Neurotrophic factors in clinical trials – A brief look to the recent past, present and years to come

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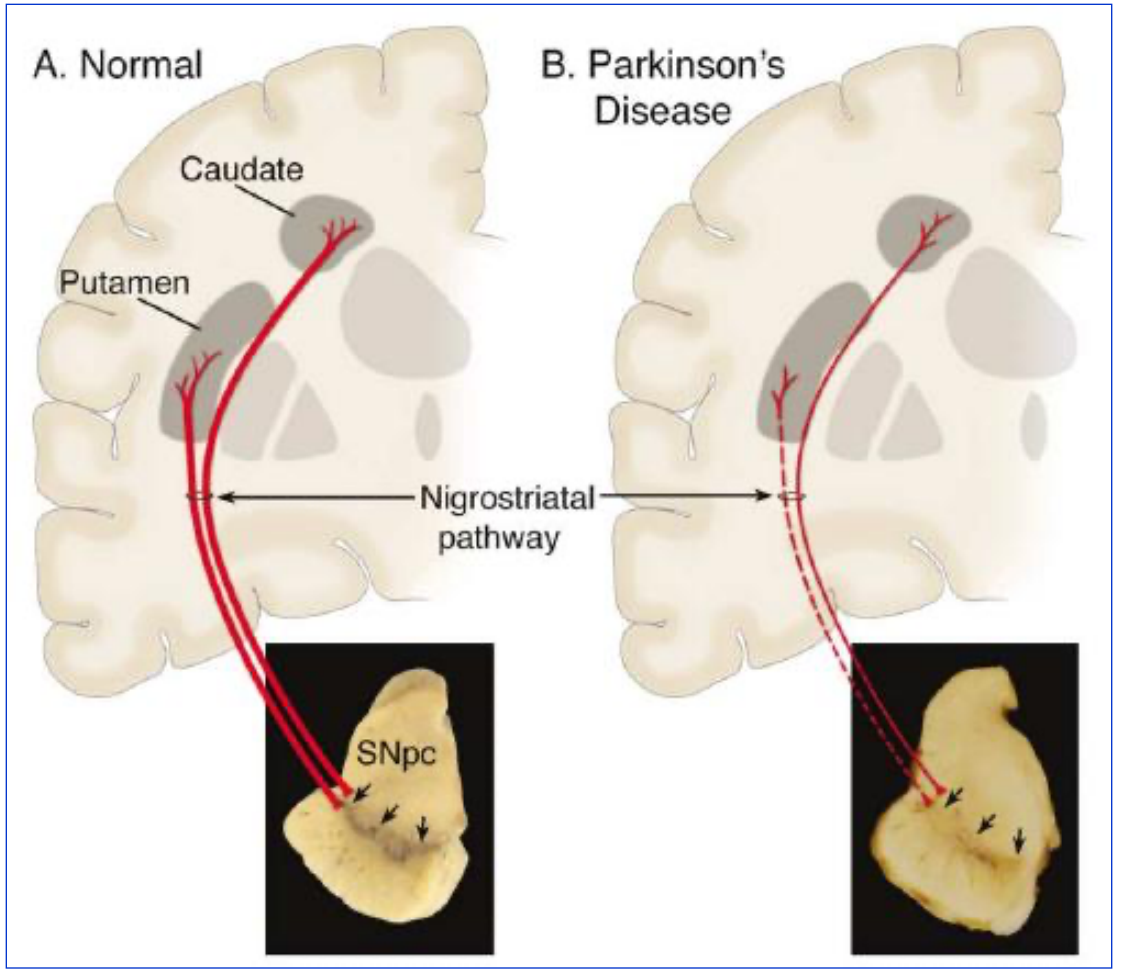
Parkinson's disease (PD): more than 10 million patients and no cure

