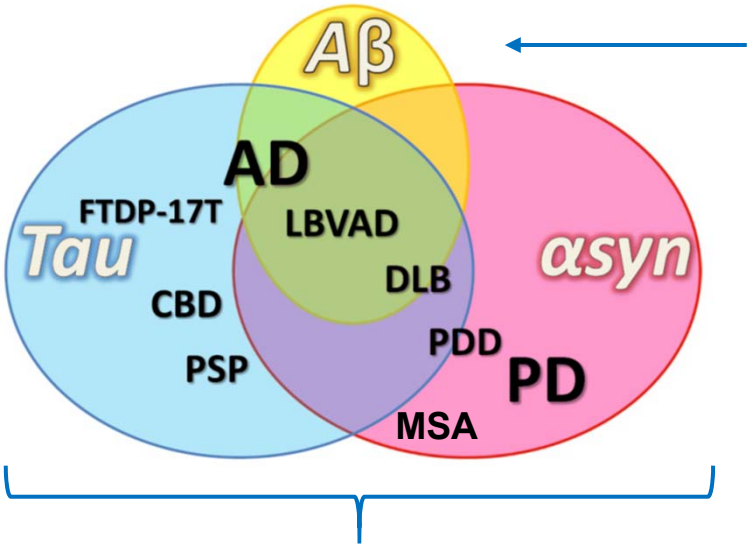
PRANA BIOTECHNOLOGY

Treatment of **Neurological Disorders**

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

January 2019

Targeting Proteins in Neurodegeneration



PBT2 (1st generation)

- Mechanism of action: Zn and Cu ionophore
- Originally developed for neurological indications by targeting extracellular protein
- Evaluating non-neurological indications for further development

PBT434 (2nd generation)

- *Targets intracellular proteins with established function: α-synuclein, tau*
- *Mechanism of action: Effluxes labile Fe*
- *Reduces α-synuclein accumulation in transgenic animal models of PD and MSA*

Current Focus

Novel Drug Candidate PBT434

- Targets key proteins implicated in neurodegeneration of Parkinson's disease and atypical parkinsonism
- Distinct scaffold and biological profile compared to PBT2

Strong Research and Development

- U.S. development team with proven track record
- Innovative discovery program
- Long standing collaborations with Harvard and Florey Institute of Neuroscience and Mental Health

Multiple Indication Opportunity

- PBT434 active in models of Parkinson's disease and atypical parkinsonism including orphan diseases such as Multiple System Atrophy (MSA)

Trading information:

ASX:	PBT
Nasdaq:	PRAN
Share price:	US$1.72
Valuation:	US$19M
Cash:	~A$23M

Approximate cash on completion of initial securities purchase agreement with Life Biosciences

Life Biosciences LLC Leads Strategic Investment of up to a $31.4 Million in Prana

January 2, 2019

US-based development team with strong drug development experience and FDA approvals

David Stamler, M.D.
Chief Medical Officer & Senior VP, Clinical Development

Former VP, Clinical Development and Therapeutic Head, Movement Disorders, Teva Pharmaceuticals and Chief Medical Officer, Auspex Pharmaceuticals.

Part of Teva's US$3.5 billion acquisition of Auspex. Led development of AUSTEDO (deutetrabenazine) for treatment of Huntington disease (approved by FDA - April 2017) and tardive dyskinesia, also in 2017.

James Kerr
VP, Chemistry, Manufacturing and controls

Previously CMC leadership at Auspex/Teva. Senior member of leadership team responsible for budget managment and operational direction of CMC team. Prior to Auspex, was Senior Director, CovX Operations at Pfizer WRD.

Margaret Bradbury, Ph.D.
VP, Nonclinical Development

Previously Non-Clinical leadership at Auspex/Teva. At Teva, led non-clinical development of several neuroscience programs. At Auspex Pharmaceuticals, led strategic planning and program management in Huntington Disease chorea from IND through NDA filing.

Cynthia Wong, M.P.H.
Senior Director, Clinical Operations

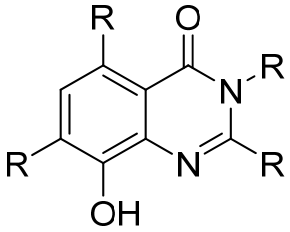
Previously Clinical Operations leadership at Auspex/Teva. At Auspex, led clinical trial activities for the registration study of AUSTEDO in Huntington Disease chorea. Prior to Auspex, led Phase 1-3 studies, including registration studies for marketing approval for Quillichew ER, Esbriet and Infergen.

