implantation diagnostic testing using invitro fertilization (PGD IVF) where the PGD IVF testing indicated that the embryo was affected when indeed the embryo did not have FSHD. Since PGD IVF does not and cannot test for the actual deletion causing FSHD, it carries with it some degree of risk that some are comfortable with and others are not.

The afternoon panel/audience discussion and question and answers was moderated by Rune R. Frants, Ph.D. and SAB members of the FSH Society.

Following the lecture series came the much anticipated face-to-face group and breakout discussion groups. There were two sequential and identical concurrent workshops so that each participant could sit in on two of the four groups.

- ◆ Workshop I: **Getting to Know You/Taking Care of Ourselves** was a session to talk with others about FSHD.

- ◆ Workshop II: **Caregivers Respite/Significant Others and Parents** was a session to talk to other caregivers.

- ◆ Workshop III: **More Q&A with Researchers and Clinicians** was a session to meet and collaborate with research professionals.

*continued on page 21*

## Patient Contact Day,

continued from page 20

◆ Workshop IV: **Self-Advocacy and Patient Advocacy** was a session to learn about patient rights and legal issues.

It was an extraordinary day and many made new friends and contacts. One of the highlights was Anne Harland, chair of the Canadian FSHD patient group and liaison to Muscular Dystrophy Canada, who presented a beautiful painting honoring the Society's work to Daniel Perez that was done by an accomplished Toronto artist named Yonas Demissie. What makes this even more special is that Yonas is one of Ethiopian identical twins, one of whom has FSHD with the other unaffected. The Society proudly displays this gorgeous piece in its office.

Anyone attending these meetings will quickly learn that a striking aspect of the FSHD patient population is its high levels of intelligence and professional achievement, and that this makes it possible for the patient and medical communities to engage in an ongoing, challenging, and productive dialogue. The FSH Society-sponsored patient, researcher, and combined patient/researcher network conferences are the centerpiece of this dialogue. The Society is proud that many of the contributors to this meeting were FSH Society fellows and members of its SAB.

The Society wishes to thank the 2006 Network Conference speakers, the 2006 Network Conference committee and all attendees for their contributions to the success of this meeting. The FSH Society expressly thanks the sponsors of the 2006 Network Conference for their generous financial support of the programs: The AFM, Athena Diagnostics, Inc., Ride-Away Handicap Equipment Corp., The Massachusetts Rehabilitation Commission (MRC) and the Muscular Dystrophy Association of Canada.

We are beginning to plan for our next biennial patient researcher day scheduled for 2008. Please contact us if you are interested in fundraising and volunteering to help with this major event!

## SCIENTIFIC RESOURCES

### FSHD International Consortium meeting

The 2006 FSHD International Research Consortium Workshop for researchers and clinicians working on FSHD was held on October 9, 2006 in New Orleans, Louisiana. The scientific chair of the meeting was Silvère van der Maarel, Ph.D. and the organizers were Daniel Paul Perez, Silvère van der Maarel, Ph.D. and William R. Lewis, Sr., M.D.

The meeting was sponsored by the FSH Society, Wyeth Pharmaceuticals, the AFM, and the MDA-USA.

The FSH Society has compiled its own forward looking tactical and strategic research plan based on the input of scientists and advisors working on FSHD. We continually ask ourselves: how can we best accelerate the rate of discovery in FSHD research? Communication of what we know, what we do not know and what we need to know is absolutely key. At these meetings we encourage the sharing of new data and new ideas to promote solutions, treatment and therapy for FSHD.

We emphasize updating all funding agencies with newly gained knowledge and insights. We ask all attendees for their highest level of collegiality and willingness to share.

FSHD IRC Workshop 2006 covered four relevant topics to FSHD.

◆ Topic 1 "**Population & Genome Wide Studies, Quantitative & Qualitative Transcriptome Analysis**" was moderated by Silvère van der Maarel, Ph.D. Presenters for Topic 1 were Meena Upadhyaya, Jessica de Greef, Ph.D., Amy Asawachaicharn, Ph.D., and Joseph Marx, Ph.D.

◆ Topic 2 "**DUX4 & Therapy**" was moderated by Melanie Ehrlich, Ph.D. Presenters were Yi-Wen Chen, D.V.M., Ph.D., and Eugénie Annseau, Ph.D., Michael Kyba, Ph.D. and Rossella Tupler, M.D..

◆ Topic 3 "**Chromatin**" was moderated by Rossella Tupler, M.D., Ph.D. Presenters were Melanie Ehrlich, Ph.D., Chunbo Shao, Ph.D., Koji Tsumagari,

Ph.D. and Frédérique Magdinier, Ph.D.

◆ Topic 4 "**Studies of A-type lamins and EDMD**" was moderated by Silvère van der Maarel, Ph.D. Presenter was Brian Kennedy, Ph.D.

FSH Society Chairman of the Board, William R. Lewis, Sr., M.D., updated the group on the FSH Society research planning meeting held July 15, 2006. Dr. Lewis, Sr. emphasized the necessity of the group and community to help us produce a series of uniform reagents (anti-bodies, cell lines and animal models) to provide consistent experimental materials. He also requested the need and willingness to propagate, share and bio-bank materials.

For the complete program and abstracts book please see the Internet link on the homepage [www.fshsociety.org](http://www.fshsociety.org) titled:

"FSH Society 2006 FSHD Research Consortium, New Orleans: Program/ Abstracts, October 9, 2006 (PDF)" or:  
[http://www.fshsociety.org/fsh/FSHD\\_ASHG\\_IRC2006\\_WorkshopProgram\\_Proof\\_04October2006.pdf](http://www.fshsociety.org/fsh/FSHD_ASHG_IRC2006_WorkshopProgram_Proof_04October2006.pdf)

The FSH Society international research meeting is an annual forum that helps the patient advocacy groups advocate for the researchers. The more insight the researchers provide, the better the Society is able to deliver research and business plans and target funding from philanthropists, foundations, businessmen, government funding agencies and volunteer health agencies.

The meeting was held as a satellite to the American Society of Human Genetics. This year's 2007 meeting will be held in San Diego, California in October.

Researchers and clinicians interested in attending the workshop should contact Daniel Perez. This meeting is one of the services that the FSH Society provides to the community to advance knowledge, networking and understanding of FSHD. Donations and contributions to support this meeting are needed and most welcome!

Call the FSH Society office at (617) 658-7878  
for ideas on how you can be a part of raising funds for research

## RESEARCHER'S REQUESTS

### *Please consider tissue donation*

The NICHD Brain and Tissue Bank for Developmental Disorder at the University of Maryland in Baltimore is a tissue resource center established by the National Institute of Child Health and Human Development 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 upon the time of 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 times it is the comparison of the unaffected with the affected which 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 perhaps, one day, 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, Project Coordinator, at (800) 847-1539 during normal business hours (9 a.m.-5 p.m. EST Monday through Friday). Melissa can be reached anytime for an emergency. Thank you for taking the time to consider tissue donation. Please visit their website [www.btbfamily.org](http://www.btbfamily.org)

Melissa Larkins, Project Coordinator  
Brain and Tissue Bank for Developmental Disorders  
University of Maryland  
655 W. Baltimore Street, 13-013 BRB  
Baltimore, MD 21201-1559 USA  
(800) 847-1539, (410) 706-1755  
(410) 706-0020  
[btbumab@umaryland.edu](mailto:btbumab@umaryland.edu), or  
[mlark001@umaryland.edu](mailto:mlark001@umaryland.edu)

### *NIH FSHD patient registry enrolling members*

The University of Rochester Medical Center has been funded by the NIH to establish the National Registry of Myotonic Dystrophy and FSHD patients and family members. The registry is a database of patients diagnosed with DM or FSHD who are interested in participating in research about these diseases. Their unaffected family members are also invited to join.

The registry assists all researchers looking for volunteers willing to participate in their studies by searching the registry data base for qualified members. The registry staff sends those members a letter announcing the project. Applications are accepted from members and researchers across the United States. To enroll, people are required to complete a comprehensive questionnaire.

If you would like to participate or have questions regarding the NIH National Reg-

istry, please contact:

The NIH National Registry of Myotonic Dystrophy and FSHD  
601 Elmwood Avenue, Box 673  
Rochester, NY 14642-8673

**Call toll free: (888) 925-4302**

(9 a.m. to 4 p.m. weekdays, EST)

Local (Rochester, NY):

(585) 276-0004 Fax: (585) 273-1255

**Email:**

[dystrophy\\_registry@urmc.rochester.edu](mailto:dystrophy_registry@urmc.rochester.edu)

**Web:**

<http://www.dystrophyregistry.org>

or

<http://www.urmc.rochester.edu/nihregistry/contact.htm>

**Please tell them you are responding to a request from the FSH Society found in this newsletter.**

### *FSHD muscle biopsies needed for research repositories*

FSHD researchers are in constant need of muscle biopsies from FSHD patients. For an interesting look at how just one research project uses muscle biopsies and the focus of that research, please go to the Fourth and Fifth FSH Society Research and Education grants awarded article on page 35 and read grant FSHS-FS-005. Patricia Arashiro, B.Sc. and Mayana Zatz, MSc., Ph.D are looking at why some individuals are more severely affected than others, and why others, who have the FSHD gene, remain healthy. Muscle biopsies play a crucial roll in this research. When considering how many other 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 and 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 5 mm deep and a few millimeters in length. An open biopsy requires making an incision or a cut that is a few centimeters in length and a sample of muscle about the size of a pea is removed and requires stitching 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 them know you are willing to donate tissues. Contact Daniel Paul Perez at the Research Office of the Society or email [biopsy@fshsociety.org](mailto:biopsy@fshsociety.org) if you are interested in making a contribution to the science that could ultimately find treatment and a cure for those suffering from FSHD.

## *Are you clinically diagnosed with FSHD but genetic testing is negative?*

Researchers are very interested in identifying FSHD patients who are clinically confirmed but have tested negative for the 4q35 deletion. Certain kinds of deletions can occur distal and proximal on the FSHD D4Z4 region causing the genetic test to be negative. If your doctor is convinced that you have FSHD and your genetic test was negative, the FSH Society would like to put you in contact with researchers. Please contact Daniel Paul Perez at the Research Office of the Society or email [non4q35@fshsociety.org](mailto:non4q35@fshsociety.org)



## *Research materials needed for embryonic stem cell research*

FSHD researchers are finding that FSHD occurs at very early stages of development and are in need of embryonic tissues to study. FSHD couples who have gone through, and had pre-implantation genetic diagnosis and in vitro fertilization (IVF PGD), are asked to consider making a valuable gift to research by donating remaining frozen IVF PGD embryos to the FSHD tissue and stem cell repositories. Please contact Daniel Paul Perez at the Research Office of the Society or email [fshdesc@fshsociety.org](mailto:fshdesc@fshsociety.org)

*The FSH Society has been instrumental in the giant advances in research to find a cure for FSHD. We need your donations to continue the fight! Please see donation form on back page.*

## **RESEARCH**

### *A discussion of early-onset or infantile FSHD*

Brouwer et al in the Netherlands defined early onset FSHD (IFSHD) as:

1. Signs or symptoms of facial weakness before age 5 years, and
2. Signs/symptoms of shoulder girdle weakness before age 10 years.

He identified only six patients who met those criteria, and their phenotypes did not differ significantly from patients with later onset. Only four of the six had documented 4q35 deletions. Brouwer's population strongly favored familial cases (only 9 of 96 patients studied had sporadic disease).

Jardine, et al in the UK reported that patients with de novo 4q35 deletions tend to have larger deletions than familial cases, and also to have more severe disease. The mean age at onset of this population was 6.8 years, 30% used a wheelchair before 18 years of age, and three had congenital facial diplegia and sensorineural deafness. This age at wheelchair use contrasts sharply with the overall statistics reporting that 20% of FSHD patients require a wheelchair by age 50 years

Arahata et al in Japan analyzed the data from 78 independent families with 4q35 FSHD. They found that 16-17% of the patients had early onset disease. Approximately one-half of these had EcoRI fragments of less than 11kb, the smallest fragments. All of the patients with these smallest fragments have early onset disease. Surprisingly, in Japan this group comprising 50% of the small fragment group of patients, had epilepsy and almost 90% had mental retardation.

Korf et al report six patients with facial diplegia occurring in the first year. All had severe progressive disability prior to adolescence.

Shapiro, Jardine, Yamanaka defined early onset FSHD as patients who exhibit gait disturbances before age 28.

Other features of early-onset FSHD are bilateral sensorineural hearing loss, retinal vasculopathy, mental retardation and epilepsy.

In Deymer's Neuromuscular Diseases from Basic Mechanism to Clinical Management, Dr. Lunt writes in his chapter: "Facioscapulohumeral muscular dystrophy

Diagnostic and Molecular Aspects" on page 47 that "In more severe infantile-onset cases, facial weakness is the earliest and most prominent sign. Thus, the infant may show little or no facial expression, appearing unable to smile, and may be initially misdiagnosed as having Mobius syndrome. Pelvic girdle weakness in the most severe cases can be prominent by age 10 years, leading to consideration of Xp21 or limb girdle types of muscular dystrophy, but unlike these conditions, FSHD is still characterized by an even greater degree of shoulder girdle weakness rather than pelvic weakness. FSHD is inevitably progressive, and an overall 20% of patients require a wheelchair by the 5th decade, although this can be required before age 20 years in many of the most severe new mutation cases."

This might suggest that very early onset FSHD represents approximately 10-20% of all cases, that these patients are more likely to have de novo mutations and that the clinical manifestations may include congenital facial diplegia, congenital deafness, mental retardation or seizures. These patients are likely to require wheelchairs in childhood.

Some ideas and new emerging definitions and criteria being put forth by researchers working on FSHD for IFSHD are:

- ◆ clinically severe FSHD; patients who report needing a wheelchair greater than 50% of the time by age 18 years; and
- ◆ those predicted to have severe FSHD; we have chosen to examine data from those patients with EcoRI fragments smaller than 15kb. This is a conservative value and is expected to identify patients with a milder phenotype in addition to the more severe. This corresponds to roughly three or fewer residual 3.3kb repeats.

FSHD researchers are interested in studying IFSHD and early onset FSHD. Please contact Daniel Paul Perez at the research office of the Society or email [ifshd@fshsociety.org](mailto:ifshd@fshsociety.org) if you meet the criteria listed above or are interested in helping research in this area.

## RESEARCH

### *Current trends in FSHD research, continued from front page*

First, there has been a renewed interest in the role of a potential gene (DUX4) which is encoded by the repeat (D4Z4) deleted in FSHD. DUX4 appears to be a transcription factor which can regulate the expression of many other genes. As the sequence for DUX4 is located in the repeat, this gene was the focus of much attention when the deletion was first identified. However, initial studies did not reveal any evidence for the expression of DUX4, and the focus moved to more proximal genes (FRG1, ANT1, FRG2).

Several recent studies suggest that DUX4 may indeed be expressed. Jane Hewitt, Ph.D. has found that the DUX4 sequence is conserved in many species. Maintenance of this sequence throughout evolution suggests that it has an important functional role. Dr. Hewitt also found that DUX4 sequences are expressed from D4Z4 repeat arrays in the mouse, giving further credence to its functional role as a gene.

The function of the potential DUX4 gene in humans has also undergone further analysis. Alberto Rosa M.D., Ph.D. identified DUX4 messenger RNAs (mRNAs) in FSHD myoblasts. These mRNAs are evidence of DUX4 gene expression. Over-expression of the DUX4 gene caused cell death, likely through the induction of the apoptotic genes caspase 3/7. He found that DUX4 is localized to the nucleus and that it causes a redistribution of emerin at the nuclear envelope. This finding is of interest in light of the localization of the FSHD-D4Z4 region to the nuclear envelope (Sara Winokur).

Alexandra Belayew, Ph.D. has dedicated much of her career over the past decade to the role of DUX4 in FSHD. She has found that DUX4 is expressed in FSHD muscle through the use of an antibody she developed. Dr. Belayew, in collab-

oration with Yi-Wen Chen, D.V.M., Ph.D., have shown that DUX4 regulates the expression of PITX1, which is a gene previously identified as mis-regulated specifically in FSH muscular dystrophy.

Gene expression studies continue to reveal the pathways and genes involved in FSHD. Dr. Rabi Tawil has performed a carefully controlled gene expression study using 19 FSHD, 12 myotonic and 30 normal muscles biopsies. Dr. Tawil found that many of the abnormally expressed genes are involved in smooth muscle or endothelial cells, which may explain the retinal vasculopathy seen in FSHD. He did not find an increase in 4q35 (FSHD region) genes, which is consistent with previous expression profiling and RT-PCR data (Melanie Ehrlich and Sara Winokur). Specifically, there was no up-regulation of FRG1, which has now also been confirmed through RNA-FISH studies of single myoblast nuclei from FSHD patients (Sara Winokur).

Patrick Reed, Ph.D., and Robert Bloch, Ph.D. examined soluble proteins from FSHD and control muscle by mass spectrometry and 2D gel electrophoresis and showed large increases in mu-crystallin, which likely has a role in the differentiation, oxidative stress, retinal and inner ear defects seen in FSHD. Macaione, Ph.D. and Vita, Ph.D. identified an increase in nuclear factor-kappa B and a receptor for glycation end products in FSHD, which also contribute to altered oxidative stress.

Perhaps one of the most significant recent findings in FSHD is that there are specific sequence variations of the 4q35 sub-telomeric region that are associated with FSHD (Richard Lemmers and Silvére van der Maarel). Drs. Lemmers and van der Maarel examined a "simple

sequence length polymorphism" (SSLP) just proximal to D4Z4, a single nucleotide polymorphism (SNP) within D4Z4 and the A/B variation distal to D4Z4. They found that the FSHD subtelomeric region exists in nine different forms (haplotypes) but that FSHD is associated with deletions in specific haplotypes, predominantly 4qA161. Further analysis of these specific sequence variations is likely to yield insight into the FSHD mechanism through protein binding or chromatin structure effects.

