PRANA BIOTECHNOLOGY

Treatment of Neurological Disorders

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

June 2018

Corporate Information

ASX Code NASDAQ Code	PBT PRAN
Share Price	A$0.043 US$1.96 (as of 25/06/2018)
Shares on Issue ADR 1:60	533,891,470
Cash Position	A$20.0m (as of 25/06/2018)
Market Capitalisation	A$24m

- Founded in Melbourne in 1997
- Operations in both Melbourne, AUS and San Francisco, USA
- Listed on the ASX (PBT) in 2000
- Listed on NASDAQ (PRAN) in 2002
- Deep drug development experience and global network of world leading expertise – including Florey Institute and Harvard
- Focus on neurological disorders including Parkinsonian diseases
- Phase 1 clinical trial commenced

Prana Biotechnology is developing first-in-class therapies to treat orphan neurodegenerative diseases

Our lead drug candidate PBT434 is in Phase 1 clinical development with the potential to treat Parkinsonian diseases, many of which have limited or no treatment options

Why Invest?

Built on Experience

Highly experienced drug development team established in the US – ex-Teva Pharmaceuticals and AUSPEX Pharmaceuticals – responsible for two FDA approvals in 2017

Published Research

Growing dossier of published research demonstrating strong activity of PBT434 in animals models of various Parkinsonian diseases

Evolving Science

Development of PBT434 builds on the experience and science of earlier therapeutic programs in neurodegenerative disease and continues to draw on the work of global leaders in diseases of the brain

R&D Program

- Chemistry – Bio21 identifying new drug candidates
- Biology screening and translational – Florey Institute
- Takeda Pharmaceuticals program focused on slowing or preventing neurodegeneration of the gastrointestinal system

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

David Stamler, MD
Chief Medical Officer & Senior VP, Clinical Development

Former VP, Clinical Development and Therapeutic Head, Movement Disorders, Teva Pharmaceuticals and Chief Medical Officer, Auspex Phamarceuticals.
Part of Teva's US$3.5 billion acquisition of Auspex. Led development of AUSTEDO (deutetrabenazine), new drug for treatment of Huntington's disease (approved by FDA - April 2017) and tardive dyskinesia, also in 2017.

James Kerr
VP, Chemistry, Manufacturing and controls

Previously Executive Direcgtor CMC Teva/Auspex Pharmaceuticals. 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 Senior Director, Teva Pharmaceuticals. At Teva, led non-clinical development of several neuroscience programs. As Executive Director at Auspex Pharmaceuticals, led strategic planning and program management in Huntington Disease-chorea from IND through NDA filing.

Board of Directors

Mr. Geoffrey Kempler

Executive Chairman, CEO
Founded Prana in 1997
Extensive experience in investment and business development
Overseen operations for the implementation of Prana's strategic plan and technology commercialisation

Mr. Peter Marks

BEc LLB Grad. Dip. Comm. Law MBA
Non-Executive Director
Director since 2005
Director of Armadale Capital
Principal of Henslow
Non-Executive Director of Emefcy Group
Previously Chairman of iSonea Ltd, formerly KarmelSonix

Mr. Brian Meltzer

B. Com., M Ec.
Non-Executive Director
30 years experience in finance
Previously Director Momentum Ventures
Director of the Australian-Israel Chamber of Commerce

Dr. George Mihaly

B. Pharm, M.Sc., Ph.D. FAICD
Non-Executive Director
Extensive experience in the pharmaceutical industry
Director of Waide
Previously Executive Chairman and Founding Director of Synermedica, one of Australia's leading consultant research organisations

Mr Lawrence Gozlan

B.Sc. (Hons)
Non-Executive Director
Leading biotechnology investor and advisor
Non-Executive Director of AusBiotech
Former Biotechnology Analyst QIC, an investment fund with over $60 billion under management
Previously Director of OncoSil Medical

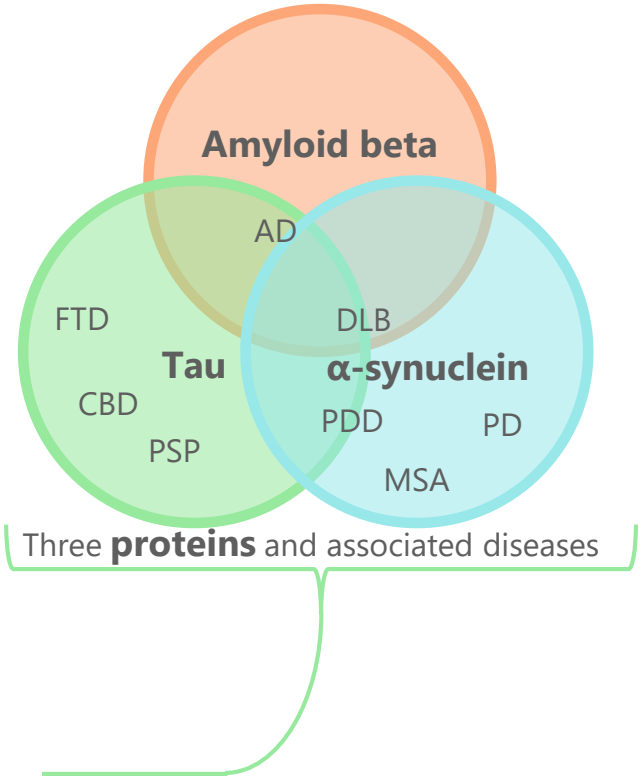
Professor Ira Shoulson

Professor of Neurology, Pharmacology and Human Science
Non-Executive Director
Chairman of our Research and Development Advisory Board
Has served as a member to several FDA advisory committees

Targeting proteins in neurodegenerative diseases

- PBT434 is the first of a new generation of small molecules designed to inhibit the aggregation of α-synuclein and tau, vital intracellular proteins that are implicated in neurodegenerative diseases such as Parkinson's disease and atypical parkinsonism.

