

## MENDING THE SPLICING DEFECT

Impressive, cutting edge, Foundation-funded research at Cold Spring Harbor Laboratory in New York has the potential to remedy the splicing defect that causes familial dysautonomia (FD). Known as the lab where RNA splicing was discovered and where eight Nobel Prize winners have worked, Cold Spring Harbor Laboratory is focusing efforts on correcting the defect, thanks to Professor Adrian Krainer's work with a technique called "antisense oligonucleotide." This technique could lead to the faster development of effective therapies for all FD patients.

Antisense technology involves short synthetic pieces of nucleic acid that can be designed to modify RNA splicing of individual genes, Krainer explained. His research team looks for short sequences to include in the antisense molecules so that they will precisely home in on the target RNA in a particular region. "If we can scan and test enough of these sequences we can usually find an oligonucleotide that will correct the splicing pattern for the target gene," Krainer said.

Krainer developed and refined the technique to efficiently correct the splicing defect in spinal muscular atrophy (SMA), an autosomal recessive disease similar to FD in that it is caused by a genetic defect that results in low levels of a particular protein. Over the course of six years, his research team, in collaboration with Isis Pharmaceuticals, developed and perfected the method in cell cultures and mouse models. Isis then partnered with Biogen-Idec to test the antisense oligonucleotide in SMA patients; it is currently in Phase 2 clinical trials at four centers in the U.S.

Krainer is now applying a similar technique to FD cell cultures and mouse models, and even though it is still in the early stages, the approach is showing considerable promise. Krainer's team has already identified an antisense oligonu-



*A researcher on Krainer's team inspects FD cell cultures.*

cleotide that corrects the defective splicing pattern of the gene mutated in FD, IKBKAP.

In addition to his specific work correcting IKBKAP splicing with antisense, Krainer projects that his experiments involving careful manipulation of RNA splicing in FD models could reveal important information about the mechanisms underlying the pathology of FD. Krainer first became aware of FD through the work of other experts years ago and also through the encouragement of an FD parent who was interested in his work on SMA. "But we did not have the resources to pursue the research in a concerted way until we had the funding from the Foundation," he said.

Krainer has set his sights high. "My hope is that this research will develop in a way that SMA has – we don't have an SMA (Continued on page 3)

## Better Respiratory Therapy

Those with FD have chronic and often severe respiratory problems. However, these ailments have been sometimes overshadowed by the focus on the many other severe issues faced by people with FD. With this in mind, the directors of the NYU Dysautonomia Center were happy to welcome pulmonologist Dr. Bat-el Bar, from the Israeli FD Center at Tel Hashomer in Tel Aviv. Her six month residence in New York enhanced our understanding of respiratory problems in FD, and gave her the opportunity to intensively study FD problems and treatment protocols. The experience she gained studying at NYU will bolster the FD treatment program in Israel.



*Dr. Bat-el Bar demonstrates her study on pulmonary function using an IOS Impulse Oscillometry unit.*

In her short time at NYU, Dr. Bar has performed pulmonary function tests to gauge the effects of two respiratory drugs on (Continued on page 3)

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## PRESIDENT'S MESSAGE

Dear Friends:

We are delighted to bring you recent news of the “FD world,” from bowlaathons and walkathons that raise both spirits and money crucial to medical care for the FD population, to new and ongoing research efforts that promise brighter futures for those with FD, to the low-cost but essential ingredient that helps us all face each day – humor – in our new online comic strip, *No Tears*.

Knowing that we have a growing community of supporters means so much to all of us involved in the FD community. It is critical to the Foundation staff and FD Board members, to the medical team at the Dysautonomia Treatment Center that we support, to the many scientists working on breakthrough treatments, and last but definitely not least, to those remarkable people who live with FD, and their devoted families and friends. All groups are vital to sustaining the complex medical care at home and in the clinic that most people blessed by good health never have to deal with.

We have vastly improved the quality of life for those with FD – and others who suffer from autonomic disorders, in countless ways over the last decade. But we are always looking ahead; there is so much more work that needs to be done. The support you are lending is what keeps us going when we feel overwhelmed by what lies ahead.

