HERANTIS PHARMA

PIPELINE PROGRAMME: XCDNF (CEREBRAL DOPAMINE NEUROTROPHIC FACTOR – BASED PEPTIDOMIMETICS)

Introduction:

Herantis is a NASDAQ Nordic-listed biotech company, founded and headquartered in Helsinki, Finland. Through strong academic collaborations, we have developed a ground-breaking biological therapy for neurodegenerative diseases such as Parkinson's disease (PD) and Lewy Body Dementia (LBD). Though a great deal is known about the cellular processes that contribute to neurodegeneration, remarkably the standard of care for Parkinson's disease has remained largely unchanged since the 1960's. Herantis is aiming to change that by introducing new therapeutics for the 21st century that are focussed on slowing, stopping or even reversing disease pathology.

The Science:

Herantis is pioneering research and development into CDNF-based therapeutics. Through years of work with our academic collaborators and rigorous preclinical studies, we have explored the multi-modal efficacy of CDNF as a neuroprotectant and modulator of proteostasis.

Proteostasis encompasses the normal synthesis and folding of proteins, and the removal of misfolded proteins. Maintaining proteostasis is critical to cell survival and function. The endoplasmic reticulum (ER) is the primary proteostasis-regulating organelle in the cell. It is responsible for the production, proper folding and export of both secretory and plasma membrane bound proteins, and also directing the degradation of unwanted proteins via the ubiquitin system. When this process falters, such as in cases of cell stress and/or aging, proteostasis is disrupted such that proteins become malformed, misfolded or dysfunctional, causing "bad" proteins to accumulate in the cell, and leading to cell dysfunction and death.

ER stress and chronic activation of the Unfolded Protein Response (UPR) have been observed in several CNS diseases (including LBD, PD and stroke), and also some metabolic diseases (NAFLD/NASH and diabetes). In neurons and glial cells in the brain, chronic ER stress can be highly problematic. Cells experiencing ER stress typically activate the UPR, a corrective mechanism for dealing with errant proteins. However, the continuous activation of UPR leads to neuronal dysfunction and cell death and contributes to neurodegenerative disease.

CDNF acts upon three key mechanisms in the ER to restore proteostasis – synthesis, folding, and degradation, by binding to several key proteins regulating UPR such as GRP78. In the context of Parkinson's disease, CDNF can rescue and potentially regenerate dopaminergic neurons in the putamen and substantia nigra (important regions of the mid-brain). However, CDNF cannot readily penetrate an intact blood-brain-barrier (BBB), which poses a familiar drug delivery challenge. To increase BBB penetrance, Herantis has explored several peptidomimetic compounds that are based on the 3D structure and sequence of endogenous CDNF. The xCDNF pipeline programme is intended to deliver optimised, metabolically stable peptidomimetic APIs that retain the neuroprotective effects of CDNF, but can readily penetrate the BBB. Herantis is currently performing lead optimisation studies on candidate compounds to maximise their plasma half-life, BBB penetrance and potency. The xCDNF optimisation program-

