

Exciting News Update!!!!!!

Hereditary Disease Foundation Symposium

Changes, Advances and Good News (CAG)_n

August 12-15, 2004, Cambridge, Massachusetts

In August 2004, the Hereditary Disease Foundation (HDF) gathered over 300 scientists – most supported by the HDF – to share their latest findings on Huntington’s disease (HD). Over the course of an intense three days and some 196 presentations, researchers offered new insights into the significance of the aggregates (clumps of abnormal “huntingtin,” the protein made by the HD gene) found in the brains of HD sufferers. They presented new understanding of how mutant huntingtin disrupts communication between cells. And they discussed new possibilities for therapies, such as a technology called “RNA interference,” the use of intrabodies (like antibodies, only inside the cell), and a drug called tetrabenazine, which shows tremendous promise for the treatment of chorea. The meeting drew both long-time HD researchers and young investigators just entering the field of Huntington’s disease research. One hundred more investigators attended this August symposium than came to the meeting two years ago, another sign of the tremendous and growing effort focused on finding treatments for Huntington’s disease. Participants came from 15 countries and 21 U.S. States. They represented over 120 different universities, government organizations and pharmaceutical companies. These included Harvard, Columbia, MIT, Johns Hopkins, Duke, UCLA, UCSF, Caltech, Salk Institute, Oxford, Cambridge, King’s College London, University of British Columbia, NIH, FDA, Novartis, Prestwick Pharmaceuticals, Inc., Forest Laboratories, Inc., Trophos, Genzyme, Vertex Pharmaceuticals, Inc., EnVivo Pharmaceuticals, and Structural GenomiX, Inc.

Aggregates

While researchers have known for some time that mutant huntingtin misfolds and can form clumps called “aggregates,” they have disagreed about whether these aggregates make the cells sick or actually protect the cells from further damage. This debate continues, but investigators presented intriguing evidence that aggregates, at different times in their lifespan, can play distinct roles – a useful insight for designing therapies. The aggregates may be toxic at the beginning, when they are just being formed, and become protective later. Researchers also presented evidence that, while cells have natural means for disposing of aggregates, the large size of the HD clumps may overwhelm the cells’ ability to get rid of them. They described new leads in developing strategies for preventing clumps from forming in the first place, as well as ways of enhancing the “garbage disposal” capacity of the cell if aggregates do appear.

Cellular Traffic Jams

Participants also presented new information about how mutant huntingtin jams the internal roadways of the cell, interferes with growth factors critical for cell survival, alters release and response to neurotransmitters critical for communication between cells, and even changes the expression of other genes. They offered new evidence for how mutant huntingtin intrudes on energy metabolism by attacking mitochondria, the powerhouses of the cell.

Therapies and Clinical Trials

RNAi: One promising therapy discussed at the meeting is called “RNA interference.” This strategy aims to turn off the RNA of the HD gene so that the problematic protein is not made at all – or only a tiny amount (DNA makes RNA which then makes protein). RNAi already works in cell models and mouse models of HD. Researchers are now developing ways to use this methodology in human cells and creating techniques for getting RNAi into the brain. This is an exciting new avenue for possible gene therapies for HD.

Intrabodies: Another possible therapeutic strategy involves “intrabodies.” These are like therapeutic antibodies but they are inside the cell itself – ordinary antibodies cannot enter the cell. These intrabodies can recognize and attack mutant huntingtin, much like antibodies attack invading bacteria or viruses. Investigators presented studies showing that, in cell models and fruit flies with the mutant HD protein, intrabodies succeeded in rescuing damaged cells. Their findings suggest that intrabodies might also be effective in human cells to rescue neurons damaged by the abnormal huntingtin.

Tetrabenazine: The newest therapy on the horizon, presented at the meeting, is a compound called tetrabenazine, which has already proven to be an extremely promising drug for ameliorating chorea. Dr. Kathleen Clarence-Smith, CEO of Prestwick Pharmaceuticals, Inc., discussed the results of a collaboration between Prestwick and the Huntington Study Group, which concluded that tetrabenazine is far superior to other drugs for treating chorea and also has fewer side effects. Although it has been available in the United Kingdom and other parts of Europe for many years, tetrabenazine is not yet approved in the United States, a situation we hope to remedy very soon. Prestwick Pharmaceuticals is committed to making the drug available as quickly as possible. The Food and Drug Administration (FDA) has granted fast-track, orphan drug status to tetrabenazine, which should help facilitate a rapid launch for the drug in the United States.

Clinical Trials: We were fortunate to have at the meeting the director of the Office of Orphan Products Development of the FDA, Dr. Marlene Haffner, who encouraged investigators to contact her with new ideas. Dr. Haffner described the Office of Orphan Products Development Grant Program, a funding project within her division, to encourage clinical development of products and help researchers run clinical trials with drugs or devices for orphan diseases. She urged scientists to expedite the time between basic science discoveries and releasing a new drug on the market.

Joining Dr. Haffner in a panel discussion of clinical trials, other scientists described novel ways of designing and analyzing clinical trials to shorten the time required to get new drugs to clinic. They discussed combining phases of clinical trials to shorten the time involved, using “historical controls” (how people with HD fared in the past compared to being on a new drug), strengthening rules to end an unsuccessful trial, and using Bayesian statistics to design and analyze studies. They discussed how creative drug trial design and innovations in clinical trials could reduce time and cost, providing greater incentives for pharmaceutical and biotechnology companies to become involved. And with more experimental therapies to be tried, more people will be able to participate in clinical trials in the future. Most individuals with Huntington’s disease lament the current paucity of drug trials and look forward to this anticipated increase.

Sleep: Researchers showed how improved sleep in animals with the HD gene actually aided the animals’ learning and memory, and lessened involuntary movements. Both mice and humans with the HD gene have lower levels of a sleep-inducing protein called “orexin.” HD mice sleep badly, just like many people with HD, who often suffer day/night reversal. When the HD mice were induced to sleep more (with medication), their movements, learning and memory improved. Just as we were told – getting a good night’s sleep really does help, even if you are a mouse! This is another promising strategy that could have significant benefits for people with HD.

Biomarkers: Meeting participants discussed the urgency of creating tools, called “biomarkers,” that can indicate if an experimental drug works, without the necessity to complete a long, expensive study. For example, in testing cancer drugs, you can measure how much tumors shrink rather than wait to see if patients survive longer. But so far we have no comparable way of measuring improvements in people with HD. Biomarkers could be measured in the blood or in brain images from MRI, CT or PET scans. Participants emphasized the high priority of creating biomarkers to expedite clinical trials in the development of new symptomatic treatments and cures.

Despite the many challenges that remain, investigators at the meeting were extremely positive about the progress achieved and highly optimistic about the future. Though much work remains to be done, all participants agreed that the time is ripe to begin translating these findings into effective therapies and cures for Huntington’s disease.