The Hereditary Disease Foundation's Research Meeting: The Milton Wexler Celebration of Life.

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Once again, the HDF has put together an outstanding meeting with three full days of speakers presenting the latest research results and 207 posters with research results for participants to view and discuss. I came away feeling encouraged by all the progress that is being made and by the enthusiasm and sense of urgency demonstrated by the researchers.

Dr. Nancy Wexler welcomed participants while pictures of her family and HDF history played on a screen in the background. It has been forty years since her mother was diagnosed with Huntington's Disease and her father started the foundation. Of all the accomplishments in his career, Dr. Milton Wexler was most proud of the HDF workshops where researchers could share research findings, discuss new ideas and plan collaborations on future studies. He had hoped to live to see the cure and in his last days continued to talk with his daughters Nancy and Alice about promising directions.

Opening Session: The Huntington's Disease Experience, Then and Now

Dr. Alice Wexler spoke about her findings in researching her new book, *The Woman Who Walked into the Sea*. Alice writes from a historian's perspective and looks at the ways that the disease and the people who developed it were viewed throughout the country's history. The woman in the book title was Phebe Hedges from East Hampton; she committed suicide when she saw signs that she was developing the disease that had affected her mother. Her mother had been diagnosed with St. Vitus Dance (which is today known as Sydenham's Chorea), however, we know that it was Huntington's Disease because family descendants have Huntington's.

Although many assume that the disease has always caused people to be stigmatized, Alice found that Mrs. Hedges was well regarded in her community and family members held many leadership positions. There may have been some ridicule or disapproval, but the family was an accepted part of the community and family members were cared for at home.

Alice has researched the witchcraft connection that gained credence when a eugenicist with his own agenda claimed that some of those executed for being witches had Huntington's Disease. She found no evidence at all that this happened and indeed, if anyone with Huntington's Disease were present in a community where accusations were being made, they would have been far more likely to be considered a victim because of their involuntary movements.

Two family members spoke to the gathering. The first was a young man who wishes to remain anonymous to avoid genetic discrimination at work. He spoke about his family history of Huntington's, his positive gene test, and coping through religious faith, antidepressants, and the hope through research. "The hope for a cure," he said, "drives my life through almost unimaginable losses." He concluded by saying that the contributions of everyone who participates in the research process are important. When a cure is found, "Together, we will be part of the most exciting research achievement in the history of mankind."

The second speaker was Kevin Baker who wrote about his mother Claire's disease and his own positive test in the June 8, 2008 issue of the New York Magazine (http://nymag.com/health/bestdoctors/2008/47566/). He spoke about his mother's life and his own and noted that his mother, now in late stage HD, still says some things that resonate profoundly. Most recently she said, "I must go through the woods." This is true of everyone dealing with the disease, but hopefully through research, we will emerge into the clearing.

Both speakers received well-deserved standing ovations.

Dr. Steven Hersch spoke about treatments for Huntington's Disease. Caring for HD families is a cradle to grave enterprise. It is important to recognize that the movement disorder is only a small part of the disease and that cognitive decline, emotional disturbances, and nutrition problems must be addressed. He said that the HD community needs more and better symptomatic treatment, evidence based approaches to optimizing care, and disease modifying therapies.

Dr. Hersch discussed observational and clinical trials, past and present. The observational trials, which are still ongoing, are Pharos, Predict, Respond, the Venezuela Project, Cohort, Track-HD, and the HD Biomarker Collaboration.

There are completed and ongoing clinical trials designed to test whether a drug or supplement improves HD symptoms. One completed Phase III trial is TREND-HD, which tested ethyl-EPA on motor symptoms; they did not improve. Another was the tetrabenazine trial which has resulted in approval of the drug to treat chorea. There are ongoing trials for citalopram and atomoxetine; it is hoped that both of these will improve executive function. Currently enrolling is HART, a trial of ACR16, a dopamine stabilizer.