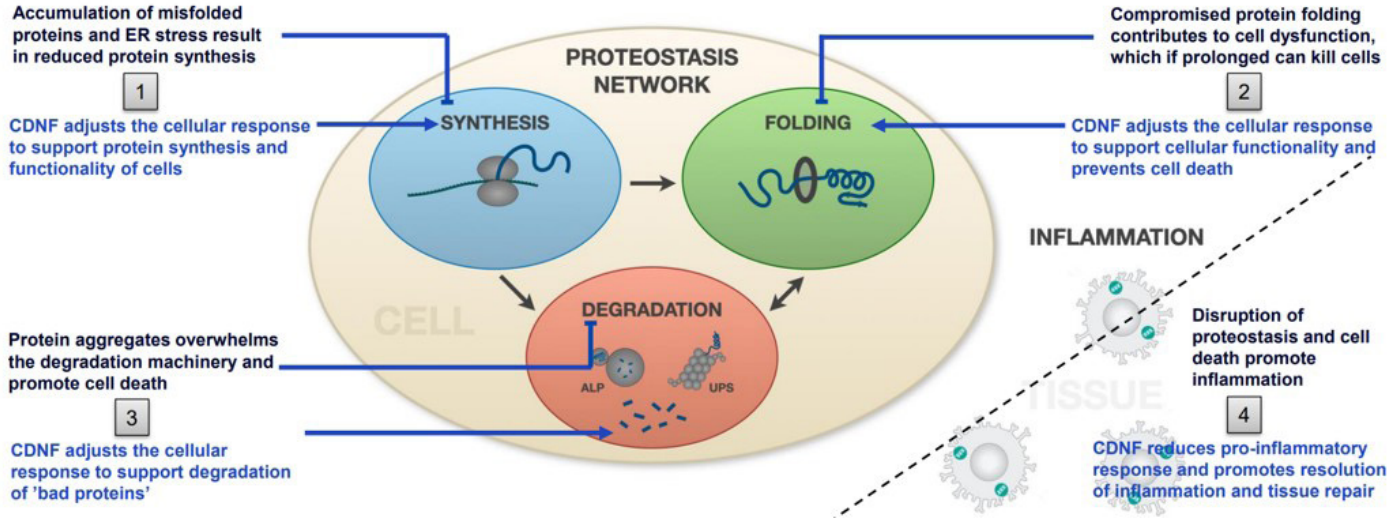


Fig 1: CDNF addresses key mechanisms in proteostasis - protein synthesis, protein folding, protein degradation, and inflammation. i) Synthesis - CDNF acts to restore normal protein synthesis by interacting with PERK, which shifts the UPR signalling from pro-apoptotic to adaptive mode. ii) Folding - CDNF interacts with a number of chaperone proteins and their regulators in the ER lumen, and modulates Unfolded Protein Response UPR signalling, which again promotes adaptive rather than pro-apoptotic response. Effects on calcium and lipid levels also may support the ER protein-folding machinery. iii) Degradation – Reduces “bad” protein accumulation, CDNF adjusts UPR signalling to support autophagy and cell survival. iv) In addition to these mechanisms, CDNF also reduces the extracellular inflammatory response (linked to UPR signalling) thus diminishing broader cellular damage.

me has already generated a number of promising NBEs with associated new intellectual property. Indeed, our current lead molecules can be delivered in therapeutic concentrations to the brain parenchyma following subcutaneous injection, as described below.

The Data:

Through extensive research into the structure and function of CDNF, Herantis has made several unexpected discoveries. Our peptidomimetic compounds retain the neuroprotective properties of CDNF and are able to penetrate the BBB. In rodent models, these compounds have been shown to be trafficked to the basal ganglia in therapeutic concentrations, following simple subcutaneous injection. More importantly, our studies have shown that as well as retaining the biological activity of CDNF, the peptidomimetic APIs can greatly exceed its potency. In 2018, Herantis successfully demonstrated first proof of concept for our previous lead peptide NG-C-101, a 61 amino acid, 7 kDa fragment of CDNF. To demonstrate efficacy of peptide NG-C-101, which is used here as a non-optimised tool compound, Herantis performed in vivo studies in 6-OHDA lesioned rats (an established PD animal model). Following subcutaneous injections of NG-C-101 (6 doses, injected twice weekly for 3 weeks), a significant improvement in motor behaviour was observed. Hence, this study suggests that the CDNF-derived peptide can exert similar neuroprotective effects as CDNF, and that it can be successfully trafficked through the BBB to the substantia nigra with simple peripheral injection.

Refinement of NG-C-101 has generated two new classes of lead peptidomimetic compounds. In further in vitro work, the neuroprotective effects of one of the optimized compounds were studied at a range of concentrations and directly compared with CDNF (whole protein). Rat mesencephalic neuron cultures were treated with the neurotoxin MPP+ and either the xCDNF peptidomimetic or CDNF. Cell survival data indicate the xCDNF API produced a maximum protective effect at a concentration of 0.5 nM, corresponding to ~10-fold increase in potency compared to CDNF (see Figure 3).

