Research Strategy: Henri Huttunen

Meeting the challenge of Parkinson's disease

A recent study on the risks of Parkinson's disease has raised interest in the neurological disorder, which has been recognised as a leading cause of disability worldwide and continues to rise in prevalence. The study, published in *Nature Medicine* on 20 April 2026, suggested that changes in the gut microbiome may signal the presence of Parkinson's disease – even before clinical symptoms appear. This highlighted the diverse nature of current research about the disease, which was first identified by the English surgeon James Parkinson in 1817, but still lacks a therapy capable of slowing, halting or reversing neurodegeneration.

This article describes research underway at Finland-based Herantis Pharma Oyj to move beyond symptomatic treatment for Parkinson's disease by developing a small peptide molecule, HER-096, that can cross the blood-brain barrier and potentially provide a meaningful treatment for patients. The molecule is poised to enter Phase 2 with the goal of establishing proof-of-concept.

A disease with a long history, Parkinson's is characterised clinically by motor symptoms – including tremor, rigidity and bradykinesia – as well as a broad spectrum of non-motor complications that significantly impact on a person's quality of life. Despite decades of research and therapeutic advances, current treatments remain largely symptomatic.

Levodopa, the gold standard of care, provides meaningful relief from motor symptoms by increasing dopamine levels in the brain. This compensates for a depleted supply of endogenous dopamine, a critical neurotransmitter and neuromodulator. Yet this dopamine supply does not address the underlying neurodegenerative process. Progressive loss of dopaminergic neurons in the substantia nigra still continues unabated, ultimately leading to disability and treatment-related complications. This limitation underscores a critical unmet need: therapies capable of slowing, halting or reversing neurodegeneration.

A path towards a more meaningful treatment was discovered in 2007. This was the identification of cerebral dopamine neurotrophic factor (CDNF), a protein encoded by the CDNF gene that protects and restores dopaminergic neurons. This is a mechanistically distinct class of neurotrophic factors[1]. Unlike classical neurotrophins that primarily signal through cell-surface receptors, CDNF exerts its effects by modulating intracellular stress pathways, particularly within the endoplasmic reticulum[2].

CDNF regulates the unfolded protein response, a homeostatic signalling network activated by protein misfolding, calcium imbalance, and other cellular stressors. Central to this system is glucose-regulated protein 78 (GRP78), a master chaperone that governs activation of the three principal unfolded protein response branches – IRE1, PERK and ATF6. CDNF binds to GRP78 and regulates its unfolded protein response-modulating activities. This helps restore proteostasis under conditions of excessive or prolonged endoplasmic reticulum stress[3].

This mechanism is highly relevant to Parkinson's disease pathophysiology, where α*lpha*-synuclein aggregation, mitochondrial dysfunction, and chronic endoplasmic reticulum stress converge to drive neuronal loss[4]. Preclinical studies demonstrate that CDNF not only protects dopaminergic neurons but can also promote functional recovery, suggesting both neuroprotective and neurorestorative effects. Notably, CDNF exhibits a *hit-and run* pharmacology: transient exposure is sufficient to induce durable biological responses, consistent with pathway reprogramming rather than continuous receptor occupancy.

Despite its promise, CDNF faces fundamental translational challenges. As a ~18 kDa protein, it does not cross the blood–brain barrier, requiring direct intracranial infusion to achieve therapeutic exposure in target regions such as the putamen[5]. This delivery paradigm imposes significant constraints.

Neurosurgical administration limits scalability, restricts treatment to later-stage patients, and reduces feasibility for chronic dosing – ironically where early intervention may yield the greatest benefit. In parallel, manufacturing large biologics entails complex expression, purification, and cold-chain logistics, contributing to high cost and limited accessibility. These challenges have catalysed efforts to capture CDNF's biology in a more drug-like format.

Engineering a solution

This format was discovered from structure–function studies which identified the C-terminal domain of CDNF – specifically its GRP78-interacting motif – as critical for unfolded protein response modulation and cytoprotection[3]. Short peptides derived from this region were shown to retain biological activity, including the ability to promote neuronal survival.

HER-096 was engineered as a ~1 kDa retro-inverso peptidomimetic designed to:

- Preserve the key pharmacophore required for GRP78 engagement;
- Resist proteolytic degradation thereby improving metabolic stability; and
- Enable transport across biological membranes, including the blood-brain barrier. This design translates a complex protein mechanism into a small, systemically deliverable molecule. Unlike CDNF, HER-096 can be administered subcutaneously, enabling repeated dosing without invasive procedures[6].

