Inside Philanthropy

A Foundation's Long Quest to Take on Huntington's Disease Picks Up Speed

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ESB PROFESSIONAL/SHUTTERSTOCK

On a Wednesday night in late January, about 30 people associated with the Hereditary Disease Foundation met at Michael's restaurant in Santa Monica to mark the end of a two-day working conference of researchers from around the country and to celebrate the beginning of the foundation's largest-ever grants program. In September of 2023, HDF awarded two grants of $1 million each, to be paid out over two years, to two research collaboratives on the cusp of therapeutic discovery for Huntington's disease.

Called "Transformative Research Awards," these grants are notable for their size. We've seen massive grantmaking for research into other diseases, such as centibillionaire Sergey Brin's reported $1 billion total giving for Parkinson's research, as IP's Paul Karon wrote recently, and for large medical schools. But philanthropic support for individual researchers working on relatively rare diseases like Huntington's tends to be given out in smaller doses.

When it comes to government funding and corporate interest, Huntington's often loses out against more common neurodegenerative diseases such as Alzheimer's. While about 30,000 people in the U.S. have Huntington's disease, and another 250,000 are at risk because one of their parents had it, those aren't big enough numbers to attract a lot of investment, said Sarah Hernandez, HDF's director of research programs. "Typically, the government gives grants this size. The Transformative Research Award ensures that we have these larger awards for Huntington's disease. It can really move the needle for research."

The two $1 million dollar grants came about as the result of an initial $3 million anonymous gift from several members of one family with a personal connection to the disease. The inaugural grants went to a team led by Dr. Beverly Davidson of Children's Hospital of Philadelphia and the University of Pennsylvania, and to a second team led by Dr. Ricardo Mouro Pinto of Massachusetts General Hospital and Harvard Medical School. Each team includes experts from different institutions and with different knowledge bases.

How a funder can shape the work

The fact that these two grant winners are multidisciplinary teams points to another important piece of this story: the role that an active, passionate funder can play in shaping how work on its issue is done.

From its inception in 1968, the Hereditary Disease Foundation has fostered and funded a highly collaborative, transparent, international research community around Huntington's disease. The foundation currently has a staff of eight (all women, interestingly enough, given the unusually cooperative nature of the work). It also has an active, volunteer scientific advisory board of nearly three dozen high-level researchers and clinicians that sets the foundation's scientific priorities, plans workshops, reviews grants and fellowship applications, and recommends the most promising research projects for funding. Before these two new awards, HDF has typically given away about $1.5 million per year in annual grant funding.

The cooperative approach of HDF is atypical in disease research. It can serve as a model for research into other diseases, several people at the dinner pointed out.

"I work on other disorders, and there really is nothing like this," Davidson said. "The Hereditary Disease Foundation is visionary about how it puts its money to work because of the way they bring teams together to work on problems. It finds ways to bring together researchers to consider various perspectives on what are the problems at hand, who are the best people to solve them, how do we get them involved? Through this, the community really grows and becomes energized to solve the problem. That's why it's such an incredible organization to be involved with."

Hernandez agreed that collaboration is one key to the success Huntington's researchers have had to date. "In Huntington's, they call themselves the 'no ego amigos.' They work together to get the answers faster. You're working against the disease, not against each other."

What is Huntington's disease?

Huntington's is a fatal, hereditary, neurodegenerative disease caused by a single gene gone awry. We all have the Huntington's gene, but in those with the disease, a faulty "expanded" copy

continues to grow over time, wreaking havoc on other systems in increasingly destructive ways. Huntington's progresses slowly, over 20 or 25 years, starting with uncontrolled, jerky, almost "dance-like" movements and gestures called chorea, and going on to erode mood and memory. In its late stages, people can longer walk, talk or feed themselves, but they are still aware of themselves and others.

Huntington's is "autosomal dominant," meaning it only takes one affected gene. In other words, a person whose parent has Huntington's disease has a 50/50 chance of inheriting the gene and therefore getting the disease, too. But if a person has the faulty gene, they don't know when the disease will start. Huntington's is a lurker disease. There are no signs of anything amiss, but then it begins to manifest itself, generally when a person is between the ages of 30 and 50 (but sometimes as young as two or even as old as 80).

Before HDF, there was almost no research on the disease or conversation about it, said Meghan Donaldson, chief executive officer of HDF. "I grew up in a family where my mother had Huntington's disease. Despite her obvious symptoms, and the fact that all seven of us siblings were at risk, we rarely talked about it as a family. In the late 1970s, there was very little research and not much hope. It was terrifying to think that one day, any one of us would develop the same disease we were watching my mother succumb to. It was very isolating. Research through the Hereditary Disease Foundation has really changed that."