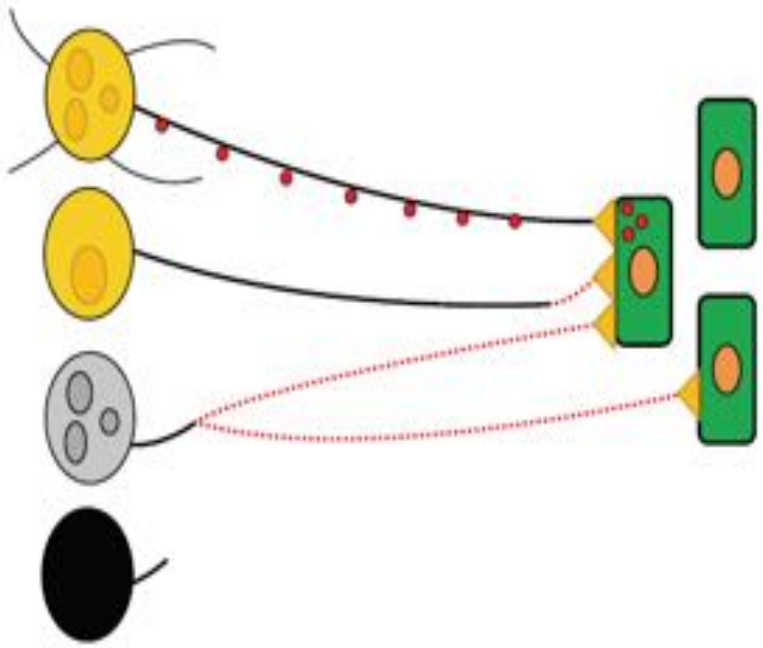
- **Progressive neurodegenerative movement disorder**
  - Loss of dopamine neurons in the nigrostriatal pathway
- Major symptoms: slowness of movement, resting tremor, rigidity and postural instability, but also non-motor symptoms
- **Motor symptoms** appear when there's ~40-50 % loss of dopamine (DA) neurons in SNpc and ~60-70 % reduction in striatal dopamine levels
- **Non-motor symptoms**: constipation, hyposmia, depression, lack of motivation, sleep disorders, cognitive decline etc. significantly decreasing quality of life



Dauer and Przedborski, 2003

Neurodegeneration in PD and current symptomatic treatments

- DA neurons lose synapses
- DA neuronal axons degenerate
- Daergic neurons lose their special phenotype and functional properties
- DA neurons finally die



- **Current therapies** (e.g. L-dopa+carbidopa+entacapone or dopamine agonists) are symptomatic and do not arrest or attenuate the progression of the disease
- **Future therapies** should include interventions that slow down or reverse the progression of the neuronal degeneration
  - prevent the degeneration and death of DA neurons
  - regenerate DA neurons
  - increase the functional activity of the remaining DAergic neurons

Why and how dopamine neurons degenerate and die?

- Postmitotic cells with very modest or no neurogenesis in mammals
- Have extensive network of neurites that is demanding for energy and intracellular trafficking (500,000 dopamine release spots per neuron!)
- Produce massive amounts of dopamine that requires strong protein synthesis and dopamine in oxidized form may be toxic
- Mutations in genes (aSynuclein, LRKK2, Pink 1 etc.) - about 20 genes identified
- **Dopamine neurons: die in aging, poisoning and in Parkinson's disease**

We know very little why and how dopamine neurons die

Brain is a very complex organ - 10^{11} neurons and 10^{14} synaptic contacts that change

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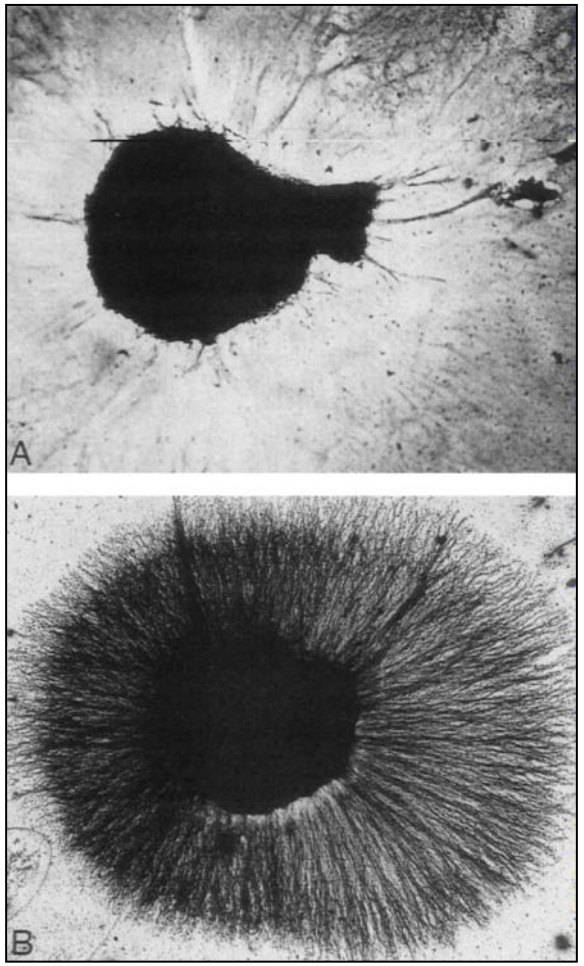
Neurotrophic factors can keep neurons alive and protect them

- Promote neuronal survival and control the number of neurons in the nervous system
- Stimulate neurite outgrowth and axonal regeneration
- Protect neurons from toxins and injury
- Regulate synaptic plasticity
- Nerve growth factor (NGF) was the first growth factor and neurotrophic factor discovered