Investment Thesis

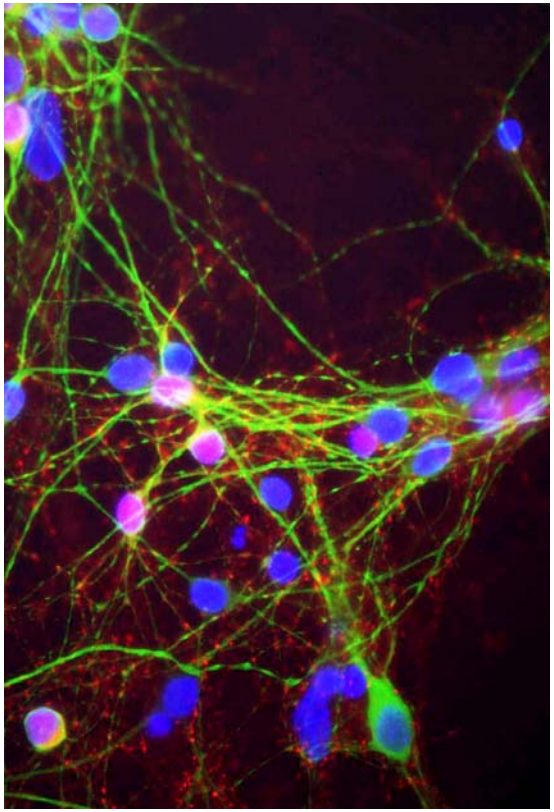
- Alpha (α)-synuclein is an intracellular protein critical for neurotransmission
- α-synulein accumulates and aggregates in many neurodegenerative diseases and is implicated in pathology
- PBT434 blocks α-synuclein accumulation and aggregation, preserves neurons and improves function in animal models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

PBT434 is an excellent drug candidate for treating neurodegenerative diseases

PBT434: Promising Drug Profile



- Good CNS penetration based on low molecular weight and lipophilicity
  - Brain concentrations 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
- Phase 1 in Healthy volunteers ongoing



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

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

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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

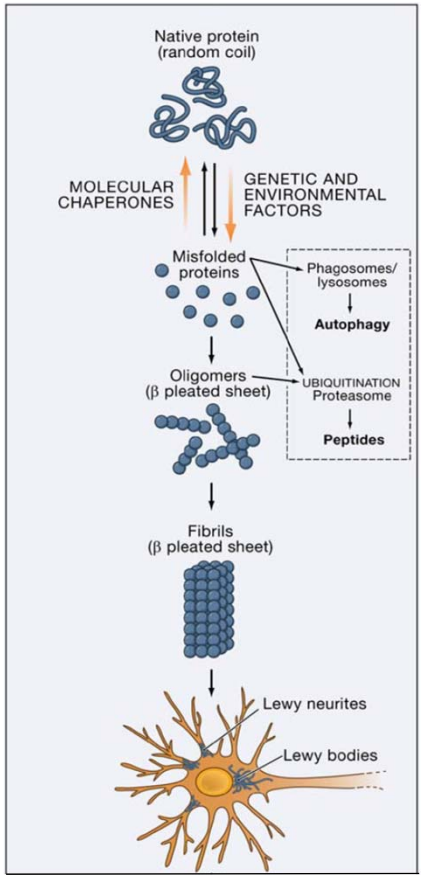
Takeda

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

Biogen

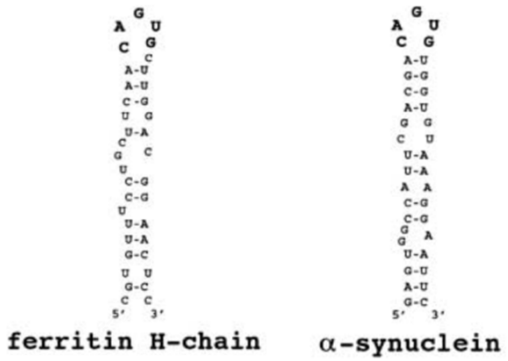
Roche

α-Synuclein as Target for PBT434



Lee and Trojanowski, 2006

- α-synuclein fibrillizes readily
- Factors regulating its production and conformation are relevant to disease pathogenesis and treatment
- Homeostasis of iron is disrupted in PD and atypical parkinsonism
- α-synuclein is highly conserved in vertebrates but only humans develop synucleinopathy
- Human α-synuclein mRNA contains an Iron responsive element



from Friedlich, Tanzi, et al. 2007

- The iron responsive element (IRE) of α-synuclein is a 5'-untranslated region of mRNA predicted to form a single RNA stem loop
- The stem loop shows striking similarity to the 5'-UTRs of mRNAs encoding ferritin and ferroportin

