PRANA BIOTECHNOLOGY

Treatment of **Neurological Disorders**

Dr. David Stamler, MD
Chief Medical Officer and SVP,
Clinical Development

January, 2018

Corporate Overview

- Developing first-in-class therapies to treat orphan and non-orphan neurological diseases.
- Lead program, PBT434, is the first of a new generation of small molecules designed to block iron-mediated accumulation and aggregation of alpha-synuclein, an abundant brain protein widely believed to be involved in the pathogenesis of Parkinson's disease and related disorders.
- Unique chemical scaffold and biological profile
- PBT434 development plan builds on a body of experience from earlier programs in Alzheimer's and Huntingdon's diseases
- Compound library of over 2000 potential therapeutic agents

Trading information:

ASX:	PBT
Nasdaq:	PRAN
Share price:	US$3.25
Cash:	AU$20M

(as at 31 December, 2017)

Board

- Ira Shoulson, MD
- Dr George Mihaly
- Lawrence Gozlan
- Peter Marks
- Brian Meltzer

An International Business

Listed on Nasdaq in 2000 (PRAN)

San Francisco, USA

- Clinical Development team

Established in 1997 in Australia, listed on ASX (PBT)

Melbourne, Australia

- Headquarters
- Discovery and Research team

Investment Highlights

Novel Drug Candidate: PBT434

- Targets key proteins implicated in the neurodegeneration of Parkinson's disease and atypical parkinsonism
- Prevents accumulation of α-synuclein and tau
- Well tolerated in repeated dose toxicology studies

Strong Research and Development

- Innovative discovery program
- Development team with proven track record
- Long standing collaborations with Harvard and Florey Institute of Neuroscience and Mental Health
- R&D Program with Takeda Pharmaceuticals

Multiple Indication Opportunity

- PBT434 is active in models of Parkinson's disease and atypical parkinsonism, such as Multiple System Atrophy and Progressive Supranuclear Palsy
- MSA and PSP are orphan diseases

Management Team

Geoffrey Kempler, Executive Chairman & CEO

- Founded Prana in November 1997
- Extensive experience in investment and business development
- Overseen operations responsible for the implementation of Prana's strategic plan and technology commercialization of our technology.

Kathryn Andrew, CFO

- Highly experienced biotechnology CFO
- Joined Prana in 2014
- CPA

David Stamler, MD, Chief Medical Officer & SVP Development

- Previous VP, Clinical Development and Therapeutic Head, Movement Disorders, Teva Pharmaceuticals
- Part of Teva's US$3.5 billion acquisition of Auspex Pharmaceuticals where he was Chief Medical Officer
- Led development of AUSTEDO® (deutetrabenazine) a new drug for the treatment of Huntington's disease, which was approved by the FDA in April 2017.
- Second neurological agent that Dr. Stamler has led through the approval process with the FDA.

Building a US team

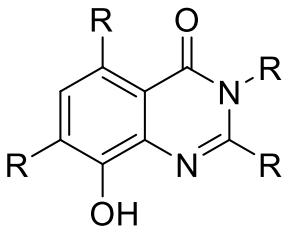
- US team expansion underway
- Office established in San Francisco
- Clinical Operations, CMC and Non-Clinical Development already hired

Investment Thesis

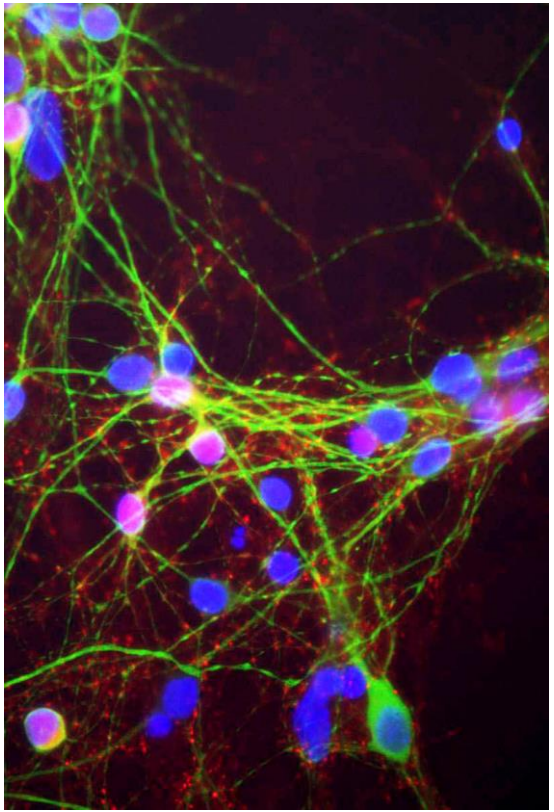
- Alpha (α)-synuclein is a soluble, intracellular protein critical for neuro transmission
- Alpha-synulein accumulates and aggregates in many neurodegenerative diseases, implicated in pathology
- PBT434 blocks α-synuclein accumulation and aggregation, preserves neurons and improves function in animal models of synucleinopathy
  - PBT434 also prevents tau accumulation and improves function in animal models of tauopathy
- There is a link between iron and the synucleinopathies
- Phase 2 data with a related compound demonstrates proof of concept in Parkinson's disease
- Clear development path for symptomatic therapy
  - Current symptomatic therapy in atypical parkinsonism has limited benefit
- Potential path for disease modifying therapy for the synucleinopathies

