



research highlights: among many research advances, early detection and biomarkers gain focus

Advances in wide-ranging areas of Alzheimer science were made in 2008, from a more complete picture of the cellular and molecular events leading to Alzheimer's to a better understanding of the influence of genetic and lifestyle factors on disease development and progression.

From among these many diverse lines of investigation, especially strong themes emerged in two related areas: the importance of early detection, including diagnosis of Alzheimer's disease before the development of symptoms, and the critical role biomarker studies will play in identifying individuals for future clinical trials. Researchers are looking to results from such efforts as the Alzheimer's Disease Neuroimaging Initiative (ADNI) II to help them identify individuals without symptoms who are at high risk of developing Alzheimer's and could be enrolled in clinical trials of drugs designed to slow or stop the progression of the disease.

These themes were discussed in an open forum at the Alzheimer's Association 2008 International Conference on Alzheimer's Disease (ICAD). Acknowledging these themes, ICAD speaker and Alzheimer's Association Medical and Scientific Advisory Council Chair Ronald Petersen, M.D., of the Mayo Clinic, remarked, "There is a movement to identify the disease earlier and earlier, and we need presymptomatic biomarkers to do this. A consistent theme has emerged of early detection for early intervention."

Several exciting discoveries in 2008 reflect these themes.



Strides in Early Detection of Alzheimer's Disease

Among the discoveries in 2008 that pointed researchers toward paths to early detection of Alzheimer's disease were those involving the imaging tool positron emission tomography (PET). A high-profile study confirmed that Pittsburgh Compound-B (PIB) binds to the telltale beta-amyloid deposits in the brains of those with Alzheimer's. PIB, combined with PET imaging, provides researchers with a tool to identify the location and distribution of beta-amyloid deposits. This is a significant step toward enabling clinicians to provide a definitive diagnosis of Alzheimer's disease in living individuals. A definitive diagnosis is now only possible after death, when brain tissue can be examined for the beta-amyloid plaques and tau tangles that are hallmarks of the disease.

PIB isn't the only compound researchers used with PET to shed light on Alzheimer's. PET combined with the radiotracer fluorodeoxyglucose (FDG) enabled researchers in another study to classify different types of dementia with a very high success rate. PET-FDG enables researchers to measure glucose metabolism in the brain. Because glucose metabolism in the brain is decreased in Alzheimer's disease, FDG-PET may prove a useful tool for diagnosing Alzheimer's in its earliest stages.

Magnetic resonance imaging (MRI) is well recognized as an instrument for research and diagnosis in many fields of medicine, and research in 2008 showed that it may be useful in Alzheimer's as well. For example, scientists found that an automated system for measuring the volume of the hippocampus using MRI can help doctors more accurately diagnose Alzheimer's at an earlier stage. The hippocampus is a region of the brain that plays a key role in memory and learning. In addition, a functional MRI (fMRI) study showed how two regions of the brain prominently affected by Alzheimer's—the hippocampus and medial parietal lobes—cooperate to form new memories and gave researchers insight into what goes wrong during age-related memory changes.

MRI also helped researchers identify abnormal structural changes in the brains of seemingly normal elderly individuals that aided detection of mild cognitive impairment, a potential precursor to

Alzheimer's disease. In addition, researchers found that MRI scans that detect shrinkage in specific regions of the mid-brain accurately diagnosed neurodegenerative disease such as Alzheimer's even before symptoms interfere with memory.

Meanwhile, researchers at the Mayo Clinic found that multiple imaging methods, including MRI, magnetic resonance imaging spectroscopy and PET-PIB, each provide valuable information about cognitive function. Using these imaging methods together allowed physicians to better predict an individual's likelihood of developing Alzheimer's disease.

Cerebrospinal fluid (CSF) assays are another tool with the potential to reveal biomarkers of Alzheimer's that could be used for early detection of the disease. For example, researchers showed that the ratio of a protein called beta-amyloid 1-42 to another protein, beta-amyloid 1-40, was reduced in the CSF of individuals who carried the gene for familial Alzheimer's disease and that levels of two other proteins, t-tau and p-tau181, were elevated before overt symptoms appeared.

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Researchers from around the world gathered in July at ICAD 2008 to share advances in areas including early detection and biomarkers. Among the advances discussed were results of a study showing that differences in levels of CD-69, a protein involved in white blood cell growth and production, distinguish between people with Alzheimer's, people with Parkinson's-related dementia and those who were cognitively normal. In other biomarker research, a study confirmed previous findings: the more beta-amyloid 1-42 in the brain (as measured by PET scans), the less beta-amyloid 1-42 in CSF.

Additional study results showed that CSF levels of apolipoprotein E (APOE), a protein involved in the

transfer of fatty substances between brain cells, are highly correlated with the levels of proteins known to be involved in the development of Alzheimer's disease: amyloid precursor protein (APP) and tau. Regulation of APOE levels may affect the levels of APP and tau in the brain.

