

26th Annual FD Day Conference

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Medical / Science Presentations Speakers and Abstracts

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Co-Director, NYU Dysautonomia Center
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Clinical Research Update

Lorenz Studer, MD

Director, Sloan-Kettering Institute Center for Stem Cell Biology
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Sloan-Kettering Institute for Cancer Research
Modeling FD in a petri dish using human stem cells - a new strategy to discover candidate drugs

Susan Slaughaupt, PhD

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Development of New Models and Therapies for FD

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Dysautonomia Day - 2011

Clinical Research Update

Presented by Horacio Kaufmann, M.D.

In the past year, we have made a number of key discoveries that have advanced our understanding and continued to re-shape the medical care of patients with FD. We have also conducted clinical trials of new treatments. Below is a short summary of some of the Dysautonomia Center clinical research endeavors over the last year.

Respiratory problems: We found that most patients with FD have a type of respiratory insufficiency called hypoventilation, meaning reduced breathing, a problem that leads to increased levels of carbon dioxide, the waste product normally cleared from the blood by the lungs. The reason for this abnormality is a malfunction of the “gas sensor” in the brain that controls breathing. The retention of carbon dioxide occurs during the day but is even more pronounced during the night while asleep. Based on these findings, a group of patients with FD started using Bilevel Positive Airway Pressure (BiPAP) or continuous positive airway pressure (CPAP) during sleep. This technique allows precise control of the frequency and depth of breathing. We were very excited to find that using CPAP/BiPAP during sleep not only prevented accumulation of carbon dioxide during the night but apparently resets the malfunctioning gas sensor in the brain and markedly improved breathing efficiency during the day, helping to normalize carbon dioxide levels. This is strong evidence that BiPAP or CPAP should become the standard of care for patients with FD.

Balance problems: We have finally found an explanation for the gait and balance problems that affect our adult population with FD. We have strong experimental evidence indicating that patients with FD lack information from muscle spindles, the tiny bundles of nerve endings that allow the brain to sense the position of the joints and limbs in space. This deficit is either because the muscle spindles themselves are absent or defective or because the nerves that transmit the information from the spindles to the brain are faulty. Understanding this peculiar sensory dysfunction that leads to gait and balance problems is the first step necessary to devise proper treatments.

Reduced Vision: We discovered recently that a very specific type of optic nerve atrophy is the primary cause of visual decline in patients with FD. We are currently working with an international team of collaborators to develop specific rehabilitation programs that “re-train” the eyes to use the unaffected part of the nerve to improve vision.

Dysautonomic crisis: We are analyzing the preliminary results from our FDA-funded trial of carbidopa as a new treatment for the disabling nausea and retching that patients with FD suffer during typical dysautonomic crises. The results are very encouraging; not only is carbidopa safe for patients with FD, but

several patients also report that it significantly reduces their nausea and retching. The trial is still on going and we are continuing to recruit patients.

Gene therapy: We are currently conducting clinical trials of potential gene therapies with kinetin and, very soon with phosphatidylserine. Using biomarkers of disease progression (such as images of the optic nerve thickness and gait agility scores), we will now test if increasing IKAP levels can alter the natural history of FD.

Blood pressure control: We continue to be pro-active about achieving tight blood pressure control. We are pleased to report that patients are less hypertensive and are less reliant on drugs that raise blood pressure to prevent fainting. We are continuing to monitor closely renal function and hope that the new blood pressure treatment guidelines we have implemented will prevent the development and progression of renal failure, and other complications, as our population ages.

We know that the best medical care requires a sound understanding of the problems at hand. With the progress made in the last year, we believe better days are coming for patients with FD.

Modeling FD in a petri dish using human stem cells - a new strategy to discover candidate drugs

Presented by Lorenz Studer, MD

Over the recent years there has been a lot of progress in stem cell research. One breakthrough finding was the demonstration that it is possible to take a piece of skin, and to convert those skin cells back to a stem cell state. Those "reprogrammed" stem cells, called iPS cells, can then be multiplied to yield millions and millions of stem cells. Each of those cells has the potential to produce any of the more than 200 cell types of the human body. If such iPS cells are generated from a patient with a disease such as FD, they will carry the same disease genes. Therefore we can now use those cells in an effort to figure out what goes wrong in FD.