Conclusion: PBT434 is an excellent drug candidate to advance to the clinic and fund through end of Phase 2

PBT434: Promising Drug Profile



- Good CNS penetration based on low molecular weight and lipophilicity
  - Concentrates in brain 2 to 3 fold higher than plasma
- Straightforward synthetic process with demonstrated ability to make kg amounts of GMP material
- Benign safety profile in GLP toxicology studies
  - Non-toxic dose exceeds efficacious dose by >10-fold based on allometric scaling



MAb to α-synuclein stains red

Importance of α-Synuclein

- α-Synuclein is an intracellular protein, abundantly expressed in the brain
- Critical for normal function of neurons
- Soluble, in highest concentration at presynaptic nerve endings
- Key regulatory protein involved in neurotransmission
  - Enables neurotransmitter release by facilitating synaptic vesicle fusion to pre-synaptic membrane

α-Synuclein is an Important Disease Target

Strong genetic and pathological link to disease

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THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

ALPHA-SYNUCLEIN PRIORITY AREA

OUR INVESTMENT IN ALPHA-SYNUCLEIN RESEARCH

The Michael J. Fox Foundation has made significant investments in research to understand alpha-synuclein and to translate it into therapeutic strategies for advancing a cure for Parkinson's disease. Our particular areas of focus to date include:

Supporting work to understand the normal function of alpha-synuclein and its role in Parkinson's disease pathogenesis;

Taking an aggressive approach in advancing alpha-synuclein therapeutics to the clinic and supporting strategies to reduce aggregation or lower protein levels of alpha-synuclein;

https://www.michaeljfox.org/research/priority-area-detail.php?alpha-synuclein

VIEWPOINT

Targeting α-Synuclein as a Therapy for Parkinson's Disease: The Battle Begins

C. Warren Olanow, MD[1,2*] and Jeffrey H. Kordower, PhD[3,4]

"Collectively these data strongly suggest that alpha synuclein is a potentially important and novel target of candidate neuroprotective therapies. Several different therapeutic strategies designed to clear or prevent the formation of toxic forms of α-synuclein are currently being investigated in the laboratory, and clinical trials have already begun."

Movement Disorders, Vol. 32, No. 2, 2017

AstraZeneca

AstraZeneca and Takeda establish collaboration to develop and commercialise MEDI1341 for Parkinson's disease 29 August 2017

Takeda

Prana commences research collaboration with Takeda for the treatment of Parkinson's disease gastrointestinal neuropathology 18 July 2017

Nature Reviews Drug Discovery | Published online 31 May 2017

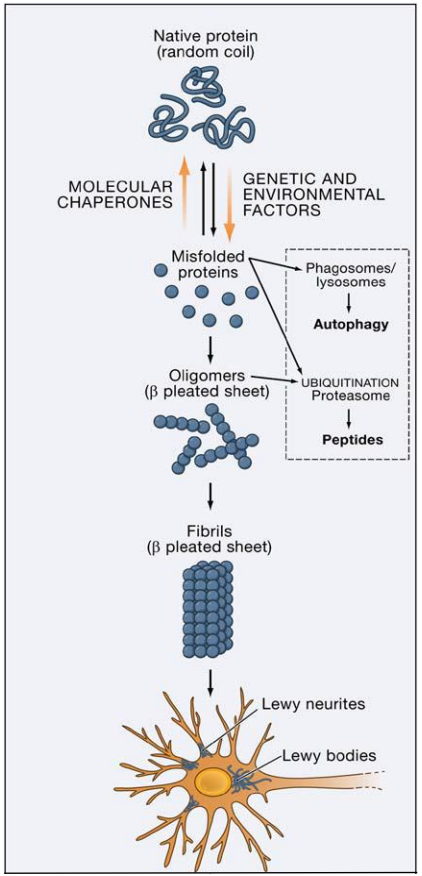
Zeroing in on neuro-degenerative α-synuclein

In the search for the first disease-modifying therapy for Parkinson disease, drug developers are advancing α-synuclein-targeted agents into proof-of-concept clinical trials.

