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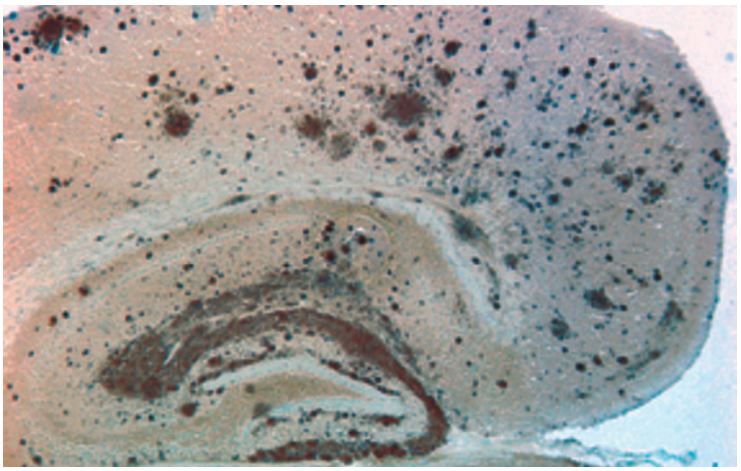
ALZHEIMER DISEASE

Plaque-specific anti-Aβ antibody shows promise in model of AD

Treatments for Alzheimer disease (AD) have largely targeted soluble amyloid-β (Aβ)—the hallmark pathological protein in this disorder—despite the fact that deposited Aβ is thought to initiate the neurodegenerative cascade, and evidence suggesting that plaques are already present at maximal levels in patients at the time of diagnosis. Now, researchers have developed a plaque-specific antibody, and have shown in preclinical studies that this therapeutic effectively clears existing plaques without causing adverse events such as microhaemorrhage.

Ronald DeMattos, a research fellow at Eli Lilly and Company, who led the study, points out that Aβ-targeted immunotherapies are believed to function via two possible mechanisms: phagocytosis or soluble equilibrium (neutralization of soluble Aβ, facilitating clearance). "Of particular interest were the early findings from multiple groups that antibodies thought to work via phagocytosis seemed to be highly efficacious at preventing Aβ deposition, yet lacked efficacy once advance deposition was in place," he says. "Our goal was to develop an antibody that can safely remove significant quantities of pre-existing deposited Aβ."

The investigators developed an antibody—termed mE8—against a modified Aβ peptide ($Aβ_{p3–42}$) that is found only in plaques, and compared its efficacy with that of 3D6 (an antibody that binds both soluble and deposited Aβ forms) in a transgenic mouse model of AD.



Brain section showing hippocampal and cortical areas stained with the mE8 antibody, which recognizes deposited amyloid-β peptide (brown staining). Image courtesy of R. DeMattos, Eli Lilly and Company.

Histological analysis of brain sections revealed that 3D6 bound plaques in only a small region of the hippocampus, whereas mE8 robustly labelled deposited Aβ plaques throughout the hippocampus and cortical regions. "The studies showed that mE8 removed pre-existing plaques in the brain, whereas 3D6 did not," says DeMattos. "Furthermore, unlike 3D6, mE8 did not produce evidence of microhaemorrhage."

Although unable to comment on the exact time-frame of development, DeMattos says that the next antibody treatment for AD from Eli Lilly and Company will be plaque specific. The results provide hope that a treatment to effectively target and remove existing Aβ plaques in the brains of patients with AD is not far from the clinic.

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Original article DeMattos, R. B. *et al.* A plaque-specific antibody clears existing β-amyloid plaques in Alzheimer's disease. *Neuron* doi:10.1016/j.neuron.2012.10.029