




alzheimer's association guides global research efforts

In 2008, the Alzheimer's Association continued to demonstrate its global leadership in nurturing Alzheimer's disease research.



This position was solidified by record-breaking attendance at ICAD 2008, as well as the funding in 2008 of more than \$26 million in research initiatives—the largest in the Association's 26-year history—to researchers in 15 countries. The Association's leadership role in advancing the World Wide Alzheimer's Disease Neuroimaging Initiative (WW-ADNI) also underscores the Association's global impact, as does the increasing visibility of the Alzheimer's Association Research Roundtable. The Roundtable is a unique forum for information sharing among members of the pharmaceutical industry in the United States and abroad, academia, the National Institutes of Health and U.S. and European regulatory agencies.

These accomplishments were made possible by the commitment of many. Among them were members from the Alzheimer's disease scientific community who participate in the Association's numerous science activities, many on a volunteer basis. These accomplishments also were made possible by leaders of organizations across the continents who share the Association's vision of a world without Alzheimer's and with whom the Association has formed essential collaborations. Last but not least, these accomplishments would not have been possible without the individuals from all walks of life who have been touched by Alzheimer's disease and have taken action through financial support of research to help ensure that Alzheimer's does not exact its grave toll on future generations.

ICAD

Historically the world's largest gathering of Alzheimer and dementia researchers, ICAD 2008 broke previous records, drawing more than 5,400 attendees to 2,000-plus plenary, symposium, oral and poster presentations. The conference attracted news 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*.

Held July 26–31 in Chicago, ICAD 2008 provided a platform for discussion of diverse areas of research, including clinical trial design, genetic factors in Alzheimer's, biomarkers as tools for early detection and social and behavioral issues in dementia.

Opening the conference, Alzheimer's Association President and CEO Harry Johns state that "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 Alzheimer's are primary strategic goals of the Association. To accelerate the pace of research and the sharing of research advances, Johns announced that the previously biannual ICAD will be held annually, with ICAD 2009 taking place July 11–16 in Vienna, Austria, and ICAD 2010, July 10–15, in Honolulu, Hawaii.

ICAD 2008 gave attendees insight into the numerous drugs in clinical trials, which incorporated an array of approaches to impact the biological processes associated with Alzheimer's. "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 and immediate past chair of the Association's Medical and Scientific Advisory Council. "Research is moving on all fronts and in unexpected directions."

The research presented included data from a six-month open-label extension trial of Dimebon showing that the drug produced results similar to those in the preceding 12-month clinical trial. Patients with

mild-to-moderate Alzheimer's who had earlier received the drug for 12 months had preservation of function close to their starting baseline on key signs and symptoms of the disease. Patients originally on placebo who received Dimebon in the extension trial showed stabilization across all key measures studied. Dimebon improves the function of mitochondria, the central energy source of cells.

Also presented were data from a study of intravenous immunoglobulin (IVIg), which resulted in statistically significant improvement in cognitive function in a Phase II trial of individuals with mild-to-moderate Alzheimer's disease. 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 the development of Alzheimer's.

Identifying Alzheimer biomarkers

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ICAD speakers also shared results of a study of methylthioninium chloride (MTC; Rember[®]) showing that the compound stabilized the progression of Alzheimer's over 50 weeks in both mild and moderate forms of the disease. MTC inhibits the aggregation of tau, the protein that forms the neurofibrillary tangles associated with Alzheimer's.

Biomarkers are an area of intense focus by researchers. Studies are under way to prove the accuracy of biomarkers in measuring the physical changes in the brain associated with Alzheimer's and tracking the progression of the disease. Identifying Alzheimer biomarkers could lead to the development of simple diagnostic tests that would be easily used in physicians' offices.

International Research Grant Program

In 2008, the Alzheimer's Association International Research Grant Program funded more than \$26 million in research initiatives, the largest annual amount in the Association's 26-year history of funding Alzheimer research. Providing more funding for Alzheimer research than any other private, nonprofit organization, the Association committed in excess of \$250 million to 1,700-plus best-of-field grant proposals between 1982 and 2008. The \$26 million includes more than \$25.4 million in five grant categories to 131 individual investigators from 15 countries and 26 U.S. states.