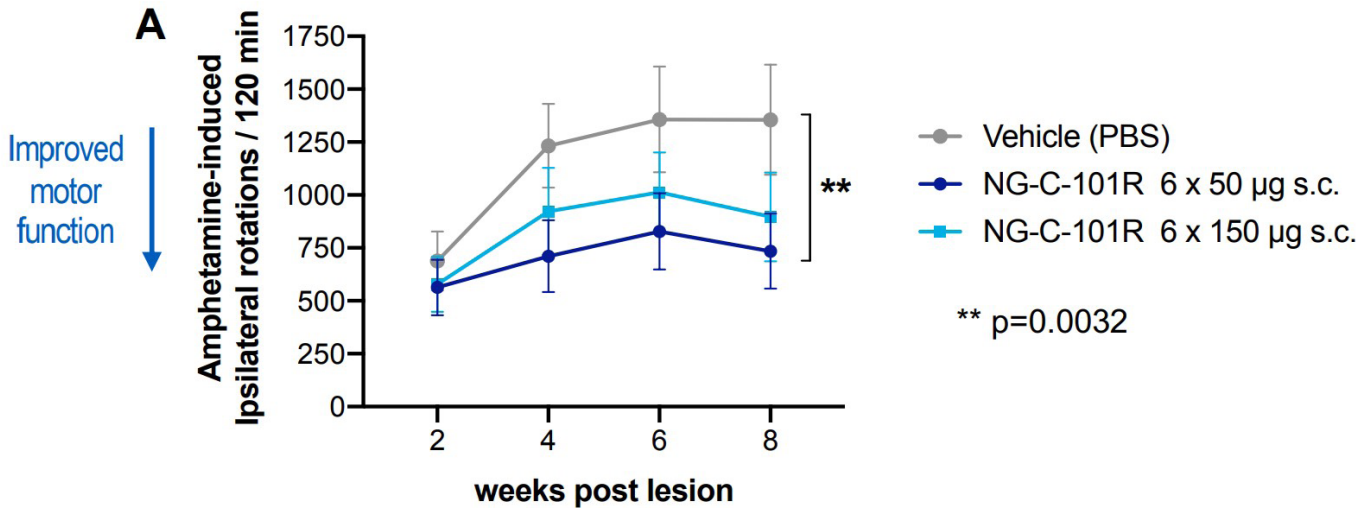


Fig 2: 6-OHDA lesion rat PD model measuring change in motor functions upon repeat dosage with NG-C-101 tool compound (50 or 150 µg, subcutaneous injection).

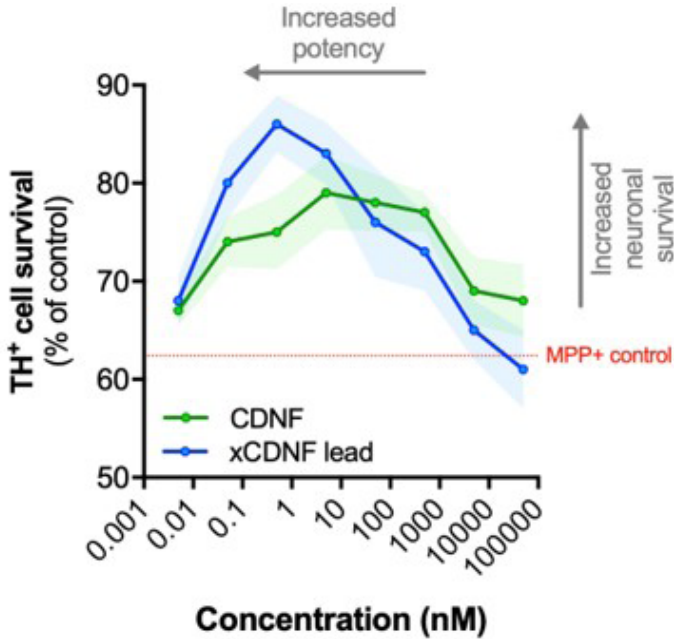


Fig 3: Rat mesencephalic neuron cultures treated with 4 µM MPP+ and increasing concentrations of either CDNF or xCDNF lead compound for 48 h, followed by immunostaining with tyrosine hydroxylase (TH), a marker of dopamine neurons, and automated image analysis; *n*=5-6.

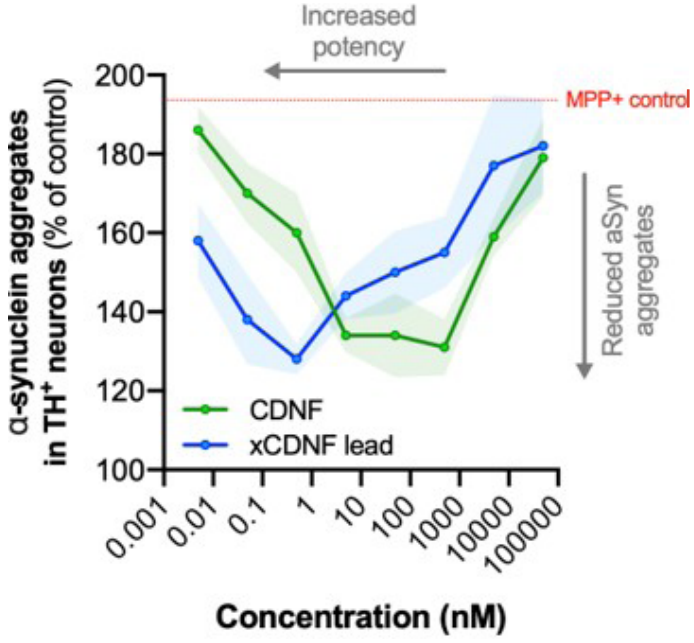
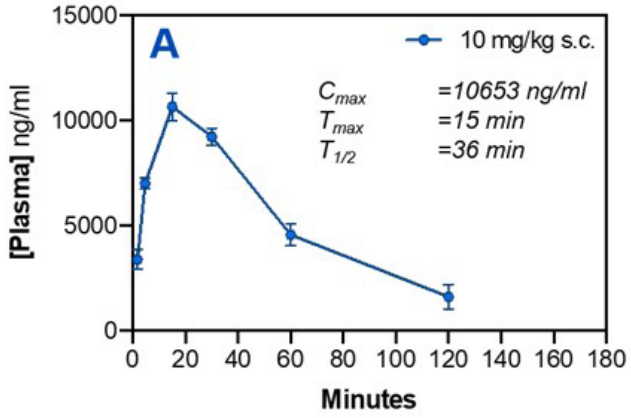


