GENECODE

Development of Disease-modifying Treatment for Neurodenerative Diseases

GDNF Mimetics Development History

GENECODE

1996

RET, identified as the GDNF receptor

BT13 GDNF receptor agonist identification

2009

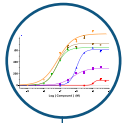
***In vivo* target engagement** with BT13 (intracranial)

2021

Improvement of motor function in rat 6-OHDA with BT44 (intracranial)

Jan. 2022

Start of lead optimization with Serge Mignani



Sep. 2022

First cpds with **same level of efficacy as GDNF *in vitro***

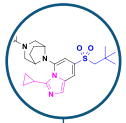
Feb. 2023

First cpd, showing both brain penetration after oral admin. and **neuroprotection *in vitro***

1. GDNF mimetic for Parkinson's management. Mahato et al., 2020.
2. GDNF receptor RET agonist for PD. Renko et al., 2021.

March 2023

Neuroprotection show in human DA neurons (EAR586, EAR685)

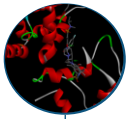


June 2023

EAR993 showing improved metabolic stability and brain penetration (MDCK)

July 2023

3 new patents filed



Aug. 2023

EAR911 showing higher neuroprotection than GDNF in human DA neurons

Jan. 2024

IND/CTA-enabling studies

March 2025

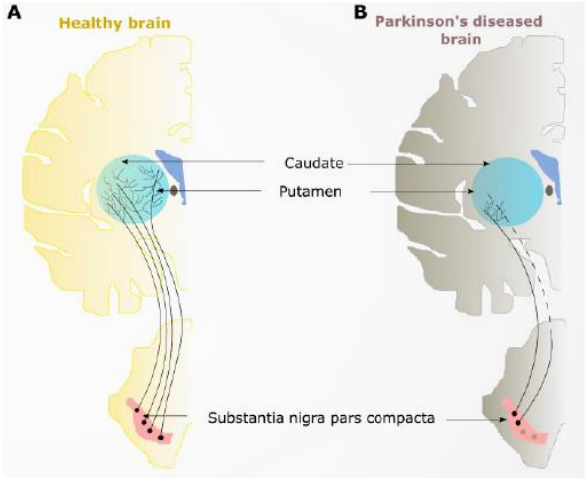
IND enabling

March 2026

March 2027

Phase 1a / Phase 2a

Neurotrophic Factors and Parkinson's Disease



- Progressive neurodegenerative disorder
- Degeneration and loss of dopamine neurons is associated with motor and non-motor symptoms of PD

Patients with Parkinson's disease:

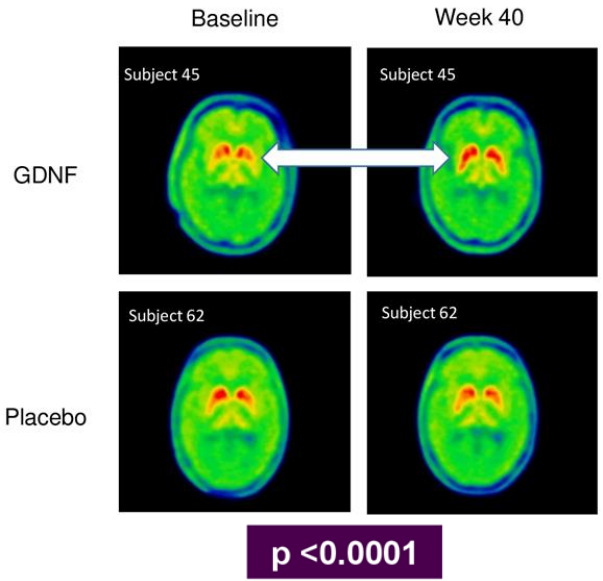
- 1% of people over the age of 65 are developing Parkinson's disease
- 10 million patients worldwide have been diagnosed with PD, with this number expected to double by 2040
- Economic Burden (US 2017) = $51B
- Motor symptoms are partially addressed but no disease-modifying drug exists to protect or restore dopamine neurons
- No treatment for non- motor symptoms

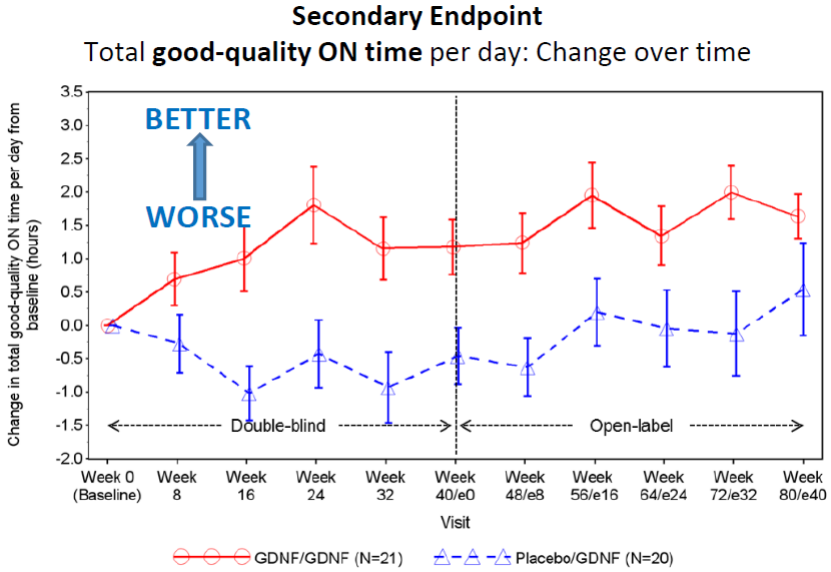
Growth factors do **not only protect but also <u>restore</u>** degenerating neurons, promote arborization and sprouting of their neurites, and enhance their functional activity