PBT434 Inhibits α-Synuclein Aggregation by Restoring Intracellular Iron Balance

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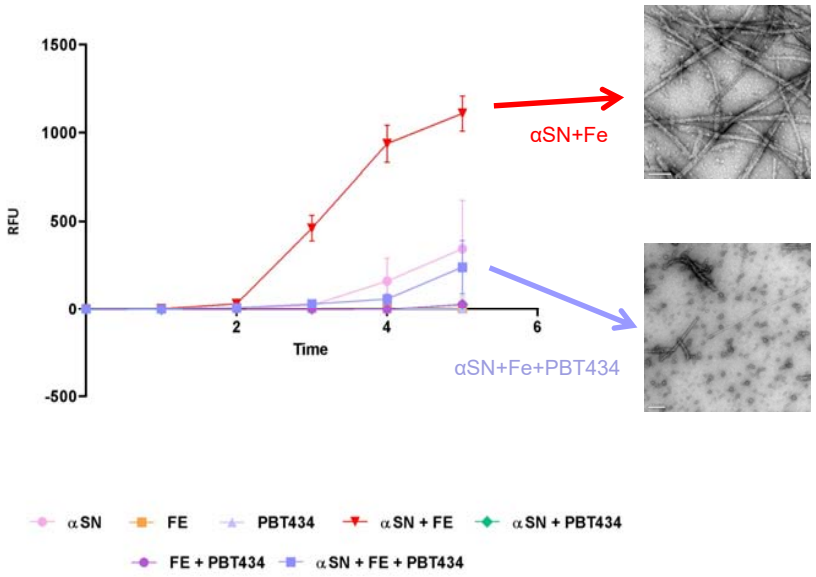
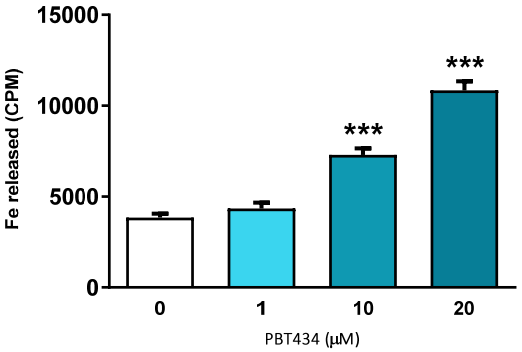
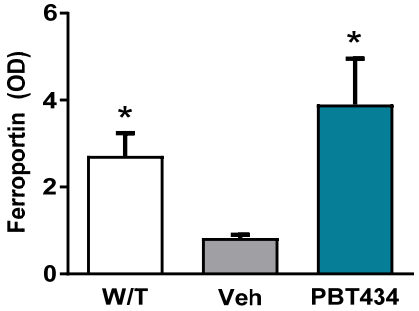
PBT434 blocks the aggregation of α-synuclein in vitro



Iron efflux from cultured M17 cells



PBT434 treatment preserves ferroportin levels in vivo



PBT434 Dose: 30 mg/kg

Alpha-synuclein Pathology and PBT434 Mechanism of Action

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

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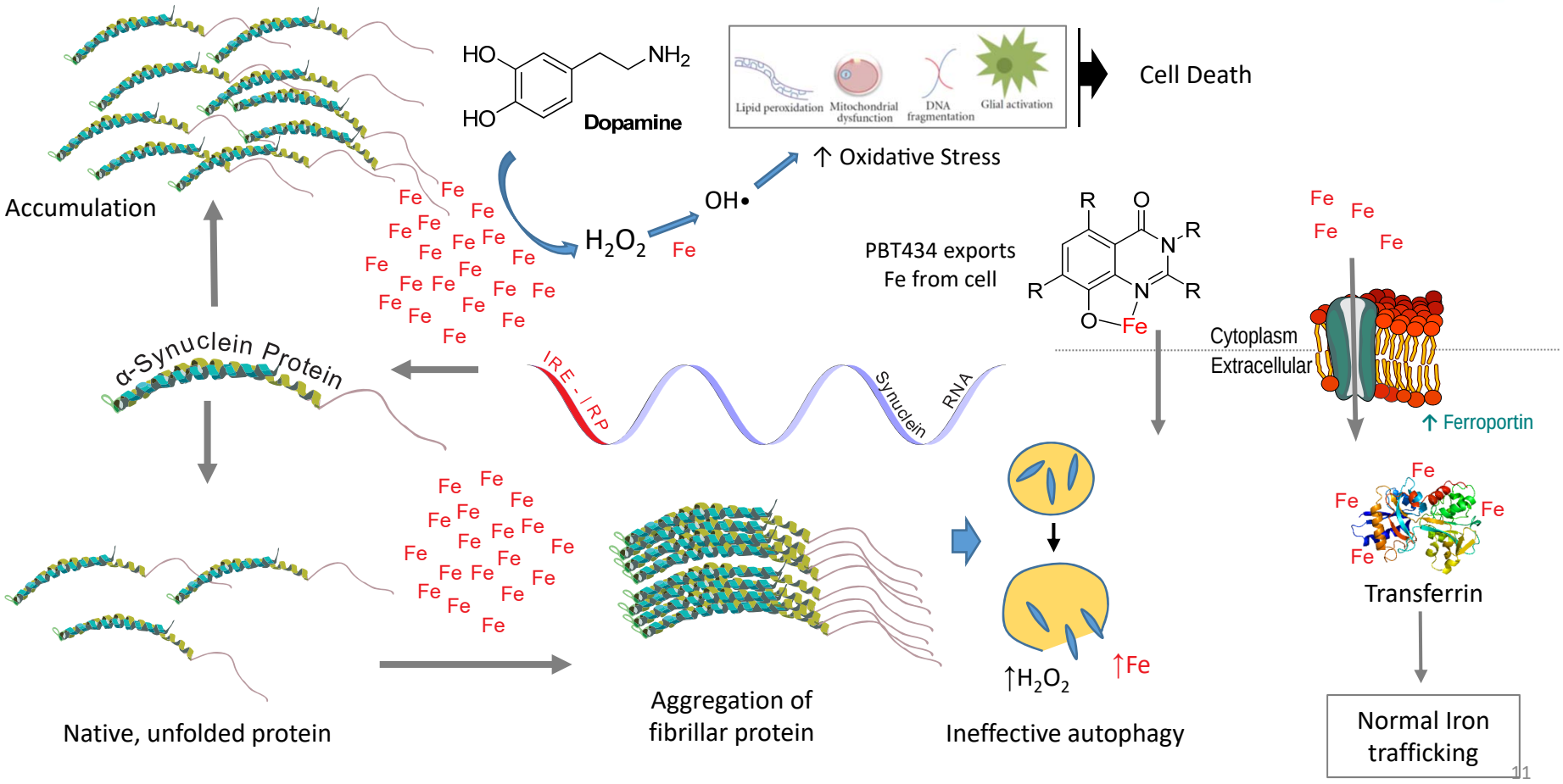

