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Huntington's disease – V. Research and Latest Developments

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Abstract

There is currently no cure for Huntington's disease (HD) and no treatment proven to delay the onset or slow the progression of the disease. This Article discusses current research into the action mechanisms of HD. Since HD is caused by a single dominant gene encoding a toxic protein, gene silencing and autophagy rate increase will be considered with aim to ameliorate the disease by reducing the production and levels of the mutant protein.

Several approaches will also be analyzed regarding neuronal survival and replacement. Inhibitors of ferroptosis will be indicated as protective in degenerative brain disorders, including HD. Potential future HD treatments and the associated clinical trials will be reviewed in detail. Lastly, latest research developments from supporting Huntington organizations will be summarized.

Abbreviations

AD: Alzheimer's disease; ASO: Allele-specific oligonucleotide; BBB: Blood-brain barrier; CAG: Cystosine-Adenine-Guanine; Cas: CRISPR-associated system; CNS: Central nervous system; CSF: Cerebrospinal fluid; CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats; CT: Clinical trial; CUHDRS: Composite Unified Huntington's Disease Rating Scale; DNA: DeoxyriboNucleic Acid; FDA: (U.S.) Food & Drug Administration; FIH: First-in-human; HD: Huntington's disease; HDI: Histone deacetylase inhibitors; HSG: Huntington Study Group; HTT: Huntington gene; Htt: Huntingtin protein; IHA: International Huntington Association; mHtt: mutated Htt; OLE: Open-label extension; PD: Parkinson's disease; PDI: Phosphodiesterase inhibitors; RNA: Ribonucleic acid; SMCI: Single-molecule counting immunoassay; TMS: Total motor score; wtHtt: wild-type Htt.

Keywords

Clinical trials; ferroptosis; gene silencing and autophagy; huntingtin protein production; Huntington action mechanisms; Huntington treatments; neuronal survival and replacement.

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As discussed in previous Articles in this series, HD is a rare inherited, progressive, incurable, and fatal neurodegenerative disorder of the central nervous system. It is caused by a defective gene characterized by an excessive number of trinucleotide (Cystosine-Adenine-Guanine) repeats - a part of the DNA code. The gene produces a protein of unknown function named Huntingtin, which is involved in the functioning of the nerve cells in the brain (neurons). When defective, the gene produces an abnormal or mutated form of this protein, which is toxic and causes selective loss of neurons. Notwithstanding the existence of several approved therapies for specific disease symptoms, there is currently no cure and there are no approved drugs that delay the onset or slow disease progression. There are, however, many new therapeutics currently undergoing clinical trials that target the disease at its origin by lowering the levels of the mutated protein.

Current research directions in HD research include determining the exact mechanism of the disease, improving animal models to aid with research, testing of medications and their delivery to treat symptoms or slow the progression of the disease, and studying procedures such as stem-cell therapy with the goal of replacing damaged or lost neurons. These several threads will now be explored.

Research into the action mechanisms of HD

Research into the action mechanisms of HD is focused on:

- Identifying the functioning of the Huntingtin protein (Htt);
- Determining how the mutant protein (mHtt) differs or interferes with Htt; and
- Understanding the brain pathology that the disease produces.

Research is conducted using in vitro methods, genetically modified animals (also called transgenic animal models), and human volunteers. Animal models are critical for understanding the fundamental mechanisms causing the disease and for supporting the early stages of drug development.

The identification of the causative Huntington's gene (HTT) has enabled the development of many genetically modified organisms including nematodes (roundworms), Drosophila fruit flies, and genetically modified mammals including mice, rats, sheep, pigs, and monkeys that express mHtt, and develop progressive neurodegeneration with HD-like symptoms.

Research currently being conducted uses many approaches to either prevent HD or slow its progression. In this regard, disease-modifying strategies can be broadly grouped into three categories:

- **Reducing the level of the mutant huntingtin protein (mHtt):** This includes gene splicing and gene silencing;
- **Improving neuronal survival:** This is accomplished by reducing the harm caused by the protein to specific cellular pathways and mechanisms (including protein homeostasis and histone deacetylase inhibition); and
- **Replacing lost neurons:** Developing strategies to accomplish this purpose.

In addition, novel therapies to improve brain functioning are under development; they seek to produce symptomatic rather than disease-modifying therapies, and include phosphodiesterase inhibitors

(PDI).