Table 1 | **Selected α-synuclein-targeted therapies in development for Parkinson disease**

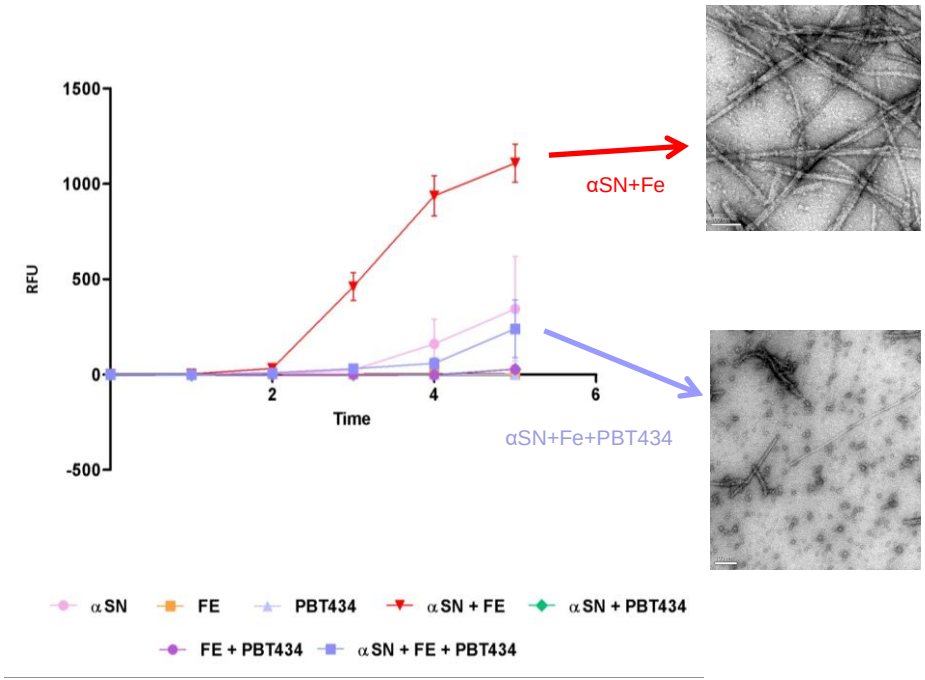
Drug	Sponsor	Modality	Status
RO7046015	Roche	α-Synuclein-specific antibody	Phase II planned to start by end of June 2017
BIIB054	Biogen	α-Synuclein-specific antibody	Phase II planned to start by end of 2017
PD01A and PD03A	Affiris	Vaccine against α-synuclein	Phase I
NPT200-11	Neuropore Therapies/UCB	Small-molecule inhibitor of α-synuclein misfolding	Phase I
NPT088	Proclara Biosciences	Small-molecule inhibitor of α-synuclein misfolding	Preclinical
SAR402671	Sanofi Genzyme	Small-molecule inhibitor of glycosphingolipid metabolism	Phase II

PBT434 Inhibits α-Synuclein Accumulation and Aggregation



Lee and Trojanowski, 2006

- α-synuclein fibrillizes in vivo; only form of synuclein to fibrillize in vitro
- Factors regulating α-synuclein production and conformation are relevant to disease pathogenesis and treatment
- Homeostasis of iron is disrupted in PD and atypical parkinsonism
- Although α-synuclein is highly conserved in vertebrates, synucleinopathy develops only in humans
- Only human α-synuclein mRNA contains an Iron responsive element which regulates its production (Friedlich, Tanzi, et al. 2007)



PBT434 blocks the aggregation of α-synuclein

Alpha-synuclein Pathology and PBT434 Mechanism of Action

Iron Chaperone, reducing α-synuclein accumulation, aggregation and preserving neurons

