

Hereditary Disease Foundation



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The Hereditary Disease Foundation Partners with Aurora Biosciences for Therapeutic Drug Discovery

1. What is Huntington's disease?

Huntington's disease (HD) is an inherited, fatal brain disorder that destroys motor control and impairs thinking and feeling.

2. What are the major effects of the disease?

Victims suffer from uncontrolled body movements, known as "chorea," which eventually leave them unable to walk, stand or even speak intelligibly. The disease also causes cognitive difficulty, memory problems, severe depression and, after 15-20 years, death. Symptoms usually begin to appear in early to mid-adulthood, but can strike as early as 2 years of age or as late as 80 years. There is no cure or treatment for the disease, but carriers of the faulty gene can now be identified by genetic testing.

3. What causes Huntington's disease?

Huntington's disease results from a genetic mutation on the fourth chromosome. This abnormality causes the death of vital nerve cells in a region of the brain known as the basal ganglia. HD is an autosomal dominant disorder which means that each child of a

parent with the disease has a 50% risk of inheriting the illness. The HD gene is considered virtually 100% “penetrant,” meaning that anyone who inherits the faulty gene will inevitably develop the disease sooner or later. All “carriers” eventually become “patients.” The disease currently affects 35,000-50,000 Americans, with 175,000-250,000 more people at risk.

4. What is the Hereditary Disease Foundation and Aurora’s new collaboration?

The Hereditary Disease Foundation and Aurora have formed an alliance that will focus on the identification of novel therapeutics for the treatment of Huntington’s disease. Aurora’s goal is to use its proprietary fluorescence assay technologies and scientific expertise to advance the discovery of new medicines and to further the scientific knowledge not only of this disease, but also of other related genetic and neurological disorders. Aurora will develop assays, conduct screening using its own extensive library of chemical compounds, and then pharmacologically profile the potentially active compounds derived from these screens. If a “hit molecule” is found, Aurora will collaborate with academic researchers to test for efficacy in animal models. Many of these investigators have been recruited and supported by the Hereditary Disease Foundation to develop models for precisely this purpose – to focus the most intensive efforts rapidly on the most promising therapies. The Hereditary Disease Foundation will provide multi-millions in funding over approximately 18 months as well as downstream revenues for potential new drugs.

5. What is the Hereditary Disease Foundation?

Formed in 1968 by Dr. Milton Wexler after his wife and all of her three brothers were stricken with Huntington’s disease, the Hereditary Disease Foundation has played a pioneering role in spearheading innovations in modern molecular genetics. In 1983, the Hereditary Disease Foundation was the first to localize the gene causing Huntington’s disease with novel strategies using DNA markers. It was the first time in history that a gene was located using DNA markers when its chromosomal assignment had been unknown. This success, heralded around the world, proved that these techniques could work for anyone who wanted to find a gene, and was a critical first step in helping to launch the Human Genome Project. The Hereditary Disease Foundation’s prescience has now been rewarded by the recent announcement of the essential completion of the mapping and sequencing of the human genome.

Once the gene had been located, the Hereditary Disease Foundation next faced the challenge of isolating the Huntington’s disease gene itself from a swath of 4 million base pairs at the top of chromosome 4. For this purpose, the Hereditary Disease Foundation organized and supported the Huntington’s Disease Collaborative Research Group, a dedicated team of over 100 international investigators. In 1993, after a decade of collaboration, their arduous work was finally rewarded with the cloning of the HD gene. This allowed the Group to characterize the mutation that causes Huntington’s disease as a subtle expansion of DNA, such that in the gene’s protein product, called huntingtin, a

stretch of repeats of the amino acid glutamine becomes longer than normal. How and why this mutation causes disease is now the subject of intensive research supported by the Hereditary Disease Foundation.

Not content to rest with the gene in hand, the Hereditary Disease Foundation continued in its proactive mission. In 1997, the Hereditary Disease Foundation formed the Cure Huntington's Disease Initiative, under the leadership of Executive Director Dr. Ethan Signer, Professor Emeritus of Biology at the Massachusetts Institute of Technology. The Cure Committee, a prestigious group of scientists including members of the National Academy of Sciences and the Institute of Medicine, pursues ways to accelerate progress toward treatments and cures by expediting the route from research to therapy.

The Hereditary Disease Foundation has also spearheaded the United States-Venezuela Collaborative Research Project, a twenty year endeavor directed by Dr. Nancy Wexler. The world's largest extended family with HD lives along the shores of Lake Maracaibo, Venezuela. The generous contributions of these family members providing clinical information and tissue samples resulted in the localization and cloning of the HD gene and is still teaching us much about the disease.