- PBT434 has been shown to reduce the abnormal accumulation of these proteins in animal models of disease by restoring normal iron balance in the brain.



PBT434 (2nd generation)

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

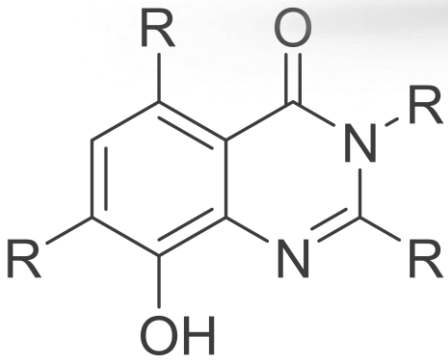
Development Rationale

- Alpha (α)-synuclein is an intracellular protein critical for neurotransmission
- 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
- Clear link between iron and the synucleinopathies and tauopathies
- 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 for the synucleinopathies

Conclusion: PBT434 is an excellent drug candidate to treat neurodegenerative diseases

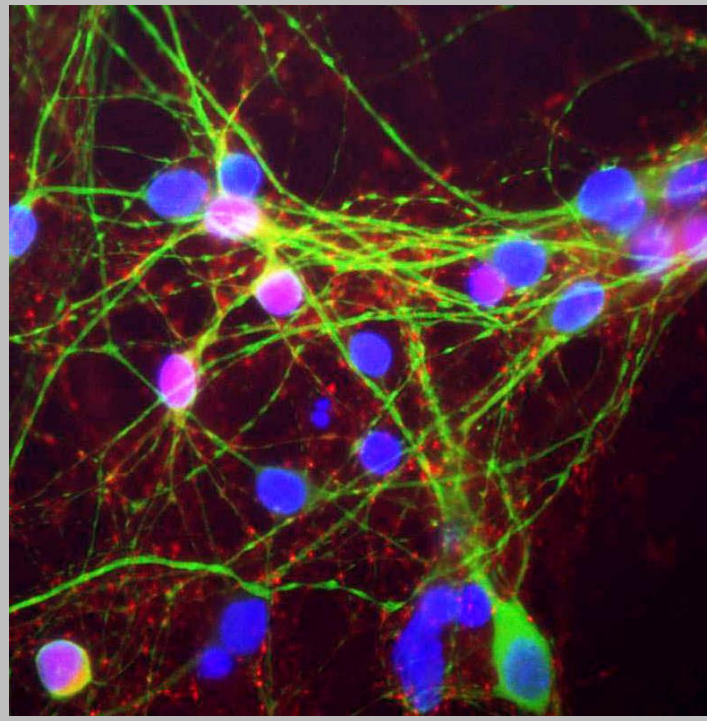
PBT434: Promising Drug Profile

- 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 scale of GMP material
- Benign safety profile in GLP toxicology studies
  - Non-toxic dose exceeds efficacious dose by >10-fold based on allometric scaling



Importance of α-Synuclein

- Essential for neurons to communicate
- α-Synuclein is an intracellular protein, abundantly expressed in the brain
- 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



MAb to α-synuclein stains red

α-Synuclein is an Established 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;

Biogen

Roche

AstraZeneca Takeda

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

VIEWPOINT

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

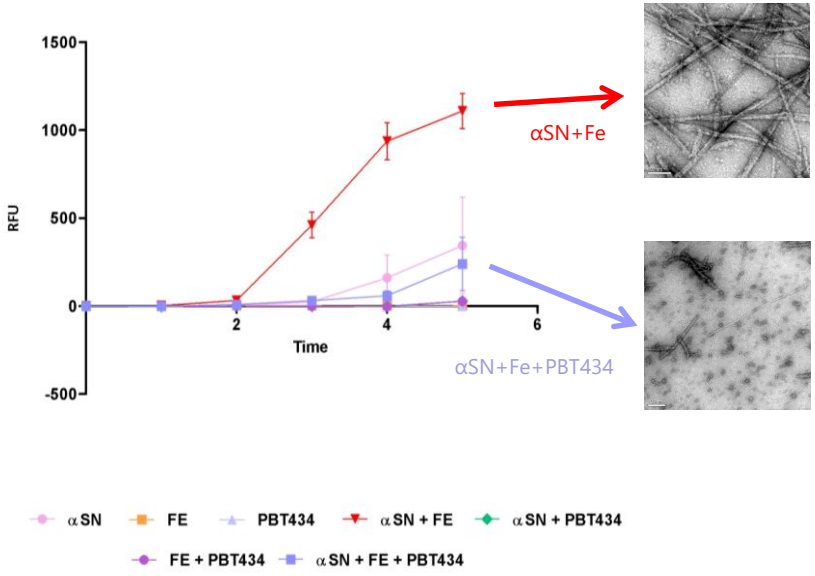
C. Warren Olanow, MD[1,2*] and Jeffrey H. Kordower, PhD[3,4]

