PRANA BIOTECHNOLOGY

Treatment of **Neurological Disorders**

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AGM 2017

Highlights

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NOVEL DRUG CANDIDATE: PBT434

- Targets key protein implicated in neurodegeneration of Parkinson's disease and atypical parkinsonism
- Prevents accumulation and aggregation of α-synuclein
- 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

MULTIPLE INDICATION OPPORTUNITY

- PBT434 active in multiple animal models of Parkinson's disease and atypical parkinsonism

Rapidly Growing Burden of Neurological Disease based on Aging Population

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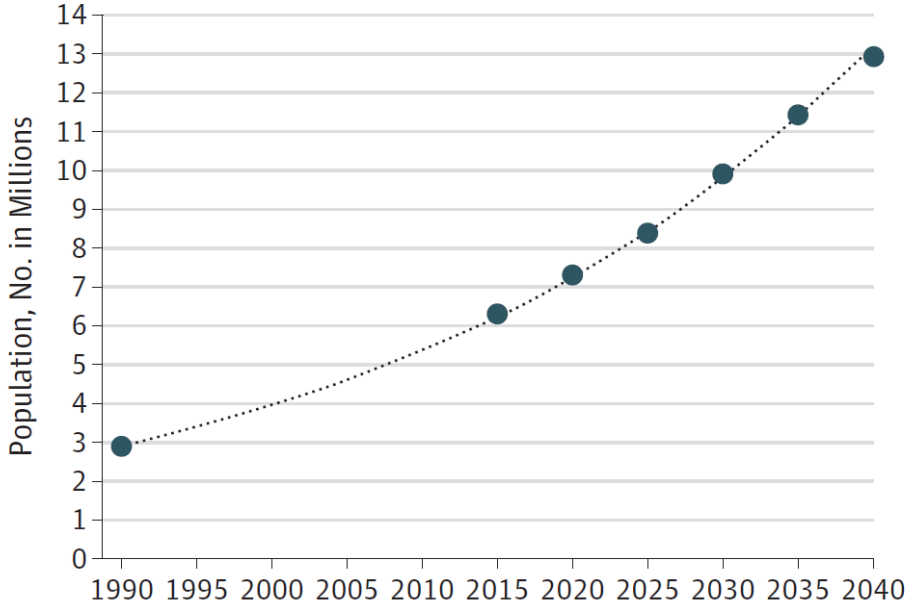
"Because the incidence of PD increases sharply with age and because the world's population is aging, the number of individuals affected is poised for exponential growth."

The Parkinson Pandemic—A Call to Action

Figure. Estimated and Projected Number of Individuals With Parkinson Disease, 1990-2040



Dorsey, Bloem. JAMA Neurology Published online November 13, 2017

PBT434 – Strong Development Rationale

- PBT434 is a 2nd generation drug to emerge from Prana's research program
  - Distinct chemical scaffold and biological profile compared to prior drug candidates
- Excellent drug candidate based on physical characteristics
- PBT434 targets α-synuclein, a biologically important protein implicated in neurodegenerative diseases
  - Widespread acceptance in scientific community
- PBT434 inhibits iron-mediated α-synuclein accumulation, preserves neurons and improves function in animal models of synucleinopathy
  - There is a strong 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
- Potential path for disease modifying therapy for the synucleinopathies