PBT434 Lowers α-Synuclein, Prevents Neuronal Death and Improves Motor Function

Transgenic Animal Model (hA53T) of Parkinson's Disease

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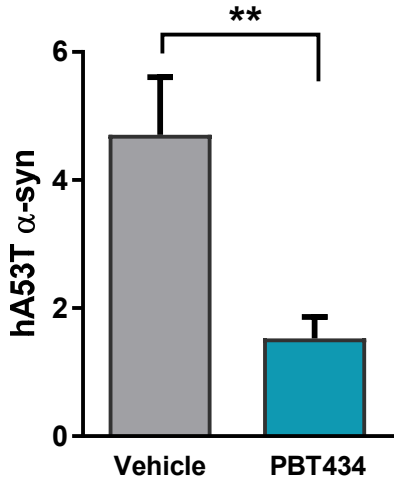
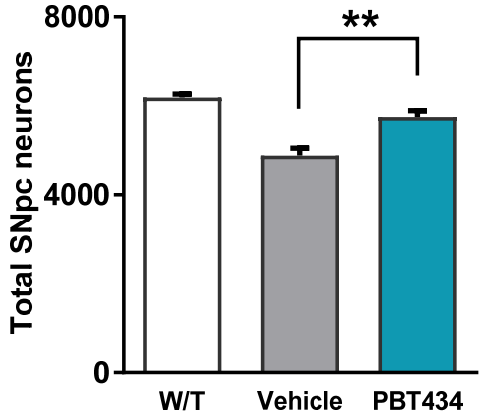
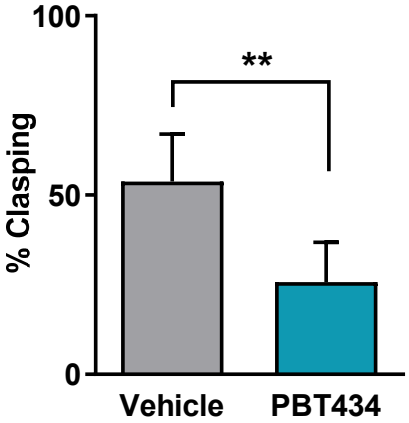
↓ α-Synuclein aggregation



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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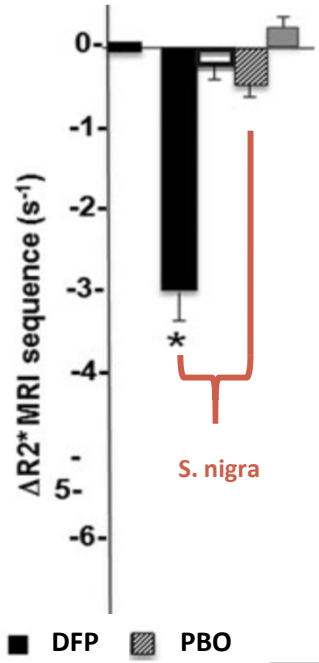
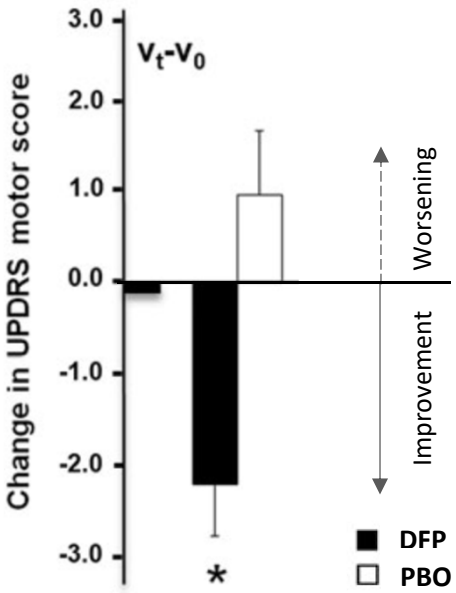
Brain Iron by MRI