Another exciting avenue of research has been through the analysis of stem cells in FSHD. Kyoko Yokomori, Ph.D. is examining chromatin structure of the FSHD region in early development, while Leslie Lock, Ph.D., and Dr. Winokur have looked at the expression of FSHD region genes in embryonic stem cells. Interestingly, many of the key genes thought to be involved in FSHD (DUX4, PITX1) are expressed very early in development. Studies are also underway in adult muscle stems cells termed mesoangioblasts (Sara Winokur). Gene expression analysis and differentiation potential compared between stem cells isolated from FSHD and control muscle biopsies.

On the clinical front, the effects of training and albuterol were examined with the conclusion that they do not have a positive or negative effect on pain, fatigue, functional status or psychological distress in FSHD (Elli van der Kooi, M.D. and George Padberg, M.D.). Electromyographic (EMG) studies of FSHD muscle were compatible with a mild, slowly progressive myopathy and that the fiber degeneration and loss was independent of regeneration and reinnervation in FSHD (J Stubgen, M.D.).

The need for additional diagnostic tests in FSHD was highlighted by an FSHD family with an extended proximal deletion encompassing the probe most often used for molecular detection, p13E-11. This family, which exhibited the typical range and severity of FSHD clinical symptoms, had an apparent absence of the contracted D4Z4 repeat when p13E-11

*continued on page 25*

*The FSH Society has funded*

**\$1,751,280** for FSHD research to date!

*Please help us continue the work by sending in your donation today. We can't do it without all of you!*

## RESEARCH

### *Trends*, continued from page 24

was used as the diagnostic probe, but upon further analysis an allele with 10 repeat units was identified (Deak, Ph.D. and Gilbert, Ph.D., Duke University Medical Center). Drs. Melanie Ehrlich and Richard Lemmers have optimized hybridization condition with a 1-kb D4Z4 sub-fragment which allows for the identification of D4Z4 alleles with p13E-11 deletions.

As evidenced by the proliferation of these significant findings in FSHD research during the past year, the definitive genetic mechanism for FSHD appears to be on the horizon. Continued support and collaboration between the patient and research communities will be essential to our common goal: identification of the FSHD mechanism and clinical treatment for this most challenging disorder.



### *Molecular diagnosis*

#### *flowchart*, continued from page 17

array of 1-10 units at 4q35. Unambiguous clinical diagnosis of FSHD depends on determining the array length at 4q35, usually with the array-adjacent p13E-11 probe after pulsed-field or linear gel electrophoresis. Complicating factors for molecular diagnosis of FSHD are the phenotypically neutral 10q D4Z4 arrays, cross-hybridizing sequences elsewhere in the genome, deletions including the genomic p13E-11 sequence and part of D4Z4, translocations between 4q and 10q D4Z4 arrays, and the extremely high G+C content of D4Z4 arrays (73%). In this study, we optimized conditions for molecular diagnosis of FSHD with a 1-kb D4Z4 subfragment probe after hybridization with p13E-11. We demonstrate that these hybridization conditions allow the identification of FSHD alleles with deletions of the genomic p13E-11 sequence and aid in determination of the nonpathogenic D4Z4 arrays at 10q. Furthermore, we show that the D4Z4-like sequences present elsewhere in the genome are not tandemly arranged, like those at 4q35 and 10q26.

PMID: 17131163 [PubMed - in process]

### *Eleventh, Twelfth, Thirteenth, Fourteenth and Fifteenth FSH Society Marjorie Bronfman Fellowship*

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



FSHS-MB-011  
Yi-Wen Chen, D.V.M., Ph.D.  
Children's National Medical Center  
"Molecular Mechanisms of Muscle Atrophy in facioscapulohumeral muscular dystrophy"



FSHS-MB-012  
Davide Gabellini, Ph.D.  
University of Massachusetts Medical School  
"Development of an Animal Model of FSHD."



FSHS-MB-013  
Melanie Ehrlich, Ph.D.  
Tulane Medical School  
"Finding the 4q35 FSHD Gene."



FSHS-MB-014  
Patrick Reed, Ph.D.  
University of Maryland School of Medicine  
"Analysis of Changes in the Proteome in Facioscapulohumeral Muscular Dystrophy."



FSHS-MB-015  
Yvonne Meijer-Krom, Ph.D.  
Leiden University Medical Center  
"Towards the Discovery of Early Developmental Defects in FSHD."



Grant: FSHS-MB-011  
Researcher: Yi-Wen Chen, D.V.M., Ph.D.  
Institution: Assistant Professors of Pediatrics  
Center for Genetic Medicine Research  
Children's National Medical Center  
111 Michigan Avenue, N.W.  
Washington, D.C. 20010 USA  
Project Title: "Molecular Mechanisms of Muscle Atrophy in facioscapulohumeral muscular dystrophy"  
\$30,000 1/1/2006 – 12/31/2006 Year 1  
**Goal** [provided by applicant]:

In preliminary studies, we studied 125 whole genome profiles of muscle biopsies from patients with facioscapulohumeral muscular dystrophy (FSHD), Duchenne muscular dystrophy, Juvenile dermatomyositis, dysferlin deficiency, Emery-Dreifuss muscular dystrophy and eight other disorders and showed that one gene, PITX1 was significantly and specifically up-regulated in patients with FSHD. Meanwhile, using data from an independent human study, we showed that the gene was up-regulated in atrophic muscles of patients with spinal cord injury. To identify molecular pathways regulated by PITX1 in mature skeletal muscles, we over-expressed PITX1 in mouse muscles, and showed that up-regulation of PITX1 leads to induction of the ubiquitin-proteasome pathways, including atrogen 1 which plays a key role in muscle atrophy.

Based on the preliminary data, we hypothesize that transcriptional pathways perturbed by the contraction of D4Z4 arrays lead to up-regulation of PITX1, and induction of atrophy pathway, which plays a critical role in the patho-physiology of FSHD. In this application, we propose to generate and evaluate a conditional muscle-specific PITX1 transgenic mouse as a potential animal model of human FSHD. The data generated in the proposed study will provide valuable findings on molecular mechanisms of muscle atrophy in general, and a potential animal model for studying FSHD.

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## RESEARCH

### *FSH Society Marjorie Bronfman Fellowship*, continued from page 25

#### LAY SUMMARY

By Yi-Wen Chen

Although many muscular dystrophies share secondary pathological changes such as muscle necrosis, regeneration, fibrosis and inflammation, the primary causes of these diseases are different. One strategy to identify the disease-specific differences

is to compare the whole-genome expression profiling data (assessing gene activities of the whole genome) of one disease to the others.

To identify genes likely involved in the early pathological process of FSHD, we compared expression profiles of FSHD to 11 other neuromuscular diseases, such as

Duchenne muscular dystrophy, Emery-Dreifuss muscular dystrophy, Juvenile dermatomyositis, and dysferlin deficiency. We identified one gene, PITX1, that specifically up-regulated in the muscle of the FSHD patients.

This gene is particularly interesting to

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### *Remarkable progress on FSHD seen at Children's National Medical Center*

On December 6, 2006 Yi-Wen Chen, D.V.M., Ph.D., principal investigator of FSH Society grant FSHS-MGBF-011, notified the Society that she would not request her second year funding based on the fact that the PI is to receive an NIH R01 award from NIAMS, National Institute of Health. Supported by the fellowship, Dr. Chen has successfully generated the proposed double transgenic mice (aim 1). Dr. Chen wrote: "we generated transgenic mice containing PITX1 under tetracycline response elements (TRE-PITX1) using the CNMC transgenic core directed by Dr. Margaret Sutherland who has extensive experiences in generating and analyzing tet-expression animal models."

They would be moving onto "characterizing the muscle-specific PITX1 transgenic mouse using molecular and functional assays" using several lines. The proposed aim 2 and 3 of the FSH Society grant will be completed under the support of the R01 grant. Dr. Chen expressed appreciation for the support of the FSH Society and Daniel Paul Perez. The study would have not been able to progress in the past year without the grant support from the FSH Society. Current findings of the proposed mouse model were included in the progress report to the Society and will be reported at the annual FSH Research workshop.

Below is the NIH project abstract for the funded R01 grant. This R01 grant is probably in the \$250,000-\$350,000 range per year for direct cost for 5 years. This demonstrates the remarkable power of leveraging this FSH Society Marjorie Bronfman fellowship from the \$30,000 to

\$60,000 range to \$1 million to \$1.5 million over five years. Please consider supporting the Society with fellowships!



#### *[NIH project summary]*

FSHD is an autosomal dominant muscle disorder that is characterized by the progressive weakness and wasting of the muscles from face, upper-arm and shoulder girdle to lower limb. While there is consensus that FSHD is a disorder of transcription and gene regulation, the molecular pathways leading to muscular dystrophy and other unique clinical features of the disease are far from clear.

Our preliminary study of whole genome profiles of 125 muscle biopsies representing 12 neuromuscular disorders showed that PITX1 gene was specifically up-regulated in FSHD patients. The significant PITX1 over-expression we observed in FSHD cannot be due to inflammation, degeneration/regeneration, or other "dystrophic" changes in muscle, as no other muscle disease (including juvenile dermatomyositis, Duchenne dystrophy, and others) showed up-regulation.

Based on our extensive preliminary data both in vitro and in vivo, we present a model where over-expression of PITX1 in adult muscle invokes key muscle atrophy pathways, and, further, that PITX1 is regulated by DUX4 expression. The goal of this current proposal is to further develop our pathophysiological model to show direct relationships between 4q35 deletions, DUX4, and PITX1. The proposed research relies heavily on temporal series, conducted both in vivo and in vitro. Gene/gene interactions will also be determined.

In aim 1, we propose to determine if PITX1 is a direct target of DUX4. We will determine whether a putative DUX4 binding site in the promoter region of PITX1 is functional, and whether it is specifically and directly regulated by DUX4. Additional DUX4 targets will be identified by temporal profiling. Interaction between DUX4 and potential target genes will be determined.

In aim 2, we propose to generate and characterize a conditional muscle-specific PITX1 transgenic mouse model. The phenotype will be evaluated for changes in various clinical, functional, biochemical, molecular and histological parameters. The phenotype of myoblasts, including appearance, proliferation, differentiation and susceptibility to oxidative stress, will also be evaluated. In addition, we will determine whether the disease phenotype is reversible.

In aim 3, we will define molecular transcriptional pathways downstream of PITX1 expression using the PITX1 transgenic mouse. Temporal expression profiling will be performed to construct the pathways regulated by PITX1. Interactions between PITX1 and potential regulatory targets of PITX1 will be further studied. Our preliminary data showed that disease-specific up-regulation of DUX4 and PITX1 and downstream changes of genes involved in muscle wasting might be involved in the pathophysiology of FSHD. The proposed research will identify key players in the pathological cascades of FSHD and define the interactions among them, which could potentially be used for developing treatments of the disease.

## RESEARCH

### *FSH Society Marjorie Bronfman Fellowship*, continued from page 26

us because it plays a significant role during embryonic limb development; it is expressed differently between the upper and lower limbs, and the effect of the gene is left-right asymmetric. These unique characteristics of PITX1 gene explain some of the major FSHD-specific clinical presentations. Since the function of PITX1 in postnatal muscles was not known, we conducted both *in vivo* and *ex vivo* experiments to study the function of PITX1 in muscles using mice and cell cultures.

The results showed that PITX1 induced expression of genes involved in muscle atrophy, including up-regulation of two critical players in the muscle atrophy pathway. We are currently conducting additional experiments to establish the regulatory relationships between the PITX1 and its regulatory targets. In addition, supported by the FSH Society, we are developing a transgenic mouse model which can selectively express PITX1 in the muscles upon induction. The goal is to generate an animal model which can be used to study the molecular mechanisms and develop therapeutic means of the disease.

■■■

Grant: FSHS-MB-012

Researcher: Davide Gabellini, Ph.D.

Institution: Howard Hughes Medical Institute Program in Gene Function and Expression

University of Massachusetts Medical School

Lazare Research Building - 6th Floor - Room 660 A

364 Plantation Street

Worcester, MA 01605 USA

Project Title: "Development of an Animal Model of FSHD."

\$37,500 1/1/2006-10/31/2006 Year 1

Goal: [provided by applicant]:

FSHD, the third most common myopathy, is an autosomal dominant neuromuscular disorder characterized by progressive weakness and atrophy affecting selective skeletal muscles. The disease has not been linked to a classical mutation within a protein-coding gene. Instead, FSHD patients

carry deletions of tandem 3.3 kb repeats, termed D4Z4, located on chromosome 4q35. An incomplete knowledge of the biochemical pathogenesis of FSHD has hampered the development of effective therapies. D4Z4 is a repetitive element with heterochromatic features. Recently, we reported that FRG1, FRG2, and ANT1, three 4q35 genes located upstream of D4Z4, are inappropriately over-expressed, specifically in FSHD muscle. We found that an element within D4Z4 behaves as a silencer providing a binding site for a transcriptional repressing complex. These results suggest a model in which deletion of D4Z4 leads to the inappropriate transcriptional de-repression of 4q35 genes resulting in disease.

To identify the gene(s) responsible for FSHD, we generated transgenic mice over-expressing FRG1, FRG2 or ANT1 selectively in the skeletal. FRG1 transgenic mice develop a pathology with physiological, histological, ultra-structural and molecular features analogous to those observed in FSHD patients. These include abnormal spinal curvature, progressive muscular dystrophy, skeletal muscle atrophy and differential involvement of muscle types. Moreover, in both FSHD patients and FRG1 transgenic mice, there is no evidence for mitochondrial involvement or alteration of sarcolemmal integrity. This latter feature distinguishes FSHD from other muscular dystrophies in which sarcolemmal disruption is the primary pathogenetic mechanism. By contrast, mice over-expressing two other putative FSHD-candidate genes, FRG2 and ANT1, are normal with regard to both phenotype and muscle histology.

FRG1 is a nuclear protein and several lines of evidence suggest it is involved in pre-mRNA splicing. We found that in muscles of FRG1 mice and FSHD patients, specific pre-mRNAs undergo aberrant alternative splicing. Collectively, our results suggest that FSHD results from inappropriate over-expression of FRG1 in skeletal muscle, which leads to abnormal alternative splicing of specific pre-mRNAs.

Here we propose a detailed study of

FRG1 mice to provide novel insights into the molecular pathogenesis of FSHD by addressing the following questions:

1. What is the biological role of FRG1? The precise mechanism of action of FRG1 is unknown. FRG1 might bind FRG1 directly, and change splicing dynamic, or it might regulate the activity of splicing factors. We plan to identify FRG1 interaction partners as a starting point for understanding its biological role.

2. How does FRG1 over-expression trigger muscular dystrophy? Understanding the role FRG1 plays in normal and diseased muscle requires methods to identify the set of RNAs it regulates *in vivo* and the use of a mouse model of FSHD for RNA target validation. To address this aim systematically, we will undertake a genome-wide screen to identify and validate FRG1 dependent, alternatively spliced transcripts in muscle.

These studies will provide relevant information to understand the molecular basis of FSHD that will help in the development of effective therapeutic strategies. FRG1 mice may be used as a preclinical model to test new therapies for FSHD.

■■■

Grant: FSHS-MB-013

Researcher: Melanie Ehrlich, Ph.D.

Institution: Hayward Genetics/SL31 Tulane Medical School

1430 Tulane Avenue

New Orleans, LA 70112 USA

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

\$35,000 7/24/2006 – 7/23/2007 Year 1

\$35,000 7/24/2007 – 7/23/2008 Year 2

Goal [provided by applicant]:

A major obstacle in research on FSHD is the uncertainty about the identity of the 4q35 gene whose activity is directly controlled by a short D4Z4 array on the same chromosome (*in cis*). Circumstantial evidence strongly indicates that inappropriate expression of this gene (the FSHD gene) in certain skeletal muscle cells is caused by having a short D4Z4 array in its vicinity. Apparently, the inappropriate expression of the FSHD gene causes the painful and

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## RESEARCH

### *FSH Society Marjorie Bronfman Fellowship*, continued from page 27

debilitating symptoms of FSHD by altering expression of other genes indirectly.

I propose to use a novel approach to screen for the FSHD gene in the 1-Mb region proximal to the D4Z4 array on 4q. There are now well-proven examples of long-distance control of human gene expression by DNA elements that have to be on the same chromosome as the gene they regulate (cis control). My lab will identify by computer analysis about 100 sequences that might contain the elusive FSHD gene, including many sequences that would not be identified by current gene search programs as potential genes.

My research group will design ~100 primer-pairs corresponding to 100-200 bp sequences in these regions and check by in silico analysis and PCR on human-rodent somatic cell hybrids and human DNA that these DNA primer-pairs work well in PCR and are unique to human chromosome 4. This broad search will compensate for the major inadequacies of available gene prediction programs and allow discovery of either a conventional or an unconventional gene such as a gene that encodes a regulatory RNA, but not a protein.

My lab will prepare and characterize myoblasts from FSHD and control patients and fix these cells. They will then be analyzed by quantitative RNA polymerase II chromatin immunoprecipitation (ChIP) assays, a DNA-based assay for engagement of the transcription machinery on specific DNA sequences. Our lab will interpret the resulting ChIP data and then, on FSHD and control myoblasts, my lab will do RT-PCR analyses to test sequences that are positive for transcription in the ChIP analysis.

These RNA-based assays will be quantitative real-time RT-PCR analyses to compare FSHD and control samples and end-point RT-PCR analyses that give another level of verification by visualization of the size of the RT-PCR product. We will do these RNA-based assays to verify that the regions are transcribed from myoblasts, to determine if we can detect increased RNA amounts for one or more of these regions in FSHD vs. control myoblasts and to test whether candidate

FSHD gene sequences are transcribed from various other cell types, including FSHD and control fibroblasts and lymphoblastoid cell lines.

The method that we will employ to screen for the FSHD gene is the best one for direct identification of transcription of genes, whatever their nature. It is independent of secondary factors that can greatly impact standard RNA analyses. These complicating factors are RNA degradation in vitro despite the use of RNase inhibitors and RNase-free reagents, RNA processing in vivo, and RNA stability in vivo. If the RNA polymerase II ChIP assays indicate differential transcription of one or more 4q35 genes in a comparison of FSHD to control myoblasts but the RNA assays do not, it could be because of one of these complications associated with RNA analysis. In that case, we will use a different type of ChIP assay to confirm the RNA polymerase II ChIP results, namely ChIP with an antibody to the general transcription factor TBP and PCR primers in the region of the putative promoter. This study holds the promise of greatly facilitating research on FSHD by elucidating the nature of the critical gene initially impacted by a short 4q D4Z4 array but unresponsive to a short, virtually identical D4Z4 array at 10q.