Reducing Huntingtin Production

Since HD is caused by the single dominant gene (HTT) encoding the toxic protein (Htt), gene silencing aims to reduce the production of the mutant protein (mHtt), Gene silencing experiments in mouse models have shown that when the expression of mHtt is reduced, symptoms improve.

The safety of RNA interference, and allele-specific oligonucleotide (ASO) methods of gene silencing has been demonstrated in mice and the larger primate macaque brain. Allele-specific silencing attempts to silence mHtt while leaving wild-type Htt untouched. One way of accomplishing this is to identify polymorphisms present on only one allele and produce gene silencing drugs that target polymorphisms in only the mutant allele. Begun in 2015, the first gene silencing trial involving humans with HD tested the safety of IONIS-HTTRx. It was produced by Ionis Pharmaceuticals and led by University of California in Irvine, Institute of Neurology.

Using a novel "single-molecule counting immunoassay" (SMCI), mHtt was detected and quantified for the first time in cerebrospinal fluid (CSF) from HD mutation-carriers. It provided a direct way to assess whether huntingtin-lowering treatments are achieving the desired effect. A phase 3 trial of this compound, renamed Tominersen, sponsored by Roche Pharmaceuticals, began in 2019 but was halted in 2021 after the safety monitoring board concluded that the risk-benefit balance was unfavorable.

A huntingtin-lowering gene therapy trial, run by Uniqure, began in 2019. Several trials of orally administered huntingtin-lowering splicing modulator compounds have since been announced. Gene splicing techniques are being looked at to try to repair a genome with the erroneous gene that causes HD, using tools such as CRISPR/Cas9.

Increasing Huntingtin Clearance

Another strategy to reduce the level of mHtt is to increase the rate at which cells are able to clear it. As mHtt (and many other protein aggregates) are degraded by autophagy, increasing the rate of autophagy has the potential to reduce levels of mHtt and thereby ameliorate disease.

Pharmacological and genetic inducers of autophagy have been tested in a variety of HD models, many of which have been shown to reduce mHtt levels and decrease toxicity.

Improving Cell Survival

Among the approaches aimed at improving cell survival in the presence of mHtt are:

- **Correcting transcriptional regulation:** This uses histone deacetylase inhibitors (HDI);
- **Modulating huntingtin's aggregation;**
- **Improving metabolism and mitochondrial function;** and
- **Restoring synaptic function.**

Neuronal Replacement

Stem-cell therapy is used to replace damaged neurons by transplantation of stem cells into the affected regions of the brain. Experiments in animal models (rats and mice only) have yielded positive results.

Whatever their future therapeutic potential, stem cells are already a valuable tool for studying HD in the laboratory.

Ferroptosis

Ferroptosis is a form of regulated cell death

characterized by the iron-dependent accumulation of lipid hydroperoxides to lethal levels. ALOX5-mediated ferroptosis acts as a cell death pathway upon oxidative stress in HD.

Inhibitors of ferroptosis are protective in models of degenerative brain disorders, including Parkinson's disease (PD), Huntington's disease, and Alzheimer's disease (AD).

Clinical Trials

Clinical trials (CTs) are prospective biomedical or biobehavioral research studies on human participants designed to answer specific questions about biomedical or biobehavioral interventions, including new treatments (such as novel vaccines, drugs, dietary choices, dietary supplements, and medical devices) and known interventions that warrant further study and comparison. They are part of clinical research at the heart of all medical advances. They look at new ways to prevent, detect, or treat diseases by new drugs or new combinations of drugs, new surgical procedures or devices, or new ways to use existing treatments. They can also look at other aspects of care, such as improving the quality of life for people with chronic illnesses. Their goal is to determine if a new test or treatment is safe and effective. Some CTs involve healthy subjects with no pre-existing medical conditions, others pertain to people with specific health conditions who are willing to try an experimental treatment. Pilot experiments are conducted to gain insights for design of the CTs to follow. A fuller discussion of CTs can be found in Article III of this series and in its Sidebar.

The number of CTs related to various therapies and biomarkers for HD that are currently recruiting may vary depending on the particular date at which the website clinicaltrials.gov is searched. Thus, in 2020, that number was 197. By 1 August 2024, that number grew to 258, an increase of ~ 30%, pointing to a heightened interest in HD. They generate data on dosage, safety, and efficacy. They can vary in size and cost, and can involve a single research center or multiple centers, in one or in multiple countries. The clinical study design aims to ensure the scientific validity and reproducibility of the results. There are two goals to testing medical treatments: (1) To learn whether they work well enough, called "efficacy" or "effectiveness" and (2) to ascertain whether they are safe enough, called "safety". Neither is an absolute criterion and both safety and efficacy are evaluated relative to how the treatment is intended to be used, what other treatments are available, and the severity of the disease or condition. In all cases, the benefits must outweigh the risks.

