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Immunizing against Alzheimer's

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William Wells
Email: wells@biotext.com

Abnormal processing and deposition of amyloid-β peptide (Aβ) in extracellular plaques are thought to be central to the pathogenesis of Alzheimer's disease. Immunization with Aβ reduces the amount of brain amyloid, and now in the 21/28 December Nature, Janus *et al*. (*Nature* 2000, **408:**979-982) and Morgan *et al*. (*Nature* 2000, **408:**982-985) report that similar immunization protocols also reduce the learning deficit seen in mouse models of Alzheimer's disease.

Janus *et al*. immunize at 6, 8, 12, 16 and 20 weeks with Aβ in β-pleated sheet conformation, and test using a Morris water maze at 11, 15, 19 and 23 weeks. The immunized mice perform significantly better than non-immunized littermates at 11 and 23 weeks, when two discrete increases in amyloid burden are detected in non-immunized mice. Immunization reduces the amount of dense-cored Aβ plaques by approximately 50%, suggesting that the elicited antibodies may inhibit assembly of Aβ fibrils rather than clear all Aβ.

Morgan *et al*. immunize monthly before assaying at 15.5 months using a radial-arm water maze that tests working memory. (Chen *et al*., reporting in the same issue of Nature, find that only the performance of tasks that require this sort of working or episodic-like memory are correlated with the age-related increase in plaque burden (*Nature* 2000, **408:**975-979).) At 15.5 months the immunized mice are better than non-immunized mice on the fourth trial, and as good as wild-type mice by the fifth trial. In contrast the mice in the Janus *et al*. study never improved to reach the performance levels of wild-type mice. Morgan *et al*., the group not affiliated with a pharmaceutical company, "strongly recommend testing" of Aβ immunization for both treatment and prevention of Alzheimer's disease.

Further links to Aβ come in the 22 December Science. Ertekin-Taner *et al*. use plasma Aβ42 levels as a surrogate for late-onset Alzheimer's disease (LOAD), and come up with a locus on chromosome 10 linked to the disease (*Science* 2000, **290:**2303-2304). Myers *et al*. confirm this observation using an analysis of affected sibling pairs, and find a significance level that suggests the new locus is as important as the E4 allele of apolipoprotein E, the only known genetic risk factor for LOAD (*Science* 2000, **290:**2304-2305). The new locus is near, but apparently distinct from, the locus identified by Bertram *et al*. (*Science* 2000, **290:**2302-2303). The latter locus is very near or identical to the gene for insulin-degrading enzyme, which may help degrade and clear Aβ.

References

1. Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse.

2. *Nature*, [http://www.nature.com/nature/]

3. *Science*, [http://www.sciencemag.org/]

4. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium.

5. Exploring the etiology of Alzheimer disease using molecular genetics.