TT-P34: a first-in-class peptide drug for treatment of neurodegeneration

Anders Dalby

Co-founder and CSO at Teitur Trophics

Disclosures

	No, Nothing to disclose
X	Yes, please specify

Company / Name	Honoraria / Expense	Consulting / Advisory Board	Funded Research	Royalties / Patent	Stock Options	Ownership / Equity Position	Employee	Other (Please specify)
Teitur Trophics				X		X	X	

Disclaimer

TT-P34 is an investigational new drug developed by Teitur Trophics and has not been approved by the FDA or EMA for any use.

Teitur Trophics – company overview

- Series A funded biotech company located in Aarhus, Denmark
- Focused on development of first-in-class macrocyclic peptides based on groundbreaking biology discovered on the receptors SorCS1*, SorCS2 and SorCS3
- 10 employees and +50 consultants supporting innovation

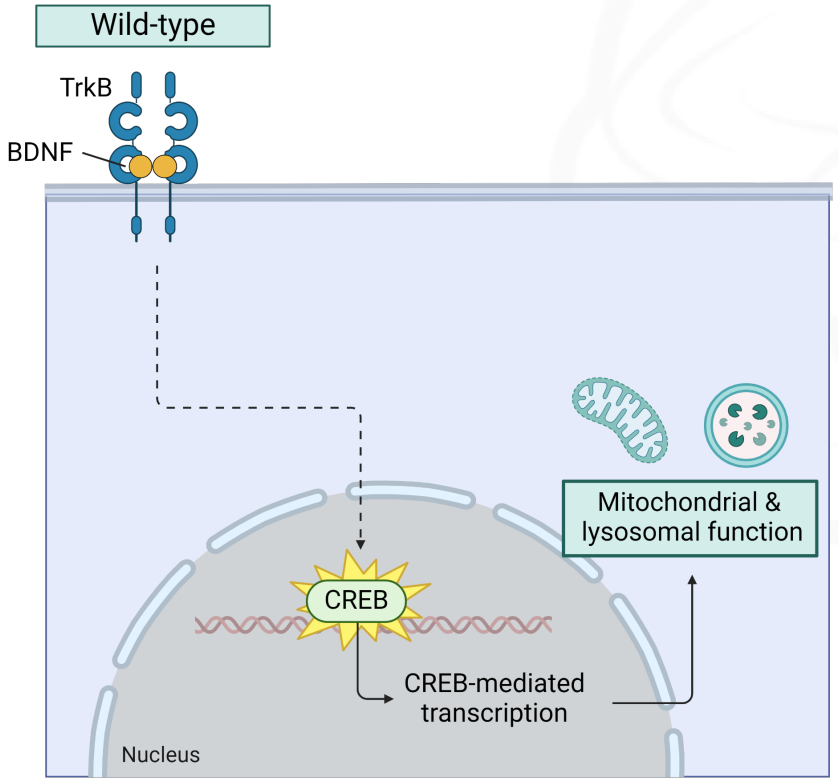
Teitur is a preclinical stage company with a pipeline of novel biology

Indication	Discovery	IND development	Phase 1	Candidate
Huntington's Disease Parkinson's Disease Frontotemporal Dementia				TT-P34
Hearing loss				Not disclosed
Not disclosed				Not disclosed

*Sortilin-related CNS expressed 1

TT-P34 has been developed on insight into BDNF/CREB pathway

- The neurotrophic factor BDNF, is critically important for neuronal health and viability
- BDNF drives synaptic plasticity and survival through activation of transcription factor CREB
- Activation of CREB leads to mitochondrial and lysosomal function driving synaptic integrity
- CREB is downregulated across numerous neurodegenerative diseases