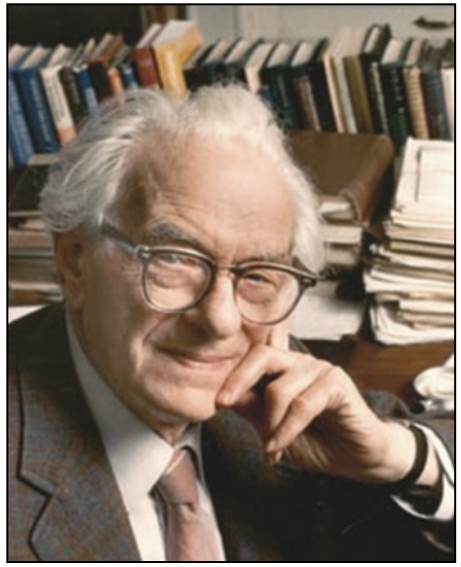
Effect of NGF on chicken sensory ganglion

The Nobel Prize in Physiology or Medicine for Levi-Montalcini and Cohen in 1986

"for their discoveries of growth factors"

Stanley Cohen
1922-2020

Rita Levi-Montalcini
1909-2012



Victor Hamburger
1900-2001

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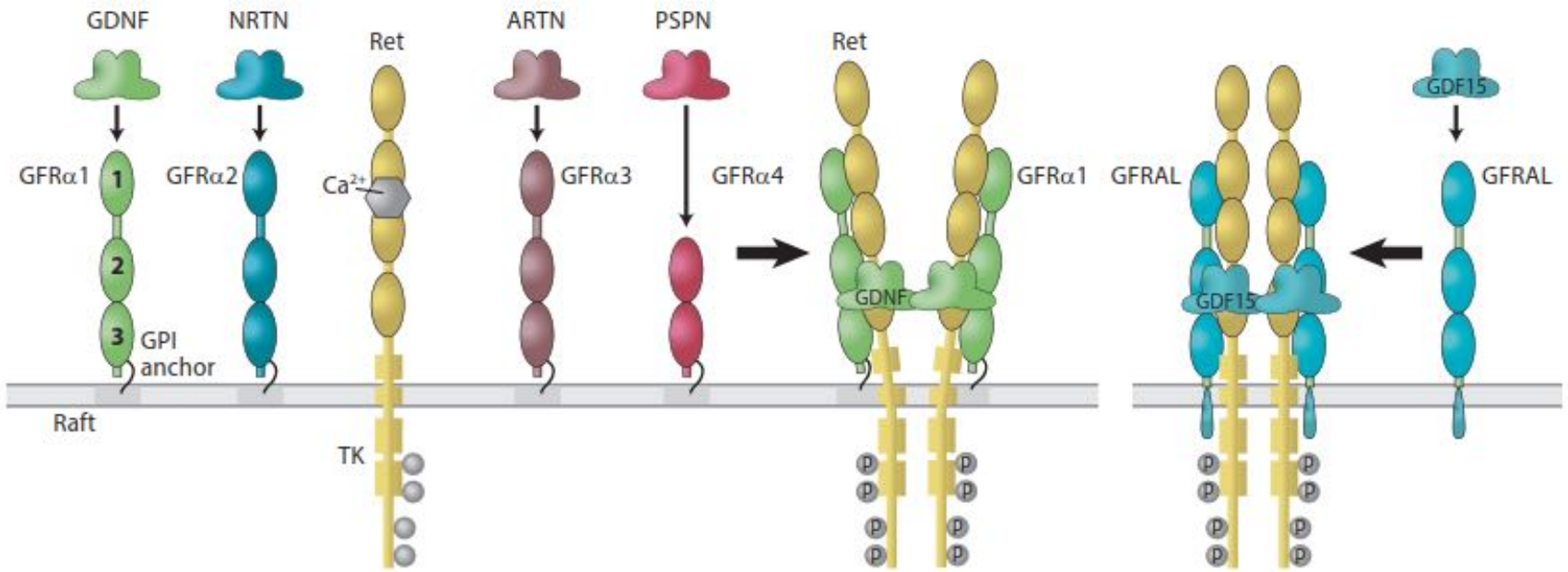
GDNF family ligands GDNF and NRTN activate GFRα-RET receptor complexes promoting survival and regenerating axons of dopamine neurons in neurotoxin animal models of PD

