

alzheimer's  association

Perspectives

in alzheimer
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Table of *contents*



Research Highlights	2
Biomarkers	3
Non-Biomarker Techniques for Early Detection	5
Modifiable Risk Factors	6
Genetic Risk Factors	9
Drug Pipeline	11
Care for People with Dementia	13
Basic Science Discoveries	15
Alzheimer's Association Research Initiatives	17
Alzheimer's Association International Conference on Alzheimer's Disease	18
International Research Grant Program	20
World-Wide Alzheimer's Disease Neuroimaging Initiative	22
Alzheimer's Association Cerebrospinal Fluid Quality Control Program	23
Research Roundtable	24
Prevalence Conference	26
Other Initiatives	27
<i>Alzheimer's & Dementia: The Journal of the Alzheimer's Association</i>	27
International Society to Advance Alzheimer Research and Treatment	27
Clinical Studies Initiative	28
Funded Research	30
Bruce T. Lamb, Ph.D., 2008 IIRG recipient, 2005 Zenith Fellows Award recipient	31
Jaya Padmanabhan, Ph.D., 2008 IIRG recipient	33
Sanjay Pimplikar, Ph.D., 2008 and 2002 IIRG recipient, 1995 PRG recipient	35
Cheryl A. Luis, Ph.D., 2009 NIRG recipient	37
Liqin Zhao, Ph.D., 2005 NIRG recipient	39
2009 Alzheimer Science Timeline	42

Research Highlights:

Discoveries underscore the predictive value of biomarkers and the potential influence of modifiable risk factors

Each year, researchers around the globe explore a diversity of topics in Alzheimer science. These topics are impressive in their breadth and depth. In 2009 topics ranged from the role of heat-shock proteins in the development of the tau tangles that characterize Alzheimer's disease to the influence of emotional closeness between an individual with Alzheimer's and his or her caregiver on the individual's rate of cognitive and functional decline.

But perhaps most visible in 2009 were discoveries supporting the potential role of biomarkers in early detection and diagnosis of Alzheimer's disease and the influence of lifestyle factors such as exercise and diet in modifying one's risk of developing Alzheimer's.

A biomarker is a substance or characteristic that can be objectively measured and evaluated as an indicator of normal body processes, disease processes or the body's response(s) to therapy. For example, blood pressure is a biomarker that indicates risk of cardiovascular disease.

During the Alzheimer's Association International Conference on Alzheimer's Disease (AAICAD) 2009, Ronald Petersen, Ph.D., M.D., chair of the Association's Medical and Scientific Advisory Council, provided the context for why Alzheimer biomarkers are needed. "With the continued aging of the population and the growing epidemic of Alzheimer's, early detection of the disease is crucial for risk assessment, testing new therapies and eventual early intervention with better drugs, once they are developed," he said.

"It is widely believed that Alzheimer's disease brain changes, including amyloid plaques and neurofibrillary tangles, begin many years before we see symptoms."

"It is widely believed that Alzheimer's disease brain changes, including amyloid plaques and neurofibrillary tangles, begin many years before we see symptoms. It is critical to identify affected individuals while they are still relatively cognitively healthy so that future therapies can preserve healthy memory and thinking function. And, in order to develop those new therapies, we need to identify 'at risk' individuals now to steer them to clinical trials," Dr. Petersen added.

Discoveries about biomarkers were matched by a wealth of findings suggesting that diet, exercise and other lifestyle choices can impact one's risk of Alzheimer's. Age and family history are known to be the top risk factors for Alzheimer's disease.

"We can't do anything about aging or family history, but research continues to show us that there are lifestyle decisions we all can make to keep

our brains healthier and that also may lower our risk of memory decline as we age," said William Thies, Ph.D., Chief Medical and Scientific Officer at the Alzheimer's Association, at AAICAD.



Biomarkers

Alzheimer's disease biomarkers were one of the highest profile areas of research discovery in 2009. The Alzheimer science community believes that disease-modifying drugs will likely be most effective when given in the very early stages of the disease and that biomarkers will play an important role in determining which individuals should receive these drugs.

Biomarkers identified through imaging techniques and analysis of cerebrospinal fluid (CSF) gained particular attention in 2009, but were joined by coverage of other biomarkers as well.

To facilitate the identification of Alzheimer biomarkers, UC-San Diego researchers developed a rapid, automated method for measuring the volume of very specific sub-regions of the brain. The method, used in combination with magnetic resonance imaging (MRI), showed that the volume of the entorhinal cortex was especially susceptible to change in the early stages of the disease and that it may be a better biomarker of Alzheimer's than

overall brain atrophy. The study involved data from 600 individuals participating in the Alzheimer's Disease Neuroimaging Initiative (ADNI).

ADNI volunteers have also been instrumental in understanding whether levels of beta-amyloid and tau in CSF are biomarkers of Alzheimer's disease. University of Pennsylvania researchers tested CSF from 410 ADNI volunteers and found that those with MCI and Alzheimer's had higher concentrations of tau and lower concentrations of beta-amyloid as the disease progressed. Levels of beta-amyloid in CSF were 96 percent accurate in detecting Alzheimer's among those whose Alzheimer's was

confirmed on autopsy. CSF levels accurately predicted conversion from MCI to Alzheimer's in 82 percent of cases.

European researchers studying CSF samples from 168 volunteers from seven countries found that those with low beta-amyloid and high tau levels in CSF had 27 times the risk of cognitive deterioration



as those without this CSF pattern. The pattern was present in all individuals with MCI who went on to develop Alzheimer's.

A study conducted in the United States and Europe backed up the potential effectiveness of CSF as a biomarker for Alzheimer's. The study involved 750 people with MCI, 529 with Alzheimer's, and 304 without these conditions. During follow-up, 271 individuals with MCI developed Alzheimer's and demonstrated an "Alzheimer's pattern" of CSF levels at baseline: low levels of beta-amyloid and high levels of phosphorylated tau and total tau.

At AAICAD, U.S. researchers presented data from a study of 85 ADNI participants with MCI that examined the potential role of a variety of biomarkers in predicting progression from MCI to Alzheimer's. Of all potential biomarkers tested, glucose metabolism in the brain as measured by positron emission tomography (PET) scans and performance on a memory recall test called the Auditory-Verbal Learning Test most accurately predicted progression from MCI to Alzheimer's. Individuals with low glucose metabolism in the brain and poor performance on the memory test had a 15-fold increased risk of developing Alzheimer's in two years.

