HERANTIS PHARMA

CDNF – Potential in prevention of dopamine neuron degeneration and stimulation of neuron regeneration

Henri J. Huttunen, CSO
Herantis Pharma Plc

TreatER webinar 18 Nov 2020

Potential To Revolutionize Parkinson's Disease Treatment

Current Standard of Care

Despairing Illness
underserved for decades

Parkinson's Currently Treated With Levodopa Since 1960's (01)

Side Effects
of current therapies undesirable and debilitating

Do not Address the Disease
no therapies capable of stopping or slowing down disease progression are available

Standard of Care Lacking

Parkinson's Disease

CDNF

01 **Action:** CDNF is a natural protein whose role is to **protect neurons**

02 **Disease Modifying:** Promotes **recovery** of dopamine terminals, stops disease progression

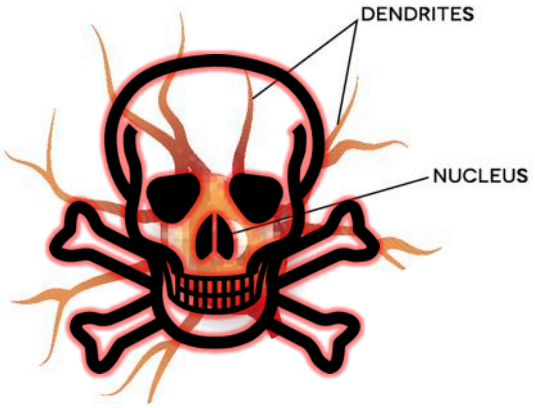
03 **Symptoms:** has potential to alleviate both **motor and non-motor** symptoms

04 **Data:** First-in-Human Phase I-II Study **Met Primary Endpoints** of Safety at 12 months

This project is funded by the European Union

Maintenance neuronal functionality and survival in long-lived organisms in challenging

- In humans, central neurons are generated during fetal development and early post-natal life, there is **very limited capacity to generate of new neurons** in adult brain
- Neurons are highly polarized and have a high rate of oxidative metabolism
- Neurons are very sensitive to disruptions in **proteostasis**
- Dopamine neurons are particularly vulnerable due to their highly complex structure and toxicity of oxidized dopamine metabolites