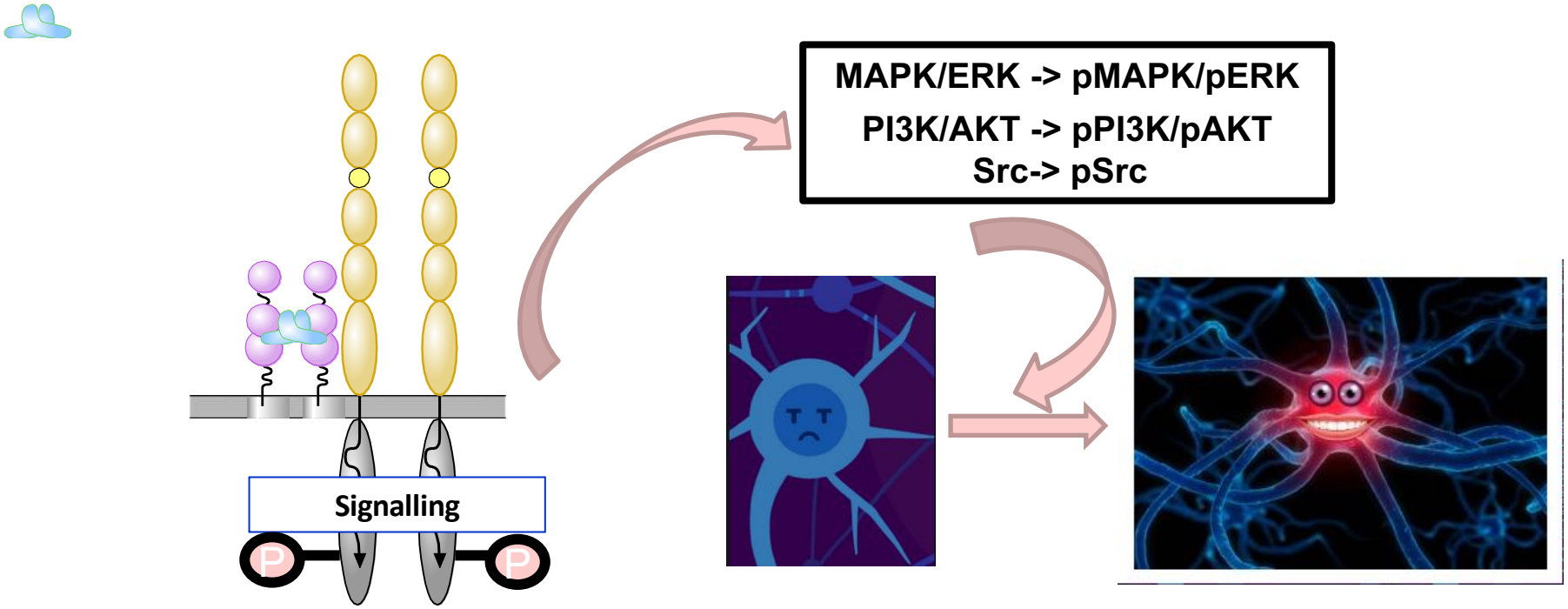


Trupp et al. *Nature*, 1996;
Durbec et al. *Nature*, 1996

Airaksinen & Saarma *Nature Rev. Neurosci.,* 2002; Andressoo & Saarma *Curr. Opin. Neurosci.,* 2008; Kopra et al. *Nature Neuroscience*, 2015; Saarma & Goldman *Nature*, 2017; Sidorova & Saarma *TIPS*, 2020

GDNF signalling

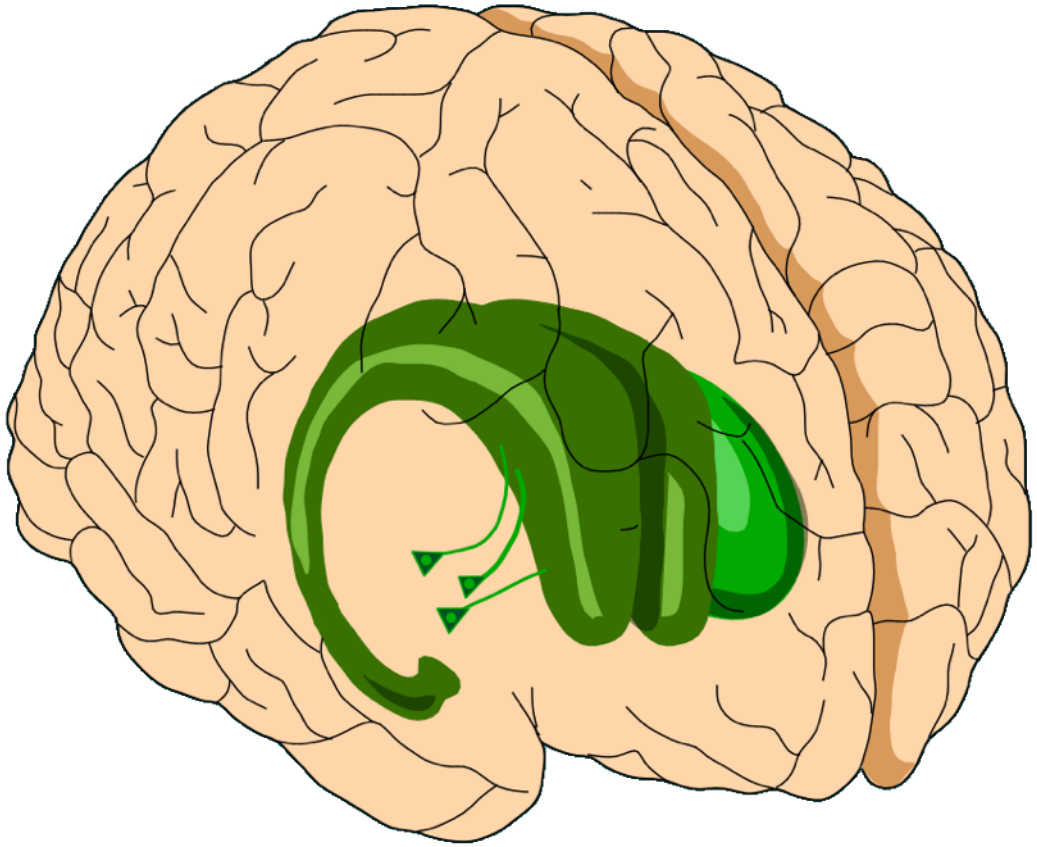
GDNF binds first to the co-receptor GFRα1 and then the complex binds to and activates RET