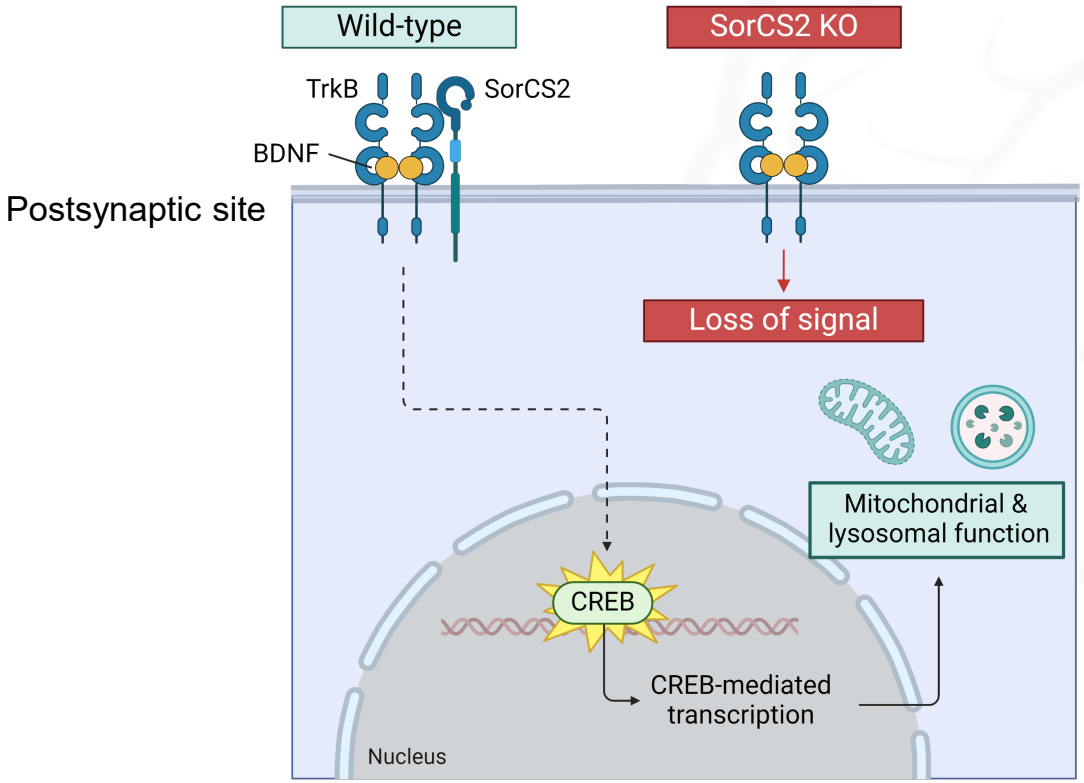


CREB downregulation across different CNS diseases

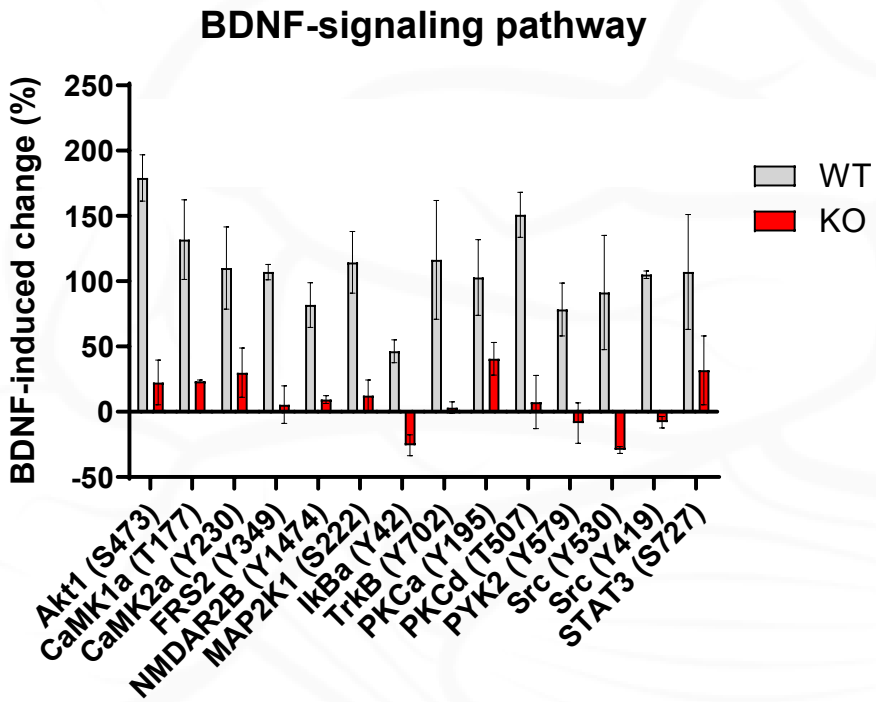
Disease	Patients	References
Parkinson's	▪ ↓ CREB activity in nigral dopaminergic neurons of post-mortem brains ▪ ↓ Downstream CREB-transcripts in post-mortem brains	Xiaoyi Xu et al. 2022, Adam Labadorf et al. 2018, Hyojung Kim et al. 2021
Huntington's	▪ ↓ Downstream CREB-transcripts in striatum of post-mortem brains	Libin Cui et al. 2006, Adam Labadorf et al. 2018, Rajnish et al. 2012
Frontotemporal dementia	▪ ↓ CREB activity in cortical neurons from patients with C9ORF72, TARDBP, MAPT mutations	Michelle Jean Gregoire et al. 2024, Josiah J. Herzog et al. 2020, M. Cecilia Ljungberg et al. 2012
Alzheimer's	▪ ↓ CREB levels in postmortem brains ▪ ↓ CREB activity in prefrontal cortex in postmortem brains	Subbiah et al. 2011, N Bartolotti et al. 2016

SorCS2 is essential for BDNF-signaling

- SorCS2 is a co-receptor for TrkB
- Knock-out of SorCS2 results in impaired BDNF-signaling



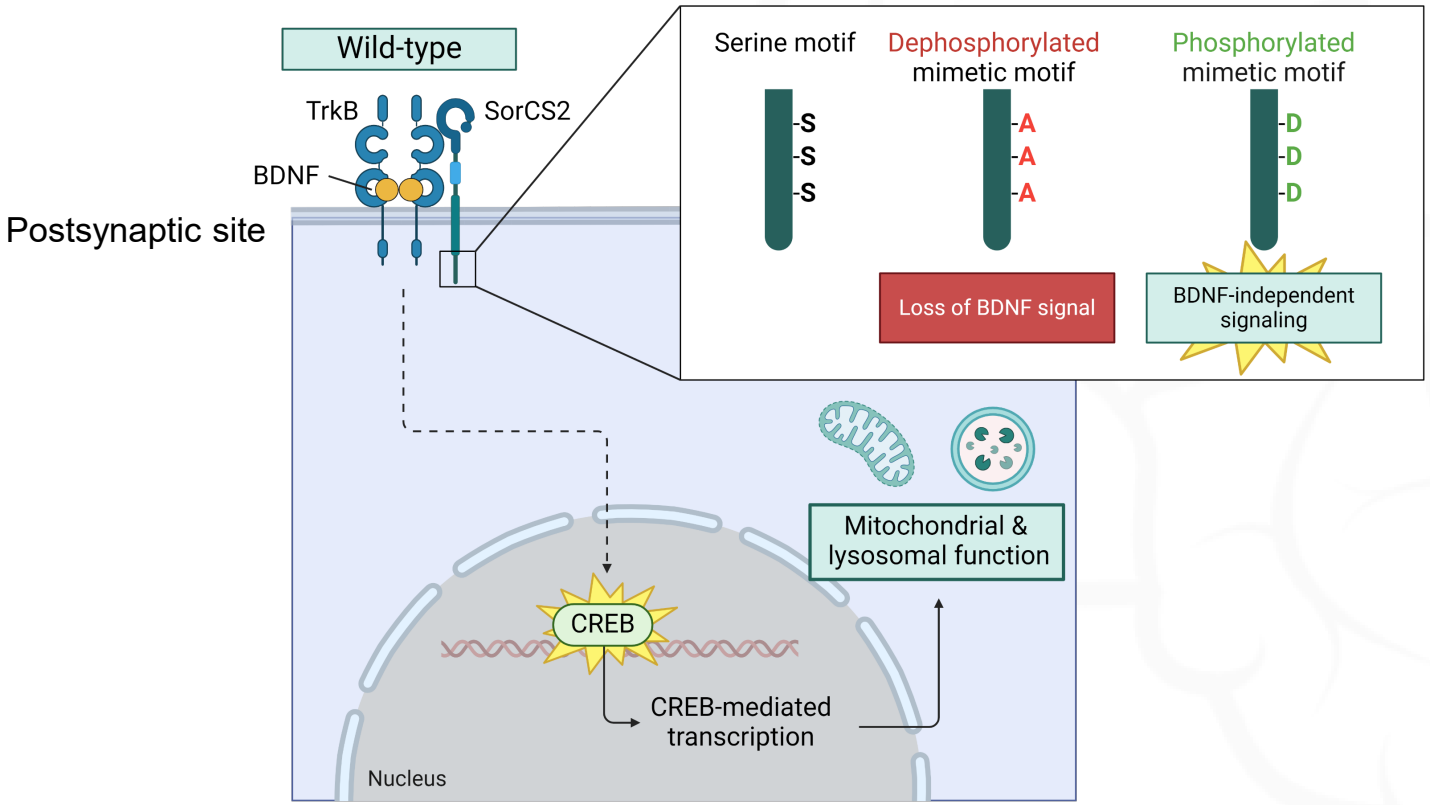
BDNF stimulation of neurons lacking SorCS2 display almost complete loss in activation of downstream signaling proteins