He discussed three completed trials of drugs hoped to be neuroprotective. Phend-HD tested phenylbutyrate, a drug designed to affect the dysregulation of gene transcription which occurs in HD. The drug is not currently moving through the research pipeline since additional, expensive animal research is required before a Phase III study could be approved.

DIMOND was a Phase II trial of dimebon, a drug which appears to act to strengthen the mitochondria. DIMOND is a symptomatic trial but the drug may also be neuroprotective and there may be future trials to show whether it can modify the disease itself. Phase III symptomatic trials are planned.

DOMINO was a futility trial for minocycline, an antibiotic which may inhibit apoptosis. This kind of trial is somewhere between a Phase II and Phase III trial and is designed to let the researchers know whether it is worthwhile proceeding to a final Phase III trial. The results of the DOMINO trial are currently being analyzed.

Two Phase III trials of supplements are currently recruiting. They are CREST-HD for creatine, which will have 650 participants and 2CARE for CoQ10, which will have 608.

Two trials are planned for those who are not yet symptomatic. Pre-CREST will enroll 70 people at risk for a trial of creatine. Prequel will enroll 90 pre-manifest participants for a trial of CoQ10.

An especially informative part of Dr. Hersch's talk was his list of ways that we can speed up the pace of the research. We need:

- More in vivo validations of hypotheses.
- More potent neuroprotection targets. Especially powerful would be those which target the HD protein itself.
- Phase II designs with efficacy readouts. If we had biomarkers, we would have better knowledge about which drugs should proceed to Phase III trials.
- Increase the pace of Phase II studies in premanifest and manifest HD.
- More Phase III studies. Again, we need biomarkers so that we can get more yes or no answers and fewer maybes about effectiveness.
- Test potential endpoint surrogates in available Phase III studies..
- First regulatory approval to set the bar for how to get there and make the market more concrete. [*Note: We have this for tetrabenazine, a treatment for chorea, but not yet for a neuroprotective treatment*.]

Imaging and Other Biomarkers:

Dr. Diana Rosas moderated a session on imaging and other biomarkers of Huntington's Disease.

A good definition of biomarker is the one used by the NINDS biomarker working group: "a characteristic that is objectively measured and evaluated as an indicator or normal biological processes, pathological processes (onset or progression), or pharmacological (pharmacodynamic) responses to a therapeutic intervention."

Dr. Rosas explained that biomarkers are needed because clinical measures are not sensitive enough. They don't take into account the clinical heterogeneity seen in patients and don't provide measurements appropriate for pre-manifest patients who will be participating in future trials of drugs designed to prevent or delay onset. It is currently taking too long to get find out if a potential treatment is effective. We now have so many compounds that might be effective based on assays and research with models, that we couldn't possibly have the resources to test all of them. Biomarkers will help with both target validation and prioritization of compounds.

Neuroimaging biomarkers have enormous potential since they are objective, reliable, and sensitive. Cortical thinning can be seen more than eleven years from predicted onset. It increases as onset nears, continues with the progression of the disease, and correlates with clinical assessment of the patient's functional capacity.

Neuroimaging studies are also showing that the different patterns of symptoms that are found from patient to patient are associated with differential patterns of cell loss in different areas of the brain. Neuroimaging would reflect the clinical heterogeneity seen in HD patients.

Dr. Rosas also presented data that showed that the volume of different parts of the brain declines before symptoms and with disease progression over time. These include the amygdale, the caudate, the hippocampus, the pallidum, the putamen, the thalamus, and the white matter of the brain in general.

Her conclusion is that Huntington's is a disease that affects the whole brain.

Modeling the disease:

A variety of models are used to study the disease and test potential treatments. There are a variety of cell models, drosophila (fruitfly) models, mouse models and now a rhesus monkey model and a sheep model. More work needs to be done on the latter two models but good progress is being made as reported in presentations from Dr. Anthony Chan and Dr. Richard Snell, respectively.

As Dr.Hersch pointed out in his presentations, treatments that work in a mouse model of the disease may not work in human patients. This has been true, for example, in ALS and stroke. We hope that our mouse models are better, but by developing a variety of models we maximize our chances of developing effective treatments.