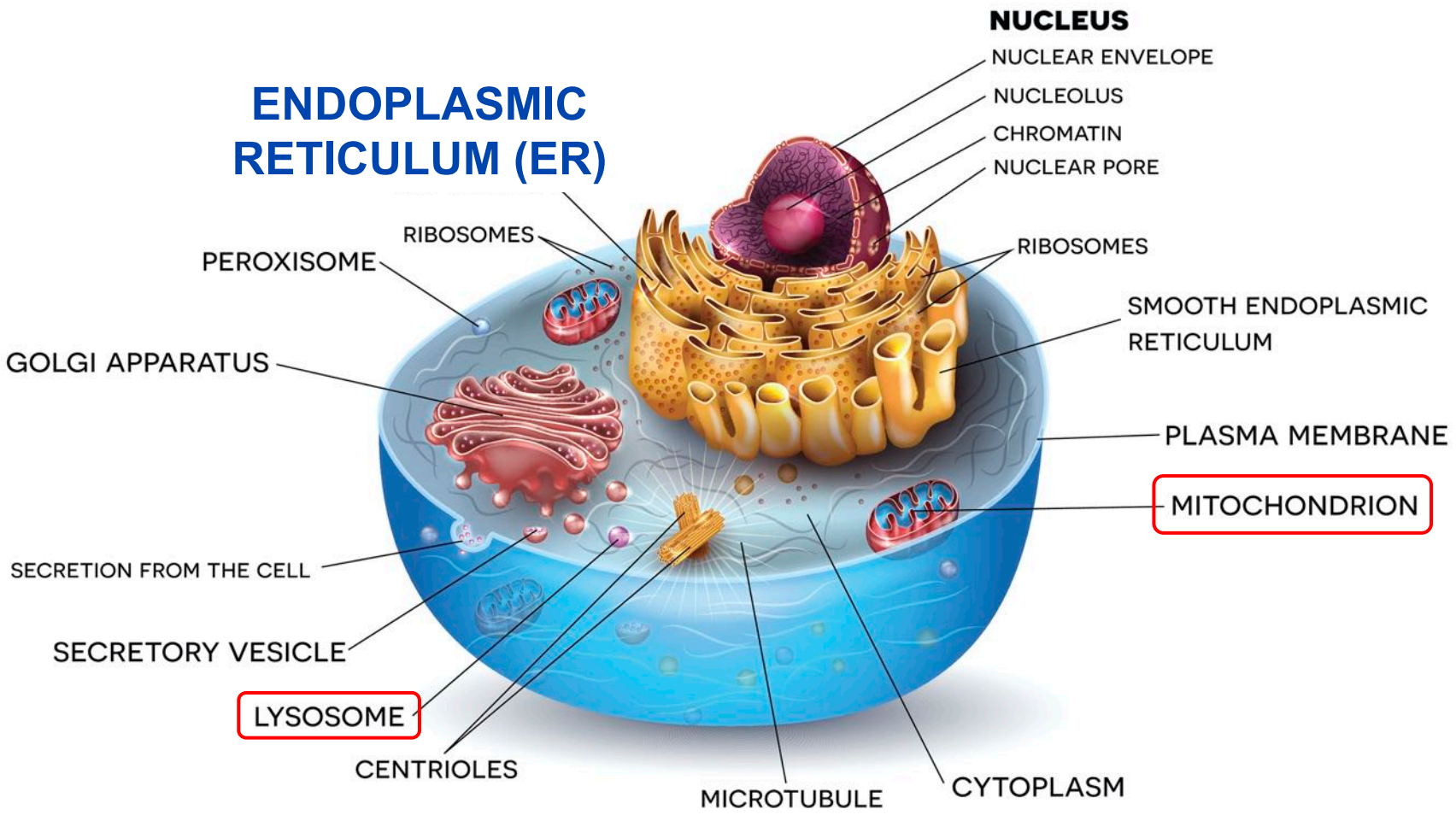


HERANTIS PHARMA

TreatER

This project is funded by the European Union

In Parkinson's disease, several cellular mechanisms important for functionality and survival are impaired



HERANTIS PHARMA

TreatER

This project is funded by the European Union

Maintenance of proteostasis

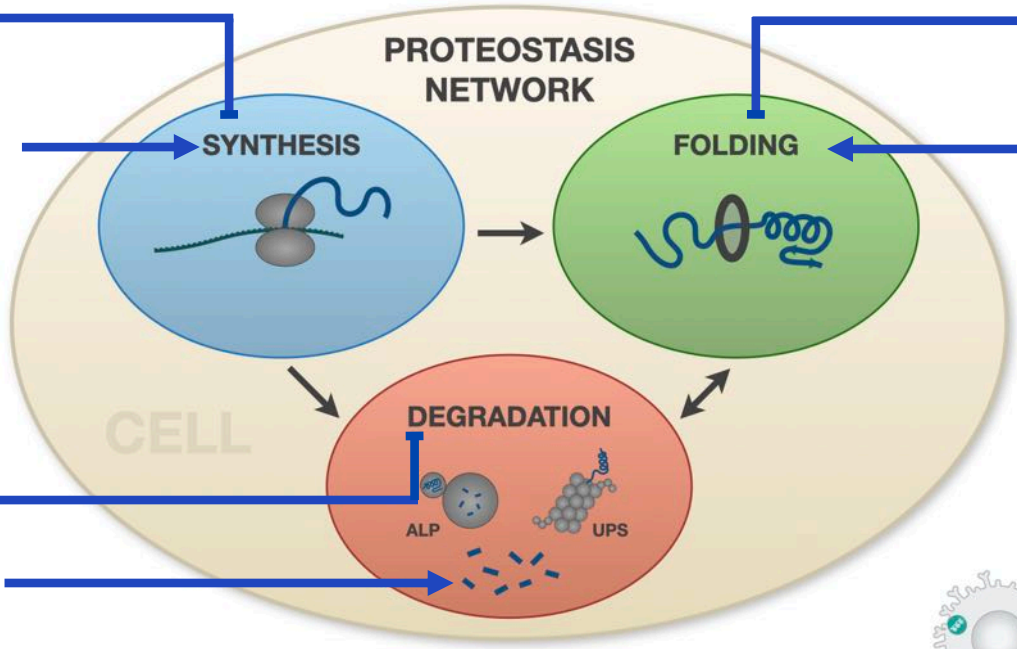
Proteins are the building blocks of everything in the body. Functionality of all cells (particularly neurons) depends on the balance of the three cornerstones of proteome regulation: synthesis, folding and degradation. If any of these becomes dysfunctional, problems will follow.

Accumulation of misfolded proteins and ER stress result in reduced protein synthesis

CDNF adjusts the cellular response to support protein synthesis and functionality of cells

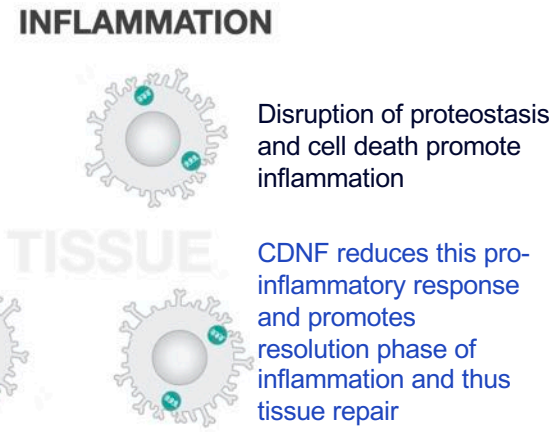
Protein aggregates overwhelm the degradation machinery and promote cell death