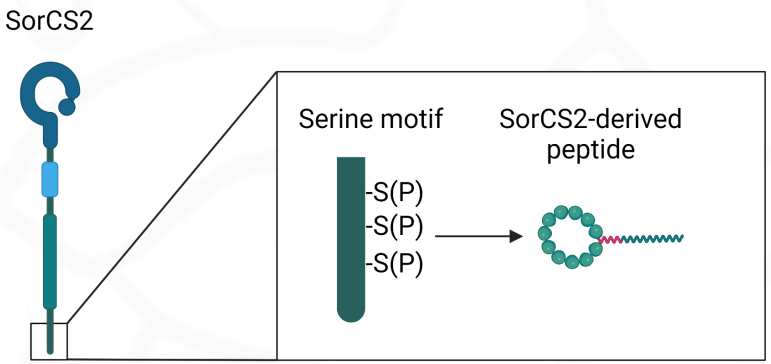


Dalby et al. 2024 preprint

SorCS2-tail contains a signaling switch in the BDNF-signaling cascade

- **Discovery**: The SorCS2-tail contains a unique serine motif
  - Modulating the SorCS2-tail motif can turn off/on neurotrophic responses
- From this, we have developed SorCS2-tail phospho-mimetic peptides

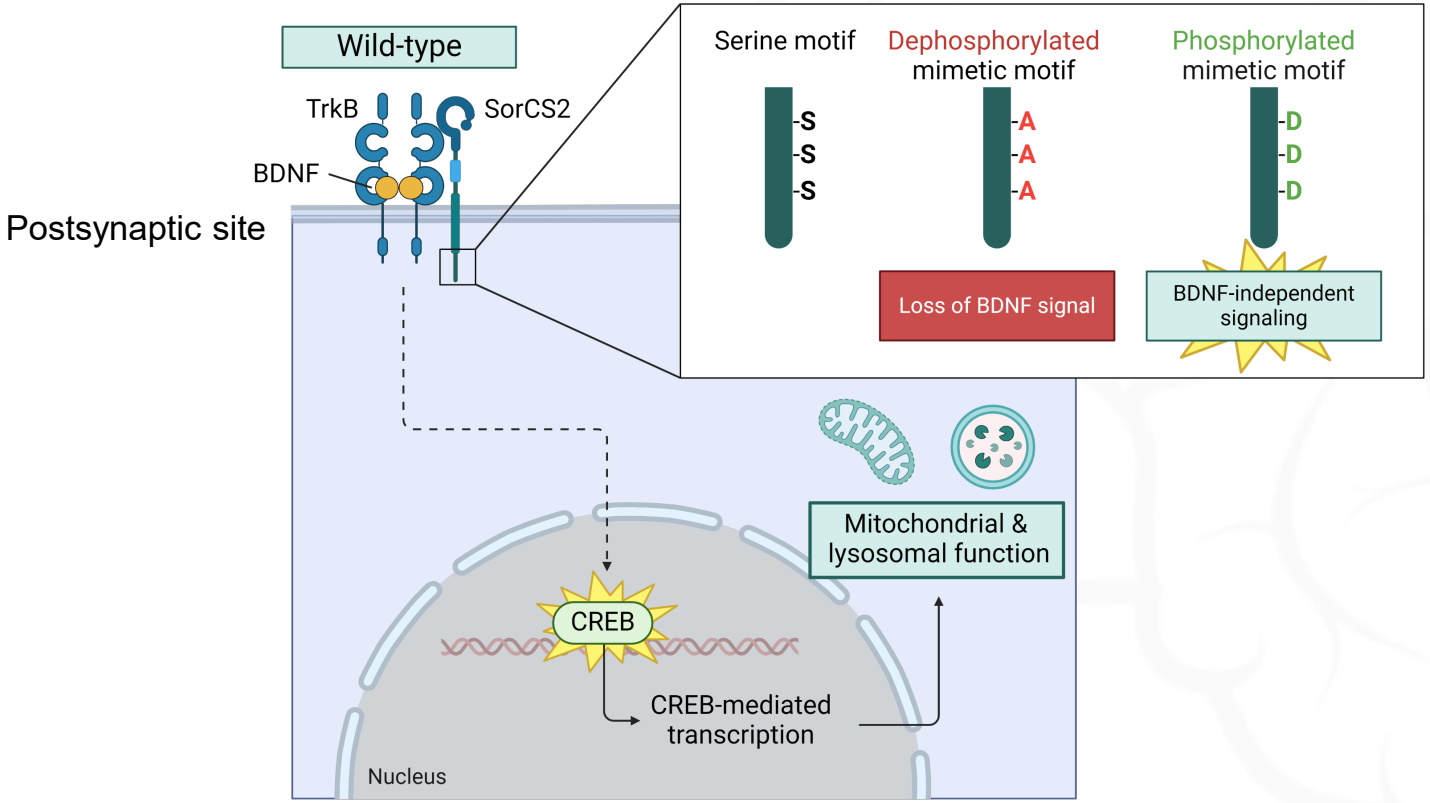


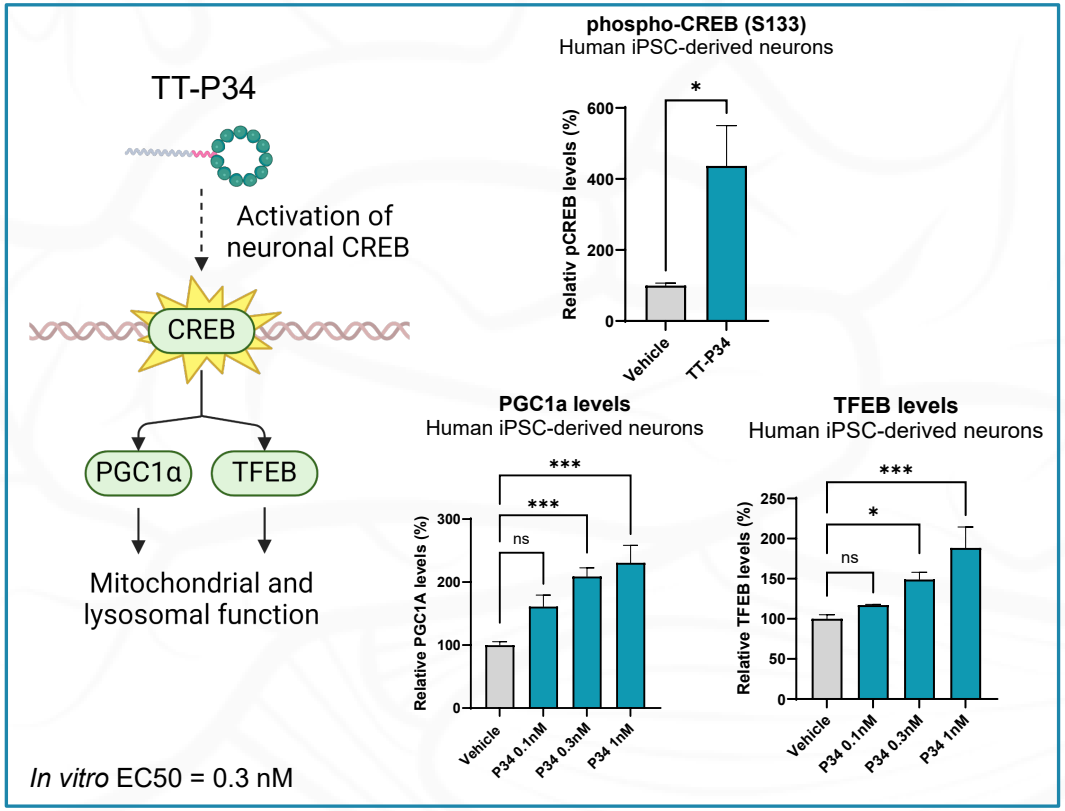


Dalby et al. 2024 preprint,

TT-P34 is derived from the SorCS2-tail

- TT-P34 is designed for a once-weekly subcutaneous delivery in patients