*Faye Ginsburg, President of the Board of Directors*



## Dysautonomia Foundation

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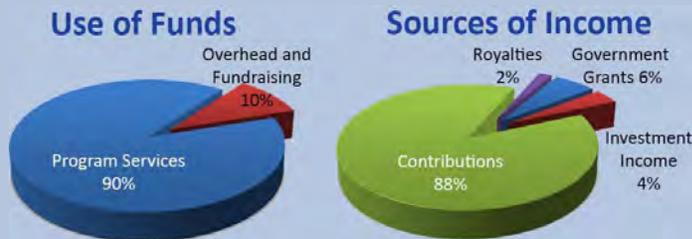
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## EXECUTIVE DIRECTOR'S MESSAGE

David Brenner

The Dysautonomia Foundation is in a privileged position, charged with the trust of three important groups: donors, FD families, and medical/scientific experts. Donors trust us to manage their contributions wisely; FD families count on us to pursue the best possible outcomes for FD patients; and doctors and researchers rely on us to support and guide their work. We strive to execute our responsibilities with diligence and enthusiasm, with the utmost respect for our stakeholders. To that end, we work hard to raise funds and spend them wisely, effectively and efficiently. The charts below illustrate how we have spent and raised our funding over the four-year period of 2010 to 2013 (figures are based on actual and projected budgets).



I am proud to lead a team of staff, volunteers and experts who make our work possible, and I take equal pride in working with directors, officers and donors who share the common goal of enabling outstanding FD treatment, research and services. To all of you I express humility and gratitude for placing your trust in me in the pursuit of our mission.





## Israeli and US Centers Collaborate

Enthusiasm is high as the transition of the Foundation-funded Israeli FD Center from Hadassah Hospital in Jerusalem to Tel Hashomer (Sheba Hospital) in Tel Aviv progresses. Director of the new Israeli Center, Dr. Ori Efrati, a pulmonology expert, has been collaborating with the doctors and researchers at the Dysautonomia Center at NYU. The NYU Center's expertise and experience with FD, with a special focus on neurological and cardiovascular systems, and the Israeli Center's tradition of integrated, comprehensive care coupled with a focus on respiratory care, form the basis for a collaborative relationship in which each can benefit from the other's strengths.

The exchange of ideas and the cross-training of personnel is well underway. Dr. Bat-el Bar from Israel recently completed six months of training at NYU, and by all accounts, it was a great success for everyone involved. Dr. Bar's pulmonology expertise has already resulted in new respiratory care protocols at NYU (see pg.1), and her newly acquired knowledge of FD treatment will be essential to rounding out the Israeli Center's FD program. As this collaboration evolves, it will undoubtedly result in continued improvements in care for patients with FD in the US and Israel.

### Respiratory Therapy *(Continued from page 1)*

the cardiovascular systems and on the lungs of FD patients. Many FD patients use these drugs, but there has never been a comprehensive study of their effects. The drugs she tested, albuterol and ipratropium, are bronchodilators that are used to enhance lung function. Albuterol affects the sympathetic nervous system, and ipratropium affects the parasympathetic system. Dr. Bar explained that in FD the sympathetic system is abnormal, thus, it is preferable, if possible, to use alternate drugs that can be more effective on the lungs with fewer side effects on the blood pressure, thereby relieving the demands placed on the sympathetic nervous system. Results of her study so far have been promising toward indicating new therapies.

Dr. Bar received her medical degree at the Universita di Bologna in Italy, and is completing her pulmonology fellowship under the guidance of Dr. Ori Efrati, director of the Israeli FD Treatment Center in Tel Aviv.

### Splicing *(Continued from page 1)*

cure yet, but I am told things look very promising in the ongoing clinical trials... I think we can probably replicate that for FD. Pushing things toward clinical trials is the best we can hope for from our end."

Krainer will be presenting his research to families, researchers and doctors at FD Day on Sunday, June 2nd, 2013.

## 28th Annual FD Day

The 28th Annual FD Day is on Sunday, June 2nd, 2013 at NYU School of Medicine. Attendees will be treated to a day of informative presentations and small-group access to researchers and doctors working on FD. Morning presentations will be given by Drs. Felicia B. Axelrod and Horacio Kaufmann along with researchers Lucy Norcliffe-Kaufmann, Adrian Krainer and Susan Slaugenhaupt.

For entertainment, *No Tears* comic artist, Mindy indy, will be present to make custom drawings (see page 4 for an example of her work). She will be joined by a balloon artist, an animal show and a photo favors booth in the morning. Kicking off the afternoon, we have a special appearance by world famous illusionist, Elliot Zimet. FD adults can also look forward to our FD casino and a private dinner party.

### FD Research Publications

These publications are authored by researchers who have been funded by the Foundation.

Hyperdopaminergic Crises in familial dysautonomia: A randomized trial of carbidopa. Norcliffe-Kaufmann L, Martinez J, Axelrod F and Kaufmann H. *Neurology*. 2013 April 23.

Phosphatidylserine increases IKBKAP levels in a humanized knock-in IKBKAP mouse model. Bochner R, Ziv Y, Zeevi D, Donyo M, Abraham L, Ashery-Pada R, Ast G. *Human Molecular Genetics*. 2013 March 29.