Using data from the Nurses' Health Study, investigators at Brigham and Women's Hospital, Boston, examined whether the ratio of beta-amyloid 1-40 to beta-amyloid 1-42 in plasma influenced the risk of developing Alzheimer's. They determined the ratio in mid-life (mean age, 63) and 10 years later for the 481 study participants. A high ratio in mid-life was associated with worse late-life cognitive decline, and a greater increase in the ratio over time was associated with faster cognitive decline.

PET combined with the tracer element Pittsburgh Compound B (PIB) provided some of the earliest evidence of potential biomarkers for Alzheimer's, and the imaging method continues to be influential. In two studies from Washington University, St. Louis, researchers found that high levels of beta-amyloid in the brains of healthy individuals are associated with a greater risk for developing Alzheimer's, loss of brain volume and declines in cognitive function.

Non-Biomarker Techniques for Early Detection

Advances were also made in non-biomarker techniques for early detection of Alzheimer's and other dementias.

Researchers examining data from 3,375 people aged 65 and older in the Cardiovascular Health Study found that after six years 480 had developed dementia. When the study began, researchers gathered data on the participants. Based on these data and which individuals went on to develop

Investigators following 444 individuals for an average of six years found that those who developed Alzheimer's experienced a decline in visuospatial skill three years before diagnosis.

sentence and perform calculations and tasks that tested verbal fluency and recall ability. Healthy individuals had an average score of 47 out of 50, while those with Alzheimer's had an average score of 33.

While memory loss is often one of the first symptoms of Alzheimer's, investigators following 444 individuals for an average of six years found that those who developed Alzheimer's experienced a decline in visuospatial skill three years before diagnosis. Overall cognitive ability declined two years before diagnosis. Verbal and working memory declined just one year before diagnosis, suggesting that visuospatial skills may be an earlier indicator of cognitive decline than memory loss.

dementia, the researchers created a 15-point scale to determine risk of developing dementia. People who scored eight points or more on the scale were at high risk of developing dementia. In addition to known risk factors such as older age and having the APOE-e4 gene, individuals who were underweight, did not drink alcohol, had undergone coronary bypass surgery and were slow at physical tasks such as buttoning a shirt were more likely to develop dementia. The scale was 88 percent accurate in identifying those who developed dementia.

Scientists in Britain developed a cognitive test that accurately detected 93 percent of people with Alzheimer's in a study of 540 healthy individuals and 139 with Alzheimer's or MCI. The test measured performance on 10 tasks, including ability to copy a

Modifiable Risk Factors

In addition to making significant contributions to the body of knowledge regarding early detection, researchers in 2009 shared study results reinforcing the association between lifestyle factors and the risk of developing dementia.

While some Alzheimer risk factors, such as genetic make-up, cannot be changed, lifestyle factors can be modified, and these modifications could lead to more years of healthy brain function.

Physical Activity

In a high-profile study commissioned by the National Football League, University of Michigan scientists found that former football players had rates of dementia, Alzheimer's and other memory-related diseases that were up to 19 times higher than national norms. Scientists conducted telephone surveys of 1,063 retired players who had played for at least three seasons. Among players age 50 or older, 6.1 percent reporting receiving a dementia-related diagnosis, five times higher than the national average. Among players ages 30 through 49, 1.2 percent reported receiving such a diagnosis, 19 times the national average. These data contribute to research linking serious head injury with an increased risk of dementia.

While physical activity in general is known to benefit both the heart and the brain, little research

has focused on the association between brain health and muscle strength in particular. To shed light on this, researchers measured the arm, leg, and abdominal strength of 970 people ages 54 to 100. Those who ranked in the top 10 percent for muscle strength were 61 percent less likely to develop Alzheimer's than those who ranked in the lowest 10 percent. The mental abilities of stronger individuals also declined at a slower rate over time.

The *Journal of the American Medical Association* reported that exercise, combined with a healthy

Researchers found that residents who were very physically active had a 33 percent lower risk of developing Alzheimer's than sedentary residents.

diet, was especially effective in lowering one's risk of developing Alzheimer's. The report was based on a study of 1,880 elderly New York City residents followed for five years. Researchers found that residents who were very physically active (1.3 hours a week of vigorous activity such as jogging or 4 hours a week of light exercise such as walking) had a 33 percent lower risk of developing Alzheimer's than sedentary residents. Residents who most often adhered to a Mediterranean diet rich in fruits, vegetables, cereal and fish but low in meat and dairy foods had a 40 percent lower risk than individuals who less frequently followed such a diet. The overall risk of developing Alzheimer's was 9 percent for those who were very active and followed a healthy diet, compared with 21 percent for those who were least active and less diet-conscious.



Diet

Another type of healthy diet called DASH (Dietary Approaches to Stop Hypertension) is similar to the Mediterranean diet and was associated with better cognitive function in a study of more than 3,800 people age 65 or older. Over the 11 years of the study, study participants' diets were scored at four different times. Scores were based on their consumption of fruits, vegetables, whole grains, low-fat dairy foods and fish (all recommended), as well as sodium, sweets and non-fish meat (recommended in limited amounts). The higher the DASH diet score, the more closely participants adhered to the diet. Investigators found that the higher the DASH score, the higher the participants' scores for cognitive function at the start of the study and over time. Four of the food groups—vegetables, whole grains, low-fat dairy food, and nuts/legumes—were independently associated with higher scores on the Modified Mini-Mental State Examination.

Drinking any amount of alcohol, be it small or large, was associated with faster cognitive decline in people with MCI.

DHA, an omega-3 fatty acid found in fish and other foods, has been the subject of much research over the years for its potential effect on Alzheimer's. In two studies reported at AAICAD 2009, researchers said that DHA did not slow memory decline over 18 months in 402 people with mild to moderate Alzheimer's, but that among 485 people with mild memory complaints, those who took a DHA supplement performed better on a computer memory test

after six months than those receiving a placebo. However, more data are needed before taking a DHA supplement can be recommended.

