

## **World Congress on Huntington's Disease 2005 Executive Summary**

The World Congress on Huntington's Disease convened in Manchester, England from September 11<sup>th</sup> to 13<sup>th</sup>, 2005, attracting more than 450 scientists, clinicians, researchers, advocates and family members from around the world. The symposium preceded a meeting of the International Huntington's Association (IHA), which was also held in Manchester.

The Congress opened with a plenary address by Sir Peter Harper, in which he recounted the history of Huntington's Disease (HD) and discussed how progress over the past 25 years has positioned HD as a model for medical genetics, genetic counseling, and genetic prediction.

Other plenary sessions were organized around the themes of pathogenic mechanisms, genetics, clinical markers, new treatments for HD, and clinical management. Concurrent sessions provided additional information on these topics as well as on experimental therapeutics, genetic counseling and testing, and late stage care. Overall, the Congress provided a broad and deep perspective on the current state of HD research and care, and energized participants about prospects for the future.

### Pathogenic mechanisms

In his plenary address on pathogenic mechanisms, David Rubinsztein suggested that the HD mutation induces a series of parallel and largely independent pathogenic pathways that may provide therapeutic targets. Only experiments will show which pathways are dominant, and thus most important therapeutically, he said. The root of the problem is the production of a mutant protein with expanded polyglutamine. Understanding the pathway for both production and degradation of this protein has been a focus of many research groups. Degradation of the protein, for example, yields toxic fragments that go on to aggregate in neurons. Thus, prevention of fragment or aggregate formation are two possible targets. Michael Hayden's group has focused primarily on the pathways that yield fragments and their toxic consequences.

Why the toxicity is concentrated in the striatum is another major question that has been investigated by many groups around the world. Jeremy Van Raamsdonk presented

evidence suggesting that nuclear localization of the mutant protein may be necessary to cause degeneration, and that this process may occur preferentially in the striatum. Other scientists discussed other biochemical or genetic modifications of the protein that may explain the differential toxicity seen in various brain regions.

Degeneration is also seen in other brain regions such as the cerebral cortex. Richard Faull presented evidence showing that whether a patient exhibits primarily mood or motor symptoms correlates with the pattern of cell loss in different brain regions. Areas of the brain that are most affected in HD patients also show other changes, such as dysregulation of gene expression. Several research groups reported studies identifying the genes that are most dysregulated in HD brains, how these changes may influence symptoms, and whether transcriptional dysregulation might itself be a therapeutic target.

Other pathogenic mechanisms were also discussed. Kerry Murphy examines the mechanisms that underlie the cognitive decline seen in HD. His studies in mice suggest that treatment with the neurotransmitter dopamine may alleviate some of the cognitive symptoms. Åsa Petersén presented research showing that degeneration may also result in neuroendocrine changes, which may be targeted to treat cognitive decline, weight loss, and sleep disturbances.

There is also evidence, discussed by Elena Cattaneo, which suggests that the normal HD protein with non-expanded polyglutamine may have a neuroprotective function that is lost when the normal protein is supplanted by mutant protein. Studies of the inhibition of this neuroprotective pathway have identified additional targets that may lead to therapeutic agents.

### Genetics

The genetics of HD have also perplexed scientists. Although the mutation itself is well defined and is known to be present in all cells of the body, why it expresses itself only in certain cells and late in life is unknown. Geneticists have developed numerous genetic animal models that reflect aspects of human disease and which are being widely used to understand HD pathogenesis. Jim Gusella discussed the advantages and disadvantages of these various models. He also described studies of genetic factors other than expanded polyglutamine that may influence symptomatology. In a mouse model that

includes the entire human HD gene, for example, Marcy MacDonald has identified a second mutation that influences the age of onset of disease.

Other geneticists are examining instability of the polyglutamine expansion over the lifetime in both human and animal models. This phenomenon, called somatic instability, may affect symptomatology. Finally, also in the field of genetics, Amanda Krause presented data about a group of patients who clinically appear to have HD but who have a mutation different from the mutation most commonly associated with HD. This disorder has been called HD type 2 (HDL2) and occurs in some patients of African ancestry.