Trialled compounds that have failed to prevent or slow the progression of HD include: *Coenzyme Q10*, *Creatine, Dimebon, ethyl-EPA, Minocycline, Phenylbutyrate, Remacemide, and Riluzole.*

Potential Future HD Treatments

Table 1 below is an overview of potential future HD treatments:

Therapy	Sponsor	Development	Administration	Allele specificity	Dosing frequency
RNA targeting ASO					
CUG7	**Bio-Marin**	**Pre-clinical**	**Undisclosed**	**Allele-specific: CAG repeats**	**Multiple doses**
Tominersen	**Hoffman-Laroche**	**Phase 3**	**Intrathecal injection**	**Allele non-specific**	**Multiple doses**
TTX-3360	**Triplet Therapeutics**	**Pre-clinical**	**Intracerebro-ventricular**	**Not applicable**	**Unknown**

			infusion (mice)		
WVE-120102/120101	Wave life Sciences	Phase 1b/2a	Intrathecal injection	Allele specific: WVE-120101,2 rs362307, 31 SNP 1, 2	Multiple doses
WVE-003	Wave life Sciences	Pre-clinical	Undisclosed	Allele specific: SNP 3 Undisclosed	Multiple doses
RNAi					
AAV.shHD2.1	Spark	Pre-clinical	Intracranial injection (delivered by AAV1)	Allele non-specific	Single dose
AMT-130	UniQure	Phase 1b/2a	Intrastriatal injection (delivered by AAV5)	Allele non-specific	Single dose
VY-HTT01	Voyager	Pre-clinical	Intracranial injection (delivered by AAV1)	Allele non-specific	Single dose
Small molecules					
Branaplam	Novartis Pharmaceutical	Pre-clinical	Oral	Allele non-specific	Multiple doses (weekly)
PTC518	PTC	Phase 1	Oral	Allele non-specific	Multiple doses (weekly)
Unnamed	Nuredis	Pre-Clinical	Gene deletion in animal model, intracerebro-ventricular bolus injection	Allele-specific: elongation co-factors required for expanded CAG repeat transcription	Single dose
DNA targeting					
Zinc protein fingers					
TAK-686	Takeda & Sangamo	Pre-Clinical	Intrastriatal injection	Allele-specific: expanded CAG repeats	Single dose
ZF-KOX1	European Research Council (undertaken by Imperial College London/Fingers 4Cure)	Pre-Clinical	Intraventricular injection	Allele-specific: expanded CAG repeat	Single dose
CRISPR/Cas9					
Unnamed	Harvard University	Pre-Clinical	N/A (in cell lines) – theoretically	Allele-specific: SNPs related to mHtt	Single dose
Unnamed	NIH and NSF, China (undertaken by Emory University)	Pre-Clinical	Intrastriatal injection	Allele non-specific	Single dose
Stem cell					
Autologous stem/stromal cells	Regeneris Medical	N/A (in clinical trial)	Intravenous injection	Not applicable	Unknown
Cellavita HD	Azidus (Brazil)	Phase 2/3	Intravenous	Not applicable	Multiple doses