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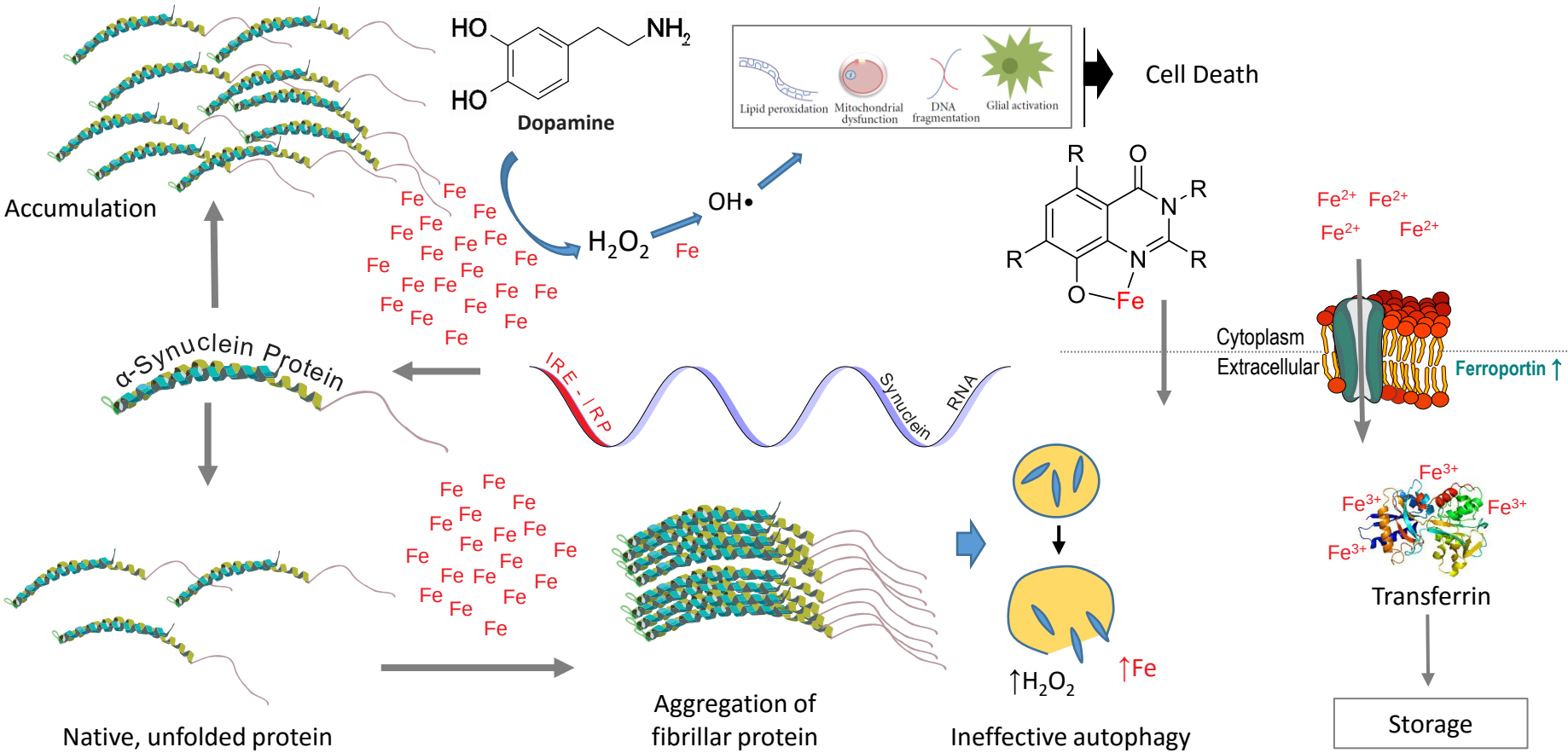


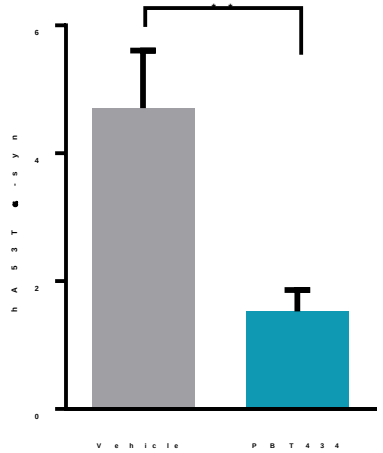
PBT434 Target Product Profile

Mechanism of Action	Inhibitor of iron-mediated protein accumulation and aggregation
Product Concept	By inhibiting accumulation and aggregation of α-synuclein, PBT434 preserves neurons and improves motor and non-motor symptoms of neurodegenerative diseases
Potential Indications	Synucleinopathy, e.g., Parkinson's disease, Multiple System Atrophy
Treatment Paradigm	Improve motor and/or non-motor symptoms Slow disease progression as monotherapy or combination therapy
Dosing	Orally administered, small molecule
Efficacy	PBT434 prevents loss of neurons in affected brain regions and improves motor and/or cognitive function in multiple animal models of synucleinopathy
Safety	Generally well-tolerated in 28-day GLP toxicology studies in rat and dog

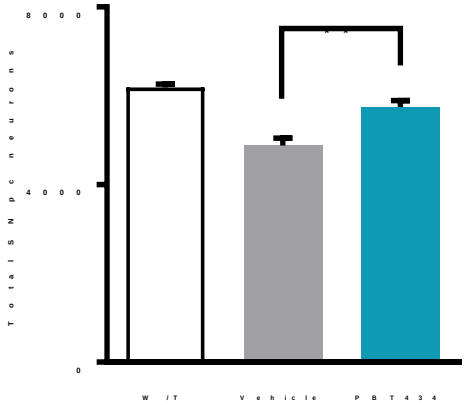
PBT434 Lowers α-Synuclein, Prevents Neuronal Death and Improves Motor Function

