Future drug treatment in Alzheimer´s disease*

Thomas A. Bayer[1], Lutz Frölich[2], Jean-Marc Orgogozo[3]

[1]Department of Psychiatry, Division of Molecular Psychiatry, University Medicine Goettingen, Goettingen, Germany; [2]Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Germany; Clinical Neurosciences, CHU Pellegrin, University of Bordeaux, France

Cumulative evidence shows that progressive cerebral deposition of beta-amyloid peptide (Abetą seems to plays a seminal role in the pathogenesis of Alzheimer's disease (AD) [1, 2]. There is great interest, therefore, in understanding the proteolytic processing of amyloid presursur protein (APP) and its proteases responsible for cleaving at the amino- and carboxy-terminals of the A region. The cause of the sporadic form of AD is unknown, probably because the disease is heterogeneous, caused by ageing in concert with a complex interaction of both genetic and environmental risk factors. Saido et al. reported that Abeta N3(pE) represents a dominant fraction of Abeta peptides in AD brain [3]. AbetaN3(pE) has a high aggregation propensity [4, 5], stability [6], and shows an increased toxicity compared to full-length Abetą [7]. Interestingly, glutaminyl cyclase (QC) inhibition leads to significantly reduced Abeta N3(pE) formation, showing the importance of QC-activity during cellular maturation of pE-containing peptides [8] making it a potential drug target to prevent Abeta N3(pE) formation. Moreover, data from transgenic mice that express human mutant APP751 with the Swedish and London mutations, and murine knock-in (KI) PS1 with two familial Alzheimers'disease (FAD) -linked mutations ($PS1_{M233T}$ and $PS1_{L235P}$) named APP/PS1KI exhibit high amounts of Abeta N3(pE). At the age of 6 months these mice develop working memory deficits [9], CA1 neuron loss, as well as abundant axonal degeneration [10, 11]. A recent review by Blennow et al. summarised the successful preclinical test for a variety of substances to reduce Abeta plaque load [12]. Many applications like secretase modulation, A immunotherapy, anti-aggregation, modulation of lipids, kinases, neurotransmitters, heavy metals appeared to work well in APP transgenic mouse models. None of these applications, however, has been yet transferred successfully into clinical practice. One possibility could be that reducing the physiological Abeta 1-40 and supposedly pathological Abeta 1-42 peptides may not be sufficient or may not even be a proper target to develop therapeutic strategies. In contrast, Abeta starting with N-terminal N3(pE) may be the real pathological peptides, which could be better suited as a target for AD treatment. Interestingly, the report by Maeda et al. [13] provides first evidence for a direct correlation of PiB (Pittsburgh Compound-B) retention analyzed by PET imaging in living APP transgenic mice. They also demonstrate that PiB labelling correlated best with plaques positive for Abeta N3(pE). These observations clearly demonstrate that the PiB compound binds specifically to those amyloid-beta (Abeta) peptides representing the dominant species in AD and DS (Down's syndrome) brain, and correlate well with neurodegeneration in the APP/PS1KI model.

These and similar findings from basic science have delivered novel treatment approaches which mainly target the amyloid cascade. However, it is yet not clear wether the amyloid cascade is the best treatment target in AD patients, as discussed above. Thus findings from AD trials, presently being conducted, will also feed back evidence on the pathophysiological relevance of the amyloid cascade hypothesis. Finally, synaptic degeneration / neurodegeneration may be maintained even when amyloid-induced toxicity is arrested. Therefore, in addition to anti-amyloid treatment approaches, anti-apoptotic or „pleiotropic" treatment approaches should not be neglected. Such approaches comprise drugs which interact with anti-inflammatory–NFkb,cholesterol-lowering mechansims [14] or RAGE antagonists [15]. All these appraoches are thought to be disease-modifying.

Immunization with aggregated human beta amyloid Abeta 1-42 (AN1792) was introduced as a therapeutic approach to stimulate clearance of amyloid plaques first in APP transgenic mice that exhibit CNS pathology remarkably similar to the histological features characteristic of AD in humans [16]. In young PDAPP mice, immunization generated robust titers of anti-AN1792 antibodies and almost entirely prevented the development of AD-like amyloid plaques, neuritic dystrophy and gliosis [17].

Single and multiple dose phase I studies were evaluated in patients with AD and an optimal dose combination for eliciting an anti-AN1792 antibody response: AN1792 225 µg and QS-21 50 µg was selected from the multiple dose study [18]. A double-blind, placebo-controlled, multicentre phase IIa study was then initiated by Elan and Wyeth to evaluate the safety, tolerability and pilot efficacy of AN1792 (QS-21) in patients with mild to moderate AD [19]. During the course of the study it was recognized that a small proportion of patients (6%) developed meningoencephalitis [20], and study drug administration was permanently discontinued. Although pilot efficacy was not measurable according to the revised protocol, the assessment of changes over time in key outcome measures, such as some items in the neuropsychological test battery (NTB), a trend towards normalization of the Abeta 1-42/tau ratio in the CSF and a response-dependant change in total brain volume at MRI were observed in that study, which provide a proof-of-concept for anti-Abeta 1-42 immunotherapy that could be important for future AD studies. The fact that some patients analysed at autopsy showed a disappearance of amyloid plaques after exposure to (Aβ)1-42 immunization [21] is a further encouragement to continue exploring this approach. Several active studies with administration of various modified Abeta 1-42 antigens, and passive studies with injection of monoclonal antibodies against epitopes of Abeta 1-4 are currently underway.