- TT-P34 drive CREB activity in a **neuron-specific manner** and improve mitochondria and lysosomal function through upregulating PGC1α and TFEB
- PGC1α and TFEB-pathways are well-established to be impaired across neurodegenerative diseases

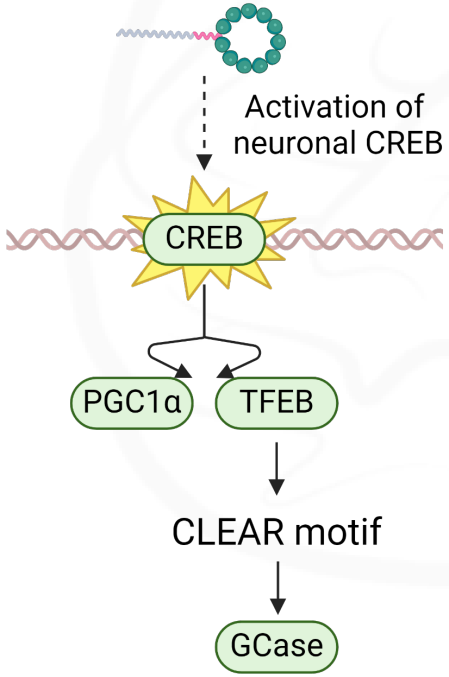


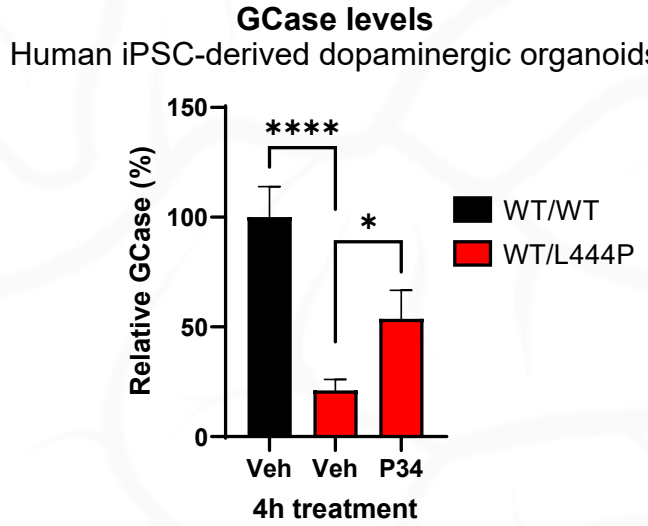


Dalby et al. 2024 preprint, Unpublished

TT-P34 – Proof of mechanism in driving lysosomal function through TFEB

- TFEB controls the expression, import, and activity of lysosomal enzymes including GCase (Glucocerebrosidase).
- TT-P34 increases GCase levels in human dopaminergic organoids with L444P mutation

