Interview: Alice and Nancy Wexler

HDBuzz interviews Alice and Nancy Wexler, the sisters at the heart of the Hereditary Disease Foundation

By Dr Ed Wild on October 20, 2012
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The Hereditary Disease Foundation, or HDF, is a key player in the world of Huntington's disease research. At the HDF's recent biennial scientific meeting in Cambridge, Massachusetts - 'The Milton Wexler Celebration of Life and Creativity' - HDBuzz met Nancy and Alice Wexler, the remarkable sisters at the heart of the HDF's work.

The Wexlers

The story of the HDF is intertwined with the story of Nancy and Alice Wexler's lives.

Alice and Nancy Wexler
Image credit: Alice Wexler

Nancy was 23, and Alice 26, when their father Milton, a prominent psychoanalyst, told them their mother Leonore had been diagnosed with Huntington's disease in 1968. As it always is, the news was a bombshell.

Milton was not one to take such news lying down, however. He approached Marjorie Guthrie, wife of folk singer Woody Guthrie. Marjorie had established the Committee to Combat Huntington's Disease after Woody had died of HD the previous year.

"Dad was always interested in research, and wanted to recruit scientists to get interested in doing research on Huntington's," recalls Alice.

It was a daunting task: the scientific landscape was dramatically different back then, says Nancy. "In 1968 nobody had even heard of Huntington's disease, and very few people did research on it. And when we started to look for people to interest in research, it was extremely difficult to get people interested".

Alice, a historian and writer, whose books on Huntington's disease include 'The Woman Who Walked into the Sea' and 'Mapping Fate', adds, "There was actually a fair amount of research going on earlier, but one problem was that much of it was aimed at identifying people who were going to get it, in order to stop them from having children."

HDF's workshops

Undeterred, Milton established the Hereditary Disease Foundation as a non-profit organization, and set out to produce a significant shift in how Huntington's disease was viewed and studied. That remains the mission of his daughters and the HDF's expert Scientific Advisory Board.

Where to begin? Get people talking. Drawing on his background as a psychotherapist, Milton organized a series of workshops - small meetings of scientists from different fields, discussing HD and exchanging ideas freely.

The HDF's workshops - which continue to this day - always began with an introductory talk to the scientists from an HD family member. "Huntington's is a very obscure disease in a lot of ways," explains Nancy. "Even doctors who treat HD patients don't actually have a conversation with them one to one as a human being. And we felt that that was critical. People would get motivated, people would get passionate."

HDF workshops have unique rules to encourage creative thinking by scientists. "They had to be small," says Nancy. "Fifteen to twenty people," adds Alice. Slides and Powerpoint presentations are banned, too, drawing the participants out of their comfort zones. "Everybody is freaked out about that, but it gets people to focus on what actually matters in the research, and what matters about the data," says Nancy.

The HDF was instrumental in bringing some big names into the Huntington's disease field, including several Nobel Prize winners. But the sisters agree that attracting and supporting young researchers has always been key. "That was a big focus - to find young people, people who were just starting their careers, and to get them to be interested in Huntington's," recalls Alice. Recruiting young researchers goes beyond the number of years ahead of them - they are free from prejudices and preconceived notions about how to approach problems, too.

Nancy, an irrepressible storyteller, slips into an affectionate parody of a senior researcher holding forth at an early workshop: "Well, this meeting's going to go on for half an hour, after which we're going to get the revealed truth, and then - nothing's going to happen!" But the younger researchers had no such fatalism - "no sense of what was impossible," as Nancy puts it.

The marker, the gene and beyond

The emphasis on unfettered thinking and using the brightest minds to strive towards the seemingly impossible has created an impressive array of HDF-supported scientific progress.

The discovery of a DNA marker for Huntington's disease in 1983, and the HD gene itself in 1993, were accelerated by the Foundation's workshops, organization and funding. "Finding the marker was radical; that absolutely changed the planet," Nancy jokes - but it's not far from the truth: the DNA marker focused the search for the HD gene. And from the HD gene we get our entire understanding of how HD causes damage, and the large repertoire of treatment targets we now have.

Beyond HD, the efforts of the “gene hunters” were central to the revolution in genetics that we hope will eventually yield treatments for many diseases including Huntington’s. “The gene hunters invented about fourteen technologies en route,” says Nancy.

Nancy is also behind the Venezuela Project - a 32-year study based in an area of that country where HD happens to be many times more common than elsewhere. Hundreds of related volunteers from those villages participated in the research that led to finding the marker and the gene. DNA from the Venezuela Project was also used to discover that CAG repeat length - the number of ‘stutters’ in a person’s HD gene - can affect the age when a person is likely to develop HD symptoms.

> “A big focus was to find young people, and to get them to be interested in Huntington’s”

Since the gene was found, HDF-supported work has led to some big advances. In 1996, Gill Bates of King’s College London developed the first HD mouse model. Called the ‘R6/2’, Bates' mice have taught us lots about how the HD mutation causes damage, and are still used today to study the disease and test possible treatments. Bates unexpectedly found clumps of protein, called ‘aggregates’, in the brains of her mice. “Nobody thought that Huntington’s had aggregates,” recalls Nancy, but spurred on by the mouse discovery, these aggregates were soon shown to be an important change found in HD patient brains, too.

