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Testing the amyloid hypothesis of Alzheimer's *in vivo*

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In the current issue, Rinne and colleagues¹ report something of a breakthrough by demonstrating the feasibility of eventually testing the “amyloid hypothesis” of sporadic Alzheimer's disease *in vivo*. According to their analysis, a passive immunotherapy protocol employing an anti-A β monoclonal antibody (bapineuzumab) was associated with a diminution in the cerebral positron emission tomography (PET) signal following administration of the amyloid plaque imaging compound [¹¹C]Pittsburgh compound B (PiB) (Figure 1). Heretofore, no one has shown *any* change in PiB signal over time, and the interpretation favored by the authors is that the new results indicate that bapineuzumab has promoted the clearance of cerebral A β . This is a logical deduction extrapolating from the dramatic changes in cerebral amyloid burden that have been consistently demonstrated in amyloid precursor protein (APP) transgenic mice following either active or passive immunotherapy². While it is conceivable that some other explanation exists (e.g., perhaps bapineuzumab-coated A β binds PiB poorly), the authors' conclusion is the most parsimonious when one considers the postmortem studies of Nicoll and colleagues³ showing surprisingly low plaque density in the cerebral cortex of subjects in an earlier active immunization trial.

At least two anti-amyloid clinical trials (homotaurine, AlzhemedTM; tarenfurbil, FlurizanTM) have been reported as failures in modifying the course of mild to moderate Alzheimer's^{4,5}. However, in neither of these trials were any amyloid biomarkers employed as endpoints. This would be the equivalent of a statin trial in which myocardial infarction was recorded as an endpoint but plasma cholesterol was not even measured. No trial can be said to be a test of the amyloid hypothesis unless there are data documenting and quantifying cerebrospinal fluid A β levels or cerebral amyloid burden in the cohort that received the drug.

On the flip side, in neither the recent Salloway *et al*⁶ bapineuzumab trial report nor the current Rinne *et al* report has there been any clinical response to bapineuzumab. “Amyloid naysayers” seize on this as proof that anti-amyloid therapy should be abandoned. This is an irresponsible and irrational response. Mutations or polymorphisms in at least four genes, each on different chromosomes, have been shown to cause or dramatically increase the risk for the Alzheimer's phenotype⁷. Each of the mutations has been demonstrated to fulfill Koch's postulates for causing or enhancing amyloid pathology in mouse models. Mice never develop a phenotype of cerebral amyloidosis except in the presence of human A β in the context of a pathogenic Alzheimer's mutation or risk factor polymorphism. These are compelling, immutable facts indicting A β in genetic forms of Alzheimer's.

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Of course, in ~97% of Alzheimer's patients, no pathogenic mutation can be identified. *APOEε4*, *SORL1*, and *CLU*, among others, have been implicated in modulating risk in this common form of the disease. It is probably not a coincidence that each of these can also be linked to Aβ metabolism in cell biology experiments⁸. However, the naysayers have a point when they favor the notion that, in common sporadic Alzheimer's, metabolic disturbances (perhaps involving calcium or oxidative stress) could plausibly lie upstream of Aβ deposition and cause some of the neurodegeneration directly and independent of Aβ⁷. This argument can be supported with authentic pathways, but, so far, not with pathogenic mutations. Still, logic dictates that Aβ cannot be causative and toxic in genetic forms of the disease and yet totally innocuous and irrelevant in common sporadic forms. Ergo, Aβ neurotoxicity must play a role in common sporadic Alzheimer's as well. The only way to settle the issue is to *prevent* Aβ accumulation by intervening, guided by biomarkers, at a pre-symptomatic age (probably in the 4th or 5th decade of life), establishing with serial biomarker measurements that the intervention prevented amyloidosis, and then following long-term (i.e., until age 80 or 90) with neuropsychological testing to determine whether the Aβ-free brain is still destined for failure.

There are some subtleties yet to be accounted for. After a century of focusing on amyloid plaques (Figure), attention has recently shifted to the less well-defined Aβ "oligomers" as the key proximate neurotoxin in Alzheimer's⁹. Moreover, PiB binds only to fibrillar Aβ and not to oligomeric Aβ, so there is, as yet, no way to visualize or quantify the cerebral burden of oligomeric Aβ. The nature of the interaction between bapineuzumab and oligomeric Aβ remains to be determined. If oligomeric Aβ is truly the key toxin, then whatever prophylaxis is employed must purge the brain of the oligomeric species as well.

It is worth noting that also on the horizon in Alzheimer's therapy is latrepirdine, a retired Russian antihistamine with surprising apparent benefit in both Alzheimer's and Huntington's diseases¹⁰. The mechanisms of action (MoA) of latrepirdine are poorly understood but they are rapidly becoming a focus of great interest. New information suggests that the latrepirdine MoA might well involve the protein aggregation phenomena that are common to both diseases. Latrepirdine has been reported to modulate Aβ metabolism *in vivo* in APP transgenic mice¹¹ and to accelerate clearance of protein deposits from synuclein transgenic mice¹². Though it is premature to say that we have effective, disease-modifying drugs in hand, these emerging data concerning both bapineuzumab and latrepirdine move us closer to the goal of understanding, treating, and, eventually, preventing major neurodegenerative diseases.

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Figure.

Cerebral amyloid plaque visualized with luminescent oligothiophenes. Each color represents a discrete misfolding state of A β (Image courtesy of Patrick Hof, Dara Dickstein, Peter Nilsson, and Sam Gandy) (Aslund A, Sigurdson CJ, Klingstedt T, Grathwohl S, Bolmont T, Dickstein DL, Glimsdal E, Prokop S, Lindgren M, Konradsson P, Holtzman DM, Hof PR, Heppner FL, Gandy S, Jucker M, Aguzzi A, Hammarström P, Nilsson KP. Novel pentameric thiophene derivatives for *in vitro* and *in vivo* optical imaging of a plethora of protein aggregates in cerebral amyloidoses. ACS Chem Biol. 2009 Aug 21;4(8):673–84. PubMed PMID: 19624097)