

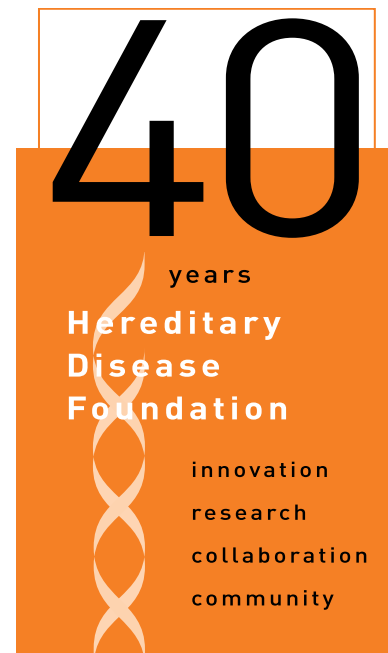
Hereditary Disease Foundation

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An Historic Meeting of Science & Celebration Honors Milton Wexler's 100th Birthday

350 scientists traveled to Cambridge, MA from around the world to attend HD2008: "The Milton Wexler Celebration of Life."

Symposium attendees honored Milton's memory by holding true to his values to communicate, collaborate, share, be candid, be courageous and seek collectively for new treatments and cures! THANK YOU SO MUCH FOR MAKING THIS EVENT SO SPECIAL!!!!

Thank you for putting all your energies into conversations, revelations, hard work, imagination and perseverance in finding new treatments and cures. Thank you for navigating across complex geographic and intellectual boundaries. Thank you for your collaborations and sharing.

Thank you for renewing and keeping Milton's spirit and the spirit of the Hereditary Disease Foundation alive! Milton created the Hereditary Disease Foundation and its inimitable workshop program 40 years ago. In almost the century of his lifetime — including many diverse accomplishments — he was proudest of these singular achievements.

We know that Milton would have enjoyed every minute and be fascinated with the outcome. [A fuller description of the meeting highlights will be posted on our website soon.](#)

The meeting encompassed the ideas of about 350 people. There were over 200 abstracts, posters and talks.

We began the conference with "The HD Experience — Then and Now." Alice Wexler started the meeting by talking about the early families with St. Vitus dance living on Long Island in the 19th century. In some ways they were better cared for and more integrated into their communities than their modern compatriots.

Alice's latest book, *The Woman Who Walked into the Sea — Huntington's and The Making of a Genetic Disease*, is about these HD families on Long Island and was released just as the symposium kicked off! For more information about the book, see our Summer 2008 Newsletter on our website.

Everyone was moved to tears by the riveting words of a passionate young man with HD who has to hide his history and experience from his coworkers for fears of losing his job and his health insurance. To read his incredibly courageous speech, see this page. To hear his speech, please visit the HDF website.

*Please see **Thank You!**, page 2*



Thank You!

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Kevin Baker, a well known writer, then described his experiences getting a genetic test for HD, finding out he has an expanded repeat, and watching his own fate reflected in his mother's face with each visit to her. His recent story, "Mind Bomb" was published in *New York Magazine* on June 8, 2008. He asks — and tries to answer — the question, "If you had a fifty-fifty chance of carrying a mutant gene that causes a fatal brain disease, would you want to know?"

The words and experiences of these two brave men gave the entire meeting a critical, urgent perspective — their lives are at stake! And they give voice to thousands of others with their same genetic destiny. Everything we accomplished, every new experiment was critiqued from the vantage point of: *Will this lead to new treatments and cures and how fast can we go?*

Finally, **Michael Levine** summed up the highlights of the meeting — even with quotes from participants about possible treatments and cures. He emphasized the importance of neighborhoods and connections as an underlying theme of the conference — on a micro and macro level.

We ended by paraphrasing the famous English poet John Donne (1572-1671) — "No 'neuron' is an island, entire of itself. Any 'neuron's' death, diminishes me, because all 'my neurons' are involved in mankind; and therefore never send to know for whom the bell tolls; it tolls for thee."

Again, many, many thanks for populating our neighborhoods.

With love and good wishes,
Nancy and Alice Wexler and the Program Committee:
Carl Johnson, Chair; Gillian Bates;
David Housman; Mike Levine;
Leslie Thompson; Anne Young ■

Making HD Visible

Speech given at HD2008: "The Milton Wexler Celebration of Life" by a scientist who chose to remain anonymous.

I would like to thank Nancy Wexler for her invitation to come to the conference. Four years ago, I attended my first HDF conference in Boston as a new graduate student. Today, I am here as an HD patient.

When Nancy first asked me to speak here, I felt honored, but my thoughts quickly raced to this question: What if the information that I'm sharing today, somehow comes back to haunt me at my current job. Unlikely, right?

As I pondered this question, I realized that I could give a full lecture just citing 'coincidences' from my life that have shown me how very small the world really is. And let's say my work does find out, would they fire me right away? Or would they wait until I made a mistake, which lots of people always do, and then correctly assume there are many more mistakes to come?

People at my job already like to make well-intended jokes about how I seem drunk, even though I don't drink, or how I'm always hitting into things and dropping others. Or how it's a miracle if I can make it to my desk without spilling a half filled mug of water. Often people cannot understand me when I speak, and I'm always being asked to repeat myself. And all this without my coworkers even being tuned into the HD symptom display.

Other symptoms that I am currently experiencing, is that I have difficulty sitting comfortably without fidgeting. Often, when I'm doing anything from a work related task to a casual conversation with friends, I can physically feel my brain short circuiting as it is trying to process the information.

Every movement and step that I take every day is earned and requires focus. And on the bad days, it seems like all the focus in the world can't get my feet and legs to do what I want them to.

These are some of the things that someone with HD has to face and think about every day. And this is why I decided that I would speak anonymously.