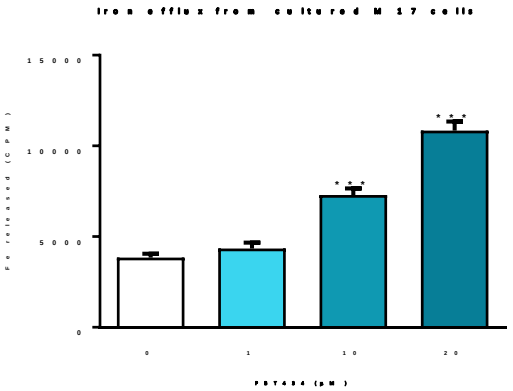
"Collectively these data strongly suggest that alpha synuclein is a potentially important and novel target of candidate neuroprotective therapies. Several different therapeutic strategies designed to clear or prevent the formation of toxic forms of α-synuclein are currently being investigated in the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

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

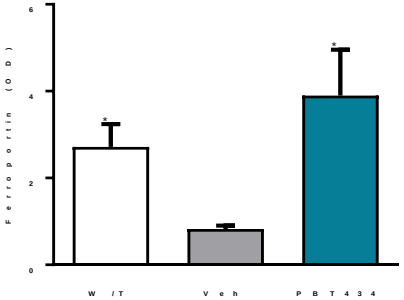
PBT434 Inhibits α-Synuclein Aggregation by Restoring Intracellular Iron Balance

PBT434 blocks the aggregation of α-synuclein in vitro





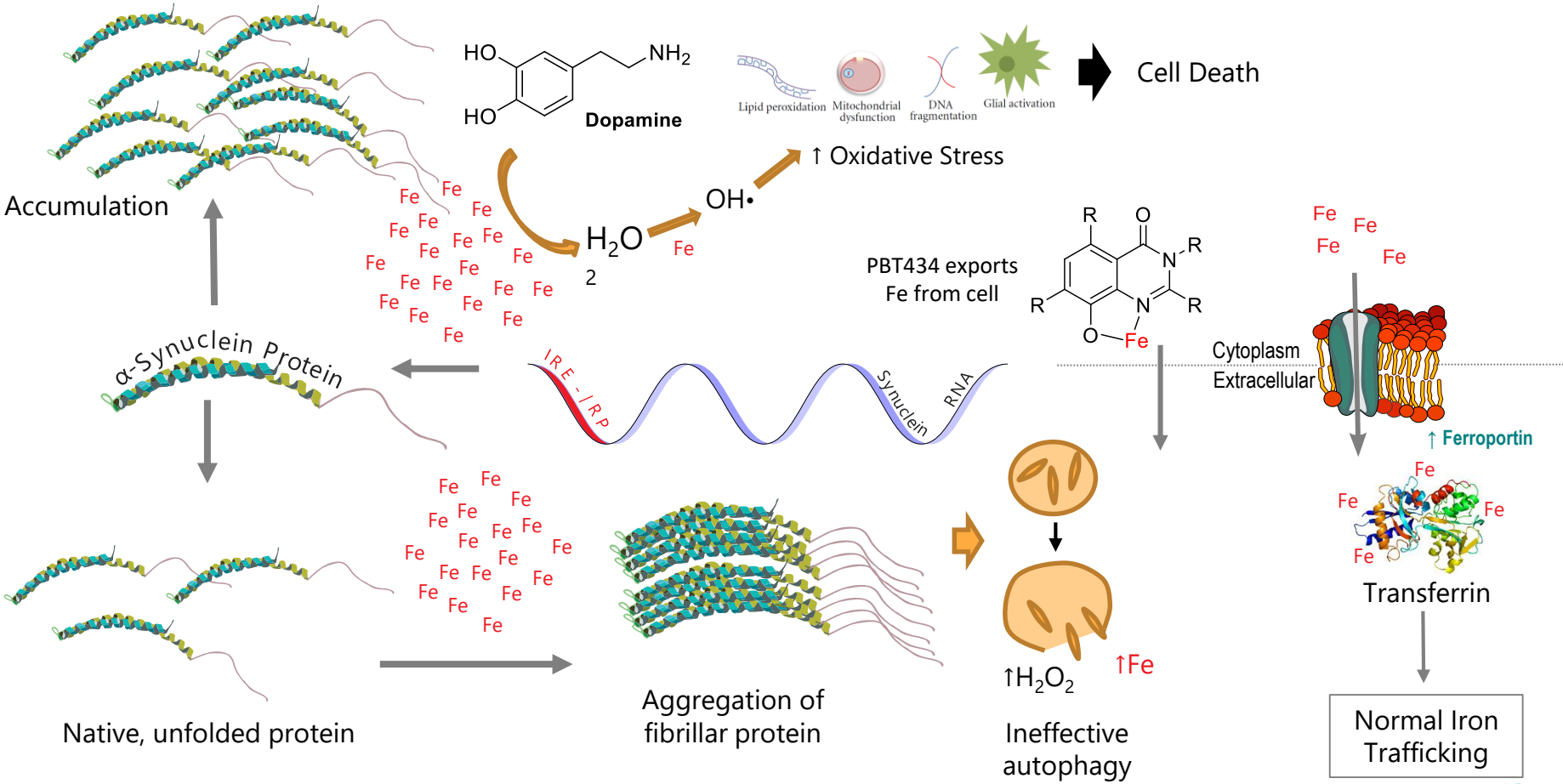
PBT434 treatment preserves ferroportin levels in vivo