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Grant: FSHS-MB-014

Researcher: Patrick Reed, Ph.D.

Institution: Department of Physiology  
University of Maryland School of Medicine

660 W. Redwood St.

Baltimore, MD 21201 USA

Project Title: "Analysis of Changes in the Proteome in Facioscapulo-humeral Muscular Dystrophy."

\$30,000 1/24/2007 – 1/23/2008 Year 1

**Goal** [provided by applicant]:

One of the largest hurdles to understanding the pathogenic basis of FSHD is identifying the molecular mechanisms that trigger the onset of muscular dystrophy. Although FSHD is linked to deletions of 3.3 kb non-coding repeats (D4Z4) near the telomere of chromosomal position 4q35, the mechanisms linking these dele-

tions to changes in gene expression, altered protein expression and consequent changes in muscle structure and function are still poorly understood.

Many muscular dystrophies are linked to changes in the stability of the sarcolemma of skeletal muscle. My previous work suggested that the sarcolemma of FSHD muscle was also affected in ways that might lead to muscle weakness, but the proteins that were altered could not be readily identified. I have now adapted a proteomic approach to identify proteins that are altered in FSHD, and to test their possible roles in pathogenicity.

The method I have chosen is high resolution, large format, two-dimensional electrophoresis (2D-GE). With the improvements I have introduced into the method, I can now detect more than 3,000 distinct protein spots in normal and FSHD muscle samples. Remarkably, my preliminary results indicate that very few proteins show changes in expression levels in FSHD muscle compared to controls. One, a spot that showed strong expression in the soluble fraction from FSHD muscle but no detectable expression in controls, has an isoelectric point of 5.07 and a molecular mass of approximately 34 kDa. I used LC/MS/MS techniques to show that this protein is mu-crystallin (CRYM; also called "thyroid hormone binding protein" THBP). Western blots confirmed that this protein is highly up-regulated in deltoid muscle from FSHD patients compared to controls. Although my analysis is still incomplete, this protein is of considerable interest because it is expressed in the retina and is responsible for high frequency hearing loss, both of which are compromised in patients with FSHD.

Furthermore, its role as a thyroid hormone binding protein places it at a potentially crucial point in the regulation of myoblast cell division and differentiation, which have recently been implicated as defective in FSHD through gene array studies. It may also be linked to sarcolemmal and sarcomeric changes, as crystallins are likely to play important roles in the assembly of intermediate filaments at these

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## RESEARCH

### *FSH Society Marjorie Bronfman Fellowship*, continued from page 28

structures in developing muscle. Finally, the autosomal dominant nature of FSHD suggests a “gain-of-function” mutation, consistent with the over-expression of a protein in FSHD that is expressed at much lower levels in healthy muscle. My novel findings therefore suggest that FSHD may be caused by up-regulation of CRYM, with consequent changes in the structural organization and thyroid hormone signaling pathways.

**My general aim is** to test the idea that up-regulation of CRYM is an important pathogenic mechanism that leads to FSHD.

**My specific aims are:**

1. to learn if increased levels of CRYM are indeed specific for FSHD by applying my improved methods for 2D-GE to complete my analysis of the proteomes of FSHD and control muscle, as well as muscles from other dystrophic samples;

2. to use cellular transfection methods to study the biology of CRYM in myoblasts and myotubes in culture; and

3. to use transgenic techniques to try to reproduce key features of FSHD in mice. If successful, my experiments should lead to a new understanding of the molecular mechanisms underlying FSHD, and provide an animal model to use in developing therapies for it.

■■■

Grant: FSHS-MB-015

Researcher: Yvonne Meijer-Krom,  
Ph.D.

Institution: Leiden University Medical  
Center (LUMC)

Department of Human Genetics  
Postal Zone S-4-P

Eindhovenweg 20; 2333 ZC Leiden  
PO Box 9600; 2300 RC Leiden  
The Netherlands

Project Title: “Towards the Discovery  
of Early Developmental Defects in  
FSHD.”

\$35,000 1/24/2007 – 1/23/2008 Year 1

\$35,000 1/24/2008 – 1/23/2009 Year 2

**Goal [provided by applicant]:**

Autosomal dominant FSHD is the third most common myopathy. FSHD is mainly characterized by an often asymmetric progressive weakness and wasting of the facial,

shoulder and upper arm muscles, typically starting in the second decade of life. FSHD is caused by contraction of the polymorphic D4Z4 repeat in the subtelomere of chromosome 4q (van Deutekom et al. 1993; Wijmenga et al. 1992). Contraction of D4Z4 is associated with DNA hypomethylation (van Overveld et al. 2003) and loss of a D4Z4 repressor complex containing the polycomb protein YY1 implying a complex epigenetic disease mechanism.

There is strong clinical evidence that FSHD should be regarded as a congenital disease with progressive character. Clinical and genetic features suggest an embryonic involvement in FSHD. These include the marked asymmetry of muscle involvement, the 1,000-fold increased occurrence of pectus excavatum unrelated to the muscle weakness and the early onset FSHD cases with complete absence of some muscle groups (Padberg 1982; Padberg 2004). In addition, two interesting candidate genes, FSHD region gene 1 (FRG1) and FRG2, located on chromosome 4, are transcriptionally deregulated in FSHD muscle culture, but not in adult muscle. Involvement of an early myogenic defect in FSHD is further supported by the observation that many of the deregulated genes in FSHD muscle are direct targets of MyoD, a key regulator of myogenesis (Figlewicz et al.

2004; Winokur, et al. 2003). Loss of YY1-Ezh2 has been demonstrated to recruit MyoD, leading to the transcriptional induction of genes involved in myogenic differentiation (Caretto et al. 2004). Therefore, we hypothesize that an unbalanced YY1 availability during early embryogenesis disturbs the myogenic program, which may render specific muscle groups more susceptible to disease later in life.

To obtain better insight in the direct targets of MyoD that are deregulated in FSHD, we will perform a transcriptome analysis of 4q-linked FSHD, phenotypic FSHD with hypomethylation of D4Z4 and control fibroblast undergoing forced myogenesis. To determine their dependency on YY1, YY1 levels will be reduced during myogenesis. In parallel, the fusion and differentiation rate of the fibroblast cell cultures will be evaluated to assess their morphologic characteristics. An advantage over the assessed gene expression profile in mature muscle is that the current application mimics the early myogenic program. Furthermore, the forced myogenic cell population will be much more homogeneous compared to primary myoblast cell cultures (Bergstrom et al. 2002; Berkes et al. 2004; Padberg 1982). We expect this study to provide new and essential information on the early (embryonic) component of the FSHD phenotype.

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### *Revisiting Bronfman Fellowship number 10*

Grant: FSHS-MB-010

Researcher: Richard Lemmers, MSc.,  
Ph.D.

Institution: Leiden University Medical  
Center

Dept. of Human Genetics  
Wassenaarseweg 72

PO Box 9503  
2300 RA Leiden  
The Netherlands

Project Title: “Refinement of the  
FSHD critical region on 4qA chromo-  
somes.”

\$35,000 6/15/2005-6/14/2006 Year 1

\$35,000 6/15/2006-6/14/2007 Year 2

**Goal [provided by applicant]:**

FSHD is the third most common myopathy with an autosomal dominant mode of inheritance. FSHD is caused by contraction of the polymorphic D4Z4 repeat in the subtelomere of chromosome 4q and the exact pathogenic mechanism is still unclear. An identical, and equally polymorphic, D4Z4 repeat is localized on chromosome 10, but this has never been associated with FSHD.

Our approach of detailed characterization of FSHD alleles, and translating these observations to disease mechanisms, has provided robust mechanistic insight in

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## RESEARCH

### *Revisiting Bronfman Fellowship number 10* continued from page 29

FSHD pathogenesis over the past years, including the mechanism of mitotic D4Z4 instability (Lemmers et al. 2004a) and the recognition of a bi-allelic 4qter variation (designated 4qA and 4qB) of which only the 4qA allele is associated with FSHD (Lemmers et al. 2002). Moreover, our laboratory provided direct evidence for a chromatin modification associated with the contraction of D4Z4 repeats by demonstrating hypomethylation of D4Z4 in FSHD alleles (van Overveld et al. 2003).

Through our expertise in pulsed-field gel electrophoresis (PFGE)-based FSHD allele characterization, we have become the international reference center for FSHD diagnosis with on average 50 referrals of atypical FSHD patients each year and culminating in a database of >1000 patient and control genotypes for D4Z4 alleles on chromosomes 4 and 10. Our PFGE-based D4Z4 examination has led to further refinement of minimal requirements to develop FSHD in several ways including exclusion of a region of 55 kb proximal to D4Z4 by identification of proximally extended deletions in typical FSHD patients (Lemmers et al. 2003). Moreover, and novel to this field, our analysis provides evidence that within an FSHD repeat, not all units are equal suggesting that intrinsic differences between individual D4Z4 units within one array may be important for PSEID pathogenesis (Lemmers et al. 2004a).

In the current application I propose to

further refine the minimal region necessary and sufficient to cause FSHD in two ways. First, I will precisely characterize three novel patients with an unusual FSHD allele. Two of these alleles carry, analogous to proximally extended deletions, deletions of sequences distal to D4Z4. The third pathogenic allele is highly unusual because preliminary data suggest that it is located on chromosome 10.

The analysis of these alleles will be combined by the full characterization of FSHD and control alleles that display repeat exchanges between chromosome 4 and 10. Moreover, I will focus on intrinsic sequence differences between 4qA-, 4qB and 10q-derived D4Z4 units, most notably that of the most proximal unit, as we provided evidence for a linkage disequilibrium (LD) between this D4Z4 unit and the distal polymorphism 4qA or 4qB (Lemmers et al. 2004a).

I expect that this proposal will generate new and essential information on the minimal region that is required to develop FSHD. Considering the complexity of the disease mechanism, further refinement of these elements is essential for a better understanding of the primary pathogenic pathway and will assist future research strategies based on candidate gene approaches and development of appropriate cellular and animal model systems.

#### FROM LEMMERS:

Two years ago, we started on the refinement of the FSHD critical region.

We first analyzed sequence differences between 4qA, 4qB and 10q alleles to further specify the pathogenic allele. Based on allele-specific sequence differences we showed the presence of nine different 4q haplotypes. Interestingly, D4Z4 contractions in only one haplotype were found to be associated with FSHD. The results of this study will be published in the October issue of the *American Journal of Human Genetics*.

As this study turned out to be more laborious than expected and generated new insights, we request an elongation of our grant for one more year to finish the other targets of our project. This includes the analysis of unusual FSHD alleles that display a deletion of the region distal to D4Z4. With these analyses we aim to refine the minimal region required to cause FSHD. In addition, we aim to analyze differences in the haplotype distribution among different populations to understand why some populations seem to be more susceptible to FSHD than others.

Currently, I am working on Grant FSHS-MGBF-010 entitled "Refinement of the FSHD critical region on 4qA chromosomes." We have identified at least eight different 4q35 haplotypes (three 4qA and five 4qB). Remarkably, only D4Z4 contractions on one of these haplotypes results in FSHD. As we have indications that sequence variation within D4Z4 (or distal from D4Z4) are present between the different haplotypes, we want to elucidate these variations.

### *FSH Society grantee awarded California embryonic stem cell research grant*

FSH Society grantee Kyoko Yokomori, Ph.D., of UC Irvine, was recently awarded a two-year \$625,000 grant by the California Institute for Regenerative Medicine (CIRM) to study "The molecular characterization of the chromatin structure of the D4Z4 repeat associated with FSHD" using human embryonic stem cells. CIRM is the California state agency created to manage California stem cell projects created by Proposition 71, the California Stem Cell Research and Cures Act overwhelmingly approved by voters in Nov., 2004.

Groups opposed to embryonic stem cell research filed a constitutional lawsuit to block the funding of the California stem cell research initiative. The initiative was upheld by the California lower court and appellate court and, on May 16, 2007, the California Supreme Court declined to hear an appeal; the Court's action effectively ended the lawsuits that had held up bond funding for the CIRM.

The FSH Society was an early and strong supporter of the stem cell research initiative. The Society congratulates Dr.

Kyoko Yokomori. FSH Society President & CEO, Daniel Paul Perez said of Dr. Yokomori's work: "this groundbreaking grant at the intersection of both FSHD and embryonic stem cell research, demonstrates the true effectiveness of the FSH Society's scientific advisors and its research funding programs. Excellent scientists pursuing needed research greatly benefit from the seed funding provided by the Society."

The CIRM website is [www.cirm.ca.gov](http://www.cirm.ca.gov)

## RESEARCH

### *First FSH Society Helen & David Younger Research Fellowship*

Grant: FSHS-HDY-001

Researcher: Kyoko Yokomori, Ph.D.,  
Associate Professor

Institution: University of California,  
Irvine

Department of Biological Chemistry  
College of Medicine,  
240D Med Sci I

Irvine, CA 92697-1700 USA

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

\$30,000 6/1/2005-5/31/2006 Year 1

\$30,000 6/1/2006-5/31/2007 Year 2

**Goal:** [provided by applicant]:

FSHD is an autosomal dominant hereditary neuromuscular disorder characterized by progressive degeneration of the upper body muscles. The majority of disease cases is linked to the deletion of the D4Z4 repeat array in the subtelomeric region of chromosome 4q (4qter). Since there appears to be no functional open reading frame in this region, it was hypothesized that the D4Z4 repeat plays a structural role in governing epigenetic regulation of gene expression critical for proper muscle cell differentiation and functions, and that the disease is caused by the inability of the shortened D4Z4 to form its specialized chromatin structure leading to dysregulation of critical gene expression. However, the exact nature of this chromatin structure, factors required for the regulation, and the target genes whose dysregulation may directly evoke disease pathogenicity remain obscure. Therefore, it is vital to understand D4Z4 function in order to address the etiology and pathogenesis of FSHD.

We found by using chromatin crosslinking and immunoprecipitation (ChIP) analysis that the heterochromatin binding protein HP1, and an essential protein complex required for chromatid cohesion termed "cohesin," specifically bind to overlapping regions within the D4Z4 repeat in human muscle cells. HP1 was shown to associate with centromeric heterochromatin through interaction with the methylated lysine 9 residue of histone H3, the hallmark of silenced chromatin, and

recruit cohesin to centromeres in *S. pombe* and chicken cells.

Consistent with this notion, we detected H3K9 methylation in D4Z4. Intriguingly, both HP1/cohesin binding and H3K9 methylation at this region are lost in FSHD mutant cells, in which the 4qter D4Z4 is deleted. These results provide the first direct evidence that 4qter D4Z4 is heterochromatic, and that this special organization is lost in FSHD. Thus, our results provide further insight into the molecular nature and pathogenic contribution of this unique repeat sequence in FSHD.

We hypothesize that human HP1 targets cohesin to D4Z4, and together they mediate proper heterochromatin structure organization required for normal D4Z4 function, which is abrogated in FSHD. To address this, we plan to carry out biochemical and cytological analyses of the mechanism and function of cohesin and HP1 binding to D4Z4. Specific aims are:

1. analysis of HP1/cohesin binding to D4Z4 in normal and FSHD cells,
2. characterization of the underlying mechanism and factor requirement for HP1/cohesin binding to D4Z4, and
3. analysis of the effect of cohesin and HP1 depletion on chromatin structure organization and function of D4Z4 at 4qter. I believe that the proposed project will make unique contributions to further understanding of the chromatin structure of D4Z4 and its role in the development of FSHD, and may lead to

possible identification of new therapeutic targets.

#### LAY SUMMARY

By Kyoko Yokomori

FSHD is the third most common muscular dystrophy but is a unique disorder in that no mutation of pathogenic gene(s) has been found. Rather, FSHD is associated with the shortening of so-called "D4Z4" repeat DNA sequences at the tip of chromosome 4. However, it was unclear how this repeat shortening leads to FSHD. In the cell DNA, which encodes genetic information, is wrapped around abundant nuclear proteins called histones to form a "string with beads"-like structure. It became apparent that these histones are actually modified to regulate gene expression.

With the kind support of the FSH Society David and Helen Younger Research Fellowship Grant, we were able to find evidence that this histone modification pattern at the D4Z4 repeat region is abnormal in FSHD cells. Importantly, the same change was observed in the cells derived from a subpopulation of FSHD patients with no shortening of the repeat sequences. Thus, histone modification abnormality at D4Z4 appears to be a hallmark of FSHD.

We found that the correctly modified histones at D4Z4 recruit factors that are possibly involved in gene silencing. We formulated a hypothesis that this complex bound to D4Z4 spreads its silencing effect to target gene(s) by long-distance interactions. To find any correlative histone mod-

*continued on page 32*

### ***U.S. DHHS NIH muscular dystrophy research plans available online***

The "Action Plan for the Muscular Dystrophies," containing a status report and comprehensive recommendations for research in muscular dystrophy produced by the Muscular Dystrophy Coordinating Committee Scientific Working Group, is available at:

[http://www.ninds.nih.gov/find\\_people/groups/mdcc/index.htm](http://www.ninds.nih.gov/find_people/groups/mdcc/index.htm)

## RESEARCH

### *Helen & David Younger Grant*, continued from page 31

ification changes in other parts of the human genome, we are carrying out high-throughput whole-genome analysis of histone modification and silencing factor binding. We are in the process of completing the analysis over the entire genome, expecting to find multiple genes that may be affected by the histone modification abnormality in FSHD. We hope that our study will help pinpoint the key regulator(s) of the disease against which a therapeutic control strategy may be devised.

