authors infused a large amount of Aβ*56 into the brain and used vehicle as the control. In view of the inordinately high levels of infused Aβ*56, it would seem reasonable to examine the effects of other 'amyloidogenic' polypeptides unrelated to Aβ, or for that matter, soluble Aβ oligomers, such as the stable trimers, on the behavioral parameters that were tested. At a fundamental level, it will be crucial to identify the cell-surface target(s) and downstream signaling pathways that impact glutamatergic neurotransmission[6] and Aβ*56-induced memory loss (**Fig. 1**).

Finally, it will be crucial to establish the presence of Aβ*56 in humans and validate the proposal put forth that Aβ*56 could serve as a valuable biomarker for preclinical diagnosis, and ultimately, provide a new therapeutic target to "...abort the disease before permanent structural changes have developed"[4].

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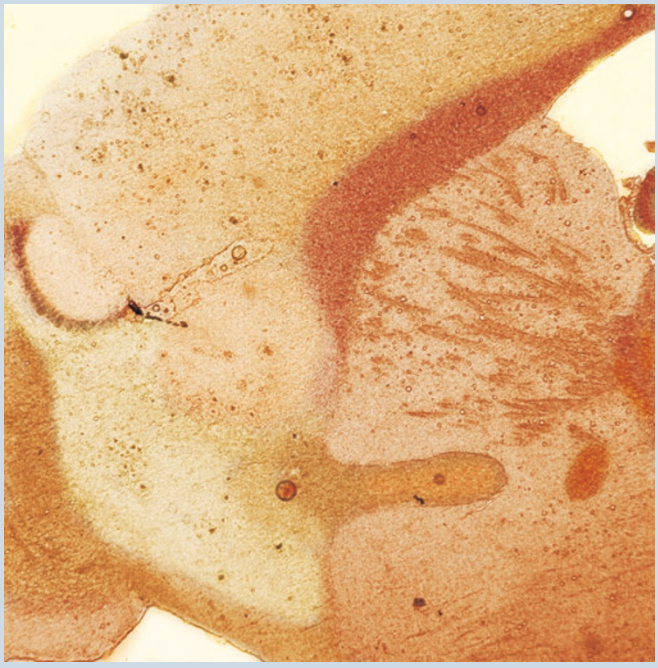
The author's perspective



Courtesy of Nature Biotechnology

Fourteen years ago, I decided to study how amyloid-β (Aβ) alters brain function as others were investigating how it changes brain structure. I have often had doubts about this choice because it has been an arduous road. When I began tackling this problem, there were no models to study the effects of endogenous Aβ on memory. It took such a long time to create a useful transgenic mouse model that I did not publish any papers the first three years I was at the University of Minnesota, which nearly cost me tenure because scientists at UCSF and Columbia wrote opposition letters, stating quite correctly that I would not receive tenure at their institutions. I was only promoted because the dean overrode the Promotions and Tenure Committee's negative recommendation. After we created the Tg2576 mouse model in 1996, it took my students and collaborators six years to determine the relationship between memory function, brain pathology and Aβ levels over the two-year lifespan of the mouse. During this time, I ran out of money to support the large aging mouse colony I needed for these experiments, and was struggling to create a lab infrastructure that could handle the volume of mouse breeding and behavioral testing. Fortunately, I had a wonderful group of lab technicians who devised a team method for generating the mice as well as the behavioral data that forms the foundation of our work. In addition, I was given two endowed chairs to support the work financially. The Aβ* hypothesis was forged in 2001, but to prove it, I needed a method for testing acute cognitive effects of minute quantities of Aβ oligomers. Luckily, two collaborators turned their labs over to solving this problem. We also lacked the expertise to find Aβ* and were stuck until Sylvain Lesné joined us in 2002. Although Sylvain's paper underwent the most rigorous set of reviews I have ever encountered, the paper that was published is much better than the first version we submitted, a clear testament to superb reviewers.

Karen H. Ashe, University of Minnesota Medical School

Highly cited clinical and epidemiological papers on Alzheimer disease published in 2003[a]

Reference	Times cited
Shumaker, S.A. *et al.* Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women—The Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA* **289**, 2651–2662	497
Reisberg, B. *et al.* Memantine in moderate-to-severe Alzheimer's disease. *N. Engl. J. Med.* **348**, 1333–1341	336
Nicoll, J.A. *et al.* Neuropathology of human Alzheimer disease after immunization with amyloid-β peptide: a case report. *Nat. Med.* **9**, 448–452	240
Hebert, L.E. *et al.* Alzheimer disease in the US population: prevalence estimates using the 2000 census. *Arch. Neurol.* **60**, 1119–1122	185
Hock, C. *et al.* Antibodies against β-amyloid slow cognitive decline in Alzheimer's disease. *Neuron* **38**, 547–554	182
Aisen, P.S. *et al.* Effects of rofecoxib or naproxen vs. placebo on Alzheimer disease progression: a randomized controlled trial. *JAMA* **289**, 2819–2826	167
Orgogozo, J.-M. *et al.* Subacute meningoencephalitis in a subset of patients with AD after Aβ42 immunization. *Neurology* **61**, 46–54	125

[a]Number of citations as of 13 June 2006. Table includes all clinical trials (including phase 1 trials), epidemiological studies, case reports and biomarker studies that have the terms 'Alzheimer' or 'Alzheimer's' in their title, abstract or keywords, and that have been cited at least 125 times. Data source: *Scopus*