### Experimental therapeutics

The search for compounds that ameliorate the disease process continues even as scientists debate the pathogenic mechanisms involved. Moreover, the search for experimental therapeutics itself reveals clues about mechanism. Erich Wanker, for example, described high throughput screening studies of compounds that inhibit aggregation; while Leslie Thompson's lab uses cell and fruit fly models to search for compounds that inhibit aggregation or reduce the toxicity of aggregates. Compounds have also been tested that target transcriptional dysregulation, production of the mutant protein, and other biochemical effects of the mutant protein. Combination therapy is also being tested in these models. Gill Bates' lab continues to work on standardizing protocols for testing drugs in the R6/2 mouse model.

### Clinical Markers

The identification of biomarkers of disease would greatly facilitate the search for new treatments. Elizabeth Aylward described her studies using neuroimaging to track disease progression. Measurement of striatal volume by magnetic resonance imaging (MRI), she said, fulfills most of the requirements of a biomarker: It can be reliably and objectively measured; it changes in a predictable manner over time; it can predict onset of symptoms; and it is associated with a known mechanism of pathology.

Other potential biomarkers were also discussed, including PET (positron emission tomography) imaging of A<sub>1</sub> adenosine receptors (A<sub>1</sub>AR) or microglial activation. Clinical

markers, however, continue to be the most commonly used for monitoring disease progression. While CAG repeat length has traditionally been considered only a marker of whether or not a person has HD (i.e., a trait marker), Adam Rosenblatt suggested that repeat length may also affect response to therapy and thus should be factored into the analysis of treatment trials.

#### Clinical trials and new treatments

Several ongoing or completed clinical trials were discussed, including the recent Euro HD trial of riluzole, which showed no significant benefits; and a preliminary trial of ethyl-EPA, which suggested the need for further study. The TETRA-HD study of Ethyl-EPA, which is being conducted by the Huntington Study Group (HSG) and in parallel by Euro HD, was also introduced. Karl Kieburtz presented a broad overview of pharmacologic therapies that have been tested for use in HD.

Newer, innovative approaches to treating HD were also described. Hank Paulson discussed RNA interference (RNAi), in which a gene can potentially be “turned off.” Steve Dunnett described transplantation cell therapies that attempt to repopulate degenerated areas of the brain with healthy brain cells. This strategy has been used with some success for treatment of Parkinson’s disease and is being studied in North America and Europe for HD.

#### Genetic counseling and testing

Several speakers discussed various aspects of predictive testing, including the controversial areas of testing children and preimplantation genetic diagnosis. There were also discussion of the psychological effects of predictive testing on at-risk individuals and their partners and family members.

#### Clinical management

Anne Rosser described the broad, multidisciplinary approach needed for the care of HD patients using both non-pharmacologic and pharmacologic treatment strategies, and taking into account family and domestic issues as well as the specific physical and psychological symptoms of the patient. Among the specific potential problems facing HD

patients, psychiatric disorders, and other mental health problems were discussed. Other speakers discussed the risks to quality of life faced by those who care for individuals with HD; and the need for guidelines and research about late stage care, advanced directives, residential care, and nursing home care.

Martha Nance provided a comprehensive overview of the clinical care and management of patients with HD throughout all stages of their illness.

#### Future directions

Anne Young concluded the Congress with an overview of the scientific sessions and comments about the future. She called this a time of “paradigm shift,” where the HD community is no longer looking only at what might be the mechanisms of the disease but also at biomarkers that will facilitate more efficient development of treatments, and at effective therapies to delay onset as well as treat symptoms. As the Congress clearly demonstrated, there is a great deal of activity currently underway ranging from genetic and neuropathologic studies to clinical therapeutic trials and clinical studies aimed at developing a clearer understanding of the natural history of the disease.