

Convention Research Notes – Research Forum

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The attendees were welcomed by **Louise Vetter** who urged people to answer the questionnaire from Project Aware which was available in the exhibition hall on computers and on paper. Without clinical trials, we will not have treatments and researchers need to know why potential participants choose to participate or not. The questionnaire can be found here: <http://surveys.supersurvey.com/survey-bin/surveys/s33876.pl>

A **video about HD research** was shown. Various researchers spoke: James Gusella, Ira Shoulson, Robert Pacifici, Don Lo, Marian DiFiglia, Michael Hayden, Marc Guttman, Neal Aronin, Chris Ross, Elena Cattaneo, and Leslie Thompson. HD was described as a model genetic disease to research since understanding HD should also lead to insights about other neurodegenerative diseases. A number of researchers talked about the unusual degree of collaboration in HD, modeled by the Coalition for the Cure. In addition, patients and families are partners in the research. Treatments are coming but in the words of Dr. Hayden, the effort is a “marathon and not a sprint.”



Dr. Rick Morimoto, Dr. Steven Finkbeiner, and Dr. Marcy MacDonald

Moderator **Marcy McDonald** talked about how **far we've come in the last 25 years.**

- 1872 described
- 1967 CCHD/HDSA formed
- 1983 HD gene mapped
- 1993 HD gene identified
- 1996 First HD mouse models
- 1997 HDSA Coalition for the Cure

- 2001 PREDICT HD begins
- 2004 HDSA Coalition forms targeted teams
- 2004 HDSA partners with CHDI and HP
- 2005 COHORT begins
- 2005 REGISTRY begins
- 2008 TRACK HD begins
- 2008 Human iPS cells
- 2009 PREDICT HDv2 begins
- 2010 5 Year PHAROS HD completed

From 150 to 200 laboratories are now working on HD. Every researcher knows other researchers and they get each other involved.

Rick Morimoto spoke about **Unlocking the Huntingtin Mysteries**. Huntington's Disease is caused by an expansion of the CAG repeat sequence. Aggregation is an invariant consequence of CAG expansion, not just in HD but in other polyglutamine diseases as well. Aggregation is a sign that protein homeostasis has been disrupted.

Proteins are essential constituents of the cells. They are the key subunits of molecular machines of life. However, they are highly sensitive to their environment and readily go awry. The cell has chaperones and other defense mechanisms to protect against misfolded and damaged proteins but they become less efficient over time. Consequently, proteins are very much at risk during aging. A promising therapeutic strategy is to restore protein homeostasis.

Researchers have been able to restore protein homeostasis in model systems with a variety of methods. Proteins are ancient and similar across organisms. One animal that has been useful for HD research is the nematode *C. elegans*. It has a three week lifespan. Using this model system, Dr. Morimoto has been able to identify genes that suppress aggregation.

Dr. Morimoto is part of the Coalition for the Cure team that is working on protein homeostasis. Other members are Gill Bates, Dave Borchelt, Ron Kopito, and Erich Wanker. Over one million compounds have been screened. The goal is to find small molecules that will restore protein homeostasis and develop them into safe and effective drugs.

Steve Finkbeiner spoke about the **Applications of Induced Pluripotent Stem Cells**. Dr. Finkbeiner's lab along with four others (Marcy MacDonald, Jim Gusella, Leslie Thompson, and Clive Swenson) are part of the NINDS HD iPS Consortium.

Induced pluripotent stem cells are adult cells which have been preprogrammed to 'turn back the clock' to become stem cells again. One possible use for iPS cells is as replacements for missing cells. There are several obstacles to overcome first. The first is production; a large number of cells would be needed. The second is the need to insure survival. It may be that the cells would come under attack by the immune system. The

third is safety. Stem cells can divide indefinitely so there is a possibility that they could produce tumors. The fourth is the difficulty of making sure that the cells become the right type of neuron. The fifth is getting the cells to talk to each other, to 'wire' correctly.

The second use of iPS cells is to improve the way drugs are screened as potential treatments. Because these are human cells with the disease, the effectiveness of assays should increase. The use of second generation robotic microscope techniques allows for rapid testing of thousands and thousands of potential treatments in a short period of time.

The third use of the iPS cells is to help researchers better understand the mechanisms of the disease.

Dr. James Gusella spoke about **genetic opportunities in observational studies.**

Observational studies are exactly that -
- observing what is going on without changing things or introducing anything. Examples include COHORT, PREDICT-HD, and TRACK-HD.



Individuals with HD vary in age of onset as well as the kind, severity, and order of appearance of symptoms. If there is a symptom that changes at a particular rate without much individual variation, this would be a good measure for clinical trials.

Without observational trials, all we have is information from doctors, most of whom will not see a large number of HD patients. We need more detail than they can provide.