Neurotrophic factors are an attractive target for supportive and neuro-restorative therapeutic approaches

Sidorova and Saarma TIPS, 2020; Mahato AK and Sidorova YA. Cell Tissue Res. 2020

Neurotrophic Effects of GDNF Revealed in Patients with PD

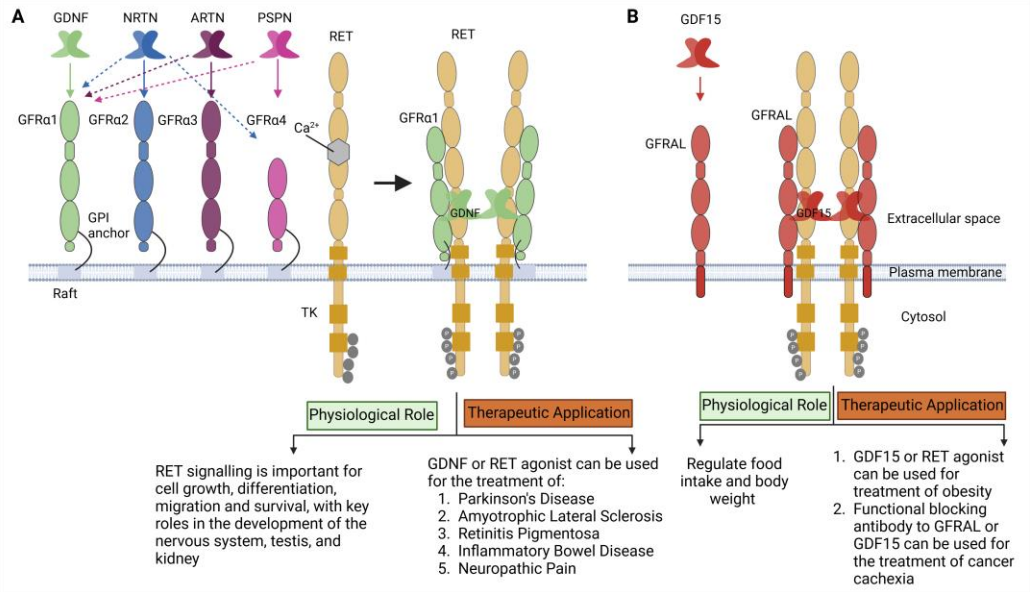




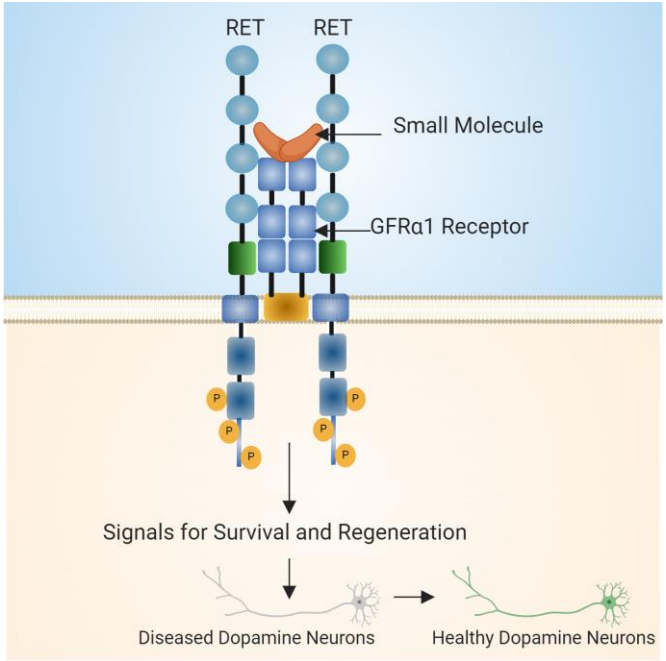
Core Treatment Details	• 21 per group, with mid-stage PD, all receiving four catheters and port (new design) • Infusion every 4 weeks for 40 weeks (GDNF-240 ug or vehicle) then all patients are rolled over into an open-label all active (40 weeks)
Efficacy Summary	• Primary efficacy outcome not statistically significant (UPDRSIII in OFF time) • Improvements in good “ON time” over baseline (will be the primary endpoint for future trials) • Biological effect demonstrated by PET Imaging. Expert: Prof. Jon Stoessl

