Mary Jennifer Selznick Interdisciplinary Workshop Program

A centerpiece of the Hereditary Disease Foundation is the Mary Jennifer Selznick Interdisciplinary Workshop Program, which brings together scientists from different fields to brainstorm in an informal setting. In small workshops throughout the year, basic scientists from different disciplines connect with clinical investigators, clinicians and families to explore new directions for research.

"This is the best meeting I've ever been to...I admit, I was skeptical at first but…I think this is great. I really think that all meetings should be run as this one. There are no slide shows. There are no politics. There are just scientists who come together to discuss the issue at hand.

Dr. Gunter Blobel
John D. Rockefeller, Jr.
Professor at Rockefeller University
Nobel laureate, 1999

Funding Opportunities

The Basic Research Grants Program supports projects that contribute to identifying and understanding the fundamental defect in Huntington's disease. Grants are considered seed money. If the project shows promise, it is hoped that other institutions will fund it thereafter.

The Milton Wexler Postdoctoral Fellowship Award is named after the founder of the Hereditary Disease Foundation. A highly competitive award, it was established in 1998 to celebrate the Foundation's thirtieth anniversary. The Hereditary Disease Foundation restricts this annual award to research highly relevant to curing Huntington's disease.

The John J. Wasmuth Postdoctoral Fellowships are named in honor of the late John Jacob Wasmuth, an essential member of the Huntington's Disease Collaborative Research Group. Our hope is that those granted fellowships bearing his name will seek John's level of imagination, rigor, creativity and spirit.

The Hereditary Disease Foundation presents annually the prestigious **Lieberman Award** to a worthy scientist, thanks to the generosity of Harry Lieberman, a trustee of the Hereditary Disease Foundation. The Lieberman Award is intended to catalyze innovative proposals leading to the treatment and cure of HD.

"The Hereditary Disease Foundation spends less…for promotion, salaries, etc. No other organization comes close. Its integrity is exemplary."

The Late Ann Landers
Chicago Sun-Times

Hereditary Disease Foundation Leadership

The *New York Times, Wall Street Journal, Los Angeles Times,* "Sixty Minutes," "Day One," and "Nova" have all acknowledged the influence of the Hereditary Disease Foundation in pioneering new approaches in science and medicine.

Dr. Milton Wexler, Chairman of the Board of the Hereditary Disease Foundation, is a distinguished psychoanalyst who did pioneering research on schizophrenia. At age 96, he still plays a strong role in guiding the Foundation. **The Wexler family – Milton and his daughters, Nancy and Alice – donate their services, as do all officers.**

Dr. Nancy Wexler, Columbia University Higgins Professor of Neuropsychology and President of the Hereditary Disease Foundation, is a member of both the Institute of Medicine of the National Academy of Science and the European Academy of Sciences and Arts, and a Fellow of the Royal College of Physicians. She has received numerous awards including a Fulbright fellowship, the Robert J. and Claire Pasarow Foundation Award, University of Michigan Alumnae Athena Award, J. Allyn Taylor Award and the Society for Neuroscience Public Advocacy Award, as well as honorary doctorates from the University of Michigan, New York Medical College and Bard College. In 1993, she received the prestigious Albert Lasker Public Service Award.

Dr. Alice Wexler, a Hereditary Disease Foundation trustee, has told the Foundation and Wexler family story in a widely acclaimed book, *Mapping Fate: A Memoir of Family, Research and Genetic Illness*. Alice's next book on the social history of Huntington's disease will be published by Yale University Press.

Dr. Carl Johnson, Executive Director for Science of the Hereditary Disease Foundation, joined the Hereditary Disease Foundation in January 2001. He is an accomplished chemist and model organism molecular geneticist. He has worked in the biotechnology industry for over 15 years. In 1990, he and HDF Scientific Advisory Board member and Nobel Prize winner H. Robert Horvitz founded NemaPharm, Inc., the first functional genomics company focused exclusively on the discovery of human therapeutics based on technologies using a well-studied model animal, the nematode (or roundworm) *Caenorhabditis elegans*.

