The Alzheimer's Pipeline

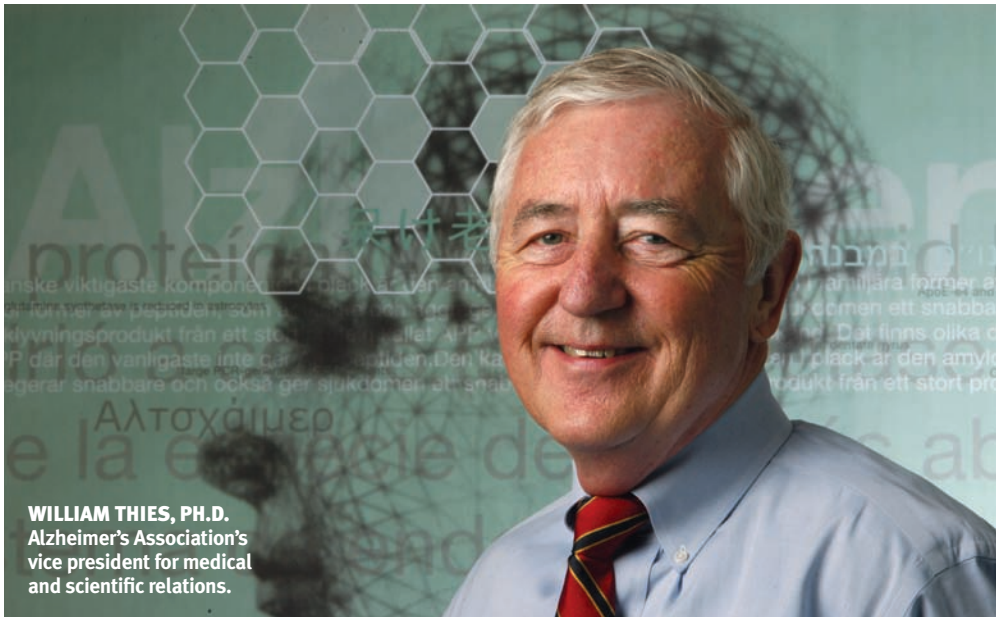
Scientists are optimistic about the slew of new treatments being tested.

BY PEGGY EASTMAN

Scientists are hopeful that new drugs to slow or even prevent Alzheimer's disease will be available soon. Alzheimer's—which causes memory loss and confusion by killing brain cells—affects more than 5 million Americans and is the fifth leading cause of death for Americans over age 65. People with the disease lose motor skills, which can lead to dangerous infections. For example, difficulty swallowing can cause patients to inhale food, resulting in pneumonia.

"We are clearly entering the era of disease-modifying treatments," says Michael W. Weiner, M.D., professor of radiology, medicine, psychiatry, and neurology at the University of California in San Francisco. "Within the near future, we hope to have a drug to slow Alzheimer's progression," he says. Coupled with early detection, these new therapies will improve the outlook for Alzheimer's patients, predicts Dr. Weiner.

William Thies, Ph.D., the Alzheimer's Association's vice president for medical and scientific relations, is also optimistic. "This is a very promising time because these drugs are being tested in *people*," says Dr. Thies.



WILLIAM THIES, PH.D.
Alzheimer's Association's vice president for medical and scientific relations.

PHOTO BY EILEEN RYAN

TARGETING AMYLOID BETA

According to the "amyloid hypothesis," Alzheimer's is caused by a brain protein called amyloid beta that forms sticky deposits in the brain. A number of investigational drugs are designed to block the protein: Bapineuzumab, for example, is a monoclonal antibody that seeks out and destroys amyloid beta. (Antibodies attack substances foreign to the body, called antigens; each antibody binds to and attacks one particular antigen.) Elan Pharmaceuticals and Wyeth Pharmaceuticals expect to release data in late July 2008 from a Phase II study of bapineuzumab in around 240 patients, and scientists are currently recruiting patients with mild to moderate Alzheimer's to participate in a Phase III multi-center study of the drug. Phase III is the last step before a company seeks Food and Drug Administration (FDA) approval.

Tramiprosate, an investigational anti-amyloid drug for mild to moderate Alzheimer's, was "fast-tracked" by the FDA last July, a process that speeds a drug through the trial phases if it has the potential to fill an unmet medical need for a life-threatening condition. However, results of a Phase III North American study of this drug fell short of expectations. Nevertheless, Paul Aisen, M.D., professor of neurology and medicine and director of the Memory Disorders Program at Georgetown University Medical Center in Washington, D.C., is confident the amyloid-blocking impetus behind the research is on the right course. "We believe the amyloid hypothesis is correct," he says.

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One way of preventing unwanted build-up of amyloid beta is to block gamma-secretase, an enzyme that helps create the protein. Eli Lilly and Company has a gamma-secretase blocker in development called LY450139, which the drug maker is studying in cooperation with researchers from the Alzheimer's Disease Cooperative Study. A Phase III clinical trial of this drug is being planned for later in 2008.

