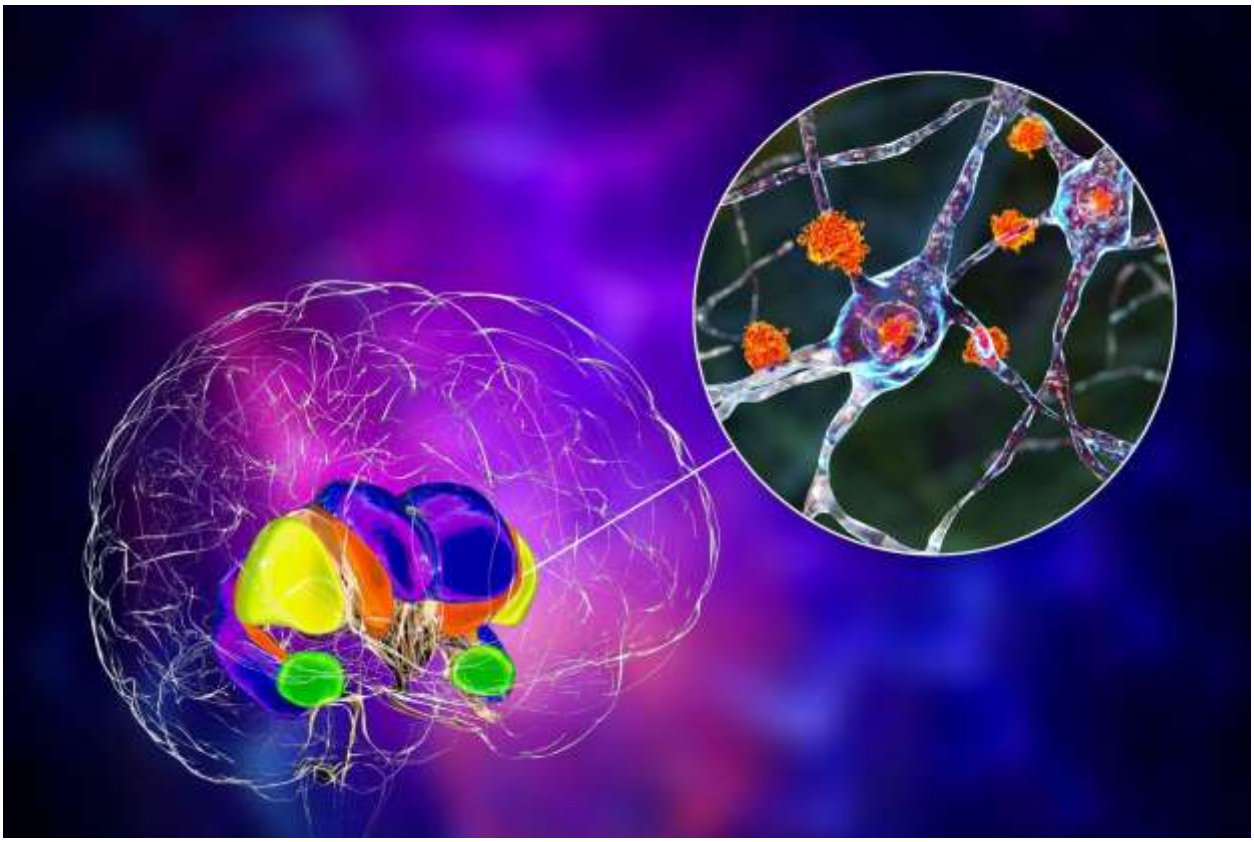
Encouraging Progress in the Hunt for a Huntington's Treatment



Described as a combination of Alzheimer's disease, Amyotrophic lateral sclerosis, and Parkinson's disease all at once, Huntington's disease is a rare and debilitating neurological disorder passed down within affected families. With a 50% chance of a child inheriting it from a parent with the HD mutation, the fatal disease often leaves a devastating family legacy.