Finding Small Molecule with same MOA as GDNF

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

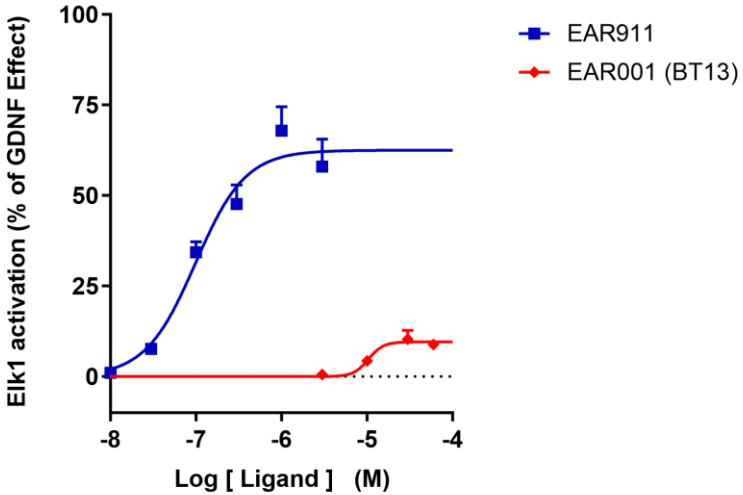


Targeting GDNF receptors with small molecules

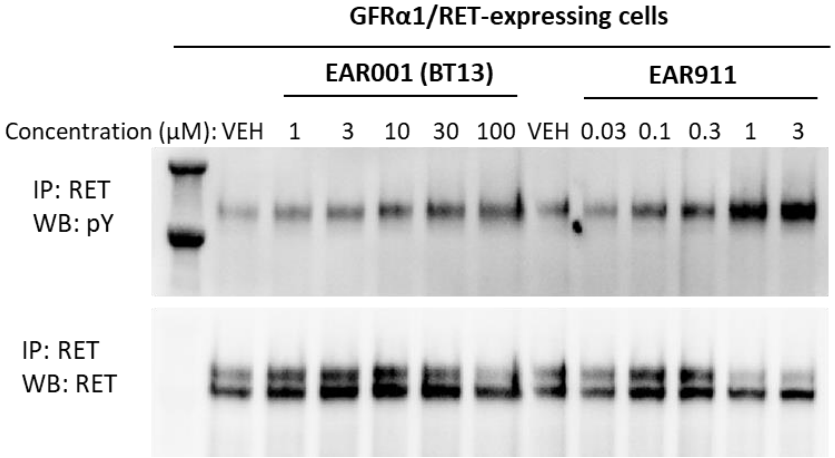


EAR911 activates GDNF signalling pathways via RET receptor

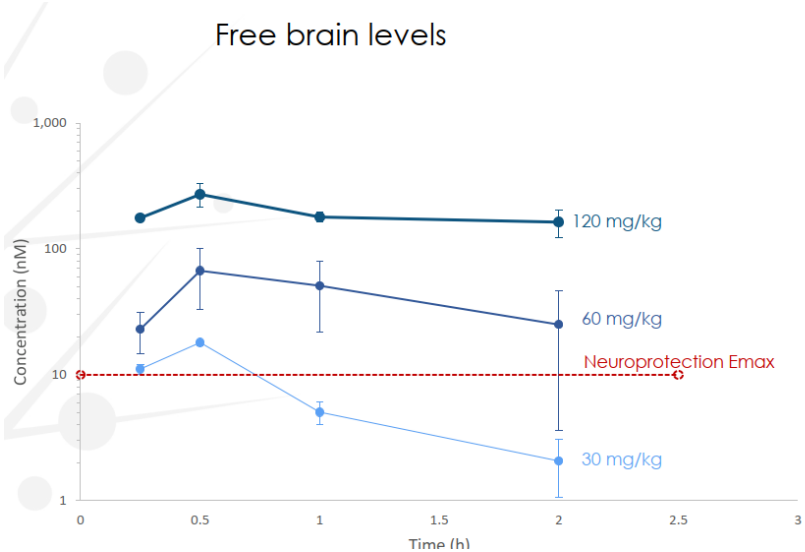
LUCIFERASE ASSAY

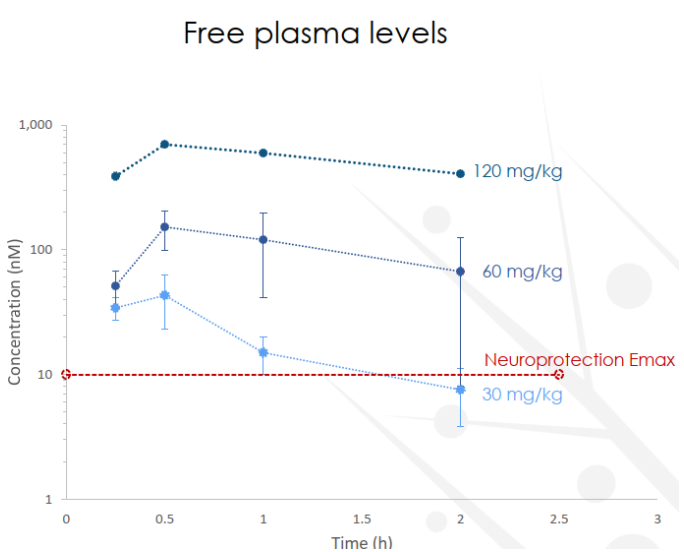


