

## **Prana's Alzheimer's Disease Treatment Strategy Validated by Independent Study**

*Accumulation and toxicity of Alzheimer's-related beta-amyloid independently confirmed to be dependent on copper and arrested with Prana's proof-of-concept MPAC.*

**MELBOURNE, March 6, 2013:** Prana Biotechnology (ASX:PBT/NASDAQ:PRAN) commented today on the publication of a landmark study in the current issue of the peer-reviewed journal *Proceedings of the National Academy of Sciences USA (PNAS)*. The findings demonstrated a dose dependent relationship between copper levels and oligomerisation of Amyloid- $\beta$  peptide ( $A\beta$ ) resulting in toxicity. Clioquinol, Prana's proof of concept Metal Protein Attenuating Compound (MPAC), rescued the metal induced  $A\beta$  toxicity, a finding consistent with the proposed mechanism of action of Prana's PBT2.

In a new publication<sup>i</sup> Professor Susan Lindquist and colleagues at the Whitehead Institute, Massachusetts Institute of Technology, Cambridge Massachusetts, described the development and validation of a novel yeast model for Alzheimer's-related beta-amyloid pathology, in which they systematically screened 140,000 drugs, including Clioquinol, for their ability to inhibit the toxicity resulting from  $A\beta$  accumulation.

One of the study's authors, Daniel Tardiff, is quoted as stating: "Our work in the yeast model shows that clioquinol decreases the amount of  $A\beta$  in the cells by 90%. That's a strong decrease, and it's dose-dependent. I've tested a lot of compounds before, and I've never seen anything as dramatic."

Both PBT2, Prana's lead MPAC in development for Alzheimer's and Huntington disease, and Clioquinol (CQ) are from the same class of 8-hydroxyquinoline compounds. Prana selected PBT2 from its library of neurologically active 8-hydroxyquinolines based on its improved safety and efficacy profile compared to CQ.

Dr Rudy Tanzi, Professor of Neurology at Harvard Medical School and Prana's Co-Founder and Chief Scientific Advisor, commented: "this very well crafted body of work from the Lindquist laboratory points to the intrinsic value of Prana's therapeutic strategy to intercede in the metal mediated toxicity of target aggregating proteins in neurodegeneration."

"However, unlike strategies which seek to merely reduce  $A\beta$  levels, our strategy is to additionally disarm target proteins of metals, neutralize toxicity, and redistribute metals to their correct neuronal compartments to restore neuronal function and neurotransmission".

In the new PNAS paper it was shown that:

- Analogues of CQ that are structurally modified not to contain its metal binding site were unable to rescue  $A\beta$  toxicity. This indicated that the toxic effect of beta-amyloid is most likely metal-mediated.
- In vitro, copper strongly promoted the formation of prefibrillar oligomeric  $A\beta$  species and CQ strongly 'antagonised' the oligomer-potentiating effects of copper.

- CQ was able to arrest toxicity in A $\beta$ -expressing yeast cells in a highly dose dependent manner.
- The rescue of A $\beta$  induced toxicity was replicated in the *C. elegans* worm model wherein A $\beta$  expressing glutamatergic neurons were preserved after treatment, in comparison to untreated controls.
- The Lindquist laboratory previously showed that A $\beta$ /metal complexes cause defects in secretory/endosomal transport pathways<sup>ii</sup>. This defect was rescued by treatment with CQ.
- CQ increased the degradation of oligomeric species of A $\beta$  in the yeast model thus preventing its accumulation and resultant toxicity. Addition of equimolar concentrations of copper exhausted the ability of CQ to reduce A $\beta$  levels.

In an earlier study<sup>iii</sup> the Lindquist laboratory reported that various 8-hydroxyquinolines were also able to rescue toxicity caused by the expression of TDP-43,  $\alpha$ -synuclein, or polyglutamine proteins in yeast models for amyotrophic lateral sclerosis, Parkinson's disease, and Huntington disease, respectively.

"The exciting new results from Lindquist and colleagues strongly support the metal hypothesis of Alzheimer's disease, as well as our therapeutic approach of competing copper away from beta amyloid in order to neutralize its toxicity. Moreover, this is the second landmark paper from the Lindquist lab that would appear to support and further inform us on the proposed mechanism of action of PBT2 in neurodegenerative disease." concluded Dr Tanzi.

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<sup>i</sup> Matlack K.E.S, Tardiff D.F, Narayan P, Hamamichi S, Caldwell K.A, Caldwell G.A, and Lindquist S. Clioquinol promotes the degradation of metal-dependent amyloid- $\beta$  (A $\beta$ ) oligomers to restore endocytosis and ameliorate A $\beta$  toxicity. PNAS 2014; published ahead of print March 3, 2014. doi:10.1073/pnas.1320586111

<sup>ii</sup> Treusch S, Hamamichi S, Goodman J.L, Matlack K.E.S, Chung C.Y, Baru V, Shulman J.M, Parrado A, Bevis B.J, Valastyan J.S, Han H, Lindhagen-Persson M, Reiman E.M, Evans D.A, Bennett D.A, Olofsson A, Dejager P.L, Tanzi R.E, Caldwell K.A, Caldwell G.A, Lindquist S. Functional Links Between A $\beta$  Toxicity, Endocytic Trafficking, and Alzheimer's Disease Risk Factors in Yeast. Science. (2011); 2;334(6060):1241-5

<sup>iii</sup> Tardiff D.F, Tucci M.L, Caldwell K.A, Caldwell G.A, Lindquist S. Different 8-Hydroxyquinolines Protect Models of TDP-43Protein,  $\alpha$ -Synuclein, and Polyglutamine Proteotoxicity through Distinct Mechanisms. J Biol Chem (2012) 287: 4107-4120.

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**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](http://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 factors 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.*