Whatever model or technique is used for studying Huntington's Disease, a number of participants stressed the importance of understanding the disease from a systems perspective. It is important to understand what is happening in a cell in the presence of mutant huntingtin. New technologies which allow a cell model or even a living cell in an animal to be observed over time continue to lead to insights about the disease. However, the disease also affects how neurons signal to each other and how various parts of the brain communicate with each other such as the cortex and the striatum. It is also important to understand how the various regions of the brain are affected and the connection between what is happening in the brain over time and the progression of the disease.

Progress in reducing the expression of the HD protein

The HD protein with its expanded polyglutamine tract causes many pathogenic processes and HD now being regarded as a disease of the whole brain. There are compounds in current clinical trials which are thought to address some of these processes such as energy deficits and oxidative damage; hopefully they will delay onset and progression. Combinations of therapies may be even more effective. The complexity of this disease, however, makes the expression of the HD protein itself a very attractive therapeutic target with the potential to perhaps be a virtual cure.

Dr. Beverly Davidson, who is known for her pioneering work in RNA interference, reported on progress in RNA interference and antisense nucleotides, based on information presented at recent workshops.

Dr. Davidson cited Ai Yamamoto's conditional model of HD as supporting this approach. In this important 2000 study, Dr. Yamamoto (then a graduate student), showed how turning off the expression of the HD gene in a mouse model lead to substantial recovery.

There are four direct ways of reducing the expression of the HD protein:

- RNA interference (RNAi)
- Antisense oglionucleotides (ASO)
- Ribozymes
- Transcriptional silencing

The first two areas are where most of the research has been done. RNA interference refers to disruption of translation of messenger RNA by introducing a short, double stranded section of RNA which matches the target RNA. Depending on the type of double stranded RNA used the target messenger RNA is either degraded or its' translation is inhibited. Antisense oglionucleotides (ASOs) are small strands of DNA which, cause degradation of messenger RNA which match the DNA sequence.

There is considerable evidence supporting the effectiveness of both approaches. A variety of HD mouse models in different labs have improved through RNAi with both viral and non-viral delivery. ASOs have been approved for treatment of AIDS patients and have been helpful in mouse models of neurodegenerative diseases.

An important question in developing these kinds of treatments is whether techniques which silence the expression of both the normal and HD protein genes would be harmful. There is some evidence to suggestion that normal huntingtin protein is needed in the brain. However, it may be safe and effective to partially knockdown both alleles. Alternately, there has been good progress in developing ways to target expression of the HD gene while the normal gene continues to be expressed (allele-specific silencing).

Another issue is directing these therapies to the appropriate parts of the brain. Will the treatment be effective if they are directed solely to the striatum? The cortex? And if so, which parts of the cortex?

Caution is needed before moving forward with human clinical trials. Progress continues in improving safety. More animal testing is needed, including longer-term studies, and testing in primates will be necessary.

Dr. Davidson concluded, "It's early days yet, but it's an exciting time."

Protein Degradation and Clearance:

Another way to address the toxicity of the HD protein is to enhance protein degradation and clearance so that the mutant HD protein doesn't accumulate and cause damage. Assays have identified drugs which induce autophagy, a cellular house cleaning process in which damaged parts of the cell, pathogens, and large proteins are surrounded and consumed. Some of the drugs which have been identified are already FDA approved for other purposes.

Ongoing research by Joan Steffan and colleagues has identified two serines on the protein which, when phosphorylated, enhance its degration and clearance.

Pharmaceutical companies

Executives from two pharmaceutical companies gave keynote addresses.

Henri Termeer, Chairman and CEO of Genzyme Corporation talked about his company's history in developing treatments for rare lysosomal storage diseases. The first treatment took ten years to develop and now, twenty-five years later there are four approved treatments with a fifth in clinical trials.

Mr. Termeer offered encouraged to the participants, reminding them that academic scientists can do things that companies can't do. "All of you have ideas and people like me are looking for ideas."