Figure 4: Rat mesencephalic neuron cultures treated with 4 µM MPP+ and increasing concentrations of either CDNF or xCDNF lead compound for 48 h, followed by immunostaining with anti-alpha-synuclein antibodies and automated image analysis; *n*=5-6.

In the same in vitro study, alpha-synuclein aggregation was quantified by immunohistochemistry with anti-alpha-synuclein antibodies. xCDNF promotes proteostasis and in this experiment significantly reduced the extent of alpha-synuclein aggregation, with maximum efficacy at a concentration of 0.5 nM. This study corroborates the increased potency of the lead peptidomimetic compared with whole protein CDNF.

Herantis has also performed in vivo studies to establish PK parameters for xCDNF peptidomimetics and to measure their BBB penetrance. Figure 5a shows the plasma PK profile following subcutaneous injection in mice (10 mg/kg).

To directly measure the concentration of xCDNF in brain interstitial fluid (ISF), a second mouse study was performed. Using a microdialysis probe implanted in the striatum, ISF samples were collected every 20 minutes following a single subcutaneous



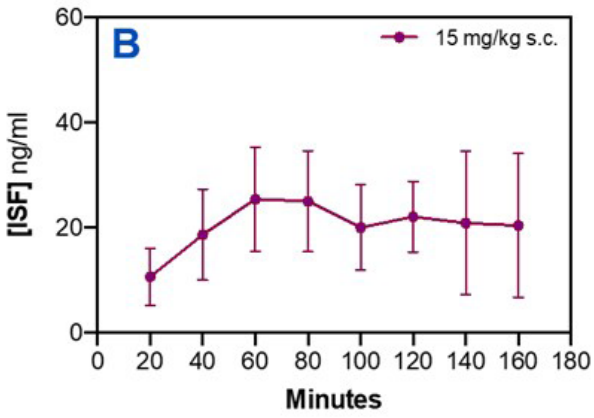


Figure 5a: PK profile following single subcutaneous injection of lead xCDNF compound in mice (10 mg/kg). The test compound was quantified by LC-MS/MS; *n*=4.

Figure 5b: Striatal ISF concentration profile for xCDNF following single subcutaneous injection of xCDNF compound in mice (15 mg/kg). Direct ISF sampling was performed via implanted microdialysis probe. The test compound was quantified by LC-MS/MS; *n*=4.

injection of xCDNF (15 mg/kg). The study showed that the peptidomimetic API successfully penetrated the BBB in therapeutic concentrations. Mean local concentrations of >20 nM were observed for >2 h after injection, suggesting the half-life and residence time of xCDNF may be substantially extended in the brain parenchyma (see Figure 5b).

The Molecule(s):

Our ongoing xCDNF programme is intended to further explore the binding affinity, metabolic stability, and BBB penetrance of a range of novel CDNF-derived peptidomimetic compounds that may be developed as new therapeutics for PD and LBD, with the key advantage of straightforward administration via subcutaneous injection.

Herantis' discovery team is now in the final stages of lead identification and structure optimisation. This involves iterative study of structure-activity relationships, e.g. impact on ER stress and BBB penetrance, synthetic route development, and target binding kinetics.

Stability and solubility results will drive further formulation work to produce an injectable preparation, and to explore alternative administration routes (subcutaneous / intramuscular). Our immediate goal is to take the lead xCDNF peptide into a formal preclinical program in 2021 and then first-in-human Phase I safety study in 2023-24.