CDNF adjusts the cellular response to support degradation of 'bad proteins'



Compromised protein folding contributes to cell dysfunction, which if prolonged can kill cells

CDNF adjusts the cellular response to support cellular functionality and prevents cell death



Disruption of proteostasis and cell death promote inflammation

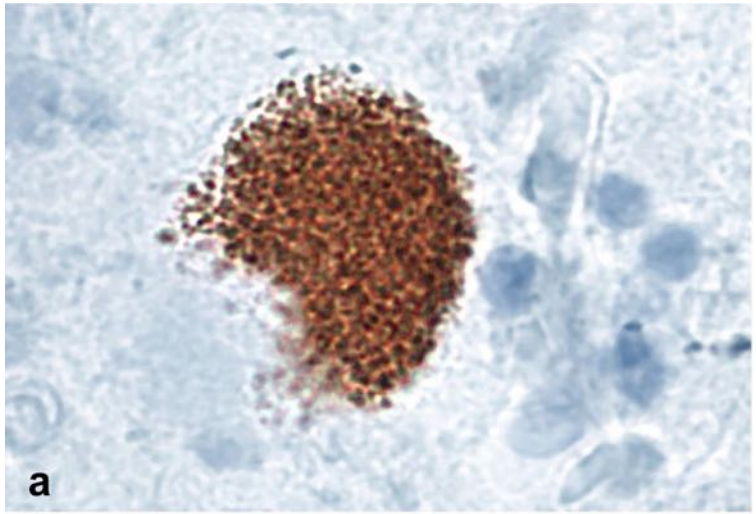
CDNF reduces this pro-inflammatory response and promotes resolution phase of inflammation and thus tissue repair

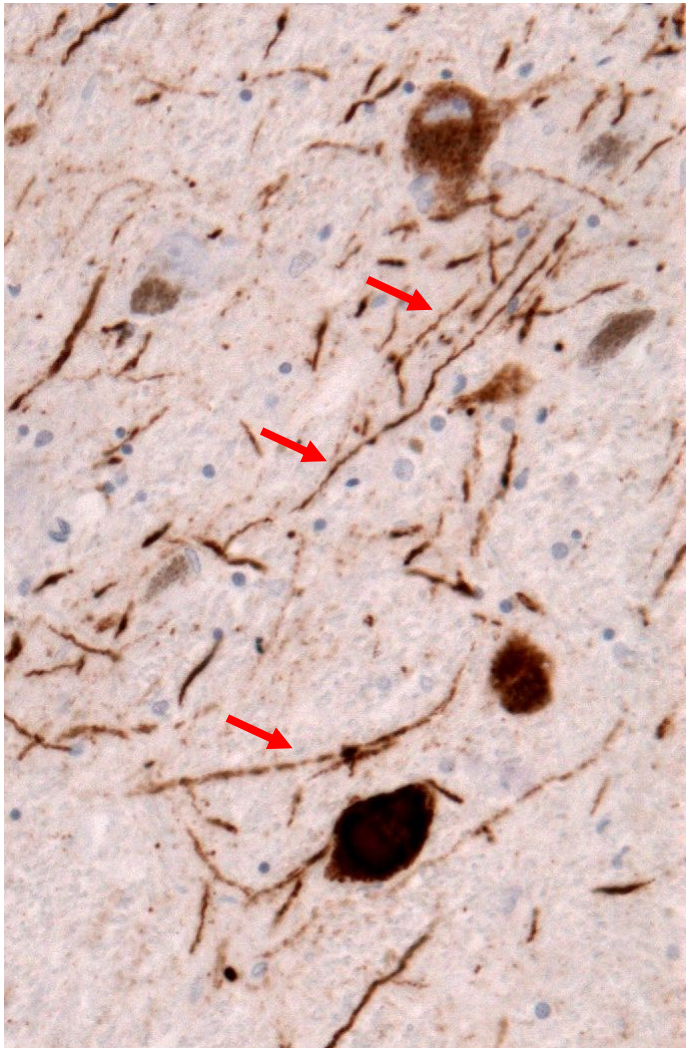
HERANTIS PHARMA

TreatER

This project is funded by the European Union

Lewy body pathology: accumulation of aggregated alpha-synuclein protein is characteristic for Parkinson's