			infusion		
Fetal stem cell transplant	**Health & Care Research Wales (undertaken by Cardiff University)**	**Phase 1**	**Intrastriatal injection**	**Not applicable**	**Single dose**
Antibody					
ANX005	**Annexon, Inc**	**Phase 3**	**Intravenous injection**	**Not applicable**	**Multiple doses**
C6-17	**AFFiRiS**	**Pre-Clinical**	**Unknown**	**Allele-specific – binds to HTT protein near the aa586 caspase-6 cleavage region**	**Unknown**
INT41	**Vybion Inc**	**Pre-Clinical**	**Intrastriatal injection (mice)**	**Allele-specific: binds to mHtt fragments**	**Single dose**
VX15/2503	**Vaccinex, Inc**	**Phase 2**	**Intravenous injection**	**Not applicable**	**Multiple doses**
W20	**National Natural Science Foundation of China, National Science and Technology Major Projects of New Drugs**	**Pre-Clinical**	**Intracerebro-ventricular injection (mice)**	**Allele-specific: binds to mHtt fragments**	**Single dose**
Other small molecules					
Fenofibrate	**University of California, Irvine**	**Phase 2**	**Oral**	**Not applicable**	**Multiple doses**
Laquinimod	**Teva Pharmaceutical Industries Ltd**	**Phase 2**	**Oral**	**Not applicable**	**Multiple doses**
Neflamapimod	**EIP Pharma Inc**	**Phase 2**	**Oral**	**Not applicable**	**Multiple doses**
Nilotinib	**Georgetown University**	**Phase 1**	**Oral**	**Not applicable**	**Multiple doses**
PBT2	**Prana Biotechnology Ltd**	**Phase 2**	**Oral**	**Not applicable**	**Multiple doses**
Pridopidine	**Prilenia Therapeutics**	**Phase 3**	**Oral**	**Not applicable**	**Multiple doses**
SAGE-718	**Sage Therapeutics**	**Phase 1**	**Oral**	**Not applicable**	**Multiple doses**
SRX246	**Azevan Pharmaceutical**	**Phase 2**	**Oral**	**Not applicable**	**Multiple doses**
Varenicline	**University of Auckland and University of Otago**	**Open label study**	**Oral**	**Not applicable**	**Multiple doses**

Source: Mackenzie, Ferguson, Connor et al., 2022, and Article III.

Table 1: Overview of potential future HD treatments

Latest news from supporting Huntington organizations

Below are latest news from some supporting HD organizations. They are intended to be indicative only, and do not represent the spectrum of latest developments across the world of HD.

International Huntington Association

The International Huntington Association (IHA) reports results of the following three programs:

- **From UniQure:** UniQure, a gene therapy company advancing transformative therapies for patients with severe medical needs, is conducting two multi-center Phase I/II clinical trials of AMT-130 in the U.S. and Europe/U.K. for the treatment of HD. On July 9, 2024, it announced updated interim data that reportedly demonstrate a statistically significant, dose-dependent slowing of the progression of HD and lowering of NfL in the CSF at 24 months. The data evidenced a potential long-term clinical benefit and reduction of a key marker of neurodegeneration. Based on the encouraging data from this interim analysis, uniQure anticipates the following next steps: A multi-disciplinary RMAT meeting with the (U.S.) Food and Drug Administration (FDA) to discuss potential expedited clinical development pathways and accelerated approval and explore AMT-130 in combination with immunosuppression.

- **From Wave Life Sciences:** Wave Life Sciences announced positive results from SELECT-HD, its Phase 1b/2a placebo-controlled trial evaluating the investigational therapy WVE-003. These results reportedly demonstrate that WVE-003 selectively lowers toxic, mutant huntingtin (mHtt) protein and preserves healthy, wild-type huntingtin (wtHtt) protein for individuals with HD. Based on this encouraging result, Wave Life Sciences will discuss with regulators the potential for accelerated approval as well as an open-label extension (OLE) study for SELECT-HD.

- **From PTC Therapeutics:** PTC Therapeutics, Inc. is developing a potential treatment for HD based on their splicing platform technology. It employs PTC518, a small molecule that can be taken orally, to reduce the production of the mutated huntingtin protein (mHtt) that leads to injury and death of neurons, resulting in disease progression. The orally bioavailable small molecule penetrates the blood-brain barrier (BBB), is selective, titratable, and not effluxed – which are key differentiation properties. On June 20, 2024, PTC shared interim results from the Phase 2 PIVOT-HD study of PTC518, showing a dose-dependent lowering of mHtt in the blood and cerebrospinal fluid (CSF). In addition, favorable trends were demonstrated on several relevant HD clinical assessments including Total Motor Score (TMS) and Composite Unified Huntington's Disease Rating Scale (CUHDRS). Furthermore, following 12 months of treatment, PTC518 continues to be safe and well tolerated. In addition, PTC announced that the FDA has lifted the partial clinical hold on the program based on review of the PIVOT-HD data.

Huntington's Study Group

On August 18, 2023, the Huntington Study Group (HSG) shared that the Phase 3 pivotal KINECT®-HD study it conducted resulted in the FDA's approval of Neurocrine's drug, Valbenazine, for the treatment of chorea associated with HD. Valbenazine, a novel vesicular monoamine transporter 2 (VMAT2) inhibitor,

reduced HD-related chorea symptoms as early as two weeks after the initial dose and was well tolerated.

