What's Function of Amyloid?

Theory *from page 1*

failure of specific drugs and possibly the failure of drug companies to follow a comprehensive and logical phase II plan.

Dr. Doody's argument reflects the disappointing results of the first phase III trials of antiamyloid therapies.Tramiprosate, a β-amyloid antagonist, was the disappointment of 2007; tarenflurbil, a gamma-secretase modulator, this year's downer. And although bapineuzumab, a passive immunotherapy, made it to phase II last summer, positive findings in its phase II trial were slim. A post hoc analysis showed that some patients with mild to moderate Alzheimer's, with no genetic risk factors, had cognitive improvement after getting the vaccine. Apparently, the finding was enough for Elan Pharmaceuticals Inc., and Wyeth Pharmaceuticals, although maybe not for Dr. Hardy.

"The data right now are neither positive nor negative. At this point, the only thing we can say about bapineuzumab is that it's not going to be a miracle therapy," he said.

A long-term follow-up study of patients enrolled in the early AN-1792 immunotherapy trial "doesn't look great for amyloid, either," he said. The AN-1792 trial was halted early, in 2002, when some of the patients developed encephalitis after getting the vaccine. The follow-up, published last summer, showed that the vaccine did clear plaques, but that clearance didn't affect cognition or survival. In fact, the authors said, "Seven of the eight immunized patients who underwent postmortem assessment, including those with virtually complete plaque removal, had severe end-stage dementia before death" (Lancet 2008;372:216-23).

Dr. Hardy doesn't think that slow progress on antiamyloid drugs negates the theory's basic truth, though—at least for a subset of patients. "There's no doubt at all that the amyloid hypothesis explains the disease in families with mutations of the amyloid precursor protein and presenilin genes. A much more open debate is whether the same process is at work in the typical Alzheimer's patient."

But drug companies must target this larger population in order to create a financially successful therapy, and the lack of progress has them fidgeting, Dr. Hardy said. "Every drug company is worried now and wondering if they should widen to other therapies, including tau-targeted drugs. And to this I say, 'Yes, of course you should have other strings for your bow.' "

The essential mystery of amyloid further complicates things, Dr. Hardy said: The protein has not yielded up all its secrets, despite years of research. "The thing that keeps me up at night is that we don't really know if amyloid has a function. It could be that amyloid is a response to vascular damage. We all ignore the fact that amyloid deposition occurs to a large extent in the vasculature. There must be a reason for this, and it could have something to do with vascular repair."

That worry also plagues Mark A. Smith, Ph.D., a professor of pathology and Alzheimer's researcher at Case Western Reserve University, Cleveland. "We have said for a long time that amyloid is doing something important in the brain. It could be acting like a vascular sealant in areas of injury. It forms structural scaffolding for blood vessels, and if you start getting rid of that scaffold, you'll see problems in the blood-brain barrier." This reaction probably caused the brain inflammation seen in the AN-1792 trial, he said.

Dr. Smith, who is a paid consultant for several companies investigating non–amyloid related therapies, is among a minority of researchers who resist the amyloid theory, although the overwhelming focus on amyloid has virtually drowned their opinion. In fact, he said, the amyloid research momentum is so strong right now that only more high-profile failures will begin to temper it.

"People still can't believe it's not working, and they're waiting for the results of the phase III vaccine trial," as well as new data on β-secretase inhibitors, theorized to reduce the buildup of plaque-forming AB-42. "I think at this point, the research community is so totally invested in amyloid that we need to either get something else that works or have an honest, sober, the-party's-over discussion of why amyloid-targeted therapies are failing—and get if off the table."

In an interview, Dr. Doody said that "Companies want their drug to be labeled as a disease-modifying agent as soon as possible; the implication is that it can then be priced at a higher rate. And because they are going for that, they are designing phase II trials that are long and costly but don't give them all the information they need."

Ideally, by the time any agent, including a potential disease-modifying compound, finishes phase II, there should be clear evidence that it is both safe and effective in the primary end point. "Neither tramiprosate nor tarenflurbil had a clear signal in phase II, and neither did bapineuzumab, although it at least had some signal. Another phase II study for bapineuzumab would have been nice to further clarify this proposed subpopulation of interest," she said.

Companies could also modify their research track to prove first that a drug confers symptomatic benefit, and then examine its possible disease-modifying properties. That is the path Medivation Inc. is following with dimebon—the only bright note in late-stage clinical trials this year. The obscure Russian antihistamine, thought to boost mitochondrial function, succeeded where the antiamyloids failed, significantly improving cognition, behavior, and function in Alzheimer's patients, although it did not modify disease progression.

"Dimebon probably is a disease-modifying drug, but proving this requires long-term studies," said Dr. Doody, primary investigator on the phase II trial. "But many pharmaceutical companies fear that a drug will be priced too low if they go for symptomatic approval first without the disease-modifying work up front."

Dr. Doody follows research on dozens of potential Alzheimer's drugs, only a

Continued on following page

Image of the Month

The cognitive-reserve hypothesis is a concept that has been proposed to account for findings that the brains of certain individuals with pathological Alzheimer's disease burden are somehow able to compensate and minimize the effect of this burden on cognitive function. It's been suggested that greater abilities in thinking, learning, and memory—which can result in part from regularly challenging the brain—makes some individuals less susceptible to the damage caused by the disease. Education is commonly used as a surrogate for cognitive function in investigations of this hypothesis.