In the United States alone, there are approximately 40,000 people with symptomatic Huntington's disease, and more than 200,000 are at risk of inheriting it. The disease causes nerve cell degeneration in the brain, leading to cognitive, psychiatric, and movement disorders. Symptoms usually appear between the ages of thirty and fifty, including difficulty with thinking and planning, lack of impulse control that can result in outbursts, involuntary movements (chorea), and impairment of voluntary movements, making work, communication, and daily activities extremely challenging. The symptoms worsen over time, often resulting in dementia and the inability to walk, speak, or feed oneself.

Huntington's disease: A toss of the coin

Jim Pryce and his family began their journey with Huntington’s disease when his mother was diagnosed with it in 1977. Jim chose to get genetic counseling and tests, and initial

tests were inconclusive but looked reassuring. However, fifteen years later, Jim began experiencing symptoms, and newer, more accurate genetic tests confirmed that he did, indeed, have Huntington's disease. By this time, Jim and his wife Barbara had four daughters.

The Pryce sisters said the most challenging part of watching their dad have Huntington's disease was the personality change. He became irritable, even mean, but looking back, they think he was likely embarrassed he could no longer care for himself. His crumbling dexterity and balance meant he could no longer continue working as a physical therapist, and after being let go, Kimberly Pryce said he shut down.

In 2003, Kimberly began considering having children and wanted to know her genetic status. All of Jim's daughters eventually chose to get tested. A flip of the coin, that's how Kim described getting tested for Huntington's disease (HD). She and her three sisters each had a 50% chance of living with a progressive, life-threatening brain disease they, in turn, could pass to their children, or they could be completely fine.

With the coin toss underway, three of the sisters landed on heads: their results were negative, and they had not inherited the disease. However, Erin Pryce, the youngest sister, landed on tails. She said that when their dad was diagnosed with HD, they were told that if any of them tested positive, there would be a treatment by the time they were old enough to have symptoms. Erin said she didn't buy this promise.

The symptoms only worsen with time and often lead to dementia and the inability to speak or feed oneself. Patients eventually succumb to pneumonia, heart failure, or other complications, with death typically occurring 10-30 years after the initial symptoms. After decades of battling the disease and receiving supportive care, in 2015, surrounded by his family, Jim Pryce died.

Unfortunately, the promise of a treatment has not yet been realized, but Erin remains active and is focusing on raising money, awareness, and participating in trials. She does not plan to have children. "The disease didn't end for our family when we lost my grandmother, and it didn't end with my father," she said. "But it will end with me."

The root of Huntington's disease: an extra-long, toxic protein

The disease is caused by a mutation in the huntingtin gene responsible for making the huntingtin protein. Typically, the huntingtin gene (*HTT*) has a specific sequence and stretch of the DNA bases cytosine-adenine-guanine (CAG) that's repeated 9-35 times. However, those with HD have an expanded version of CAG repeats, which produces an extra-long, toxic huntingtin protein (mHTT). It is hypothesized that the body degrades the abnormal protein, but over time, mHTT proteins accumulate and clump together in brain cells, causing neurons to degenerate and eventually die, leading to the symptoms seen in Huntington's disease.

While there are currently no disease-modifying treatments, scientists are looking at different approaches to lower the HTT protein levels in people with HD. Although there

have been some setbacks, recently there have been many positive results from early clinical trials.

Previous setbacks in HD therapies: modest but inconsistent results

Wave Therapeutics had a setback in 2021 when its Phase 1b/2a trials for Huntington's disease yielded disappointing data. The results for the antisense therapies — WVE-120101 and WVE-120102 — showed modest but inconsistent reductions in mHTT protein, prompting the company to shelve the therapies. The announcement came only one week after Roche halted its Phase 3 trial in HD patients for its antisense drug, tominersen.

Tominersen was designed by Ionis and developed by Roche to treat HD by targeting the HTT messenger RNA, preventing it from producing the huntingtin protein, which lowers the concentrations of all forms of it and thus slows the disease progression.

While tominersen's Phase 1/2a trial showed it to be generally safe and able to effectively lower concentrations of mHTT in the cerebrospinal fluid, its subsequent Phase 3 GENERATION-HD1 trial was halted on the advice of an Independent Data Monitoring Committee (DMC). Intended to determine safety and efficacy in a larger group and if it improved symptoms; the results showed that the high-dose group was doing worse than the placebo group on some measures.

