

## Milton Wexler Workshop Program

A centerpiece of the Foundation is the interdisciplinary Workshop Program which sponsors Workshops held many times during the year. Milton Wexler began the Program to bring scientists together from different academic disciplines to brainstorm - without prepared lectures or slides - and explore new directions for research. They often share unpublished data.

**“This is the best meeting I’ve ever been to...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. Günter Blobel, Nobel laureate, 1999  
John D. Rockefeller, Jr. Professor at Rockefeller University

## Funding Opportunities

**The Basic Research Grants Program** supports projects that contribute to identifying and understanding the fundamental defects in Huntington’s disease and related disorders.

**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 Lieberman Award** is presented annually to a worthy scientist, thanks to the generosity of Harry Lieberman, a trustee of the Hereditary Disease Foundation.

**The Milton Wexler Postdoctoral Fellowship Award** is named after the founder of the Hereditary Disease Foundation. The Hereditary Disease Foundation restricts this annual award to research highly relevant to curing Huntington’s disease.

### Giving to the Hereditary Disease Foundation

Donations are accepted by **check** and **credit card**. For other ways of giving or more information, see the Give to HDF section of our website at [www.hdfoundation.org](http://www.hdfoundation.org) or call Karen Dean, Controller, at 212.928.0420.

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

**“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, The 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**, Founder of the Hereditary Disease Foundation, was a distinguished psychoanalyst who did pioneering research on schizophrenia. Until his death in March, 2007 at age 98, he played a strong role in guiding the Foundation. Learn more about him on the HDF website.

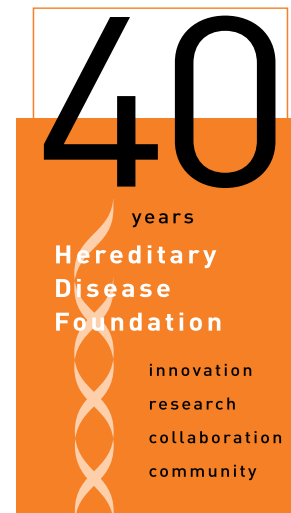
**Dr. Nancy Wexler**, Columbia University Higgins Professor of Neuropsychology and President of the Hereditary Disease Foundation, is a member of the Institute of Medicine of the National Academy of Sciences, the American Academy of Arts and Sciences, and the European Academy of Sciences and Arts, and 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 Prize and the Society for Neuroscience Public Advocacy Award, as well as several honorary doctorates. In 1993, she received the prestigious Albert Lasker Public Service Award. In 2007, she was awarded the Benjamin Franklin Medal in Life Science from the Franklin Institute.

**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, Risk, and Genetic Research*. 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 HDF in January 2001. He is an accomplished chemist and model organism molecular geneticist. He has worked in the biotechnology industry for over 20 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*.

The **HDF Scientific Advisory Board (SAB)** is made up of 29 scientists from around the world, including Nobel laureates, members of the National Academy of Science and its Institute of Medicine, members of the American Association of Arts and Sciences, among others.

For a complete listing of SAB members and HDF Leadership, please visit [www.hdfoundation.org](http://www.hdfoundation.org).



## Hereditary Disease Foundation

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In 1968, a biomedical detective story began with one family’s personal heartache. It eventually stretched from the poorest villages of Venezuela to the most advanced research laboratories in the world.

The **Hereditary Disease Foundation (HDF)** aims to cure genetic illness by supporting basic biomedical research. The HDF was started by Dr. Milton Wexler in 1968 when his wife was diagnosed with Huntington’s disease (HD). The 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.

Huntington’s disease 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 has a 50% risk of inheriting HD, usually in the third or fourth decade of life, though children as young as two years and adults in their eighties may also develop symptoms.

The Hereditary Disease Foundation uses Huntington’s disease as a model for hereditary disease research because it is triggered by a mutation of one single gene. Progress toward treatment or a cure could be instrumental in finding ways to treat other illnesses with more complex genetics, including Parkinson’s, Alzheimer’s, Lou Gehrig’s disease (ALS), depression, schizophrenia, and cancer.

The Hereditary Disease Foundation has given over \$50 million to support pioneering research in genetics, gene therapy, molecular and cell biology, cell survival and death, animal models, neurophysiology, neuropharmacology and other areas relevant to understanding inherited diseases.

The Hereditary Disease Foundation played a key role in the discovery of the HD gene, which was localized in 1983 and isolated in 1993. The HDF recruited and supported more than 100 scientists worldwide who worked together as the Huntington’s Disease Collaborative Research Group in a ten-year search 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 the HD gene search - supported by the Hereditary Disease Foundation - have been widely used in mapping genes for other disorders including cystic fibrosis, Parkinson’s, Alzheimer’s, cancer, heart disease and mental illness. These successes helped to launch the Human Genome Project.