HERANTIS PHARMA

TreatER

This project is funded by the European Union

The discovery of CDNF

Nature 5 July 2007
Vol. 448, pp. 73-77

Letter

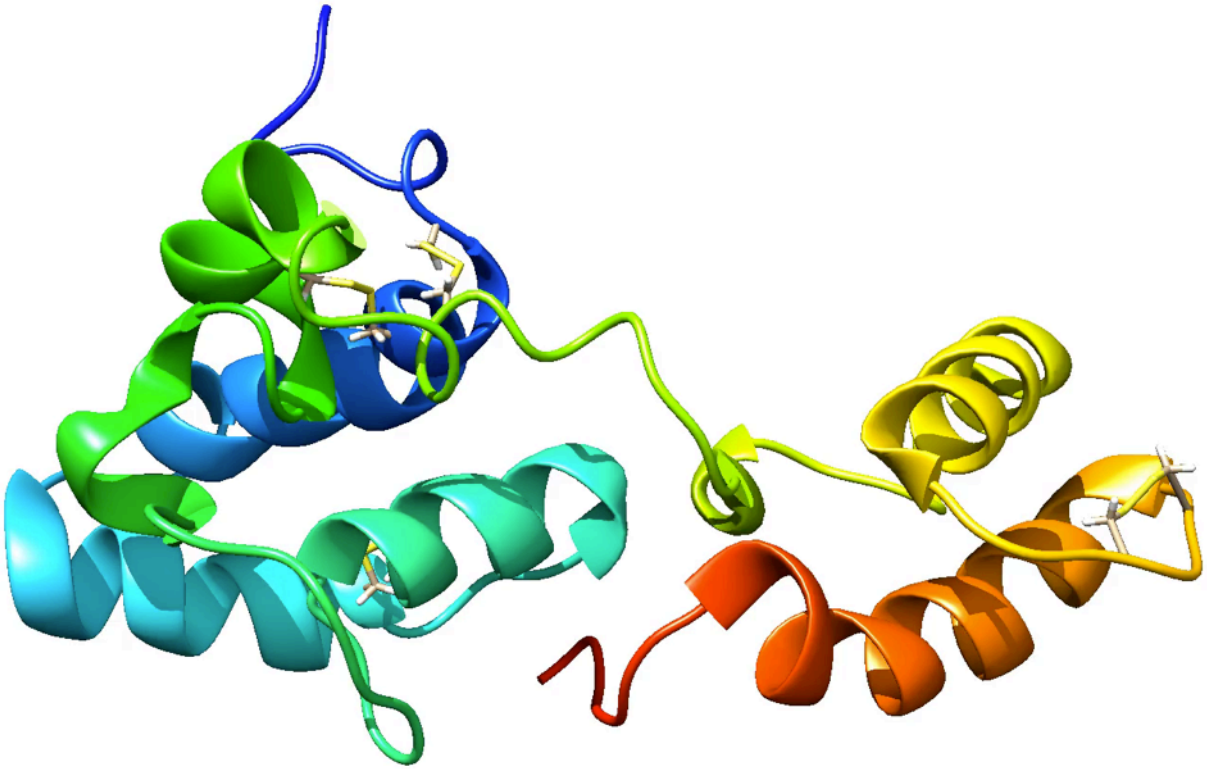
Novel neurotrophic factor CDNF protects and rescues midbrain dopamine neurons in vivo

Päivi Lindholm[1], Merja H. Voutilainen[2], Juha Laurén[1,4], Johan Peränen[1], Veli-Matti Leppänen[1], Jaan-Olle Andressoo[1], Maria Lindahl[1], Sanna Janhunen[2,4], Nisse Kalkkinen[1], Tõnis Timmusk[1,3], Raimo K. Tuominen[2] & Mart Saarma[1]

In Parkinson's disease, brain dopamine neurons degenerate most prominently in the substantia nigra. Neurotrophic factors promote survival, differentiation and maintenance of neurons in developing and adult vertebrate nervous system. The most potent neurotrophic factor for dopamine neurons described so far is the glial-cell-line-derived neurotrophic factor (GDNF). Here we have identified a conserved dopamine neurotrophic factor (CDNF) as a trophic factor for dopamine neurons. CDNF, together with its previously described vertebrate and invertebrate homologue the mesencephalic-astrocyte-derived neurotrophic factor, is a secreted protein with eight conserved cysteine residues, predicting a unique protein fold and defining a new, evolutionarily conserved protein family. CDNF (Armetl1) is expressed in several tissues of mouse and human, including the mouse embryonic and postnatal brain. In vivo, CDNF prevented the 6-hydroxydopamine (6-OHDA)-induced degeneration of dopaminergic neurons in a rat experimental model of Parkinson's disease. A single injection of CDNF before 6-OHDA delivery into the striatum significantly reduced amphetamine-induced ipsilateral turning behaviour and almost completely rescued dopaminergic tyrosine-hydroxylase-positive cells in the substantia nigra. When administered four weeks after 6-OHDA, intrastriatal injection of CDNF was able to restore the dopaminergic function and prevent the degeneration of dopaminergic neurons in substantia nigra. Thus, CDNF was at least as efficient as GDNF in both experimental settings. Our results suggest that CDNF might be beneficial for the treatment of Parkinson's disease.