University of California, San Francisco

The University of California, San Francisco, reported on 2 studies:

- Clinical trial of AMT-130: This trial is a Phase I/II, randomized, multicenter, multiple dose, double-blind, imitation surgery, first-in-human (FIH) study of AMT-130 in patients with early manifest HD (see also UniQure above). It was designed to establish safety and proof-of-concept (PoC).

- Enroll-HD: This is a longitudinal, observational, multinational study that integrates two former HD registries-REGISTRY in Europe, and COHORT in North America and Australasia-while also expanding to include sites in Latin America. The primary objective is to develop a comprehensive repository of prospective and systematically collected clinical research data (demography, clinical features, family history, genetic characteristics) and biological specimens (blood) from individuals with manifest HD, unaffected individuals known to carry the HD mutation or at risk of carrying the HD mutation, and control research participants (e.g., spouses, siblings or offspring of HD mutation carriers known not to carry the HD mutation). Enroll-HD is conceived as a broad-based and long-term project to maximize the efficiencies of non-clinical research and participation in clinical research. With more than 150 active clinical sites in 23 countries, Enroll-HD is now the largest HD database available and is accessible to any interested researcher.

Conclusions and take-aways

- Research into the mechanism of HD is focused on: Identifying the functioning of the huntingtin protein (Htt) and how its mutated form (mHtt) differs or interferes with it. It also involves the brain pathology that the disease produces.

- Research is conducted using in vitro methods, genetically modified animals (also called transgenic animal models), and human volunteers. Animal models are critical for understanding the fundamental mechanisms causing the disease and for supporting the early stages of drug development.

- The identification of the causative gene has enabled the development of many genetically modified organisms and mammals that express mutant huntingtin and develop progressive neurodegeneration and HD-like symptoms.

- Research is being conducted using many approaches to either prevent HD or slow its progression. Disease-modifying strategies can be broadly grouped into three categories: Reducing the level of the mutant huntingtin protein; improving neuronal survival; and replacing lost neurons. In addition, novel therapies to improve brain functioning are under development.

- Since HD is caused by a single dominant gene encoding a toxic protein, gene silencing aims to reduce the production of the mutant protein, Gene silencing experiments in mouse models have shown that, when the expression of mHtt is reduced, symptoms improve.

- The safety of RNA interference, and allele-

specific oligonucleotide methods of gene silencing has been demonstrated in mice and the larger primate macaque brain.

- A huntingtin-lowering gene therapy trial run by Uniqure began in 2019, and several trials of orally administered huntingtin-lowering splicing modulator compounds have been announced. Gene splicing techniques are being looked at to try to repair a genome with the erroneous gene that causes HD, using tools such as CRISPR/Cas9.

- Another strategy to reduce the level of mutant huntingtin is to increase the rate at which cells are able to clear it. Increasing the rate of autophagy has the potential to reduce levels of mHtt and thereby ameliorate disease. Pharmacological and genetic inducers of autophagy have been tested in a variety of HD models, many of which have been shown to reduce mHtt levels and decrease toxicity.

- Among the approaches aimed at improving cell survival in the presence of mutant huntingtin are: Correcting transcriptional regulation; modulating huntingtin's aggregation; improving metabolism and mitochondrial function; and restoring synaptic function.

- Stem-cell therapy is used to replace damaged neurons by transplantation of stem cells into affected regions of the brain. Experiments in animal models (rats and mice only) have yielded positive results.

- Ferroptosis is a form of regulated cell death characterized by the iron-dependent accumulation of lipid hydroperoxides to lethal levels. Inhibitors of ferroptosis are protective in models of degenerative brain disorders.

- In 2020, there were 197 clinical trials related to varied therapies and biomarkers for HD listed as either underway, recruiting or newly completed. In 2024, that number grew to 258, a growth of ~ 30% in 4 years, pointing to the increased interest in HD.

- Compounds trialled that have failed to prevent or slow the progression of HD include: Coenzyme Q10, Creatine, Dimebon, ethyl-EPA, Minocycline, Phenylbutyrate, Remacemide, and Riluzole.

- An overview of the several potential future HD treatments has been provided in a convenient tabular form.

- Some of the latest news from some supporting HD organizations have been presented. They are intended to be indicative only, and do not represent the spectrum of latest developments across the world of HD.

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