PBT434 drug candidate shows potential as "next-generation" disease-modifying treatment in Parkinson's Disease

Data featured in Plenary Lecture and 'Blue Ribbon Highlights' conference presentations at the 17th Movement Disorders Congress of Parkinson's Disease and Movement Disorders.

Thursday, 20 June, 2013: Melbourne-based Prana Biotechnology (ASX:PBT / NASDAQ:PRAN) today welcomed the release of data which indicates its drug candidate PBT434 shows significant disease-modifying capability in multiple animal models of Parkinson's Disease (PD) with potential utility in a range of movement disorders.

PD is caused by the death of specialized neurons in the region of the brain called the *substantia nigra*. This is the only part of the brain where iron, dopamine (a neurotransmitter) and the alpha synuclein protein are all present at high concentrations. In PD, iron binds to dopamine, preventing it from functioning normally, and creating toxic free radicals. Iron also binds to alpha synuclein, causing it to aggregate. The aggregation of this protein is a well-established pathological feature of PD, and a target for new disease-modifying therapies.

PBT434 prevents alpha synuclein from aggregating and also prevents the toxic consequences of iron combining with dopamine,

In a further sign of the potential of PBT434 as an effective treatment, its therapeutic benefits were seen to be dose-dependent. Increasing increments of the drug resulted in increased preservation of neurons and increased improvement in motor function.

"These data are highly positive and support the advancement of PBT434 as a first-in-class drug that could change the course of Parkinson's Disease and related movement disorders," said Geoffrey Kempler, Prana's Chairman and CEO. "This would be a major step forward in therapy as existing treatments are focused on symptomatic relief and offer little in the way of halting neurodegenerative decline once it has begun. The drug is progressing through the development process, with the aim of first clinical trials in 2015".

These findings are being presented today at the *17th Annual Congress of Parkinson's Disease and Movement Disorders* in Sydney by Professor Colin Masters, Director of The Mental Health Research Institute at the Florey Institute of Neuroscience, in a plenary presentation, and Associate Professor David Finkelstein, Head of the Parkinson's Disease Laboratory also at the Florey Institute.

"What we have known for some time is that dopamine and iron, together in the brain, form a combustible mix and this drives alpha synuclein aggregation and toxicity," said Associate Professor Finkelstein.

“What we’ve seen with PBT434 is two beneficial modes of action - it prevents cell death by inhibiting the interaction between dopamine and iron and it also stops this accumulation of alpha synuclein.”

This is the first molecule designed to inhibit the neurotoxic build-up of alpha synuclein in the brain and PBT434 could support the “next generation for PD therapies,” Associate Professor Finkelstein also said.

The full Poster is attached.

About Prana Biotechnology Limited

Prana Biotechnology was established to commercialise research into Alzheimer's Disease and other major age-related neurodegenerative disorders. The Company was incorporated in 1997 and listed on the Australian Stock Exchange in March 2000 and listed on NASDAQ in September 2002. Researchers at prominent international institutions including The University of Melbourne, The Mental Health Research Institute (Melbourne) and Massachusetts General Hospital, a teaching hospital of Harvard Medical School, contributed to the discovery of Prana’s technology.

For further information please visit the Company’s web site at www.pranabio.com.