My sister also has HD and she is more affected than I am. A year or so ago, she worked as a teacher's aide. One day, she was having a hard time, or more accurately, a harder than usual time with her symptoms. She felt that this had caused her to have difficulties dealing with one of the kids, so she started to cry. One of her co-workers tried to help and talk with her. During this conversation my sister confessed to having HD. A few short weeks later, and she was let go. Of course, all that they had to say was that she was not performing well. More recently, she lost her job. This time it was because her HD symptoms truly made her job impossible to do. About the same time, she got a DWI, without even having a drink. She had to face the bitter reality that she could not drive anymore, something she refused to accept. As horrible as this sounds, I am relieved that she finished driving without hurting or killing someone else or herself.

This is what HD does, as it is whittles away a person, it forces impossible choices under the most difficult of conditions.

Make no mistake about it, my sister and I are in the most difficult of conditions. The only hope we have is that science will produce a cure. For people like me, the hope for a cure is my reason for being. It is the reason that I can get out of bed in the morning. It is the reason that

I can keep fighting HD in spite of the tremendous losses that I have already suffered. I cannot stress enough the importance of this to my survival.

It is because of this, that I feel the need to express my deep, genuine and heartfelt gratitude to all of you. This is my main motivation for speaking today. From my family to everyone, "WE THANK YOU." What I hope to accomplish with this speech is to provide more clarity to the big picture of why we are all here today.

With that said, I hope to give you further insight into what HD does to people, and their families. I was born to a loving family. My parents loved each other, and both me and my sister very much. My father was a good and kindhearted man. Even though, I have very limited memories before his HD began, there are some things I remember clearly.

My father had an endless patience and would stand outside pitching me waffle balls, until I would declare that I was tired. As a kid, I always knew to go ask my father for whatever it was that I wanted. Somehow, I sensed that he felt guilty saying no to me.

Overtime, as the HD first began to take hold of him, his movements when throwing a ball became increasingly erratic. Slowly, but surely, playing catch occurred less often, then not at all. His ability to think things through also deteriorated. He stopped driving and closed his optician shop business around the same time. He had been making bad business decisions and as a result, racked up some serious debt. The patient man that was my father, turned into an easily angered, irritable person. The man who loved talking with me and telling me that he loved me, morphed into someone

who rarely communicated verbally at all. The man, who seemed to be able to do everything and then some, could no longer cut the lawn, cook, or even walk the dog. He couldn't teach me how to shave, or talk to me about girls.

When you add all of these changes up, it's a very ugly picture. HD had cut down a man in his prime, and replaced him with a shell of my father. Piece by piece, HD relentlessly carved him away, until he more resembled a child, than he did a grown man. It was very painful for me to be stuck watching helplessly, as bit by bit he was taken from me.

In effect, I had to mourn my father because that man was gone. And yet I still had to see his shell every day. I still had to face the inhuman condition that HD left him in. Of course, when he finally passed 13 long years later, and 3 short months before today, I was deeply saddened. And so, I am mourning my father for the second time in my life. I know he is in a better place, but it's hard for me to think that I can't see even the shell of him anymore.

I don't remember when exactly I became aware that the same thing that happened to my father could happen to me. The time when I discovered both that I could inherit HD, and that there was a genetic test available, was the point that I knew that I wanted to know. For me it wasn't a long drawn-out, decision-making process. Rather it was a relatively clear-cut choice with enormous stakes. More accurately, I needed to know. The way I saw it, even though there was a 50% chance of me inheriting the gene, there was also a 50% chance that I didn't.

That was enough odds for me to step up and bet it all on black. The power of seeing my future was too alluring; I could not stop myself from looking into the crystal ball. I saw two very different paths in front of me,

and I needed to know which one was my fate, so that I could plan accordingly. I had to wait a number of years before I turned 18.

On my 18th birthday, I went into the clinic to start the long testing process. After I found out that I was gene positive, the psychologist at the clinic asked me what I was going to do now that I had the result. I said to her that the one thing I was completely sure of was that I would never get married or have kids. I would never let HD do to my own family what it had done to my father's.

I then got up, went to bathroom and splashed some water repeatedly into my face. As I looked up into my eyes in the mirror, I realized that I no longer recognized myself. The realization that I was gene positive set off an atom bomb inside me that I didn't even know existed.

This atomic explosion destroyed all the weak, the normal and the child-like parts of me that growing up with HD had not killed already. All that remained were the strongest, most battle-tested remnants of my former self from which I would begin to build a person who could live in the shadow of the HD monster.

I floundered around psychologically in the few years directly following my test. And during this time, I thought constantly about what I wanted to do with myself and what life I still had left that was mine.

When I started college, I didn't have any ideas about a career in medicine or science. The more that I thought about it, the more unhappy I was with the classes and directions that I did take. I decided I would try to be a doctor and treat patients like my father. I tried out some science classes and did well.

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One day around this time, I was in a bookstore and happened to come across a book called Genome. The book has 23 chapters, each one dedicated to a different human chromosome and a gene on it. The author uses that gene to show how it controls a specific human trait or life characteristic that we think of as uniquely our own. Chapter 4, was entitled 'Fate.' It discusses how a simple genetic mutation in one of our genes can determine the fate of our lives. It talks about the huntingtin gene, HD and, of course, it told the story of HD. I learned of their astonishing success in finding the HD marker and then the gene and mutation. Further, I learned of how they were still searching tirelessly for a cure by funding critical scientific research.

I was so blown away and inspired by the story; I must have reread the chapter 50 times. The knowledge that people were working on a solution to the very problem that plagued me and my family filled me with hope. I learned there might be a way out of my fate, and I wanted to be a part of it. The more that I learned about the state of knowledge and treatment in the HD field, the more I continued to be drawn to research. Ultimately, I decided to go to grad school, where I could focus on HD research.