Child with juvenile Huntington's disease with Hereditary Disease Foundation's president Nancy Wexler.
- By Peter Ginter

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The Hereditary Disease Foundation aims to cure genetic illness by supporting basic biomedical research. Started by Dr. Milton Wexler in 1968, the Hereditary Disease Foundation uses a variety of strategies – workshops, grants, fellowships, and targeted research contracts – to solve the mysteries of genetic disease and develop new treatments and cures.

The Hereditary Disease Foundation supports research in genetics, gene therapy, molecular and cell biology, cell survival and death, animal models, neurophysiology, neuropharmacology and other fields relevant to the understanding of inherited diseases. The Hereditary Disease Foundation uses Huntington's disease as a model since it destroys so many functions – physical, mental and emotional – with a single genetic change. When we find a way to prevent and treat the devastation of Huntington's disease, we will use this knowledge to develop treatments for other illnesses with more complex origins, including Parkinson's, Alzheimer's and Lou Gehrig's disease (ALS), depression, and schizophrenia.

Huntington's disease (HD) is a fatal, dominantly inherited, genetic, neurological disorder causing involuntary movements, severe emotional disturbance and progressive cognitive loss over ten to twenty years. Each child of an affected parent runs a 50% risk of inheriting the same illness, usually in the third or fourth decade of life, though children as young as two and adults in their eighties may also develop symptoms.

"**Through the active recruitment of new ideas, new technologies and new researchers, the Hereditary Disease Foundation has set the stage for important progress in our understanding of HD pathology in the near future. Their commitment to collaboration and community building within the HD field serves as a model for all scientific groups tackling human diseases."**

Nature Medicine, October 2000

The Hereditary Disease Foundation played a key role in the discovery of the Huntington's disease gene, which was localized in 1983 and isolated in 1993. The Hereditary Disease Foundation recruited and supported more than 100 scientists who worked together as the Huntington's Disease Collaborative Research Group in a decade-long effort to capture the gene. *The New York Times* called the quest for the HD gene "legendary in less than a decade"; the gene, itself, the most "coveted treasure in molecular biology." New technologies developed during this search have been widely used in mapping genes for other disorders including cystic fibrosis, Parkinson's, Alzheimer's, cancer, heart disease and mental illness. Treatments developed for Huntington's disease will also lead to therapies for many other ailments.

Equally important, the success of the Hereditary Disease Foundation proved that these strategies worked and helped to launch the Human Genome Project.

"Through the years, I have been greatly blessed to work with superb and dedicated people, and I count the three of you, Milton, Nancy and Alice Wexler, to be at the top of that list."

Dr. Francis Collins, Director
National Human Genome Research Institute
National Institutes of Health

Hereditary Disease Foundation Supports and Catalyzes Critical Achievements Toward the Cure

1968 - **Dr. Milton Wexler** forms the **Hereditary Disease Foundation** after his wife and all of her three brothers are stricken with Huntington's disease. **The Hereditary Disease Foundation begins its pioneering role in spearheading innovations in modern molecular genetics which has continued for 36 years.**

1979 - Nancy Wexler, *President, Hereditary Disease Foundation, Higgins Professor of Neuropsychology, Columbia University*, initiates the ***U.S.-Venezuela Huntington's Disease Collaborative Research Project***, an ongoing study of the world's largest HD community living along the shores of Lake Maracaibo. This work is the longest and largest prospective, longitudinal study of HD worldwide. The Venezuela kindred is comprised of over 18,000 people, most from one extended family originating from a woman living in the early 1800s. The collaborative study provides critical elements for molecular and clinical research.

1983 - James Gusella, *Harvard University*, Nancy Wexler, P. Michael Conneally, *Indiana University*, David Housman, *Massachusetts Institute of Technology,* and others ***discover the general location of the Huntington's disease gene*** near the top of chromosome four. This is the first time that a gene is located using DNA markers when its address on a chromosome is completely unknown. Our success, heralded around the world, proved that these techniques could work for finding genes, and was a critical first step in helping to launch the **Human Genome Project** - called "the most important scientific undertaking of our time."