The scientific community is conducting research to validate these PET, MRI, CSF and other biomarker data. Validated biomarkers will play a key role in identifying individuals in the earliest stages of

Alzheimer's. With this knowledge, individuals are empowered to take action, such as participating in a clinical trial of drugs aimed at slowing or stopping the progression of Alzheimer's or modifying diet, exercise and other lifestyle factors to improve brain health.

Scientific discoveries in Alzheimer research in 2008 also shed light on a number of other areas of research focus that promise to influence how Alzheimer's disease is viewed in the years to come.

New Biological and Genetic Risk Factors Uncovered

A vast amount of research in 2008 examined why a person may develop Alzheimer's disease. Scientists studied factors ranging from levels of vitamins and protein in blood to genetic factors.

Results of one study suggested that low levels of folate, a B vitamin, can triple the risk of developing dementia in older people, while other scientists found that a decrease in the blood protein cystatin C in men ages 70–77 was associated with a 29 percent increased risk of developing Alzheimer's. Studies examining the ability of blood levels of beta-amyloid 1–42 to predict an individual's predisposition for developing Alzheimer's had conflicting conclusions.

Whether dietary supplements have a role in preventing or treating Alzheimer's has long been queried. Research results published in 2008 included data from one study showing that using vitamins C and E alone or in combination did not improve cognitive function, but another study showed that those with Alzheimer's who took vitamin E lived 26 percent longer than those who did not. Vitamin B supplementation also did not slow cognitive decline. Additional studies are needed to determine whether dietary supplements have a role in treating Alzheimer's disease.

A person's genetics may also play a role in the development of Alzheimer's. Having two parents with Alzheimer's is associated with a 42 percent increased likelihood of developing Alzheimer's by age 70, according to one study. Researchers also found that those who have a mother with Alzheimer's may be predisposed to the disease. The link may be a malfunction in how the brain metabolizes glucose—something that's probably genetic and starts years before symptoms of Alzheimer's appear, researchers said. The researchers found that people with a mother with Alzheimer's had a much faster reduction in the use of glucose in areas of the brain affected by the disease compared with people who had a father with Alzheimer's or parents without the disease.

In other genetics research, after studying the genetic profiles of two large Georgia families with high rates of late-onset Alzheimer's, researchers found a variation in a large family of genes—called TRPC4AP—that may help explain the high rates of Alzheimer's. The genetic variation is believed to regulate calcium. Calcium is needed throughout the body but abnormal levels can cause inflammation, nerve cell death and possibly plaque formation in the brain.

Some risk factors for heart disease also appear to increase one's risk of developing Alzheimer's disease. For example, having health conditions such as diabetes and stroke may impact a person's risk, reported researchers. In a study involving men only, those who developed diabetes in midlife were one-and-a-half times more likely to develop Alzheimer's disease than those without diabetes. In another study, individuals who have experienced a stroke and carry the APOE-e4 gene are at greater risk for dementia than individuals with just one—or none—of these factors.

In addition, several studies released in 2008 supported previous reports that those with a diagnosis of depression appear to be at greater risk of developing Alzheimer's disease than those without a history of depression.

Biological and genetic risk factors for Alzheimer's such as these provide researchers with a valuable window into the potential causes of the disease and may inform future scientific investigations.

Lifestyle Factors Influence Risk

Individuals cannot change their genetic make-up, but they can change their lifestyles, and doing so may influence their likelihood of developing dementia. Research results published in 2008 strengthened evidence that exercise, diet, education and an active lifestyle can contribute to maintaining brain health.

Physical fitness may significantly influence one's risk for developing Alzheimer's disease. One study suggested that people with larger bellies in their 40s were more likely to have dementia when they reached their 70s. In fact, obesity may increase the risk of Alzheimer's disease up to 80 percent, said some researchers. Regular, moderate exercise in one's 50s and 60s may help protect against mild cognitive impairment, and people with early-stage Alzheimer's who were physically fit as measured by performance on a treadmill test had four times less brain shrinkage than those who did not exercise.

What one consumes may also help ward off Alzheimer's disease. Flavonoids, compounds found in many fruits and vegetables, may reduce levels of the protein beta-amyloid that goes on to form the amyloid plaques that characterize Alzheimer's. Investigators also found a benefit in a nutrient-rich drink that might

eventually offer a new option in managing Alzheimer's disease. On the flip side, heavy alcohol consumption (more than two drinks per day) and heavy smoking (one or more packs per day) may hasten the onset of Alzheimer's by as many as five years.

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The old adage of “use it or lose it” gained ground in several research studies. Scientist discovered that, in babies, the brain generates roughly double the number of nerve cells it needs to function. Cells that receive chemical and electrical stimuli from other cells survive and cells that don't ultimately die. This could help explain why in one study older persons who had at least a high school education lived 2.5 years longer without cognitive loss than those without a high school education. It also offers insight into how, according to one study of male twins, maintaining social activities and engaging in cognitive activities cut the risk of dementia by 26 percent.