Previous studies have suggested that a greater amyloid β (Aβ) burden in the brain is required among individuals with more education to manifest mild dementia of the Alzheimer type (DAT) than in those with less education.

Catherine M. Roe, Ph.D., a research instructor in neurology, and her colleagues at Washington University in St. Louis used Pittsburgh Compound-B (PIB) PET imaging to test whether education and level of fibrillar brain Aβ interact to affect cognitive function in both nondemented individuals and those with DAT.

"We were really interested in the association between the amyloid uptake, their scores on these tests, and how education might mediate that," said Dr. Roe.

The data were obtained from participants in longitudinal studies conducted at Washington University's Alzheimer's disease research center.

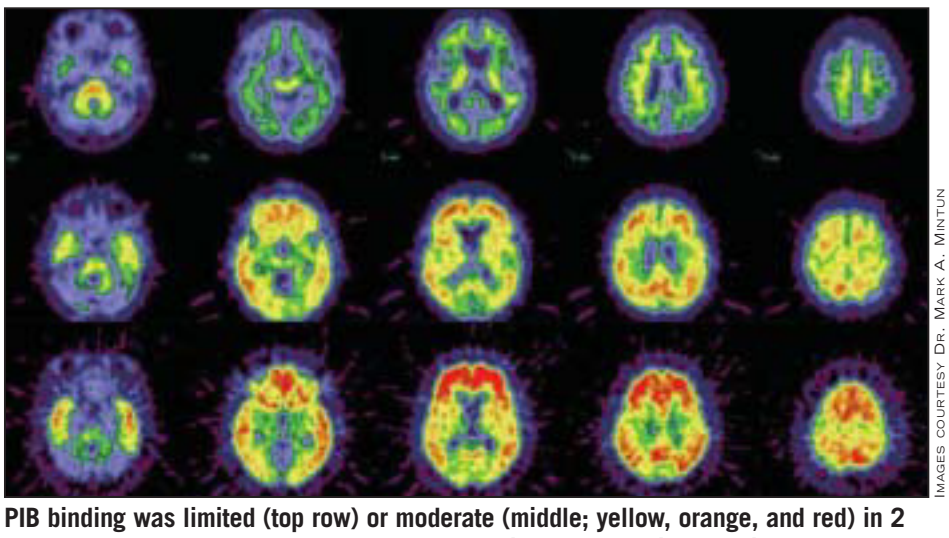
All of the participants underwent PET imaging using PIB, as well as anatomical T1-weighted MRI. Each participant's MRI was registered to a standard atlas target to minimize bias due to atrophy. PET images were aligned with the MR images. For the analysis, the cerebellum was chosen as the reference region because there is little specific PIB binding in this region, even in individuals with Alzheimer's.

Binding potentials (BPs) were calculated for each region of interest. "Binding potential is a number that is essentially proportional to the number of binding sites. It's a number that combines both the number of binding sites and the affinity of that particular molecule [in this case, Aβ] for the binding sites," said Dr. Mark A. Mintun, a professor of radiology, psychiatry, and bioengineering at Washington University, and also the director of the center for clinical imaging research there. Theoretically, BP should be very highly related to the amount of amyloid present.

Mean BP was calculated for the prefrontal cortex, gyrus rectus, lateral temporal cortex, and precuneus regions.

"These regions were chosen based on previous work that we've done, where we looked at patients who had a clinical diagnosis [of DAT] with very obvious amyloid plaques using PIB scans," said Dr. Mintun. For this study, "we looked at the four regions that we thought were the most clearly associated with Alzheimer's disease."

It's been hypothesized that amyloid plaques would show up first in those areas for individuals who were previously healthy.



Images courtesy Dr. Mark A. Mintun

PIB binding was limited (top row) or moderate (middle; yellow, orange, and red) in 2 nondemented women but was very pronounced in a woman with Alzheimer's (bottom).

Mean BPs from these regions were used to calculate mean cortical BP based on regions known to have high PIB uptake among patients with DAT. The participants were categorized based on their mean cortical BP.

In all, 198 participants were included: 161 who were cognitively normal and 37 with DAT. In all, 139 were determined to be PIB negative and 59 PIB positive. the participants were also categorized based on their level of education: high school or less; some college or college graduate; and post college. Among the PIB-negative group, 22 had a high school education or less, 69 had some college or had graduated from college, and 48 had postcollege education. In the PIB-positive group, 16 had a high school education or less, 29 had some college or had graduated from college, and 14 had postcollege education.

"What we found on the global tests is that the people who had little PIB uptake (the people who had few if any plaques at all) all scored very well and basically had no dementia. It was kind of a ceiling effect," said Dr. Roe.

In that group, scores on the tests were unrelated to education. "For the people who had high PIB uptake—more plaques in their brains—the scores were related to the amount of education that they had."

These findings lend support for the cognitive-reserve hypothesis because those with greater education maintained better global cognitive functioning in the presence of Aβ pathology.

—Kerri Wachter