Like DHA supplementation, alcohol consumption is a topic of wide interest in terms of its potential impact on Alzheimer's. In a six-year study of more than 3,000 people aged 75 and older, researchers found that drinking one or two alcoholic beverages daily was associated with a 37 percent lower risk of developing dementia, but that individuals consuming more than 14 alcoholic beverages per week were twice as likely to develop dementia. Drinking any amount of alcohol, be it small or large, was associated with faster cognitive decline in people with MCI.

Co-existing Health Conditions

Diet is often a contributor to health conditions that previous studies have shown increase the risk of developing Alzheimer's. Results of large-scale studies published in 2009 add to the growing evidence of diabetes, high cholesterol and high blood pressure as risk factors for Alzheimer's. For example, a study supported in part by a grant from the **Alzheimer's Association** found that among 13,000 twins, those who developed diabetes before age 65 had a 125 percent increased risk of Alzheimer's disease. Twin studies are valuable in that they enable researchers to eliminate genetic differences that might cause disease.

Data from nearly 20,000 participants in the Reasons for Geographic and Racial Differences in Stroke study served as the basis for an evaluation of the role of blood pressure on brain function. In these participants, all age 45 or older, the higher one's blood pressure, the greater one's chances of having

cognitive impairment. In fact, with each 10-point increase in diastolic blood pressure, the chance of cognitive impairment increased 7 percent. Diastolic blood pressure measures the force on arteries



when the heart is at rest. When diastolic blood pressure rises, it can cause thickening of the arterial walls in the brain, decreasing blood flow. Systolic blood pressure, the force on arteries when the heart contracts, wasn't associated with impaired brain function.

In a remarkably long four-decade study of nearly 10,000 individuals who were followed beginning in their 40s, researchers found that high cholesterol (240 mg/dL or higher) in midlife is correlated with a 66 percent increased risk of Alzheimer's disease

People with metabolic syndrome, a condition that is characterized by several heart disease risk factors including high blood pressure and low levels of good cholesterol, are at higher risk of developing Alzheimer's.

later in life. Borderline high cholesterol (200 to 239 mg/dL) was correlated with a 52 percent increased risk. The results are another reminder that midlife health can foreshadow health in one's later years and that taking action on modifiable risk factors such as high cholesterol may have significant rewards in decades to come.

Likewise, people with metabolic syndrome, a condition that is characterized by several heart disease risk factors including high blood pressure and low levels of good cholesterol, are at higher risk of developing Alzheimer's, according to researchers. In a four-year study of nearly 5,000 women with an average age of 66, 36 percent of women with metabolic syndrome developed cognitive impairment, compared with just 4 percent of women without metabolic syndrome.

Post-traumatic stress disorder (PTSD) is a health condition that has gained increased attention over the years, and researchers in 2009 showed that PTSD is associated with a higher risk of dementia. They studied more than 180,000 veterans aged 55 and older over seven years and found that the rate of new cases of dementia was 10.6 percent in those with PTSD compared with 6.6 percent in those without. Results were similar when those with histories of traumatic brain injury, substance abuse and depression were excluded. Researchers note that much more research is needed to understand the link between dementia and PTSD but that evidence such as this underscores the importance of physicians paying particular attention to early signs of dementia in patients with PTSD.

Other Risk Factors

Smoking is a known risk factor for Alzheimer's disease, but is second-hand smoke a risk factor too? To find out, investigators tested saliva samples from 4,800 nonsmokers age 50 and older for levels of cotinine, a product of nicotine that stays in the

saliva for about a day after exposure to smoke. Investigators found that people with the highest levels of cotinine had a 44 percent higher risk of cognitive impairment than people with the lowest scores and that impaired cognitive function increased with the amount of exposure to second-hand smoke. The findings underscore the importance of limiting one's exposure to smoke in maintaining brain health.

Numerous studies have suggested that completing more years of formal education produces a "cognitive reserve" that delays the onset of Alzheimer symptoms. But does this cognitive reserve affect the rate at which one's cognitive abilities decline once symptoms are present? Different studies have had varying answers to that question. Research conducted in 2009 involving 6,500 individuals age

72 and older suggests that it does not. Study participants' education levels ranged from eight or fewer years of schooling to 16 or more. Their memory and thinking skills were measured every

Researchers in 2009 showed that post-traumatic stress disorder is associated with a higher risk of dementia.

three years. While those with more years of education performed better on tests at the beginning of the study, once they started having memory problems their rate of cognitive decline was no slower than that of individuals with fewer years of education.

Genetic Risk Factors

Researchers believe that people develop Alzheimer's disease as the result of a combination of different factors, including genetic, lifestyle and environmental factors.

Mutations in three genes guarantee that individuals will develop Alzheimer's, but only a very small percentage of individuals with Alzheimer's (1–5 percent) carry these genes. The e4 form of the gene apolipoprotein E (APOE-e4) is carried by about 25 percent of individuals and increases the risk of developing Alzheimer's, but does not guarantee that individuals will develop the disease. Aware that genetics plays a role in Alzheimer's, researchers continue to study genetic variations and their association with Alzheimer's to better understand the disease and to identify factors that might aid in early detection.

Mayo Clinic researchers reported in the journal *Nature Genetics* the discovery of the first sex-specific gene that increases one's risk of Alzheimer's disease. Located on the X chromosome, PCDH11X

is a common gene that exerts its influence most strongly when a woman inherits it from both parents. Examining genetic data from 2,400 people with Alzheimer's and 3,800 without, they found that women with Alzheimer's disease were twice as likely to have two copies of the gene as women in the control group. Inheriting just one copy of the gene also increased one's risk, but to a smaller extent than having two. Researchers noted that the discovery does not necessarily mean women are at higher risk than men, as yet-undiscovered male-specific genetic risk factors may exist.