We also found that the correct histone modification at D4Z4 appears to be established early in development and can be observed in human embryonic stem cells. This raises the possibility that the functional abnormality of muscles in later

stages may be pre-conditioned during early development. Recently, we received a two-year research grant called the "Scientific Excellence through Exploration and Development (SEED) Grant" from the California Institute for Regenerative Medicine (CIRM) to establish embryonic stem (ES) cells from FSHD embryos that were graciously donated by families of FSHD patients. We plan to perform a comparative analysis of normal and FSHD ES cells during skeletal muscle differentiation. We hope to generate valuable reagents for the FSHD research community to further scientific understanding of the origin and progression of the condition as well as to develop therapies for patients suffering from FSHD.

*The FSH Society advocates for all of those who are affected and not affected by FSHD. Your financial support makes it possible to continue to educate Congress and fight for NIH grants. Please consider sending in a contribution today. Thank you.*

### *7th & 8th Delta Railroad Construction Company research fellowship grants awarded*

The FSH Society Delta Railroad Construction Company fellowship program continues to help FSHD research efforts by awarding research grants that provide immediately 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 Laurrello, and their family for this groundbreaking effort on behalf of the FSHD community. Initiated in 1998, the seventh and eighth grants along with the previous six Delta Railroad Research Fellowship Grants are yielding tremendous insights in new and novel areas of FSHD research. We hope this collaboration will continue and the members of the Society will consider matching this \$30,000 gift annually.

University of California, Irvine  
Irvine, CA 92697 USA  
Project Title: "Coding and non-coding RNA expression in FSHD."  
\$35,000 7/1/2005-6/30/2006 Year 1

#### **Goal [provided by applicant]:**

More than a decade after the position effect hypothesis was first proposed, the fundamental question of whether altered chromatin structure in FSHD affects RNA expression at 4q35 has not been answered. Several independent laboratories have addressed this question yielding disparate and contradictory results.

In part, this is due to the variability in tissues and cultures utilized by various laboratories, which are provided by different sources and often obtained and preserved using different methods. In addition, all of the experimental techniques used to examine RNA expression thus far have relied on pooled sources of RNA from tissues or cell cultures. These techniques include non-quantitative RT-PCR, real-time RT-PCR, and expression profiling. These studies assayed differential RNA expression between FSHD and control muscle and, by nature of the experimental design, detect-

ed average RNA levels emanating from both alleles and multiple cell types.

In contrast, examination of RNA expression in a single cell context is more suited to address the question of whether an altered chromatin structure on the contracted D4Z4 allele influences RNA expression. RNA-FISH (fluorescence in situ hybridization) utilizes antisense RNA or dsDNA as hybridization probes to nascent nuclear RNA transcripts followed by fluorescence detection of conjugated hap- tens or antibodies. Transcription of both coding and non-coding RNAs from each of the alleles (normal and D4Z4 contracted) can be readily identified by RNA-FISH followed by hybridization with D4Z4 and 4q specific DNA probes. In addition, the specific cell type expressing the RNA can be readily identified using this technique, either in culture or within tissue sections.

We propose to utilize RNA-FISH to answer to following questions:

1. Which 4q35 genes are transcribed in proliferating myoblasts and differentiated myotubes?;
2. Are the levels of transcription dif-

*continued on page 33*

Grant: FSHS-DR-007

Researcher: Sara Winokur, Ph.D./Ulla Bengtsson, Ph.D.

Institution: 202 Sprague Hall  
Biological Chemistry

## RESEARCH

### *7th & 8th Delta Railroad Constructionfellowship grants*, continued from page 32

ferent between normal and FSHD myoblasts/myotubes?; and

3. Is there an allele specific transcription in FSHD myoblasts/myotubes? That is, do the contacted and normal alleles display different levels of RNA transcription within single cells?

For these studies, 3' hyper-biotinylated antisense oligos corresponding to 4q35 genes will be used as probes for coding RNA expression in myoblasts and differentiated myotubes.

If chromatin structure is altered in FSHD leading to aberrant RNA expression, then we should not assume that such a mechanism would affect coding RNA exclusively. Non-coding RNA has increasingly come to light as a significant player in the regulation of both transcription and translation. Although several approaches to the detection of non-coding RNAs exist, we propose to use the same technique (RNA-FISH) to examine non-coding RNA within a defined region proximal to the D4Z4 repeat. Genomic clones (cosmids) will be used to hybridize to these RNAs as the specific non-coding transcripts cannot be identified a priori.

Lastly, RNA transcription of genes affected in FSHD (as identified by expression profiling) will be examined in FSHD and control myoblasts/myotubes. A recent finding in FSHD research within the past year has been the unique and consistent localization of the 4q telomeric region to the nuclear periphery. While the biological significance of this localization is not yet known, the existence of nuclear domains either permissive or repressive of transcription is well documented. Therefore, genes affected in FSHD will be examined by RNA-FISH to determine whether colocalization with the FSHD region at the nuclear periphery might affect RNA transcription from these genes.

NG7 2UH

UK

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

\$29,658 7/24/2006-7/23/2007 Year 1

**Goal** [provided by applicant]:

We have recently demonstrated conservation of the open reading frame and the tandem array organization of DUX4 homologues in a wide range of mammalian species suggesting a protein-encoding function for the array and a requirement for a high copy number. We hypothesize that the conservation of the open reading frame and the tandem array organization of DUX4 homologues in a wide range of mammalian species indicates a protein-encoding function for the array and a requirement for a high copy number. This function may be disrupted by the FSHD deletion and hence play a role in the disease mechanism.

The identification of the mouse homologue (DUX4) provides a model organism in which to genetically manipulate the DUX4 array in vivo. In the work proposed in this application we plan to generate a set of resources that will then enable us to generate mouse lines that either a) have reduced repeat numbers within the DUX4 arrays or b) in which the entire DUX4 array is deleted. In specific aims 1 and 2 we will complete the physical and the sequence map of this locus. In specific aim 3, using information from this region obtained in aims 1 and 2, we will generate gene targeting constructs using the Mutagenic Insertion and Chromosome Engineering Resource (MICER), developed in the UK at the Sanger Genome Centre.

#### LAY SUMMARY OF CLAPP ET AL.

By Jane Hewitt, Ph.D.

FSHD is caused by a DNA rearrangement near the end of human chromosome

4. There is an unusual segment of DNA at this location that usually contains many copies of a 3300 base pair piece of DNA (D4Z4). The D4Z4 unit copy number varies between individuals from 11-100 copies. In FSHD patients, the number of copies of this D4Z4 unit is reduced to less than 11. Although some scientists think that this DNA rearrangement causes FSHD by altering the amount of gene product of genes located elsewhere on chromosome 4q35, this is still controversial.

Work initiated and funded by the FSH Society and subsequently funded by the MDA-USA from Jane Hewitt, Ph.D.'s laboratory has shed new light on the possible function of D4Z4. Although it has been known for a long time that D4Z4 could encode a protein (DUX4), it has generally been considered that D4Z4 no longer can function as a gene and that this protein is not produced.

However, Professor Hewitt's group has now shown that D4Z4 sequences are present in other mammals, including mice, rats and elephants. By examining these D4Z4 sequences, her group has shown that the potential of D4Z4 to produce a DUX4 protein has been conserved for over 100 million years of evolution. This implies that an important function of D4Z4 is to make this DUX4 protein, which is predicted to act as a regulator of gene expression. In addition, the fact that mice have a D4Z4 sequence means that it may be possible to make a mouse model of FSHD. This work will be published in The American Journal of Human Genetics in 2007.

#### Reference:

J Clapp, LM Mitchell, DJ Bolland, J Fantes, AE Corcoran, PJ Scotting, JAL Armour and JE Hewitt. "Evolutionary conservation of a coding function for D4Z4, the tandem DNA repeat mutated in facioscapulohumeral muscular dystrophy" The American Journal of Human Genetics (in press).



Grant: FSHS-DR-008

Researcher: Jane Hewitt, Ph.D.

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

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*The membership form is on the back cover. Thank you!*

## RESEARCH

### Third Society Roberts Foundation Grant awarded

The FSH Society Sam E. and Mary F. Roberts fellowship program continues to help bridge the FSH Society's FSHD research efforts and the Robert's Foundation nutritional research and education efforts by awarding research grants that provide novel and unique opportunities to study nutrition and FSHD. The FSH Society is grateful for the opportunity to pursue nutrition research and to begin to incorporate more work with MRI/MRS and clinical efforts that will help provide data and tools for clinical trials and nutrition research.

■ ■ ■

Grant: FSHS-SMRF-003  
 Researcher: Hermien Kan,  
 Ph.D./Arend Heerschap, Ph.D.  
 Institution: Head Biomedical Magnetic  
 Resonance group  
 Department of Radiology (667)  
 Radboud University Nijmegen Medical  
 Center  
 PO Box 9101  
 6500 HB Nijmegen  
 The Netherlands  
 Project Title: "Assessment of the meta-  
 bolic inter-muscular heterogeneity,  
 and muscular creatine uptake and  
 turnover in FSH patients vivo."  
 \$30,000 8/14/2006-8/13/2007 Year 1  
 \$15,000 8/13/2007-2/14/2008 Year 2

#### Goal [provided by applicant]:

Although substantial progress has been made in the molecular biology of FSHD, still, little is known about its pathophysiology such as possible defects in skeletal energy metabolism. Asymmetric dysfunctioning of muscles is a typical feature of FSHD but characteristic metabolic profiles of the affected muscles are lacking, and objective biomarkers to assess therapies, e.g. creatine supplementation which possibly has beneficial effects, are not available. MR spectroscopy (MRS) is an ideal tool to study metabolism in muscle in a non-invasive way.

#### Hypothesis:

The application of MRS to FSHD patients will uncover metabolic abnormalities that can serve as non-invasive biomarkers to assess and better understand

the severity of disease in specific muscles. The signals of creatine can serve as non-invasive biomarkers to assess creatine uptake, phosphorylation and turnover in skeletal muscle of patients in creatine supplementation treatment.

#### Study objectives:

1. To discover metabolic abnormalities in skeletal muscle of FSHD patients by MRS as biomarkers for the severity of the disease in specific muscles;

2. to determine if the level of Cr and PCr, by quantitative MRS is decreased in muscle of FSHD patients;  
 3. to determine creatine uptake, phosphorylation and turnover in different skeletal muscles in healthy volunteers (which is not known); and  
 4. in the muscles of FSHD patients.

#### Study design will consist of two parts:

I. A metabolic profile of muscles will be assessed using phosphorous 31 (31P) and tritium (1H) MRS

*continued on page 35*

### Revisiting results of the first FSH Society Roberts Foundation Grant

Grant: FSHS-SMRF-001  
 Researcher: Graham J Kemp, M.D.  
 Institution: Faculty of Medicine  
 University of Liverpool  
 Liverpool L69 3GA, UK  
 Project Title: "Muscle damage by reactive oxygen species, muscle atrophy and effects of creatine supplementation in FSHD."  
 \$48,650 1/1/2003-5/01/2005 Year 1.5  
 "Oral creatine supplementation does not change muscle strength, body composition or muscle biochemistry in patients with FSHD."  
 Graham J Kemp, Bryan RF Lecky, William E Bimson, Graeme L Close, Neil Roberts, Malcolm J Jackson  
**Aim.** To examine the effects of oral creatine supplementation on markers of ROS (reactive oxygen species) damage and defense mechanisms, body composition and muscle strength in FSHD.

**Background.** Creatine supplementation has been reported to increase strength in some muscular dystrophies, but this has not been specifically examined in FSHD. There has been interest in ROS mechanisms in this and other dystrophies and creatine-mediated enhancement of mitochondrial function is a possible beneficial mechanism.

**Methods.** Four female and seven male genetically confirmed FSHD patients aged 34-64 received 5g/d creatine orally for three months. They were assessed before and after by spirometry; manual muscle testing and quantitative isometric strength testing (grip, neck, elbow, shoulder, hip, knee, ankle); time to travel 30 feet; SF-12; body composition assessment by body mass, bioimpedance and quantitative MRI; plasma creatinine and liver function tests; and in biceps muscle biopsy, markers of ROS damage (malondialdehyde) and protective mechanisms (reduced and total glutathione, catalase, superoxide dismutase and glutathione peroxidase) and total creatine content. One subject withdrew.

**Results.** Creatine supplementation had no significant effect except to increase plasma creatinine by 7% ( $P < 0.05$ ). Of technical interest is the strong correlation ( $r = 0.96$ ) between aggregate MRI measures of muscle cross-sectional area and average isometric strength, which both correlate ( $r = 0.7$ ) less tightly with fat-free mass by bioimpedance.

**Conclusion.** As recently reported in DM, creatine supplementation at 5 g daily has no effect on muscle mass or strength in FSHD, probably because of failure of muscle uptake of creatine. It has no effect on measures of ROS damage and defense. Further study of the apparent limiting factor, muscle creatine uptake, seems desirable.

Funded by an FSH Society Roberts Foundation Nutrition Research Grant.

## RESEARCH

### Fourth and Fifth FSH Society Research and Education grants awarded

■ ■ ■

FSHS-FS-004  
Alexandra Belayew, Ph.D.  
Université de Mons-Hainaut  
"Study of DUX4 mRNA and Protein  
Expression in FSHD."

■ ■ ■

FSHS-FS-005  
Patricia Arashiro, B.Sc., Mayana Zatz,  
MSc., Ph.D.  
Universidade de São Paulo  
"Clinical Variability in Patients Affected  
by FSHD."

■ ■ ■

Grant: FSHS-FS-004  
Researcher: Alexandra Belayew, Ph.D.  
Institution: Lab. Biologie Moléculaire  
University Academy Wallonia-Brussels  
Université de Mons-Hainaut  
Pentagone 3A, Avenue du Champ de  
Mars,  
B-7000 Mons  
Belgium  
Project Title: "Study of DUX4 mRNA

### Roberts Grant,

*continued from page 34*

and possible differences between affected and non-affected skeletal muscles will be studied (objective 1). Specifically, differences in Cr and PCr concentrations will be monitored (objective 2). Simultaneously, Cr turnover and PCr/Cr ratios after Cr supplementation will be studied in healthy volunteers (objective 3).

II. Depending on the results of the volunteer studies of Cr uptake, phosphorylation and turnover will be assessed in a single location or in several skeletal muscles of FSHD patients to meet objective 4.

#### Expected results:

A metabolic profile will be established to serve as a non-invasive biomarker for the severity of disease in specific muscles and to monitor therapy in FSHD. Differences in Cr uptake and turnover between skeletal muscles in healthy persons and FSHD will guide the optimization of Cr supplementation strategies in FSHD patients.

and Protein Expression in FSHD." \$30,000 1/24/2007-1/23/2008 Year 1  
**Goal [provided by applicant]:**

In this research proposal, we want to focus on expression of the DUX4 gene we mapped in each unit of the D4Z4 repeat array that is contracted in FSHD. The gene was identified several years ago, but demonstration of its expression in patient muscles proved technically very challenging because of its low level, toxicity and homology to hundreds of DUX genes unlinked to FSHD.

We could demonstrate expression in myoblasts and biopsies of the homologous non-toxic DUX4c protein encoded by an isolated D4Z4 element 42 kb centromeric of the repeat array. We have recently been able to develop very sensitive and specific tools and procedures to detect DUX4 expression at the mRNA and protein level. In our mRNA studies we detected two introns downstream from the D4Z4 stop codon: their occurrence allowed unambiguous identification of RT-PCR products as bona fide mRNA (not genomic DNA) copies in four FSHD myoblast lines but not three controls. We raised a monoclonal antibody against the DUX4 carboxyl-terminal domain that specifically detects the DUX4 (52 kDa) and homologous DUX4c (47 kDa) proteins on Western blots performed with extracts of cells transfected with p-CI-neo-DUX expression vectors.

The Western blot sensitivity was recently increased about 20-fold by use of a new peroxidase substrate (Pierce) and allowed DUX4 detection in four additional FSHD myoblast lines provided by Denise Figlewicz, M.D. and Drs. D. Laoudj-Chenivresse and J. Mercier.

1. With these tools, our first aim is to evaluate DUX4 mRNA and protein expression in additional myoblast lines and in muscle biopsies of patients with FSHD and different D4Z4 copy numbers, or FSHD not linked to 4q35 as well as in controls and other neuromuscular disorders. Biopsies will be provided by Drs. D. Laoud, J. Chenivresse and J. Mercier as well as by P. Lunt, M.D. and Y.W. Chen, D.V.M., Ph.D. Primary myoblast lines established from muscle biopsies have

been provided by Dr. Figlewicz and additional ones will be by Drs. D. Laoudj-Chenivresse and J. Mercier.

2. Our second aim is based on the observation that the DUX4 mRNA 3' ends we detected mapped outside of the D4Z4 repeat array. This region differs between the chromosome 4qA allele and the 4qB one that was never found associated with FSHD. We want to evaluate whether such DUX4 mRNA's might also be produced from the chromosome 4qB allele.

In conclusion, we expect these studies to demonstrate whether or not there is a correlation between DUX4 gene or protein expression and the presence of the FSHD phenotype.

■ ■ ■

Grant: FSHS-FS-005  
Researcher: Patricia Arashiro, B.Sc.,  
Mayana Zatz, MSc., Ph.D.  
Institution: Universidade de São Paulo  
Instituto de Biociências  
Centro de Estudos do Genoma  
Humano  
Departamento de Genética e Biologia  
Evolutiva  
R. Matão, 277 - sala 211  
05508-900 São Paulo, SP  
Brazil

Project Title: "Clinical Variability in  
Patients Affected by FSHD."

\$15,000 3/1/2007-3/1/2008 Year 1

**Goal [provided by applicant]:**

Previous studies from our and other groups have shown that usually males are on average more often and more severely affected than females, with approximately 20% of patients becoming wheelchair-bound (Padberg et al, 1991; Zatz et al, 1998).

We have previously observed in Brazilian FSHD families that asymptomatic carriers are present in about 30% of the families and some genealogies seem to concentrate more on non-penetrant cases (Tonini et al, 2004). This observation is in accordance with van der Maarel et al (2000) who have also observed a female predominance of mosaic asymptomatic carriers.

