

## Exciting News Update!!!!!!

### Hereditary Disease Foundation Symposium HD 2006: Changes, Advances, and Good News (CAG)<sub>n</sub>

August 10-14, 2006, Royal Sonesta Hotel, Cambridge, Massachusetts

Summary prepared by Marina Chicurel, Ph.D.

#### Summary

Two years ago, the Huntington's disease community was impressed with the magnitude and scope of the "HD 2004: Changes, Advances, and Good News (CAG)<sub>n</sub>" meeting. Over 300 scientists, giving 196 presentations, attended the meeting—100 more than the previous meeting two years earlier. Remarkably, the number of attendees and presentations grew again in 2006: over 360 scientists participated, giving 230 presentations. Equally impressive was the scientific progress achieved in two years, ranging from a greater depth of understanding of the mechanistic underpinnings of HD to new clinical advances.

A major lesson emerging from this year's meeting was the importance of context. The focus of many studies in HD research has been understanding how the expanded polyglutamine region that characterizes mutant huntingtin triggers misfolding and toxicity. However, as underscored at this meeting, there are many non-polyglutamine determinants of toxicity. Participants presented data indicating that intramolecular, intermolecular, intracellular, timing and genetic contexts play key roles in shaping HD pathogenesis. Non-polyglutamine sequences within huntingtin, as well as the presence and conformational state of other cellular proteins are important. Also, huntingtin's aggregation state is key for determining toxicity. Two years ago, the physical diversity of aggregates was discussed; this year, distinct physiological effects, including detrimental and beneficial ones, were correlated with the presence of specific aggregate forms. Furthermore, a major step in identifying genetic modifiers of HD was reported.

The extent of the contributions of cell autonomous mechanisms versus cell-cell interactions in HD pathology was another fundamental question addressed at the meeting. In 2004, a few observations suggested a potential role for cell-cell interactions. This year, new findings strongly bolstered this proposal, implicating alterations in synaptic transmission and corticostriatal trophic support. In addition, the likely importance of cell types that do not display visible signs of degeneration, particularly glial cells and interneurons, was underscored.

Participants also offered new insights into the transcriptional dysregulation associated with HD. For example, a link between transcriptional dysfunction and mitochondrial pathology was identified. In addition, studies of histone post-translational modifications in HD provided clues as to how histone deacetylase inhibitors, discussed as therapeutic candidates in 2004, might exert their effects. Other HD-associated pathologies examined at the meeting included bioenergetic alterations and the interaction of mutant huntingtin with cellular clearance systems.

In addition, participants expressed a renewed appreciation for comparisons of HD to other neurodegenerative disorders, particularly those with repeat expansions. For example, the potential implications of studies indicating that bidirectional transcription across repeats and RNA-mediated toxicity may contribute to pathology in myotonic dystrophy, spinocerebellar ataxia type 8, and Huntington's disease-like 2 were discussed. Although the contribution of these processes to HD remains unknown, preliminary data suggest antisense transcripts are generated from the mutant huntingtin gene.

Important advances in therapeutic approaches presented in 2004 were also reported. For example, participants described advances in the optimization of delivery, stability and safety of RNAi molecules to reduce the expression of mutant huntingtin. Addressing a major question in the application of this approach, new findings indicated that silencing wildtype, in addition to mutant, huntingtin in adult organisms does not appear to have major deleterious effects. The feasibility of inducing the specific knockdown of mutant huntingtin was also discussed. At the protein level, participants described recent advances in the development of intrabodies, antibody fragments against huntingtin which can alter misfolding kinetics or interfere with mutant huntingtin's access to other cellular components. Cystamine's potential as a therapeutic candidate was re-visited, and potential advantages of its reduced form, cysteamine, were noted. Furthermore, the 2004 examination of dopamine antagonists was extended noting these compounds' potential neuroprotective effects. Also, an update on the status of one of the small molecules identified in an anti-aggregation screen described in 2004, C2-8, was presented.

Participants also reported on several new candidate compounds and targets. For example, a compound that increases cellular ATP levels and one that inhibits chaperone function, show promise for decreasing mutant huntingtin toxicity. In addition, the anti-apoptotic factor XIAP was reported to confer neuroprotection and amelioration of motor symptoms in cell and animal models of HD. The sirtuins, a class of histone deacetylases that may help link metabolic rate to aging, were also discussed as therapeutic targets. Another promising new approach involves the stimulation of neurogenesis by adenoviral delivery of brain-derived neurotrophin factor (BDNF), together with Noggin, an inhibitor of the signaling pathway involved in astrocyte genesis. This treatment resulted in the reduction of motor symptoms and increased survival in a mouse model of HD.

Two therapeutic candidates in clinical trials, creatine and cell transplantation, were also discussed. Cell transplantation has yielded some positive results, but it is in the early stages of testing and several technical and theoretical challenges remain to be addressed. The creatine studies suggest that high doses of the compound have therapeutic effects, but larger studies are needed to confirm the findings.

Participants also discussed the identification of biomarkers of HD progression. Confirming predictions made in 2004 regarding the potential use of brain imaging techniques to monitor HD, this year, imaging of cortical thinning emerged as a powerful biomarker to streamline clinical drug trials. In addition, an update of the PREDICT-HD project suggests that cognitive tests have the potential to reveal improvements in pre-symptomatic clinical trials. Advances in the potential use of neuropeptides as biomarkers were also presented. Moreover, 'omics' approaches yielded important new data. For example, a transcriptomics study suggested that gene expression patterns can be used to classify HD progression states. In addition, a metabolomics study revealed the importance of taking gender into account when searching for biomarkers of disease.

The development and use of new tools to answer key questions in HD was also described. For example, a system that automatically monitors the fates of cells over time and correlates the risk of death or dysfunction with other cellular parameters was presented. The system should help sort the myriad alterations observed in HD into causal relationships, compensatory changes, and epiphenomena. In addition, participants described new models of HD, including stem cell-based and conditional mouse models in which mutant huntingtin can be selectively turned on or off in specific cell types. Results illustrating the power of a biolistics-based slice model of HD to evaluate candidate drug targets were also presented. Moreover, participants were informed of the ongoing COHORT project which will generate a widely available source of biological samples from HD families linked to a longitudinal database including neurological data, as well as medical and family histories.