

to avoid the organ failure that presents clinically as dementia. The problem is that techniques to identify presymptomatic individuals at high risk to develop Alzheimer disease are imperfect, and offering preventative treatments must await highly sensitive and specific biomarkers of approaching disease. There is also a need to tailor therapeutic study design to include subjects with the very earliest preclinical signs of

pathological changes. Since such a therapeutic approach requires long-term treatment until efficacy is ascertained, it will also be necessary to gain a better understanding of potential long-term toxicities of the drugs being tested. Finally, it will be crucial to develop medical and regulatory agreement that detection of a biomarker for approaching dementia is a sufficient indication to treat. These are complex issues, but the

welcome promise of an effective anti-amyloid agent will force us to deal with them soon.

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## The author's perspective

Our study detailed the findings from a phase 2 clinical trial of A $\beta$  immunotherapy in individuals with Alzheimer disease. Trial participants received an average of two immunizations of A $\beta$ <sub>42</sub> peptide before the trial was interrupted due to the development of meningoencephalitis in 6% of the participants. The first four individuals that presented with this side effect were located in France, and we originally thought that these individuals had viral meningitis. Subsequently, however, trial participants in other countries presented with similar symptoms, and no virus could be identified in these individuals. As the chair of the safety monitoring committee, I felt that the trial should be interrupted, and the two companies involved, Elan and Wyeth, came to the same conclusion at the same time. Most of the trial participants who presented with meningoencephalitis recovered, although a small number of them remain impaired. Despite interruption of the trial, we demonstrated through cognitive analyses and biomarker testing that A $\beta$  immunotherapy had a positive clinical impact on Alzheimer disease. Subsequent neuropathological examinations strengthened the findings by showing decreased A $\beta$  deposits in individuals who had been immunized. The positive effects in this study provided proof of concept of the value of immunotherapy in the armamentarium to treat Alzheimer disease and strengthened our conviction that additional research would reveal the pathogenesis of the meningoencephalitis and permit us to continue with this approach to therapy. Indeed, investigations into the cause of the meningoencephalitis support the view that the full A $\beta$ <sub>42</sub> peptide that was used in the trial induced the generation of a T-cell response, and this T-cell epitope found within A $\beta$  can be engineered out of future active immunotherapeutic molecules, thereby avoiding the generation of these cross-reactive T cells. To this end, a phase 1 clinical trial has been initiated which is examining immunization with A $\beta$  peptides that lack this T-cell epitope. Additionally, a phase 2 trial has been investigating the potential efficacy of 'passive' immunization using antibodies against A $\beta$  in individuals with Alzheimer disease. These ongoing and future clinical studies will explore the potential role that A $\beta$  immunotherapy may have in changing the course of this dreadful disease.

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## Amyloid at the blood vessel wall

John Hardy & Karen Cullen

**An APP gene duplication found in French families with  $\beta$ -amyloidopathy suggests a link between dementia and the vasculature.**

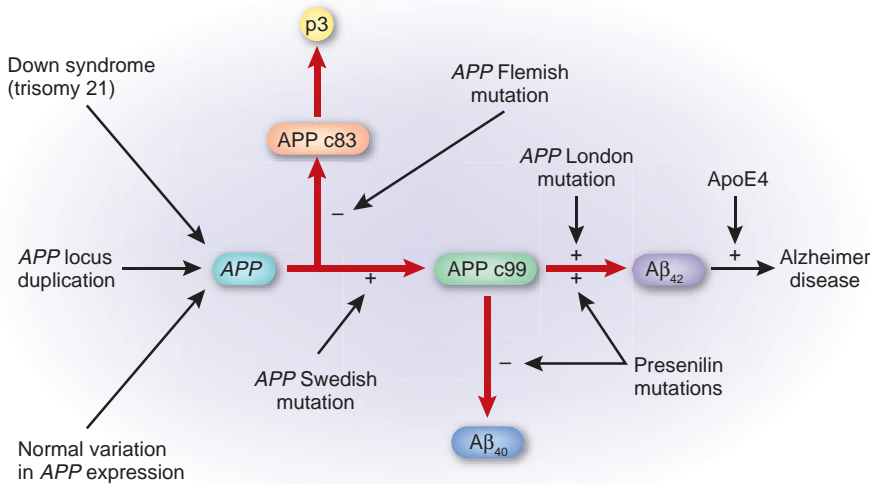
Rovelet-Lecrux and colleagues' demonstration that duplications of the amyloid precursor protein gene (*APP*) in French families cause  $\beta$ -amyloidopathy<sup>1</sup> is strong evidence for the amyloid hypothesis<sup>2</sup>, which states that Alzheimer disease is caused by increased production of amyloid- $\beta$  (A $\beta$ ), a cleavage product of APP. The phenotype of individuals with *APP* duplications is variable, with some individuals having a purely demented phenotype, others having a

