Prana Details Data Showing that PBT2 Reduces Cognitive Impairment Caused by Tau Protein Accumulation

Summary of new data presented at the 11th International Conference on Alzheimer's and Parkinson's Disease

Melbourne – 8th March, 2013 Prana Biotechnology (NASDAQ:PRAN; ASX:PBT). Following on from the announcement released on 4th March, 2013 and at the request of the Australian Securities Exchange, the company is pleased to provide further detail in respect to the presentation of the new data demonstrating the ability of PBT2 to reduce the damage to brain cells, caused by the accumulation of the tau protein and preventing subsequent cognitive impairment.

The data was generated in an animal model that over produces the tau protein giving rise to 'tangle like' inclusions similar to those which cause neuronal death in Alzheimer's disease (AD). Importantly, whilst the anti-aggregation effects of PBT2 on Abeta have been well documented[1], these results were generated in a model which is independent of the presence of Abeta, indicating that PBT2 has the ability to prevent neuronal damage via multiple metal mediated pathways, including Abeta and tau aggregation.

The data is being presented by Prana scientist Associate Professor Paul Adlard on 9th March 2013 in his presentation entitled, "Metal Chaperones are novel therapeutic agents for tauopathy".

"These findings provide further evidence that by targeting specific metal imbalances in the brain, PBT2 possesses the ability to ameliorate Alzheimer's pathology in relevant mouse models for both senile plaques and neurofibrillary tangles. This data, in combination with the previously reported Phase IIa clinical trial results[2] for PBT2 in Alzheimer's disease further support PBT2 as a potentially promising therapy for this devastating disease", commented Rudy Tanzi, the Joseph P. and Rose F. Kennedy Professor of Neurology at Harvard Medical School and Prana's Chief Scientific Advisor.

Associate Professor Robert Cherny, Prana's Head of Research commented,"Prana scientists have shown that the Metal Protein Attenuating Compound, PBT2 improves cognitive impairment, Abeta burden and tau hyperphosphorylation in the APP/PS1 transgenic mouse model of AD which overexpresses Abeta[1]. Recent literature supports the notion that metals modulate the properties of tau and may affect the formation of neurofibrillary tangles (NFTs)[3,4,5] which are a feature of several neurodegenerative diseases. In human beings, certain mutations in the gene encoding the tau protein lead to hereditary fronto-temporal dementia (FTD) and Parkinsonism collectively known as *tauopathies.* Indeed AD itself has been defined as an "Aβ-mediated tauopathy".

PBT2 is currently in a 12 month Phase II Alzheimer's disease clinical trial, the IMAGINE trial, which is now fully enrolled and will be completed at the end of the year.

Experimental Methodology

The rTg(tau_{P301L})4510 mouse line[6] is a transgenic mouse model of human tauopathy. From an early age rTg($taup_{301L}$)4510 mice display neurofibrillary tangles (NFT) like pathology in the neocortex which progresses into the hippocampus and limbic structures with increasing age. This is manifested biochemically by an age-dependent transition of accumulating tau species from soluble 55 kDa to insoluble hyperphosphorylated 64 kDa. The mice develop significant cognitive impairments from 4 months of age. In our study, rTg(tau_{P301L})4510 mice (n=10-15/group) were aged to approximately 12 months at which time they were administered either vehicle or PBT2

(30mg/kg) by daily oral gavage for six weeks. Prior to culling and tissue collection the cognitive performance of the animals was examined using a standard test of cognition, the Y-maze. A stereological analysis of NFT burden and neuron number was conducted by histology and other biochemical endpoints assessed by Western blot.

Results

Administration of PBT2 resulted in significant improvement in performance in the Y maze, a significant reduction in the number of NFTs and a significant increase in cortical and hippocampal neurons in the rTg(tau_{P301L})4510 mouse model. A significant increase in the levels of the PP2A protein (implicated in tau phosphorylation events) in PBT2 treated animals suggest that the drug may directly act upon biochemical pathways which lead to NFT formation as well as any potential interaction with tau itself [4].

References

[1] Adlard P, *et al* (2008) Rapid restoration of cognition in Alzheimer's transgenic mice with 8-hydroxy quinoline analogs is associated with decreased interstitial Abeta. Neuron 59:43-5510.

[2] Lannfelt *et al.* Safety, efficacy, and biomarker findings of PBT2 in targeting Aβ as a modifying therapy for Alzheimer's disease: a Phase IIa, double-blind, randomised, placebo-controlled trial. Lancet Neurology (2008) vol. 7, pp. 779-86. Lannfelt *et al.* **Errata:** Lancet Neurology (2009) vol. 8, pp. 981.

[3] Insook K, *et al* (2011) Zinc stimulates tau S214 phosphorylation by the activation of Raf/mitogen-activated protein kinase-kinase/extracellular signal-regulated kinase pathway. Neuroreport: 22:839–844.

[4] Craddock TJA *et al*, The Zinc Dyshomeostasis Hypothesis of Alzheimer's Disease. PLoSOne e33552. doi:10.1371/journal.pone.0033552.

[5] Xiong *et al* (2013) Zinc induces protein phosphatase 2A inactivation and tau hyperphosphorylation through Src dependent PP2A (tyrosine 307) phosphorylation. Neurobiol Aging. 34:745-56.

[6] Ramsden M *et al* (2005) Age-Dependent Neurofibrillary Tangle Formation, Neuron Loss, and Memory Impairment in a Mouse Model of Human Tauopathy (P301L). J Neurosci, 25: 10637-10647.

About Prana Biotechnology Limited

Prana Biotechnology was established to commercialize research into age-related neurodegenerative disorders. The Company was incorporated in 1997 and listed on the Australian Securities 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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