Transgenic Animal Model (hA53T) of Parkinson's Disease

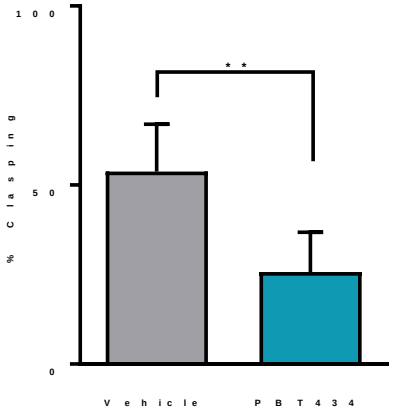
↓ α-Synuclein aggregation



Preserves neurons in S. nigra



Foot Clasping



Treatment
- Randomly allocated
- 4-8 months of age
- ~30 mg/kg/day (via feed)

Assessments done in blinded manner

Finkelstein et al. Acta Neuropath Comm (2017) 5:53

Strategy Supported by Proof of Concept with Deferiprone

6 month placebo controlled data in Parkinson's disease patients

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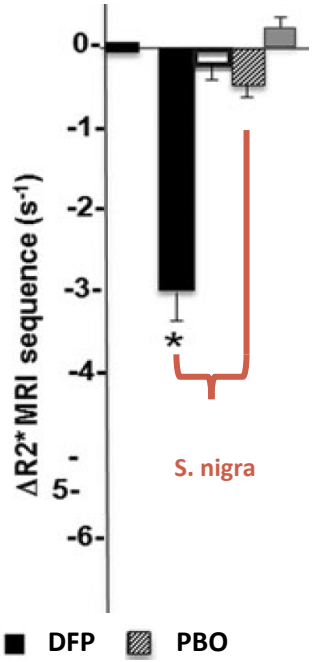
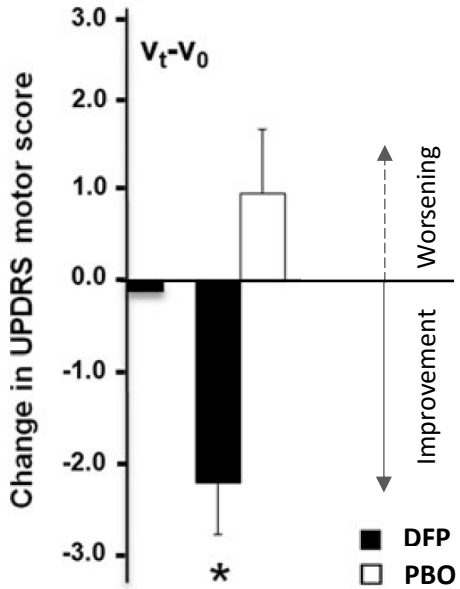
Brain Iron by MRI



Motor Function – UPDRS III



Deferiprone

- Indicated for Treatment of Iron Overload
- Black Box for neutropenia and agranucloctyosis
- Iron Binding Affinity $Kb=10^{36}$

PBT434

- Iron Binding Affinity $Kb=10^{10}$

Reducing excess iron improves motor function

Devos et al. Antiox. and Redox Signaling. 2014; 21: 195

Link Between Iron and Severity of PD

The Relevance of Iron in the Pathogenesis of Parkinson's Disease

Gotz et al. Ann N.Y. Acad Sci. 2004

The nigral increase in iron levels identified biochemically in the postmortem brain from parkinsonian patients appears to be confirmed and is related to the severity of the disease in the living patient as assessed by magnetic resonance imaging (MRI).[53–56]

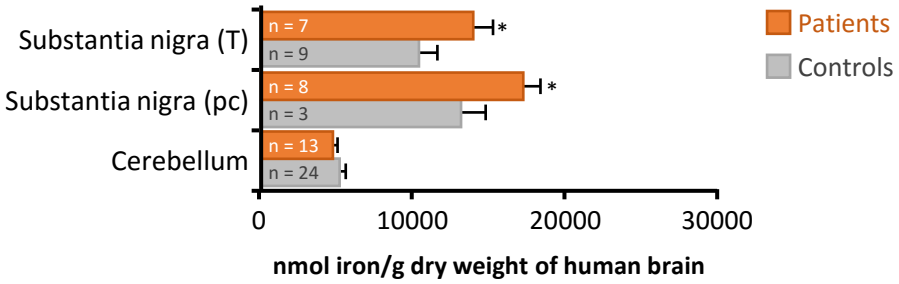
However, biochemical studies have reported increased iron content in the nigra in PD,[2-4] with the changes most marked in severe disease (PD)[5]

