# AD Prevention Initiative Could Lead to Large Trials

BY JANE SALODOF MACNEIL

SANTA FE, N.M. — A privately funded initiative is gearing up to do proof-of-concept prevention trials sooner rather than later in motivated volunteers who carry susceptibility genes for early Alzheimer's disease, but have not yet presented with cognitive impairment.

If any treatments can be shown to prevent precursor brain imaging and biomarker changes, the investigators plan to launch large clinical trials in people who have put their names into an Arizona Alzheimer's Consortium registry of potential participants.

Dr. Pierre N. Tariot announced the initiative at an annual psychiatric symposium sponsored by the University of Arizona. An advisory group of leading investigators will meet in Phoenix in October to set priorities in preparation for requesting a grant from the National Institutes of Health, he told attendees.

**Estrogen, antioxidants, omega-3 fatty acids, exercise, memantine, and other emerging therapies are among the interventions under consideration.**

"The Holy Grail is either to delay the onset of the illness or prevent it altogether," said Dr. Tariot, director of the Memory Disorders Center at Banner Alzheimer's Institute in Phoenix. "If we can delay the onset by 5 years we could cut the numbers in half. That is a huge impact. We think that is an achievable goal."

The general schema, as outlined by Dr. Tariot, is to genotype asymptomatic people who are in their early 40s and come from families with a history of early Alzheimer's disease. Those who screen positive for genes that predict they will develop dementia within the next decade could be invited to participate in one of a series of small placebo-controlled studies.

Within 2 years, the investigators expect to see whether an intervention can alter the course of changes leading to the disease. Rather than waiting years more to see whether the disease is prevented in these subjects, the project would start a clinical trial of a promising therapy in a larger population drawn from the registry at this point.

"The development work has already been done showing what happens to your brain with various types of imaging and biomarkers before you get the illness. … If I have an anti-amyloid therapy I am going to test it in 100 people—50 on drug and 50 on placebo. That is enough to answer the question of whether the trajectory is altered or not," Dr. Tariot said.

Estrogen, antioxidants, omega-3 fatty acids, exercise, memantine, and other "emerging experimental therapies" also are among the potential interventions under consideration for proof-of-concept studies. Therapies that failed in Alzheimer's intervention trials would not be ruled out, but they must be proven safe, Dr. Tariot said. Hormonal therapies, in particular, might be effective in preventing the disease, even if they cannot stop its progression.

"We think that right now there are roughly a dozen Alzheimer's prevention interventions that might work," he said.

Except for the publicly funded registry, the investigators are relying on private philanthropy to jump-start the initiative. Dr. Tariot was optimistic that the NIH will be receptive as the project matures, but noted that, despite unanimous enthusiasm for the concept, industry and government have been cautious thus far.

"It is so out of the box, we are not getting any funding," he said. "So we are actually using philanthropic dollars to launch this initiative. We think once we get going, the field will be changed forever."

Building an infrastructure for clinical trials is a priority for Dr. Tariot and his colleagues. Along with the research registry, this entails writing protocols for an administrative structure and a scientific and ethical review process, including data and safety monitoring boards that could be in place when the larger trials are funded and ready to start.

The Arizona Alzheimer's Consortium hosts the registry at its Web site, www.azalz.org. People willing to participate in clinical trials are invited to enroll if they are aged 50 or above, whether or not they have memory problems.

Based on their responses to a detailed questionnaire and their location in the state, volunteers are referred to research studies at one or more of the consortium's eight member institutions: Arizona State University, Banner Alzheimer's Institute, Barrow Neurological Institute, Mayo Clinic Arizona, Sun Health Research Institute, Translational Genomics Research Institute, Tucson VA, and the University of Arizona.

Efforts are underway to expand the registry, and thereby the pool of potential volunteers, to other Western states."There are so many therapies in development that the biggest threat to finding a way to put Alzheimer's disease behind us is not discovery any more. It is clinical trials," Dr. Tariot said.

He disclosed relationships, including consulting fees and research support, with about 24 companies engaged in Alzheimer's research, but emphasized that he has no investments to disclose and does not serve on any speakers bureaus. Banner Alzheimer's Institute is part of the nonprofit Banner Health System, and has the Banner Alzheimer's Foundation as a philanthropic resource. ■

# *Dimebon's Action May Challenge Amyloid Theory*

BY MICHELE G. SULLIVAN

VIENNA — Dimebon—the abandoned Russian antihistamine that burst onto the Alzheimer's study scene with the only positive clinical data of 2008—may throw yet another curve ball into a research world that for years has focused almost entirely on the amyloid hypothesis.