Pooling DNA data for 16,000 people across Europe and the United States, scientists identified three potential new genetic risk factors for late-onset Alzheimer's: variants of the genes PICALM, CLU and CR1. This was the largest genome-wide association

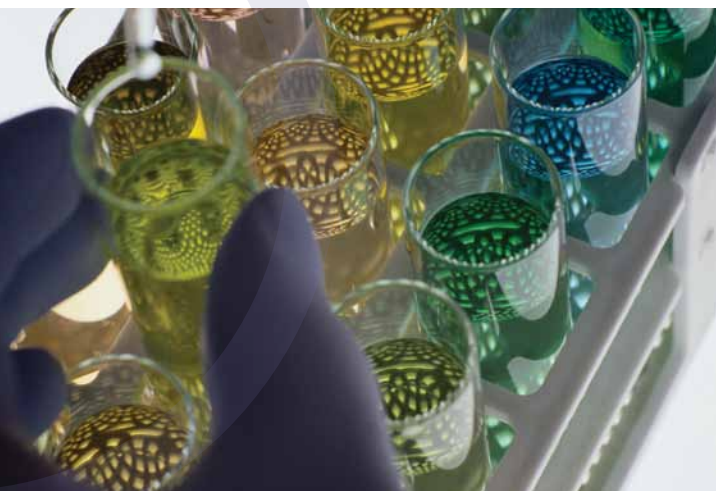
study reported to date for Alzheimer's. Genome-wide association studies aim to identify genetic associations with a disease by studying the DNA on all of the chromosomes in a specific population. PICALM is located on chromosome 11, CLU on chromosome 8 and CR1 on chromosome 1. These

The gene is the first recessive genetic trait found for Alzheimer's, meaning that two copies of the gene must be inherited for the disease to develop.

genes normally have helpful functions in the brain. CLU is thought to suppress the deposition of beta-amyloid, PICALM is believed to help keep synapses healthy, and CR1 may help remove beta-amyloid from the brain. However, the newly reported variants of these genes appear to have negative effects on the brain, with further research needed to understand how they might act to increase Alzheimer risk.

In a family carrying the mutant gene A673V, Italian researchers found that those carrying two copies of the gene were destined to develop Alzheimer's

while those with one copy or no copies of the gene did not develop the disease. The gene is the first recessive genetic trait found for Alzheimer's, meaning that two copies of the gene must be inherited for the disease to develop. Scientists studied cells from family members with zero, one or two copies of A673V, with fascinating results. While cells with two copies of the mutation produced more beta-amyloid, and the beta-amyloid was more likely to clump together, cells with one copy of A673V produced less beta-amyloid clumps than cells with no copies of A673V.



Drug Pipeline

Each year brings a remarkable growth in knowledge of Alzheimer's disease, and clinical trials of new drugs are essential to expanding that knowledge and identifying improved treatments.

Randy Nixon, Ph.D., professor of psychiatry and cell biology at New York University and vice chair of the Association's Medical and Scientific Advisory Council, remarked at AAICAD 2009, "There are currently dozens of drugs in Phase II and III clinical trials for Alzheimer's. This, combined with advancements in diagnostic tools, has the potential to change the landscape of Alzheimer's in our lifetime." Results of numerous Phase II and Phase III studies made headlines in 2009.

Docosahexaenoic acid (DHA), the most abundant omega-three fatty acid in the brain, has been of interest as a treatment for Alzheimer's for some time. Results of two studies presented at AAICAD 2009 showed that DHA did not slow cognitive decline in people with mild or moderate Alzheimer's but was associated with improved performance on a memory test in volunteers with mild memory complaints. "These two studies—and other recent Alzheimer's therapy trials—raise the possibility that treatments for Alzheimer's must be given very early in the disease for them to be truly effective," said William Thies, PhD., chief medical and scientific officer at the Alzheimer's Association.

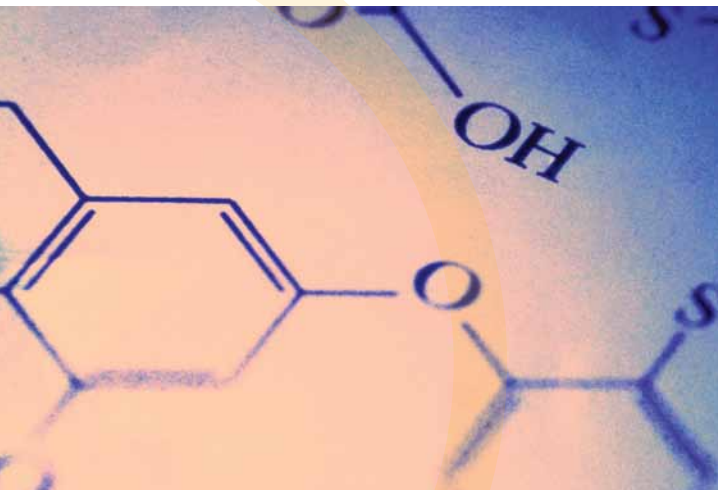
The larger of the two trials, funded by the National Institute on Aging, lasted 18 months and involved 402 people with Alzheimer's at 51 sites across the United States who received either a placebo or 2 grams of DHA daily. While DHA levels in the brain increased in the treatment group, it did not slow the rate of change on tests of mental function, dementia severity, activities of daily living or behavioral symptoms. Interestingly, it did slow the rate of decline on a mental function test in those with the APOE-e4 gene. "One of the issues raised by this study—and other recent Alzheimer's and mild cognitive impairment therapy trials—concerns a

possible interaction between certain therapies and genetic status. This issue needs to be explored more completely in future trials," Dr. Thies added.

The smaller of the two studies lasted six months and involved 485 older people who received either placebo or 900 milligrams of DHA daily. Volunteers' performance on a visuospatial memory test was measured at the beginning and end of the study. Those who received DHA made significantly fewer errors on the test at the end of the study than those who did not.

Beta-amyloid is a protein that is the main constituent of amyloid plaques found in the brains of people with Alzheimer's disease.

While Phase III clinical trials of dimebolin (Dimebon®) were under way in 2009, researchers shared results of a study aimed at shedding light on how the drug appeared to stabilize function in people with mild or moderate Alzheimer's who participated in earlier studies. Researchers conducted experiments in cells and in mouse models of Alzheimer's to assess the effects of dimebolin on beta-amyloid and other brain proteins known to be related to Alzheimer's disease. Beta-amyloid is a protein that is the main constituent of amyloid plaques found in the brains of people with Alzheimer's disease. It is widely considered a key player in the development and progression of Alzheimer's. The goal of anti-amyloid drugs in clinical trials is to reduce beta-amyloid levels in the brain. In a surprising result, researchers found that treatment with dimebolin caused an acute increase



in brain beta-amyloid levels in mice. “This result is highly unexpected in what may prove to be a clinically beneficial Alzheimer’s drug,” said one of the researchers. “We need more research to further clarify how dimebolin affects beta-amyloid levels in the brain.”