The Hereditary Disease Foundation is currently directed by Dr. Milton Wexler, an active Chairman of the Board at age 92; Dr. Nancy Wexler, President, winner of the prestigious Albert Lasker Public Service Award; Dr. Allan Tobin, Scientific Director of the Hereditary Disease Foundation and Director, Brain Research Institute, University of California at Los Angeles; and Dr. Ethan Signer, Executive Director, Cure Huntington's Disease Initiative. The Hereditary Disease Foundation supports grants and fellowships as well as the inimitable Mary Jennifer Selznick Workshop Program of small, interdisciplinary workshops designed to recruit new researchers and facilitate new ideas.

6. How will the Hereditary Disease Foundation and Aurora's new collaboration function?

In order to expedite drug discovery, the Hereditary Disease Foundation's Cure Huntington's Disease Initiative supported the creation of the first transgenic mouse models of Huntington's disease, as well as some of the first "knock-out" and "knock-in" mouse models. The Initiative likewise supported some of the first *C. elegans* (worm) models, *Drosophila* (fruit fly) models and tissue culture models. The vast array of investigators recruited and supported by the Foundation now form a network that, together with Aurora's scientists, will make possible rapid characterization of promising compounds identified by the Aurora assays. Secondary screening and testing in these animal and tissue culture models will establish efficacy and toxicity, as compounds are refined to the point where they can be evaluated in clinical trials.

7. Why did the Hereditary Disease Foundation choose to partner with Aurora?

Aurora Biosciences is a leader in the development of new technologies for drug discovery. It is recognized worldwide for its outstanding team of scientists and engineers and its enabling bioassay technologies and instrumentation. Aurora has developed a broad platform of proprietary and highly sensitive fluorescence assay systems, as well as the ability to perform ultra-high throughput screening (testing daily generates in excess of 100,000 compounds or datapoints). In this partnership, Aurora's capabilities will be used to translate the basic science findings of Hereditary Disease Foundation-supported researchers into several assays for rapidly identifying interesting candidate compounds from among hundreds of thousands of test chemicals with potential for development into treatments for Huntington's disease. Highly miniaturized assay formats unique to Aurora provide the speed and efficiency to achieve this end.

The Hereditary Disease Foundation's advisors, in academia and industry, were aware of Aurora's highly sophisticated techniques for drug discovery, their interest in collaboration with voluntary health organizations, and their willingness to tackle difficult biological challenges intractable to standard approaches. Even though the HD gene has been cloned and the protein it produces has been identified, both the function of the normal protein and also the pathological function of the mutant protein are still a mystery. The Foundation is confident that Aurora's proprietary technology and expertise in drug discovery will be of enormous value in the race to find a cure for Huntington's disease.

8. Explain the drug discovery process in brief.

First, specific biological molecules (often proteins such as receptors, enzymes or ion channels) are identified as potential "targets" for drug action on the basis of data suggesting they play a role in the disease process in question. Most drugs work by binding to a target and modulating that target's function. Compounds demonstrating the appropriate activity in a laboratory test system have potential as new drugs. "Assays" are the specific tests used to identify those compounds, typically very few, that have appropriate activity against the target, and to assess each compound's relative effects. Assays are designed so that they are relevant to the disease process, mimicking the biology of key control points in this process to the greatest extent possible. "Screens" are assays run in a miniaturized and high throughput format to test very large numbers of compounds. Aurora has unique fluorescence assay technologies that have been developed by altering a gene called "green fluorescent protein" which is extracted from jellyfish in the Puget Sound. This gene has been altered to increase its brightness, permitting greater miniaturization, and, by color, indicate activity of test chemicals in these laboratory systems. This information is automatically captured, analyzed and stored by computer in sophisticated databases, and active compounds are identified as "hits." These hits are further tested to evaluate properties such as selectivity, potency, activity in other test systems such as animal models - if available for the disease in question - general pharmaceutical properties and safety. Compounds with favorable

profiles based on these tests become “lead compounds.” Medicinal chemists, biologists and pharmacologists work together to optimize lead compounds in an iterative cycle of chemical modification of the lead and repeated testing in assays and animal models. Successful lead optimization programs result in compounds termed “development candidates” that are on the path to clinical testing in humans. This will be performed by pharmaceutical, biotechnology or clinical research organizations with experience in planning and conducting clinical trials.

9. How far does this project go?

Aurora will develop a number of drug screening assays for Huntington’s disease, utilizing its proprietary fluorescence technologies. It will test one-half million compounds from its compound libraries with its automated Ultra-High Throughput Screening System (UHTSS) in these assays, and re-evaluate, validate and perform secondary assays on the resulting hits. At that point, the Hereditary Disease Foundation and Aurora will decide together how to proceed, determining how much chemistry and optimization is required, and whether proof of concept can be demonstrated in animal models that the Hereditary Disease Foundation’s network of basic and clinical investigators have developed. The Hereditary Disease Foundation and Aurora will work with the Food and Drug Administration (FDA) to seek Orphan Disease registration for lead compounds resulting from this project. The National Institutes of Health (NIH) will also be engaged to help in the early evaluation of candidate therapies.

10. How long will this take and how much will it cost?

This project should be completed within the next eighteen months. Actual costs will depend on the progress of drug discovery.