A remarkable, but often neglected,

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## RESEARCH

### *FSH Society Research and Education grants awarded, continued from page 35*

observation in many families and populations is the occurrence of elderly individuals who inherit disease genes but who nevertheless remain healthy (Nadeau, 2006). The tendency for health to persist despite the presence of susceptibility genes has several explanations, including modifier genes and protective alleles that confer genetic resistance to disease (Nadeau, 2001).

The purpose of the present proposal is

to look for modifying genes or mechanisms involved in protecting some individuals against the deleterious effect of the FSHD deletion. Understanding this mechanism may help us to develop new tools for prognosis of the disease and also for future treatment.

In order to compare the gene expression in patients with discordant phenotypes, we are currently collecting muscle and skin samples from families with clini-

cally affected and asymptomatic carriers. Total RNA will be isolated from muscle (biceps/ deltoid) tissue using TRIzol (Invitrogen) method and their quality verified using gel electrophoresis and spectrophotometry. Sample handling and microarray hybridizations will be done in collaboration with Dr. Louis M. Kunkel, Ph.D. The gene expression datasets will be performed on the Affymetrix GeneChip platform. Affymetrix MAS 5.0 software and custom software (<http://db.chip.org>) will be used for initial data processing, noise analysis, and quality control. Data analysis will also be done in collaboration with Dr. Louis M. Kunkel, Ph.D.

Transcript analysis offers many technical advantages over protein analysis in that the mRNA molecules possess high affinity and specificity binding partners. Additionally, mRNA molecules exhibit equivalent biochemical properties and can be amplified. Moreover, proteomics deal with unavoidable problems of limited and variable sample material, sample degradation, vast dynamic range (more than 10<sup>6</sup>-fold for protein abundance alone), developmental and temporal specificity, and disease and drug perturbations (Tyers, 2003).

Other aspects that must be considered are that many signaling and regulatory proteins are present in the cell at very low levels; only a small percentage of proteins are soluble and are expressed at a level compatible with structural analysis (Thornton, 2001), and more than a third of all gene products are poorly soluble membrane proteins of considerable functional importance (van Regenmortel, 2001).

The collection of informative FSHD families in whom we have identified symptomatic and unaffected members (asymptomatic carriers and non-carriers) and who are willing to be submitted to a muscle biopsy for research purposes (after informed consent), is extremely difficult in practice. It has been possible due to many years of research from our group. In addition, the comparison of gene expression from asymptomatic carriers and affected patients is a novel approach that might bring important results.

### *A brief word on current directions of the FSH Society research portfolio and outreach*

The FSH Society research and patient's programs focus on five broad areas. These are some of the areas that we are working on and for which we need increased funding. The FSHD disease mechanism research is the bulk of what we are pursuing at this time. Areas of focus and in need of funds and funding are:

- ◆ Gene Expression Chromatin Structure
- ◆ Chromatin Remodeling Allelic Specificity: D4Z4 DUX4; mRNA PITX1/DUX4; PITX2/DUX4 NLS (nuclear localization signals); and FRG1/FRG2; DNA structure
- ◆ HSS (hypersensitive sites); specific DNA sequences with 4qA
- ◆ Candidate Genes; Model Systems
- ◆ Epigenetics; Unusual FSHD cases
- ◆ RNAi

Many of the seed grants and starter projects initiate new data and insights that help with screening for FSHD, better genetic testing and ultimately with diagnosis.

Also . . .

- ◆ In the area of therapy/treatment we have launched two groundbreaking and novel nutritional research projects covering creatine, MRI/MRS and better biomarkers, and techniques to measure clinical trial outcomes and endpoints. We have reviewed and written the first-ever brochure and article covering physical therapy for both patients and professionals.
- ◆ Respiratory insufficiency is a serious complication that can happen with FSHD and we are assembling a knowledge base, guidelines and disseminating information on respiratory care and insufficiency in FSHD.
- ◆ The Society helped advise, network and consult with the clinical and patient communities and Wyeth to bring about the anti-myostatin inhibitor trials of MYO-029. We are still awaiting word from Wyeth on the outcome of the trials. Time-frame at this moment might be August to the fall, 2007.
- ◆ The Society met with Acceleron Pharma in 2006 to make the case for FSHD and muscular dystrophy for their anti-myostatin inhibitor called ACE-031. This has led to excellent progress as well.
- ◆ In the area of quality of life and FSHD, the Society had a stellar biennial international patient-researcher conference in Cambridge, MA during July, 2006. We are still providing peer support, on-line resources and helping to build a better picture of what living with FSHD entails.
- ◆ FSH Society staff has been focusing on the Society's infrastructure, research resources, and research coordination. We have also drafted an 18 page short- and long-term research plan to help rapidly find solutions for FSHD.

## RESEARCH

### Third Lewis Family Research grant awarded

FSH Society Chairman of the Board William R. Lewis, Sr., M.D., board member William R. Lewis, III, M.D. and their families established a research fund in late 2000 to help with FSHD research. One of the strengths of this fund is to allow the FSH Society to help researchers

and projects in need of bridge funds to keep working on FSHD in the event they find themselves not funded by larger agencies such as the NIH, MDA-USA, AFM, etc.

All project proposals are peer-reviewed by the FSH Society SAB. This research fund allows the Society to be extremely responsive in keeping needed lines of investigation open. Many times in the past, larger funding agencies have rejected cutting edge research in their peer review process because the research was too novel or not well accepted. An excellent example is the FSH Society's nine year track record of supported projects studying the D4Z4 repeats producing DUX4 (Belayew, Ostlund, Rosa).

We are proud that while it was not believed or accepted that junk DNA could have real biological activity, the FSH Society kept these lines of investigation open. Now that junk DNA is seen as transcriptionally active and is the hot area of science, proposals in these areas are fairing better. Sadly, much of FSHD research is like this and it is critical to keep funds flowing to the Society to support multiple lines of investigation. Due to funds such as the Lewis family fund, Dr. Winokur has continued her work and begun receiving larger grants from larger funding agencies to continue working on an essential and important piece of the FSHD puzzle.



(L-R) Bill Lewis Sr., M.D. & William Lewis III, M.D., FSH Society Board of Directors & SAB Members

Institution: 202 Sprague Hall  
Biological Chemistry  
University of California, Irvine  
Irvine, CA 92697 USA  
Project Title: "Coding and non-coding RNA expression in FSHD."

\$30,000 3/1/2006 - Bridge Fund Year 1

#### Goal [provided by applicant]:

More than a decade after the position effect hypothesis was first proposed, the fundamental question of whether altered chromatin structure in FSHD affects RNA expression at 4q35 has not been answered. Several independent laboratories have addressed this question, yielding disparate and contradictory results.

In part, this is due to the variability in tissues and cultures utilized by various laboratories, which are provided by different sources and often obtained and preserved using different methods. In addition, all of the experimental techniques used to examine RNA expression thus far have relied on pooled sources of RNA from tissues or cell cultures. These techniques include non-quantitative RT-PCR, real-time RT-PCR, and expression profiling. These studies assayed differential RNA expression between FSHD and control muscle and, by nature of the experimental design, detected average RNA levels emanating from both alleles and multiple cell types.

In contrast, examination of RNA expression in a single cell context is more suited to address the question of whether an altered chromatin structure on the contracted D4Z4 allele influences RNA expression. RNA-FISH (fluorescence in situ hybridization) utilizes antisense RNA or dsDNA as hybridization probes to nascent nuclear RNA transcripts followed by fluorescence detection of conjugated hapten or antibodies. Transcription of both coding and non-coding RNAs from each of the alleles (normal and D4Z4 contracted) can be readily identified by RNA-FISH followed by hybridization with D4Z4 and 4q specific DNA probes. In addition, the specific cell type expressing the RNA can be readily identified using this technique,

either in culture or within tissue sections.

We propose to utilize RNA-FISH to answer to following questions:

1. Which 4q35 genes are transcribed in proliferating myoblasts and differentiated myotubes?
2. Are the levels of transcription different between normal and FSHD myoblasts/myotubes? and
3. Is there an allele specific transcription in FSHD myoblasts/myotubes? That is, do the contracted and normal alleles display different levels of RNA transcription within single cells?

For these studies, 3' hyper-biotinylated antisense oligos corresponding to 4q35 genes will be used as probes for coding RNA expression in myoblasts and differentiated myotubes.

If chromatin structure is altered in FSHD leading to aberrant RNA expression, then we should not assume that such a mechanism would affect coding RNA exclusively. Non-coding RNA has increasingly come to light as a significant player in the regulation of both transcription and translation. Although several approaches to the detection of non-coding RNAs exist, we propose to use the same technique (RNA-FISH) to examine non-coding RNA within a defined region proximal to the D4Z4 repeat. Genomic clones (cosmids) will be used to hybridize to these RNAs as the specific non-coding transcripts cannot be identified a priori.

Lastly, RNA transcription of genes affected in FSHD (as identified by expression profiling) will be examined in FSHD and control myoblasts/myotubes. A recent finding in FSHD research within the past year has been the unique and consistent localization of the 4q telomeric region to the nuclear periphery. While the biological significance of this localization is not yet known, the existence of nuclear domains either permissive or repressive of transcription is well documented. Therefore, genes affected in FSHD will be examined by RNA-FISH to determine whether co-localization with the FSHD region at the nuclear periphery might affect RNA transcription from these genes.

■■■ Grant: FSHS-LEWI-003

Researcher: Sara Winokur, Ph.D./Ulla Bengtsson, Ph.D.

## RESEARCH

*Three additional U.S. NIH Paul D. Wellstone MDCRCs are funded*

The second round of NIH Senator Paul Wellstone MD CRCs to boost U.S. MD research were announced Friday, November 4, 2005. The Wellstone centers are mandated by the MD-CARE Act written in part by Daniel Paul Perez and the FSH Society and passed by Congress. The Wellstone centers are designed to work individually and collaboratively. Their purpose and mission is to encompass basic, clinical and behavioral research projects, and will be overseen by a steering committee. For more information, see NIH press release "New Muscular Dystrophy Cooperative Research Centers Announced" at <http://www.nih.gov/news/pr/nov2005/niams-04.htm>

The Society had originally requested the law to require the establishment of three-to-five CRCs in the legislation. The NIH, in turn, used the CRC U54 mechanism to achieve the same result. NIAMS, NINDS, NICHD, NHLBI and parts of the NIH funded three new CRCs in November 2005 making a total of six Wellstone Centers. The Wellstone Centers have approximately \$1.5-\$2 million in direct costs per center, per year, for five years. This can be nearly doubled with indirect costs to the recipient institutions.

The first three centers funded for five years (2003-2008), principal investigators, responsible NIH institute funding agencies, and areas of research include:

◆ **The University of Pittsburgh,**

Joseph C. Glorioso, Ph.D., director.

NIAMS and NICHD are funding this center at a level of \$1.5 million per year (\$1.2M NIAMS, \$250,000 NICHD) direct costs. This center is titled: "Gene and Cell Therapy of Duchenne Muscular Dystrophy." The center's home page is at University of Pittsburgh:

<http://www.mgb.pitt.edu/mdcrc/>

For an excellent detailed overview of the projects and cores at this center see Internet link:

<http://www.wellstone-dc.org/>

OtherInformation/OtherWellstoneSites/MDCRCPittsburgh/tabid/296/Default.aspx

◆ **The University of Washington,**

Seattle, Jeffrey S. Chamberlain, Ph.D, director.

This center is funded by the NICHD at a level of \$1.5 million per year direct costs. This center will conduct studies to develop new gene therapies for DMD. The center's online Internet home page is at University of Seattle:

<http://depts.washington.edu/mdcrc/index.html>

For an excellent detailed overview of the projects and cores at this center see Internet link:

<http://www.wellstonedc.org/OtherInformation/OtherWellstoneSites/MDCRCSeattle/tabid/295/Default.aspx>

◆ **The University of Rochester,** New York, Richard T. Moxley, III, M.D, director.

The co-director of the center is Rabi Tawil, M.D. This center is funded by the NINDS at a level of \$1.6 million per year direct costs. The center is titled the "Muscular Dystrophy Cooperative Research Center." Drs. Moxley and Tawil will be researching skeletal muscle at the cellular and molecular level for insight into what causes muscle wasting. This center focuses on DM and FSHD. The center's Internet home page is at University of Rochester:

<http://www.urmc.rochester.edu/MDCrc/Index.cfm>

For an excellent detailed overview of the projects and cores at this center see Internet link:

<http://www.wellstone-dc.org/OtherInformation/OtherWellstoneSites/MDCRCRochester/tabid/293/Default.aspx>

The fourth through sixth, or second set of three Wellstone MD CRC centers, funded for 5 years (2005-2010) principal investigators, responsible NIH institute funding agencies, and areas of research include:

◆ **The University of Iowa, Iowa City,** director and co-director, Kevin Campbell, Ph.D. and Steven Moore, M.D., Ph.D. This center is funded by NINDS at a level of \$1.4 million per year direct costs. The center is titled the "Muscular Dystrophy Cooperative Research Center." Drs. Campbell and Moore are expert in basic, translational and clinical research on muscular dystrophy. This center is pursuing novel strategies for treatment of DMD and

LGMD, including using muscle progenitor cells. This center also facilitates the development of diagnostic tools and collection of materials for muscular dystrophy research. The center's online home page is at the University of Iowa:

<http://www.medicine.uiowa.edu/mdcrc/links.asp>

For an excellent detailed overview of the projects and cores at this center see:

<http://www.wellstone-dc.org/OtherInformation/OtherWellstoneSites/MDCRCIowa/tabid/292/Default.aspx>

◆ **The University of Pennsylvania, Philadelphia,** and Johns Hopkins University, Baltimore, Maryland, director and co-director, H. Lee Sweeney, Ph.D. and Kathryn Wagner, M.D., Ph.D. This center is funded by NIAMS at a level of \$1.6 million per year direct costs. The center is titled the "Modulation of Muscle Growth for the Muscular Dystrophies" and is pursuing increasing muscle mass via inhibition of myostatin or by IGF-1 treatment; and blocking muscle degeneration with protease inhibitors. A clinical trial with Bowman-Birk Inhibitor Concentrate (BBIC) is being conducted in DMD patients. A core at the center assesses muscular dystrophy mouse models. Daniel Paul Perez currently serves on the scientific and advisory committee for this center helping to advise and give patients' perspectives on the research. The center's online Internet site is at Children's National Medical Center:

<http://www.wellstone-dc.org/>

For an excellent detailed overview of the projects and cores at this center see Internet link:

<http://www.wellstonedc.org/OtherInformation/OtherWellstoneSites/MDCRCUPennHopkins/tabid/294/Default.aspx>

◆ **The Children's National Medical Center, Washington, D.C.,** director and co-director Eric P. Hoffman, Ph.D., and Diana M. Escolar, M.D. This center is funded by NICHD at a level of \$1.4 million per year direct costs. This center will focus specifically on DMD and work to identify genetic modifiers of the natural history of DMD, as well as the response of

## RESEARCH

### *NIH funds three innovative FSHD pilot projects through Wellstone MD CRCs*

Each year the award to each NIH Wellstone MD CRC Center contains \$50,000 for new pilot projects and collaborative activities. A portion of these funds are used for travel to the annual meeting of the Wellstone Center investigators. The remainder of funds goes toward supporting new collaborative projects involving center investigators or for pilot projects led by non-center investigators. These new project proposals are approved by the Wellstone steering committee, composed of the

center directors and co-directors, the three NIH program directors and a patient advocate representative.

The following projects have been approved by NIH and the Steering Committee using the above Wellstone Center administrative core funds:

◆ **University of Pittsburgh, Wellstone Center**

Bridget Deasy, University of Pittsburgh, "Human Umbilical Cord Endothelial Cells for Cell Therapy for DMD"

Hiroyuki Nakai, University of Pittsburgh, "Development of an Improved Therapeutic Regimen for rAAV-Mediated Body-Wide Muscle Gene Transfer Based on in vivo Vector Biology"

◆ **University of Rochester, Wellstone Center**

Matthew Disney, University of Buffalo, "Development of Ligands Targeting (CUG)<sub>n</sub> Repeats"

Benjamin Miller, University of Rochester, "Use of Resin-Bound Dynamic Combinatorial Chemistry to Identify High Affinity Ligands for CUG Expansion RNA"

Rabi Tawil, University of Rochester, **"Comprehensive Genotyping of a Large FSHD Population"**

◆ **University of Washington, Wellstone Center**

Galina Filippova, Fred Hutchinson Cancer Research Center, **"Analysis of Chromatin Structure and CTCF Binding to the 4q D4Z4 Region in Phenotypic FSHD"**

Andre Lieber, University of Washington, "Analysis of Blood Interactions, Tissue Sequestration and Innate Toxicity Following IV Administration of rAAV6"

Stanley Riddell, Fred Hutchinson Cancer Research Center, "Analysis of T-cell Responses to AAV Capsid Proteins and Microdystrophin in Dogs that Receive AAV Gene Therapy for Muscular Dystrophy"

Barbara Trask, Fred Hutchinson Cancer Research Center, **"Study of Aberrant Nuclear Organization in FSHD Using Circular Chromosome Conformation Capture"**

◆ **University of Pennsylvania/Johns Hopkins, Wellstone Center**

H. Lee Sweeney, University of Pennsylvania, "Myostatin Inhibition in a Dog Model of DMD"

Three of the projects listed above, Galina Filippova, Barbara Trask, and Rabi Tawil and Silvere van der Maarel are extremely timely projects that will significantly impact our understanding of the chromatin structure, gene expression, and allelic variations involved in FSHD.

### *Wellstone MDCRCs*

*open, continued from page 38*

patients to glucocorticoids. One goal of this center is to connect the Wellstone network with the CINRG network. For an excellent detailed overview of the projects and cores at this center see Internet link online site:

<http://www.wellstone-dc.org/Home/tabid/228/Default.aspx>

Though the Society was instrumental in laying the ground work it does not go unnoticed that most of these investments are made in DMD. A number of reasons for this include that DMD research is well established, that the DMD families have a very aggressive and strong lobby in Washington, D.C. and that FSHD and other non-DMD dystrophies are challenging diseases that have not traditionally fared well in the NIH grant reviews/peer review process.