The Alzheimer's Association grant program supports researchers at every stage of their careers. New Investigator Research Grants provide the next generation of scientists with funding that enables them to gather preliminary data, test procedures, and develop hypotheses. Investigator-Initiated Research Grants fund established scientists exploring questions across the research spectrum, from basic neurobiology and genetic risk factors to evidence-based care and disease-modifying treatments designed to slow or stop the progression of Alzheimer's. Providing \$450,000 in research funding over three years, the Zenith Fellows Awards support senior scientists who have made significant contributions to the field and continue to pursue promising lines of investigation about disease mechanisms, diagnosis, novel treatments and quality care.

The Association grant program also funds the Senator Mark Hatfield Award in Clinical Research and the Everyday Technologies for Alzheimer Care (ETAC) Grants. Awarded in partnership with Intel Corp., ETAC grants fund research exploring how computers, monitoring devices and other electronics can be used to meet the day-to-day needs of individuals with Alzheimer's as well as their caregivers.

In 2008, the Alzheimer's Association also helped fund the Australian ADNI (A-ADNI), which aims to bring key Australian imaging and biomarker studies in line with ADNI protocols. If successful, A-ADNI will greatly expand the pool of ADNI data and samples available to researchers. Funding also was given to provide an additional year of support to the ADNI Genotyping Project. This research studies the amounts of tau and beta-amyloid in the CSF of individuals who are cognitively normal, individuals with MCI and individuals with Alzheimer's. Documenting changes in CSF concentrations over time will help establish the potential role of these biomarkers in early detection.

In addition, the Association contributed \$100,000 toward the establishment of the Tomorrow's Leaders in Alzheimer's Disease Research Award, co-sponsored by the Cure Alzheimer's Fund and Lou Ruvo Brain Institute. This award recognizes outstanding new M.D. or Ph.D. investigators who have made pivotal contributions to early detection, treatment and prevention of Alzheimer's disease.

WW-ADNI

The Alzheimer's Association leads the WW-ADNI effort, which complements the efforts of ADNI. ADNI is a \$60 million, 5-year, public-private partnership to test whether imaging technologies (such as MRI and PET), other biomarkers, and clinical and neuropsychological assessment can be combined to measure progression toward Alzheimer's. ADNI is the first study to examine a number of candidate Alzheimer's biomarkers in the same individuals. The study is expected to be a landmark for identifying Alzheimer's biomarkers, with data widely available to researchers. ADNI is primarily funded by National Institute on Aging, part of the National Institutes of Health (NIH), with private sector support through the Foundation for NIH. The Alzheimer's Association is an ADNI sponsor.

The goal of WW-ADNI is to establish standardized methods across the globe for testing neuroimaging and fluid biomarker tools such as MRI and PET scans and CSF assays. These standardized methods will enable biomarker data obtained at sites worldwide to be pooled, analyzed and used by researchers without concern for the inter-site variability of biomarker data that has played a role in the failure of some clinical trials.

In this role, the Association coordinates WW-ADNI efforts, seeks funding for the continuation and

expansion of WW-ADNI and provides support for WW-ADNI partners. It also ensures the steady flow of information among principal investigators conducting WW-ADNI research and facilitates communication between the research community and pharmaceutical companies. By serving as a liaison for the exchange of information between researchers and pharmaceutical companies, the Association plays a critical role in accelerating the pace of clinical trials. When pharmaceutical companies are ready to begin a clinical trial, they can draw upon the information gleaned from Association-led communication activities to identify which researchers have the tools and expertise to lead those trials.

WW-ADNI comprises the North American ADNI (57 sites), European Union ADNI (EU-ADNI, seven operational sites), Japanese ADNI (J-ADNI, 36 active sites) and A-ADNI (two active sites). Specific Association-sponsored WW-ADNI initiatives include financial support for the establishment of EU-ADNI and for activities to ensure integration of A-ADNI data into the North American ADNI database. The Association also fostered discussions to ensure that J-ADNI is carried out in a way that is fully compatible with the North American ADNI and is playing a visible role in cultivating sites for the potential development of ADNI sites in China.