With such a crazy life, in such a crazy world, pursuing science made a lot of sense. I realized that even if I was unsuccessful with scientific findings, I would be better off knowing that I had tried, than always wondering 'what if?' This let me add a few lines of color to the pitch black canvas that was my future. It would eventually bring in the eye of the HD storm, a period of time when I was the

most at peace with the presence of HD in my life.

On an interesting side-note, when I was a grad student, I took a Human Genetics course. Halfway through, we were all given a copy of the 1983 paper that first describes the HD gene marker. Our assignment was to explain the significance of the findings. I felt it was a tremendous stroke of luck and that I was more than enough prepared to answer that question. I quickly hammered out a paper, discussing all the key points that I could think of, from the genetic test to the research that has been done and the possibility of a cure. I handed it in, content that I had just nailed an A paper. When I got the paper back, there was a big 'C' on it. That was the lowest grade I got as a Grad Student. When I questioned my professor, he thought he was being generous. He promptly explained to me that nowhere in my paper did I even attempt to discuss how this critical, initial discovery opened the door for the era of modern human genetics, and the myriad of significant findings that followed.

As is usually true, I learn the most from my mistakes. I was awestruck by how much more important this paper was than I originally thought. I was excited thinking about the possible ripple effect that one of my findings as a scientist might have, beyond even my dream of a cure.

There is an interesting paradox that exists living with HD. HD has revealed to me the true value of things in life, in a way I would have never believed, had I never lived through it. This truth was so important to me, that a number of years ago, I was so happy and proud of the person I had become, that I wouldn't have traded my gene positive status back in, if it meant that I would also have to trade in the person that I had become.

Speaking now I can tell you that I would trade in everything that I have learned and all that I am. If God came to me one night in a dream and said, "You can choose your life. The door on the left is your life as it is now. The door on your right is your life with the thread of HD completely removed, so that all that you have learned since then is gone." I would run so fast to the door on the right, I'd light the ground on fire — the reason being to avoid the incredible pain and torture that HD is inflicting on me and my family. Even though HD has vividly illuminated all the incredible beauty that exists in the world, it subsequently has thrown up an impenetrable barrier that separates me from it all.

The symptoms started when I was in my third year of grad school. For years, I had been extremely vigilant, always looking for the signs of HD. The mild physical and mental symptoms began to occur frequently enough that I could no longer write them off as my own paranoia. I began to grow concerned over how many variables I might be introducing into my experiments. And if not now, how much longer before I wouldn't be able to do science experiments anymore? I wondered how much time before I would no longer be able to work? Then, what would I do for money after I couldn't work anymore? The answer to these questions told me that it was time to leave grad school.

After leaving grad school, HD continued beating me down a steady spiral, far into a deep hole. I had been depressed a number of times in my life, but I found myself in a place that was so much darker and deeper than I had ever experienced before. I lost the ability to laugh. I could only recognize that situations were supposed to be funny, and then give my best impersonation of a laugh.

I was unemployed and there wasn't any job that I could do; not any physical labor, a janitor or even a cashier. Hope was non-existent in my life. I became disconnected from life, stuck watching the bad movie that was my life from far inside my shell.

I also became disconnected from the people that I care about. I knew they were there for me, just a simple phone call away. But even thinking about calling anyone made my mind numb before I even had to engage in a conversation.

Every single thing that I did would drain my brain and make my symptoms worse, at which point, I could do nothing besides sleep or watch TV. This reminded me of my father. When I was down in the hole, I also became filled with regret and negative emotions or thoughts.

As an example, I started to believe how I shouldn't have gone to grad school because, in the end, I only found negative data, and the money that supported me as a grad student could have been used to support someone who would finish and ultimately make positive findings.

I remember one of these dark days, I looked at my reflection. And I realized that for the second time in my life, I didn't recognize the person in the mirror.

I didn't think that things would ever get better. I was barely surviving. I just hung on and did the best that I could. Thankfully, I have found both God and anti-depressants, and I haven't let go of either one since. This one-two punch combo has pulled me out of the hole and got me back into the fight with HD.

Now, I can stand here today and say that I am 100% confident that a cure will come. This isn't even



Longtime Hereditary Disease Foundation friend **Courtney Blethen** and her Seattle team "**Klimb for the Kure**" are climbing Mt. Kilimanjaro in February 2009 to raise \$1,000,000 for the Hereditary Disease Foundation to find the cure for Huntington's disease. Check out their website — www.klimbfortheKure.com. **THEY ARE WILLING TO FIGHT TILL THE END! BE PART OF SOMETHING SPECTACULAR! PLEASE HELP!** Your contribution brings them one step closer to achieving their goal!

Courtney Blethen had a genetic test two years ago and found she has the expanded version of the Huntington's disease gene, which means that HD is definitely in her future. In her race against time, Courtney is having the climb of her life. (To learn more about Courtney, please read our Summer 2008 Newsletter available online at www.hdfoundation.org.)

Climbing Kilimanjaro will be one of Courtney's greatest physical and emotional challenges. She is hopeful that her training regimen and the Kilimanjaro climb will provide her with additional strength and enthusiasm for her continued campaign to raise money for finding a cure for Huntington's disease. We're all rooting for her!!!

Join Courtney and her team on their climb!
www.klimbfortheKure.com
klimbfortheKure@gmail.com ■

a question I ask myself. The real question is WHEN will it happen? I am very hopeful that this will be sooner, rather than later. If I didn't have this very crucial hope, I wouldn't be able to be up here speaking today.

I am very excited to learn about your latest results and ideas. I thank you all for the work you have already done, and the work you continue to do. From the grad student who contributes various pieces of negative data (like myself), all the way up to the PI compiling

numerous publications, we are all part of the process that will ultimately produce the cure for HD.