GDNF and NRTN activate via RET transcription factors inducing long-lasting effects

Leppänen et al. *EMBO J.,* 2003; Parkash et al. *J Biol Chem.,* 2008; Saarma & Goldman *Nature,* 2017

Intracranially injected GDNF & NRTN can protect and repair DA neurons in moderate neurotoxin animal models of PD



GDNF and NRTN can protect and repair DA neurons in neurotoxin-induced animal models of PD

GDNF and NRTN are basic proteins and diffuse poorly in mammalian brain

GDNF has no effects on AAV2-α-synuclein model of PD

GDNF works poorly in severe 6-OHDA and MPTP models

Saarma et al. *Movement Disorders*, 2012; Lindahl et al. *Neurobiol. Dis.*, 2017

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GDNF and NRTN in phase I-II clinical trials for Parkinson's disease

- There have been 3 phase II clinical trials with GDNF protein and the outcome is:

a) no clear clinical benefit in two first trials

b) promising results with GDNF in the third trial

- Two phase II clinical trials with NRTN gene therapy with statistically significant, but modest clinical effect

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Clinical trial I: Intraventricular infusion of GDNF (Nutt et al. 2003)

50 patients; placebo (n=12), various monthly doses of GDNF (25 to 4 000 micrograms)

- randomized, double-blind (8 months), open-label up to 20 months
- no improvement of UPDRS motor score
- adverse events common: e.g., paresthesias, nausea, weight loss

- GDNF did not reach putamen and substantia nigra

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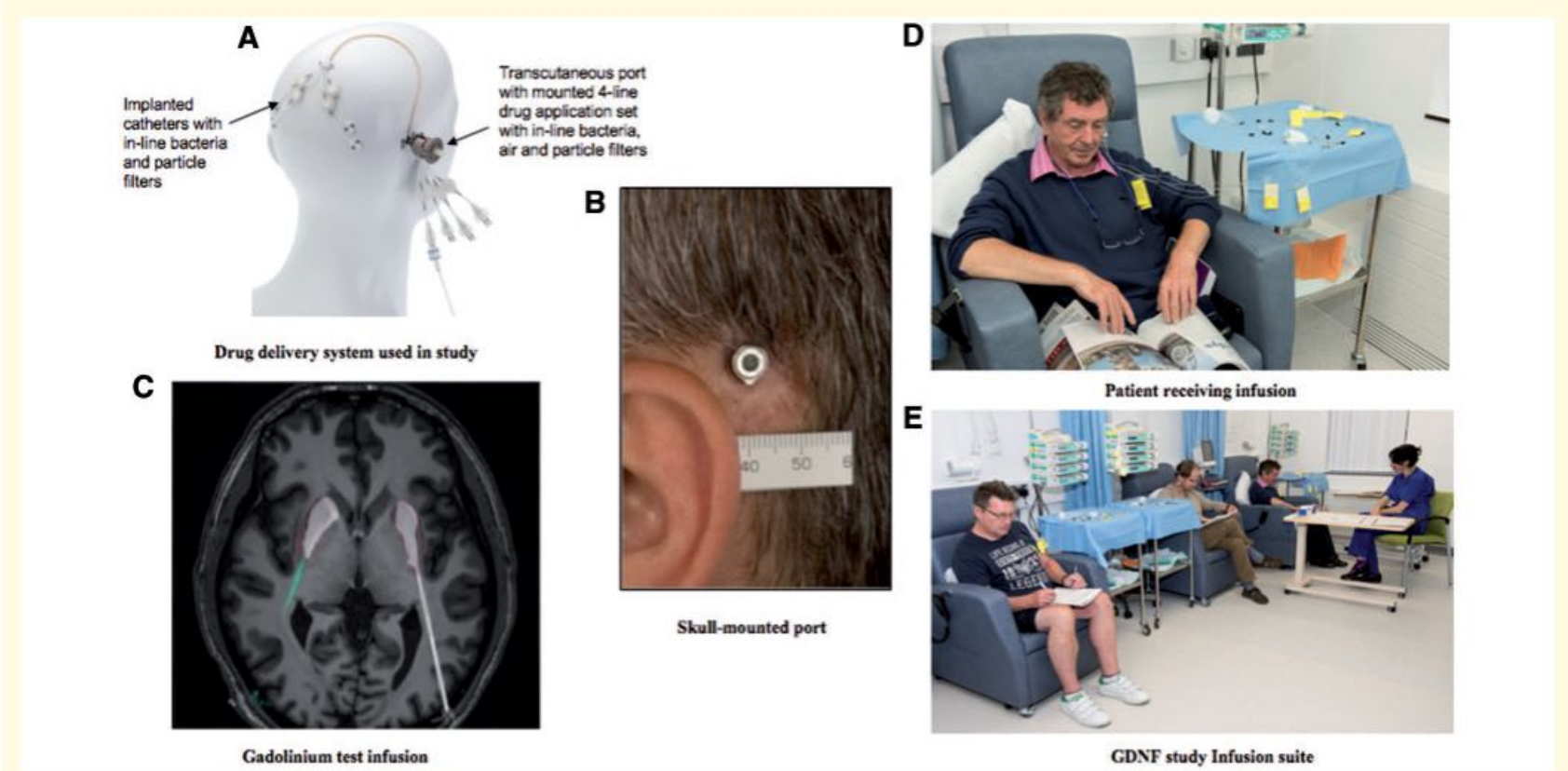
Clinical trial III: Dr. S. Gill, Dr. A. Whone and Medgenesis Ltd. used intermittent GDNF protein delivery