1993 - The ***Huntington's Disease Collaborative Research Group***, an international consortium of over 100 investigators led by the Hereditary Disease Foundation, ***isolates the actual Huntington's disease gene*** on chromosome four, identifying the mutation as an expanded trinucleotide repeat. During its ten-year search for the gene, the Group develops 14 new technologies used in subsequent investigations to find disease genes. It also provides a powerful new model for collaborative biomedical research.

1995 - Scott Zeitlin and Argiris Efstratiadis, *Columbia University*, create the ***first HD "Knock-Out" mouse*** - removing the mouse's own version of the Huntington's disease gene, almost identical to its human counterpart. They reveal that the HD gene performs an essential function for life.

1996 - Gillian Bates, *Guy's Hospital, London, UK,* develops the ***first transgenic mouse model of Huntington's disease*** by placing a portion of the human HD gene in a mouse, providing an invaluable and continuing gold mine of information about HD.

1997 - Scott Zeitlin and Argiris Efstratiadis, *Columbia University*, create a ***"Knock-In" mouse*** by increasing the size of the mouse's own HD gene. The mouse shows subtle disease symptoms.

1997 - Gillian Bates, *Guy's Hospital*, London, and Stephen Davies, *University College London*, U.K. ***discover aggregates*** of the HD protein in the nuclei of HD mice, leading to the astonishing discovery of these same aggregates in humans with HD.

1997 - The Hereditary Disease Foundation launches the ***Cure Huntington's Disease Initiative***, designed to accelerate progress from research to therapy. ***The goal-oriented, task-force strategy aims at stimulating and coordinating research in both academia and private industry, targeting approaches with potential for drug discovery.*** The Initiative proactively solicits research proposals, making grants to numerous investigators studying potential new drugs, developing screening methods for quickly assessing the effectiveness of new drugs, and studying the mechanism of disease and potential drug targets.

A **Cure Committee** of the best and most visionary scientists brings their formidable collective intellect and wide-ranging expertise to guide the Initiative, generously donating their time:

- Dr. Kenneth Fischbeck, Director, Neurogenetics Branch, *National Institutes of Neurological Disorders and Stroke, National Institutes of Health*;
- Dr. H. Robert Horvitz, 2002 Nobel Laureate in Physiology or Medicine; Professor of Biology, *Massachusetts Institute of Technology;* Investigator, *Howard Hughes Medical Institute*;
- Dr. David Housman, Ludwig Professor of Biology, Center for Cancer Research, *Massachusetts Institute of Technology*;
- Dr. Richard Mulligan, Investigator, *Howard Hughes Medical Institute*, Children's Hospital, Boston; Mallinckrodt Professor of Genetics, *Harvard Medical School*; and winner of a MacArthur "genius" award;
- Dr. Allan J. Tobin, Professor Emeritus, *UCLA*; Scientific Director Emeritus, Hereditary Disease Foundation;
- Dr. Nancy Wexler, Higgins Professor of Neuropsychology, *Columbia University* and President, Hereditary Disease Foundation;
- Dr. Anne Young, Julieanne Dorn Professor of Neurology, *Harvard Medical School* and Chief, Neurology Service, *Massachusetts General Hospital.*

Ethan Signer, Professor Emeritus, *MIT*, was the first Executive Director of the Initiative, followed by Carl Johnson, and Minka vanBeuzekom as Managing Director.

1998 - George Jackson and Larry Zipursky, *UCLA*, create the ***first fruit fly* (Drosophila) *model of HD***.

1998 - James Olson, *Fred Hutchinson Cancer Research Center*, Washington, forms the ***Huntington's Disease Array Group,*** which comprises 50 investigators representing eight laboratories throughout the U.S. and Canada. The Group uses "microarray chips" in animal models and in human tissue to search for genes "turned on or off" in HD. The Group's findings initiate a therapeutic drug trial in mice.

1999 - Flint Beal, *Weill Medical College of Cornell University*, establishes the ***first Mouse House***, a facility for testing potential drug candidates in several different HD mouse models.

1999 - Jenny Morton, *University of Cambridge, UK,* begins a large project assessing the therapeutic effects of different drugs on behavior, symptoms and longevity of HD mice.

