Comment on Vicki Brower's article 'Harnessing the immune system to battle Alzheimer's' in *EMBO reports*, March 2002

The Elan Corporation has been testing a possible cure for Alzheimer's disease (AD) using vaccinations against amyloid- β (A β), the presumed neurotoxic component of the neuritic plaques in the brains of AD patients. In February 2002, Elan terminated its phase 2A clinical trials of the vaccine AN-1792 after 15 out of 360 patients developed symptoms of central nervous system inflammation (Check, 2002; Weiss, 2002). Whereas the article in the March issue of *EMBO reports* was very positive about the future prospects of the vaccination approach for the treatment of AD, we are less optimistic. Despite its potential, we believe that the risks underlying deliberately provoked autoimmune responses against A β have been underestimated.

The aim of vaccination against A β is to eliminate fibrillar A β from neuritic plaques by antibody-mediated phagocytosis. Such a process appears to occur in the brains of transgenic mice that over-express human amyloid precursor protein (APP), the parent protein of A β . These mice develop A β plaques and associated memory impairment; when these mice are vaccinated with human A β , they produce antibodies to the protein, the plaques are cleared and memory is improved (Schenk *et al.*, 1999; Arendash *et al.*, 2001). Crucially, the endogenous form of A β in mice has a different molecular sequence to human A β and so is spared by these antibodies.

In humans, the difficulty lies in being able to limit the immune response to the fibrillar (β -sheet) conformation of A β , since it shares a 40–42 amino acid sequence with the soluble form and with the full-length APP. If induced B-cell responses cannot be limited solely to β -conformation-specific antibodies, then

soluble A β will also be targeted, and it is possible that this form of the peptide may contribute to normal brain function. In addition, APP is known to play a key role in assisting neuronal recovery and repair following brain injury, and soluble APP fragments have trophic properties. Antibodies that bind to APP on the cell surface will lead to complement activation and subsequent opsonisation of the cell prior to its phagocytosis. If the cases of nervous system inflammation in the AN-1792 trials involve such a response, patients with a lower titre of antibodies may also develop this autoimmune reaction a long time after the initial vaccination, reminiscent of multiple sclerosis. A β vaccination also carries the risk of activating TH₁ cells, which are the predominant T-cell population in the elderly. These cells produce pro-inflammatory cytokines such as interferon- γ that can stimulate microglia to secrete neurotoxic factors, including TNF- α and nitric oxide (McMillian *et al.*, 1995). In addition, the A β -specific T-cell line repertoire contains a high percentage of cytotoxic T cells (Grubeck-Loebeinstein *et al.*, 2000), and any increase in the level of the T-cell-mediated neuro-inflammatory response has the potential to accelerate neuronal loss in AD patients.

Therefore, while the vaccine approach does have the potential to clear neuritic plaques from the brains of AD patients, it is a strategy that risks producing serious brain inflammation and neurodegeneration. Until these risks have been greatly reduced, neuroprotective drugs such as NMDA antagonists, free-radical scavengers and non-steroidal anti-inflammatory drugs remain the most promising approaches to AD treatment (Rösler *et al.*, 1998).

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