Although the CAG count is negatively correlated with the age of onset, two individuals with the same CAG count can have an onset that is 40 years apart. Dr. Gusella and other researchers are looking for genetic modifiers that influence an earlier or later than average age of onset. These genetic modifiers should be good clues to effective treatments. It should be possible to find them using DNA from observational studies but thousands of participants will be needed.

Mice can teach us a lot about biochemical effects of the HD mutation and they can be used as a first test of potential drugs. Because mice are mice, mice tend to teach us more about what's important to mice as opposed to teaching us what's important to people. Observational studies of people have advantages both for the patient and the researcher.

Advantages of doing observational studies to the patient:

- The course of their disorder can be followed over time by expert HD clinicians.
- They can contribute to improving the ability of the research community to design and carry out the most effective clinical trials to test potential treatments for HD

- The information gathered in the observation study can indicate that they have the characteristics needed for participation in a clinical trial to test new medicines for HD.

Advantages to the researcher:

- More efficient, more effective clinical trials.
- Clues to the fundamental mechanisms that operate during the course of HD = clues to new targets for treatment
- Clues to differences between individuals in the symptoms that develop, the timing with which they occur and the rate with which they progress.
- Biological samples (DNA, cell lines and biological fluids) to investigate HD at the molecular level.
- Because of rapid advances in the technical tools for performing genetic studies in humans, it should be possible to find these genetic modifiers using information and DNA from the HD observational studies.
- Since modifier genes alter the course of HD in human patients, they may provide direct clues to effective treatments.

The power of these studies is directly related to how many people participate in the studies. Dr. Gusella urged the audience to participate in these studies.



Dr. Jane Paulsen spoke about **PREDICTing Care – the Value of Pre-Diagnostic Observation**. She thanked the many participants in the study. Another 80 participants are needed each year so there are still opportunities to join the study. In addition to doing assessments of cognition and motor function and the MRIs, they are now working on measuring psychiatric problems.

In the nine years that the study has been operating, it has achieved the following results:

- Able to reduce the sample size for pre-HD clinical trials
- Identified markers 15 years prior to diagnosis.
- Developed a database of scans, bloods, DNA, phenotypic assessment
- Data is used to develop the models of disease.
- Facilitated the collaboration of clinical research teams, papers, presentations, new investigators, additional grants
- Policy statement for disability legislations.
- Diagnostic consensus conference planning.

Your participation keeps the science moving forward.

Dr. Robert Pacifici spoke about **Clinical Horizons: An Update on Therapeutic Directions.** Dr. Pacifici is the Chief Scientific Officer for CHDI which is a very special biotech company. Their mission is to rapidly discover drugs that delay the onset or slow the progression of Huntington's disease. CHDI is a not for profit biotech company. The bottom line is time, not money. It is foundation funded with about 80 million spent each year. It is exclusively dedicated to HD



CHDI utilizes the virtual or outsourced model. They do not have their own labs. All experimentation is done via collaboration with other labs.

CHDI's goal is to 'get the whole world to work on HD.' To that end they have focused on:

- Collaborative enablement – providing funding, reagents, an informational website, etc.
- Lowering the barriers for entry into HD research
- Leveraging integrated biotech firms
- CHDI driven targets

CHDI's outreach to pharmaceutical companies has created new interest in HD. Pharmaceutical companies have thousands of compounds on the shelf which are not being used as drugs. CHDI will screen them while the company retains the rights to them. Each compound may have ten to fifteen years of research going into it so if something is promising for HD, they have a jumpstart.

Why is it taking so long to develop treatments? Instead of using old compounds, CHDI is working to develop new chemical entities for novel targets.

Right now there are sixteen full speed ahead projects, five which have been discontinued as ineffective, and more that are just getting started.

Several drugs are being optimized including an HDAC inhibitor and targets which target KMO (kynurenine 3-monooxygenase) TG-2 (tissue transglutaminase), JNK3 (C-June N-terminal kinases), Sirt1, caspases, and PDHK (pyruvate dehydrogenase kinase).

Inhibiting Histone Deacetylase 4 (HDAC-4) is looking like a promising target. Crossing HD mice with mice missing HDAC-4 results in significant increase in survival time.

The most validated target is of course the HD protein itself. There are several approaches to this, RNAi, zinc finger proteins which target a DNA sequence, and antisense. In addition, they are also researching safe methods of delivery.

CHDI is working with Isis to develop antisense therapy for HD: The objective is to identify an antisense oligonucleotide based therapeutic that reduces the levels of huntingtin in the brain. At this point there are some unknowns and uncertainties but it is possible that if all goes well, clinical trials could start at the end of 2011.

There are several drugs nearly the stage where an Investigation Drug Application (IND) will be filed. These include a CoQ10 analogue, an autophagy inducer, and a pro-cognitive compound.

Autophagy is a means of clearing the cell of damaged proteins. They are working with Link Medicine to research their compound LNK574. This compound, which upregulates autophagy, was developed as a cancer treatment.