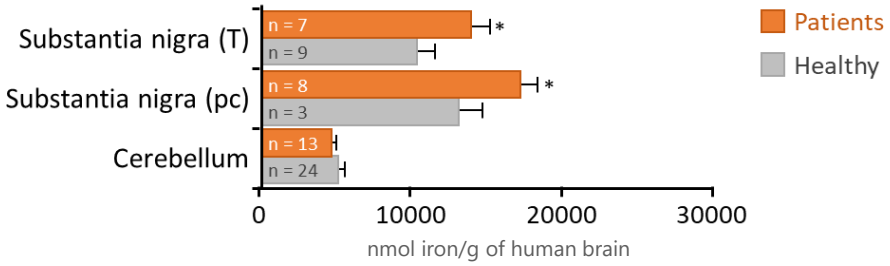
PBT434 Dose: 30 mg/kg

Alpha-synuclein Pathology and PBT434 Mechanism of Action

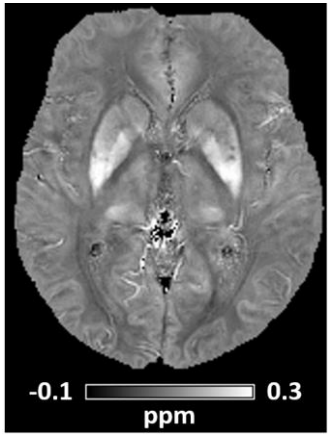
Iron Chaperone, reducing α-synuclein accumulation, aggregation and preserving neurons



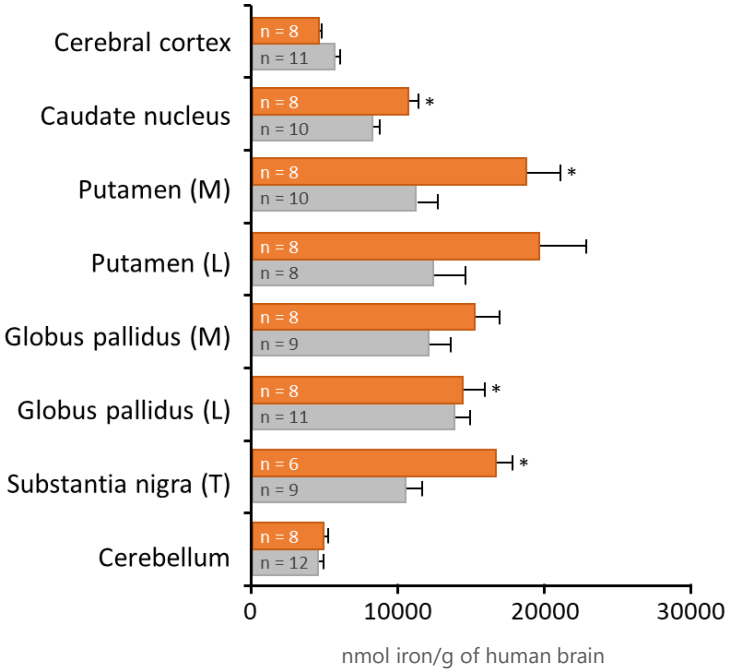
Brain Iron Increased in Parkinson's Disease Patients



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



And In Multiple System Atrophy Patients

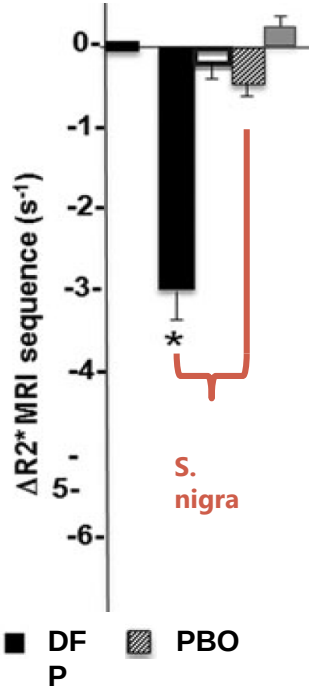


Dexter. Brain.1991;114
Langkammer. PLoS ONE 11(9): e0162460. 2016

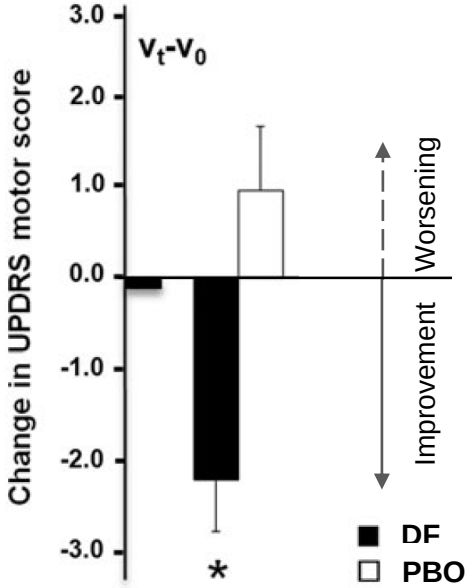
Strategy Supported by Proof of Concept with Deferiprone