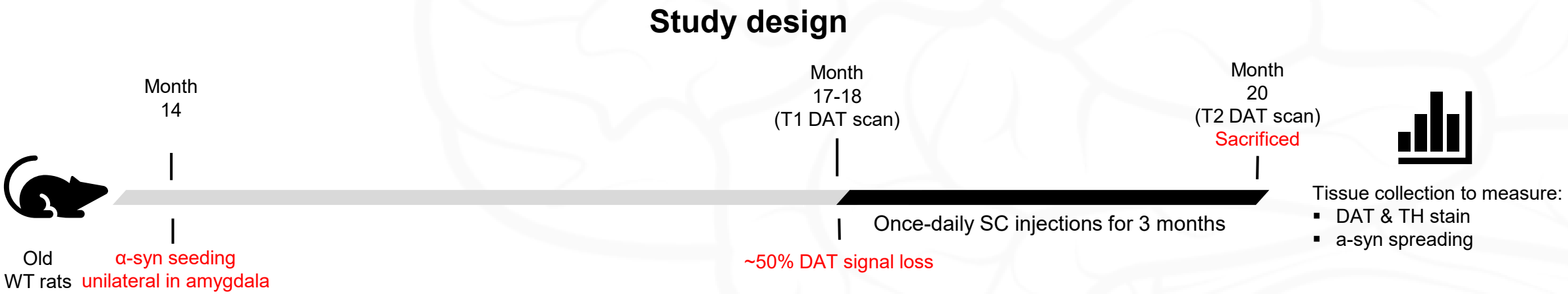




Halting disease progression in a PFF rat model of PD

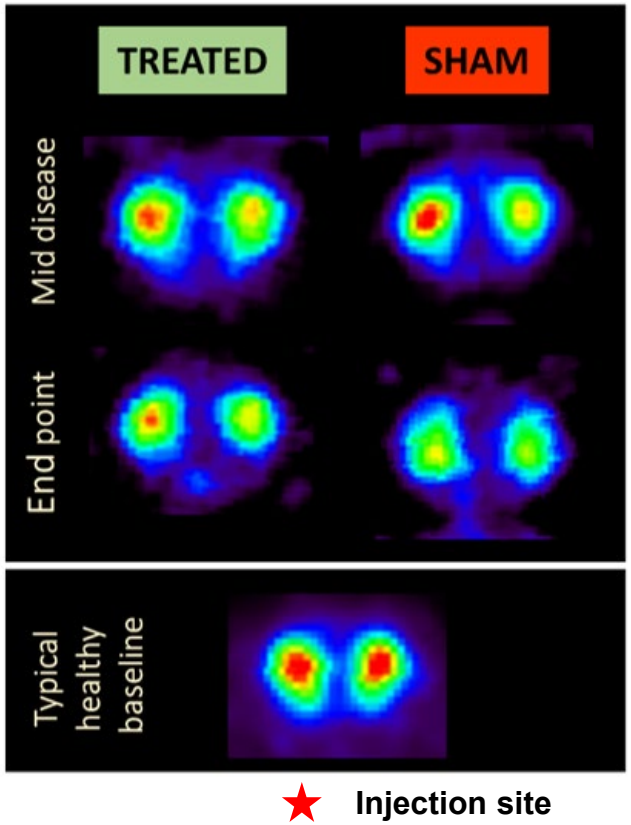
- TFEB controls the expression, import, and activity of lysosomal enzymes including GCase (Glucocerebrosidase).
- TT-P34 increases GCase levels in human dopaminergic organoids with L444P mutation

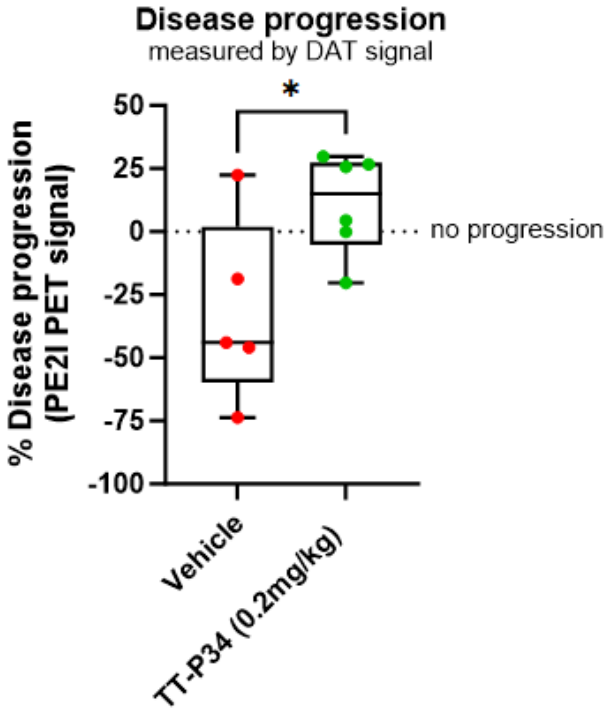
Question 1: Does the engagement in TFEB-pathway lead to clearance of α-synuclein in a PFF seeding model?