Forward Looking Statements

This press release contains "forward-looking statements" within the meaning of section 27A of the Securities Act of 1933 and section 21E of the Securities Exchange Act of 1934. The Company has tried to identify such forward-looking statements by use of such words as "expects," "intends," "hopes," "anticipates," "believes," "could," "may," "evidences" and "estimates," and other similar expressions, but these words are not the exclusive means of identifying such statements. Such statements include, but are not limited to any statements relating to the Company's drug development program, including, but not limited to the initiation, progress and outcomes of clinical trials of the Company's drug development program, including, but not limited to, PBT2, and any other statements that are not historical facts. Such statements involve risks and uncertainties, including, but not limited to, those risks and uncertainties relating to the difficulties or delays in financing, development, testing, regulatory approval, production and marketing of the Company’s drug components, including, but not limited to, PBT2, the ability of the Company to procure additional future sources of financing, unexpected adverse side effects or inadequate therapeutic efficacy of the Company's drug compounds, including, but not limited to, PBT2, that could slow or prevent products coming to market, the uncertainty of patent protection for the Company's intellectual property or trade secrets, including, but not limited to, the intellectual property relating to PBT2, and other risks detailed from time to time in the filings the Company makes with Securities and Exchange Commission including its annual reports on Form 20-F and its reports on Form 6-K. Such statements are based on management’s current expectations, but actual results may differ materially due to various factions including those risks and uncertainties mentioned or referred to in this press release. Accordingly, you should not rely on those forward-looking statements as a prediction of actual future results.

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PBT434, a novel 8-hydroxyquinazolinone, preserves nigro-striatal circuitry, improves motor performance and inhibits alpha synuclein accumulation in animal models of Parkinson's disease by modulation of iron homeostasis.

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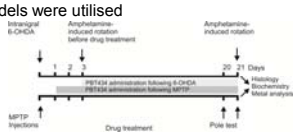
OBJECTIVE AND BACKGROUND:

Objective: To develop a disease modifying treatment for Parkinson's disease (PD) **Background**: Iron dysregulation is implicated in damage to neurons of the substantia nigra pars compacta (SNpc) in PD. Animal models of PD also display acute and/or chronic alterations in brain iron distribution. We have been developing drugs for neurodegenerative diseases designed to re-establish normal metal homeostasis (Adlard, et al. 2008. Neuron 59, 43-55; Lannfelt, et al. 2008. Lancet Neurol 7, 779-786). A library of novel, orally bioavailable, moderate iron affinity, redox silencing blood brain barrier penetrant 8-hydroxyquinazolinone compounds was developed.
Hypothesis: Remediation of brain iron dys-homeostasis will be of therapeutic use in PD

METHODS:

- 6-OHDA and MPTP models were utilised and animals treated daily (30 mg\kg orally, 21days)



- Transgenic mice (hA53T α-syn) were treated for 4 months.

Readouts: Neuroanatomical: Preservation of SN neurons and striatal terminals following MPTP or 6-OHDA intoxication. Behavioural: Amphetamine (6-OHDA)elicited rotations, pole test (MPTP). Neurobiological: TH, Ferroportin (iron export protein). Etiopathological: α-syn, iron, 8-OHdG (oxidative damage marker).

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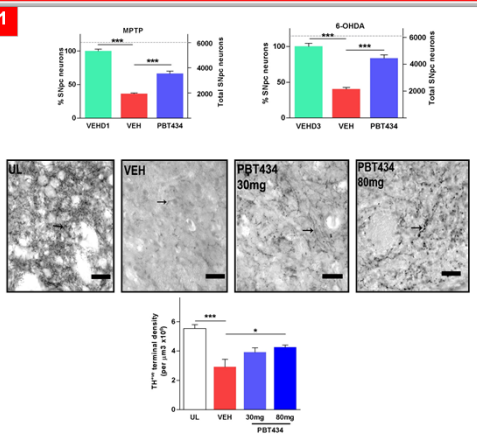

Protection of nigral neurons in both the MPTP and 6-OHDA models (upper panels). The photomicrographs show the morphological preservation of TH positive terminals in the dorsal lateral CPu. The lower panel displays stereological quantification of terminal density with the different treatments.

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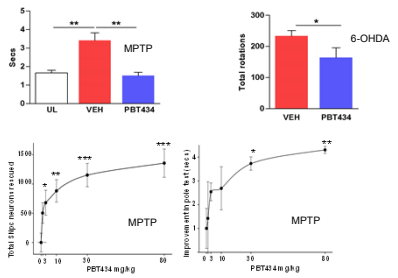

Motor performance is improved following treatment with PBT434 in the MPTP and 6-OHDA toxin models. Lower figure: Dose dependent improvement in SNpc neuron viability and pole-test behaviour.