However, in January 2022, Roche announced the tominersen research program would continue with a new Phase 2 trial in younger adults with early and subtle symptoms. The company stated that a new, exploratory post hoc analysis of the GENERATION-HD1 trial suggested that low exposure to tominersen may benefit younger adult patients with a lower disease burden and that tominersen at lower levels avoids NfL increases above baseline while still lowering CSF mHTT and has the potential to lower NfL. According to information shared at this year's August Hereditary Disease Foundation conference, the clinical trial, called GENERATION HD2, has begun and is now at ~75% enrollment of trial participants, with 15 sites open in six countries, and is planned to take place across more than 70 locations in 15 different countries. GENERATION HD2 is different from its predecessor studies in that it will involve lower doses of 100 or 60 mg versus the 120 mg used in previous trials; it will also have a reduced dosing frequency and not use a loading dose.

Tominersen is not the only candidate in clinical trials. In the last six months, a spate of other pharmaceutical companies, including PTC Therapeutics, Skyhawk Therapeutics, UniQure, and Wave Life Sciences, announced the results of their early clinical trials.

PTC Therapeutics: favorable results announced

After displaying favorable clinical trends in a mid-stage study, this June, the FDA lifted a partial clinical hold on HD drug candidate PTC518. The FDA had put a clinical hold on PTC518 in October 2022 after requesting more data to support the drug dosing and duration proposed in the 12-month study. However, in a press release at the time, the company stated, “there have been no treatment-related adverse events reported in the

US or outside of the US," and the 12-month PIVOT-HD trial proceeded in Australia and several European countries.

PTC518, created by PTC Therapeutics, is an mRNA splicing modifier that can be taken orally and reduces the production of the mutated huntingtin protein. This splicing modifier has been designed to modulate splicing of the *HTT* pre-mRNA, resulting in the inclusion of an inducible pseudoexon that contains a premature termination codon. This causes a nonsense mutation that leads to rapid *HTT* mRNA degradation, preventing the production of full-length HTT protein.

The favorable results showed lowered mHTT levels in participants' blood by 22% and 43% at 5 and 10mg doses, respectively. Patients mHTT levels in the CSF were also reduced by 21% at the 5mg and 43% at the 10mg dosage. Favorable trends were also found in clinical assessments, including Total Motor Score and Composite Unified Huntington's Disease Rating Scale.

PTC518 was also well tolerated, with no treatment-related serious adverse events or reports of peripheral neuropathy. The most common adverse events were nasopharyngitis, influenza, headache, and falls, which were experienced across all treatment groups, including placebo.

Skyhawk Therapeutics: positive results in Phase I trial

Skyhawk Therapeutics clinical trial for SKY-0515, its small molecule candidate targeting HD, recently announced positive results for parts A and B of its Phase I clinical trial, evaluating the drug in healthy volunteers.

SKY-0515 is an investigational small-molecule RNA splicing modifier similar to PTC518, the experimental small molecule described above. SKY-0515 was designed to reduce the RNA expression of both the HTT protein and PMS1 protein and to slow disease progression. PMS1 protein is another key driver of HD pathology and somatic CAG repeat expansion, so it is possible that reducing PMS1 protein in addition to HTT protein could have greater therapeutic benefit.

The multiple ascending dose trial revealed an average HTT mRNA reduction of 72% at a daily oral dose of 9mg and was safe and generally well tolerated at all doses tested. Recruitment has begun for part C, a double-blind, placebo-controlled, parallel design study of two dose levels of SKY-0515 in individuals with early-stage HD.

WVE-003: safe and well-tolerated, with statistically significant results

On June 25th, 2024, Wave Life Sciences shared their clinical trial results for WVE-003, a therapy designed to treat Huntington's disease (HD).

WVE-003 is an allele-selective antisense oligonucleotide (ASO) designed to lower the mutant huntingtin (mHTT) protein and maintain the healthy, wild-type huntingtin (wtHTT) protein. Wave says the drug is expected to address approximately 40% of individuals with HD.

Tominersen, AMT-130, and PTC518 lower the levels of both regular and expanded HTT. The approach of Wave Life Sciences, however, only targets the expanded form of HTT while leaving the regular form unchanged.