Dr. Paolo Paganetti, senior research investigator at the Novartis Institutes for BioMedical Research in Basel Switzerland, informed participants about Novartis Pharmaceutical's program to develop treatments for Huntington's Disease. Novartis is collaborating with Massachusetts General Institute for Neurdegenerative Disease and MIT in an impressive commitment to develop treatments for the disease.

Novartis has developed high throughput assays to screen for compounds which rescue the dysregulation of gene transcription and for compounds which enhance protein degradation and clearance. The dysregulation of gene transcription is a major pathology in HD. Some genes are downregulated, some are upregulated; some of these changes occur early on and some later in the disease. It may be that the HD protein exerts direct effects but also that some changes in gene transcription are a result of the neurodegeneration itself. They have found 500 compounds with positive effects, and are now triaging. A key question in the research is which biomarkers will tell us that rescue of transcription has taken place.

Inducing protein degradation and clearance is a very promising therapeutic strategy. Two possibilities are Novartis's rapamycin analogue to induce autophagy and an inducer of heat shock transcription factor 1. Novartis has screened a million and a half compounds, found 5,000 preliminary hits, verified 2,000 and is continuing to triage.

Gene Transcription:

In addition to the work at Novartis, research on gene transcription is also continuing in other labs. Progress is being made in understanding how gene transcription is dysregulated in Huntington's Disease and how it can be restored.

One focus has been on the inhibition of histone deacetylases (HDACs). HDACs play an important role in regulating gene transcription and there is evidence that inhibiting them can restore the function of downregulated genes. However, multiple compounds which are known to be HDAC inhibitors have been tested and not found effective. The one that

has (SAHA) has a narrow therapeutic window and toxic effects. Gillian Bates and researchers in other labs have been working on narrowing the target to specific HDACs.

Other areas:

Research into other promising areas continues. As articles are published, we will be reading about studies identifying potential new biomarkers and studies investigating the therapeutic potential of caspase 6 inhibition, stem cells, phosphorylation of the HD protein, and a variety of drugs identified for the research pipeline from high throughput assays.

Summary and Conclusions:

The goals of the HDF's meetings are to share ideas and research findings, and develop collaborations. Some of the research findings are preliminary and/or unpublished and can't be included in this report. However, I have tried to give an overview of how the research has advanced and I will be better prepared to cover the new studies when they are published.

The research is cumulative and collaborative. Many of the questions raised by researchers at the HDF conference two years ago have been answered as a result of ongoing work and collaboration by teams of scientists in various labs around the world. As an HD family member, I was encouraged at the level of collaboration and the enthusiastic discussion of ideas and findings. Some speakers even updated power point presentations at the last minute to take into account new findings discussed at the conference.

The research has been carried out with funding by the National Institute of Health, the Hereditary Disease Foundation, HDSA, CHDI, the High Q Foundation, and other foundations. We are also seeing more involvement by pharmaceutical companies, a very welcome development.

Much progress has been made in the last two years. More is known about HD pathology and the normal functions of the huntingtin protein and a lot of work has been done to identify and validate targets for drug discovery and development. High throughput screening has identified a number of drugs that might become treatments. Steady progress has been made in the development of techniques to target the HD protein while maintaining expression of the normal protein.

Basic research continues to be important. Evidence for nearly 300 different pathological processes in Huntington's Disease has been presented in at least one research paper over the years. Research is still need to identify which processes are indeed pathogenic and not compensatory or harmless, which are early events and which occur downstream, how they fit together, and which are most critical to address with treatments. Most important for the HD patient community is the narrowing of therapeutic targets to increase efficacy and reduce side effects.

Although basic research needs to continue, enough is known about Huntington's Disease for some clinical trials to be already underway. In the longer term, the ongoing basic research is likely to pay off with the development of drugs which precisely target a variety of pathologies and which have, either singly or in combination, even more potential to prevent or delay onset and/or slow disease progression. At the same time, progress continues with methods to reduce the level of the mutant huntingtin's protein such as RNA interference or antisense drugs which may have the potential to function as virtual cures.