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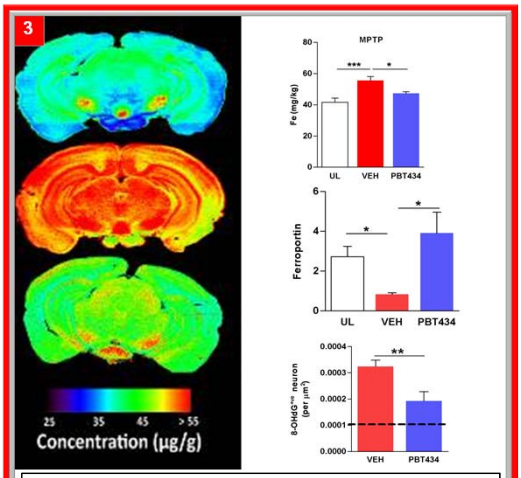

Reduction in iron by PBT434 quantified in the SNpc by Laser Ablation Mass Spectrometry. The reduction caused by PBT434 was observed after MPTP lesion but not in control mice. SNpc Ferroportin (cellular iron export protein) levels rise, promoting reduction in local iron levels. Oxidative stress damage (8-OHdG) is reduced (consistent with diminished presence of redox-competent iron). The dotted line is the wildtype levels.

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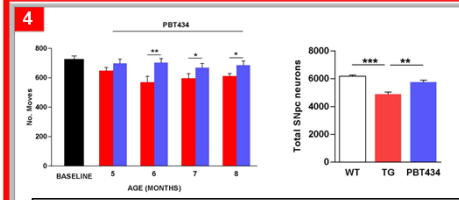

Treatment of alpha synuclein transgenic mice (hA53T α-syn) with PBT434 for 4 months prevents motor dysfunction and significantly protects SNpc neurons from α-syn induced toxicity.

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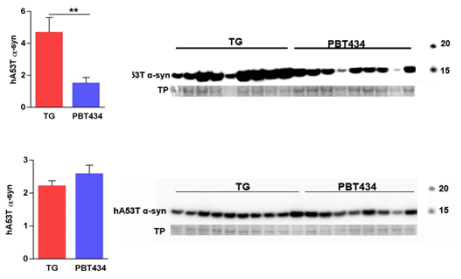

Four months of treatment with PBT434 significantly reduced accumulation of the insoluble fraction of α-syn in α-syn transgenic mice (hA53T α-syn, upper panel). PBT434 had no effect on soluble α-syn.

Wild type mice intoxicated with MPTP show an elevation in total SNpc α-syn (**UnL**esioned compared to **VEH**icle treated MPTP). PBT434 prevents the rise in α-syn in MPTP-affected PBT434-treated wild type mice

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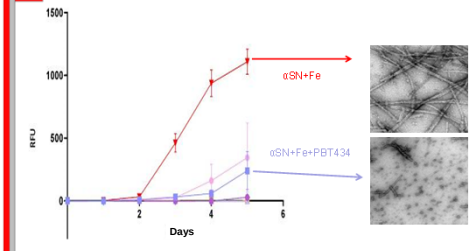

An *in vitro* Thioflavin T assay demonstrates the accelerated formation of α-synuclein fibril formation in presence of iron. α-synuclein fibril formation is prevented by co-incubation with PBT434. Electron microscopy supports the THT assay data.

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CONCLUSIONS:

- Iron is a component of the etiopathological cascade in PD: PBT434 buffers iron to effectively reduce insoluble α-syn formation *in vivo* and prevent α-syn fibril formation *in vitro*.
- Compounds designed to target iron dyshomeostasis can preserve SNpc neurons and striatal connectivity.
- Iron chelation (i.e. depletion) is not required for therapeutic benefit
- Neuronal survival is dose-dependent and correlates closely with improvement in motor function
- PBT434 represents a plausible addition to current PD therapies

We acknowledge the support of the M J Fox Research Foundation