



Huntington's Disease Foundation

Dedicated to Research

Milton Wexler Interdisciplinary Workshop

With support from the Parvin Foundation

Huntingtin Structural Biology and Proteostasis: Molecular Mechanisms of PolyQ-Mediated Aggregation and Protein Quality Control

Public-Facing Workshop Report

Prepared by Dr. Leora Fox, Fox Scientific Consulting

*The Huntington's Disease Foundation (HDF) held a workshop **January 9-10, 2026** in **Santa Monica, California**, which brought together leading scientists from inside and outside of the Huntington's disease (HD) field to discuss huntingtin (HTT), the protein at the heart of the disorder. HDF's workshops are a model long recognized for speeding research discovery by promoting discussion and data-sharing among colleagues in a relaxed and collaborative environment. Workshop participants delved into the structure and function of the HTT protein, its many forms and roles within the cell, how it is labeled and re-formed over time, and how it is removed, with attention to how this knowledge can drive the development of therapeutics.*

A family perspective

To kick off the workshop, Dr. Yvette Bordelon, a neurologist, interviewed a woman with symptomatic HD, and her husband, who shared their family's experience with HD. They discussed her diagnosis and primarily movement-based symptoms, and spoke candidly about balancing openness and privacy, parenting two at-risk teens, and navigating genetic testing. The wife emphasized her interest in clinical trial participation, the challenge of navigating information, and the value of supportive care and physical activity.

Discussion topics and goals

Day 1 of the workshop focused on huntingtin (HTT) structure and function, and Day 2 on how HTT is broken down (degradation) and how its expansion may influence the protein balance inside of cells (homeostasis). The discussion touched on various lengths, forms, structures, and species of HTT, their roles within the cell, how they bind together into potentially toxic clumps (aggregates), and "tags" that modify their function and properties. Participants discussed published and unpublished data from their laboratories, applying many established and emerging techniques to query how HTT interacts with other proteins, how it assembles into structures and is degraded by cellular machinery, and the influence of different lengths of CAG repeat expansion, the underlying genetic alteration that causes HD.

Throughout the workshop, the meeting co-chairs emphasized key goals: identifying remaining questions in the field and gaps in knowledge, and brainstorming collaboratively to fill them.

Big-picture questions guiding the discussion

- What are participants each studying individually, and how can they collaborate?
- What tools are needed to better answer these questions?
- What can be learned from other similar disorders?
- Which disease models are most relevant to answering these questions?
- How can findings be translated into therapeutics?

Age-old questions, challenges, and novel insights

Over the course of the workshop, participants shared insights from their own research and the literature, highlighting how the field continues to grapple with some of the most fundamental questions about HD and HTT: Why and in what form is HTT toxic, what are normal functions of HTT, and how does CAG repeat expansion lead to cell death and disease symptoms?

Despite progress, researchers face technical and conceptual hurdles, including the difficulty of studying an enormous and sometimes unstable gene and protein. They acknowledged that existing models do not fully capture all aspects of HD, and that results can vary across species and systems. Identifying the most important aspects of HTT's structure, function, and potential toxicity remains complex.

Despite these challenges, the discussion revealed questions which can finally be explored, thanks to emerging technology and collaborative momentum fostered by the workshop. These include determining the location of HTT within cells, visualizing how aggregates and other HTT structures form and behave dynamically, understanding the relationship between aggregation and CAG repeat expansion, and studying donated human brain tissue using modern molecular and computational tools. In learning about how peers inside and outside of the HD field are applying new techniques and information, researchers came away with ideas for new experiments, plans for cohesive publications, and commitments to follow-up conversations.

Future tools and strategies

Participants emphasized that progress in HD will depend on developing and sharing emerging tools to study HTT forms that are most relevant to human disease, including cells that have the full-length form of the protein with long polyglutamine (polyQ) repeats and methods to distinguish different forms of HTT. Improved methods to visualize HTT in living cells, analyze brain tissue, and thoughtfully apply AI-based tools were seen as especially promising. These advances could help researchers better understand where HTT is in the cell, how it changes over time, and which forms are most closely linked to disease symptoms.

Equally important were strategies to improve collaborative efforts across the field. Participants discussed the value of shared standards for models, reagents, and data interpretation, as well as new efforts to explore historical findings with modern tools. Many also emphasized the importance of shared resources and digital forums that would make it easier to exchange data, test ideas across systems, create easier entry for researchers new to HD, and tackle the field's most persistent questions.

Conclusions and next steps

This workshop reinforced how much we have learned about the HTT protein and helped to define questions that still remain. The HDF will use these insights to help guide its support for collaborative efforts that apply innovative approaches to the study of HTT and HD, while maintaining a commitment to centering the lived experiences of affected families.