The makers of bapineuzumab, an Alzheimer vaccine designed to reduce levels of beta-amyloid in the brain, announced that the highest dose of the drug would be dropped from two Phase III clinical trials due to increased risk of vasogenic edema, a type of brain swelling caused by accumulation of water in brain tissue. The 0.5 mg/kg and 1.0 mg/kg doses in these two trials will continue as planned. The trials involve people with mild or moderate Alzheimer’s who do not have the APOE-e4 gene. The decision had no impact on two other ongoing studies testing a single 0.5 mg/kg dose of bapineuzumab in APOE-e4 carriers. The Phase III program for

bapineuzumab is the largest clinical program ever initiated in Alzheimer’s disease. Approximately 4,000 patients are expected to be included across all four studies.

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The two highest doses of ELND005, an Alzheimer drug from the makers of bapineuzumab, were dropped from a Phase II trial due to serious adverse events including an increased number of deaths in those receiving the highest doses. Nine deaths were reported in the groups receiving 1,000 mg or 2,000 mg twice daily. The Phase II trial enrolled approximately 353 patients with mild to moderate AD, who were divided into three treatment groups and one placebo group. ELND005 is designed to reduce deposits of beta-amyloid in the brain by preventing the formation of beta-amyloid oligomers, which recent research has shown may be the most toxic form of beta-amyloid.

Care for People with Dementia

Until new therapies to slow or stop the progression of Alzheimer's disease are developed, more than 5 million Americans with Alzheimer's will continue to require assistance from family or other caregivers to cope with the symptoms and declining function brought on by the disease.

The challenges experienced by people with the disease and their caregivers and physicians is an area of expanding investigation by the scientific community.

A study conducted in Australia involving 289 people with dementia aged 60 and older found that those whose care was person-centered and based on dementia-care mapping had less agitation when the study ended and four months after the study. Person-centered care makes the person with dementia a central part of care-planning and focuses on their individual needs. Dementia-care mapping is a tool to improve person-centered care that scores factors related to the individual's well-being, such as enjoyment of eating, touching and interacting. While training in dementia-care mapping is expensive and labor-intensive, training in person-centered care is quickly taught and one-fourth the cost of dementia-care mapping. The authors suggest that patient-centered approaches to care be standard practice in residential care homes.

Death rates for individuals with Alzheimer's who receive antipsychotic medication are significantly higher than for individuals who do not take this medication, reinforcing the guideline that the medication only be used as a last resort and for as short a period as possible. In a three-year study, 128 people with Alzheimer's were assigned to either continue to receive one of several antipsychotic medications or to be switched to a placebo. At the end of the study, the risk of death was 42 percent lower among those on the placebo. After two years' follow-up, 46 percent of those taking antipsychotics were alive, compared with 71 percent of those taking a placebo. After three years, 30 percent of

people receiving antipsychotics were alive, compared with 59 percent of those on placebo.

Half of family caregivers admitted to abusive behavior while caring for an individual with dementia, according to an article in the *British Medical Journal*. Of 220 caregivers surveyed, 52 percent reported occasionally screaming or yelling at the individual, 33 percent reported "significant" abuse such as frequently insulting or swearing at the individual, and 1 percent (3 caregivers) reported physically abusing a family member. As dementia progresses, individuals can become aggressive, and in some cases caregivers were reacting to being the subject of aggressive behavior. Some caregivers wished that physicians had asked them how they were coping with being a caregiver and said this might help prevent abusive behaviors.

Dementia-care mapping is a tool to improve person-centered care that scores factors related to the individual's well-being, such as enjoyment of eating, touching and interacting.

While the study highlights the fact that it's not paid caregivers alone who abuse vulnerable individuals, it also highlights the need for increased support services for caregivers.

Up to one-third of individuals with severe dementia receive nutrition via a feeding tube, yet a review of seven studies involving 409 such individuals found

that there was not significant evidence that feeding tube use increased survival or improved quality of life. Because individuals at this stage of dementia are unable to give informed consent, they often continue to receive tube feeding. The researchers highlighted the importance of individuals with dementia having advance directives to prevent what may be unwanted use of a feeding tube at this stage of their illness.

While cholinesterase inhibitors can temporarily help improve the memories of those with Alzheimer's disease, they do come with risks, one of them being an increased risk of fainting caused by slowed heart rates. Researchers used healthcare databases in Ontario, Canada, to identify nearly 20,000 people with dementia who were receiving cholinesterase inhibitors and 61,000 who were not and found that those taking the medications were almost twice as likely to be hospitalized for fainting. They were also 49 percent more likely to have a pacemaker implanted and 18 percent more likely to suffer hip fracture. The researchers said the study served as reminder that the benefits of cholinesterase inhibitors should be carefully weighed against their risks before being prescribed.



Individuals with Alzheimer's who are hospitalized may experience delirium as a result of a change in environment and daily routines, and according to scientists, the delirium may have unexpectedly serious consequences. The scientists studied 400 people with Alzheimer's over 15 years and found

that the rate of cognitive decline in those with an episode of delirium during hospitalization was three times that of those who had not experienced delirium. They noted that up to 40 percent of delirium episodes can be prevented by measures such as telling individuals that they are in the

Higher rates of emotional closeness were associated with significantly slower cognitive and functional decline.

hospital so they are better oriented to their surroundings, allowing as much uninterrupted sleep as possible and avoiding unnecessary medications.

To better understand the effect of emotional closeness between caregivers and individuals with Alzheimer's disease, researchers studied 167 people with Alzheimer's and their caregivers every six months for up to four years. Those with Alzheimer's underwent physical, cognitive and functional tests, while caregivers were interviewed and completed a survey in which they were asked to rate their degree of emotional closeness to the individual with Alzheimer's. Researchers found that higher rates of emotional closeness were associated with significantly slower cognitive and functional decline and that the effect was similar to that of some of the cholinesterase inhibitors used to treat Alzheimer symptoms. More research is needed to understand the "closeness effect," but one of the investigators said it was possible that feelings of closeness result in caregivers being more attentive to the individual's needs and more likely to encourage them to participate in cognitively and socially stimulating activities that promote cognitive and functional health.

Basic Science Discoveries

Basic science discoveries form the foundation of advances in medicine.