The Society needs significantly more support from its membership to allow us to advocate even more strongly for addressing the disparity and unevenness of funding for FSHD and similar dystrophies. For those wishing to make a major shift in emphasis in NIH government funding for FSHD, please consider making a major contribution to support these advocacy and educational efforts. Please see article on Daniel Paul Perez's work and efforts on the U.S. President's federal advisory committee called the Muscular Dystrophy Coordinating Committee on page 14.

### *NIH awards three large grants on FSHD through a special initiative*

In April 2006, due to input from the federal advisory committee, researchers and the FSHD Society, the NIH (U.S. DHHS NIH) released two Requests For Applications (RFAs) for FSHD research requesting grant applications from both domestic and foreign investigators.

RFA-NS-07-001 (R01) and RFA-NS-07-002 (R21) focus on the "Nuclear Structure-Function Defects in the Pathogenesis of Muscular Dystrophy." R21s are high risk research track grants and R01s are basic research track grants. The amount set aside between the two announcements was \$2 million for direct costs. For complete details, see Internet link:

<http://grants.nih.gov/grants/guide/rfa-files/RFA-NS-07-001.html>

or

<http://grants.nih.gov/grants/guide/rfa-files/RFA-NS-07-002.html>

The MDCC Action Plan for the muscular dystrophies, towards which Daniel Paul Perez made significant contributions, contains a section called "Mechanisms Section: Disease-Specific Mechanisms." Two sub-sections call for "Define the molecular pathogenetic mechanisms that lead to FSHD" and,

"Establish mouse (and cellular) models for FSHD, specific to

*continued on page 40*

## RESEARCH

### U.S. NIH funding opportunities

The NIH has eleven ongoing programs that request grant applications in muscular dystrophy and FSHD. Below are initiatives grouped by Announcement Number, Issuing NIH Institute, Expiration Date, Type of Funding Mechanism, Program Title and Internet Hyperlink. We encourage FSHD researchers to keep the excellent flow of FSHD R21 and R01 applications going and to pursue translational and research training initiatives. FSHD patients should encourage FSHD researchers and clinicians to continue to have discussions and open a dialogue with

the muscular dystrophy program staff at the NIH.

One of the surest ways that the FSHD research and clinical communities can grow funding through the NIH is for the research community to keep applying for grants under ongoing announcements and initiatives offered by the NIH.

We are aware that it is becoming increasingly difficult to secure funding worldwide due to dwindling research dollars. We are also aware of the excellent caliber of researchers and the numerous training, clinical trial, and translational

opportunities present in the FSHD community. We know that FSHD will acquire a greater percentage of funding in the total dystrophy portfolio if a greater number of applications are submitted to the NIH.

### GRANT OPPORTUNITIES AND INITIATIVES TO CONSIDER

PA-07-125  
NIAMS  
01/03/2008  
R01  
Muscular Dystrophy: Pathogenesis and Therapies (R01)  
<http://grants.nih.gov/grants/guide/pa-files/PA-07-125.html>

PA-06-508  
NIAMS  
11/02/2007  
R21  
Muscular Dystrophy: Pathogenesis and Therapies (R21)  
<http://grants.nih.gov/grants/guide/pa-files/PA-06-508.html>

PAR-07-184  
NICHD  
11/06/2009  
R01  
Innovative Therapies and Clinical Studies for Screenable Disorders (R01)  
<http://grants.nih.gov/grants/guide/pa-files/PAR-07-184.html>

PAR-06-342  
NICHD  
11/02/2009  
R21  
Innovative Therapies and Clinical Studies for Screenable Disorders (R21)  
<http://grants.nih.gov/grants/guide/pa-files/PAR-06-342.html>

PAR-06-341  
NICHD  
11/02/2009  
R03  
Innovative Therapies and Clinical Studies for Screenable Disorders (R03)

### NIH awards grants on FSHD, *continued from page 39*

emerging candidate genes and/or disease genomics, to understand the epigenetic mechanisms and for the development of novel intervention strategies.”

The NIH requested research projects that focus on basic biology and mechanistic studies of EDMD, FSHD, LGMD 1B, and OPMD. Over the years, the FSH Society has continually emphasized the need to capitalize on the scientific opportunities presented by FSHD, EDMD, and OPMD. Many of the research areas highlighted in the request are areas that the FSH Society has provided seed money for e.g. “biology of the nucleus, studies of the nuclear envelope dysfunction, perturbations in chromatin structure, disruption of the cytoskeleton-nuclear envelope-chromatin linkage, and/or dysfunction of transcriptional control mechanisms (including altered gene silencing).”

The response from the FSHD research community was robust, showing the NIH that there are many FSHD researchers seeking research funding from the NIH. In an investigator-driven model it demonstrates that NIH is indeed receiving many applications for FSHD.

In June 2007, the NIH made mention of six grants being awarded out of this special one time contract program designed to help the under-studied and under-represented dystrophies in the NIH portfolio. Six grants were awarded or were to be awarded.

The NIH muscular dystrophy program directors are continuing to work with other applicants for resubmission of non-funded applications. There was a good disease balance with three FSHD, two EDMD and one OPMD grants awarded.

Of the three FSHD grants, two were R21s and one was a R01. The R21s were awarded to Silvere van der Maarel, Ph.D., to study FRG1 gene expression in FSHD, and William W. Mattox, M.D., to study FRG1 and alternative RNA splicing in *drosophila* (fruit fly).

The R21s are for two years and in the \$200,000-\$250,000 direct costs range per year. The R01 was awarded to Peter L. Jones, Ph.D., to study early events in a FSHD-like model of *Xenopus* (frog) and FRG1 expression. The R01 is for five years and is probably in the \$200,000-\$250,000 direct costs range per year.

The FSH Society has kept Dr. Jones apprised of developments in FSHD and has met with his post-doctoral student, Ryan Wuebbles, M.S. Ryan and his father, who is a professor at the University of Illinois, attended the FSHD patient conference in Rockville, MD 2002 to discuss research and ways to encourage the development of research at the university. Dr. van der Maarel started his FSHD research as a FSH Society fellow and the Society is currently funding several post-doctoral candidates in his laboratory.

*continued on page 41*

## RESEARCH

### U.S. NIH funding opportunities, *continued from page 40*

■■■

PAR-06-227

NINDS

08/15/2008

F05

International Neuroscience Fellowship  
(F05)

<http://grants.nih.gov/grants/guide/pa-files/PAR-06-227.html>

■■■

PAR-06-203

NINDS

09/02/2007

R21

Exploratory/Developmental Program for  
Translational Research in Muscular  
Dystrophy (R21)

<http://grants.nih.gov/grants/guide/pa-files/PAR-06-203.html>

■■■

PAR-06-044

NINDS

11/02/2008

U01

Translational Research in Muscular Dys-  
trophy (U01)

<http://grants.nih.gov/grants/guide/pa-files/PAR-06-044.html>

■■■

PA-05-052

NIAMS

12/06/2007

F32

Ruth L. Kirschstein National Research  
Service Awards for Postdoctoral Fel-  
lowships in Muscle Disease Research

<http://grants.nih.gov/grants/guide/pa-files/PA-05-052.html>

■■■

PA-05-051

NIAMS

03/02/2008

K08, K23

Mentored Clinical Investigator Career  
Development Awards in Muscle Dis-  
ease Research

<http://grants.nih.gov/grants/guide/pa-files/PA-05-051.html>

■■■

NOT-NS-07-005

NINDS, NIAMS, NICHD, NHLBI

Release Date: February 8, 2007

U54

Notice of Intent to Issue an FOA  
(RFA) to Continue the Senator Paul D.  
Wellstone Muscular Dystrophy Coopera-  
tive Research Centers Program

<http://grants.nih.gov/grants/guide/notice-files/NOT-NS-07-005.html>

The NIH now has new mechanisms for  
support of therapeutic development in  
neurological disorders in general:

<http://grants.nih.gov/grants/guide/pa-files/PAR-05-158.html>

and

<http://grants.nih.gov/grants/>

[guide/pa-files/PAR-05-157.html](http://grants.nih.gov/grants/guide/pa-files/PAR-05-157.html)

and for muscular dystrophy in particular:

<http://grants.nih.gov/grants/guide/pa-files/PAR-06-044.html>

and

<http://grants.nih.gov/grants/guide/pa-files/PAR-06-203.html>

We encourage you to contact the FSH  
Society for additional information on any  
of these programs. Consult the NINDS  
and Neuroscience Blueprint websites to  
learn about available tools, resources and  
training opportunities for neuroscientists.

## FSH Society compiles tactical and strategic research plan to solve FSHD

The FSH Society Scientific Advisory  
Board Tactical and Strategic  
Research Plan was written and derived, in  
part, by presentations made to the SAB by  
research team leaders currently funded by  
the FSH Society at a meeting conducted at  
the Charles Hotel in Cambridge, MA on  
Saturday July 15, 2006.

The meeting was generously sponsored  
by the FSH Society, MDA-USA, William  
Herzberg, M.D. and family, Genzyme Cor-  
poration, and the AFM.

Present were members of the FSH Soci-  
ety SAB and FSH Society Board of Direc-  
tors, FSHD researchers, funding agencies  
and industry.

### FSH Society Scientific

#### Advisory Board members:

David E. Housman, Ph.D.; Michael R.  
Altherr, Ph.D.; Rune R. Frants, Ph.D.;  
Louis M. Kunkel, Ph.D.; William R. Lewis,  
M.D.; William R. Lewis III, M.D.; George  
W.A.M. Padberg, M.D.

#### FSHD Researchers:

Silvère van der Maarel, Ph.D.; Sara  
Winokur, Ph.D.; Melanie Ehrlich, Ph.D.;  
Kyoko Yokomori, Ph.D.; York Marahrens,  
Ph.D.; Davide Gabellini, Ph.D.; Rossella  
Tupler, M.D., Ph.D.; Shree Pandya, P.T.;  
Stephen Tapscott, M.D., Ph.D.; Katherine  
Mathews, M.D., Ph.D.

### Funding Research Agencies:

John D. Porter, Ph.D.; Bill Moore,  
Ph.D.; C. Theo Verrips, Ph.D.; M. Caron,  
AFM

### Industries:

Gyongyi Molnar, M.D., Ph.D.  
Research team leaders were given the  
charge to present major findings by their  
groups, but not necessarily their most cur-  
rent data. An open, free-flowing discussion  
accompanied many of the presentations.

Finally, the researchers were asked to

*continued on page 42*

## FSH Society Scientific Advisory Board

- ◆ David E. Housman, Ph.D.,  
Chairman
- ◆ Michael R. Altherr, Ph.D.
- ◆ Robert H. Brown Jr., M.D./D.Phil.
- ◆ Rune Frants, Ph.D.
- ◆ Robert C. Griggs, M.D.
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- ◆ George W. A. M. Padberg, M.D.
- ◆ Paul Schultz, M.D. \*
- ◆ Rabi Tawil, M.D.

\* Board Member Emeritus

## RESEARCH

### *FSH Society strategic research plan to solve FSHD*, continued from page 41

identify their perception of the most important issues impacting FSHD research both as individuals and the field as a whole.

The presentations were kicked off with an outstanding overview of the phenotypic spectrum of the disease. This talk, and many that followed, began to identify a number of focal points that would further facilitate our understanding of FSHD pathogenesis.

A number of excellent reviews on the clinical picture in FSHD have been published recently but will not be summarized here. Of particular note, the discussion on the marked asymmetry and different developmental lineages of the muscles involved sparked consideration of the parallels to the plethora of effects caused by developmental pattern regulatory genes.

A recurring theme appeared in the next several talks that involved understanding the difference between normal vs. disease state and the absence of a natural history of both normal and disease muscle at the molecular, cellular, physiological and histological levels. This is something that could be facilitated by a systems biology approach.

The subsequent presentation provided what was probably one of the most stimulating discussions of the day and focused on two enormously interesting and related issues. One group has made significant progress in using ectopic expression of suspect coding sequences to produce a mouse model. Although not completely concordant with the disease phenotype (e.g. how do you evaluate facial weakness in the mouse?), there are a number of important parallels between the mouse model and human disease and a number of observations suggest a potentially important role for FRG1 in disease.

Strikingly, a previously unappreciated facet of FRG1 mis-regulation was initially identified in the aberrant mRNA splicing mouse construct. This phenomenon was subsequently confirmed in the processing of FSHD patient's RNA from derived cell

lines. Similar mouse constructs using other coding segments from the suspect genomic segment failed to produce significant altered phenotypes. These findings appeared in conflict with those of another group, who apparently attempted to create similar constructs but without significant effect. Unfortunately, those studies, largely negative in their findings, have not been published. Nonetheless, the "availability" of the affected mouse drives an enormous amount of experimental interest.

While the discordant findings are initially disquieting, much of the later discussions focused on the epigenetic potential to modulate gene expression by nuclear localization and chromatin modifications associated with the contraction of D4Z4 repeats, leading one to believe that it might even be expected.

For example, the choice of promoter or other aspects of the construct, the site of trans gene integration, or even the subsequent chromatin modifications of the trans gene could have profound impacts on the resultant phenotype. The quixotic nature of this disease and phenomena associated with it suggest to always expect the unexpected. The disparate mice results were not the only incongruities to be identified during the day and the complexity of the problem screams out for well defined controls, reagents and uniformity in experimental execution.

There was nearly complete uniformity and consensus of opinion among the investigators for the need to establish a process to arbitrate experimental discrepancies leading to paradoxical findings

through independent validation, third party, or double blind studies; and for the production, utilization and distribution of baseline reagents and detailed protocols in an effort to eliminate variability resulting from subtleties associated with experimental materials and techniques.

While the Society's research budget is modest compared to that of NIH or even MDA-USA, the Society could greatly facilitate the research endeavor by adopting a centralized coordinating role. This could be accomplished by expanding the current Society web site to be a resource for researchers. A number of specific recommendations are included, both short term (tactical) and longer term (strategic), that will be needed to expedite and synergize the current research efforts and move the experimental paradigm toward strategies that have the potential to ameliorate the consequences of this disease.

The FSH Society research plan initial draft was prepared by Michael R. Altherr, Ph.D. after an executive meeting of the FSH Society SAB following the meeting. The 17 page research plan outlines the steps and programs that are necessary to facilitate breakthroughs in FSHD through the work of the Society, researchers, FSHD community and industry. We are currently in need of substantial funds to implement the programs, projects and strategies. Those interested in helping to fund this essential and critical program of projects should contact Daniel Paul Perez, David Housman and Nancy Van Zant for further details.

***Your contribution to the FSH Society is tax-deductible  
and ensures the on-going work of YOUR advocacy  
group. We need your continued support.***

***Please send your donation now.***

***The donation form can be found on the back page.***

## RESEARCH SUMMARIES FROM OUR FSH SOCIETY GRANTEES

### *Gaining insights into differentiation of muscle stem cells into myoblasts*

By Michael Rudnicki, Ph.D.

This work has helped us understand that the transcriptional regulation of Pax7 expression is complicated and involves more than just Wnt signaling. Dr. Oliveira has demonstrated that 10kb containing the proximal promoter is insufficient to confer expression in primary myoblasts. This has led to focus on GC islands located in introns 3 and 4. The reason why this basic research is of relevance to FSHD is that this work will: help to define the molecular events that regulate the differentiation of this population of muscle stem cells into myoblasts; contribute to our understanding of adult muscle regeneration; and may also result in identification of new therapeutic targets that will be valuable for the development of new therapies to treat many neuromuscular diseases, such as FSHD.

■ ■ ■

Grant: FSHS-NYSS-001  
 Researcher: Daniela M. Oliveira, Ph.D.  
 Institution: Ottawa Health Research Institute  
 501 Smyth Road  
 Ottawa, Ontario  
 Canada K1H 8L6  
 Project Title: "Identification of the mechanism regulating the Wnt-dependent activation of muscle progenitor cells."

\$30,000 1/1/2005-12/31/2005 Year 1

**Goal:** The overall goal of the project is to identify genes regulated by the Wnt signaling pathway that are responsible for the myogenic differentiation and proliferation of CD45+/Sca-1+ muscle cells. In addition, muscle satellite cells — another stem cell population within muscle (CD45+/Sca-1+ muscle cells) — plays a physiological role in muscle regeneration. Identification of new therapeutic targets can be used to help stimulate the Wnt-target genes that might be used to enhance stem cell transplant in FSHD.

### *FSHD arises when patients are missing a number of randomly repeated DNA sequences*

By York Marahrens, Ph.D.

Genes are short segments of genetic material — the chromosomal DNA molecules. Our chromosomal DNA molecules range from having tens of genes to thousands of genes. The DNA molecules do not exist as "naked DNA" in the cell. Instead, the DNA molecules are packaged in protein coats called chromatin. Several different types of protein coats (chromatin) exist and different regions of a chromosome are packaged in different protein coats. The various types of chromatin can be placed into two broad categories: euchromatin and heterochromatin.

Euchromatin refers to all of the loose protein coats that allow genes that reside in the euchromatin to be expressed. Heterochromatin refers to all of the tight protein coats that cause genes to be silenced. The tandemly repeated sequences within our chromosomes are packaged in heterochromatin.

FSHD arises when patients are missing a number of tandemly repeated DNA sequences, called D4Z4, that are located near the end of chromosome 4. It is thought that one or more unidentified disease genes, located somewhere far away from the repeats, malfunction when the repeats are missing. Since the tandem repeats are packaged in heterochromatin, FSHD patients have smaller regions of heterochromatin near the end of chromosome 4 than healthy people.

There is evidence that heterochromatin spends a certain proportion of its time sticking to other heterochromatin and that the most frequent sticking interactions are between two regions of heterochromatin that are nearby on the same chromosome. Therefore, we suspect that the heterochromatin structure that exists at the D4Z4 repeats loops around and sticks to certain heterochromatin structures elsewhere on the chromosome. We hypothesize that the looping interactions allow the repeats to influence the gene expression.

We are attempting to identify the FSHD genes by attaching a chemical to the repeats in live cells that modifies the chromosomal sites that it contacts. The FSHD genes are then identified by virtue

of their modification that occurs when they touch the repeats/chemical.