DIRECT RET PHOSPHORYLATION ASSSAY



EAR911- Mouse PO pharmakokinetics

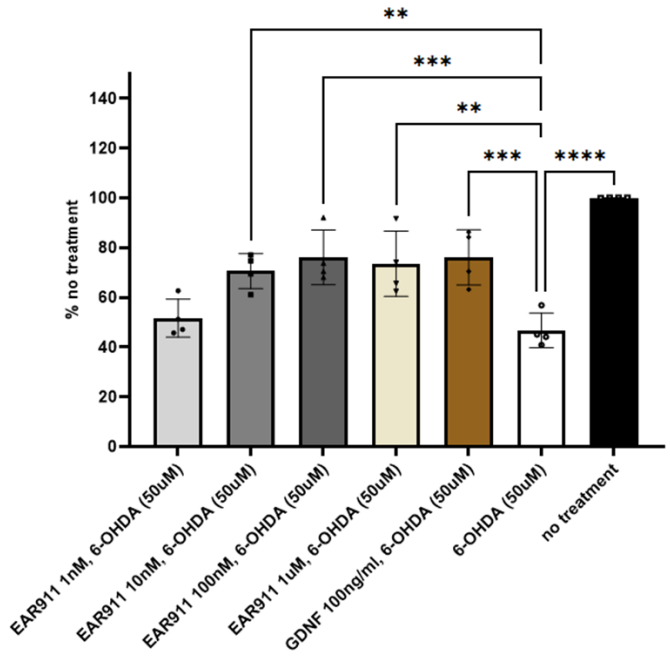




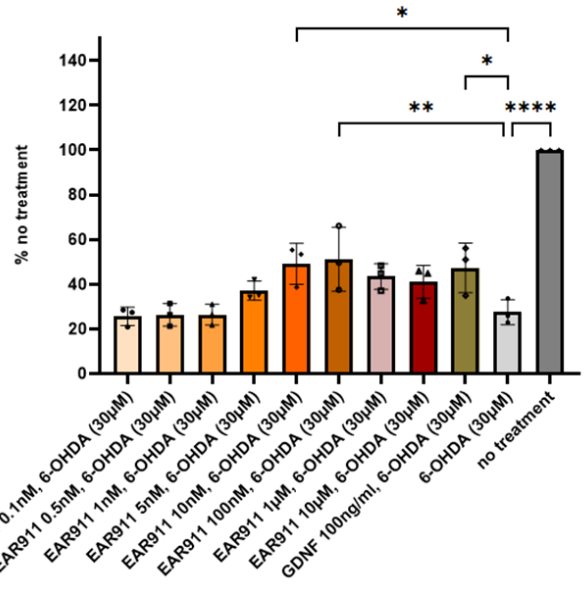
Formulation: 10 % DMSO, 10 % Solutol H15, 40% PEG 200, 40 % 0.01% Tween 80 in 10 mM Tris buffer pH8

EAR911 protects both wild-type and α-synuclein mutated human dopamine neurons from neurotoxin-induced cell death