The fact that new drugs for Alzheimer's disease are entering Phase III trials is a "landmark" because so many new drugs fail at the Phase I or Phase II stage, says Samuel E. Gandy III, M.D., Ph.D., associate director of the Mt. Sinai Alzheimer's Disease Research Center in New York, NY. However, trials of promising new drugs are difficult and unpre-

dictable, especially for Alzheimer's. And there is a danger in pushing drugs through the pipeline too quickly. "Neurochem has changed its name to Bellus Health and announced plans to sell [tramiprosate] despite its failure," Dr. Gandy says. "The compound was proven ineffective and should either be tested in different situations or abandoned."

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OTHER RESEARCH FRONTS

New data from a Phase II, 12-month study on a novel drug called Dimebon, which blocks multiple targets within brain cells, is promising enough to proceed with the U.S. new-drug approval process in 2008, says Rachelle Doody, M.D., Ph.D., Effie Marie Cain professor in Alzheimer's disease research at Baylor College of Medicine's Department of Neurology and Alzheimer's Disease Center in Houston, TX.

Dimebon was available in Russia in the 1980s as an antihistamine, a drug that blocks the effects of a chemical— histamine—released during allergic reactions. Dr. Doody says 70 percent of 183 patients with mild to moderate Alzheimer's in an 11-center Russian study who stayed on Dimebon for a year showed improvement, such as an increased ability to cope with activities of daily living. Medivation, a California company, is now researching Dimebon for Alzheimer's.

Another approach to blocking brain-cell death in Alzheimer's patients is to give these cells an energy source other than glucose (sugar) to nourish them, says Lauren Costantini, Ph.D., vice president for clinical development at Accera, Inc. On brain-imaging (PET) scans, doctors can see that the brain cells of Alzheimer's patients are unable to metabolize glucose. Dr. Costantini is studying a new investigational drug, AC-1202, which is taken every morning in beverage form and is converted to substances normally found in the body called ketone bodies that can be metabolized by brain cells even when they cannot metabolize glucose.

WANTED: ALZHEIMER'S VACCINE

A safe, effective Alzheimer's vaccine against amyloid beta would be a long-term fix. One promising vaccine, AN1792—a synthetic form of the amyloid protein and a cooperative effort of Elan and Wyeth—had a setback in its first clinical trial, which had to be stopped because about six percent of participants developed brain inflammation.

The encouraging news is that the 59 participants who developed antibodies to amyloid beta (showing that their bodies mounted an immune response) continued to show lower but persistently elevated levels of these antibodies in a follow-up study four and a half years later, says Michael Grundman, M.D., M.P.H., vice president of clinical development in the Alzheimer's disease program at Elan.

The vaccine responders were less dependent on their caregivers after four and a half years and tended to show less memory decline. The follow-up study included 129 patients who took the vaccine, 25 of whom mounted an immune response to amyloid beta. There were no more cases of brain inflammation. In patients who died after the study was finished, autopsies showed a reduced build-up of amyloid beta in their brains, Dr. Grundman notes. What the vaccine studies seem to point to is that amyloid beta may be an important culprit and worthwhile target for treatment studies.

Still, questions of safety linger. "A vaccine may be the best long-term solution, but safety concerns are paramount," cautions James Mortimer, Ph.D., professor of epidemiology and biostatistics at the University of South Florida in Tampa, FL, and co-principal investigator of the Nun Study, a long-term study of Alzheimer's disease in elderly nuns.

According to Dr. Gandy, the variable response to the vaccine is not surprising, because there is variability in people's immune systems—especially as they age. This is why not all elderly people given influenza shots respond, Dr. Gandy says.

If a vaccine proves to be beyond reach, there may be other ways of combating amyloid beta, such as by stimulating the body's immune system to react against it. Several studies presented at the American Academy of Neurology meeting in April 2008 looked at intravenous immunoglobulin (IVIg), a substance containing antibodies against amyloid beta, as an Alzheimer's treatment. "We need to know whether in the course of aging, these antibodies are overwhelmed by the toxic forms of amyloid beta," says Norman A. Relkin, Ph.D., M.D., associate professor of clinical neurology and neuroscience and director of the Memory Disorders Program at Weill Cornell Medical College in New York, NY.

It is important, says Dr. Thies, to confirm that amyloid beta is the right target in Alzheimer's. If so, researchers can intensify their efforts in their attack on the protein, and if not, they can then refocus their work on other areas. NN

Peggy Eastman is an award-winning medical writer whose work has appeared in many publications, including SELF, AARP Bulletin, *and* Washingtonian.

For more information on clinical trials in Alzheimer's and other diseases, see RESOURCE CENTRAL on page 37