6 month placebo controlled data in Parkinson's disease patients

Brain Iron by MRI



Motor Function – UPDRS III



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

PBT434
- Iron Binding Affinity $Kd=10^{-10}$

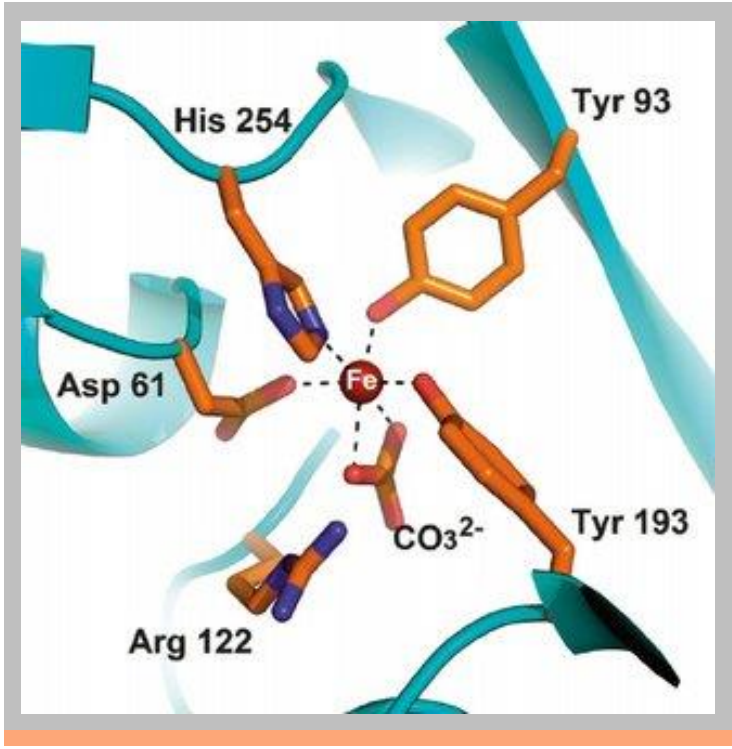
Reducing excess iron associated with improved motor function

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

Initial Disease Targets

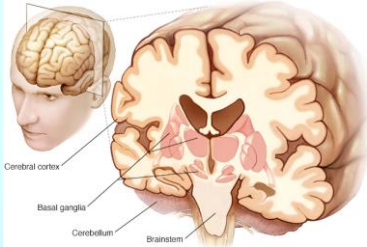
Multiple System Atrophy (MSA) and Progressive Supranuclear Palsy (PSP) are two forms of atypical Parkinsonism with no approved therapies.

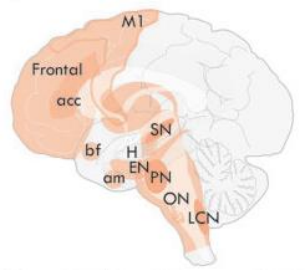
Sufferers experience especially rapid deterioration compared to Parkinson's disease and typically have motor symptoms that respond poorly to available treatments.

Patients with MSA have difficulty maintaining blood pressure along with bowel and bladder dysfunction whereas PSP patients have unsteady gait, frequent falls, visual difficulties and cognitive impairment.

Multiple System Atrophy (MSA)

- Progressive neurodegenerative disorder leading to severe disability and impairment in quality of life
- Sporadic, typically presents in 50s to 60s
- Orphan disease: Prevalence ~5 per 100,000 in the U.S.
- Characterised by a variable combination of
  - Parkinsonism, which responds poorly to Levodopa
  - 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

Progressive Supranuclear Palsy (PSP)

- Fatal and rapidly progressive neurodegenerative disease
- Typically presents in 50s
- Orphan disease: Prevalence ~5 per 100,000 in the U.S.
- Characterised by a variable combination of
  - Parkinsonism, which responds poorly to Levodopa
  - Loss of coordination, unsteady gait (walking pattern)
  - Vision difficulty
- Characterised by Parkinsonian movements with typical stiffness and lack of coordination, eye movement is also limited. An MRI may show a shrinking of the brainstem
- Aggregated tau is associated with PSP