My lab was first to develop the tools to coax human stem cells to specifically produce peripheral nerve cells, the cells most affected in FD. When we applied those tools to the iPS stem cells that carried the mutant FD gene, we were able to detect several disease related problems in the cells ("disease phenotypes"). We next demonstrated that we can use our iPS disease model system to test promising candidate drugs to treat FD such a kinetin. Even more recently, we were able to test many thousands of additional drugs in our stem cell based assay, and we found several compounds that may be even more potent than kinetin. We think that our new stem cell disease model technique offers us a new window into FD and may help in developing ultimately an effective treatment for the disease.

Development of New Models and Therapies for FD

Presented by Susan Slaughaupt, Ph.D.

Work in the Slaughaupt lab is focused on characterizing our FD mouse models and developing new therapies for FD.

We have a mouse model in which the *IKBKAP* gene is 'knocked-out', which allows us to examine which genes are turned on or off when you knock-out *IKBKAP*. We also have mice that carry the human *IKBKAP* gene, and we are using these to figure out why mRNA splicing of *IKBKAP* in neurons is so poor. By crossing the knock-out strain with the mice carrying the human gene, we can prolong development and determine which genes are turned on when human *IKAP* is present.

We are collaborating with Dr. Ioannis Dragatsis to cross our 'humanized' mice to his 'FD-like' mice so we can test kinetin and other compounds to see if they improve FD symptoms. We sent our 'humanized' mice to Dr. Dragatsis a few months ago and he is working to cross the mice and make a new line that will have FD symptoms.

Last year, we received an award to make a high-throughput screening assay in order to identify new compounds that modify splicing of the FD gene, *IKBKAP*. This assay is now complete and we have used it recently to initiate structure and function studies on kinetin to see if we can improve activity and reduce the dose. Structure and function (SAR) studies involve testing related compounds and making chemical modifications to the structure to improve the qualities of a drug. The NIH has a new program focused on drug development for rare diseases, and we hope that they will choose to help us with the FD project and bring a new drug to FD patients.

Updates on all of these studies will be presented.

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Presented by Felicia B. Axelrod, M.D.

Dr. Axelrod presents her traditional update. Information is provided on current patient statistics and progress regarding clinical trials of agents that may affect expression of the FD gene. World-wide registration has reached 655 patients with 55% from the United States and 34% from Israel. At present our youngest patient is 6 months and the oldest is 66 years. The adult population continues to increase as 56% are now 18 years or older. In addition, more adults are achieving independence and better function. They are attending college, living independently, marrying and even going on to have their own families. Because we have known the gene since 2001 and population screening was instituted shortly thereafter, there has been a gradual decline in new FD births so that in 2010, for the first time, none were born in USA and the total birth rate reached an all time-low of two (2). Both new births for 2010 were in Israel.

Two agents have been reported to modify the FD gene so that more normal IKAP protein is produced. The first is kinetin. This is a naturally occurring compound which actually affects the genetic error and corrects splicing so that the gene works correctly to produce normal IKAP. Dr. Slaugenhaupt's team at Massachusetts General/Harvard discovered this agent in 2004 and in 2007 the Center started preliminary studies to determine effective dose and assure kinetin's safety. The first study was performed in parents (carriers of one copy of the splicing mutation) who were well but whose white blood cells had measurable decreases in IKAP. The second study was a short 8-day study in 8 FD patients to see if FD patients processed the drug the same way as carriers. In August 2010 we started a long-term study to see if we can achieve neurological improvement and change the natural history of FD. Six patients are presently in the trial and we are continuing to add patients. To date it has been very well tolerated but it is too early to see if there has been an effect on neurological function.

The second agent was reported by Dr. Ast's team in Israel. It is phosphatidylserine or PS. It is also a naturally occurring compound. It works differently than kinetin since it does not actually correct missplicing. Instead it stimulates the entire gene so that more normal IKAP is made but also more mutant IKAP is made. Although the report is promising, confirmation of its good effects by other laboratories is still pending. However, since it is a compound that is readily available, we are preparing to assess its value objectively and perform clinical trials starting in July 2011.

Dr. Axelrod also announces this year's four FD Distinguished Adults –Scott Fass from Woodmere NY, Steve Schwartzberg from Edmonton Canada, and Gali Tirosh and David Miller who are both from Israel.