

**International Conference
on Alzheimer's Disease:**

**Highlights
of Research Findings**

Introduction

Does one protein mechanism underlie the development of plaques and tangles? Which risk factors most accurately predict the development of dementia? How does the communication style of caregivers affect the quality of life of individuals with Alzheimer's disease (AD)? The Alzheimer's Association 2008 International Conference on Alzheimer's Disease (ICAD), held July 26–31 in Chicago, sought to answer these and other questions in diverse areas ranging from drug trials to genetics, neuroimaging, diagnosis and social and behavioral issues in AD and other forms of dementia.

Historically the world's largest gathering of AD and dementia researchers, ICAD 2008 broke previous attendance records, drawing more than 5,400 attendees to more than 2,000 plenary, symposium, oral and poster presentations. The conference attracted media attention both in the United States and abroad, with coverage by outlets including ABC, the BBC, CBS, CNN, NBC, the Associated Press, Reuters, The Wall Street Journal and USA Today.

Opening the conference, Alzheimer's Association President and CEO Harry Johns thanked the attendees for the work they do every day to unlock the mysteries of dementia and shared some of the Association's strategic goals, including "raising Alzheimer's from a disease to a cause that is embraced worldwide," increasing financial support to researchers, and enhancing advocacy efforts to heighten awareness of the epidemic of AD. The disease and other dementias cost the United States more than \$148 billion annually in Medicaid and Medicare services and in indirect costs to businesses that employ AD and dementia caregivers.

According to one study, providing care for the estimated 29.3 million people worldwide with AD cost \$315 billion in 2005.

To accelerate the pace of research and the sharing of research advances, Johns announced that the usually biannual ICAD will be held annually. The 2009 meeting will take place July 11–16 in Vienna, Austria.

Disease mechanisms and therapeutic strategies

Researchers' and clinicians' keen interest in the development of drugs that will slow or stop the progression of AD was especially evident on the second day of the event, when a symposium on disease-modifying drugs drew a full house. The symposium featured six speakers who reflected the global focus on disease modification. The speakers and their topics were Bruno Vellas, M.D., Ph.D., of Purpan-Casselardit Hospital in Toulouse, France (Recommendations and Outcomes of Disease-Modifying Drugs); Eric Siemers, M.D., of Ely Lilly and Company in Indianapolis, Indiana, United States (Disease Modification: Will We Know It When We See it?); Yasuo Ihara, M.D., University of Tokyo, Japan (Why a Beta-Amyloid Vaccine?); Colin Masters, M.D., Ph.D., of the Mental Health Research Institute, University of Melbourne, Parkville, Australia (Rational Therapeutic Strategies for Modifying AD: Beta-Amyloid Oligomers as Validated Targets); Roger Nitsch, M.D., of the University of Zurich, Switzerland (Beta-Amyloid Immunotherapy in AD); and Bengt Winblad, M.D., Ph.D., of the Karolinska Institutet, Stockholm, Sweden (Safety, Tolerability and Immunogenicity of the Beta-Amyloid Immunotherapeutic Vaccine CAD106 in a First-in-Man Study in AD Patients).

ICAD 2008 gave attendees insight into the broad range of drugs in clinical trials. They incorporate an array of approaches to impact biological processes associated with AD. “The overarching message is how robust the pipeline is,” said speaker Sam Gandy, M.D., Ph.D., of the Mount Sinai School of Medicine in New York, New York, United States. “Research is moving on all fronts and in unexpected directions.”

- A six-month open-label extension trial of Dimebon produced results similar to those in the preceding 12-month clinical trial. Patients with mild-to-moderate AD who had earlier received the drug for 12 months had preservation of function close to their starting baseline on key signs and symptoms of AD. Patients originally on placebo who received Dimebon in the extension study showed stabilization across all key measures studied. Originally developed in Russia as an antihistamine, Dimebon improves the function of mitochondria, the central energy source of cells. Recruitment for a Phase III study has begun.
- Treatment with intravenous immunoglobulin (IVIg) over nine months resulted in statistically significant improvements on both cognitive and global clinical measures in a Phase II trial of individuals with mild-to-moderate AD. On the market for more than 25 years as a treatment for autoimmune diseases, IVIg contains antibodies that bind to the beta-amyloid aggregates thought to be central to AD. A Phase III clinical trial is under way.
- A 24-week, Phase II trial of methylthioninium chloride (MTC) followed by a 60-week extension trial found that at 24 weeks MTC produced a significant improvement relative to placebo. The compound stabilized the progression

of AD over 50 weeks in both mild and moderate AD. MTC, which dates from the 1930s, inhibits the aggregation of tau, the protein that forms the neurofibrillary tangles of AD. Among its earlier uses, it was used as an antibiotic. A Phase III trial is planned.

Paul Aisen, M.D., of the University of California, San Diego, United States, discussed the significant challenges facing those who conduct clinical trials. Among the challenges is the slow decline of placebo groups in clinical trials. For a drug to show that it stops or slows the progression of AD, the group that receives a placebo must fare worse. This requires longer trials lasting at least 18 months, because that’s how long the placebo group needs to show a decline. Phase III clinical trials, which can cost \$200–\$300 million, still carry a high risk of failure because of the potential of larger sample sizes and longer trial durations to produce results different from smaller, shorter Phase II trials. Strategies to employ in Phase II trials to decrease the risk of Phase III trials include aiming for “hints of clinical efficacy” and showing proof of the drug’s mechanism of action through biomarker studies.

