PLoS ONE Journal Publishes Mechanistic Model of Alzheimer's Disease Endorsing Prana's PBT2

Melbourne – 26 March, 2012: Prana Biotechnology (NASDAQ:PRAN; ASX:PBT) today announced the publication in the journal PLoS ONE, of an article that strongly endorses PBT2's potential to treat Alzheimer's Disease. The paper, entitled "The Zinc Dyshomeostasis Hypothesis of Alzheimer's Disease"[1] presents an integrated explanation of the major pathological features of Alzheimer's Disease, based upon a combination of new experimental data and mathematical modeling.

The senior author on the paper is Professor Rudy Tanzi, the Joseph P. and Rose F. Kennedy Professor of Neurology at Harvard University and Prana's Chief Scientific Advisor.

Dr. Tanzi explained that "the hallmark pathological features of Alzheimer's Disease are the amyloid plaques, composed of the Abeta protein, and neurofibrilliary tangles (NFTs), composed of Tau protein. Everything we have learned from the genetics of Alzheimer's Disease indicates that the disease is caused by excessive accumulation of the Abeta protein in the brain. We also know that hyperphosphorylation of the Tau protein which forms NFTs is the feature of the disease which correlates with neuronal damage and cognitive loss. Prana's drug PBT2 reduces levels of both Abeta and hyperphosphorylated tau in animal studies[4] and improved cognition and lowered Abeta in a Phase 2a clinical trial of Alzheimer's Disease patients[2,3].

"So, Alzheimer's Disease can be defined as an amyloid-induced tauopathy. The big question is this – how does amyloid aggregation lead to NFTs? In this paper we propose that at least part of the answer to that question is zinc dyshomeostasis, that is to say, abnormal distribution of zinc in the brains of Alzheimer's Disease sufferers. The drug PBT2 directly addresses this problem by binding zinc and normalising its distribution. This bodes very well for the current PBT2 clinical trial that is in progress" concluded Dr. Tanzi.

This paper builds on Prana's previously published findings that as we age our ability to maintain normal zinc distribution deteriorates. Abeta forms amyloid by capturing and holding zinc, which in turn further reduces our ability to maintain normal zinc distribution. "This is a vicious pathological cycle. PBT2 interrupts this cycle, re-distributing zinc needed for healthy brain function", commented Prana's Head of Research, Associate Professor Robert Cherny.

Supporting this, the Journal of Alzheimer's[5] Disease recently published data from an independent laboratory showing the ability of the brain to move zinc in and out of neurons deteriorates with the progression of Alzheimer's Disease. These two papers are the latest of a number of high profile scientific articles that have been published on the role of metals in neurodegenerative diseases, supporting Prana's therapeutic strategy to treat these disorders.

Prana has recently commenced clinical trials for Alzheimer's Disease and Huntington's Disease, both using the drug PBT2.

Synopsis of PLoS ONE paper

In the paper the authors propose that sequestration of zinc by Abeta-amyloid deposits (Abeta oligomers and plaques) not only drives Abeta aggregation, but also disrupts zinc homeostasis in zinc-enriched brain regions important for memory and vulnerable to Alzheimer's Disease pathology, resulting in intra-neuronal zinc levels, which are either too low, or excessively high. Moreover, they carry out modeling to suggest that this can lead microtubule instability and the abnormal tau pathology, including neurofibrillary tangles (NFT).

To evaluate this hypothesis, the authors:

1) used molecular modeling of zinc binding to the microtubule component protein tubulin, identifying specific, high-affinity zinc binding sites that influence side-to-side tubulin interaction, the sensitive link in microtubule polymerization and stability.

2) performed kinetic modeling showing zinc distribution in extra-neuronal Abeta deposits can reduce intra-neuronal zinc binding to microtubules, destabilizing microtubules.

3) used metallomic imaging mass spectrometry (MIMS) to show anatomically-localized and age-dependent zinc dyshomeostasis in specific brain regions of Tg2576 transgenic, mice, a model for Alzheimer's Disease. We found excess zinc in brain regions associated with memory processing and NFT pathology.

They present a theoretical framework and support for a theory of Alzheimer's Disease linking extra-neuronal Abeta amyloid to intra-neuronal NFTs and cognitive dysfunction.

The connection, they propose, is based on beta-amyloid-induced alterations in zinc ion concentration inside neurons affecting stability of polymerized microtubules, their binding to MAP-tau, and molecular dynamics involved in cognition.

This theory supports novel Alzheimer's Disease therapeutic strategies targeting intra-neuronal zinc homeostasis and microtubule dynamics to prevent neurodegeneration and cognitive decline, such as PBT2.

[1] Craddock TJA et al The Zinc Dyshomeostasis Hypothesis of Alzheimer's Disease. PLoS ONE (2012) 7(3): e33552. doi:10.1371/journal.pone.0033552
[2] Lannfelt *et al.* "Safety, Efficacy, and biomarker findings of PBT2 in targeting Abeta modifying therapy for Alzheimer's Disease: a controlled phase IIa, double-blind, randomized, placebo-controlled trial", Lancet Neurology (2008) 7: 779-86.
[3]Lannfelt *et al.* **Errata:** Lancet Neurology (2009) 8: 981.
[4]Adlard PA *et al* Rapid Restoration of Cognition in Alzheimer'sTransgenic Mice with 8-Hydroxy Quinoline Analogs Is Associated with Decreased Interstitial Aβ. Neuron (2008) 49: 43-55
[5] Beyer, N *et al* Zinc Transporter mRNA Levels in Alzheimer's Disease Postmortem Brain. J Alz Dis (2012), 28: 1-11

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.

Contacts:

Australia
Prana Biotechnology Ltd
T: +61 3 93494906
E: info@pranabio.com

US – Investor Relations
Leslie Wolf-Creutzfeldt
T: 646-284-9472
E: leslie.wolf-creutzfeldt@grayling.com

US - Media
Ivette Almeida
T: 646-284-9455
E: ivette.almeida@grayling.com