The Hereditary Disease Foundation's HD2024: Milton Wexler Biennial Symposium brought together almost 300 of the world leaders in Huntington's disease research in what proved to be a meeting filled with exciting research, hope, and inspiration.

Young Investigators in the field of HD research began a day early with a workshop modeled on those that the HDF initiated decades ago fueling ideas to advance HD research. These Young Investigators shared research findings and initiated exchanges that will be used to build collaborations and advance gaps in current work. Discussions focused on many aspects of HD research, including genetic modifiers, somatic instability, biomarkers, disease progression, and therapeutics. 2023 HDF Transformative Research Award recipient Dr. Beverly Davidson joined the meeting to discuss the successful navigation of the path to tenured positions, which is critical to ensure the future of HD research and clinical trials. HDF has long supported the careers of Young Investigators and early-stage researchers through postdoctoral fellowships and is proud to continue this mission, providing a network through which these talented scientists can build relationships, establish collaborations, and drive HD research into the future.

HD2024 kicked off on Wednesday evening with two keynote talks, one delivered by Dr. Fyodor Urnov covering CRISPR therapeutic advancement for HD and a clinical trials update from Dr. Ed Wild. Compared to the somber messaging of the 2022 meeting when the conference was held shortly after the announced failure of three huntingtin-lowering clinical trials, the opening talks of the 2024 conference were an invigorating dose of hope and optimism with the realization of just how far we've come in two short years. Dr. Urnov shared that in 2023 the world learned about Casgevy, the first regulatory agency-approved CRISPR treatment for Sickle Cell Disease and Beta Thalassemia, which paves the way for using CRISPR-based drugs to treat other diseases, including HD. Dr. Wild treated the audience to a deluge of positive HD clinical trial news that the community has had in just the first quarter of 2024, with positive data announcements from *five* ongoing clinical trials.

The first full day of the conference opened with an HDF tradition – an interview between a neurologist and one of their patients living with HD. Not only is this interview the first time many of the researchers have met someone living with HD, giving them a true sense of what HD is and how it affects someone's life, but it also opens the meeting by solidifying what everyone is working for and motivates them to continue to put countless hours into their research.

The remainder of day 1 was filled with exciting talks that discussed the function of the wild type version of the huntingtin protein, the effect of the CAG repeat in somatic expansion, and the effects that HD has on the brain, which are similar to what is observed in other brain diseases. To learn from other fields, the group heard a keynote talk from Dr. Ed Lein, who has created an atlas of cells from the human brain for Alzheimer's disease. This has allowed that field to deeply understand the effects of the disease and map vulnerable and resilient cell types, something that the HD field hopes to do.

Day 2 dove deeper into HD biology, with research talks related to pathogenic contributions across cell types in the brain, somatic instability and DNA repair, and RNA dynamics. Day 3 moved toward the clinic, with talks from both academia and industry on pre-clinical studies as well as clinical physiology. HD has, excitingly, caught the attention of drug developers, who are showcasing their

trial-related research at various therapeutics conferences. HD2024 proudly highlighted up and coming pre-clinical research and approaches from both academia and industry that will fill the trial pipeline in the coming years.

As the inaugural year for HDF's Transformative Research Awards (TRA) was just last year, HD2024 brought the first occasion to feature the work from the awardees. The TRAs are the largest award mechanism the HDF has ever supported, with grants of up to $1,000,000 given over two years for work that will significantly move the needle toward a disease-modifying treatment for HD. The audience heard from both 2023 TRA recipients. Dr. Ricardo Mouro Pinto shared his work on gene therapies targeting molecules that control somatic expansion. Dr. Beverly Davidson wowed the crowd with stunning images that show impressive penetration of her novel viral delivery system to deep structures of the brain at very low doses. Both teams are working to advance their research toward the clinic. You can learn more about their work in our recent HDF Research Spotlight Webinars.

The Hereditary Disease Foundation presents two awards annually to recognize extraordinary scientific work – the Leslie Gehry Prize for Innovation in Science and the Nancy S. Wexler Young Investigator Prize. The Leslie Gehry Prize for Innovation in Science recognizes scientists who have made extraordinary contributions to the field of Huntington's disease research. The Nancy S. Wexler Young Investigator is presented to an early career researcher whose work reflects the highest caliber of excellence, diligence, and creative thinking.

HD2024 highlighted the work of the 2023 Nancy S. Wexler Young Investigator Prize winner Dr. Chiara Scaramuzzino. She shared her work in understanding how molecules move differently down the long axons of neurons when they're affected by HD, which contributes to the breakdown in communication between brain cells. At HD2024, the 2024 Wexler Prize was awarded to Dr. Rachel Harding for the collaborative spirit she embodies while successfully driving her research as a structural biologist forward, focusing on defining the structure and function of the huntingtin protein. Dr. James Gusella received the 2024 Leslie Gehry Prize for his monumental role in helping to map the gene that causes HD and define modifiers of age of symptom onset through the GeM-HD Consortium. Few people have changed the research landscape of HD as much as Dr. Gusella and the HDF is honored to support his inventiveness and imagination that have been used to shift paradigms and lead to new advances in seeking a cure for HD.

Additionally, there were HD-focused scientific writers at the 2024 conference. HDBuzz was back this year to live tweet updates to the HD community in real time, as data was being presented throughout the meeting. HDBuzz is a trusted source for high-quality HD research news and clinical trial data, written in plain language, by HD clinicians and scientists. If you were unable to catch the updates live or would like to learn more, you can go to the HDBuzz website. Researchers were also joined by Dr. Ken Serbin, aka Gene Veritas, who writes the blog *At Risk for Huntington's Disease*. Ken's coverage of the conference will include two articles related to the meeting on his website, which you can visit to read more.

HDF's 2024 meeting began with a swell of hope from recent trial updates and clinical approaches, was punctuated with bold new ideas to fill the clinical trial pipeline, and ended with the realization that the field of HD research is in a very different position than it was just two short years ago – a very positive position! It seems that as the number of pharmaceutical companies in the HD space increases, so too do the number of ideas that can be used to approach the problem of this disease. As we march forward together in our battle against HD, it's clear that treatments are on the horizon.