Motor Function – UPDRS III



Deferiprone

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

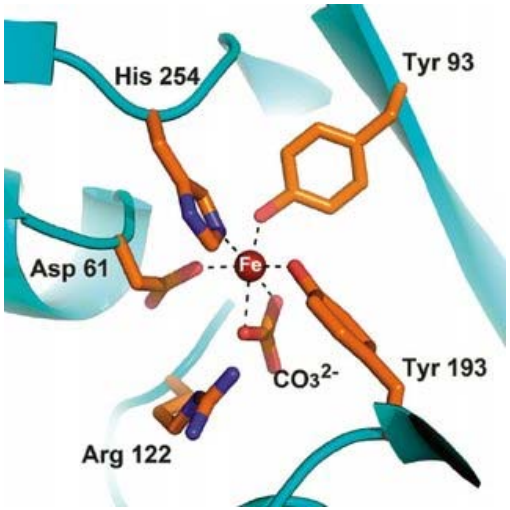
Reducing excess iron associated with improved motor function

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

PBT434 has Optimal Iron Binding Affinity for Efficacy and Safety

Agent/Protein	Kd for Fe^{3+}
α-Synuclein	10^{-5}
PBT434	10^{-10}
Ferritin	10^{-22}
Transferrin	10^{-23}
Deferiprone	10^{-36}

Stronger binding



Davies et al. PLoS ONE. 2011; 6; 1; e15814. doi.org/10.1371/journal.pone.0015814
Aisen P and Listowsky I. Ann Rev Biochem 1980 49: 357-393
Aisen P, Leibman A, Zweier J. J Biol Chem. 1978; 253:1930-1937
Kline MA and Orvig C. Clin Chem (1992); 38: 562-565

Link Between Iron and Severity of PD

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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]

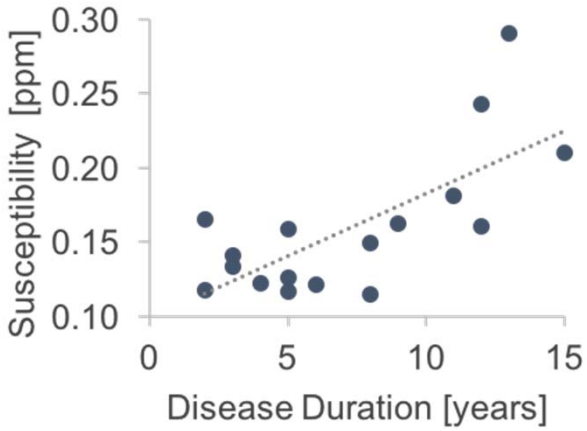
Midbrain iron content in early Parkinson disease

A potential biomarker of disease status

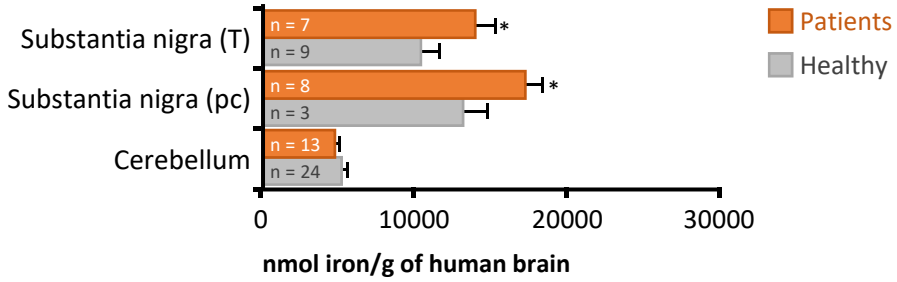
Martin, et al. Neurology 2008;70:1411–1417

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]