In a more clinical context, the concept of disease modification in Alzheimer's disease is controversial and the design of these trials raises new problems. Which populations should be studied? For how long? Which are the correct principal and secondary endpoints? Are surrogate markers available? A European consensus on disease-modifying trials in Alzheimer's disease, agreed under the auspices of the European Alzheimer's Disease Consortium has been proposed on these issues [22]. The design and conductance of randomised clinical trials (RCT's) has to be amended from the present practice according to the new needs and new diagnostic principles [23]. Specific recommendations are still under debate. Because of the moderate magnitude of drug effects to be expected, the proof of efficacy of new drugs will remain a major challenge. An ideal treatment should arrest the progression ot the pathological process of AD as early as possible, even at a stage when the diagnosis cannot be made with certainty on clinical and neuropsychological criteria. To make that possible we desperately need biological or brain imaging methods which could make the diagnosis of AD feasible early in the pre-dementia stage. The recently rapid development in the field of in vivo amyloid imaging is promising [24,25]. It is important to verify by imaging the reduction of amyloid in brain that is expected to obtained after immunization therapy and relate the in vivo reduction in amyloid load in brain to cognitive function.

** This session is held at the occasion of the ECNP Targeted Expert Meeting 2007 Dementia, 12-13 October 2007, Vienna, Austria. For further details see the ECNP website www.ecnp.eu*

References

1. Hardy, J.A. and G.A. Higgins, *Alzheimer's disease: the amyloid cascade hypothesis.* Science, 1992. 256, 184-5.
2. Selkoe, D.J., *The molecular pathology of Alzheimer's disease.* Neuron, 1991, 6, 487-98.
3. Saido, T.C., et al., *Dominant and differential deposition of distinct beta-amyloid peptide species, Abeta N3(pE), in senile plaques.* Neuron, 1995, 14, 457-66.
4. He, W. and C.J. Barrow, *The A beta 3-pyroglutamyl and 11-pyroglutamyl peptides found in senile plaque have greater beta-sheet forming and aggregation propensities in vitro than full-length A beta.* Biochemistry, 1999, 38, 10871-7.
5. Schilling, S., et al., *On the seeding and oligomerization of pGlu-amyloid peptides (in vitro).* Biochemistry, 2006, 45, 12393-9.
6. Kuo, Y.M., et al., *Irreversible dimerization/tetramerization and post-translational modifications inhibit proteolytic degradation of A beta peptides of Alzheimer's disease.* Biochim Biophys Acta, 1998, 1406, 291-8.
7. Russo, C., et al., *Pyroglutamate-modified amyloid -peptides - AbetaN3(pE) - strongly affect cultured neuron and astrocyte survival.* Journal of Neurochemistry, 2002. 82, 1480-1489.

8. Cynis, H., et al., *Inhibition of glutaminyl cyclase alters pyroglutamate formation in mammalian cells.* Biochim Biophys Acta, 2006, 1764, 1618-25.
9. Wirths, O., et al., *Deficits in working memory and motor performance in the APP/PS1ki mouse model for Alzheimer's disease.* Neurobiol. Aging, 2008, 29, 891–901.
10. Casas, C., et al., *Massive CA1/2 Neuronal Loss with Intraneuronal and N-Terminal Truncated A{beta}42 Accumulation in a Novel Alzheimer Transgenic Model.* Am J Pathol, 2004, 165, 1289-1300.
11. Wirths, O., et al., *Age-dependent axonal degeneration in an Alzheimer mouse model.* Neurobiol Aging, 2007, 28, 1689–1699.
12. Blennow, K., M.J. de Leon, and H. Zetterberg, *Alzheimer's disease.* Lancet, 2006, 368, 387-403.
13. Maeda, J., et al., *Longitudinal, quantitative assesment of amyloid, neuroinflammation and anti.amyloid treatment in a living mouse model of Alzheimer's disease enabled by PET.* J Neurosci, 2007, 27, 10957–10968.
14. Spark D.L. et al., Atorvastatin for the treatment of mild to moderate Alzheimer disease: preliminary results.. Arch Neurol 2005, 62, 753-757
15, Stuchbury G., et al., Alzheimer's associated inflammation, potential drug targets and future therapies. J Neural Transm 2005, 112, 429-453.
16. Games, D., et al., *Alzheimer-type neuropathology in transgenic mice overexpressing V717F beta-amyloid precursor protein.* Nature, 1995, 373, 523-527.
17. Schenk, D., et al., *Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse.* Nature, 1999, 400, 173-7
18. Bayer, A.J., et al., *Evaluation of the safety and immunogenicity of synthetic Abeta42 (AN1792) in patients with AD.* Neurology, 2005, 64, 94-101
19. Gilman, S., et al., *Clinical effects of Abeta immunization (AN1792) in patients with AD in an interrupted trial.* Neurology, 2005, 64, 1553-62
20. Orgogozo, J.M., et al., *Subacute meningoencephalitis in a subset of patients with AD after Abeta42 immunization.* Neurology, 2003, 61, 46-54
21. Nicoll, J.A., et al., *Neuropathology of human Alzheimer disease after immunization with amyloid-beta peptide: a case report.* Nat Med, 2003, 9, 448-52
22. Vellas, B., et al., *Disease-modifying trials in Alzheimer's disease: a European task force consensus.* Lancet Neurol, 2007, 6, 56-62
23. Dubois, B., et al., *Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria.* Lancet Neurol, 2007, 6, 734-46
24. Nordberg A.Amyloid imaging in Alzheimer´s disease. Current opinions in Neurology, 2007, 20, 398-402
25. Mathis CA, Lopresti BJ, Klunk WE. Impact of amyloid imaging on drug development in Alzheimer´s disease. Nucl Med Bio, 2007, 34, 809-822