Clinical trial III: Dr. S. Gill, Dr. A. Whone and Medgenesis Ltd.

Table I Demographic and Parkinson's disease characteristics at screening

Characteristic	GDNF (n = 17)	Placebo (n = 18)
Age, years	57.7 ± 8.2	55.1 ± 7.5
Male sex, *n* (%)	7 (41.2)	11 (61.1)
Race, *n* (%)		
White	17 (100)	17 (94.4)
Asian	0	1 (5.6)
OFF-state Hoehn and Yahr stage, *n* (%)		
Stage 2	8 (47.1)	5 (27.8)
Stage 2.5	4 (23.5)	8 (44.4)
Stage 3	5 (29.4)	5 (27.8)
Disease duration, years		
Since first motor symptom	10.8 ± 5.0	10.9 ± 5.8
Since original diagnosis	8.6 ± 4.3	7.9 ± 3.7
UPDRS motor score		
OFF state	37.1 ± 7.2	35.8 ± 6.1
ON state	16.9 ± 5.2	16.9 ± 4.5
Levodopa response, %[a]	54.2 ± 9.4	52.8 ± 9.4
OFF-time per day, h	6.3 ± 2.2	6.1 ± 2.1

[a]Percentage improvement in UPDRS motor score following a levodopa challenge.

With all patients pooled UPDRS score did not show significant differences between the groups either

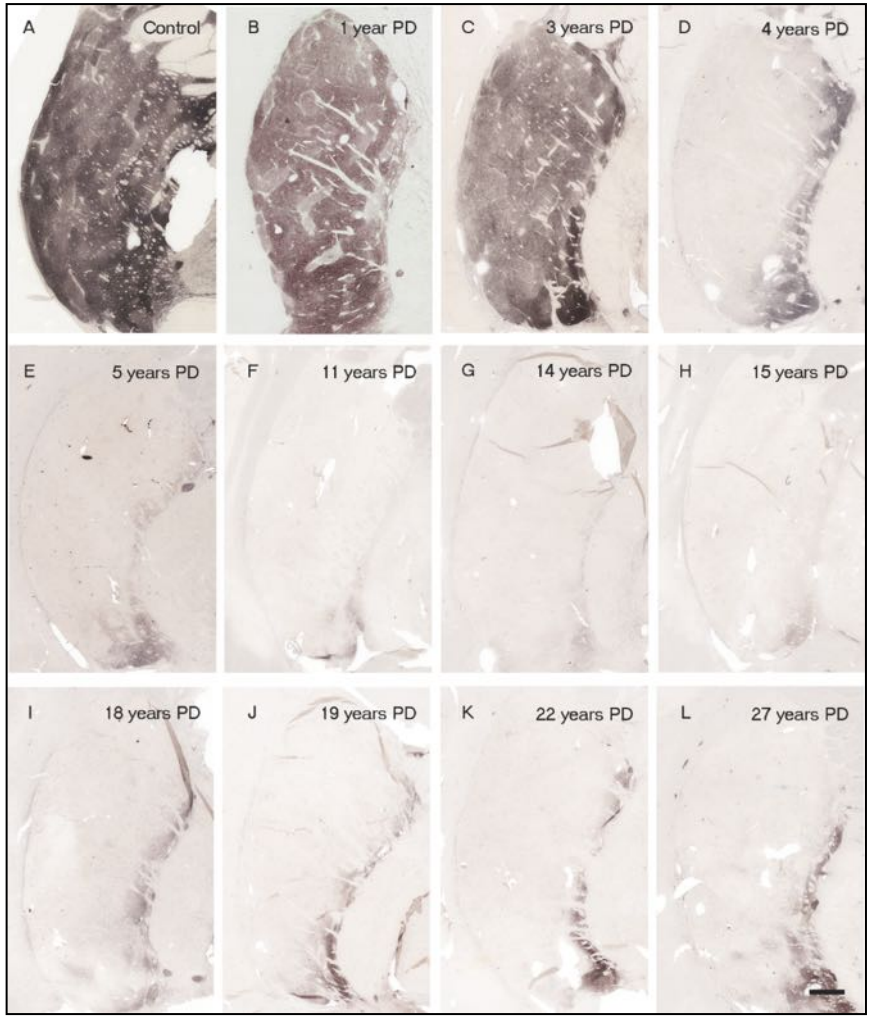
A post hoc analysis found nine (43%) patients in the active group but no placebo patients with a large clinically important motor improvement