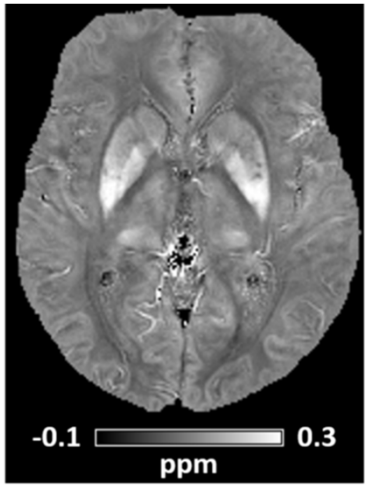
Iron concentrations increase with disease severity



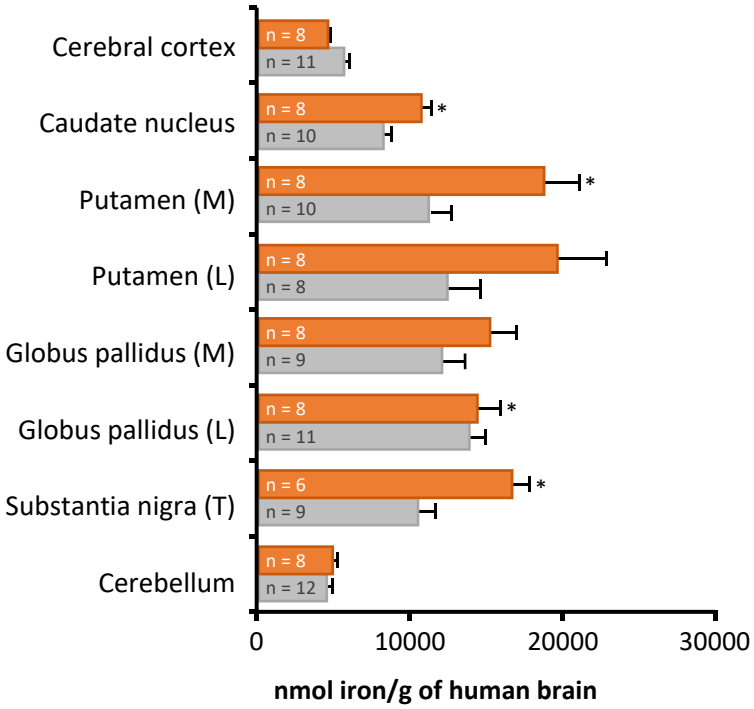
Brain Iron Increased in Parkinson's Disease Patients



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



And in Multiple System Atrophy Patients

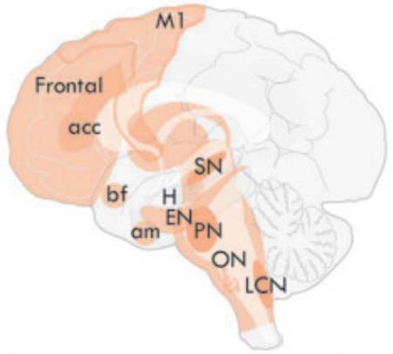


Dexter. Brain.1991;114
Langkammer. PLoS ONE 11(9): e0162460. 2016

Multiple System Atrophy

A form of Atypical Parkinsonism

- Rapidly 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
  - Cerebellar impairments: impaired gait and speaking
  - Autonomic failure: Orthostatic hypotension, bladder dysfunction, erectile dysfunction, constipation
- MSA patients have neuron loss in multiple brain regions
- The hallmark of MSA is the accumulation of α-synuclein within neurons and glial support cells

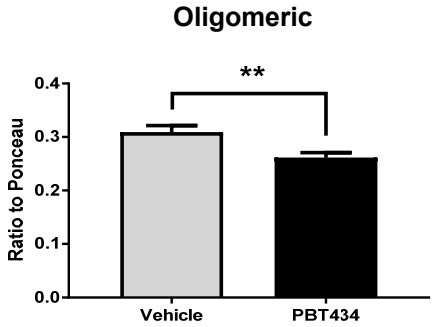


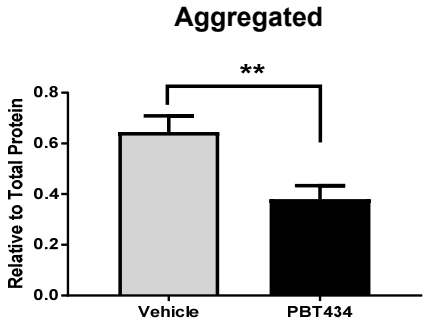
Halliday 2015, based on
Brain 2015: 138; 2293–2309

PBT434 reduces Alpha-synuclein and Lowers Glial Cell Inclusions

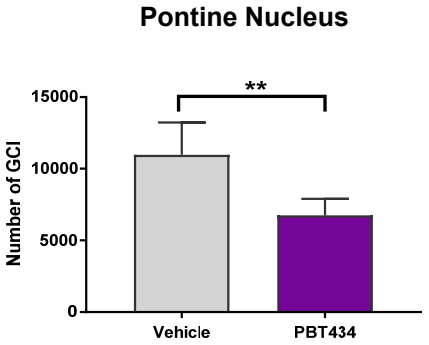
Transgenic Mouse Model (PLP)-α-SYN of MSA