Midbrain iron content in early Parkinson disease

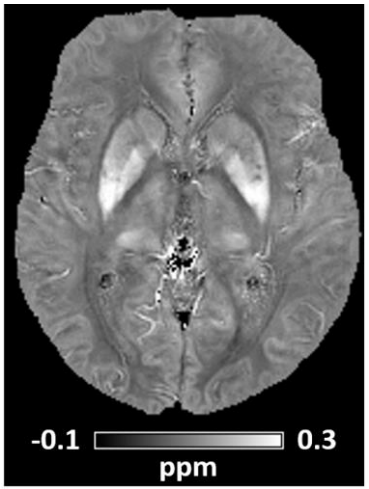
A potential biomarker of disease status

Martin, et al. Neurology 2008;70:1411–1417

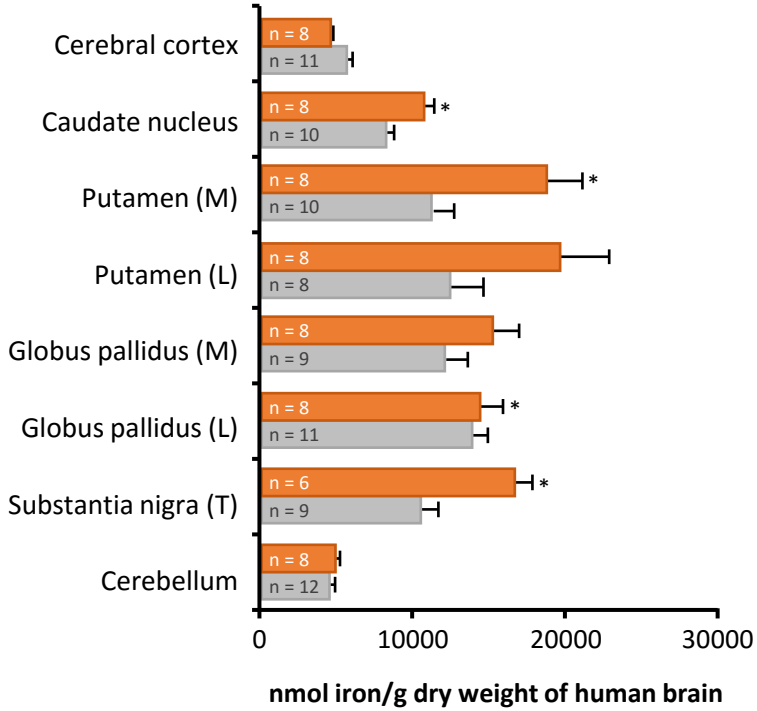
Brain Iron Increased in Parkinson's Disease Patients



Specialized MRI Technique (QSM) to Non-invasively Quantify Brain Iron (PD Patient)



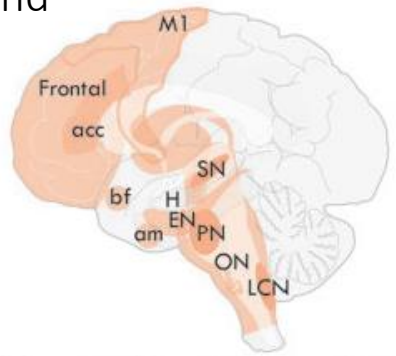
And in Multiple System Atrophy Patients



Dexter. Brain.1991;114
Langkammer. PLoS ONE 11(9): e0162460. 2016

Multiple System Atrophy

- Progressive neurodegenerative disorder leading to severe disability and impairment in quality of life
- Sporadic, typically presents in 50s to 60s
- Orphan Indication: Prevalence ~5 per 100,000 in the U.S.
- Characterized by a variable combination of
  - Parkinsonism, which responds poorly to levodopa responsive
  - Autonomic instability: Orthostatic hypotension, bladder dysfunction, erectile dysfunction, constipation
  - Cerebellar impairments
- MSA patients have neuron loss in multiple brain regions
- The hallmark of MSA is the accumulation of α-synuclein within neuronal cells and glial support cells



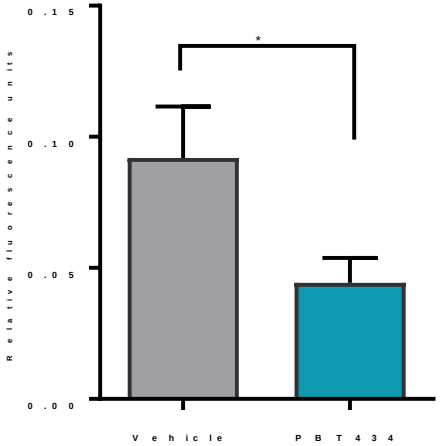
Halliday 2015, based on Brain 2015: 138; 2293–2309

