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Untangling huntingtin's mysteries

We have reached a critical juncture in the search for a cure for Huntington disease (HD), and nowhere was this more apparent than in Boston recently at the annual research conference sponsored by the Hereditary Disease Foundation (HDF, www.hdfoundation.org), Huntington Disease 2000: Changes, Advances and Good News (CAG). The symposium provided a forum for the expanding community of Huntington researchers to share their latest results. A rather unique format—talks were kept short (usually no more than 10 minutes), candid and to-the-point by the prodding and charisma of chairpersons Anne Young and Allan Tobin, and more than ample time was provided for questions and lively group discussion—a welcome departure from the lengthy and stale presentations that seem to dominate many scientific conferences. Although many fundamental questions regarding the pathogenesis of the disease are still unresolved, powerful new tools and strategies are being developed, and several promising new therapeutics have been identified—a mere seven years after the discovery of the Huntingtin gene.

The open, interactive nature of the symposium is in large part a legacy of the founder of the HDF, famed Los Angeles psychologist Milton Wexler. Wexler's charm and Hollywood connections were critical to the assembly of the foundation's Board of Trustees, which includes such notables as Carol Burnett, Julie Andrews and architect Frank Gehry. A non-profit, basic science organization dedicated to the cure of HD, HDF directs an impressive 100% of all publicly donated funds to the support of biomedical research; the trustees pick up the tab for administration. Formed in 1968, the HDF organized the Venezuela Collaborative HD Project, which led to the identification in 1983 of a genetic marker for the disease. The foundation also oversaw the HD Collaborative Research Group, which in 1993 zeroed in on the disease gene—one of a newly identified class of disease genes whose signature is an excess of trinucleotide repeats.

The focus has now shifted to the huntingtin protein and specifically the mutant form that incorporates an expansion of a polyglutamine tract within its first exon, a result of the additional trinucleotide repeats. Although the identification of marker and gene was rapid, the protein has been much more refractory to giving up its secrets. The pay-off of unraveling its mysteries could be great, however, as HD is only one of a group of related diseases characterized by an expanded polyglutamine tract. Despite its mammoth size (approximately 350 kDa), huntingtin comprises surprisingly few recognizable functional domains, providing few clues as to its function. Moreover, its ubiquitous expression belies the uniquely neuronal pathology conferred by the mutant protein. The lack of understanding of wild-type huntingtin function, although frustrating, is not as serious a problem as one might think. Polyglutamine repeats themselves are toxic to neurons and have been shown to give rise to neuronal pathology in animal models. It is now well-established that the repeats mediate aggregation of their 'host' protein, and this aggregation appears to trigger the cascade of events leading to cell death. Just how this occurs is still under intense study, but data presented in Boston point to altered protein-protein interactions both with and within the amyloid-like huntingtin aggregates, and support therapeutic strategies based on an inhibition of this aggregation.

Nevertheless, this 'toxic aggregates' or 'gain-of-function' model of polyglutamine repeat diseases does not predict the idiosyncratic nature of the different neuronal pathologies, and investigators are turning to the wild-type protein for clues. Striatal neurons are selectively vulnerable to mutant huntingtin, and workers are also examining more closely both molecular and phenotypic changes in these cells. Changes in gene transcription profiles, caspase pathways and neuronal electrophysiology have all provided powerful new leads.

If the molecular details of the mechanism of neuronal death in HD are slowly being untangled, it is due in no small part to the strongly proactive role the HDF has taken in exploiting their financial resources to attract a diverse set of bright new investigators into the field. Cases in point are cell death researchers Robert Friedlander and Junying Yuan, both contacted and actively recruited by the HDF within the last few years. Friedlander's group reported that activation of caspase 1 accompanied HD pathology (*Nature* **399**, 263; 1999) and recently found that the caspase inhibitor minocycline could delay mortality in a transgenic mouse model of HD (*Nature Med.* **6,** 797; 2000). The compound will be tested soon in HD patients in a phase I/II clinical trial. Yuan's group identified caspase 8 as a mediator of polyglutamine pathology, but have more recently turned their attention to the identification of small molecules that inhibit polyglutamine repeat aggregation in murine models of HD.

Through the active recruitment of new ideas, new technologies and new researchers, the HDF has set the stage for important progress in our understanding of HD pathology in the near future. Their commitment to collaboration and community building within the HD field serves as a model for all scientific groups tackling human diseases.