The Disease(s):

Parkinson's disease is understood to be caused by the deterioration and eventual death of dopamine-producing (dopaminergic) neurons in two principal regions of the mid-brain (the putamen and the substantia nigra). In healthy adults, dopaminergic neurons make up around 3-5% of all neurons in these regions. In Parkinson's patients, this number decreases gradually as the disease progresses over decades. PD is characterised by the progressive deterioration of motor functions, resulting in tremor, muscle stiffness & rigidity, and bradykinesia; and over time the appearance of neuropsychiatric, non-motor symptoms such as Parkinson's dementia, sleep disturbance and depression. A long-standing, but as yet unrealised therapeutic hypothesis is that by rescuing and restoring the function of these dopaminergic neurons, the progression of PD can be halted, and its symptoms alleviated. While the exact cause of dopaminergic neuron degeneration has not been definitively established, an important hallmark of Parkinson's disease is the formation of aggregated protein structures comprised of insoluble alpha-synuclein and misfolded ubiquitin-tagged proteins. As stated, misfolding and accumulation of "bad" proteins occur when cellular proteostasis is perturbed, and this is a common characteristic in neurodegenerative diseases.

Lewy body dementia (LBD) is a neuronal synucleinopathy that is related to PD but affects different regions of the brain and produces different symptoms such as visual hallucinations, depression and other cognitive problems. The aggregation of misfolded alpha-synuclein and formation of Lewy bodies are strongly linked to the onset of LBD. Hence, the potent neuroprotective activity of xCDNF peptides should be highly effective in preventing further neuronal degeneration by eliminating misfolded alpha-synuclein.

Herantis intends to pursue preclinical development programmes for both PD and LBD. Since the therapeutic hypothesis for these indications is the same, these programmes will likely be complementary and are likely to involve similar in vivo efficacy models. This is expected to simplify development and accelerate overall progress.

The Market:

Comprehensively, the total available market for neurodegenerative diseases was estimated to be worth €29Bn in 2018 and is projected to reach €54Bn by 2026 (CAGR = 7.2%).

Parkinson's disease alone represents a serviceable market of €3.75Bn, growing to €5Bn by 2024. PD is the second most common form of neurodegeneration, affecting 7 to 10 million people worldwide, with over 60,000 new diagnoses in the US each year. In 2010, the annual societal cost of PD in Europe was calculated to be approximately €14 billion. A further study estimated that a disease-modifying therapy capable of stopping PD progression could create a societal cost saving of €400,000 per patient. PD is poorly served, with few durable therapies, none of which are able to stop or slow disease progression.

LBD is thought to be the second most common form of dementia, accounting for between 5 and 10% of cases. The market is difficult to precisely define, as it obviously overlaps with Parkinson's dementia and Alzheimer's. However, it has been estimated to reach €1.25 – 1.7 Bn in 2025, representing an attractive opportunity for Herantis. Treatments for LBD are limited to Acetylcholinesterase (AChE) inhibitors, such as donepezil (Aricept), and Levodopa, which treat the symptoms of the disease by increasing neurotransmitter production, but do not affect the underlying disease state.

Based on the market share of incumbent therapeutics for PD (e.g. Levodopa & Deep Brain Stimulation), we project the overall obtainable market opportunity for xCDNF in PD and LBD to be ~€4.2Bn.
xCDNF peptidomimetics have the potential to be disease-modifying therapeutics for PD and LBD. Moreover, they have the great advantage of a simple delivery route (i.e. via subcutaneous injection). We anticipate xCDNF will be launched as a simple injectable formulation, with a straightforward regulatory route and numerous patient-friendly administration possibilities.

The IP:

Herantis is well positioned to exploit a significant opportunity to change PD and LBD treatment with xCDNF by launching first in class disease-modifying therapeutics. Herantis' assets, including the xCDNF programme, are broadly protected by patents, trade-secrets and know-how. Herantis maintains a portfolio of 79 global patents across 11 families, which protect the form and function of our xCDNF therapeutics. Our recent filings (2019) ensure continued patent protection until 2040, and several new applications are currently in preparation.

Herantis derives a strong competitive advantage from know-how and trade-secrets relating to the manufacture and control of trophic factors, which we estimate provides at least a five-year head-start over potential competitors. Additionally, upon approval of the first xCDNF therapeutic, Herantis expects to be granted 5 and 8 year periods of data-exclusivity for its preclinical and clinical trials in the USA and EU, respectively.