**“If one looks back in the development of human genetics in our current form, I think the Hereditary Disease Foundation played really the same role that the Rockefeller Foundation played in the 30s and 40s, when it permitted the development of molecular biology. It was a small group of people who weren’t waiting around, but were giving money to the right people, with the thought that it was sensible.”**

November 1, 2005

Dr. James D. Watson

Chancellor, Cold Spring Harbor Laboratory  
Nobel laureate, 1962



Photo by Peter Günter

Child with juvenile HD with HDF President Nancy Wexler

## Hereditary Disease Foundation Supports and Catalyzes Critical Achievements Toward the Cure

**1968** - 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.**

**1979** - Nancy Wexler 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 has over 18,000 people, most from one extended family originating in the early 1800s.

**1983** - James Gusella, *Harvard University*; Nancy Wexler; P. Michael Conneally, *Indiana University*; David Housman, *MIT*; 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 launching pad for 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 goldmine of information about HD.

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

**1997** - Gillian Bates and Stephen Davies, *University College London*, UK, **discover aggregates** of the HD protein in the nuclei of HD mice, leading to the discovery of these same aggregates in humans with HD.

**1997** - The Hereditary Disease Foundation launches the **Cure Huntington's Disease Initiative** to accelerate progress from research to therapy. The strategy aims to stimulate and coordinate research in both academia and private industry.

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

**1998** - James Olson, *Fred Hutchinson Cancer Research Center*, forms the **Huntington's Disease Array Group**, comprised of 50 investigators from eight labs in the US 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** - M. 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, *UCLA*, and C.J. Li, *Weill Medical College of Cornell University*, **create the first transgenic mice which contain a piece of bacterial artificial chromosome (BAC).** The HD gene can be targeted to precise areas of the mouse brain, revealing much about intricate brain circuitry damaged by the HD protein.

**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*, and José Lucas, *Center for Molecular Biology*, Madrid, Spain, **produce the first reversal of symptoms in an HD mouse.** The human HD gene is placed 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!

**2001** - HDF provides **funding** for research aimed at developing **RNA interference(RNAi)-based treatments for HD.**

**2002** - HDF holds its **first workshop on RNAi-based treatments for HD** with leading experts in the field, including 2006 Nobel laureates Andrew Z. Fire, *Stanford University School of Medicine*, and Craig C. Mello, *University of Massachusetts Medical School*, co-discoverers of RNAi.

**2002** - Leslie Thompson, Joan Steffan and Lawrence Marsh, *UC, 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.

**2002** - The Hereditary Disease Foundation initiates a "virtual company" of drug screening. These include primary, secondary and tertiary screens - from **cells and yeast to worms, flies and mice.** **HDF supports screening of all FDA-approved drugs as well as additional "libraries."**

**2003** - Gillian Bates shows that suberoylanilide hydroxamic acid (SAHA), 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 new ways of selectively "turning off" the HD protein, leaving the normal protein intact and functional using RNAi.** 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.**

**2005** - Beverly Davidson publishes groundbreaking research on RNAi therapy for HD, showing that **delivery of RNAi to the brain** of mice expressing the mutant HD gene **has a significant beneficial impact on the symptoms and progression of the disease.**

**2005** - William Yang generates mouse models which show, for the first time, that a large fraction of the **neuronal toxicity observed in HD may be caused by toxic cell-to-cell interactions** between neighboring cells.

**2005** - Steven Finkbeiner, *UC, San Francisco*, uses a microscope to **elucidate which forms of mutant huntingtin are most poisonous, which could reveal how mutant huntingtin causes degeneration and may lead to specific therapies that block it.**

**2006** - Beverly Davidson and Krystof Bankiewicz, *UC, San Francisco*, begin **developing methods for delivering RNAi-based therapy to the brain and testing the safety in animal models of an RNAi-based therapeutic product being developed for HD.**

**2006** - David Housman and Ruth Bodner, *MIT*, together with Aleksey Kazantsev and Bradley Hyman, *Harvard University*, **identify a compound that interferes with the pathogenic effects of HD**, which could lead to **development of new treatments for the disease.**

**2006** - Michael Hayden and colleagues, *Centre for Molecular Medicine and Therapeutics*, Vancouver, Canada, discover that by **preventing the cleavage of the mutant huntingtin protein** responsible for HD in a mouse model, the **degenerative symptoms underlying the illness do not appear and the mouse displays normal brain function.** **This is the first time that a cure for HD in mice has been successfully achieved.**

**2006** - William Yang generates a bacterial artificial chromosome (BAC) transgenic mouse model with the full-length mutant human HD gene inserted into the mouse genome. The study **reveals that BACHD mice exhibit progressive and robust behavioral and neuropathological phenotypes that closely match that of the human disease.** This model is also the **first full-length mutant HD gene model in which expression of the toxic protein can be switched off in different cells, making it an ideal model to study cell-to-cell interactions in HD.**

**2007** - Robert Hughes, *Buck Institute for Age Research*, and colleagues **identify more than 200 new proteins that bind to normal and mutant forms of the protein that causes HD.** These proteins are **modifier genes** which **lessen or increase the severity of Huntington's disease or advance or delay onset.**



Photo by Steve Uzzell

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