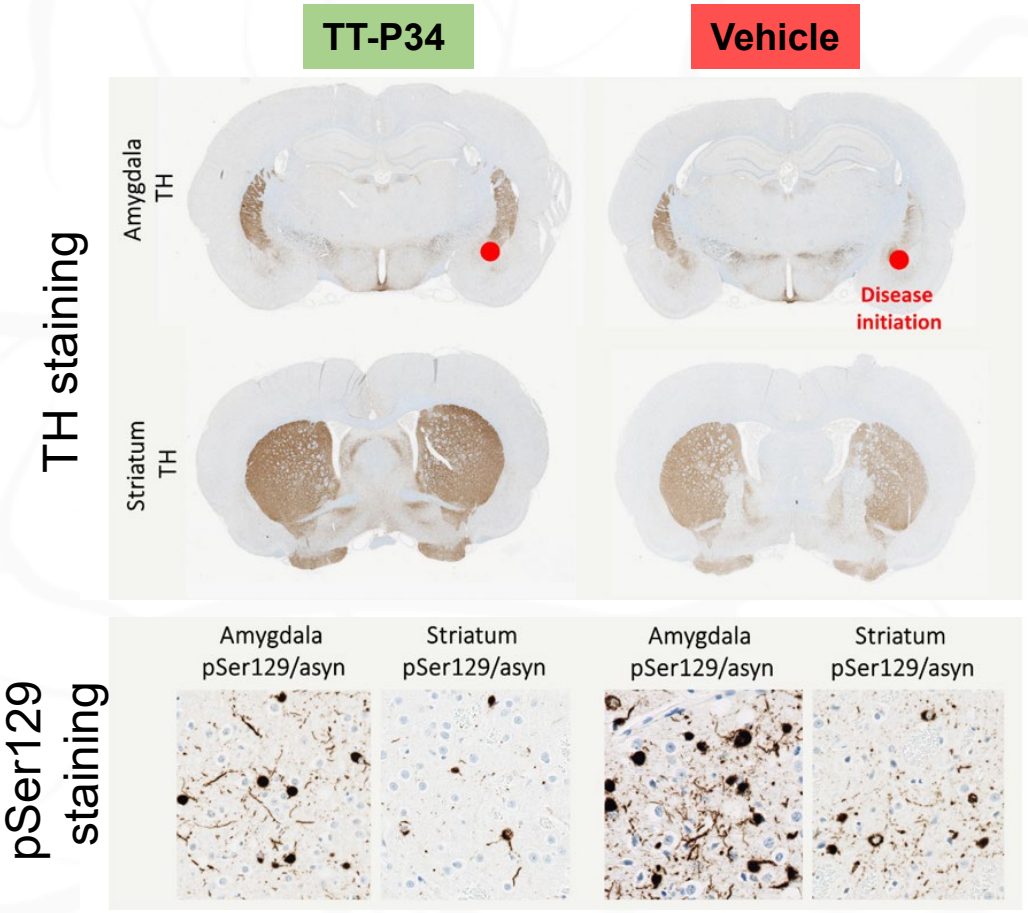


Halting disease progression in a PFF rat model of PD

- Treatment with TT-P34 prevents further loss of DAT signal
- This was accompanied with significant rescue of TH+ terminals and DAT stains (IHC)
- This was accompanied with significant reduction (50-75%) in phospho-aSyn (S129)







Preclinical proof of concept: improved pathology through TFEB

TT-P34 treatment in 3 other PFF rat seeding models of Parkinson's

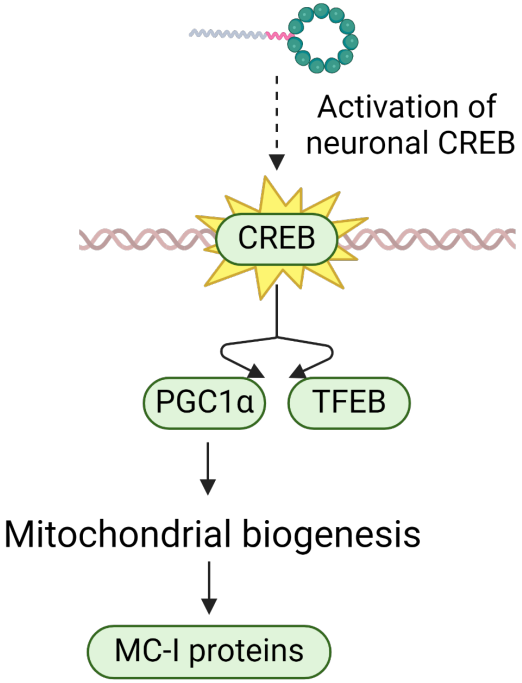
- Across all models, TT-P34 clears alpha-synuclein aggregates and increases dopaminergic survival

4 different PFF rat seeding model studies

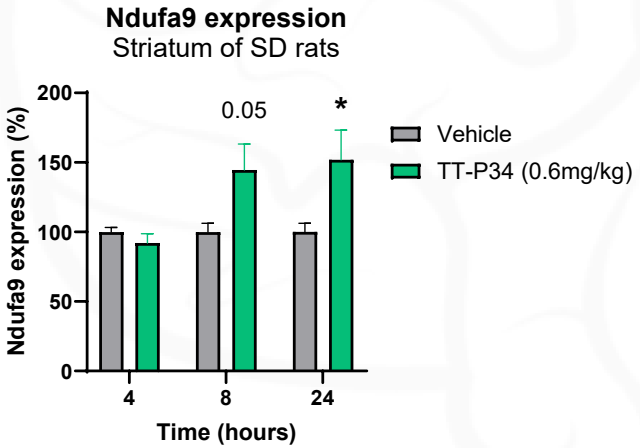
Model	Age of rats, injection site	Treatment period	Reduction in α-synuclein aggregation	Other assessments
Brain first	14 months, Amygdala	1 month immediately after injection	▪ -75% SNpc ▪ -75% amygdala	▪ Increased TH in striatum
Brain first	14 months, Amygdala	3 months after 50% loss in DAT signal	▪ Reduced in striatum ▪ Reduced in amygdala ▪ Reduced in SNpc ▪ -50% stomach	▪ Increased TH & DAT in striatum ▪ Increased 18F-PE2I in striatum
Brain first	17 months, Amygdala	6 months immediately after injection	▪ -50% amygdala ▪ -50% striatum ▪ -50% SNpc	▪ Increased 18F-PE2I in striatum ▪ Increased TH in striatum ▪ Increased NPY CSF
Gut first	16 months, Duodenum	2 months immediately after injection	▪ -60% cadiac nerves	