Advances in Alzheimer's disease are no exception. Our understanding of the roles of beta-amyloid, tau and the amyloid precursor protein (APP) in the development of Alzheimer's has evolved from science discoveries made in the lab. Likewise, science discoveries made in the lab hold the key to developing new treatments for Alzheimer's disease and other dementias.

The plaques that characterize Alzheimer's begin as individual fragments of APP called beta-amyloid 1-42 that clump together and go on to impede the functioning of synapses in the brain. In 2009, U.S. researchers studying why some nerve cells self-destruct during normal embryonic development discovered that a second APP fragment, N-APP, was a key part of the programmed cell death that occurs. They believe that the mechanism that causes excess nerves to be destroyed as the brain and spinal cord develop, a process that is supposed to stop early in life, may be turned on in Alzheimer's, killing healthy brain cells. The researchers were able to block nerve destruction in human embryonic cells. The next step is to find out if the process can be stopped in adult brain cells. If successful, the method used to stop cell destruction could be tested as a potential new treatment for Alzheimer's.

In a surprising discovery, investigators reported in the journal *Nature Neuroscience* that nerve cells in the brain make a form of collagen called collagen VI and that collagen VI attempts to protect nerve cells from the toxic effects of beta-amyloid. This may help explain why levels of collagen VI are increased in the brains of people with Alzheimer's. Looking more closely, they found that small clusters of beta-amyloid called oligomers (which are much smaller than beta-amyloid plaques and are believed by many to be more toxic than plaques) bind to vulnerable neurons in the brain, but that collagen VI interrupts that binding and may help move the oligomers away from the neurons. If the role of collagen VI in cell models of Alzheimer's is borne

out in more advanced models, collagen VI could prove to be a new weapon against Alzheimer's disease.

Astrocytes, star-shaped nervous system cells that make up about half the volume of the brain, typically support normal brain function. However, researchers at the MassGeneral Institute for Neurodegenerative Disease in Boston found that



the beta-amyloid plaques of Alzheimer's activate the astrocyte network in the brain and may cause the harmful effects of beta-amyloid to be spread cell by cell in waves to distant parts of the brain. Researchers are now trying to determine whether increased astrocyte signaling harms brain cells or may actually be an effort by the body to protect brain cells.

Researchers have known for some time that clusters of beta-amyloid contribute to the nerve cell damage that leads to Alzheimer's. However, they haven't always understood which clusters were most harmful: the large clusters called plaques, the small clusters called oligomers, or clusters somewhere between.



Recent studies have suggested that oligomers are most toxic, and in 2009 researchers at UCLA narrowed in on exactly how toxic they are. The researchers created beta-amyloid clusters in the lab that exactly matched those that form in the brains of people with Alzheimer's. They found that toxicity increases dramatically as the clusters grow from two to three or four beta-amyloid molecules. Clusters consisting of two molecules are three times as toxic as one-molecule clusters, and three- and four-molecule clusters are more than 10 times as toxic as one-molecule clusters. Detailed study of the atomic structure of these clusters will make development of anti-toxicity drugs much easier and likely more successful, said researchers.

The **Alzheimer's Association** played a key role in funding research showing that inhibiting a protein called heat-shock protein 70 (Hsp70) reduces levels of hyperphosphorylated tau in the brain. Hyperphosphorylated tau disrupts the movement of nutrients in brain nerve cells and threatens the very structure of nerve cells. Hsp70 is a "chaperone" protein that guides the activity of tau inside cells. The researchers originally thought that activating Hsp70 would cause the protein to remove hyperphosphorylated tau. However, instead of attaching to tau and removing it, Hsp70 attached to tau and continued to hold on to it, allowing it to accumulate

inside cells. Researchers are now working to identify a compound to effectively inhibit Hsp70 that could be tested as a treatment for Alzheimer's.

Research on the role of brain-derived neurotrophic factor (BDNF) was a focus of attention in 2009. In February, **Alzheimer's Association**-funded researchers reported in *Nature Medicine* that injecting the BDNF gene or protein slowed and even stopped the progression of Alzheimer's disease in animal models. BDNF is produced in the entorhinal cortex, which is involved in memory. Alzheimer's disease affects the entorhinal cortex and is associated with decreased production of BDNF. In September, a second group of researchers found that injection of neural stem cells into the brain in animal models of the disease resulted in improved performance in memory tests. The stem cells secreted BDNF,

The Alzheimer's Association played a key role in funding research showing that inhibiting a protein called heat-shock protein 70 (Hsp70) reduces levels of hyperphosphorylated tau in the brain.

which caused existing tissue to sprout new neurites, strengthening and increasing the number of connections between neurons. The discovery gives researchers hope that stem cells or a derivative of them, such as BDNF, may one day be used to treat Alzheimer's.

Alzheimer's Association Research Initiatives:

Expanding the Association's Reach in the Global Science Community

Advancing research has been a core element of the Alzheimer's Association mission since its founding in 1980. In 1982, the Association awarded its first research grants, and in each successive year has broadened its reach to researchers throughout the world. Research initiatives undertaken in 2009 were no exception.

In addition to established forums that cultivate research collaborations, including the Alzheimer's Association International Conference on Alzheimer's Disease 2009 and meetings of the Research Roundtable consortium, the Association launched its Cerebrospinal Fluid Quality Control Program to aid standardization of Alzheimer biomarkers, continued to raise the profile and scope of the World-Wide Alzheimer's Disease Neuroimaging Initiative, held its first conference on the global prevalence of Alzheimer's and offered new funding opportunities to scientists through its International Research Grant Program.

This expansion occurred in a global economic climate that caused many nonprofit organizations to scale back their efforts. That the Alzheimer's Association continued to move forward its research agenda in such a challenging year is a striking testimony to the commitment of many. These include individuals who, although diverse in age and background, are joined by their personal experiences with Alzheimer's disease and are dedicated to eradicating it through financial support of the Association, advocacy efforts and efforts to raise awareness of the disease. Their commitment is matched by that of members of the Alzheimer's disease science community who help guide and carry out the Association's research initiatives, as well as leaders of partner organizations worldwide who share the Association's vision of a world without Alzheimer's.

That the Alzheimer's Association continued to move forward its research agenda in such a challenging year is a striking testimony to the commitment of many.