1999 - Robert Friedlander, *Harvard University*, treats HD mice with an experimental therapy resulting in the ***first improvement of symptoms***.

1999 - Paul Patterson, *Caltech*, creates ***monoclonal antibodies*** named after Hereditary Disease Foundation founder Milton Wexler that reveal new properties of the huntingtin protein.

1999 - William Yang at *UCLA*, and C.J. Li, *Weill Cornell Medical School*, ***create the first transgenic mice, which have a piece of bacterial artificial chromosome (BAC).*** Some of these mice have only a ***tiny piece of the HD gene*** while others have the ***entire gene***. These genes can be targeted to precise areas of the mouse brain with great eloquence and specificity, revealing much about intricate brain circuitry damaged by the HD protein. ***They are finding new therapeutic targets***.

2000 - Peter Detloff, *University of Alabama, Birmingham*, creates a ***"Knock-In" mouse*** with a huge expansion that causes severe HD symptoms and early onset.

2000 - Ai Yamamoto and René Hen, *Columbia University*, ***produce the first reversal of symptoms in an HD mouse.*** Ai and René place the human HD gene in a mouse with a special genetically engineered "switch" that can be turned off long after symptoms appear. When no longer exposed to HD's "poisonous protein," the mouse's brain cures itself!

2000 - The Hereditary Disease Foundation forms a ***collaboration with Aurora Biosciences*** (now Vertex Pharmaceuticals Inc.), San Diego, to use their innovative gene fluorescence technology (based on a protein found in jellyfish) to identify therapeutic compounds for potential drugs for HD.

2001 - Robert Hughes, *University of Washington*, organizes the ***first Cure Network*** to prepare for drug discovery and development, testing for effectiveness and toxicity. Working with the Huntington's Disease Array Group, a major effort is expended to recruit and support scientists to develop model systems to mimic the effects of HD.

2002 - The Hereditary Disease Foundation initiates a partnership with ***Structural GenomiX*** to purify the HD protein and determine its ***crystal structure*** – a formidable feat.

2002 - Leslie Thompson, Joan Steffan and Lawrence Marsh, *University of California, Irvine*, demonstrate that drugs called histone deacetylase (HDAC) inhibitors ***reverse the degeneration*** of neurons and ***prevent early death*** in their fruit fly *(Drosophila)* model of HD. ***Dysregulation of transcription and drugs which reverse it*** become a hot new area for Hereditary Disease Foundation-funded research.

2002-2004 The Hereditary Disease Foundation initiates a "virtual company" of drug screening. This entails many collaborations with HDF-funded investigators. These include primary, secondary and tertiary screens – from ***cells and yeast to worms, flies and mice***. ***We supported screening of all FDA-approved drugs*** as well as additional "libraries" or collections of drugs purchased by HDF for the purpose.

2003 - Gillian Bates, *Guy's Hospital*, London, shows that SAHA (suberoylanilide hydroxamic acid), an HDAC inhibitor, dramatically ***improves the movement impairment*** in a mouse model of HD.

2003 – Beverly Davidson and Henry Paulsen, *University of Iowa,* and Neil Aronin and Phillip Zamore, *University of Massachusetts*, ***discover extraordinary new ways of selectively "turning off" the HD protein, leaving the normal protein intact and functional***. They use a phenomenon called ***RNA interference***. These discoveries are ***virtual cures for HD***, if they can be transferred to the brain!

2004 - Nancy Wexler and the U.S.-Venezuela Collaborative Research Project show that the ***age at which HD starts is not determined solely by the HD gene, as previously believed, but is strongly influenced by genes other than the HD gene and by environmental factors.*** This discovery suggests there are more ways to attack Huntington's than investigators realized and raises hope that scientists can mimic protective genetic and environmental factors with drugs.

Some of the many Venezuelans at risk for HD whose donations of DNA samples helped find the gene.

- By Steve Uzell

To make a donation to the Hereditary Disease Foundation, please go to our website **www.hdfoundation.org** and click on the "Make a Donation" link or send a check to
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