the EphA4 receptor or ephrinB3 did not alternate rhythmically, but tended towards an abnormal synchronous pattern that results in the rabbit-like gait of these mutants. *EphA4*-null mice exhibited aberrant projection of fibres across the midline of the cord, indicating that correct wiring of the neuronal networks that control locomotion relies on recognition of ephrinB3 in the midline by EphA4 receptors.

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NEURODEGENERATIVE DISORDERS

# Fighting fire with fire

Since the pioneering work of Edward Jenner in the late 1700s, the idea of creating immunity to disease by challenging the immune system with a pathogenic agent has formed the basis for numerous successful immunization programmes. Research in mice has indicated that Alzheimer's disease (AD) might be amenable to this approach, although clinical trials were halted because of potentially serious side effects. However, despite this setback, some encouraging findings have emerged, as Nicoll and colleagues now report in *Nature Medicine*.

Their paper describes the case of a 72-year-old woman with a five-year history of AD. The woman was immunized with amyloid-β (Aβ) peptide — one of the main constituents of the plaques that accumulate in the brains of patients with AD. Previous studies in mice had shown that immunization with Aβ caused animals to mount an immune response against the endogenous peptide, leading to breakdown of many of the plaques. The mice also showed evidence of cognitive improvement — one of the principal goals of any AD therapy.

As the new paper illustrates, the human trials seemed to be considerably less successful than their animal counterparts. The woman described by Nicoll *et al.* showed no obvious signs of improvement in her AD symptoms, and several months into the trial, her overall condition deteriorated rapidly. Like several other patients that received the vaccine, she showed signs of brain inflammation. Twenty months after the start of the treatment — and twelve months after she received her last injection — she died from a pulmonary embolism. The trial was terminated at the beginning of 2002.

The prospects for the vaccine looked bleak at this stage. However, a *post mortem* examination has now shown that the woman's brain contained significantly fewer plaques than would be expected for a person at this stage of the disease. Moreover, some of the remaining Aβ was associated with microglia — the cells that are believed to be important for clearing Aβ from the brain — implying that removal of Aβ might still have been taking place at the time of her death.

So, what does the future hold for the Alzheimer's vaccine? These new findings seem to indicate that it is worth pursuing, but the side effects will clearly need to be resolved. One problem with the Aβ vaccine is that it seems to provoke a T-cell-mediated immune response, which results in a harmful encephalitis. The T-cell

response might be bypassed by immunizing with antibodies against Aβ, rather than with the peptide itself. Alternatively, as the Aβ epitope that elicits the strongest immune response is in the amino terminus, it might be preferable to immunize with a fragment of Aβ instead of the full peptide. Assuming that the problems can be ironed out, it will be necessary to show that the vaccine can actually relieve the symptoms of AD in humans, or even prevent them if administered before the disease process starts. This is important both from a clinical and a research perspective — it is widely believed that amyloid plaques are at least partly responsible for the cognitive decline in AD, and the vaccine has the potential to allow the further exploration of this idea.

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