AAICAD

The Alzheimer's Association International Conference on Alzheimer's Disease 2009 (AAICAD) brought 3,800 researchers from 74 countries to Vienna, Austria, July 11–16, to share new discoveries on the cause, diagnosis, treatment and prevention of Alzheimer's disease and related disorders.

The 2009 meeting debuted AAICAD as an annual event, with the increased frequency aimed at expanding opportunities for collaborations among



scientists and speeding the sharing of information that is essential to research advances.

Over six days, attendees had the opportunity to hear the latest in Alzheimer research from more than 1,600 presenters. Topics included biomarkers as tools for early diagnosis; lifestyle and other risk factors for Alzheimer's disease; Alzheimer incidence and prevalence; and results of recently completed clinical trials and trials under way. New to AAICAD in 2009 were a designated track on prevention research and an expanded focus on social, behavioral and care research.

Media coverage brought AAICAD research discoveries to more than 104 million individuals. Radio delivered AAICAD news to nearly 40 million listeners. Television audiences totaling more than 28 million learned about research findings reported at AAICAD through shows including *Good Morning America*, *CNN Newsroom* and *ABC World News*. An additional 26 million individuals found out the latest in Alzheimer research through AAICAD coverage in publications such as *The Wall Street Journal*, *The Washington Post* and *USA Today*. More than 500

stories appeared online at sites including CNN.com, WebMD.com, and Forbes.com, delivering an additional 10 million audience members for the cutting edge research released at AAICAD.

Among the data presented were results of studies of docosahexaenoic acid (DHA), the most abundant omega 3 fatty acid in the brain. DHA has long been of interest as a potential treatment for Alzheimer's disease, but study data showed mixed results for DHA. An 18-month study of 402 volunteers with mild to moderate Alzheimer's disease conducted by the Alzheimer's Disease Cooperative Study found that DHA did not slow the

Decreased glucose metabolism in the brain, combined with poor memory recall, were the most effective predictors of conversion from MCI to Alzheimer's.

rate of change on tests of mental function, global dementia severity, activities of daily living or behavioral symptoms. However, a six-month study of 485 healthy older adults with mild memory complaints found that those in the treatment group performed significantly better on a visuospatial test of memory than those in the placebo group.

In a surprising discovery, the experimental drug dimebolin (Dimebon®), in phase III clinical trials at the time, was found to increase levels of the protein beta-amyloid in mouse models of Alzheimer's disease. Beta-amyloid is thought to be a key player in the development and progression of Alzheimer's.

Numerous study results shared at AAICAD shed new light on risk factors for Alzheimer's. Several garnered media attention across the globe, including a study examining whether post-traumatic stress disorder (PTSD) influences one's risk of developing dementia. Researchers Kristine Yaffe, M.D., and colleagues studied 181,093 veterans age 55 and older without dementia, following up on their cognitive function over seven years. Of the total study participants, 53,155 had been diagnosed with PTSD when enrolled. Researchers found that veterans with PTSD were nearly twice as likely to develop dementia as veterans without PTSD.

Also gaining the spotlight were results of a study indicating that moderate alcohol intake may significantly decrease one's risk of developing dementia. Kaycee Sink, M.D., M.A.S., and colleagues studied alcohol intake and development of dementia in 3,069 community-dwelling adults age 75 and older without dementia. Nearly 500 participants had mild cognitive impairment (MCI). Participants were examined every six months for up to six years for changes in memory or thinking abilities. Researchers found that consuming one to two alcoholic beverages per day was associated with a 37 percent lower risk of dementia in participants with normal cognitive function at baseline. This was not the case for those with MCI, however. Any amount of alcohol consumption among those with MCI at baseline was associated with faster rates of cognitive decline.

The potential role of diet and exercise in influencing one's risk of developing dementia was a much discussed topic at AAICAD. Researchers reported that following the Dietary Approaches to Stop Hypertension (DASH) diet was associated with higher scores for cognitive function and that four food groups from the diet—whole grains, vegetables, low-fat dairy foods, and nuts and beans—may be especially beneficial for cognitive function in later life.

Other researchers found that maintaining or increasing physical activity throughout life may slow cognitive decline with age. In one study, older adults who were sedentary had the lowest levels of cognitive function at the beginning of the study and the fastest rate of decline. In an intriguing twist, a study of post-menopausal women found that those who regularly participated in moderate-intensity physical activity had improved cognitive function in later life, while those who regularly participated in strenuous physical activity were at increased risk of cognitive impairment later in life.

Using data from the Alzheimer's Disease Neuroimaging Initiative, Susan Landau, Ph.D., and colleagues investigated which biomarkers best predicted decline in cognitive function in those with MCI and which individuals with MCI would go on to develop Alzheimer's disease. Their data showed that decreased glucose metabolism in the brain, combined with poor memory recall, were the most effective predictors of conversion from MCI to Alzheimer's. People with MCI who fared poorly in these tests were 15 times more likely to go on to develop Alzheimer's disease than those with normal test results.



Glucose metabolism was a key focus of research conducted by investigators at the Center for Brain Health at New York University School of Medicine. The investigators developed an automated scanning

method that rapidly samples glucose metabolism in 32 brain regions. Study participants were divided into seven subgroups based upon their initial diagnosis and results of subsequent memory and thinking tests performed up to three years after their original scan. Investigators found a significant correlation between decreased glucose metabolism in several brain regions and the progression from “stable normal” to “normal with subsequent clinical decline” and to subcategories of MCI and Alzheimer’s. They also found that glucose metabolism in the hippocampus was a sensitive predictor of decline and a discriminator between disease stages.

In the area of potential genetic biomarkers for Alzheimer’s disease, Allen Roses, MD, shared results of a small study in which inheriting the long-repeat version of the Tomm40 gene, in addition to the e3 form of the apolipoprotein E (APOE) gene, was associated with an increased risk of developing Alzheimer’s and an increased risk of developing it at an earlier age. Individuals in the study carrying both genes developed Alzheimer’s an average of seven years earlier—at about age 70—than individuals who inherited the APOE-e3 gene but not the Tomm40 gene. If this association is confirmed in larger studies, the presence of both genes could prove a tool for identifying those at increased risk of Alzheimer’s.