A quest for knowledge — and a cure

In the late 1800s, George Huntington, a doctor in Long Island, wrote about a malady he was seeing in certain families in his community. His father and grandfather, also doctors, had observed the same condition within these families. But it took more than 100 years, and the work of HDF, to discover the gene that caused what has come to be known as Huntington's disease.

In the late 1960s, Dr. Milton Wexler, a psychoanalyst to the stars in Los Angeles, learned that his former wife had Huntington's disease, meaning their two daughters were at risk. There was still scant information about the disease: No one knew what gene caused it, what chromosome that gene lived on, how it functioned, or what, if anything, could be done about it.

Milton Wexler founded HDF, and threw himself into corralling leading doctors and researchers from different disciplines and convincing them to work on the disease. His 2007 obituary in the *New York Times* reported that he applied his expertise of working with creative people to researchers. "His strategy was one he developed for group therapy among creative people: no-holds-barred discussion toward a common purpose in a nonthreatening climate."

Wexler's youngest daughter, Nancy, then a graduate student in psychology, not only helped persuade researchers to collaborate, but also learned about a community of families in a remote part of Venezuela, where Huntington's disease was widespread. She brought a team of scientists and doctors to Venezuela every year, from 1978 through 2002, to provide basic healthcare while also collecting tissue samples of these families for genetic experts in the U.S. to analyze. This led to the identification of the gene marker or "neighborhood" — the chromosome that the Huntington's gene is on — in 1983.

After another decade of work, researchers, many funded by HDF, identified the gene that causes the disease. The story of the quest for the cure reads like a whodunnit. Alice Wexler, Milton's eldest daughter and the secretary of HDF, tells this story in her book "Mapping Fate," which came out in 1995. (A 2020 article in *The New York Times* describes the Venezuelan project and Nancy's revelation that she herself has Huntington's.)

There is still no disease-modifying treatment or cure, but through the support from HDF, researchers have made monumental strides in understanding Huntington's disease. While Huntington's impacts many systems, it primarily affects the brain, and findings on it may be beneficial for other neurodegenerative disorders, such as Parkinson's, Alzheimer's and Lou Gehrig's (ALS) disease.

New money leads to a new funding approach

The Hereditary Disease Foundation has long given one- or two-year grants of $75,000 each, per year, to researchers (a set amount it upped to $100,000 per year in 2024). The $3 million gift was a chance for the foundation to try something new. "I thought we should really do something outside our usual grants program with this funding," Donaldson said. Working with its scientific advisory board and the donors, HDF created a steering committee, which in turn developed specific criteria for these much-larger new grants, and a request for applications.

Parameters for the Transformative Research Award are specific: The research must be novel, be a collaborative effort among different labs and people with different expertise, and be moving toward clinical trial. "The funders were so impressed with the process that we put in place that they pledged another $1 million," Donaldson said. This is good news because the HDF hopes to keep these $1 million grants going and plans to increase its fundraising efforts to that end.

The winning teams

Both of the Transformative Research Award winners are focusing on gene therapy and somatic instability, a "hot topic" in Huntington's research. Each team is working on other genes that affect the Huntington gene. Davidson's team is looking at inhibiting two genes that have been shown to make Huntington's progress faster and researching a safer, more potent vector to transport the inhibitors into the brain. The ultimate goal is to develop a single-dose treatment that will alter the progression of Huntington's disease.

As Davidson explained it to nonscientist me, there are two parts to gene therapy: some way of impacting an existing gene, and some way of getting a gene or gene-editing machinery into the body using a harmless virus. (For more information on gene therapy, check out the American Society for Gene & Cell Therapy's educational content.) "The viruses are like a car, and the passengers are the genetic cargo," Davidson said.

Her team has identified new and improved "cars," or vectors. "We've discovered viruses that have better distribution in brains and that require much lower doses to achieve gene delivery to the cells affected by mutant Huntington's. So it's safer, as it doesn't expose the entire body to these viruses or to the genetic cargo that they encode. We've gone from a Miata to a Lamborghini — not to disparage one automaker over another," she said. "These viruses also have the bonus of lowering

manufacturing cost, which means more patients could be treated for the same cost, a real concern in this field."

The funding will allow her team to continue their work and try it out on animals with larger brains that more closely resemble humans. "This will get us to the point where we can have conversations with the FDA about what else is needed to move to a clinical trial. I think this is exceedingly doable — getting close to clinical trial readiness and then eventually slowing down Huntington's disease," she said.

The other winning team is led by Ricardo Mouro Pinto of Harvard Medical School and Massachusetts General Hospital and includes seven other researchers. This second team is taking a different approach and targeting three genes, including one of the same ones that Davidson's team is looking at, MSH3.

As Davidson said at the dinner, the Transformative Research Grant request for applications was exciting. "This will let us push our work forward to file with the FDA and move to the next step. This jumpstarts the process."

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