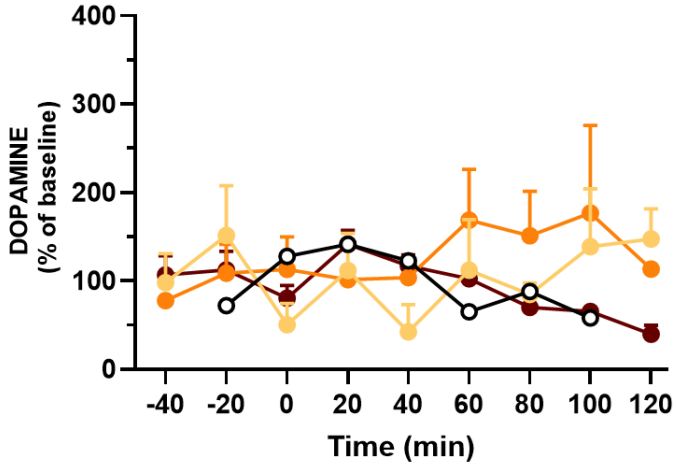
Wild-type Human Dopamine Neurons

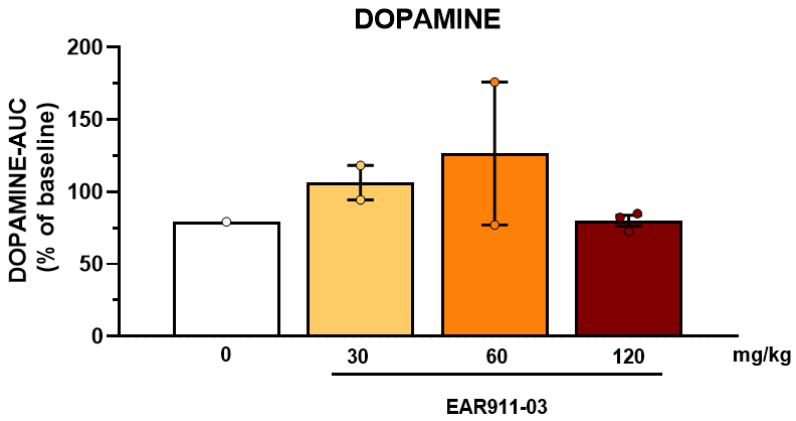


α-synuclein A53T-Mutated Human Dopamine Neurons

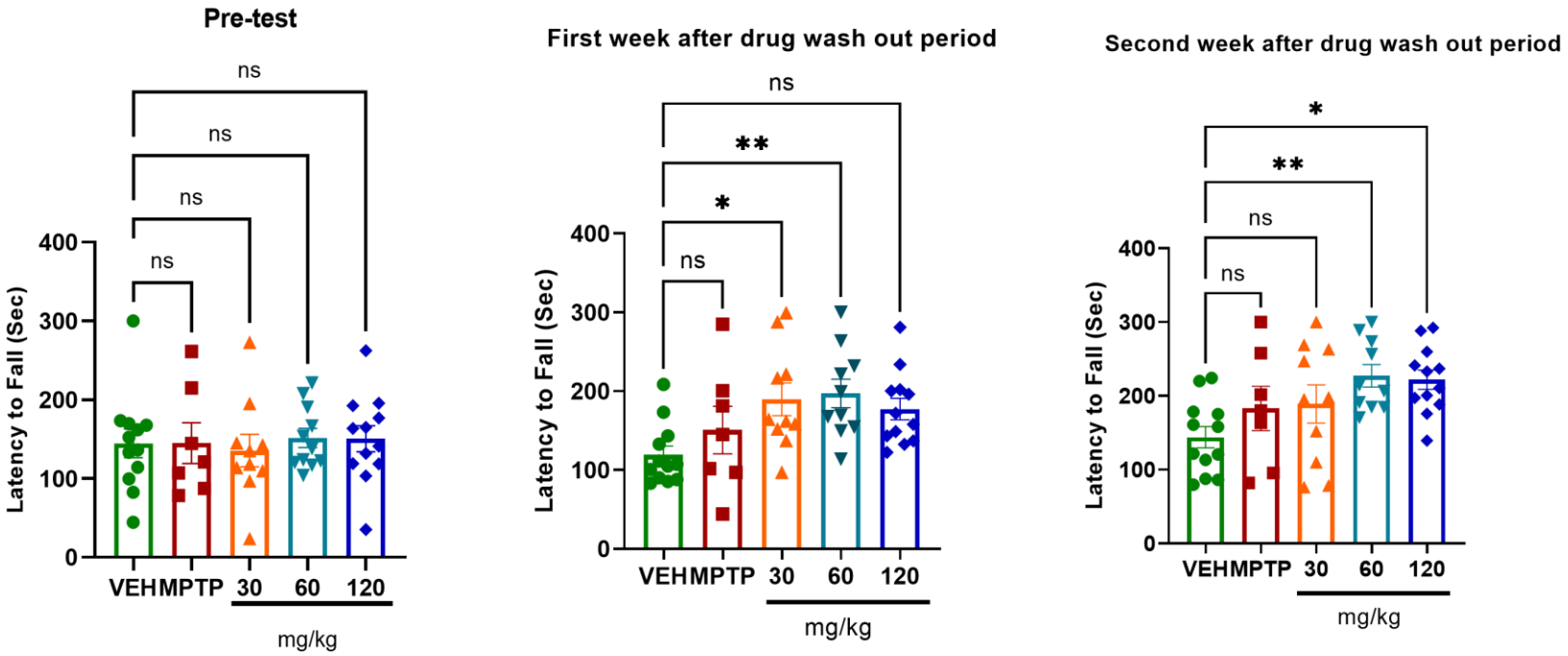


EAR911 penetrates blood-brain barrier and increases dopamine release

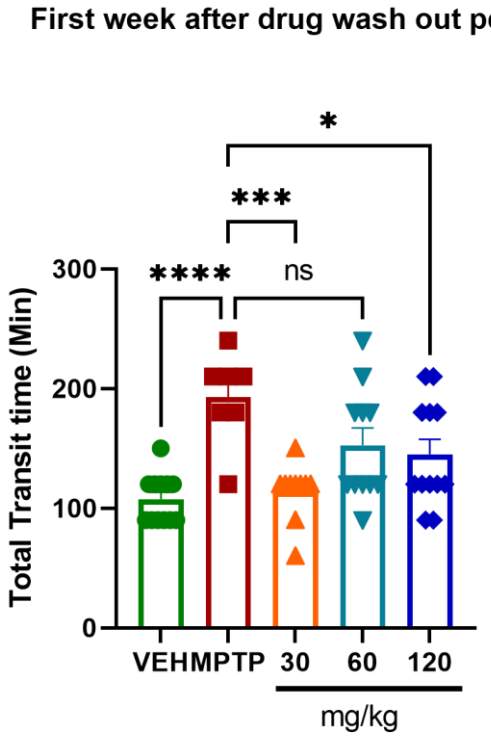




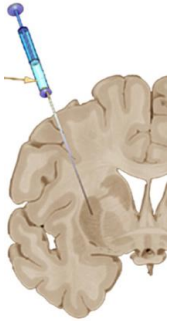
Systemic delivery of EAR911 improves motor coordination and motor learning in rotarod test in the MPTP-Probenecid mouse model of Parkinson's disease



EAR911 rescues gastrointestinal tract dysfunction in the MPTP-Probenecid mouse model of Parkinson's disease



From biological concept to small-molecule drug



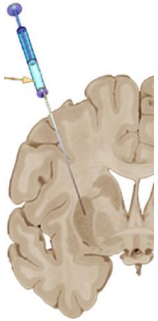
GDNF

EC_{50} = 5 nM

Efficacy= 100%

Active in patients

Intraputaminal administration



BT13

EC_{50} = 13000 nM

Efficacy= 10%

Active in rodents models of Parkinsons's disease

Intraputaminal administration

EAR911

EC_{50} = 5 nM (Neuroprotection)

Efficacy= 100%

Active in patients

Neuroprotection in human dopamine neurons, penetrates BBB and stimulates dopamine release, improves both motor and non-motor symptoms in MPTP model of PD