Research Roundtable

The mission of the Research Roundtable is to facilitate the development and implementation of new treatments for Alzheimer's disease by uniting researchers with diverse affiliations to collectively address issues and obstacles related to Alzheimer research. Begun in 2003 with four sponsors, the Research Roundtable is an undeniable success story. The consortium now includes more than 20 corporate sponsors from the pharmaceutical, biotech, imaging

and cognitive testing industries. Each sponsor sends several senior scientists to the Roundtable to benefit from the collegial interactions and networking opportunities available at this unique forum. Additional attendees include scientists from academia; regulatory agencies such as the U.S. Food and Drug Administration and its European equivalent, the European Medicines Agency; and the National Institutes of Health.

The spring 2008 Research Roundtable, held April 29–30, in Washington, D.C., addressed the use of scales as outcomes measures of Alzheimer's disease clinical trials. Bringing focus to the meeting, William H. Thies, Ph.D., Alzheimer's Association chief medical and scientific officer, remarked, "Without scales, how do we tell if drugs are doing any good? And how do we know what the outcome measures of scales mean in patients' everyday lives?" Added Roundtable co-chair Ronald Black, M.D., senior director of clinical research at the pharmaceutical company Wyeth, "Measurement is at the core of clinical trials. If you care about clinical trials, you care about scales."

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Topics at the Roundtable meeting included existing scales and scale development, measures sensitive to change in early Alzheimer's, computerized measures, and measures useful for early-phase trials. When disease-modifying medications become available, scales will play a key role in identifying patients who might benefit from these medications as well as assessing their effectiveness.

Researchers returned to Washington October 20–21 to share "lessons learned" in designing clinical trials of disease-modifying drugs. Attendees also heard about the role of biomarkers in clinical trials and about trial design strategies employed in studies under way.

Keynote speaker Richard Mohs, Ph.D., of pharmaceutical company Eli Lilly & Company reflected on a Roundtable meeting he led in 2005 that addressed optimal trial design for disease-modifying drugs for

Alzheimer's. "In 2005, looking at fields such as multiple sclerosis and rheumatoid arthritis, the lessons learned were that for each condition, multiple therapies were on the market; biomarkers were used in the diagnostic process, each in different ways; and there were many potential paths for new drugs," he said. "Since then the science underneath Alzheimer's has advanced to show potential underlying drivers of Alzheimer's.... And we have candidate drugs we can test because of this basic science knowledge. Compared with 2005, we now have better tools to measure the pathogenesis of Alzheimer's."

These tools include biomarkers such as brain volume and rate of change of brain volume over time; measurements of glucose metabolism and beta-amyloid plaques and other beta-amyloid aggregates in the brain; and levels of beta-amyloid, tau and phosphorylated tau in CSF. With these and other biomarkers, said Dr. Mohs, "It is incumbent upon us to pick the ones that will be most informative in clinical trials."

The complexity of Alzheimer's, he added, is that unlike clinical trials that led to the development of disease-modifying statin drugs for heart disease, Alzheimer drugs aimed at disease modification do not have a discrete set of outcomes (such as low-density lipoprotein level in heart disease), but a continuum of outcomes because Alzheimer's disease progresses on a continuum.

Lessons learned about clinical trial design were shared by scientists involved in the testing of such high-profile drugs as Alzhemed® and Flurizan®, which ultimately were not successful in meeting their desired outcomes, as well as other drugs, including huperzine A, phenserine, LY450139 and bapineuzumab.

Other Initiatives

In 2008, the Alzheimer's Association's role in advancing Alzheimer science was also evident by the success of its bimonthly, peer-reviewed journal, *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*; new professional society, the Alzheimer's Association International Society to Advance Alzheimer Research and Treatment; and Clinical Studies Initiative.