This project is funded by the European Union

Structure of human CDNF protein



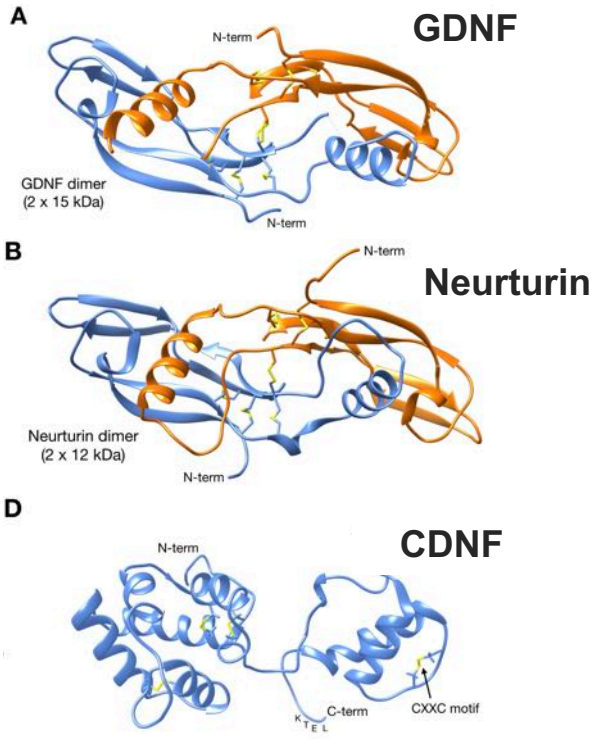
HERANTIS PHARMA

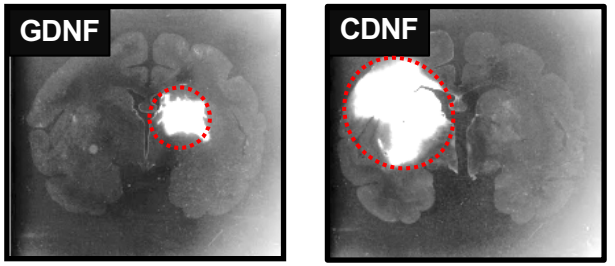
TreatER

This project is funded by the European Union

CDNF is not another GDNF! Many important differences…

- **Structure**
  - In biology, structure dictates function
  - The structure of CDNF differs from all known growth factors or neurotrophic factors
  - Structure also is relevant for pharmaceutical manufacturing and stability
- **Target pathway / mode of action**
  - Growth factors, like GDNF, bind to specific cell-surface receptors and activate secondary signaling cascades that promote cell survival
  - CDNF modulates intracellular targets in the ER that regulate cellular proteostasis
  - CDNF modulates alpha-synuclein toxicity and pathology while GDNF does not
- **Ability to diffuse in brain tissue**
  - CDNF diffuses much more broadly in brain tissue compared to e.g. GDNF and neurturin