hemorrhagic phenotype and still others having a mixture of both. This phenotype is similar to the disease caused by a mutation in the *APP* gene (the so-called 'Flemish' mutation) and is intermediate between that of Dutch amyloid angiopathy, in which amyloid deposition along blood vessels causes brain hemorrhage, and Alzheimer disease, where although there is pathological evidence of amyloid angiopathy, there is no clinical evidence of hemorrhages (Fig. 1). The report that overexpression of *APP* initiates this syndrome fits with the general pattern of observations in many neurodegenerative diseases characterized by protein deposition: mutations in or duplications of the loci encoding these proteins cause inherited forms of these diseases, and genetic variability in the expression of these loci contribute to the risk of 'sporadic' disease<sup>3</sup>. The

chromosomal alterations that cause the disease are duplications of between ~600 kb (just framing the *APP* gene) and large, 7 Mb duplications that encompass many other genes on chromosome 21 besides *APP*<sup>1</sup>.

There are some unexpected features of the disease that warrant further consideration and investigation. In Down syndrome (trisomy 21), as in the French families, individuals have three copies of the wild-type *APP* sequence. But in contrast to the French families, there is no evidence that individuals with Down syndrome have large-vessel hemorrhages. Why this should be the case is not clear, though it may relate to differences in the vasculature in individuals with Down syndrome. The variable and vascular phenotypes of individuals with the *APP* duplication is almost certainly why

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**Figure 1** The pathway by which Alzheimer disease pathogenesis is initiated.

families with these duplications had not been identified before. Perhaps clinicians had not appreciated that family members with a stroke phenotype and related family members with a dementia phenotype had the same underlying lesion, particularly because evidence of a stroke is part of the exclusionary criteria for making the diagnosis of Alzheimer disease.

In general, the relationship between the vascular and parenchymal lesions in all the  $\beta$ -amyloidopathies deserves re-examination in light of this overlap between angiopathy and plaque and between hemorrhage and dementia. This reinvestigation is also important because it is likely that the T lymphocyte-mediated meningoencephalitis seen in the  $A\beta$  vaccination (AN-1792) trial for Alzheimer disease may have been caused by antibody-induced damage to the microvasculature<sup>4</sup>. Recent data have corroborated an old

view of amyloid plaques: that at their center they have amyloid fibrils extruding from an angio-pathic blood vessel<sup>5-7</sup>. In addition, there is clear evidence that amyloid plaques represent the sites of microhemorrhages in Alzheimer disease<sup>8,9</sup>. Ironically, this new view comes close to the long-discredited notion of Alzheimer disease as being caused by hardening of the arteries. Whatever the history of this idea, these findings all suggest that it is crucial we understand the vascular deposition of  $A\beta$  in Alzheimer disease. Such an understanding may be necessary not only to understand the initiation of the disease, but also to avoid potential side effects of treatment.

One hundred years after Alois Alzheimer's description of the plaques and tangles in the first reported case of Alzheimer disease, we have looked at the proteins that make up these deposits as pathologies and have not extensively

investigated their physiologic roles. Perhaps we should consider the possibility that  $A\beta$  has a function that relates directly to its involvement in vascular pathology. We know, for example, that APP is involved in blood clotting<sup>10</sup> and that  $A\beta$  drains from the brain along the walls of the microvasculature<sup>11</sup>. Perhaps we should consider the possibility that  $A\beta$  has complementary damage-response roles: (i) as an emergency sealant of the vasculature during hemorrhage and (ii) as a neuronal depressant<sup>12</sup>. As a depressant, it would reduce the brain's oxygen requirement during an ischemic event and thus help control the extent of hypoxic damage in a hemorrhage. This physiologic view would fit with the observation of a continuum of  $A\beta$  pathology between the blood vessels and the plaques, which is especially seen in the individuals with APP duplications. Research over the last 20 years has focused on  $A\beta$  pathology; perhaps we should now shift our focus to understanding  $A\beta$  physiology in order to garner further information as to the process which leads to dementia.

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<sup>a</sup>Number of citations as of 13 June 2006. Table includes all primary research articles that have the terms 'Alzheimer' or 'Alzheimer's' in their title, abstract or keywords, and that have been cited at least 50 times. Table does not include reviews. Data source: *Scopus*