^{18}F-DOPA PET imaging demonstrated a significantly increased uptake throughout the putamen only in the active group

GDNF appeared to be well tolerated and safe, and no drug-related serious adverse events were reported

Whone et al. *Brain*, 2019

Dopamine neurons degenerate and die in the midbrain of PD patients



Kordower, 2013

Starting from 4-6 years after diagnosis PD patents have very little TH-positive fibres of dopamine neurons in the caudate putamen

In animal models neurotrophic factors do not work when more than 80% of the fibres have been lost

GDNF can slow down neurodegeneration in PD patients – first time in the treatment of a chronic neurological disease?

What can we do better?

Treatment should be started **as soon as possible** after diagnosis – ethical considerations connected to invasive surgery do not allow to treat early stage patients

Develop **mammalian cell produced or modified neurotrophic factors** with improved properties and ability to pass through the BBB to avoid brain surgery

Develop compounds that can increase **the levels of endogenous brain neurotrophic factors**

Develop small molecules that **mimic the actions of neurotrophic factors**

Search for **new neurotrophic factors** with better therapeutic properties

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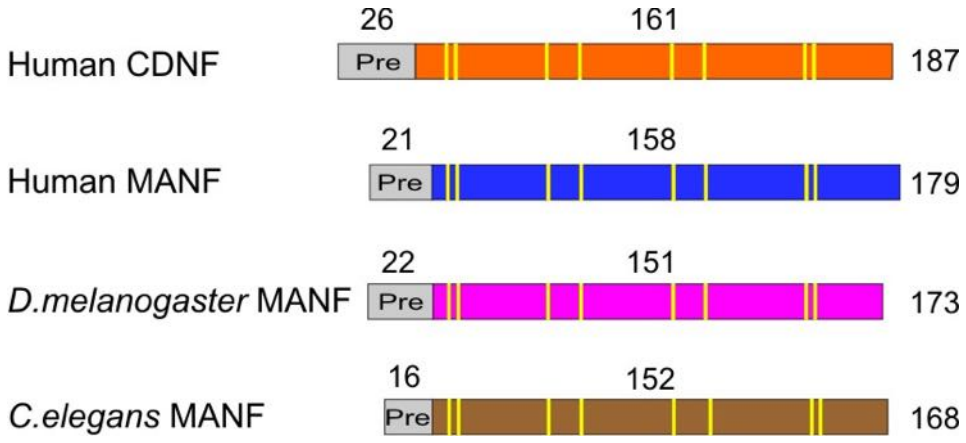
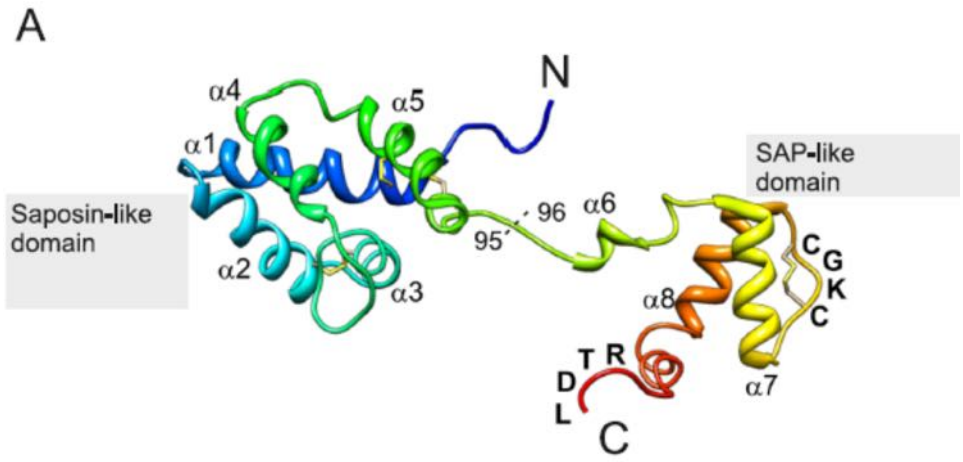
CDNF discovery - has unique sequence, 3D structure, mode of action and forms with MANF a novel group of unconventional neurotrophic factors