Take-Home Message

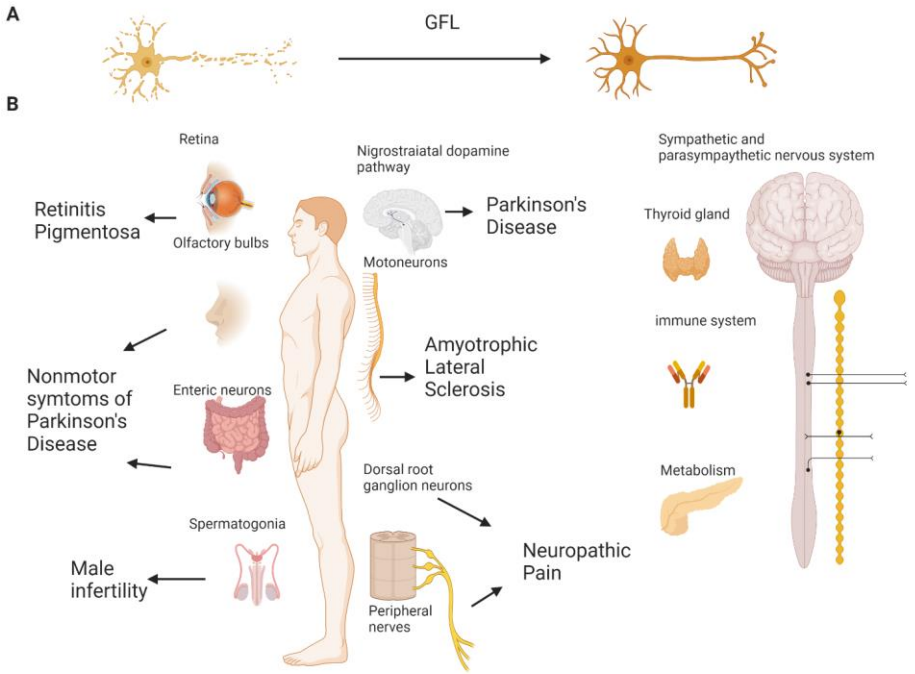
- EAR911 penetrates BBB and stimulates dopamine release
- EAR protects and regenerates human iPSC-derived wild-type and α-synuclein mutated dopamine neurons
- EAR911 in mouse model of Parkinson's disease improves global motor behavior of mice
- Most importantly, systemically delivered EAR911 dramatically reduced constipation and normalized the function of gastrointestinal tract (GIT)
- Currently, we are analyzing the brain tissues from MPTP study by immunohistochemistry

Possible Targets of GDNF Mimetics

- Successfully continuing PD development means that GeneCode has a **wide range of potential follow-up activities based on the GDNF Mimetics** platform development.

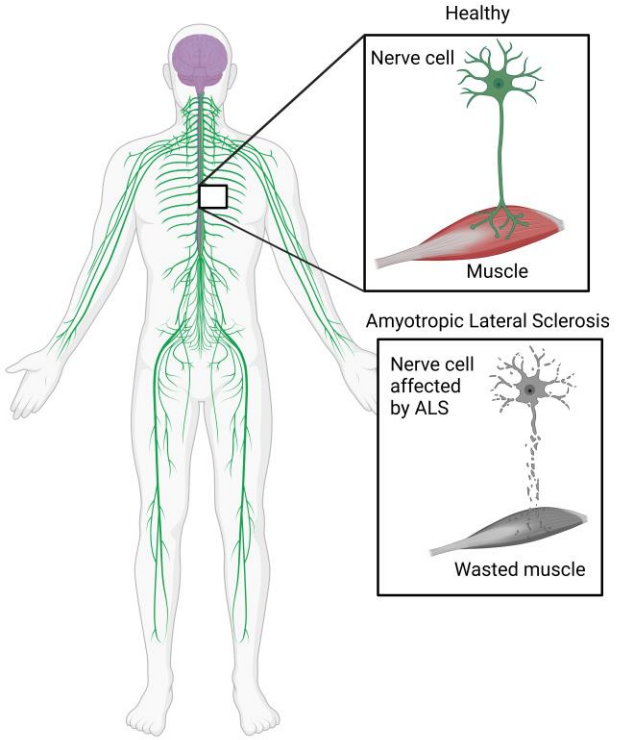
- Our preliminary studies indicate that **the 3 most promising indications are: Amyotrophic Lateral Sclerosis (ALS), Retinitis Pigmentosa (RP), and Inflammatory Bowel Disease (IBD).**

- **As a proof of concept, we have started studying GDNF mimetics *both in vitro* and *in vivo* model of ALS, RP and IBD**



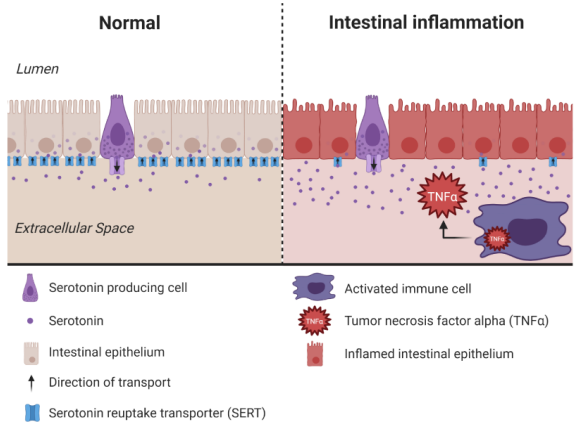
Neurotrophic factors and Amyotrophic lateral sclerosis (ALS)

- ALS is fatal neurodegenerative disease affecting both upper and lower motor neurons
- The progressive loss of motor neurons causes rapid loss of motor control, leading to paralysis and death within 3-5 years of symptom onset
- Glial cell line-derived neurotrophic factor (GDNF) has the potential to support the survival and maintenance of motor neurons with 100 times more efficacious than other trophic factors
- A recent Phase I/II safety study was conducted by transplanting human progenitor cells (hNPCs) engineered to produce and secrete GDNF unilaterally to the lumbar spinal cord. In this safety trial, the primary endpoint of safety was met, and the results from postmortem tissues grafted cells survived and produced GDNF
- **<u>The second clinical trial is underway to evaluate the cortical delivery of hNPCs-GDNF</u>**



Neurotrophic factors and Inflammatory bowel disease (IBD)