PBT434 Lowers α-Synuclein, Prevents Neuronal Death and Improves Function

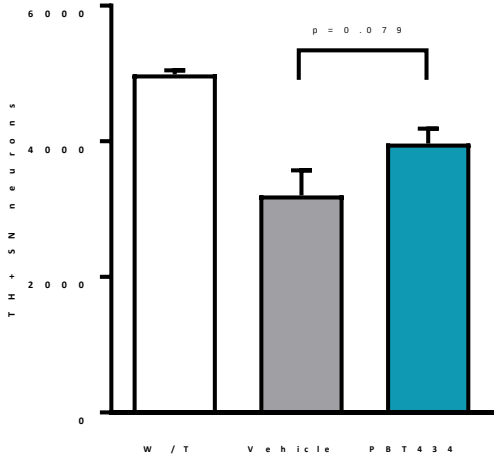
Transgenic Animal Model of MSA [(PLP)-α-SYN] of Multiple System Atrophy

Preliminary Data

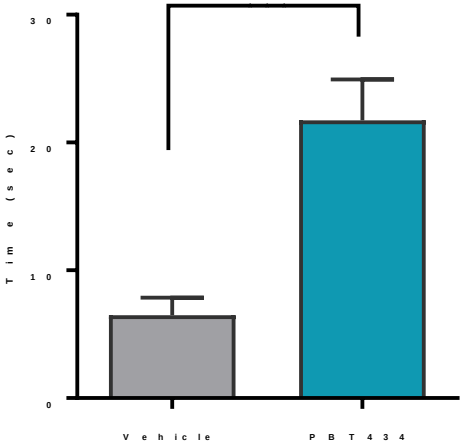
↓ α-Synuclein aggregation



Neurons in S. nigra



Rotarod Test

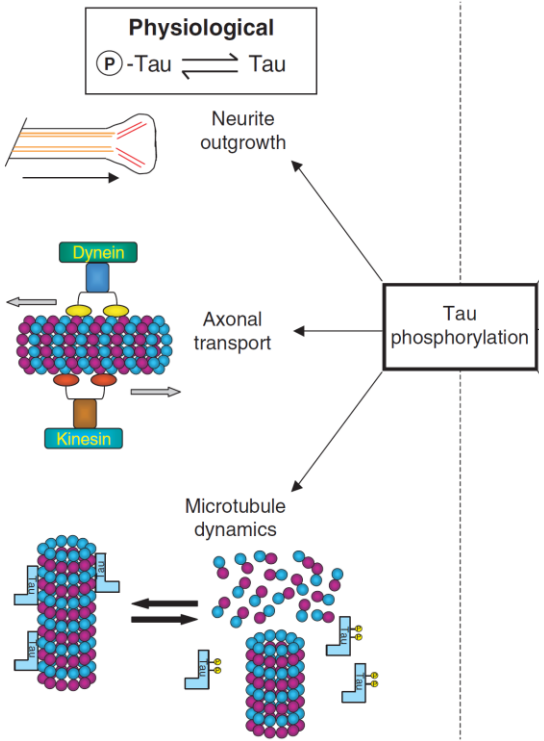


Treatment
- Randomly allocated
- 7-12 months of age
- ~30 mg/kg/day (via feed)

Assessments done in blinded manner

Structure and Function of Tau

PBT434 Prevents Abnormal Tau Accumulation



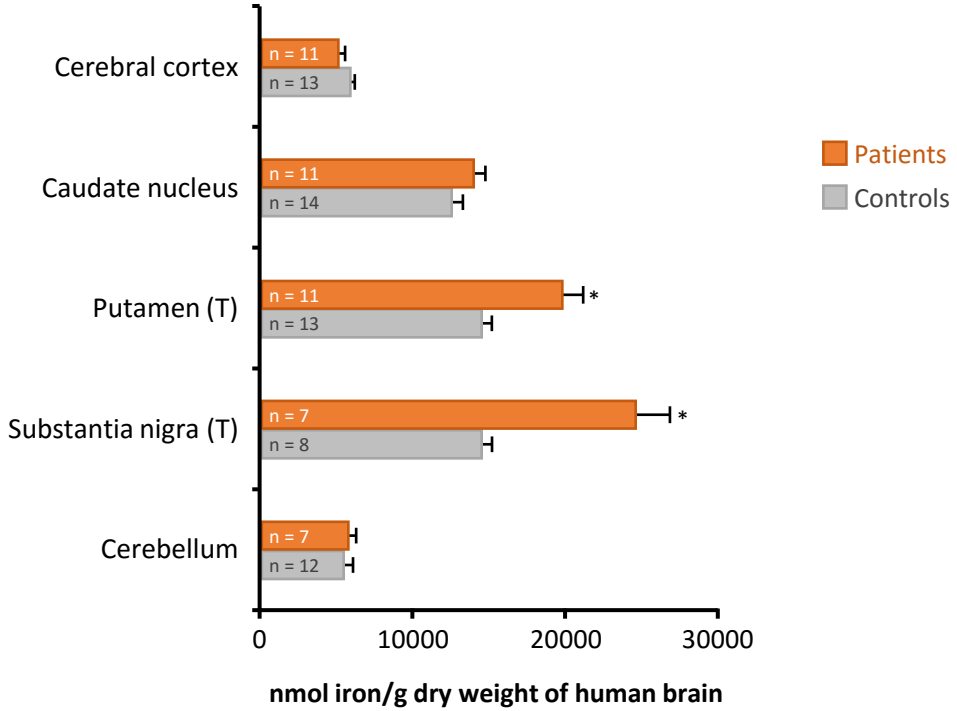
- Tau is an intracellular protein expressed in neurons and glial support cells
- Natively unfolded, highly soluble protein
- Primary role is to regulate and stabilize microtubules inside cells, which is critical to normal cellular function
- Tau promotes neurite outgrowth, axonal transport of synaptic vesicles, and microtubule dynamics involved in memory formation
- Normal activity of tau is regulated by phosphorylation, which is highly sensitive to iron levels
- In disease, hyperphosphorylation leads to protein aggregation and disrupted cellular function

