Commentary

Amyloid- β Vaccination: Testing the Amyloid Hypothesis?

Heads We Win, Tails You Lose!

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The goal of science, at its most fundamental level, is to construct hypotheses and thereafter to devise experiments that either disprove the hypothesis or, by not disproving it, provide additional support for the hypothesis. In the field of Alzheimer's disease (AD), the predominant hypothesis is the Amyloid Cascade Hypothesis, the original version of which posited that insoluble fibrillar amyloid β ($A\beta$) is central to disease pathogenesis.¹ In support of this hypothesis, $A\beta$ fibrils have been found to be toxic *in vitro*,² and, since then, considerable effort has been and continues to be made on developing therapeutic modalities that target $A\beta$ fibrils. In this regard, transgenic mice that overexpress mutant forms of the $A\beta$ protein precursor ($A\beta$ PP) and develop extensive fibrillar $A\beta$ -senile plaque deposits³ have become invaluable, despite the fact that such mice do *not* provoke neurodegeneration or other features of AD, which would seem to disprove the hypothesis. That withstanding, such transgenic mice have become important screening tools for potential therapeutics, and of the many agents found to "treat" these mice (ie, reduce $A\beta$ plaque deposits and rescue cognitive deficits), none has raised as much enthusiasm and expectations as the vaccination strategy.^{4,5}

Around the same time that the vaccination approach was entering into human clinical trials, the original Amyloid Cascade Hypothesis¹ underwent a slight modification in which the emphasis switched to oligomeric, rather than fibrillar, forms of $A\beta$.⁶ Today, oligomeric $A\beta$ is viewed, almost universally in the field, as the most toxic and, therefore, most important species.⁷ What impact did

this have for the clinical trial that targeted fibrillar amyloid? Before this question was answered, the clinical trial was suspended because of the development of encephalitis in a small percentage of individuals, an event that was subsequently blamed on the adjuvant.⁸ However, two alternate explanations may be more relevant in explaining such an unexpected outcome. First, while initial studies in mice supported vaccination-mediated decreases in both fibrillar and oligomeric species,⁴ the paper in this issue of *The American Journal of Pathology*⁹ shows that oligomeric amyloid may, in fact, increase in human patients who received the vaccination (Figure 1). Specifically, while senile plaques were disaggregated in AD patients who received the vaccination, the amount of soluble amyloid was substantially *increased* when compared with nonvaccinated AD patients. Based on these findings, the authors suggest that the elevated pool of soluble amyloid may further impair neuronal function, reduce neural transmission, and promote neuroinflammation.⁹ In our opinion, such neuroinflammation may be a potential cause of the negative outcome of vaccination in some patients (ie, encephalitis). While the results of a related trial involving passive vaccination, to avoid adjuvant issues, are eagerly anticipated, the present findings essentially remove any "doubt" (sic) that amyloid is indeed responsible for AD. Simply, if patient health improves, it is because $A\beta$ fibrils are removed. On the other hand, if patients fare worse, it is because of increases in oligomeric $A\beta$. Success or failure will equally support the Amyloid Hypothesis. However, as cited, in subgroup analysis, a percentage of patients may have benefited from the vaccination.^{10,11} Perhaps in such patients, clearance mechanisms enable rapid removal of $A\beta$ oligomers, with the benefit lying in removal of fibrils. Thus, the ques-

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Figure 1. In both human AD and transgenic models of AD, amyloid A β is in dynamic equilibrium between soluble monomeric and soluble oligomeric forms and between soluble oligomeric and fibrillar forms. According to the two versions of the Amyloid Cascade Hypothesis, either fibrillar or oligomeric forms are viewed as toxic. Vaccination in transgenic animals shifts both equilibria to the left, resulting in decreases in both fibrillar and oligomeric forms of the protein. In contrast, in human patients with AD, vaccination may only shift the equilibria of fibrillar to oligomeric but not that between oligomeric and soluble forms. This could be detrimental (increase in oligomers) or beneficial (removal of fibrils) dependent on the version of the Amyloid Cascade Hypothesis under consideration.

tion now becomes explaining this finding so future therapeutic efforts can be more successful. Such investigations are no doubt pending. Nonetheless, this vaccination strategy does result in an increase in soluble (oligomeric?) amyloid in some people, and this would be viewed as detrimental according to the current construct of the Amyloid Cascade Hypothesis.

While the two mainline amyloid theories consider amyloid as toxic, a second alternate role for A β in AD must also be considered. We predicted originally that vaccination strategies were likely to fail,^{12,13} not because of an increase in oligomeric amyloid, but because we suspect that A β is a protective consequence of the disease, *not* a cause of disease.^{14,15} Our Alternate Amyloid Hypothesis¹⁶ posits that A β serves as a protective antioxidant and that its removal will exacerbate, rather than treat, disease. The paper by Roher and colleagues⁹ in this issue of the *AJP* gives us pause for thought on our original prediction^{12,13}—perhaps, by increasing oligomeric A β , the vaccination strategy may work by increasing protective A β .

In other words, for both the Amyloid Cascade Hypothesis and the Alternate Amyloid Cascade, the results of the immunization trial are the same: Heads we win, tails you lose!

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