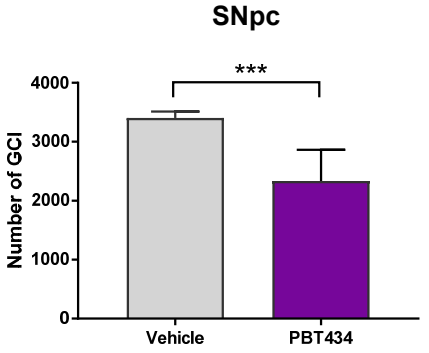
↓ α-Synuclein





Glial Cell Inclusions

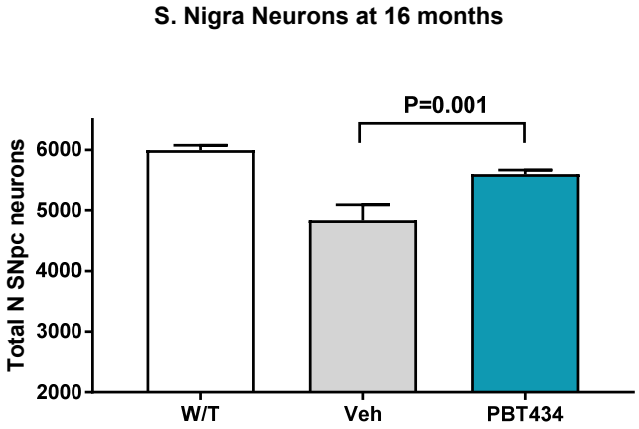


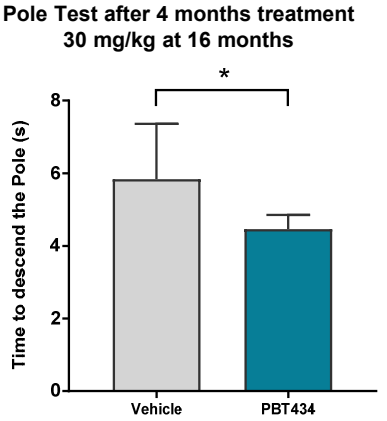


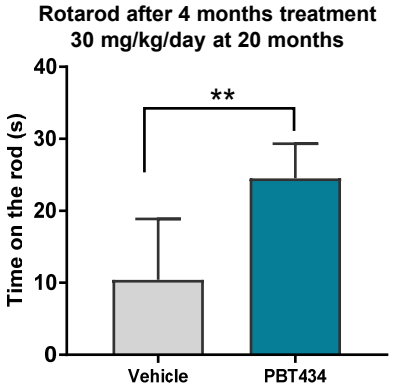
Treatment: Randomly allocated, 4 months, ~30 mg/kg/day or Vehicle (Veh)
Data presented are for animals at 16 mo age

PBT434 Preserves Neurons and Improves Motor Function

Transgenic Mouse Model (PLP)-α-SYN of MSA





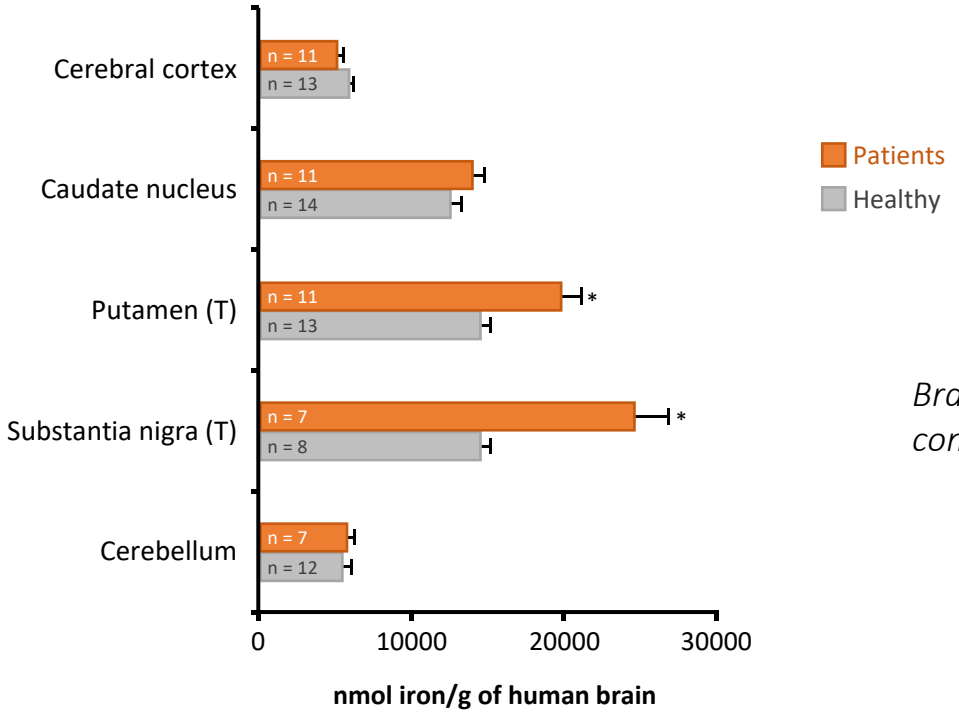


Treatment: Randomly allocated, 4 months, ~30 mg/kg/day or Vehicle

Brain Iron is also Increased in **Tauopathies**

Progressive Supranuclear Palsy (PSP)