TT-P34 – Proof of mechanism in driving mitochondrial function through PGC1α

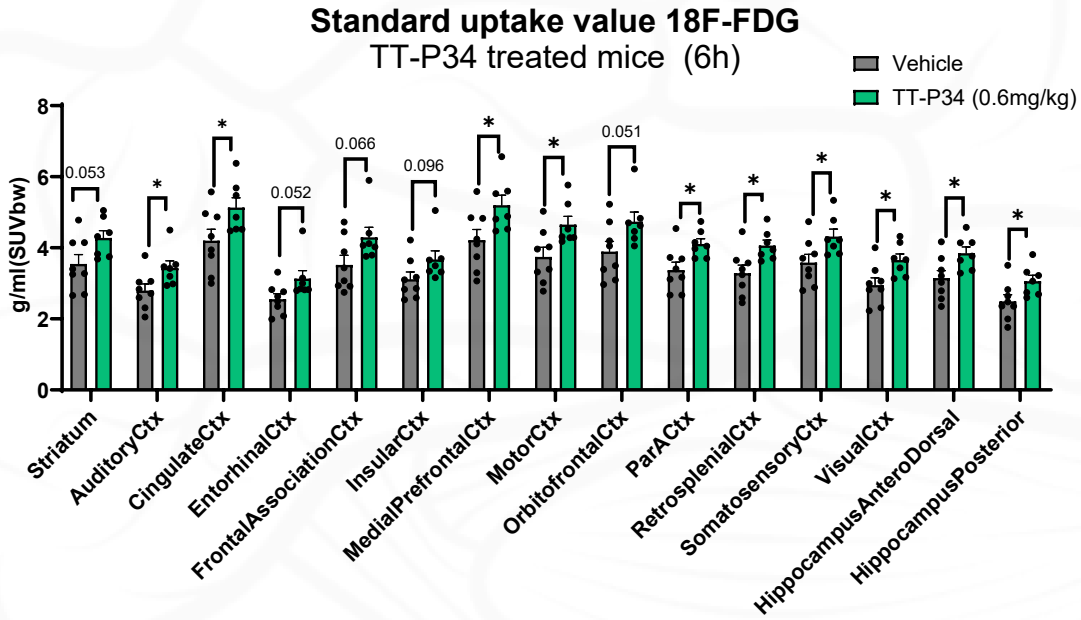
- PGC1α drives mitochondrial biogenesis and controls the expression of mitochondrial proteins important for energy metabolism and synapse formation
- TT-P34 acutely increases mitochondrial biogenesis and glucose metabolism *in vivo* in brain of healthy rats



PGC1α downstream target



Brain glucose metabolism

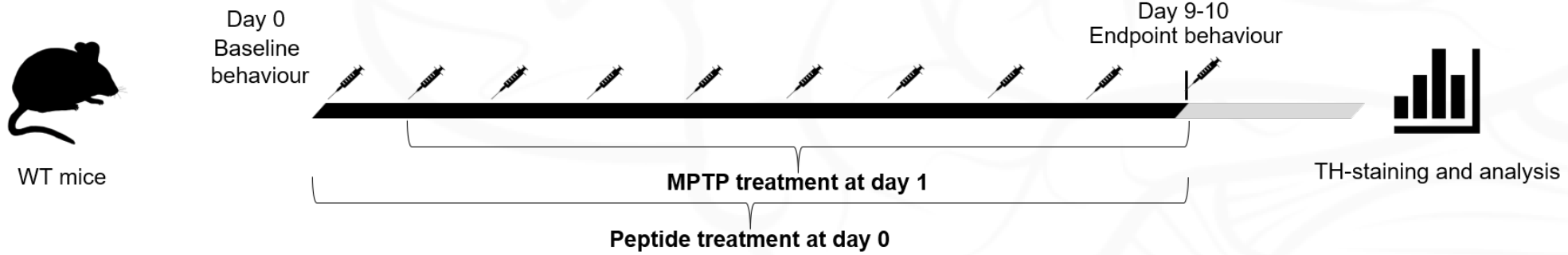


Preclinical PoC: improving motor function in a MPTP mouse model of PD

- PGC1α drives mitochondrial biogenesis and controls the expression of mitochondrial proteins important for energy metabolism and synapse formation
- TT-P34 acutely increases mitochondrial biogenesis and glucose metabolism *in vivo* in brain of healthy rats

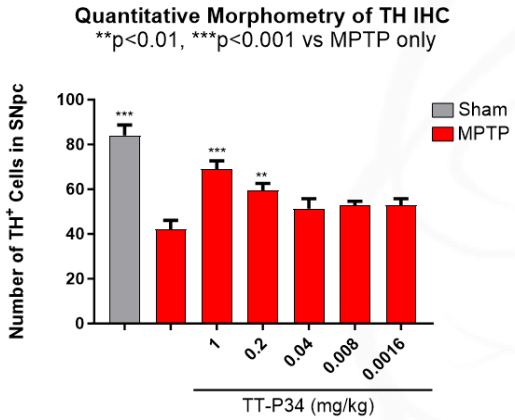
Question 2: Does the engagement in PGC1α-pathway lead to neuroprotection in mitochondrial model (MPTP mouse model of PD)?