The Phase 1b/2a SELECT-HD trial had a single-dose group consisting of 45 people who received a single shot of the drug at various doses and were followed over almost 90 days, as well as a multi-dose group composed of 23 people who received three repetitions of the lowest dose given at eight-week intervals and were tracked for nearly 200 days. Both groups had a placebo control group who received spinal taps that did not administer the drug.

In the single-dose group, the participants' side effects were the same as those receiving the placebo, suggesting a safe dosing regime and well-tolerated drug. Patients in the multi-dose group receiving the drug experienced more mild and moderate side effects. No serious adverse events were observed at 30mg for either group.

Significant drops in mHTT protein were observed throughout the 28-week assessment of the multidose group. At 24 weeks, the mean mHTT lowering in cerebrospinal fluid (CSF) was 46% compared to placebo. At 28 weeks, the mean mHTT lowering was 44% versus placebo, supporting quarterly or less frequent dosing.

The wild-type huntingtin (wtHTT) protein was preserved during the assessment period, validating allele-selective silencing. Additionally, statistically significant increases were observed in wtHTT protein versus placebo. This could be positive news, demonstrating that WVE-003 seems only to be changing the levels of the expanded HTT protein while leaving the regular HTT levels stable.

The trial also examined neurofilament light protein (NfL) levels, a biomarker of brain health. NfL levels often increase over time in patients with HD. The trial found that many patients treated with the drug had similar changes to their NfL levels as those receiving the placebo, but others had NfL levels that increased above the 95% CI in placebo. Of these, some patient's NfL levels decreased by the end of the study, while some patients' increases remained. However, the significance is not understood at this time.

All trial participants were monitored with clinical evaluations, MRI brain scans, and spinal fluid samples at regular intervals. The MRI scans examined if a brain region called the caudate changed over time, as it typically becomes smaller in people with HD. The trial found that those in the multi-dose arm of the trial seemed to have slightly less change in their caudate size over time. Nevertheless, these findings were not statistically significant and need further examination in subsequent studies.

Additionally, the trial evaluated Total Motor Score (TMS), which assesses movement symptoms in HD patients. A higher score means more advanced symptoms, but the data found a slight decrease in TMS for people in the trial receiving WVE-003 for just over six months compared to the placebo. However, a more extensive study is needed to evaluate potential clinical outcomes.

Wave's next step is to create a clinical development path for WVE-003 to support a potential accelerated approval and to submit its opt-in package to program partner Takeda.

UniQure: expected to meet with FDA for expedited clinical approval

In July, therapeutic company UniQure announced updated interim data for the ongoing U.S. and European Phase 1/2 clinical trials of its drug, AMT-130, designed to treat HD. At 24 months, a statistically significant, dose-dependent slowing in disease progression was found in patients receiving the high dose of AMT-130.

The investigational gene therapy is the first one-time administered treatment to enter clinical testing for the treatment of HD. AMT-130 is given once by neurosurgical procedure and works by using a vector to deliver a gene encoding miRNA that will recognize, bind, and non-selectively lower the human huntingtin protein.

Patients receiving high-dose AMT-130 showed an 80% slowing of disease progression in the composite Unified Huntington's Disease Rating Scale (cUHDRS) at 24 months compared to a propensity score-weighted external control. Additionally, a statistically significant lowering of CSF neurofilament light protein (NfL) compared to baseline at 24 months in patients treated with AMT-130 was found. The drug was generally well-tolerated, with a manageable safety profile at both doses.

The drug was granted the first-ever Regenerative Medicine Advanced Therapy (RMAT) designation for Huntington's disease, and the company expects to meet with the FDA in the second half of 2024 to discuss the potential for expedited clinical development and accelerated approval.

Data-Driven Progress: the path to treating HD

Many additional efforts in preclinical research add to the clinical work to date, and with tominersen being tested in patients with lower disease burden, as well as many additional investigational agents being tested in early trials that are beginning to report some positive results, the HD community is offered tentative hope. Regardless of the outcomes, the data obtained from these trials is invaluable, bringing us closer to finding safe, effective treatments for HD.