



News

2008-09-28

Nature Medicine Publication Elucidating Probiodrug's New Treatment Paradigm for Alzheimer's disease

Halle/Saale, September 29th, 2008, 08:00 Uhr MESZ -- Probiodrug AG (Probiodrug), a developer of small molecule inhibitors for the treatment of inflammatory and neurodegenerative diseases, today announced the *publication of in vivo data in Nature Medicine* supporting the finding that inhibition of the enzyme Glutam(in)yl Cyclase (QC) can be considered as a potentially causative new treatment of neurodegeneration in Alzheimer's Disease (AD).

The paper demonstrates that QC is overexpressed in the brain of AD patients and that QC is responsible for the formation of a certain, neurotoxic variety of the amyloid- β peptide, which promotes the formation of the typical plaques in the brain of AD patients. Moreover, the paper includes data on murine models demonstrating that oral administration of a QC inhibitor results in significant memory improvement. The data strongly support the Company's hypothesis that the enzyme QC plays a major role in initiation and progression of Alzheimer's disease and that the disease can be modified by compounds inhibiting QC.

"Today, the available treatment options can only temporarily slow down progression of Alzheimer's disease", said Hans-Ulrich Demuth, CSO of Probiodrug, "and so far all efforts to come up with a disease modifying treatment have failed. There are many approaches aiming at the reduction of plaques and tangles found in brain of AD patients, but no attempt to break down these structures or to prevent their formation has been successful so far." Probiodrug believes that it has identified a causal mechanism explaining neurotoxicity and neuron loss in the brain of AD patients, thereby providing a unique proprietary target to stop or prevent neurodegeneration and subsequent plaque formation. "We have compelling evidence that a certain variation of the amyloid- β peptide ($A\beta$), i.e. a pyroglutamyl-modified $A\beta$, plays a major role in Alzheimer's disease", Demuth added. "The variation is caused by a cyclization of an N-terminal glutamate residue of the peptide. As a result, the modified peptide is uncharged and thus hydrophobic and degradation resistant, while it exhibits a very strong tendency to aggregate."

In addition, its occurrence correlates with dementia in AD patients and neuron loss in animal models. While plaques frequently present in the brain of non-demented elderly consist primarily of full-length $A\beta$, the plaques of AD patients mainly consist of pyroglutamated $A\beta$ peptides. The pyroglutamated peptides unfold profound seeding capacity, thus forming the core of plaques found in AD patients' brains. The Company has also demonstrated that pyroglutamated derivatives of $A\beta$ are much more toxic and degradation-resistant than unmodified $A\beta$. Moreover, in animal models of AD, inhibitors of QC reduce both pGlu- $A\beta$ and total $A\beta$, and improve memory.

Our company has a long-standing expertise in elucidating the role of enzymes modifying peptides", Demuth added. „Already, we invented the inhibition of the enzyme DP-4 as a treatment for diabetes. By blocking DP-4, we prolong the life-time of intestinal peptide hormones which guard against excess of blood glucose and helps monitor the emptying of

the stomach. These inhibitors led to several marketed drugs that generate annual sales of more than EUR 1 billion."

Over the last five years, successful cooperation within a network of academic partners specialized in neurobiological as well as in protein structure and molecular genetic research at the Universities of Erlangen, Göttingen, Halle, Leipzig and the Institute for Neurobiology, Magdeburg have greatly advanced the Company's ongoing neurodegeneration research. Probiodrug AG and the University of Göttingen Medical School are members of the Alzheimer Ph.D. Graduate School entitled "Neurodegeneration in Alzheimer's disease – mechanisms, consequences and therapy" (NEURAD). This Marie Curie Early Stage Training Ph.D. program is funded by the European Commission in order to promote young scientists in the field of AD (<http://www.neurad-alzheimer.de>). In addition, the collaborative work with CROs such as JSW-CNS Research G.m.b.H. in Graz, Austria, specialized in all aspects of preclinical and clinical CNS research, and the Research Institute for Applied Neurosciences GmbH (FAN GmbH Magdeburg) have supported and strengthened Probiodrug's fundamental research program.

With several key patents already granted in the U.S., Probiodrug's new therapeutic approach now receives further international recognition by publishing important results of its ongoing target validation and drug discovery program in Nature Medicine.

About Probiodrug AG:

Probiodrug is a biopharmaceutical company focused on the development of innovative small molecule drugs for the treatment of neuronal, inflammatory, and autoimmune diseases. In these areas, Probiodrug is focusing on innovative targets with the prospect of first and best in class therapeutics. The Company has a dominant position in the area of glutaminyl cyclase (QC) inhibition, an enzyme central for the pathogenesis of Alzheimer's disease (AD). In this field, Probiodrug is pioneering a completely novel therapeutic approach. In addition, the Company is pursuing further novel approaches in the area of inflammatory diseases.

Probiodrug's core expertise is based on its long-standing, unique experience with the structure and function elucidation of enzymes central for the maturation of hormones. The Company has pioneered the field of DP4-inhibition for the treatment of type-2 diabetes. Compounds and technology patents of its DP4 (dipeptidyl peptidase 4) program in diabetes were licensed to various pharmaceutical companies. In 2004, all metabolic assets were sold to (OSI) Prosidion. The first drug based on Probiodrug's technologies reached the market in late 2006. Proceeds of these transactions have been reinvested to fund the novel approach for the treatment of AD:

The Company was founded in 1997 by Dr Konrad Glund and Prof Dr Hans-Ulrich Demuth and has raised a total of \$52 million. In 2007, it acquired Ingenium Pharmaceuticals AG. Probiodrug is located in Halle (Saale), Germany, and operates a subsidiary in Martinsried/Munich, Germany. For more information, please visit www.probiodrug.de.

Contact:

Prof Dr Hans-Ulrich Demuth
Probiodrug AG
Weinbergweg 22
D-06120 Halle/ Saale

Germany
Tel.: +49 345 55599-00
Fax: +49 345 55599-01
Mail: *Hans-Ulrich.Demuth @probiodrug.de*

Dr Ludger Weß
akampion
Saseler Loge 6b
D-22393 Hamburg
Germany
Tel.: +49 40 88 16 59 64
Fax: +49 40 88 16 59 65
Mail: *ludger @akampion.com*

Probiodrug NEWS

Probiodrug AG

Weinbergweg 22 / 06120 Halle (Saale) / Germany / Phone: +49 345 5559901 / E-Mail: info@probiodrug.de