- IBD is a term for two conditions Crohn's disease (CD) and ulcerative colitis (UC) and is characterized by chronic inflammatory process of patient's gut
- Disruption of intestinal epithelium layer is a semi permeable physical barrier might play role in the development and progression of IBD
- **GDNF and its receptors** are significantly expressed in intestine and play important role regulating epithelia tight junction in the intestinal epithelial barrier (IEB) and protect intestinal cell invasion from bacterial infection
- **GDNF also acts as anti-inflammatory agent in murine models of colitis**
- Recent finding indicate that GDNF was significantly reduced in IBD patients with CD and UC, indicating disease-relevant contribution to the development of IEB dysfunction
- **Our recent finding shows that GDNF mimetics recues gastrointestinal dysfunction which indicates that GDNF mimetics can be drug for IBD**



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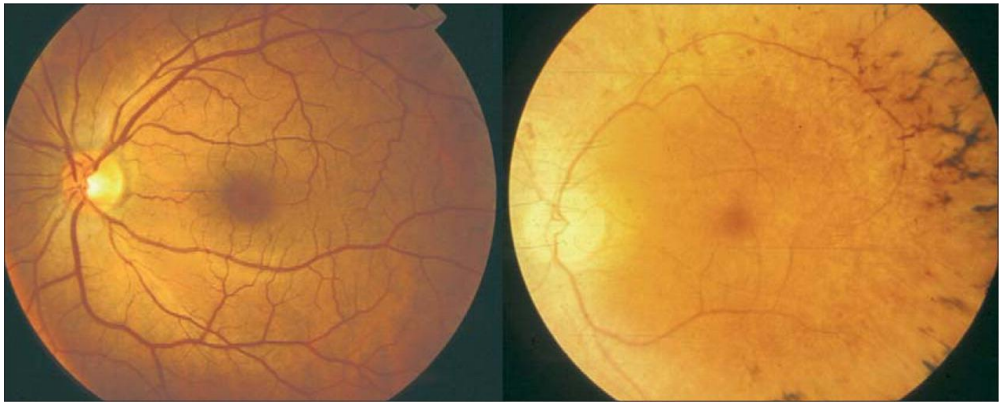
Patients with IBD:

- About 4 million females and 3 million males are living with IBD worldwide and cases is on rise
- The prevalence of IBD was reported to range from 252 to 439 cases per 100 000 population in the USA.

Neurotrophic factors and Retinitis pigmentosa (RP)

- RP is a group of inherited disorders characterized by the progressive dysfunction of predominantly rod followed by cone photoreceptor cells
- **GDNF receptors are predominantly expressed in retinal ganglionic cells as well as in Müller cells of the retina**
- Both *in vitro* as well as *in vivo* studies show that GDNF promotes the survival of photoreceptor and ganglionic cells after injury
- Recently, subretinal injection hNPCs-GDNF has shown significant neuroprotection and enables the extended survival of photoreceptor cells in transplanted animal eyes
- **Phase I/IIa clinical trial of transplanting hNPCs-GDNF into the subretinal space of RP patients is ongoing**

HEALTHY RETINA RETINITIS PIGMENTOSA



Patients with Retinitis Pigmentosa:

- The worldwide prevalence of retinitis pigmentosa is about 1 in 4000 for a total of more than 1 million affected individuals.
- Currently, there are no treatment available to stop the disease progression and restore the vision
- **As a proof of concept, we are studying GDNF mimetic in both *in vitro* and *in vivo* models of RP**

Development Overview

An Estonia-based biotech company focused on developing small molecule GDNF mimetics with the potential for disease-modifying treatments for nervous system disorders

Drug Development Launch **2007**

HQ in **Tallinn, Estonia**

Team of **20+**

EUR 14.2m Funding to date

GeneCode is developing novel small molecule GDNF mimetics with the potential for disease-modifying treatments for nervous system disorders

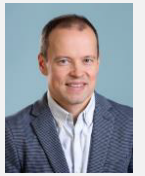
Genecode's lead compounds for PD will enter the IND phase in 2024

Pre-clinical Trials	IND Phase	Clinical Trials
finalized in 2024	2024-2025	2025+

Management Team

Paavo Pilv, EMBA
CEO, Partner

Prof. Dr. Mart Saarma
CSO, Partner



Prof. Dr. Tarmo Tamm
Lead Scientist

Patents x3 x1

The annual listing of 10 companies in the EU that are at the forefront of providing Drug Discovery and Development solutions, impacting the industry in the region

Key Partners: University of Helsinki, University of Tartu, European Innovation Council

EUR 14.3m Equity investment commitment from EIC

Core Team

Dr. Mehis Pilv, The Company Founder

Prof. Dr. Mart Saarma, Research Director and Professor at the Institute of Biotechnology, University of Helsinki, Sr Partner of GeneCode, CSO, JMC member of Kevad Bio

Paavo Pilv, EMBA, CEO of GeneCode, JMC member of Kevad Bio

Prof. Dr. Tarmo Tamm, University of Tartu, lead scientist of GeneCode

Arun Mahato, PhD, Institute of Biotechnology, University of Helsinki, lead scientist of GeneCode

Yves Ribeill, PhD, Partner, Entrepreneur-In-Residence, Co-founder of Argobio Studio, JMC member of Kevad Bio