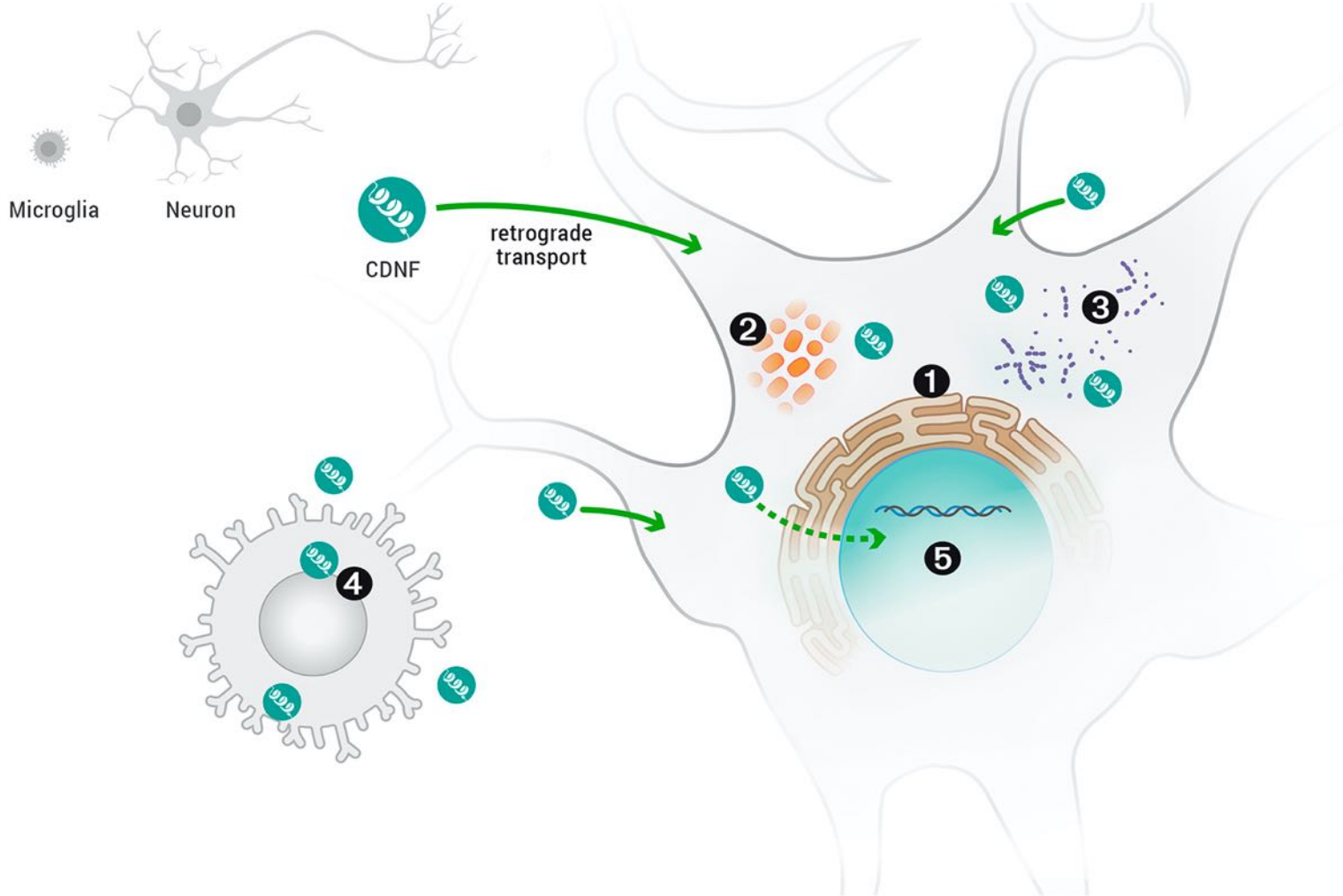
www.herantis.com

HERANTIS PHARMA

TreatER

This project is funded by the European Union

CDNF promotes neuronal survival and recovery through multiple disease-relevant mechanisms



1. CDNF promotes neuronal survival and functionality by reducing endoplasmic reticulum (ER) stress
2. CDNF promotes neuronal survival by activating Protein Kinase B (Akt)
3. CDNF inhibits α-synuclein oligomerization and toxicity
4. CDNF suppresses production and secretion of proinflammatory cytokines by glial cells
5. CDNF supports maintenance of neuronal functions by enhancing transcription of genes involved in e.g. dopamine synthesis and metabolism