Phase I Clinical trial of PBT434 commenced

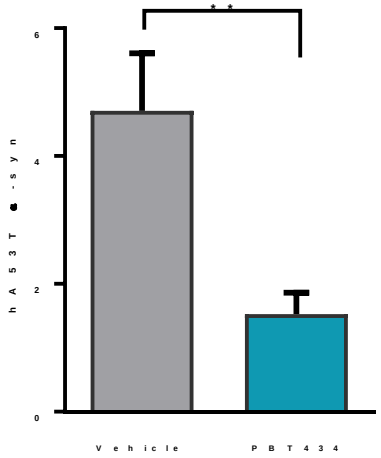
- Ethics approval received for a clinical trial evaluating first in human dosing of PBT434
- First cohort dosed
- Study conducted by the Nucleus Network in Melbourne
- The study will recruit healthy adult and elderly volunteers, with the primary goal of assessing the safety and tolerability of PBT434 after single and multiple ascending dose administration.
- Secondary endpoints include a range of pharmacokinetics measures to understand how PBT434 is absorbed and metabolized by the body

Scientific evidence growing for PBT434

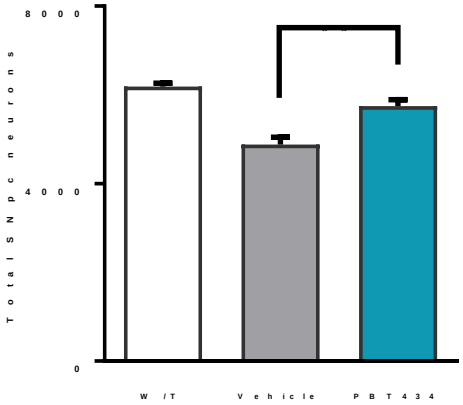
PBT434 Lowers α-Synuclein, Prevents Neuronal Death and Improves Motor Function

Transgenic Animal Model (hA53T) of Parkinson's Disease

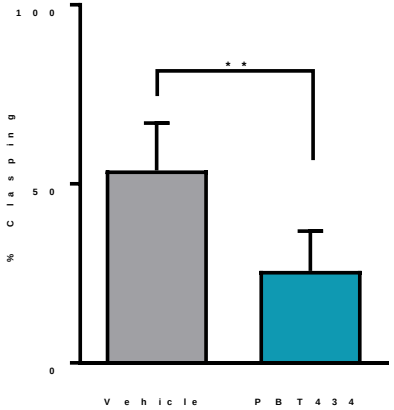
↓ α-Synuclein aggregation



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

PBT434 Lowers Glial Cell Inclusions, Preserves Neurons and Improves Motor Function

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

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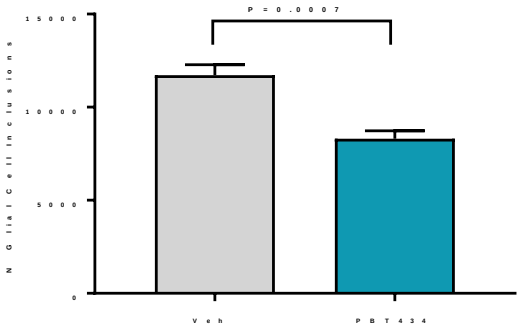
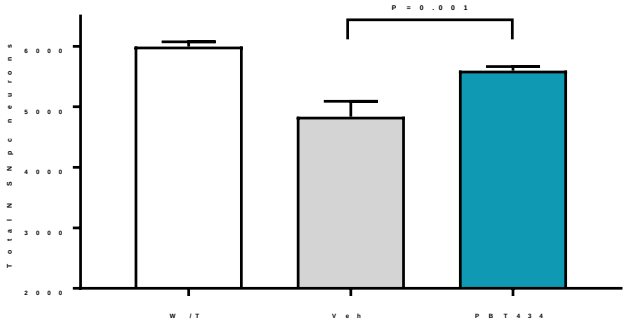
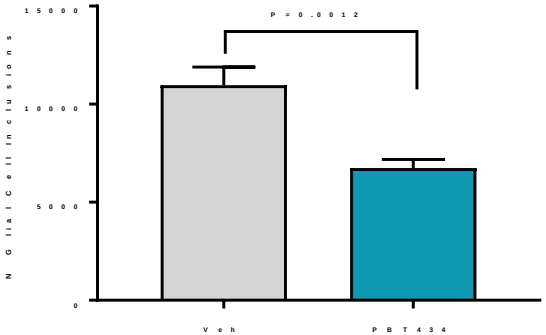
Glial Cell Inclusions Substantia nigra



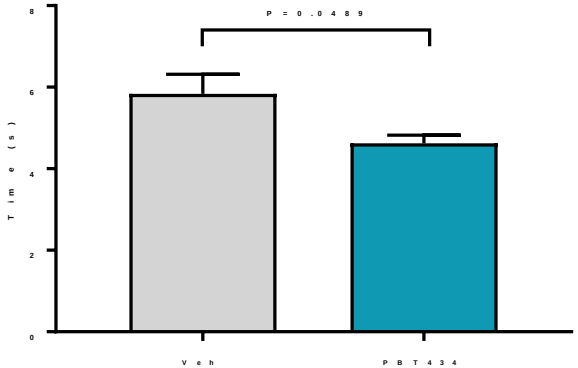
Substantia nigra Neurons



Glial Cell Inclusions In Pons



Pole test (motor function)