Alzheimer's & Dementia: The Journal of the Alzheimer's Association

In July 2008, publishing company Elsevier announced that *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* (www.alzheimersanddementia.org) had been selected for inclusion in MEDLINE. MEDLINE is the bibliographic database of the National Library of Medicine, containing more than 16 million journal article citations, with a concentration on biomedicine. MEDLINE is a key information source for biomedical researchers.

"The entire editorial board and I are extremely pleased that *Alzheimer's & Dementia* is being added to the MEDLINE journal collection so soon after its launch in 2005," *Alzheimer's & Dementia* Editor Zaven Khachaturian, Ph.D., commented. "Inclusion in this prominent database signals recognition of the journal's scientific merit and contribution to the field of Alzheimer's research. More importantly, MEDLINE indexing will help researchers and other interested parties worldwide locate articles published in *Alzheimer's & Dementia*."

As the official journal of the Alzheimer's Association, *Alzheimer's & Dementia* is circulated to the members of the Association's International Society to Advance Alzheimer Research and Treatment, as well as other subscribers and libraries. *Alzheimer's & Dementia* addresses challenges facing researchers, clinicians and health policymakers and features breakthrough research and new thinking across diverse areas of investigation. The interdisciplinary journal provides the impetus for new scientific initiatives and offers probing, thought-provoking studies, articles, and reviews from the leading minds in the field.

Alzheimer's Association International Society to Advance Alzheimer Research and Treatment (ISTAART)

Bringing together researchers and clinicians from a broad range of fields to accelerate progress in Alzheimer's and other dementia research is the mission of ISTAART, which was launched in January 2008.

ISTAART provides a forum for the sharing of cutting edge research advances from diverse disciplines. The society welcomes members from fields including biochemistry, genetics, geriatrics, molecular and cell biology, neurology, neuroscience, pathology, pharmacology, psychiatry, psychology, radiology and the social sciences.

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Steven T. DeKosky, M.D., dean of the University of Virginia School of Medicine and former director of the Alzheimer's Disease Research Center at the University of Pittsburgh, chairs ISTAART's Executive Advisory Committee. Says Dr. DeKosky, "Over the past 20 years, Alzheimer researchers and the Alzheimer's Association have worked together to advance research in the disease, provide information for dissemination to the public and inform Congress and the press about the disease and its implications for social, economic and personal well-being. Now the Alzheimer's Association has initiated ISTAART, an organization of and for Alzheimer researchers, to foster research in the disease and facilitate interaction among researchers. It is our hope that ISTAART will enable convenient and productive collaborations among members and speed progress in defeating Alzheimer's."

By year's end, ISTAART had nearly 1,000 members.

Clinical Studies Initiative

The pilot program of the Alzheimer's Association Clinical Studies Initiative was launched in April 2007 to address daunting facts. Among them were statistics indicating that of the more than 9,000 interventional studies under way in the United States, 80 percent were delayed because of enrollment shortfalls. The challenge of recruiting and retaining study participants has become a significant impediment to developing next-generation drugs.

The Clinical Studies Initiative was formed to find effective ways to mobilize and motivate study participants in an effort to accelerate clinical research. Recruitment strategies were tested with the assistance of Association chapters headquartered in five pilot cities: Atlanta, Georgia; Indianapolis, Indiana; Providence, Rhode Island; San Francisco, California; and Tulsa, Oklahoma.

After completion of the pilot program, 38 percent of respondents at pilot sites reported that calls about participation in Alzheimer clinical studies had increased, while respondents at non-pilot sites said it remained the same (71 percent) or decreased (21 percent). In addition, 54 percent of respondents at pilot sites said the number of individuals screened for Alzheimer clinical studies had increased, while 57 percent of respondents at non-pilot sites said it had decreased.

With these successes as a springboard, in 2008 the Association announced the expansion of the Clinical Studies Initiative to 10 chapters headquartered in the following locations: Phoenix, Arizona; San Diego, California; Chicago, Illinois; Timonium, Maryland; Watertown, Massachusetts; Portland, Oregon; Philadelphia, Pennsylvania; Fairfax, Virginia; and Seattle, Washington.