Each of us has already contributed our own grains of sand to a pile. When this pile of knowledge gets high enough, it will give us a cure. When that cure comes, as I have no doubt that it will, in the end, we will find that we were all part of one of the most powerful and incredible stories in the history of science. ■

2008 Funding Decisions

Hereditary Disease Foundation grants, postdoctoral fellowships and research contracts are helping identify routes to the development of cures and treatments for Huntington's disease and other similar hereditary disorders. The HDF's Scientific Advisory Board, comprised of world-renowned experts in genetics, neurology, neuroscience, and therapy development, approves funding for groundbreaking research. The following projects were funded in 2008:

RESEARCH GRANTS

Jocelyn Caboche, Université Pierre et Marie Curie, Paris, France. Restoration of mitogen and stress-activated kinase: a new therapeutic approach to HD?

Wenzhen Duan, Johns Hopkins University School of Medicine. Exploration of SIRT1 as a potential target for HD treatment in mouse models of Huntington's disease.

Kenneth Hensley, Oklahoma Medical Research Foundation. Metabolic thioether derivatives for Huntington's disease.

Ruth Luthi-Carter, Écoles Polytechnique Fédérale de Lausanne, Switzerland. Mutant huntingtin-related changes in striatal responsiveness to BDNF and gene expression correlates of BDNF-mediated neuroprotection.

Dennis Steindler and Florian Siebzehrubl, University of Florida. SVZ stem/progenitor cell migration and differentiation in Huntington's disease.

Alan Tartakoff, Case Western Reserve University. Protection against low level synthesis of mutant huntingtin.

POSTDOCTORAL FELLOWSHIPS

2008 Milton Wexler Postdoctoral Fellowship Recipient:

Andrey Tsvetkov, Gladstone Institute, University of California, San Francisco. Mentor: Steven Finkbeiner. Metabolism of huntingtin in health and disease.

Elodie Bruel-Jungerman, University of Rochester. Mentor: Steven Goldman. Can AAV4-BDNF/Noggin induce striatal neurogenesis and delay symptoms in R6/2 HD mice?

Shulin Ju, Rosenstiel Center, Brandeis University. Mentor: Gregory Petsko. Structural and functional characterization of huntingtin using yeast two hybrid and x-ray crystallography.

Erik Kvam, Wadsworth Center. Mentor: Anne Messer. A therapeutic approach for Huntington's disease using cell-permeable intrabodies.

Antonio Valencia, Massachusetts General Hospital, Harvard University. Mentor: Marian DiFiglia. Role of lipid rafts in the AKT-dependent survival pathway in Huntington's disease.

RESEARCH CONTRACTS

Elizabeth D. Abercrombie and James M. Tepper, CMBN, Rutgers University. Dysfunctions of the basal ganglia circuitry in mouse models of Huntington's disease in vivo: Dopaminergic mechanisms and implications for understanding pathophysiology and treatment.

Beverly Davidson, University of Iowa. Testing viral-encoded RNAi as a potential HD therapy.

Donald Lo, Duke University Medical Center. Collaborative studies on mechanism and drug target evaluation using a brain slice-based assay for Huntington's disease.

Alexander Osmand, The University of Tennessee. Polyglutamine aggregation in Huntington's disease.

Leslie M. Thompson and J. Lawrence Marsh, University of California, Irvine. Role of SUMOylation, T3 phosphorylation and altered protein interactions influenced by post-translational modification in HD pathogenesis.

with

Joan S. Steffan, University of California, Irvine. The IKK complex phosphorylates Huntingtin and targets it for degradation by the proteasome and lysosome.

Ronald Wetzell, University of Pittsburgh. Characterization and manipulation of exon1 aggregate species.

X. William Yang, University of California, Los Angeles. A BACHD-genetic modifier platform for efficient testing of candidate pathogenic mechanisms in a full length mutant huntingtin mouse model.

Scott Zeitlin, University of Virginia School of Medicine. Generation of a knock-in mouse model expressing 140Q-huntingtin with a precise deletion of its proline-rich region.

An Evening with the Gerstenhabers, HDF Board Members



Family and friends, old and new, were warmly welcomed into the gorgeous home of Hereditary Disease Foundation Directors **Kelly Posner Gerstenhaber** and **David Gerstenhaber** on Monday, June 23, 2008. Their apartment was featured in the May 2007 issue of *Architectural Digest* (www.architecturaldigest.com).

From glorious flowers to playful nibbles to gracious and loving hosts, it was a perfect, phenomenal and very special event!!!

We welcomed **Liz Weber** and **Stone Gossard** into the Hereditary Disease Foundation family. Stone is the fantastically talented rhythm guitarist for the band, **Pearl Jam**. Pearl Jam was stopping in New York City to play two nights of sold out shows at Madison Square Garden before continuing their multi-city tour.

Kelly Posner Gerstenhaber is as brilliant as she is beautiful. She was selected as one of the most influential people in health in the May 8, 2006 issue of *New York Magazine* as part of a team of scientists from Columbia University Medical Center. Kelly is a world-renowned expert on the relationship between antidepressants and suicide in children. She and her colleagues created standards for defining “suicidal behavior,” leading the FDA to put “black box” warnings, the most serious FDA alert, on antidepressant labels and led to a heightened awareness of the effects of potent drugs on children. This critically important work was featured on the front page of *The New York Times* on January 24, 2008 in a story by Gardiner Harris, “FDA Requiring Suicide Studies in Drug Trials.” (Visit our website — www.hdfoundation.org — to read it.) “A Renaissance Mom,” an article about Kelly from a cover story, is being re-run in the December 2008 issue of *New York Family*.