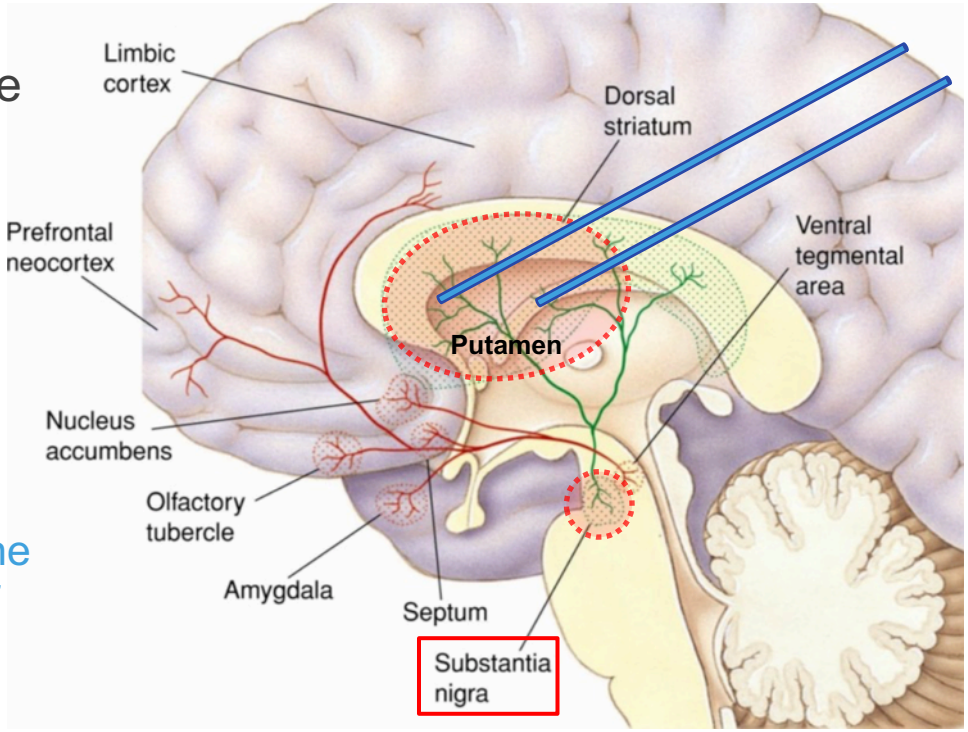
HERANTIS PHARMA

TreatER

This project is funded by the European Union

Intraputamenal CDNF infusions in Parkinson's

- Parkinson's is caused by the **degeneration and death of dopaminergic neurons** of the nigrostriatal pathway
  - Reduced striatal dopamine levels
  - Motor symptoms
- Based on preclinical data:
  - CDNF promotes functional recovery of dopaminergic terminals in the putamen
  - CDNF is transported from the putamen to the substantia nigra to protect the cell bodies of dopaminergic neurons
  - **Intermittent protein therapy** is the optimal way to modulate CDNF's target pathways
- Blood-brain barrier is a common challenge for drug delivery in brain
  - CDNF is dosed directly to the target brain area with a sophisticated medical device

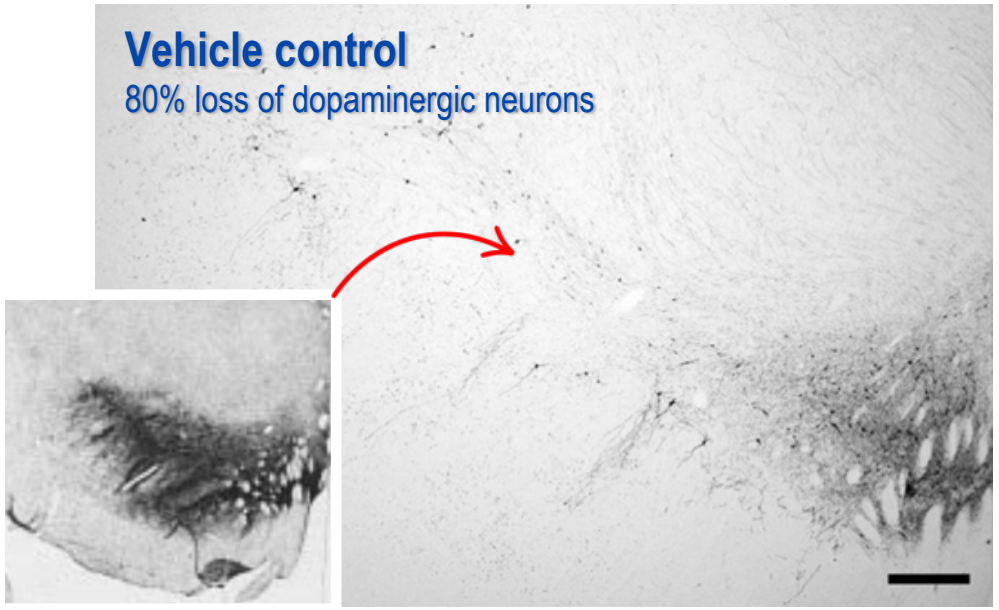


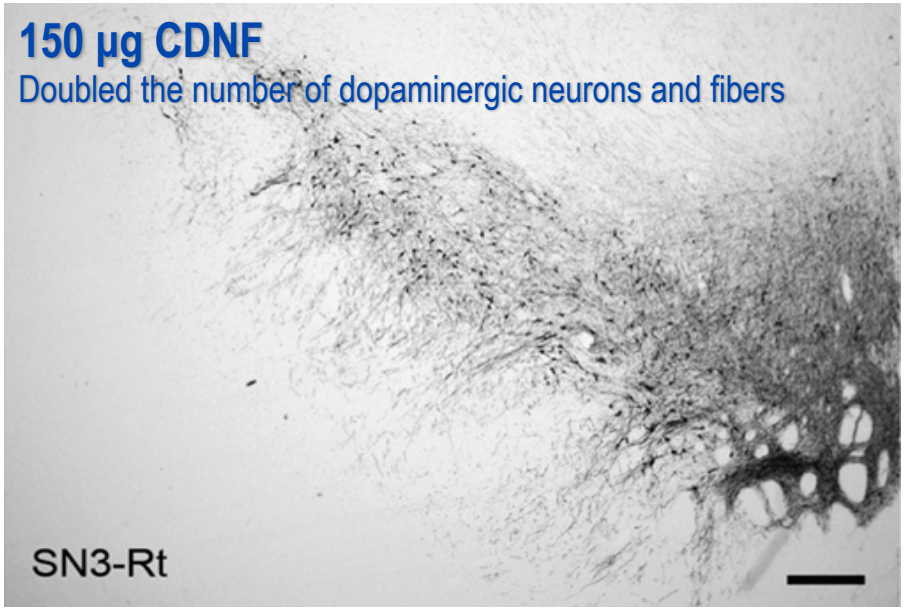
HERANTIS PHARMA

TreatER

This project is funded by the European Union

CDNF protects and recovers dopaminergic neurons in a rhesus monkey PD model





- Model: **Established** MPTP lesion in aged Rhesus monkey
  - → True neurorestoration study with 80% loss of DA neurons (dark staining)
  - → Treatment was started 6 weeks post-lesion
- Three monthly CDNF doses **doubled the number of DA neurons**
- Significant improvement in gross motor function, fine motor function, and **for the first time in the world**, non-motor symptoms