Another game-changing moment was the 2000 study by Ai Yamamoto, who bred an HD mouse in which the abnormal gene could be artificially ‘switched off’. To everyone’s surprise, switching off the gene allowed mice that had already developed symptoms to get better. Nancy is particularly pleased to recall that breakthrough, because the HDF had nurtured Yamamoto from early in her career. “We funded her to do her graduate work. She didn’t even have a doctorate!” she laughs.

Yamamoto’s work paved the way for the gene silencing or huntingtin lowering treatments that are now close to being tested in Huntington’s disease. In 2002, the HDF held the first workshop on using RNA-based drugs to ‘switch off’ the HD gene, and HDF-supported researchers like Beverly Davidson - whom we recently interviewed for our ‘EuroBuzz’ feature - remain central to advancing those treatments to clinical trials as quickly and safely as possible.

Today and tomorrow

After the discovery of the gene, why has Huntington’s disease has proven such a tough nut to crack? “Biology is really complicated; we’re really complicated, our cells are really complicated,” explains Nancy. “Every time you look under a rock for what the Huntington gene’s doing, you find something fascinating and interesting, maybe relevant and maybe not. And so even figuring out what’s relevant is tricky.”

Nancy challenges an oft-mentioned piece of conventional wisdom in the HD field - the idea that we've 'cured the mice' in many different ways, and the problem now is 'translating' those successes into human patients. "I think that we haven't had very much success in models, frankly. One thing that did work was gene silencing in mice."

One success Nancy considers convincing is a drug called SAHA, which Gill Bates first tested on HD mice in an HDF-supported study in 2002. The SAHA story is a good example of why progress in science can feel so painfully slow to the people waiting for the big breakthroughs.

SAHA was thought to restore normal gene switching, which goes wrong in HD. "The mice got better. And they improved their grip strength and they improved survival a little bit. But SAHA's toxic. Gill dedicated years of her life to studying how it worked."

Ten years later, Bates presented the latest results of her work at the HDF meeting where we met the Wexlers. "She just figured out it works by doing something in the cell - not in the nucleus where the DNA is. And she just presented that at our meeting, ten years later. And Gill does more work than anyone I've ever met in my life!" It's a vivid example of how long it can take from a discovery, to a fuller understanding of the mechanisms behind it.

So, bearing in mind the amount of work to be done, and the optimism surrounding recent progress towards effective treatments for Huntington's disease, what's the HDF's focus for the near future? "Push the envelope," volunteers Nancy with characteristic enthusiasm.

"We try not to put all of our eggs in one basket," adds Alice, "but also to not be all over the place. Gene silencing has been one approach we feel is worthwhile. Then there's the issue of biomarkers - how do you measure whether a potential treatment is actually working in humans - that's another big question. I also think because clinical trials are so expensive and so hard to do, that we really need to insist that the work is done properly in the mice"

Helping to move the best possible treatments into the best-designed clinical trials is a major focus, too. "We hold a lot of workshops looking at designing clinical trials," says Nancy.

The 'blue sky thinking' tradition of the HDF remains apparent in its work, too. The Foundation's biennial scientific meeting, where we met the Wexlers, is renowned among scientists as a place where exciting new ideas are presented and discussed. As well as big-ticket items like gene silencing techniques and the chemical tagging of the huntingtin protein, HDF-supported projects presented at the meeting included studies as diverse as what bacteria live in the gut of HD mice; new ways of rapidly measuring gene switching problems; studying the HD gene in fruit flies; and genetically engineering cells to produce antibodies to protect against the harmful mutant protein.

We finish the interview by asking what the next few years may bring for HD research. "It does feel to me like an historic moment," admits Alice. "But we don't know. I think we still face the balance between optimism and realism, in a way. Maintaining that balance to me is a big challenge."

When we ask what the next decade of HD research may bring, Nancy's answer is shorter, and rather beautiful. "I'll go to heaven and dance," she says, and smiles.

The authors have no conflicts of interest to declare. For more information about our disclosure policy see our FAQ...

Glossary

huntingtin protein The protein produced by the HD gene.

gene silencing An approach to treating HD that uses targeted molecules to tell cells not to produce the harmful huntingtin protein

CAG repeat The stretch of DNA at the beginning of the HD gene, which contains the sequence CAG repeated many times, and is abnormally long in people who will develop HD

aggregate Lumps of protein that form inside cells in Huntington's disease and some other degenerative diseases

nucleus A part of the cell containing genes (DNA)

R6/2 a mouse model of Huntington's disease. R6/2 mice have been genetically altered with an abnormal gene that makes them produce a harmful fragment of the mutant huntingtin protein

SAHA an HDAC-inhibitor drug. Its full name is Suberoylanilide hydroxamic acid.

RNA the chemical, similar to DNA, that makes up the 'message' molecules that cells use as working copies of genes, when manufacturing proteins.