David Gerstenhaber is recognized as one of the foremost macroeconomic strategists and hedge fund managers. He is Founder, President and Portfolio Manager of Argonaut Capital Management, a hedge fund manager offering investment vehicles using global macro and long/short equity investing strategies. He is also a talented photographer and we, as his guests, were fortunate to have the opportunity to see his stunning images on display around his home!!!

Alice Wexler Featured on the Diane Rehm Show on NPR

On October 1, 2008, HDF Director **Alice Wexler** offered a phenomenal interview as the featured author on The Diane Rehm Show, **National Public Radio's** flagship broadcast on books and critical issues of the day. The topic of the interview was Alice's new book, *The Woman Who Walked into the Sea: Huntington's and the Making of a Genetic Disease*.

Alice's fantastic interview can be heard via the HDF website - www.hdfoundation.org.

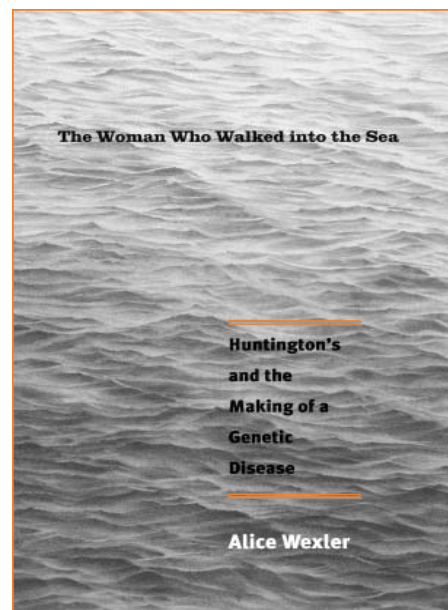
Alice has published 4 books, including: A two-part biography of Emma Goldman: *Emma Goldman: An Intimate Life* and *Emma Goldman in Exile: From the Russian Revolution to the Spanish Civil War*; *Mapping Fate: A Memoir of Family, Risk and Genetic Research*, a profound and provocative insider's look at the discovery of the Huntington's disease gene.

Now in her latest book, *The Woman Who Walked into the Sea*, Alice uses a historical magnifying glass to illuminate traces of the past that tell unique stories. She ties these together into a creative web that gives translucence to modern trends, influences and questions in her inimitable way.

“For more than 25 years, The Diane Rehm Show has offered listeners thoughtful and lively conversations on an array of topics with many of the most distinguished people of our times.”

More than 1.7 million listeners tuned in to Alice's compelling and original voice on one of NPR's most-listened-to programs.

You can learn more about Alice's book, published by Yale University Press, from Amazon.com. ■



HDF Scientific Advisory Board Member and UCI Stem Cell Researcher Awarded \$1.4 Million to Study Huntington's Disease

Irvine, California, June 30, 2008

The governing board of the California Institute for Regenerative Medicine, the state's stem cell agency, Friday awarded nearly \$1.5 million to UC Irvine researchers under two separate grant programs. One will fund research for the development of new lines of human stem cells, and the other will fund the planning stages of innovative research teams that will collaborate on therapies for disease.



Leslie M. Thompson, professor of psychiatry and human behavior, with joint

appointments in neurobiology and behavior and biological chemistry, was awarded nearly \$1.4 million to develop new stem cell lines for use in treating Huntington's disease. She received an additional \$54,618 disease team planning grant to coordinate the Huntington's disease study. The neurodegenerative disease causes physical impairment, psychiatric symptoms and cognitive dysfunction and usually strikes at middle age. It inevitably leads to death and currently there is no treatment or cure.

"We are thrilled that these grants were awarded," she said. "The cell lines will enable us to better understand how the disease starts and progresses and to test new drugs to stop it. The disease team approach allows us to harness diverse expertise across the state of California. We are grateful for the support and involvement of the patient community and their efforts in raising awareness of HD."

UCI researchers joining Thompson in the new cell line study include Peter Donovan, biological chemistry

and developmental and cell biology professor, and Sue and Bill Gross Stem Cell Research Center co-director; Hans Keirstead, anatomy and neurobiology professor, and Sue and Bill Gross Stem Cell Research Center co-director; and Dr. Neal Hermanowicz, health sciences clinical professor and Movement Disorders Program director. The disease team planning group includes those researchers and J. Lawrence Marsh, developmental and cell biology professor.

A second disease team planning grant for \$37,367 went to Dr. Henry Klassen, a UCI ophthalmologist, who is looking into the use of stem cells to treat retinitis pigmentosa, a disease that destroys light-sensing cells in the retina causing blindness. Klassen plans to use modified stem cells to both secrete a growth factor for light-sensing cells and to develop into those cells themselves.

The relatively modest disease team planning grants allow scientists to assemble multi-disciplinary teams that will prepare proposals for major clinical trial grants. The goal is to fund disease teams whose work will result in a therapy or diagnostic tool for a particular disease or serious injury.

In all, CIRM awarded \$24 million to 25 California institutions.

"California, through CIRM, is leading the world in providing funding for innovative stem cell research," said Susan V. Bryant, vice chancellor for research at UCI, "and it is thrilling to see our UCI faculty competing so successfully for these awards."

Dr. Alan Trounson, president of CIRM, said the ultimate goal "is to apply the knowledge gained in basic research toward treatments and cures for patients." ■

Tetrabenazine Updates

Tetrabenazine Approved by FDA!

On August 18, 2008, after months of impatiently waiting, the U.S. Food and Drug Administration (FDA) approved tetrabenazine to treat chorea, the movements associated with Huntington's disease.

This marks the first and only drug approved by the FDA for use in the United States to treat Huntington's disease! The action came after an advisory panel unanimously voted on December 5, 2007, to advise the FDA to make the medication available to treat the disease.