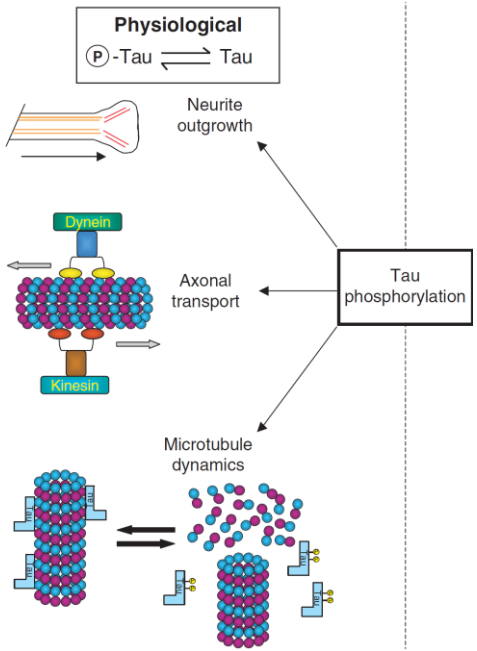
Treatment: Randomly allocated, 4 months, ~30 mg/kg/day or Vehicle (Veh)
Data presented are for animals at 16 mo age

Brain Iron is Increased in Synucleinopathies (PD, MSA) and also *Tauopathies (PSP)*

Structure and function of Tau

- Tau is an intracellular protein expressed in neurons and glial support cells
- Natively unfolded, soluble protein
- Primary role is to regulate and stabilize microtubules inside cells
- 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 disrupted cellular function/cell death
- Loss of tau function exacerbates iron dysregulation

Tau in health

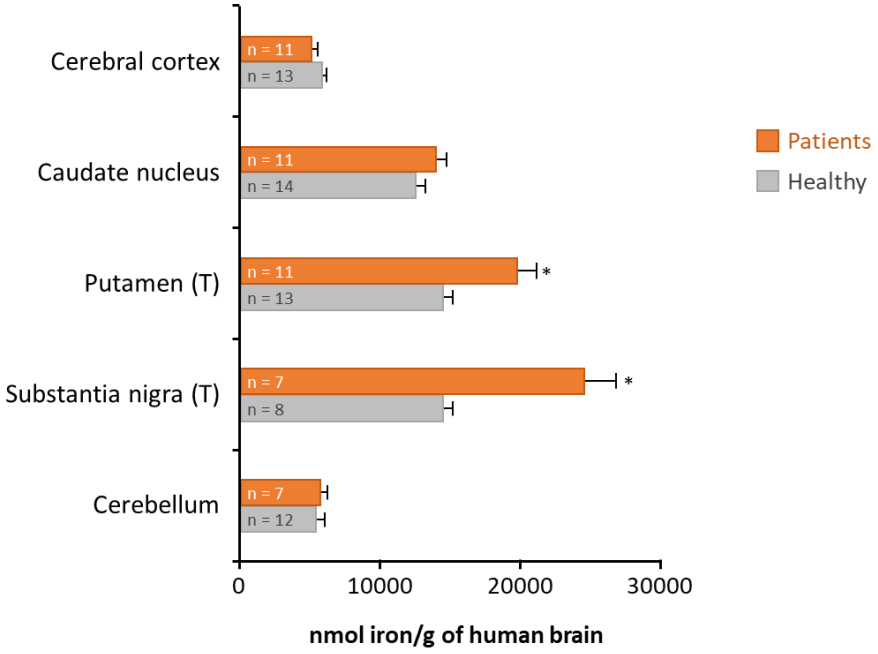


Yamamoto, 2002; Ahmadi 2017

J. Cell Science 117, 5721-5729; 2004

Progressive Supranuclear Palsy (PSP): A Tauopathy

Brain Iron increased compared to Healthy controls

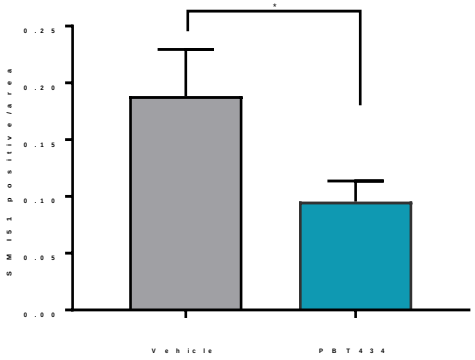


Dexter et al. Brain. 1991;114:1953.

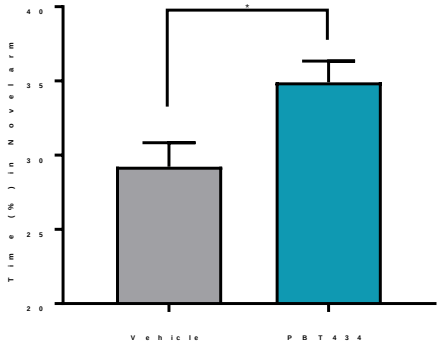
PBT434 Prevents Tau Accumulation and Improves Cognitive Function

Transgenic Animal Model of Tauopathy (rTg4510)