Research collaboration with University of Helsinki and University of Pittsburgh, funded by the Michael J. Fox Foundation. Manuscript in preparation.

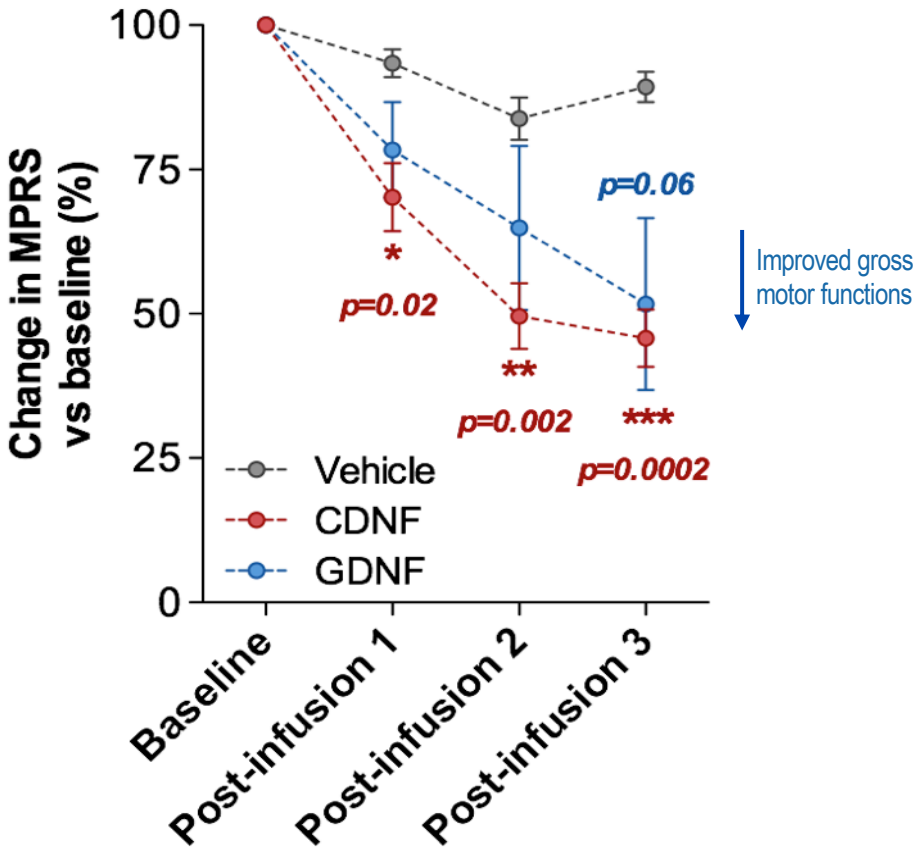
HERANTIS PHARMA

TreatER

This project is funded by the European Union

CDNF improves gross and fine motor symptoms in a rhesus monkey PD model

CDNF significantly improves motor symptoms by 53% in a MPTP rhesus model of PD at 3 months



Improvement in Motor Symptoms

- **Gross motor functions** measured with monkey Parkinsonian disability rating scale (MPRS)
- **Fine motor functions** measured with monkey movement analysis panel (mMAP)
  - Improvement shown in recovery of the use of the affected-side hand

Research collaboration with University of Helsinki and University of Pittsburgh, funded by the Michael J. Fox Foundation. Manuscript in preparation.

This project is funded by the European Union

Summary

- In Parkinson's, **dopamine neurons** die slowly and treatments like CDNF have in preclinical studies shown significant therapeutic potential in functional recovery of the degenerating neurons and neuronal functions
- Optimally, a **neurorestorative** treatment like CDNF would be started soon after the onset of symptoms. The further the disease progresses, the less there are neurons left to protect and the effects are expected to become weaker.
- **Alpha-synuclein** pathology lies at the core of Parkinson's and appears to be an important mediator of disease progression. CDNF improves cellular **proteostasis** and protects neurons from alpha-synuclein toxicity and may modulate progression of alpha-synuclein pathology.
- Based on CDNF pharmacology and mode of action, **intermittent protein therapy** offers several benefits over continuous infusion or gene therapy – despite the challenging intracranial route of administration.

This project is funded by the European Union