The D4Z4 repeats are one example of many types of repetitive sequences that make up approximately 50% of the human genome. We, and others, have obtained evidence that a subset of these repeats form an interaction network throughout each of the chromosomes. Only genes that are flanked by high concentrations of these repeats are tied into this network. The main repeat responsible for this network is called LINE-1 which is a very abundant repeat. However, we have evidence that other repeats also participate in these networks. It has struck us that the D4Z4 repeats might be tied into this network. This would provide a way in which the D4Z4 repeats influence the expression of distant genes. We are currently looking for evidence that would suggest that this is indeed the case.

■ ■ ■

Grant: FSHS-NYSS-002  
 Researcher: York Marahrens, Ph.D./Nieves Embade, Ph.D.  
 Institution: Department of Human Genetics  
 David Geffen School of Medicine  
 University of California, Los Angeles  
 Gonda Center, Room 4558  
 695 Charles E. Young Drive  
 Los Angeles, CA 90095 USA  
 Project Title: "Testing whether D4Z4 Perform Long Distance Gene Silencing via the Chromosome 4 Inactivation Network."

\$22,652 11/1/2004-10/31/2005 Year 1

**Goal:** A high risk and novel approach to understanding chromosome interactions, epigenetics: to test the hypothesis that long repetitive sequence on a chromosome, regardless of sequence, is tied into the network of long repeats responsible for chromosome inactivation; and particularly with FSHD, the case of non-random mono-allelic autosomal inactivation; to test the hypothesis that the tract of D4Z4 repeats at 4q35 is tied into the chromosome 4 inactivation network; and that D4Z4 deletions disturb chromosome 4 inactivation resulting in abnormal gene expression.

## RESEARCH SUMMARIES FROM OUR FSH SOCIETY GRANTEES

### *Does the envelope surrounding the cell nucleus have a role in FSHD?*

By Cecilia Östlund, Ph.D.

All human cells, except for red blood cells, have a nucleus. The cell nucleus harbors our DNA in chromosomes, which contains our genes. All cells in a person have the same DNA, but different genes are activated (expressed) in cells from different tissues, which enables the cells to fulfill their specialized functions. In most cases, the expression of a gene leads to production of a specific protein for which that particular gene is the "blueprint."

The content of the nucleus is separated from the rest of the cell by the membranous nuclear envelope. This separation is very important for correct activation of genes at correct times and in the right cells. Besides its main lipid (fat) component, the nuclear membranes also contain different proteins which are important to maintain the structure of the cell nucleus. Proteins are also believed to be important for the regulation of gene expression.

Our laboratory at Columbia University, led by Dr. Howard Worman, studies the role of nuclear envelope proteins in human disease. During recent years, at least two nuclear envelope proteins, called emerin and lamin A, have been shown to be mutated in persons with EDMD. Mutations in lamin A have also been shown to cause one type of LGMD, as well as partial lipodystrophy (loss of fat tissue) and progeria (premature aging). Lamin A form a protein network which lines the inside of the nuclear envelope and although the detailed function of this protein is not yet understood, it is important for the integrity of the cell nucleus and binds to many other nuclear proteins.

Recently, part of our work has been focused on FSHD. This work has greatly benefited from a research fellowship from the Majorie and Gerald Bronfman Foundation, given to me through the FSH Society. In collaboration with a Belgian group led by Professor Alexandra Belayew, we are investigating the role of a protein called DUX4. The gene from which this protein is produced is present in the region of chromosome 4 that is affected in most cases of FSHD. We want to compare the

amount of DUX4 protein between individuals with FSHD and unaffected individuals. One hypothesis is that while normally the DUX4 gene is not activated, the FSHD mutation makes the gene active, causing DUX4 protein to be made. This could have toxic consequences for the muscle cells.

DUX4 is localized to the cell nucleus, and may interact with other proteins in this area. One interesting question we want to address is if DUX4 and other proteins affected by FSHD mutations interact with lamin A, emerin or other known nuclear proteins. This could help us understand if the mechanisms behind the different muscular dystrophies have common features. One way we are analyzing the interaction between DUX4 and other proteins is by studying if DUX4 can move freely within the nucleus, or if it is immobilized in some specific area of the nucleus. If the protein is immobile, it suggests that it binds to other proteins or structures in the nucleus.

Another interesting hypothesis recently put forward by Sara Winokur and her colleagues (Masny et al., Hum. Mol. Genet. 2004) suggests that lamin A, or a protein interacting with lamin A, binds to chromosome 4 itself. The region of this

chromosome mutation in most cases of FSHD is consistently found close to the nuclear envelope consistent with such an interaction. A disturbance of the interaction between the nuclear envelope proteins and the chromosome may cause abnormal activation of the genes on this chromosome leading to FSHD.

In conclusion, there is growing evidence that the nuclear envelope plays an important role in several human diseases, and there is indication that this structure may have a role in FSHD as well as in other muscular dystrophies.

■ ■ ■

Grant: FSHS-MB-008

Researcher: Cecilia Ostlund, Ph.D. / Howard Worman, Ph.D.

Institution: Columbia University  
Departments of Medicine and  
Anatomy and Cell Biology

P & S 10-518

630 W 168th St

New York, NY 10032 USA

Project Title: "The role of DUX4 in  
facioscapulohumeral muscular  
dystrophy."

\$30,000 2/1/2003-1/31/2004 Year 1

\$30,000 2/1/2004-1/31/2005 Year 2

■ ■ ■

## ONLINE COMMUNITY

### *Visit us @ [www.fshsociety.org](http://www.fshsociety.org)*

By Daniel Paul Perez

Visit us and bookmark the FSH Society at its Internet location: [www.fshsociety.org](http://www.fshsociety.org). The website is still going strong and we are seeing a tremendous increase in both domestic and international traffic. We are getting the word out about FSHD! The home page at [www.fshsociety.org](http://www.fshsociety.org) contains a rich resource of material for those interested in FSHD. For those not familiar with the site, the FSH Society home page contains information on the following: the FSH Society; FSHD; the FSH Society online bulletin board and chat room; and previous FSH Society publications and information. The chat room, hosted by Paul Closson, meets every Sunday 2 p.m. and 9 p.m. eastern time zone. Professional web designers and web architects who would like to volunteer their time and services are encouraged to contact us.

We fully appreciate the contributions and donations made to date to the Society to support this important and timely resource. Please consider making a donation to the FSH Society Internet fund. We look forward to seeing you on-line!

## RESEARCH SUMMARIES FROM FSH SOCIETY GRANTEES

### *Developments on D4Z4, DUX4 and cell death*

By Alberto Rosa, M.D., Ph.D.

Most of our previous work with DUX4 has recently been accepted for publication in the Journal Neuromuscular Disorders NMD. The reference is now available at PubMed. Alexandra Belayew, Ph.D., Denise Figlewicz, M.D., Fédérique Coppée, Ph.D., Cecilia Conde, Ph.D., Cristina Arias, Ph.D. and E. Daniel Corona, Ph.D., all supported or partially supported by the FSH Society, are co-authors in the paper. It is a important contribution to FSHD research. We continue working with DUX4 mutants as well as exploring some interesting side aspects of DUX4 expression. I have some support from CONICET and FONCYT (Argentina).

■■■

“The DUX4 gene at the FSHD1A locus encodes a pro-apoptotic protein”

#### ABSTRACT:

FSHD patients carry contractions of the D4Z4-tandem repeat array on chromosome 4q35. Decrease in D4Z4 copy numbers is thought to alter a chromatin structure and activate expression of neighboring genes. D4Z4 contains a putative double-homeobox gene called DUX4. We identified DUX4 mRNAs in cells transfected with genomic fragments containing the DUX4 gene. Using RT-PCR we also recognized expressed DUX4 mRNAs in primary FSHD myoblasts. Polyclonal antibodies raised against specific DUX4 peptides detected the DUX4 protein in cells transfected with D4Z4 elements. DUX4 localizes in the nucleus of cells transfected with CMV-DUX4 expression vectors.

A DUX4-related protein is endogenously expressed in nuclei of adult and fetal human rhabdomyosarcoma cell lines. Overexpression of DUX4 induces cell death, caspase 3/7 activity and alters emerin distribution at the nuclear envelope. We propose that DUX4-mediated cell death contributes to the pathogenic pathway in FSHD.

■■■

Grant: FSHS-MB-009  
 Researcher: Alberto Luis Rosa, M.D., Ph.D.  
 Institution: Laboratory of Neurogenetics  
 Institute for Medical Research “Mercedes y Martín Ferreyra”  
 INIMEC-CONICET, National Research Council of Argentina  
 Friuli 2434, B Col. Velez Sarsfield, 5016 – Córdoba, Argentina  
 Project Title: “Role of nuclear localization signal (NLS) and H1/H2 motifs in DUX4-mediated cell Death.”

\$43,750 8/1/2004-7/31/2005 Year 1

\$14,690 8/1/2005-7/31/2006 Year 2

**Goal:** To gain understanding of the molecular and cellular mechanism underlying the pathogenesis of human FSHD. To study DUX4, a putative double homeobox-containing protein encoded by a 3.3 kb polymorphic tandem repeat (D4Z4), at the locus FSHD1A on the human chromosomal region 4q35. It is hypothesized that abnormal temporal or spatial expression of DUX4 has a toxic effect for muscle cells causing FSHD. The study will help identify the mechanism(s) by which DUX4 causes cell death.

■■■

Grant: FSHS-DR-001  
 Researcher: Alexandra Belayew, Ph.D./Stephane Plaisance, Ph.D.  
 Institution: Lab. Biologie Moléculaire  
 Université de Mons-Hainaut  
 Pentagone, Avenue du Champ Mars 6  
 B - 7000 - Mons  
 Belgium  
 Project Title: “Characterization of a protein expressed from a 3.3 kb element not linked to FSHD.”

\$15,000 6/1/1998-12/31/1998 Year 1

“Small laboratory equipment for research on FSHD.”

\$15,000 2/15/2001-open Year 1

**Goal:** To initiate research on the role of DUX, DUX1, DUX4, DUX4C and to elucidate the role of DUX in FSHD and within the D4Z4 region.

### **CFC #10239**

#### *& United Way*

Federal employees and military personnel can donate to the FSH Society, Inc. 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, Inc. CFC code is #10239. For more information about the CFC you may visit the OPM website at:

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

■■■

### **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/>

■■■

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 on YOUR contributions  
 to continue its work!**

**Please consider a  
 tax-deductible  
 contribution today!**

## ACKNOWLEDGEMENTS

### Thank you!

The FSH Society wishes to acknowledge the following for their contributions to our efforts:

- ◆ Ann Biggs-Williams of Alabama, for leading the caregivers group at the July 2006 patient day conference in Cambridge, MA
- ◆ Booth hosts for Salt Lake City ASHG meeting Oct. 2005: Duncan and William R. Lewis, M.D., Z. John Stekly, D.Sc. and Dawn and David Young
- ◆ Alan and Paula Cartoun of Connecticut, for their advice and counsel on our mailings
- ◆ Howard and Michele Chabner of California, for fundraising efforts and co-leading a group at the July 2006 patient day
- ◆ Paul Closson of Florida, for hosting the FSH Society Bulletin Board and Chats
- ◆ Justin Cohen of New York, for donating funds from the sale of his art cards to the FSH Society
- ◆ Arlene Endres of Maryland, for raising funds for the FSH Society through her annual read-a-thon
- ◆ FSH Society members and donors around the world for their generosity, 2005-2007
- ◆ Kyle Gilligan of Illinois, for donating profits from the sale of his book, "My Special Visit with Dad," to the FSH Society
- ◆ Anne Gillespie of Virginia, for her fundraising efforts on behalf of her daughter, Catherine
- ◆ Judy and William Herzberg, M.D. of Oregon, for their fundraising for our Research and Education Fund and assistance at the conference July 2006
- ◆ Prof. David Housman, Chair, Scientific Advisory Board, for continued dedication to FSHD issues
- ◆ The Kelly family of Massachusetts, for their fundraising mail campaign to family and friends on behalf of the FSH Society and especially to YanNi and Lia Kelly for putting stickers on all the envelopes (see article on page 5)
- ◆ Judy and Don Lokerson of Maryland, for co-leading a group and assistance at the July 2006 patient day conference in Cambridge, MA
- ◆ Stefanie Pace of New Jersey, for the fundraiser she held on behalf of the FSH Society at the Coleman School Super Bowl Chili event
- ◆ Charles Perez and Susan Perez of Massachusetts, for continued administrative support of the FSH Society
- ◆ Robert and Patti Smith of Massachusetts, for hosting the welcome at the July 2006 conference in Cambridge, MA
- ◆ Chris Stenmon of Massachusetts, for his successful bar crawl fundraiser on behalf of the FSH Society
- ◆ Dawn Young of Canada, for welcoming patients and families to the July 2006 patient day conference in Cambridge, MA



### Foundations

- ◆ Marjorie and Gerald Bronfman Foundation
- ◆ Catalogue for Philanthropy
- ◆ The William J. Conners, III and Barbara S. Conners Charitable Foundation
- ◆ Delta Railroad Construction
- ◆ Greater Kansas City Community Foundation
- ◆ New York Community Trust
- ◆ Tides Foundation

### July 2006 Conference Support

- ◆ Association Française Contre les Myopathies
- ◆ Athena Diagnostics, Worcester, MA
- ◆ Genzyme Corporation
- ◆ Dr. Bill and Judy Herzberg
- ◆ Leiden University Medical Center
- ◆ Linda Mason
- ◆ Massachusetts Rehabilitation Commission
- ◆ William Michael
- ◆ Harry Mulholland
- ◆ Muscular Dystrophy Canada
- ◆ Ride-away Handicap Equipment Corp.
- ◆ Edward & Betty Schechter
- ◆ Doris Walter
- ◆ Wyeth Pharmaceuticals



### Other Support

- ◆ Leiden University Medical Center for 2004 Toronto FSHD Consortium Meeting and for FSHD Consortium meeting October 25, 2005 and October 9, 2006

***Your donations keep  
the FSH Society  
advocating for you!  
Please remember the  
Society when considering  
your tax-deductible  
charitable giving.***

## **ACKNOWLEDGEMENTS**

### *In honor of...*

4/1/2005-3/31/2007

- ◆ Amy Bekier: Merrill Block
- ◆ Richard A. Lefebvre's Birthday: Marie Bortone
- ◆ Ashley Bryan: Helme-Shaw Foundation, Wallace Lyle Mueller
- ◆ Paul Closson: Janice Caldwell, David Closson
- ◆ Justin Cohen: Grandparents Stuart & Harriet Cohen, Judith Cotler, Glorine Schweitzer, Caryn Stoner
- ◆ Leah Cohen's Bat Mitzvah: Melvin Klipper
- ◆ Brian Colella's Birthday: Terry & Rick Colella
- ◆ Melanie Ehrlich's heroic efforts during Hurricane Katrina: Ann Biggs-Williams and the Gulf FSHD Support Group
- ◆ Sarah Love Davis: Grandfather Charles M. Fitts, Jr.
- ◆ Sixto Garcia: Aunt Bettina G. Welsh
- ◆ Catherine Gibson: Yvonne Gillespie, Carol Hagy, Nancy C. Hunter, Robert & Deborah Hunter, Sharon Perry, Ruth Tarter
- ◆ Meredith Huml: Catherine Coyle
- ◆ Dr. & Mrs. Frank Katz's 50th Anniversary: Eli & Honey Schindelheim
- ◆ Katz Family: Linda Ketelaar
- ◆ William Klipper on his Bar Mitzvah: Rose Kanter
- ◆ Shelia Lieberman's 60th Birthday: Miriam Brown
- ◆ Jessica Pease: Grandmother Patricia Tompkins
- ◆ Dan Perez's great work: Paul & Annabelle Closson
- ◆ Irving Rappaport: Rose Kanter

- ◆ Ethel Russom: Paul & Annabelle Closson
- ◆ Jessica Ryley: Grandparents Gerry & Joanne Smith
- ◆ David & Helen Younger: Rosalind Devon

**Please call the FSH Society at 617-658-7878 if you need an extra newsletter, a patient or P.T. brochure, or other materials to share with your doctor or someone interested in FSHD.**

### *Estate planning*

#### *How to make a bequest for the benefit of the FSH Society*

For many donors, a bequest is the most realistic way of making a significant gift to the FSH Society. You may provide assistance to the work of the FSH Society by naming the Society as a beneficiary in a new will, in a codicil to your present will, under your revocable trust, or by designating the FSH Society as the beneficiary of your retirement plan or insurance policy.

To ensure that your exact intentions are carried out, wills, codicils, and trusts should be prepared by and with the advice of your attorney. The FSH Society executive staff is available for additional information on the various methods of designating a bequest to the FSH Society or for guidance in planning a gift.

A bequest or beneficiary designation to the FSH Society should name "the FSH Society," which is the common name of the Facioscapulohumeral Society, Inc. Unless otherwise specified, a bequest to "the FSH Society" is interpreted as an unrestricted donation to the Society for use as directed by its board of directors.

If you desire to restrict the use of the donation for research or education, then to ensure that your bequest is properly directed and credited to the FSH Society Research & Education Fund, rather than to the Society without restriction, it is important that you specify that it be paid to the "the FSH Society, for the benefit of the FSH Society Research & Education Fund."

#### **Sample Bequest Forms**

##### **A general bequest, unrestricted as to purpose:**

"I give (\_\_\_ dollars) or (\_\_\_ percent of my estate) to the FSH Society, a 501(c)(3) non-profit charitable corporation based in Massachusetts, or its successor, to be used for general purposes of the organization."

##### **A bequest for a specific purpose:**

"I give (\_\_\_ dollars) or (\_\_\_ percent of my estate) to the FSH Society, a 501(c)(3) non-profit charitable corporation based in Massachusetts, or its successor, for the benefit of the FSH Society to be used for (state the purpose). If, in the future, in the opinion of the FSH Society, all or part of this gift cannot be usefully applied to the above purpose (or in the above manner), it may be used for any purpose within the corporate powers of the Society that will most nearly accomplish my wishes and purposes."