Tau accumulation in hippocampus



Performance in Y-maze



Treatment
- Randomly allocated
- Started at 10.5 months
- 30 mg/kg/day x 1.5 mo

Assessments done in blinded manner

PBT434 has Potential for Wide Application in Neurodegenerative diseases

α-Synuclein and Tau proteins share pathogenic features

Parameter	α-Synuclein	Tau
Localisation	Intracellular	Intracellular
Native form	Soluble	Soluble
Physiologic function	Facilitates synaptic function	Microtubule assembly and stabilization
Genetic evidence for disease	Yes (SNCA gene)	Yes (MAPT gene)
Iron dysregulation in associated disease	Yes	Yes
Iron promotes phosphorylation and protein aggregation	Yes	Yes
PBT434 effective in animal models	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

Building Momentum

- ✓ Phase I clinical trial of PBT434
- ✓ Prana presents at B. Riley FBR China Healthcare Investment and Partnering Symposium in Hangzhou, China
- ✓ PBT434 poster presented at the 6th International Multiple System Atrophy Conference, New York
- ✓ Prana presents at Biotech Showcase, San Francisco
- ✓ Prana receives $3.02m cash refund under the Australian Government's R&D
- ✓ Prana expands with San Francisco office

Scientific Appendices

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]

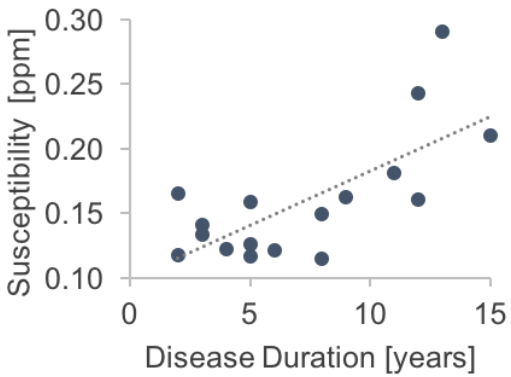
Midbrain iron content in early Parkinson disease

A potential biomarker of disease status

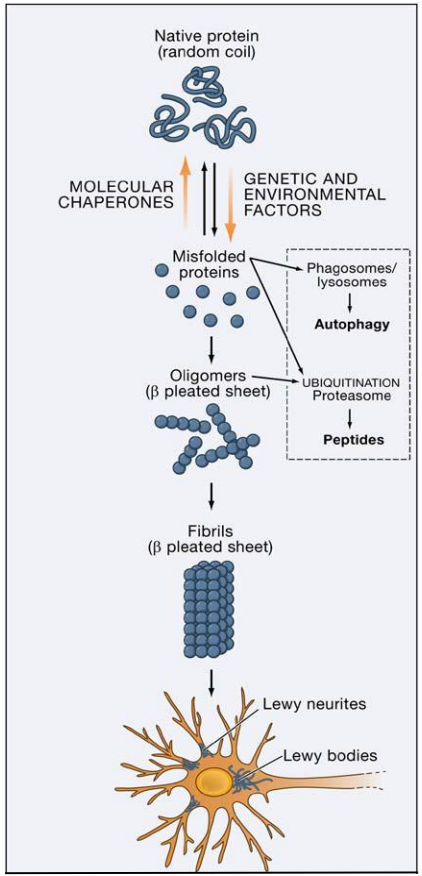
Martin, et al. Neurology 2008;70:1411–1417

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

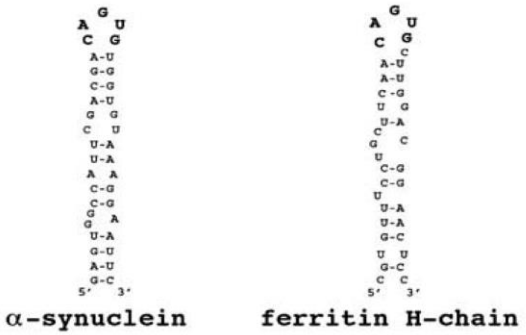


α-Synuclein as Target for PBT434



Lee and Trojanowski, 2006

- α-synuclein is unique in that it 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
- Although α-synuclein is highly conserved in vertebrates, only humans develop synucleinopathy
- Only human α-synuclein mRNA contains an Iron responsive element



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

Frontotemporal Dementia – A Tauopathy

Iron Content assessed by Brain MRI in FTD Patients

Table 2: Iron content (micrograms of iron/gram of tissue) of each region in bvFTD, PPA, and the control group

				Bonferroni-Corrected *P* Value[a]		
Region	Controls	bvFTD	PPA	bvFTD vs Controls	PPA vs Controls	bvFTD vs PPA
LSFG	13.17 ± 5.78	24.35 ± 10.02	18.61 ± 4.23	<.001[b]	.123	.09
RSFG	12.55 ± 5.51	25.36 ± 9.82	18.45 ± 5.11	<.001[b]	.75	.03[b]
LTP	13.72 ± 5.44	21.90 ± 8.69	19.67 ± 5.16	<.001[b]	.041[b]	1.00
RTP	13.25 ± 5.9	23.41 ± 8.71	18.77 ± 4.35	<.001[b]	.07	.166

Evidence for increased Iron in the Frontal and Temporal lobes

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PBT434 Prevents Tau Phosphorylation in Dose Dependent Manner

In vitro demonstration of anti-tau activity