Tetrabenazine License Agreement

On September 17, 2008, OVATION Pharmaceuticals, Inc. acquired from Prestwick Pharmaceuticals the exclusive license to commercialize tetrabenazine (Xenazine®) in the U.S. Subsequently, Biovail Corporation, Canada's largest publicly traded pharmaceutical company, acquired Prestwick.

Under the terms of the agreement, Biovail and OVATION will jointly develop additional follow-on indications for Xenazine and related products in the U.S. in conjunction with Cambridge Laboratories Limited, the worldwide license holder of the drug. OVATION expects to launch the product in the U.S. by the end of this year. ■

October 28, 2008



(See www.hdfoundation.org for more.)

Doctors, Families Fought For Approval of Huntington's Drug

By Rita Rubin

Jonathan Monkemeyer, an engineer by training, worked long and hard on the heartfelt four-minute talk he presented at a packed Food and Drug Administration advisory committee meeting last December. But even without saying a word, Sheryl Monkemeyer was far more expressive than her husband could ever be.

While seated, Monkemeyer's wife moved constantly. Her legs jerked so much that she kicked off her boots and scooted her chair back 6 inches, nearly into the lap of the person behind her. She couldn't help it. The former registered nurse, 45, has Huntington's disease, an inherited, incurable degenerative brain disorder that killed her father.

The uncontrolled movements that characterize the disease make it difficult for her to ride in a car, but she and her husband had driven 125 miles from their suburban Philadelphia home to the FDA meeting in a Sheraton Hotel ballroom in Beltsville, Md. Their goal: to help convince panelists that the FDA should approve tetrabenazine, which would be the first drug approved in the USA for any symptom of Huntington's disease. Huntington's afflicts 30,000 Americans, as many as cystic fibrosis, another, better-known genetic disorder.

The story of how tetrabenazine finally won FDA approval is one of desperate Huntington's disease families and dedicated doctors who were used to having their hopes dashed when one experimental drug after another failed to live up to its promise.

More than a dozen family members testified before the advisory committee about the horrors of Huntington's and the benefit of tetrabenazine, and, says Barbara Boyle, executive director of the Huntington's Disease Society of America, "when they finished there wasn't a dry eye."

Tetrabenazine neither cures nor slows the disease — no drug yet has been shown to do that — but it's the most effective treatment for the uncontrolled

movement called chorea, Greek for "dance." (The disease is sometimes still referred to as Huntington's chorea.) Typically, Huntington's symptoms first appear in middle age, and death occurs 10 to 30 years later.

The FDA advisers voted unanimously to recommend approval. In August, the agency gave Prestwick Pharmaceuticals in Washington, D.C., permission to market tetrabenazine as Xenazine. Last month, Ovation Pharmaceuticals in Deerfield, Ill., acquired the U.S. license from Prestwick.

"Recognizing that patients have been waiting a long time for this treatment, we are working diligently to expedite availability of Xenazine, which we expect will happen before the end of the year," Ovation spokeswoman Sally Young said Friday.

Columbia University neurologist **Nancy Wexler**, who spearheaded the research leading to a genetic test for Huntington's, says she had hoped the FDA wouldn't need an advisory committee meeting "because the merits of this drug were so obvious." But, says Wexler, whose mother died of Huntington's, "I think there were a lot of misconceptions about how debilitating these incredibly engulfing, abnormal movements are."

Three people were needed to feed her mother, Wexler says: one to hold her head still, one to hold her arms and one to spoon food into her mouth.

"Even if you have just a tiny bit of abnormal movement," says Wexler, president of the Hereditary Disease Foundation, "it can make it difficult to do anything normal: brushing your teeth, eating, doing the dishes."

At his tidy, plant-filled home on a leafy street in Newtown Square, Pa., Jonathan Monkemeyer apologizes for the faint food stains on the ceiling above the kitchen sink and for the plastic tumblers in which he serves iced tea.

In another family's home, the stains and plastic cups would suggest the presence of an active toddler. At the Monkemeyers, they are mute testimony to the disease that began attacking his wife's brain a decade earlier.

"My wife bites her lip, her tongue, the sides of her mouth," Monkemeyer, 42, told the FDA advisers. "She grinds her teeth together and smashes into them with utensils. Unless she sits in the middle

(car) seat, she smashes the side of her head into the passenger door window. Even with my help and padded walls in our shower, she split open her head on the towel rack."

After the meeting, Monkemeyer began getting tetrabenazine directly from Cambridge Laboratories, its Irish maker. He has become adept at splitting the pale yellow, aspirin-sized pills in half and, if need be, into quarters, and then serving them in applesauce. Too much tetrabenazine, and he has found his wife becomes sleepy and depressed. Too little, and her chorea worsens.

"I think Sheryl would be really, really far gone if she didn't have it," Monkemeyer says.

After her first dose, his wife could eat without choking, a common complication that can lead to deadly pneumonia if food goes down the wrong pipe.

Even on the medication, Sheryl Monkemeyer still fidgets non-stop as she sits on their couch, repeatedly knocking pillows off. Her speech is hard to understand, and you can feel her bones when you hug her. All that excess movement can burn thousands of calories a day, Wexler says.

But when her husband showed a reporter his prototype for an online gathering place for Huntington's researchers, she got off the couch and stood behind him at the computer for at least 15 or 20 minutes without falling.

At a graduation party this past summer, Monkemeyer says, his wife tickled guests by whacking a whiffle ball two times in a row. And she has amazed their neighbors by hitting a tennis ball in the front yard with their 10-year-old son, who's also named Jonathan.

Since his mom started taking tetrabenazine, "she's a lot more normal," says Jonathan, a fifth-grader who inherited his mother's delicate features and her love of reading and writing. He already has figured out that, like any child of an affected parent, he has a 50-50 chance of having inherited Huntington's disease.