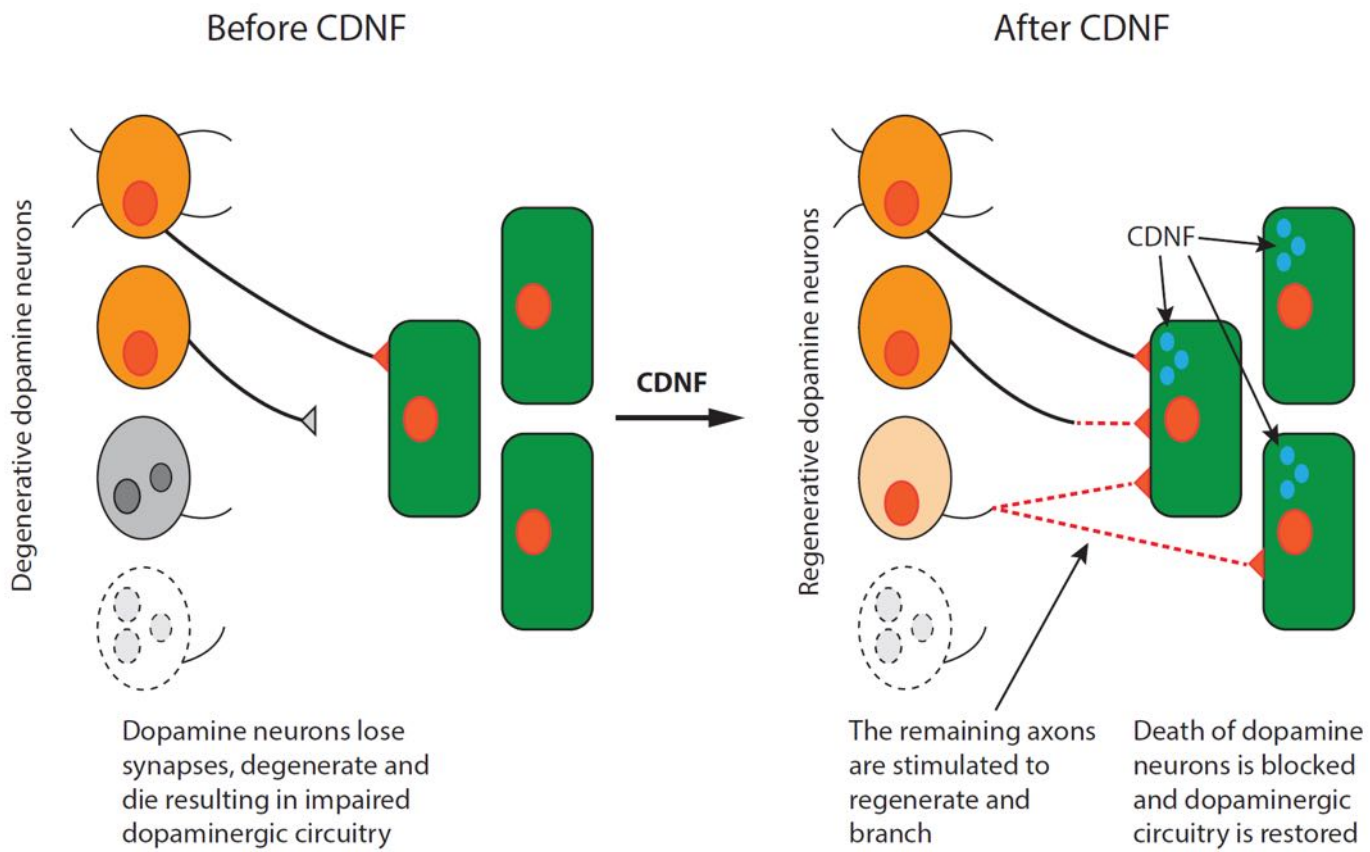
Päivi Lindholm

- MANF and CDNF in vertebrates; single CDNF/MANF homolog in invertebrates (50% homology).
- No sequence homology with other proteins
- Mainly located and operate in the ER
- Have no effects on naive cells

CDNF & MANF mode of action is emerging

Lindholm et al. *Nature*, 2007
Voutilainen et al. *J. Neurosci*, 2009
Lindahl et al. *Cell Reports*, 2014

CDNF protects and rescues dopamine neurons in animal models of Parkinson's disease and also affects some non-motor symptoms



We formed a biotech company Herantis Pharma Ltd. that has started to develop CDNF-based drugs

Thank you for your attention!