After extensive research, the scientists at Herantis Pharma have been able to design a small peptide that has the features of CDNF without the translational challenges. HER-096 recapitulates CDNF's core mechanism by interacting with GRP78 and modulating unfolded protein response signalling in a coordinated manner. This contrasts with earlier approaches that selectively target individual unfolded protein response branches, often with limited efficacy in complex

disease settings.

By restoring endoplasmic reticulum homeostasis, HER-096 acts to normalise maladaptive unfolded protein response signalling and rebalance cellular stress responses. This integrated mode of action influences proteostasis, inflammation and mitochondrial function – processes closely linked to Parkinson's disease pathobiology. This systems-level activity provides a mechanistic basis for the broad neuroprotective and restorative effects observed in preclinical models.

A key differentiator of HER-096 is its ability to achieve central nervous system exposure following peripheral dosing [6]. The company's preclinical pharmacokinetic studies show:

- A rapid systemic clearance with a plasma half-life of approximately 30 minutes;
- Brain exposure corresponding to about 20% cerebrospinal fluid-to-plasma ratio and extended cerebrospinal fluid half-life compared to plasma and;
- Cerebrospinal fluid pharmacokinetics that mirror interstitial fluid exposure, supporting cerebrospinal fluid as a surrogate for brain levels.

Despite its short systemic half-life, HER-096 retains the hit-and-run pharmacodynamic profile observed with CDNF, suggesting that sustained brain exposure is not required for efficacy. This enables intermittent dosing strategies that may improve tolerability and reduce off-target effects. While the exact mechanism of blood-brain barrier penetration remains incompletely understood, the peptide's small size and engineered stability are thought to support blood-brain barrier penetration, addressing one of the most persistent challenges in neurotherapeutics.

In an aged mouse model of synucleinopathy – featuring progressive dopaminergic neuron loss, microgliosis, and elevated endoplasmic reticulum stress – subcutaneous HER-096 administration produced robust neuroprotective effects. Treatment resulted in a 50%–60% preservation of dopaminergic neurons in the substantia nigra[6]. Moreover, striatal dopamine levels were normalised and motor symptoms alleviated, suggesting that HER-096 treatment supports functional restoration of the nigrostriatal system.

Target engagement was confirmed by decreased activation of key unfolded protein response markers, including phosphorylated IRE1 and nuclear ATF6, consistent with the proposed mechanism of action, alongside reductions in aggregated α-synuclein and inflammatory marker levels. Early clinical studies have translated these findings into humans.

In a Phase 1 trial, single ascending subcutaneous doses of HER-096 were safe and well tolerated. Crucially, measurable levels of HER-096 were detected in cerebrospinal fluid, confirming blood-brain barrier penetration in humans. Subsequent multiple-dose evaluation in Parkinson's disease patients has further supported tolerability and provided initial biomarker evidence consistent with biological activity, reinforcing confidence in the translational relevance of the mechanism.

Towards proof-of-concept

HER-096 is advancing toward Phase 2 clinical evaluation to establish proof-of-concept for disease modification in Parkinson's disease. Herantis has received support from Horizon Europe, the European Union's programme for research and innovation, including €8 million in funding. If successful, HER-096 could represent a shift from symptomatic management to mechanism-based intervention. Its compatibility with standard-of-care therapies such as levodopa also opens the possibility of combination strategies that address both symptoms and disease progression.

Beyond Parkinson's disease, the underlying biology – centered on endoplasmic reticulum stress and unfolded protein response/proteostasis dysregulation – extends to a range of neurodegenerative disorders. These potentially include amyotrophic lateral sclerosis, Huntington's disease, and Alzheimer's disease[4]. Moreover, recent findings in healthy brain ageing point to unfolded protein response as a potential regulator of neuronal maintenance and stress adaptation, supporting exploration of unfolded protein response-modulating approaches, including HER-096, not only in disease modification but also in preserving neuronal function across the lifespan.

By translating the biology of neurotrophic factors and proteostasis modulation into a brain-penetrant, systemically deliverable therapy, HER-096 exemplifies a new direction in central nervous system drug development – one that aligns mechanistic sophistication with clinical practicality.

References:

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