A form of Atypical Parkinsonism



Brain Iron increased compared to Healthy controls

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

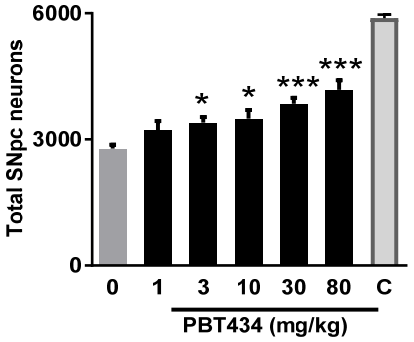
PBT434 in an Animal Model of Acute Oxidative Stress

MPTP mouse model

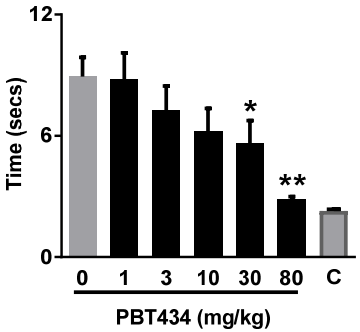
- MPTP is a potent inhibitor of complex 1 of the mitochondrial electron transport chain
- Significant neuron loss in SNpc and motor impairment

- Rapid and sustained elevation of iron in the SNpc
- Causes acute elevation in ROS and oxidative damage
- PBT434 or vehicle treatment† started 1 day after toxin administration

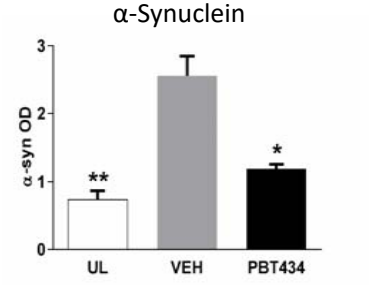
Total SNpc neurons



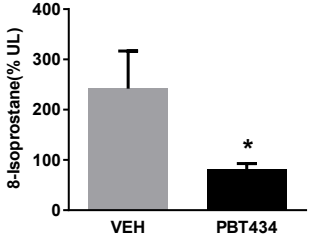
Pole test



α-Synuclein



Lipid peroxidation



For α-synuclein, lipid peroxidation: PBT434 dose 30 mg/kg/d
† Treatment randomly allocated, assessors blinded
*P<0.05, **P<0.01, ***P<0.001

PBT434 preserves neurons, improves motor function and reduces α-Synuclein accumulation and oxidative stress in the MPTP mouse

Development Milestones

- Phase 1 Completion 1H ‘19
- Initiate LT toxicology 1H ‘19
- Initiate Phase 2 planning study 1H ‘19
- Initial Patient study start 2020

Preliminary Market Assessment (U.S. only)

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Substantial Unmet Need

- Severely debilitating, fatal illnesses with no current treatments are ripe for new entrants targeting what may be the actual cause of the disease, even if only motor symptom endpoints

Non-Competitive Landscape

- PBT434 likely to be used in combination with symptomatic treatments and alpha-synuclein antibodies given it works differently and targets different aspects of MSA and PSP

$1-1.7B potential commercial opportunity for PBT434 in MSA and PSP*

Unique MOA

- Inhibition of iron-mediated protein accumulation and aggregation is a novel mechanism of action that may ultimately prove in clinical practice to impact more than motor symptoms

Ease of Use

- Given similar efficacy, clinicians will likely prefer PBT434's once or twice daily oral administration vs. the monthly IV infusions or injections required for any alpha-synuclein or tau antibodies that come to market

*Additional market research required to validate preliminary opportunity assessment.

Summary

- PBT434 is an excellent drug candidate to prevent alpha-synuclein aggregation and reduce oxidative stress by targeting intracellular reactive iron
- Brain iron pathologically increased in Parkinson's disease and atypical parkinsonism
- PBT434 has demonstrated efficacy in various animal models of neurodegeneration and has been shown to prevent acute oxidative damage *in vivo*
- Multiple indication opportunity, with potential for treating PD and atypical parkinsonism such as Multiple System Atrophy, an orphan disease
- Significant commercial opportunity given limited treatment options which target underlying cause of disease