The physical changes to the brain in AD begin years before clinical symptoms such as memory loss develop. Disease-modifying drugs will likely be most effective before individuals develop clinical symptoms. A significant task before the research community is showing that impacting putative biomarkers of AD, such as levels of beta-amyloid in cerebrospinal fluid (CSF) and patterns of brain loss seen on imaging tests such as magnetic resonance imaging (MRI), results in cognitive benefit in the clinical setting. Doing so could elevate biomarkers to the status of surrogates for AD in the eyes of regulatory agencies that establish the requirements

for clinical trials. This would enable researchers to set biomarker changes as evidence of a clinical trial's success.

“There is a movement to identify the disease earlier and earlier, and we need presymptomatic biomarkers to do this,” said speaker Ronald Petersen, M.D., of the Mayo Clinic, Rochester, Minnesota, United States. “A consistent theme has emerged of early detection for early intervention.”

Biomarkers

Biomarkers have been an area of intense focus by researchers. Identifying biomarkers could lead to the development of simple tests such as blood tests that would be easy to use in the clinical setting and more readily accepted by the public than more complicated tests. Neuroimaging, which is able to detect changes as small as one millimeter in the structure of the brain, can show both the degree of brain loss at any given time as well as the rate of loss of brain volume over time. Some presenters believe rate of brain loss may be more important than brain volume alone in the early detection of AD and other dementias.

- Researchers reported that levels of CD-69, a protein involved in white blood cell growth and production, were more than 80 percent accurate in distinguishing those with AD from those who were cognitively normal and more than 90 percent accurate in distinguishing individuals with AD from individuals with Parkinson's dementia. Healthy brain cells do not undergo the process of division and replication (the cell cycle) that is common to other cells in the body. In AD, however, brain cells may prepare to re-enter this

cell cycle, which may increase the likelihood of cell death. The same cell cycle defect is found in the white blood cells of people with AD.

- According to researchers, computer analysis of MRI scans can accurately capture the severity of AD-related neurofibrillary tangles. The analysis is used to establish a score on the new Structural Abnormality Index (STAND). A STAND score is assigned by comparing the degree of atrophy in an individual's brain with atrophy patterns of 160 individuals with AD and 160 cognitively normal persons. Researchers recorded STAND scores for 101 individuals before death and compared them with scores from postmortem BRAAK staging, the “gold standard” for assessing tangle severity. The STAND scores were 90 percent accurate in distinguishing MRI scans of individuals with AD from cognitively normal individuals.

Risk factors and prevention

Beginning in the mid-1990s, large epidemiologic studies were undertaken to identify factors that contribute to brain health as well as to cognitive decline. These studies had consistent findings, showing that factors such as physical and mental inactivity were associated with higher risk of cognitive decline. However, these studies were conducted with individuals in late life and lasted for only a few years. More recent studies provide data from individuals beginning at mid-life and ending in late-life.

- Using risk factor information from a pooled European database of more than 16,000 nondemented individuals over age 55 and

conducting follow-up studies up to 15 years later, researchers determined the risk factors with greatest accuracy of predicting dementia. In order, the most predictive variables were impairment in executive function (planning), memory problems as measured on tests, subjective memory or cognitive complaints, apolipoprotein e-4 genotype, use of psychotropic medication, severe head trauma, diabetes, stroke and language difficulties.

- A study of 422 healthy elderly persons over age 60 showed that those with metabolic syndrome had an almost 35 percent higher level of cognitive compromise than those without metabolic syndrome, a group of heart disease risk factors that includes abdominal obesity, high blood pressure, high triglycerides, high blood sugar and low HDL cholesterol. Researchers used a battery of scales to assess cognition, depression, planning abilities and activities of daily living. Individuals with metabolic syndrome had significantly lower scores on all neurofunctional tests, reinforcing the importance of good physical health in reducing one's risk for cognitive decline.
- “Elderspeak,” defined as overly caring, controlling and infantilizing communication, by caregivers increases resistance to care by nursing home residents with dementia, said researchers. Individuals with dementia were more likely to cooperate with care activities such as bathing and dressing if normal adult communication was used. The probability of resistance to care was .55 with elderspeak and .26 with normal communication.
- As AD progresses, individuals have increasing difficulties with communication. These difficulties are related to cognitive changes such as impaired word finding, shortened attention span and impaired memory. A study from the University of California at Los Angeles found that healthy family members' responses to unanticipated comments from individuals with AD followed predictable patterns. When a response disrupted the flow of conversation, healthy family members often continued to speak as if the person with AD had not spoken or tended to pause, indicating they had heard the comment, but did not respond verbally. Such responses frame the individual with AD as a nonparticipant in the conversation. The results of the study will be used to develop training programs to facilitate conversation among all family members.

Communication style and quality of life

The quality of life of individuals with AD and other dementias is affected by numerous factors. Some factors are well known, such as the importance of the individual continuing to engage in enjoyable activities and creating a safe physical environment for the individual. Less well known is the effect of caregiver communication style on quality of life. However, researchers have discovered that the impact is significant.