One welcome side effect of tetrabenazine's approval has been hope, says Boyle of the Huntington's Disease Society. "This is something that said to our families: You know, we have a drug. We can get others. We're on our way to treating a disease." ■

In 2000, the Hereditary Disease Foundation supported research using the green fluorescent protein (GFP) in a jellyfish to analyze the potential effectiveness of drugs among thousands of already existing chemicals. Dr. Martin Chalfie, Columbia University, first determined how to use the jellyfish's GFP as a biological tag. Dr. Roger Tsien, University of California, San Diego, then re-engineered the GFP gene so that the protein it makes glows much brighter than usual. As a result, it can be used in very rapid test systems meant to spot potential drugs.

In 2008, Martin Chalfie and Roger Tsien, along with Osamu Shimomura, an emeritus professor at the Marine Biological Laboratory and Boston University Medical School, won the Nobel Prize in Chemistry.

CONGRATULATIONS ON THIS FANTASTIC ACCOMPLISHMENT! WE'RE PROUD TO HAVE BEEN AN EARLY BELIEVER!

September 12, 2000

THE WALL STREET JOURNAL

A Jellyfish Aids Scientists in Unraveling Gene Secrets --- Its Green Glow May Shed Light On How Some Diseases Arise And Ways to Combat Them

By Michael Waldholz, Copyright Dow Jones & Company Inc.



A jellyfish from Puget Sound off the Washington state coast is helping scientists tackle one of the most daunting challenges facing drug-hunting researchers: quickly turning the spate of new gene discoveries into innovative medicines.

The jellyfish species, *Aequorea victoria*, emits a green fluorescent flash when it's agitated — likely an attempt to defend itself by confusing enemies. Scientists at Aurora Biosciences Corp., a small biotech company in San Diego, are harnessing the chemical responsible for the sea animal's eerie green glow in experiments designed to literally illuminate new ways to attack a host of gene-related illnesses.

Today, Aurora will announce that it will soon begin experiments using the gene that generates the jellyfish's green fluorescent protein, or GFP, to search for a long-elusive treatment for Huntington's disease, an inherited disorder that erupts without warning at midlife, causing severe muscle gyrations, degeneration of brain function and, eventually, death.

Although the gene and its illness-causing defect responsible for Huntington's was identified seven years ago, following an

intense 25 year gene-sleuthing effort, no headway has been made in finding a treatment. Drug makers have been unwilling to stake the funds needed to find a cure because the gene defect is complicated and the number of people with the disease — about 35,000 to 50,000 Americans have it — is relatively small.

"We've been terribly frustrated because we had found what causes the disease but we couldn't get any company to look for a drug to counter the defect's devastating effects," says **Nancy Wexler**, the co-founder, along with her 92-year old father, Milton, of the **Hereditary Disease Foundation**. The Foundation launched a quest for the Huntington's disease gene in 1968 after Dr. Wexler's mother developed the illness that had also claimed her mother's three brothers.

"One major problem we've faced is that, despite years of research, we still don't know the role the gene plays in the body and how, when defective, it causes disease," says Dr. Wexler, who has a doctorate in psychology and is a professor of neuropsychology at Columbia University.

Researchers hope that the jellyfish-produced green light will not only help show how a defective gene gives rise to disease, but will also provide a simple, visual way to determine which drugs can inactivate a gene's deadly effect.

Roger Tsien, a biochemist at the University of California, San Diego, has tinkered with the jellyfish's gene, making

a new gene that produces a very bright version of the light. Aurora researchers, in turn, have created techniques that allow them to fuse the light-making portion of the proteins with portions of disease-causing genes, such as the one that causes Huntington's disease. In Aurora's coming experiments, researchers plan to test hundreds of thousands of chemical compounds to see if any of them can prevent or slow the death of cells caused by the bits of Huntington's gene. In the technique developed by Aurora, any drug that inactivates the fused protein or modifies its activity would cause a change in the color of the light emitted. In most instances, the color changes from green to yellow or to a color in between the two.

"In the past there was no way to tell if a test compound was having any effect on the gene or the protein it makes," says Brian Pollok, senior director of discovery biology at Aurora.

The light-emitting gene may also help determine which parts of the defective gene are causing harm and need to be attacked by experimental drugs, Dr. Pollok says. "What we'll try to do is fuse GFP with many parts of the Huntington's gene, and we'll track which of the fused proteins make cells sick or die."

If successful, the green-light technique could benefit other drug makers trying to exploit the flood of gene discoveries arising from the human genome project. While scientists are linking thousands of previously unknown genes to illnesses both rare, such as Huntington's, and common, such as heart disease and

arthritis, how these genes function in sickness or in health is largely unknown.

Indeed, in the past year or so a new discipline of science, called “functional genomics,” has arisen as researchers in academia, giant pharmaceutical companies and start-up biotech firms race to figure out what newly discovered genes do and why, when defective, they cause disease. But, researchers at major drug makers acknowledge, if they have to wait until scientists elucidate the function of genes before they can initiate drug-discovery projects, it could take decades before new gene-based medicines are found.

“What we’ve developed is an ability, using GFP, to test thousands of chemical compounds against [disease-related] genes without having to know what the gene does in cells or why alterations to the gene results in disease,” says Dr. Pollok, who has a doctorate in biochemistry.

In recent months, published scientific reports of Aurora’s ability to track down drugs against disease-related genes before knowing function has led a number of major drug makers, such as Pfizer Inc., Bristol-Myers Squibb Co., and Merck & Co., to employ the company’s drug-hunting technique in deals worth tens of millions of dollars each.