Rather than lowering amyloid beta (Abeta) levels, as two failed investigational drugs—tramiprosate and tarenflurbil—have attempted, dimebon appears to almost immediately increase them, raising Abeta by as much as 200% in three mouse models of Alzheimer's disease (AD), Dr. Samuel Gandy reported at the International Conference on Alzheimer's Disease.

While preliminary, the findings—combined with the nearly unprecedented cognitive benefit dimebon conferred in its phase II trial—could be enough to dethrone the long-reigning amyloid hypothesis, according to Mark A. Smith, Ph.D., an Alzheimer's researcher. "This drug is clearly not targeting amyloid, but increasing it acutely," said Dr. Smith of Case Western Reserve University, Cleveland. "If you believe the dogma, therefore, you should believe that this increase will cause Alzheimer's. These results question that dogma. If this holds up, it could be enough to wound the amyloid theory, potentially mortally."

Dimebon's 2008 phase II study found that patients with mild to moderate AD who took the drug for 12 months gained about 2 points on the Alzheimer's Disease Assessment Scale-Cognition (ADAS-cog), while those taking placebo declined almost 6 points from baseline (Lancet 2008;372:207-15). A 6-month open-label extension trial found similarly positive results. Patients who completed a full 18 months of dimebon continued to show benefit on ADAS-cog. Former placebo patients who crossed over to dimebon stabilized their cognitive decline.

Dr. Gandy of the Mount Sinai School of Medicine, New York, investigated the drug's effect on amyloid in three models of the disease: cultured nerve cells, isolated synaptic terminals, and brains from mice that overexpress human amyloid. "In every single system dimebon stimulated amyloid secretion," Dr. Gandy said in an interview. "The levels of the amyloid peptides in the interstitial brain fluid roughly doubled whenever the drug was given. If we think about the increased risk of Alzheimer's in Down syndrome patients who have a 50% increase in amyloid, this acute increase with dimebon could be significant over a period of many years of prescribed use."

Dr. Gandy noted that similar results were obtained by John Cirrito, Ph.D., and Dr. David Holtzman of Washington University, St. Louis, who collaborated with him in studying the brains of freely moving transgenic mice that overexpress human Abeta.

Dr. Gandy's suggested that this acute release may be followed by a chronic lowering of Abeta—something he is now investigating. Combined with dimebon's positive clinical data, this finding would imply that neurons benefit from dumping their intracellular amyloid load.

"This is reminiscent of the evidence suggesting that healthy nerve cells seem to release more amyloid," Dr. Gandy said, referring to another study from the Dr. Holtzman group, in which they reported that brain amyloid release increased as head-injured patients began to recover. "Why do happy, functioning neurons release more amyloid beta? The challenge now is how to reconcile that with research that is trying hard to develop medications to lower amyloid levels."

The clinical and lab data highlight the essential mystery of amyloid, both researchers said. "It all seemed so simple when we discovered genes that implicated amyloid," Dr. Gandy said. "It was all amyloid toxicity and that was the end of it. But the truth is, we still don't really know what amyloid does locally. It is clear to me that amyloid beta causes the rare genetic forms of Alzheimer's, but there remains the possibility that some injurious event [e.g., calcium dysregulation or oxidative injury] is both directly neurotoxic and pro-amyloidogenic. Gary Gibson, Ph.D., of Cornell University and I have seen this in an experimental oxidative stress model, and if something like this is the case in common forms of AD, then lowering amyloid won't be sufficient. Still, I don't think we'll know that until we succeed in purging the brain of amyloid oligomers at an early age and follow the natural history of the amyloid-free brain."

Some researchers, including Dr. Smith, have contended that amyloid is not the direct cause of AD, but a downstream product of some other dysfunction. The plaques themselves might be largely inert, or even be protecting the brain by binding and neutralizing neurotoxins.

"It could very well be that releasing Abeta is good, and that's why drugs that lower it are ineffective, or even damaging," Dr. Smith said. A wealth of recent data seems to support that idea: in the last 2 years, four antiamyloid agents have failed their phase III trials, and both active and passive immunotherapy studies have seen about a 10% rate of vasogenic brain edema associated with plaque dissolution.

"We have to face it," Dr. Smith said. "We don't know what amyloid is doing in the brain and just trying to get rid of it may not be a good thing."

Neither Dr. Gandy nor Dr. Smith had any relevant disclosures. ■