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

Biogen

Roche

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

Takeda

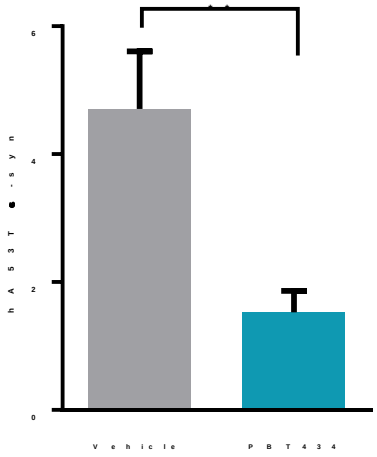
AstraZeneca

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

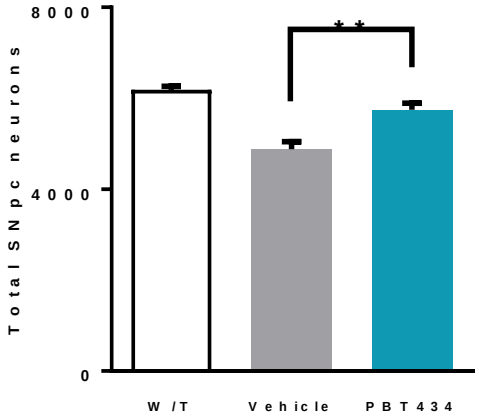
PBT434 Lowers α-Synuclein and Prevents Neuronal Death

Transgenic Animal Model (hA53T) of PD

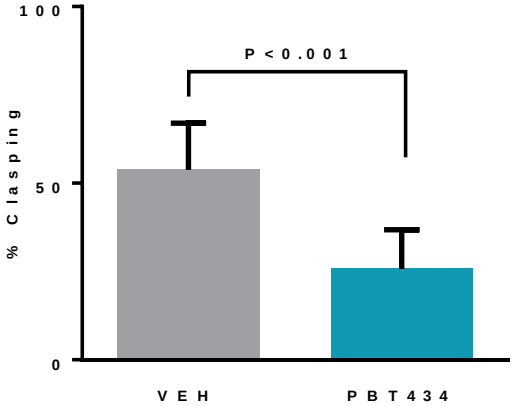
↓ α-Synuclein aggregation



Preserves neurons in S. nigra



Improves Motor Function



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

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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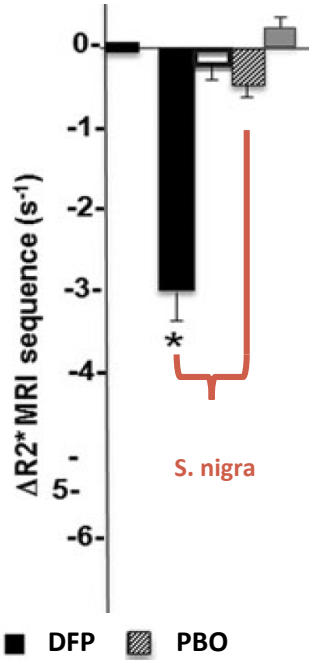
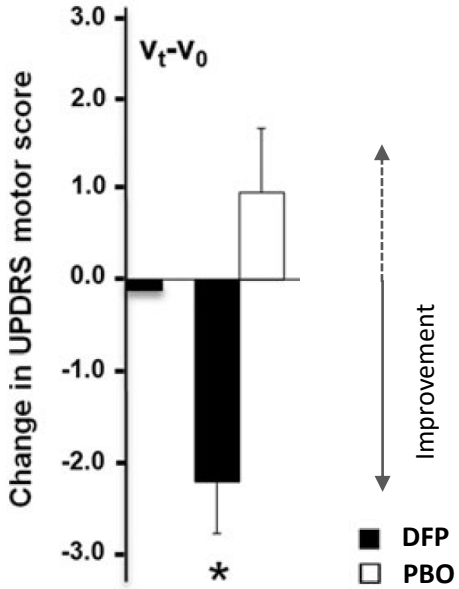
Brain Iron by MRI



Motor Function – UPDRS III



DFP Fe binding Affinity Kb=10^{36}

Reducing excess iron improves motor function

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

Summary

- PBT434 targets α-synuclein, a biologically important protein implicated in neurodegenerative diseases
- Iron is increased in the brain of patients with target diseases
- PBT434 restores iron homeostasis and blocks the accumulation and aggregation of this protein
- PBT434 has shown clear efficacy in multiple animal models of disease
- Potential indications include the synucleinopathies
  - Significant unmet needs in treating certain Orphan diseases, e.g., Multiple System Atrophy
  - Urgent need for disease modifying therapies
- Phase 1 study to commence in mid-2018