Herantis Pharma Plc
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Protecting the proteome from Parkinson's disease

Herantis is capitalising on the power of the natural protein Cerebral Dopamine Neurotrophic Factor (CDNF) to restore proteostasis and slow, stop, or even reverse neurodegeneration.

Despite great strides in understanding the roots of neurodegenerative conditions such as Parkinson's disease (PD), few effective therapies exist, most offering only symptomatic relief for a limited time by correcting the dopamine deficiency caused by loss of dopaminergic neurons, rather than targeting the neurodegenerative disease process itself.

As populations have aged the need for transformative therapies has never been greater. Herantis Pharma, headquartered in Helsinki, Finland, is using groundbreaking science to bring PD therapies into the 21st century with a first-in-class disease-modifying treatment.

A common theme in neurodegenerative diseases is a defective proteome due to dysregulation of proteostasis, a key system that ensures all proteins within a cell are synthesized, folded, trafficked and degraded appropriately to maintain a functional cell proteome. In neurodegenerative diseases, proteostasis goes wrong. Herantis is developing CDNF, a natural protein that plays a key role in proteostasis (Fig.1), as a new therapy for PD and other neurodegenerative diseases. In addition, Herantis has also created a range of novel CDNF-derived peptidomimetic compounds (xCDNF) that are capable of crossing the blood–brain barrier (BBB), and is exploring their potential in PD.

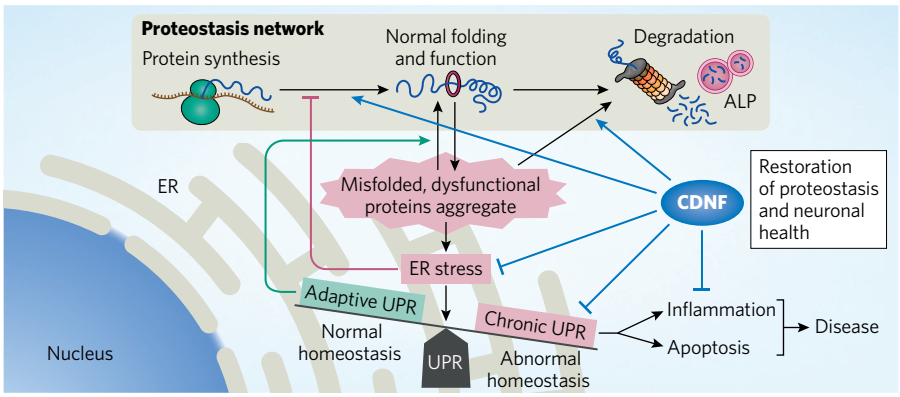

Fig. 1 | CDNF and proteostasis. The proteostasis network maintains a functional proteome in cells. Dysregulated proteostasis plays a major role in development of disease. In Parkinson's disease, accumulation of misfolded proteins induces endoplasmic reticulum (ER) stress leading to reduced protein synthesis and activation of the unfolded protein response (UPR), which if prolonged leads to apoptosis. CDNF acts to normalize proteostasis by restoring adaptive UPR signalling, supporting cell survival and normal degradation of misfolded proteins.

CDNF—a powerful natural protein

CDNF was first identified at the Institute of Biotechnology, Helsinki, in 2007. In animal models, intrastriatal injection of CDNF powerfully restored dopaminergic function and promoted restoration of the nigrostriatal system. Over the past decade, Herantis has further developed CDNF, making fundamental discoveries in proteostasis and neurodegenerative disease. In a primate study, CDNF demonstrated restorative effects on damaged dopaminergic neurons, with improvements observed in motor function, as well as non-motor PD symptoms, including anxiety and motivation—the first time such benefits have been observed with a PD therapeutic.

Safety: CDNF is already being tested in humans, where Herantis has completed a 12-month phase 1 safety study in PD patients, which demonstrated excellent tolerability of CDNF administered directly into the brain. In addition, although these studies were carried out in PD patients with advanced dopaminergic loss, the patients remained relatively stable over the 12-month assessment period, which is a promising result in a disease that normally deteriorates over time.

Biomarkers: Even more significantly, these studies revealed biomarker changes in the cerebrospinal fluid suggesting a biological response to CDNF treatment. Notably, these biomarker changes were correlated with improvements in motor function and enhanced dopamine signalling in several patients. Biomarkers specific to proteostasis were also found to be modulated following CDNF treatment, supporting the mechanism of action of CDNF.

Genetics: Around one-third of patients treated with CDNF were found to have relevant mutations in genes implicated in the pathogenesis of PD, including LRRK2 and GBA. A LRRK2 mutation patient showed substantial motor improvement as well as enhanced dopamine imaging, together with biomarker response, when switched from placebo to CDNF therapy. Herantis is evaluating these genetic patient subpopulations in more detail.

Administration: Getting PD therapies into the midbrain remains a challenge; the BBB prevents large molecules including CDNF from entering the brain, which effectively rules out subcutaneous and intravenous administration. In the first CDNF clinical study, CDNF was administered directly into the brain via a surgical mechanical device, but this is highly invasive and places a considerable burden on patients and limits the target patient populations. To address these delivery challenges, Herantis is developing CDNF formulated for intranasal administration, which previous data has suggested can achieve pharmacologically active concentrations in the brain.

xCDNF—a smartly engineered peptide

Herantis is also working on another solution to the delivery obstacles through its xCDNF program. Driven by insights gained from studying natural CDNF, Herantis has generated several peptidomimetic compounds based on endogenous CDNF that can cross the BBB while retaining the neuroprotective effects of CDNF. Because xCDNF peptides can penetrate the BBB, they open up the possibility of easy and effective subcutaneous delivery. By running both programs, with comparable potency but different routes of delivery, Herantis has balanced and de-risked its CDNF portfolio.

In animal models, xCDNF administered subcutaneously penetrates the BBB and achieves therapeutic concentrations in the brain, including basal ganglia, with a long half-life that increases its therapeutic effects. xCDNF has also been shown to protect dopaminergic neurons against the PD-inducing neurotoxin MPP+, and also strongly reduces and even normalises a-synuclein aggregates and neuroinflammation in a mouse model of PD based on intranigral injection of a-synuclein oligomers. Herantis is currently taking the lead xCDNF peptide into formal development.

Herantis has established a compelling science base that has been safely translated into humans, and increasing evidence that CDNF and xCNDF therapeutically affect key biological systems. The company is in a strong position to leverage its assets to meet the therapeutic needs of patients through strategic out licensing collaborations with big pharma partners to advance CDNF and xCDNF through to market where independent projections suggest the CDNF opportunity could reach peak sales of $8 billion.

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