Since the Huntington’s disease gene was found, researchers who have been supported in large part by Dr. Wexler’s small foundation have found that the defect involves a very strange bit of evolution. In people born with the defect, who are fated to develop the disease by the time they are 40 or 50 years old, the gene contains a tiny segment of DNA that is abnormally repeated over and over — an accordion-like expansion of genetic material that is also found in people with other neurodegenerative illnesses such as Alzheimer’s or Parkinson’s.

There is reason to believe that Huntington’s disease arises when mutant proteins made by the defective gene begin sticking together inside nerve cells, and that over time this accumulated mass of material simply gums up the machinery inside the cell. This gradual buildup may explain why the disease takes decades to arise.

“The idea would be finding a drug that blocks this protein aggregation,” says

The Hereditary Disease Foundation has been supporting this ground-breaking research since 2000.

October 8, 2008

The New York Times

Three Chemists Win Nobel Prize

By Kenneth Chang

One Japanese and two American scientists won this year’s Nobel Prize in Chemistry on Wednesday for taking the ability of some jellyfish to glow green and transforming it into a ubiquitous tool of molecular biology to watch the dance of living cells and the proteins within them.

Osamu Shimomura, an emeritus professor at the Marine Biological Laboratory in Woods Hole, Mass. and Boston University Medical School, Martin Chalfie of Columbia University, and Roger Y. Tsien of the University of California, San Diego, will share the \$1.4 million prize awarded by the Royal Swedish Academy of Sciences.

The green fluorescent protein, or G.F.P. for short, was observed in 1962 in the jellyfish *Aequorea victoria*, which drifts in the ocean currents off the west coast of North America.

Dr. Shimomura was able to identify the protein and showed that it glowed bright green under ultraviolet light.

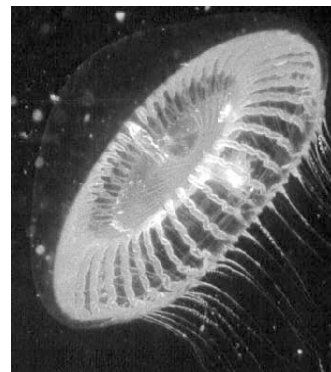
Dr. Chalfie showed how the protein could be used as a biological identifier tag by inserting the gene that produces the protein into the DNA of an organism.

In an early experiment, he inserted the protein into six cells of a transparent roundworm. When placed under ultraviolet light, those cells glowed green, revealing their location.

Dr. Tsien was able to make glowing proteins of colors other than green, allowing biologists to track different cellular processes at the same time.

Biologists now routinely use green fluorescent proteins for tracking the growth and fate of specific cells like nerve cells damaged by Alzheimer’s disease.

The technique can even track specific proteins within cells. In one experiment, the brain of a mouse was transformed into a kaleidoscope of color by tagging different nerve cells with different fluorescent proteins. ■



Ronald Wetzel, a protein chemist at the University of Tennessee at Knoxville. The trick to finding such a drug is devising an experiment that can measure the impact of thousands of chemical compounds that might interfere with the gene’s lethal action.

Dr. Pollok says once Aurora begins its experiments in the next few months, it expects within a few weeks to come up with about 5,000 compounds that have some impact on the Huntington’s gene. The researchers then plan to

ship these compounds off to academic scientists who will begin to test these compounds in other cell experiments. The hope is that, perhaps within a few years, scientists may find drugs that can be taken for life by people who have inherited the gene but haven’t yet developed the disease. The new medicine, it is hoped, would work by simply blocking the gene’s deadly action, though exactly what that action is may still not be known for many years, even after a drug is available. ■

A Focus on Giving



Mrs. Phyllis Parvin with HDF Lifetime Director Mary Carol Rudin

Since 2002, the **Albert Parvin Foundation** has been generously supporting the Hereditary Disease Foundation's annual January Workshop. To date, we have received almost \$100,000 from them! A big thank you to Hereditary Disease Foundation Lifetime Director **Mary Carol Rudin** for fostering this relationship and to **Mrs. Phyllis Parvin** and the **Albert Parvin Foundation** for their wonderful and very important generosity.

At the January Workshop, researchers discuss their latest findings and determine next steps. The support from the Albert Parvin Foundation enables us to keep looking ahead towards the CURE!!! THANK YOU!!! ■

Upcoming Workshops

- **“Suspended animation — can treatment with H₂S alter the pathogenesis of HD?”**
Tentatively scheduled for mid-January 2009
Seattle, Washington
- **“Pipelines and Pathogenesis and Future Directions for the HDF”**
January 24-25, 2009
Santa Monica, California
- **“Milton Wexler Workshop Symposium: Gene Therapy and Neurodegeneration,”** a collaborative meeting of the Hereditary Disease Foundation and the Keep the Memory Alive Foundation
Spring 2009
Las Vegas, Nevada
- **“Neuroinflammation in the pathogenesis and treatment of HD”**
Tentatively scheduled for mid-to late-Spring 2009
New York, New York

For workshop reports and other research updates, please check our website:
www.hdfoundation.org.

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Ways of Giving

There are many creative ways of giving to the Hereditary Disease Foundation to help us find treatments and cures for Huntington's disease and other hereditary illnesses. Your gift will serve as a catalyst for other donors to contribute, and will help ensure the continued success of the Foundation.

You can make a gift of cash or appreciated securities, or include the HDF in your estate planning. You can make a bequest to HDF simply by asking your attorney to include HDF in your will or codicil.

For more information about making a donation or how your legacy gift today can fund the discoveries of tomorrow, call Karen Dean, Controller, at 212.928.0420 or e-mail her at karendean@hdfoundation.org.

For more information about Ways of Giving, please visit our website - www.hdfoundation.org.

The Hereditary Disease Foundation is a non-profit 501(c)(3) organization. ■