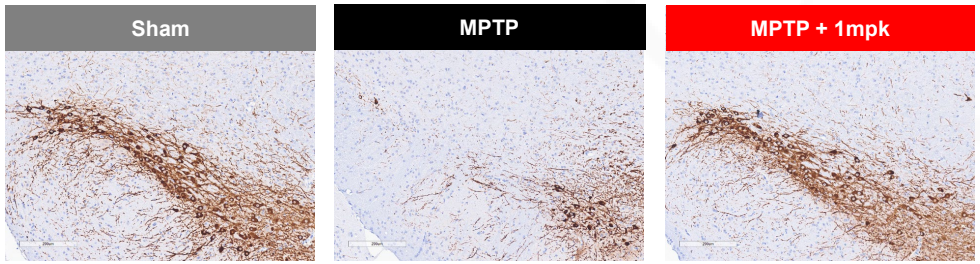
Study design

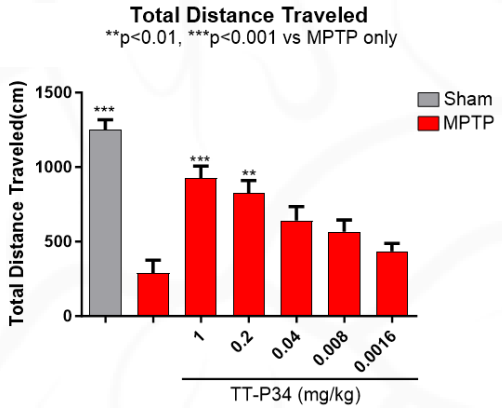


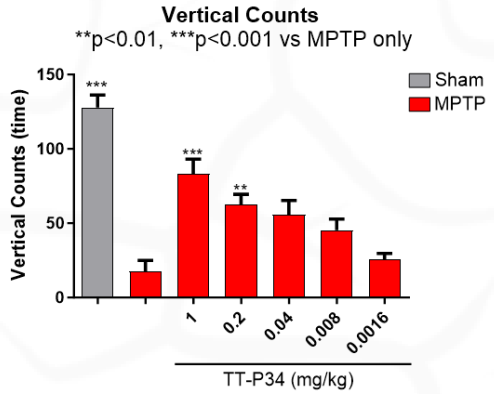
Preclinical PoC: improving motor function in a MPTP mouse model of PD

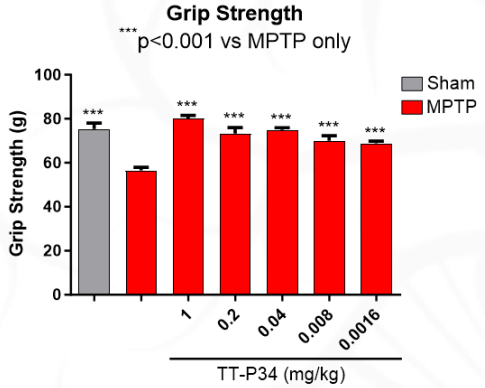
- TT-P34 chronic treatment of MPTP-injected mice rescued dopaminergic cell loss (measured by TH staining)
- TT-P34 treatment of MPTP-injected mice rescued motoric phenotype measured in open-field and grip-strength
- TT-P34 increased NPY CSF as explorative indirect target engagement biomarker

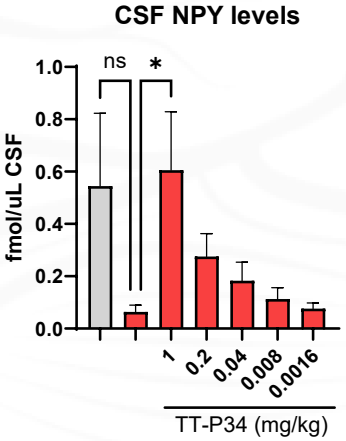












TT-P34 efficacy across several neurodegenerative models

- Activation of CREB is beneficial across several neurodegenerative diseases
- TT-P34 displays ameliorative effects across models of HD and FTD.

TT-P34 treatment in models of Huntington's and Frontotemporal dementia

Disease	Model	Treatment period	Behavior	Post-mortem analysis
Huntington's	R6/2	3 months	▪ Reduced clasping ▪ Improved median survival	
Huntington's	zQ175DN KI	9 months	▪ Rescue of motor function in beam test ▪ Rescue of phenotype in home-cage analysis	▪ Restoration of mitochondrial and synaptic proteins ▪ Restoration of dopamine and serotonin ▪ Rescue in striatal markers
Frontotemporal dementia	Grn+/-	1 week		▪ Increased GRN expression ▪ Normalized LAMP1 levels

Clinical development – phase 1

Phase 1 design

- Start in mid-2025
- Double blind, randomized, parallel group, placebo-controlled study of single and multiple ascending subcutaneous doses of TT-P34 in healthy subjects
- Potential MAD patient cohort add-on

Clinical Endpoints of SAD/MAD

Administration

- Dosing subcutaneously (MAD = once weekly)

Primary:

- Safety and tolerability of a single subcutaneous (SC) dose and multiple SC doses of TT-P34

Secondary:

- Plasma pharmacokinetic (PK) profile of TT-P34 following a single SC dose and multiple SC doses
- Evaluate the exposure of TT-P34 in CSF following a single SC dose and multiple SC doses.

Exploratory

- Pharmacodynamic effect of TT-P34 in CSF following a single SC dose and multiple SC doses on exploratory biomarkers including NPY

Summary

- TT-P34 is a first-in-class macrocyclic peptide designed for a once-weekly subcutanous administration in patients
- TT-P34 can cross the blood-brain barrier in non-human primates follow sc. dosing (kpuu across species = 1)
- TT-P34 induces activation of neuronal CREB leading to PGC1α and TFEB expression ultimately driving lysosomal and mitochondrial function
- TT-P34 demonstrated preclinical proof of concept across PD, HD and FTD models
- TT-P34 did not show adverse events within the anticipated therapeutic window over 28-day GLP tox studies
- TT-P34 will enter the clinic mid-2025 to assess safety, PK and CSF exposure in humans

Acknowledgements

Team

Simon Molgaard
CEO & co-founder

Ed Browne
CDO

Anders Dalby
CSO & co-founder

Andreas Borta
CMO

Emil Gregersen
Senior Scientist

Sanne Nordestgaard
Lab technician

Anne Kathrine Pedersen
Senior Scientist

Mathias Ollendorff
Preclinical R&D
& co-founder

Mia Aaboe Jorgensen
Clinical project manager

Maya Tyssøy
Office Manager &
Executive Assistant

50+ Consultants

Aarhus University

Nathalie van den Berge

Vasileios Theologidis

Mark Denham

Muwan Chen

Palle Juul-Jensens Blvd., 8200 Aarhus N, Denmark

VIASOM SCIENCE

AARHUS UNIVERSITY