J. Cell Science 117, 5721-5729; 2004

Yamamoto, 2002; Ahmadi 2017

Brain Iron is also Increased in Tauopathies

E.g.: Progressive Supranuclear Palsy



Dexter et al. *Brain. 1*991;114:1953-1975.

PBT434 Lowers Tau accumulation and Cognitive Function

Transgenic Animal Model of Tauopathy (rTg4510)

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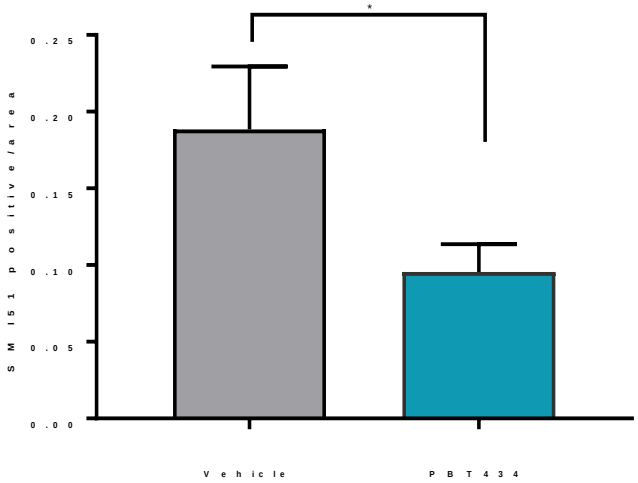
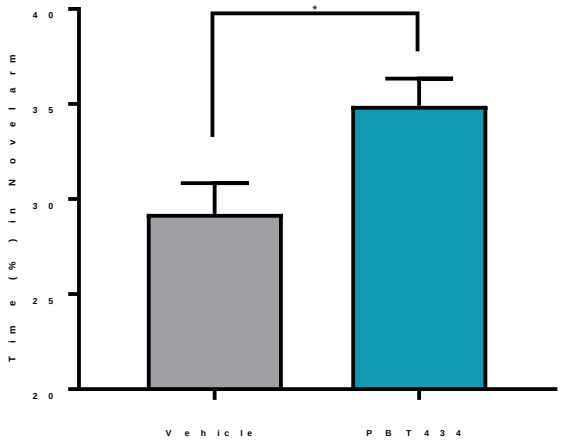
Tau accumulation in hippocampus



Performance in Y-maze



Treatment
- Randomly allocated
- Started at 10.5 months
- Low: 1 mg/kg/day x 3-4 mo
- High: 30 mg/kg/day x 1.5 mo

PBT434 has Potential for Wide application in Neurodegenerative diseases

α-Synuclein and Tau proteins Share Pathogenic Features

Parameter	α-Synuclein	Tau
Localization	Intracellular	Intracellular
Native form	Soluble	Soluble
Physiologic function	Facilitates synaptic function	Microtubule assembly and stabilization
Genetic evidence for disease	Yes (*SNCA*)	Yes (*MAPT*)
Iron dysregulation in associated disease	Yes	Yes
Iron promotes phosphorylation and protein aggregation	Yes	Yes
Abnormal protein accumulates in disease	Yes (Lewy body, Glial cell inclusions)	Yes (Neurofibrillary tangles)
Potential Target Diseases	Multiple System Atrophy Parkinson's Disease	Progressive Supranuclear Palsy Frontotemporal Dementia

Development Milestones

- GMP Manufacturing 1Q ‘18
- Phase 1 (SAD/MAD) start mid ‘18
- Initiate LT Toxicology 2H ‘18
- New IND 2H ‘19
- Phase 2 start 1H ‘20