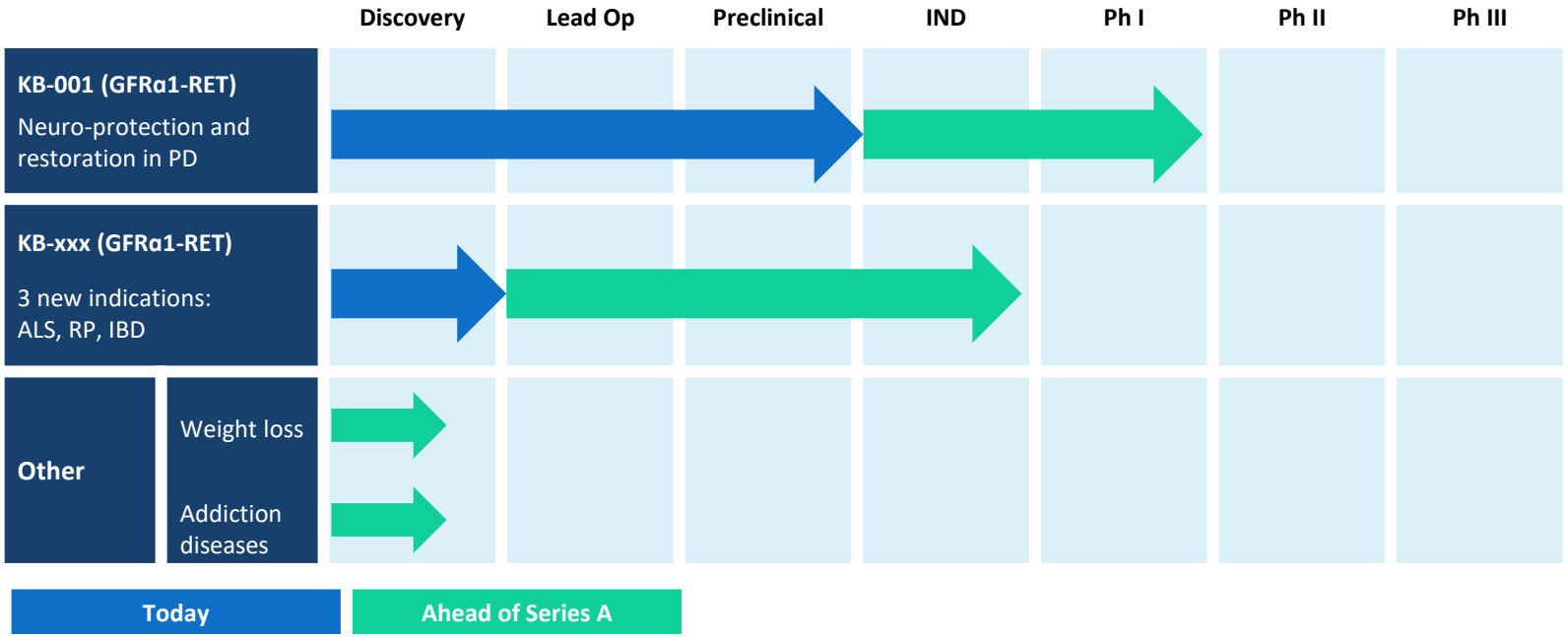
Delphine Charvin, PhD, Operating Partner at Argobio Studio, JMC member of Kevad Bio

Mélanie Rouillier, MSc, PMP, Scientific Project Manager at Argobio Studio

Serge Mignani, PhD, Consultant in Medicinal Chemistry for Argobio Studio

Timeline

Building a Valuable Pipeline



Market analyses

Building a Valuable Pipeline

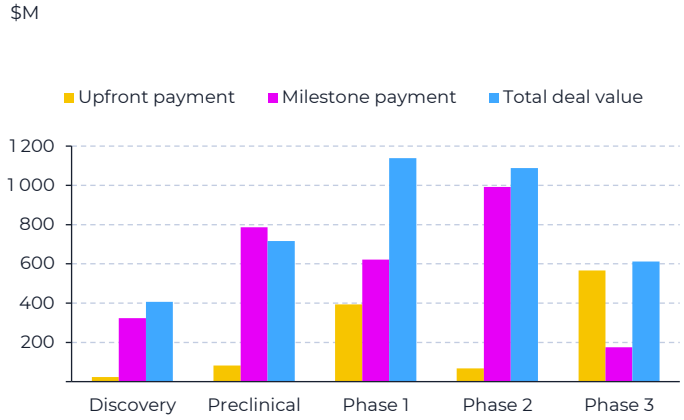
Indication	Patients	Compound annual growth rate (CAGR)	Market value	Future market value
PD	Over 10 million worldwide	14,5%	Global market value 2022 $3.4 billion	$7,1 billion by 2029
ALS	4-6 cases per 100,000 individuals	13,9%	$282 million in 2019 within the 8 MM	Exceed $1.04 billion by 2029
RP	Affects approximately 1 in every 3,000	7,3%	Global market value 2021 $11.57 billion	$20.33 billion by 2029
IBD	6-8 million individuals worldwide	5,7%	Global market value 2022 $25.18 billion	$37 billion by 2029

ARE WE TALKING ABOUT A POTENTIAL NEW UNICORN?

Existing drugs are generic and have very similar treatment paths. The GeneCode drug is **the first one that restores the neurons affected by PD**.

The strategy is to secure a strategic corporate partnership with an industry-leading pharmaceutical company. The core takeaway from the deal/transaction comparable analysis shown here is that **there are multiple key time points where GeneCode can expect to secure a corporate partnership (i.e., preclinical, Phase 1, 2, 3)**.

Parkinson's Disease - Deal Comparables: Segmented by Stage of Development



The main drive behind these very lucrative financial deals is innovative PD drug treatments offering 'disease-modifying' abilities. GeneCode is developing novel PD therapies that also have this important attribute of disease-modifying potential.

Contact

GENECODE

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