Cyclic Vomiting Associated with Excessive Dopamine in Riley-Day Syndrome. Norcliffe-Kaufmann, L, Axelrod, FB, Kaufmann, HK. *Journal of Clinical Gastroenterology*. 2013 Feb.

### New Social Worker at the FD Center

Melissa Kleinman, MSW, has come to the Dysautonomia Center after seven years of working with children and adolescent trauma survivors both at NYU Medical Center and Boston Children's Hospital. Kleinman has her license to practice social work in both New York and Massachusetts. Kleinman is also a certified yoga instructor and has hopes of using yoga as a therapy for FD patients to improve balance, regulate breathing and calm anxieties. Kleinman can be reached by calling the Center. Her office hours are Wednesday 8am to 4pm, Thursday 9am to 5pm and Friday 1pm to 5pm.



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## Walk for FD

Originally scheduled for November, but then postponed due to complications surrounding Hurricane Sandy, the Third Annual Walk for FD took place on a sunny and unseasonably warm Sunday in March. More than 150 people walked the seven mile circuit from Manhattan's Greenwich Village up the Hudson River Greenway on March 10th. Spirits were high, and more than \$30,000 was raised. Our thanks go to **Sarah Strongin, Shira Falk, Jessica Raab and Tova Cohen** for once again organizing this wonderful event.



*Walk for FD Co-Chairs Shira Falk, Tova Cohen, Sarah Strongin and Jessica Raab.*

## FD Bowlathon



*FD Bowlathon Co-Chairs Sydney Sirota, Lexi Sirota and Ally Kaplan.*

The 8th Annual FD Bowlathon on Sunday, April 14th at Woodmere Bowling Lanes on Long Island, New York was a resounding success with 100 friends in attendance. The event, co-chaired by

**Ally Kaplan, Lexi Sirota and Sydney Sirota**, whose cousin, Scott Fass, has FD, drew great support from the community and raised more than \$25,000. The event, which is held in honor of Scott, has been organized by one or more of his many cousins since its inception, and has become one of our most inspiring events.

## Mitzvah Projects Raise Thousands

**Zachary Vexler**, whose cousin, Kyra Slive, has FD, has raised more than \$15,000 for FD treatment and research since the end of February through his mitzvah project. Instead of accepting presents for his bar mitzvah, Zachary educated people about FD and encouraged them to make donations. He follows in the footsteps of his siblings, Caroline and Jonathan who both did similar fundraising projects for FD. Those of us at the Foundation are always humbled and extremely grateful to our young advocates who commit their time and energy to the FD cause. Thank you, Zachary!



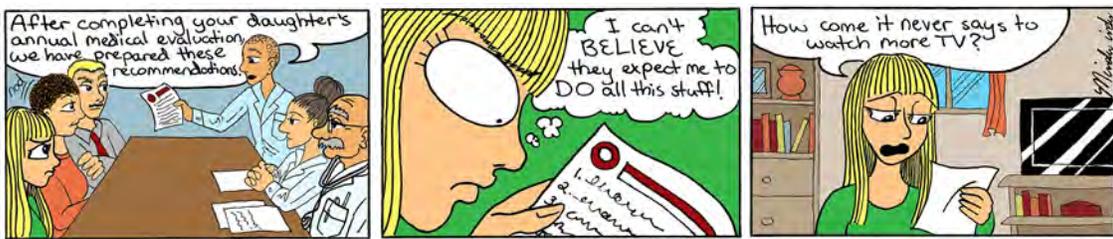
*Kyra Slive with her cousin, Zachary Vexler.*

**Jeremy Lieberman** came up with a fun and creative way to raise money and awareness for FD treatment and research. For his mitzvah project, Lieberman motivated his classmates at Liberty Middle School in Liberty, New York, to jump rope and raise funds through sponsors in April. He is inspired by his cousin Jack Posnack, who is 6 and has FD. Jeremy told local news, "Jack is my role model, because he is smiling every day of his life, inside and out." Jeremy called the event "Jump for Jack." In 2007, Jeremy's brother, Jonathan, organized a "Walk-the-Track for Jack" event at his elementary school.

## No Tears: Life With FD



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## Laughter as Medicine

This year, the Foundation collaborated with a local artist to create a comic strip that communicates the trials and tribulations of having a chronic illness like FD. We hope to make you laugh and nod in agreement with the weekly series. A new comic is posted every Friday afternoon. For the full collection, visit us at [www.famdys.org/comic](http://www.famdys.org/comic) or follow us on Facebook at [facebook.com/famdys](https://www.facebook.com/famdys).