The Hereditary Disease Foundation held a topic-specific workshop focused on "Cell-Type Specific Biology in Huntington's Disease" in Santa Monica, CA, from January 30-31, 2024. This was the HDF's second workshop in 4 months, signifying the revival of an HDF tradition that had been inactive for a decade. HDF workshops have served as an uncommon, visionary model that led to the discovery of the causal gene for HD. These workshops promote conversational research discussions to share ideas, establish collaborations, and advance the field's understanding of complex problems. The workshop brought together 20 of the world's leading experts on cell-type specificity from both academia and industry that work on Huntington's disease (HD) as well as other diseases and disorders. Attendees included senior researchers as well as trainees in postdoctoral and graduate student positions. Following an interview-style discussion with an HD family member, workshop participants delved into deep discussions surrounding neuropathology, selective vulnerability of certain brain regions and specific cell types, and big picture discussion to synthesize the group's understanding of where we are and what needs to be done next to get us to a treatment for HD.

A Huntington's disease advocacy champion

The meeting opened as all previous workshops have, with someone directly impacted by HD sharing their story. We were joined by Dr. Kenneth Serbin. In 1995, on the cusp of turning 36, he received a letter about his mother's HD diagnosis, having never heard of the disease. Ken started going to support groups immediately, stating at the workshop that finding support has been a key component of his journey. With genetic discrimination in mind, both Ken and his daughter (prenatally) tested anonymously. In 2005, he began sharing his journey in a blog, entitled "At Risk for Huntington's Disease," CureHD.blogspot.com, under the pseudonym Gene Veritas. Through this lens, he became a voice for the community and was able track the progress of HD research. His blog has registered a positive trend: HD research has actually become more difficult to follow as it has gained momentum, with more people joining the field and a large increase in the number of HD-related publications. Ken went public with his story in 2011 with a keynote address at the annual CHDI HD Therapeutics Conference. He mentioned that "coming out of the HD closet" allowed him to advocate fully for this disease. Ken spoke about his mother's more rapid trajectory with this disease; even though they both have 40 CAG repeats, she experienced onset in her late 40s, dying at age 68, whereas he has reached 64 still able to function. He strongly feels that finding purpose and meaning in life have been instrumental in stalling his own disease onset. A key theme of his talk was that knowledge is power – knowing about HD before it was at his doorstep was an advantage that his mother didn't have. He cited the hope that comes from having HD-specific treatments that weren't in the field 30 years ago when the focus was on "treatments" like Coenzyme Q10 and creatine. He urged the workshop participants to continue to diversify targets – having those that directly target HTT as well as other potential targets that may get us to a cocktail treatment. Ken also celebrated the collaborative nature

of HD research, noting that at meetings HD researchers leave their egos at the door for keep their focus solely on making research advances.

Ken wrote about his experience at the HDF workshop in his blog, which you can find **HERE**.

Day 1 focused on cell-type specific differences in neuropathology, for the purpose of AAV therapeutic delivery, and selective vulnerability of striatal medium spiny neurons.

There were several key points raised during the morning session of day 1, which included 1) understanding temporal changes of disease progression, 2) the lack of an organized collection of HD brains for systematic neurodissection, and 3) the need for a central brain bank repository. There were differing opinions on the need for defining temporal disease progression to advance therapeutics. While some felt this is critical for understanding disease pathology and progression for therapeutic advancements, others postulated that the field could better serve the patient community by focusing on what is needed to understand disease mechanisms that could improve aspects of the disease compared to what is needed for developing a cure for HD. The conversation included ways to address some of these gaps, such as alternative methods for assessing rare and precious human tissue that would extract as much information as possible.

The afternoon sessions of day 1 focused on the selective vulnerability of striatal medium spiny neurons with discussions about how we can increase the granularity of techniques to identify cellular subtypes within this brain region. Species-specific differences in cell type were explored along with regional differences observed across models and diseases. The group postulated on the determinants for vulnerability and if these are driven intrinsically or extrinsically for medium spiny neurons. The role of somatic instability and the relationship of expansion to cell type-specific death was raised.

Day 2 focused on the role of cortical and other neuronal cell types in HD pathogenesis, non-neuronal cells in HD (astrocytes, oligodendrocytes, microglia, and BBB cell types), and a big picture breakdown of cell type specificity in HD.

The morning of day 2 started with discussions around CAG expansions and cell death. While expansions don't appear to be sufficient to cause cell death since cells that don't die also expand (i.e. Betz cells), expansion does appear to be coupled to transcriptional dysregulation. As in day 1, there was also talk of the need for a central repository for HD brain tissue coordinated by a collaboration between biologists and neuroanatomists. The debate about findings from animal models vs human tissue also continued, with a discussion about the requirement of CAG repeat expansion for transcriptional dysregulation. While the relationship between the two appears linked in human tissue, in mice transcriptional dysregulation can occur without expansion. When looking across diseases to spinocerebellar ataxias, multiple mechanisms have been identified as regulating pathology in a cell type-specific manner, so models driving pathology in one cell type may differ from those driving pathology in another. The morning session also included a discussion on the role of non-neuronal cell types in HD pathology.

The afternoon of day 2 began by continuing the discussion from the morning on the role that non-neuronal cell types play in HD pathology with a specific focus on cell types of the BBB. As changes at the BBB precede overt disease changes in various neurodegenerative disease, causality was raised. Transcriptional profiling of the BBB suggests endothelial cells have homeostatic dysregulation because of HD and have alterations in proteins responsible for barrier fidelity. The workshop ended with a big-picture discussion where workshop participants shared how they think about cell specific changes in HD, what experiments need to be done, and what treatment approaches all this points toward. These conversations will be used by the HDF so that we can catalyze these ideas to target for future funding and workshops.