## ACKNOWLEDGEMENTS

### *In memory of...*

■■■

4/1/2005-3/31/2007

- ◆ Richard Manning Allan: Patricia L Langdon
- ◆ Seneth Baltés: Paul & Annabelle Closson
- ◆ Ruth Berkowitz: Agnes Farkas, Iris Kislin, Thomas & Lori Imperiale, Rubin & Sally Laskoff, Anna Marantz, Calvin & Myra Marantz, Steven & Leslie Marantz, Keith & Larissa Marantz, Milton & Joanne Yatvin
- ◆ Jean Bond: Judy & W. D. Ross
- ◆ Ron Brennan: Miriam Brown
- ◆ Harriet Brodsky: Joseph & Miriam Kaplan, Rose Kanter
- ◆ Harry Daum: Judy & W. D. Ross
- ◆ Nancy Duca: Elizabeth L. Niner
- ◆ Gordy: Miriam Brown
- ◆ Joseph Grech: Jeff & Jennifer McInnes
- ◆ Lady W. Hall & Lady Beth Hall: William E. Hall
- ◆ Tom Higgins: Judy & W. D. Ross
- ◆ Brent N. Jacobsen: Barry & Nancy Carlson, Rachel Delmore, Rosalie Ferguson, Carla Jacobsen, D. & M. Suhre
- ◆ Dr. Stephen Jacobsen: Ann Biggs-Williams, Paul & Annabelle Closson, Delta Railroad Construction Company, Melaine Ehrlich, Robert & Patti Smith
- ◆ Karen Johnsen's Dream: Jilliam Abrams, All Saints Lutheran Church, Jean & Randy Anastasi, Annapolis Lodge No. 622, Anonymous Donor New York Community Trust Foundation, Michael Aquilino, Jeffrey & Barbara Bache, James W. Barry, Bay Ridge Lawn & Landscape, Inc., Daniel & June Beck, Chesapeake Hearing Centers, Inc., Jeanne Chicca, Thomas & Dana Delaney, Arlene & Patrick Endres, Dean Ferris, Jill Fleisher, Carlos & Beatriz Garcia, Anne Harland, Arlene & Marvin Hoffmann, Karen Johnsen's Dream for a Cure Fundraiser Raffle Event, Kiwanis Club of the Severn, Elaine Kolakowski, David & Mary McCaffrey, Robert B. Meek, MD, Shirley Novotny, Louis, Ellen & Meredith Pease, Carol Prier, Rotary Club of Columbia-Patuxent, Clara & Gregory Segreti, Alain Thys, Jaime Vives, Kenneth & June Webb
- ◆ Jules Kanter: Miriam Brown
- ◆ Joseph Kaplan: Fred & Joyce Claar, Tammy & Evan Cohen, Rose Kanter, Alfred & Sydell Herrick
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- ◆ Dean Ledford: Judy & W. D. Ross
- ◆ Jerry Leduc: Jeri Blom
- ◆ Bill Luttmann: Charles & Carol Perez, Cyrina Wolf
- ◆ William N. Merkle: Jeffrey & Eileen Barthelmes, Catherine Bauer, BDO Seidman, LLP, Lawrence & Lisa Boyle, Lorraine Casler, Suzanne Corradini, Lawrence & Patricia De Felice, Gerald & Jill Dean, Denney Electric Supply of Amber, Inc., Benjamin & Barbara Denny, Mary Jo Di Nardo, Sharon Diab, Christine M. Fitz Patrick, William & Danielle Franz, James Gavin, Michael Gazzara, Scott J. Heller, Theresa Ives, Gary & Susan Klaiss, Mita & Christopher Martino, Lawrence & Robin Osman, Suzanne Park, Henry & Louise Rauch, Natalie Rivers, Eleanor & Willard Turner, Janette Wyman-Babikian, Frank & Susannah Zoltowski
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- ◆ Harry O. Miller: William Lacker, Carol Miller, Sharon Nordberg, Mason Schafer, Sandra Stewart, Beryl & Anthony Brant, Donald & Helen Fitz, Mary Sue & Jerry Proudfoot, Harvey Kunnen
- ◆ Barbara Nesnow: Katherine Abrams, Avis & Mannie Brenner, Alan & Ardeth Millner, Lois A Obrion, Carol & Charles Perez, Susan & Daniel Paul Perez, Ruth Rinder, Andrew & Claudia Scholtz, Robert & Patti Smith, Virginia Stackfleth, Helene Stein, John & Suzanne Stekly
- ◆ Paul Nord: Charles & Carol Perez
- ◆ Thomas Oxenreider: Elizabeth L. Niner
- ◆ Klara Pogany: Linda Brey, Brian Lemon, Charles Waymaster, Dorothy Williams
- ◆ Mildred Rabinowitz: Rose Kanter
- ◆ Irving Rappaport: Rose Kanter, Joseph & Miriam Kaplan
- ◆ Doris Raskin: Iris Kislin
- ◆ Shirley Renders: Judy & W. D. Ross
- ◆ Angelina D. Richino: Miriam Brown
- ◆ Herrman Rotter: Edith Schwartz
- ◆ Elizabeth "Betty" Smith: Agnes Boyer
- ◆ Jean E. Soldan on his Birthday, Christmas Day and for Father's Day: his daughter, Linda Mason
- ◆ Henry Spritzer: Milton & Joanne Yatvin
- ◆ John Stephenson: Elizabeth Stephenson
- ◆ Janine Thys: Anonymous donor New York Community Trust Foundation, Susan Parker Brauner, Allan Coukell, John Davidow, Donald & Patricia Herring, Nellie Kanter, Melvin Klipper, Donald & Judith Lokerson
- ◆ Winnifred Tiley: Elizabeth L. Niner
- ◆ James W. Weyenberg: Beverly Weyenberg

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4/1/2005- 3/31/2007

- ◆ Amgen Foundation,
- ◆ Anheuser Busch,
- ◆ Goldman, Sachs & Co.
- ◆ Hewlett-Packard Co.
- ◆ IBM Employee Services Center
- ◆ Johnson & Johnson
- ◆ M.I.T. Annual Community Giving Campaign
- ◆ Merrill Lynch
- ◆ Merck Employee Giving Campaign
- ◆ Morgan Stanley
- ◆ Pepsico
- ◆ Raytheon
- ◆ Schering Plough
- ◆ Schering Plough United Way
- ◆ United Way of Central Maryland
- ◆ CFC

■ ■ ■

### Special Events

- ◆ **Bear Creek Elementary School, Baltimore, MD 2005 and 2006 Read-A-Thon Fundraiser:** 2006 was the tenth annual fundraiser to raise funds to support the FSH Society & educate their community about FSHD. Honoring Arlene Endres, mother of Jessica Ryley & teacher at the Bear Creek School.
- ◆ **Howard Chabner's friends & family for the FSH Society:** David Brownstein & Grace Shohet, Buffalo Rides Inc. (Elliott & Sharon Slusky; and Dr. Harvey & Lisa Slusky), Bernard & Joyce Chabner, Barbara Chabner & Marshal Datkowitz; Daniel F. Cooley; Michael & Marla Craven, Howard & Dr. Carol Fine; Morton Frank,

Stewart & Rochelle Grill Philanthropic Foundation, Lisa & Michael Heyison; Jennifer Jackson; Sherwin & Betty Korey, Dr. Jerome & Marsha Kraut, Mannan & Margaret Latif; John & Lynn Peterson, Michael & Lisa Radin; Seymour & Barbara Regal, Judith & Allan Rosenblum, Jacqueline Savoy, Dr. Seymour & Lois Siegel, Michael & Stephanie Smerling; Denise & Steven Soberanis, Dr. Gerhard & Ethel Spiegler; Dr. & Mrs. Herbert Stein, Ronald & Susan Stern; Barry & Joan Swirsky; Kathryn Thyret, Rosalyn & Judd Wenner

- ◆ **Justin Cohen's Art Card Project – proceeds to the FSH Society:** On Sunday, July 16, 2007, Justin Cohen's work was acknowledged at the International FSH Society Conference.
- ◆ **Coleman School – Superbowl Chili Cooking Event - January 2007 for the FSH Society:** 3rd grade teacher Stefanie Pace at the Coleman School in Glen Rock, NJ donated the proceeds of this annual charity fundraiser.
- ◆ **Jeff Johnston's Friends & Family 2006 Christmas Gifts for the Research & Education Fund:** Christine & Jeff Bridges, Frank J. & Dolores E. Bridges, Kenneth & Jean Bridges, Ray Bridges, Richard J. & Patricia K. Hall, Jeff Johnston, Curtis Newell
- ◆ **Kyle Gilligan's book sale:** On Sunday, July 16, 2007, 8 year old Illinois author Kyle Gilligan's work for the Society was acknowledged at the International FSH Society Conference. Kyle's first book is entitled "My Special Visit with Dad" and his grandfather, Joseph Donald Hawkins, has illustrated the cover. In honor of his grandfather, proceeds from Kyle's book are donated to the FSH Society. Information about purchasing a copy of Kyle's book can be found on

www.booksbybookends.com or by contacting:

Long Dash Books  
89 Walnut Street  
Montclair NJ 07042  
Phone: 973-746-5496  
Email: longdash@gmail.com

- ◆ **Bill & Judy Herzberg's friends & family for the Research & Education fund:** Richard & Marci Abramowitz, Norman & Sandra Arky, Linda Barker, Kerry & Mia Barnett, Joseph Bendavid, Susan Bloom & Mac Kieffer, Andrea Borsuk, Philip & Barbara Borsuk, Ernesto & Connie Brauer, Stanley & Judith Broadwin, T. J. Browning, Ariel & Mariela Dybner, Michael & Marie Ferragamo, John Freedman & Lisa Cohen, Claudio & Andrea Giesen, Max & Eva Giesen, Jaime Gildengers, Barbara Gilson, Louis Goldstein, Alan & Harriet Gordon, Lynda Gordon, Stephen & Alice Goshorn, Enrique & Ruth Gutman, Howard Haberman & Martha Lybarger, Roberta Harris, Peter F. Herzberg, Mark Herzberg & Patricia Sheridan, William Herzberg & Judy Marantz, Mitchell & Marci Heskell, Steven & Linda Hill, Elisa & Bill Hirschberg, Ruth & Alan Hirschberg, Beno & Fredalee Hubler, Karen & Eric Hubler, Paul & Jane Jacobsen, Seymour & Lola Kamp, Margaret Katz, Maria Katz, Barbara Kim, Iris Kislin, Samuel & Shirley Knopf, Cheryl Kollin & Bill Franz, Jonathan Koomey, Peter Korn & Betty Smith, Rubin & Sally Laskoff, Kenneth Lerner, Anna Marantz, Calvin & Myra Marantz, Myra & Marvin Marantz, Scott Marantz & Susan Laskoff, Katherine McDowell, Cathy May Miller, Enrique More, David & Elsie Napell, Ina Nelson & Cheryl Minkoff, Dr. Leon & Barbara Nesis, Marty Paddock, Joan Rockhill, Ingrid Rosenthal, Norman Schlesinger, Mitchell Schoenbrun,

*continued on page 50*

## ACKNOWLEDGEMENTS

### *Special Events*, continued from page 49

Drs. Ernesto & Mirta Seldman, Gerald & Pearl Siegel, Morty & Zeta Sudler, Vancouver Neurologists PS, Ernest Weiss, Milton & Joanne Yatvin

◆ **Kelly family fundraiser – 2006:**  
(See article on page 5)

Kagan Abbott II, David & Ann Adams, David Alessandro, Dr. & Mrs. Robert Alperin, Allen & Susan Artmann, Benny, Gear & Jeannette Augusto, Mitra & Bijan Bakhtian, Paul & Regina Bastón, Maria & Kenneth Bishop, Kathy Black, James & Pamela Boyer, Bill & Ann Burke, Tom & Pam Burkhart, Cynthia Cassinello, Valerie Chistophilos, Pauline Chusid, Louis & Paula Cianca, Justine & Linda Cirrone, Mary & Eugene Cookson, Alice & Joseph Culhane, John & Antoinette Cuoco, Pauline Cuoco, Richard & Joan Davis, Arlene Deardorff, Robert & Emily DeSantis, Ann DeVellis, Mary Ann & Anthony DiCeglie, Rosemary Donovan, Virginia D. Doyle, Joseph V. Elia, Jane & David English, Frances & Leona Ferullo, Lewis Ferullo, Robert & Barbara Ferullo, James Ficociello, Jeanne Ficociello, John Flaherty, Henry Garvey, Maria & Robert Gauvain, Nancy Gerson, Richard Godfrey, Dr. Mark Gorovoy, Rose & Linda Grafton, Paula Grant, Melissa Gregorio, Richard & Susan Gregorio, Gene & Jeanne Grindlinger, Vicki Gusso, Carl & Marion Harris, Nancy & Brian Harris, Paula Hartwell-Bell, Pat & Bob Hauser, Arthur Higgins Jr., Albert & Jean Marie Hodgkin, Robin & Bruce Humphreys, Irish American Club, Inc. of Woburn, Joseph Janeliunas, Sam & Li-Su Javedan, James & Cynthia Kavanaugh, Julie Keeling, James, Grant & Paula Keith, James Kelly, Julie Kelly, Maureen Kelly, William & Odette Kent, Daniel & Jeanette Kohlbrenner, Maureen Lanpher, Donna

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- ◆ **Karen Johnsen's Dream for a Cure 2006 fundraiser raffle event:** Thanks to Robert & Doris Eck for sponsorship
- ◆ **Christopher Stenmon's seventh & eighth annual "End of the 2005 & 2006 Tax Season Bar Crawl":** Alba Bar & Grill, Andrea & Dorothy Anderson, Lara Apovian, Bad Abbots, Robin Basler, Lillian Battles, Beachcomber, BNJ Inc., Robert Boch, Ed Boyle, Sheri Buckingham, Ed Buiser, Kevin Burke, Lauren Carnes, Lisa Christopoulos, Club 58, Steven Cohen, Jacqueline Colebourn, Stephen Colella, Lisa Contursi, Guy Corter, Crosshaven

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## ACKNOWLEDGEMENTS

### *New & renewing members*



From 4/1/05 to 3/31/07, the following individuals have requested to be acknowledged in the FSH Watch.

- ◆ Kathleen Aument, NV; Amy Bekier, CA; Jane Barton, CA; Sandy Batkin, NY; Doris Geddes Berg, IL; Ann Biggs-Williams, AL; Barbara Birnbaum, CT; Stephen & Jane Bradford, CA; J. D. Brown, Corp., WA; Miriam Brown, PA; Don Burke, VA; Lori Calandro, MI; Deborah Calhoun, AZ; Lloyd Campbell, CA; Gary Cohen, M.D., NY; Josh Comfort, CO; Laurie & Bill Daniels, CA; Mary Doto, NY; Don Drinkwater, FL; Sally Petit Dunlap, TX; Mollie Egert, NY; Kathryn Ecenbargen, CA; Audrey Falk, MN; Barbara Finlay, Canada; Carlos & Beatriz Garcia, MD; Carlos & Mimi Garcia, CA; Anne M. Gillespie, VA; Manuel Gomez, DC; Ken Gordon, TX; James Haas, IN; Glenn & Petrina Hasman, OH; Eric Heiberg, MI; Arlene & Marvin Hoffman, MD; Richard Holmes, MA; Linda Hoover, WA; Michael Hough, CA; Bob & Libby Humphreys, SC; Kevin Kirby, GA; John & Donna Kirtz, TX; Elaine Kolakowski, MD; Elizabeth Kompel, MA; Florence Koplow, MA; Ruth & Daniel Krasner, NY; Kryn Krautheim, NC; Bryan Kromholtz, Switzerland; Russell Lai, CA; Stuart Lai, NY; William Lewis Sr., CA; David Lokerson, MD; Donald & Judith Lokerson, MD; Ryan & Shannon Maguire, NJ; Sara McCloskey, MA; Jeff & Jennifer McInnes, CA; Wilma Metros, AZ; Katherine Michael, MA; Paul & Marva Monical, OR; Gwen M. Moore, MN; Terry Moreau, IL; Peggy Morris, FL; Harry Mulholland, North Ireland; Reed & Dorothy Murtagh, FL; Jai Narayan, NJ; Havuva & Jacob Ner-David, Israel; Edward & Melissa O'Dell, NY; Godfrey & Virginia Padberg, MO; Nancy Petersen, MD; Glenn

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MA; Mrs. Leonard Schwartz, NY; Carole Jane Shirk, CA; Allan Silverstein Family Foundation, NY; Joan Smith, SC; Stephanie Staley, CO; Kelly Tutaj, IL; Dorothy & George Verbel, NJ; Doris Walter, MD; Lindsey Welcome, CA

- ◆ Professional Membership: Steven Blier, NY



### *Reflecting on advances made by the Society*

When we look back over the past 18 years, we see the incredible advances made toward understanding FSHD and finding a cure. In 1989, we didn't even know which chromosome affected FSHD! Since then we have watched as new pieces of the FSHD puzzle fall into place. We have celebrated the victories and mourned the losses — not only research that didn't work out, but also friends and colleagues who did not live to see a cure.

Each day brings its own victories and challenges. We stand firm in our commitment to beat this disease, and we are able to do so because we do not stand alone. We value all of you who have worked side-by-side with us to get where we are today and welcome those of you who are new to the Society. Thank you for your continued support; we couldn't do it without you.

#### **Society board members, researchers and friends working together to fight FSHD & support one another**



On March 27, 2007, FSH Society members Don, Dan and Judy Burke (Don not shown) were present in the U.S. House chamber while Daniel Paul Perez gave oral testimony to the U.S. House Committee on Appropriations, Subcommittee on Labor, Health and Human Services, Education and Related Agencies. Daniel's testimony was regarding FY2008 appropriations for the NIH programs on FSHD research.

Researchers, SAB members and FSH Society board members worked diligently side-by-side as a community of peers to focus their efforts to develop a Tactical and Strategic Research Plan on July 15, 2006.



A group of old and new friends gathered after the 2006 International Patient Researcher Network and Contact Day for FSHD held in Cambridge, Massachusetts on July 16, 2006.

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**YES! I want to help the FSH Society and its efforts to solve FSHD!**

### Individual Membership

- I                    \$50 +  
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