Alzheimer Drug Pipeline Reflects Breadth of Research

In the ongoing quest for more effective Alzheimer's disease treatments, 2008 brought both advances and setbacks.

For example, individuals with mild-to-moderate Alzheimer's disease who received the experimental drug Dimebon experienced improvement in all five outcome measures studied by researchers. What's more, Dimebon's benefits seemed to hold, and by some measures even increase, through the trial's six-month extension study. These persistent benefits distinguish the small-molecule drug from existing approved therapies for mild-to-moderate Alzheimer's—none of which have shown increasing improvement past 12 months.

Several other drug trials showed promising results. A nasal spray called AL-108 significantly improved some measures of memory in individuals with mild cognitive impairment. The drug targets the fibrous tangles caused by the abnormal build-up of the protein tau. Another drug that aims at breaking up tau tangles in the brains of those with Alzheimer's is Rember®. Rember showed promise for halting the progression of the disease by improving memory and thinking in people with Alzheimer's disease.

Phase II results of an anti-beta-amyloid monoclonal antibody—LY2062430—suggested that the drug may begin to dissolve amyloid plaques in the brains of people with Alzheimer's. Individuals receiving Gamagard, an intravenous therapy derived from human plasma, showed maintenance of cognitive function and, in some cases, improved cognitive function. The drug PBT2 was associated with improved brain function in people with early-stage Alzheimer's and reduction in the amount of beta-amyloid in CSF.

The vaccine AN-1792, however, cleared beta-amyloid plaques but did not slow the progression of Alzheimer's disease. The experimental drug bapineuzumab, also designed to remove beta-amyloid plaques in the brain, was linked to a brain-swelling side effect and showed

no benefit in the 65 percent of individuals in the study who carried the APOE-e4 gene. But people with Alzheimer's who did not carry the gene scored an average of five points higher on a 70-point cognitive test. Flurizan®, a drug designed to decrease the production of the protein beta-amyloid, failed to help individuals with Alzheimer's in its Phase III trial, and Huperzine A, a drug hoped to offer multiple different types of action against Alzheimer's disease, did not meet its primary study endpoints in its Phase II trial.

Clinical trial results reported in 2008 also included results from studies involving drugs originally developed for conditions other than Alzheimer's. Results from the largest study of statin drugs, developed for individuals with high cholesterol levels, showed no significant differences in cognition or overall function compared with placebo and Aricept® in people with mild-to-moderate Alzheimer's. However, a separate study showed that people at high risk for dementia who used statins were half as likely to develop dementia as those who did not take statins.

People who used the painkiller ibuprofen regularly for five years had a 25 percent lower risk of developing Alzheimer's according to one study. These findings, though, don't put to rest the debate about the role of non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen in preventing and treating Alzheimer's. Another study published in 2008 found that NSAIDs do not appear to improve cognitive function in older adults.

These clinical trial results point to the complexity of finding new treatments for Alzheimer's, as well as the wide array of approaches being used in an attempt to tackle the disease. While several existing medications can improve the symptoms experienced by individuals with Alzheimer's, none slows or stops the nerve cell death in the brain that is the central cause of Alzheimer's. Drugs that slow or stop nerve cell death are essential for stemming the epidemic of Alzheimer's.

Discoveries Advance Understanding of the Disease Process

Clinical trials represent the culmination of years of basic and preclinical research. Without basic research, clinical trials are not possible. In 2008, scientists made numerous basic and preclinical discoveries that helped the field understand how Alzheimer's develops and progresses.

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For example, an advanced imaging technique showed that beta-amyloid plaques can develop in just one day. In addition, a three-dimensional electron microscopy image of aggregated beta-amyloid was created in 2008 that helped researchers understand the structure and development of beta-amyloid clumps.

In another study, researchers found that blocking a common immune system molecule, transforming growth factor-beta, greatly diminished the formation of beta-amyloid plaques in the brains of mice. It also enabled treated mice to recover some lost memory. Researchers hope the new approach may one day overcome one of

the biggest obstacles to the development of new dementia medications—the difficulty in finding drugs that can safely cross the blood-brain barrier.

Another team of researchers learned that elevated levels of the protein ATP-binding cassette transporter (ABCA) 1, which helps move lipids such as cholesterol through the body, sharply reduced the buildup of plaques, potentially slowing the development of Alzheimer's disease. The study also highlighted a new possibility for Alzheimer treatment: altering the brain's use of lipids. A separate study showed that naturally occurring lipids found throughout the brain can dissolve plaques. These findings offer new targets for disease intervention.

In other research, lithium was found to inhibit glycogen synthase kinase (GSK) 3 β in vivo by disrupting its signaling. GSK-3 β is of interest to Alzheimer researchers because inhibiting GSK-3 β may decrease formation of the tau tangles that are hallmarks of Alzheimer's.

Basic science studies such as these provide only a glimpse into the many advances in research made in 2008 toward a better understanding of the development of Alzheimer's.