International Research Grant Program

Eighty-four Alzheimer’s researchers from around the globe were awarded a total of more than \$13 million in funding through the Alzheimer’s Association 2009 International Research Grant Program. Since its founding in 1982, the program has awarded over \$279 million to more than 1,900 best-of-field grant proposals, making the Association the world’s largest private, nonprofit funder of Alzheimer research. Funded projects in 2009 represented the proposals ranked highest by 1,400-plus reviewers from 30 countries who volunteered their time to the Association.

Twenty-six percent of funded studies examine the underlying pathology of Alzheimer’s; 24 percent, the molecular mechanisms and chemical changes related to Alzheimer’s; 22 percent, brain imaging, biomarkers and clinical tools that may result in earlier diagnosis and intervention; 11 percent, methods for improving care for people with dementia through new technologies and for exploring the values and beliefs of diverse cultures that impact use of health services; and 7 percent, other factors that may contribute to Alzheimer’s, such as vascular and genetic factors.

Grants were awarded in eight categories. Zenith Society 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 (four awarded). Zenith Award recipients will examine such topics as whether a molecule that helps control iron storage in the brain also regulates production of beta-amyloid and the amyloid precursor protein; the role of a

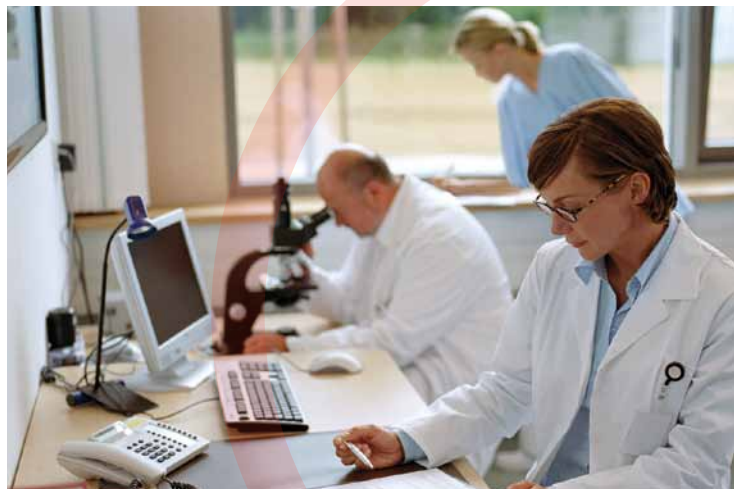
Zenith Society Awards support senior scientists who have made significant contributions to the field and continue to pursue promising lines of investigation about disease mechanisms, diagnosis, novel treatments and quality care.

protein called p38alpha MAPK in the brain cell damage and brain inflammation of Alzheimer's; if tangles of the protein tau may actually be beneficial in Alzheimer's; and whether specific compounds can prevent beta-amyloid oligomers from binding to synapses in the brain.

Investigator-Initiated Research Grants fund established scientists exploring important questions across the entire research spectrum, from basic neurobiology and genetic risk factors to disease-modifying treatments and evidence-based, quality care (29 awarded). New Investigator Research Grants provide the next generation of scientists with funding that enables them to gather preliminary data, test procedures and develop hypotheses. These grants advance research while supporting the early career development of researchers who have earned their doctoral degrees within the last 10 years (40 awarded). The Senator Mark Hatfield Award in Clinical Research focuses on strategies to make earlier and more accurate diagnoses (one awarded).

Everyday Technologies for Alzheimer Care Grants were awarded—in partnership with Intel Corporation—to investigators exploring how computers, monitoring devices and other electronics can be used to meet the day-to-day needs of people with Alzheimer's disease and those who care for them (three awarded).

In 2009 the Association offered three new grant programs, including a program focused on molecular imaging and two that aim to increase the number of individuals from underrepresented groups in the field of Alzheimer science. New Investigator Research Grants to Promote Diversity (NIRGD) funded underrepresented investigators in Alzheimer's or related dementias research who were conducting basic, clinical and social/behavioral research (two awarded). Like the NIRGD, the Mentored New Investigator Research Grants to Promote Diversity (MNIRGD) were funded to help close the gap between diverse and non-diverse



investigator populations, but incorporate the presence of a mentor in the research process (two awarded).

Molecular Imaging in Alzheimer's Disease Grants were awarded to stimulate further research into new approaches to image molecular changes associated with early neurodegenerative processes in living humans, animal models and cells (three awarded). Grants were given to researchers in the United Kingdom, Canada, and the United States. The first study examines whether a new imaging method can detect very early brain changes of Alzheimer's by detecting small clusters of beta-amyloid while the beta-amyloid is still inside nerve cells but before it aggregates into plaques. The second study aims to improve the imaging of beta-amyloid in the brain by developing dyes that bind to beta-amyloid and can be used with magnetic resonance imaging. The third explores how normal age-related changes and Alzheimer's-related changes affect the ability of dyes to permeate the blood-brain barrier. The Molecular Imaging in Alzheimer's Disease grant program is supported by a gift from Dana and Dave Dornsife.

World-Wide Alzheimer's Disease Neuroimaging Initiative (WW-ADNI)

The Alzheimer's Association leads WW-ADNI, which complements the efforts of ADNI. ADNI is a 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 to Alzheimer's.

WW-ADNI is a global consortium of countries using ADNI protocols and is the umbrella organization for neuroimaging initiatives being carried out through the North American ADNI (NA-ADNI), European ADNI (E-ADNI), Japanese ADNI (J-ADNI), and Australian ADNI (AIBL).

Sponsored by the Alzheimer's Association, WW-ADNI unites leading international investigators in a common effort to help predict and monitor the onset and progression of Alzheimer's disease; establish globally recognized standards to identify and diagnose Alzheimer's disease; document cognitive changes linked to physical changes; and share data across the international research community

Specific Association-sponsored WW-ADNI initiatives include financial support for the establishment of E-ADNI and for activities to ensure integration of AIBL data into the NA-ADNI database. The Association also fostered discussions to ensure that J-ADNI is carried out in a way that is fully compatible with NA-ADNI and is playing a visible role in cultivating WW-ADNI sites in China, Argentina, Korea and Taiwan.

In 2009, the Alzheimer's Association cosponsored the first WW-ADNI symposium in Sendai, Japan, with Japan's Research Association for Biotechnology and Society for Dementia Research. The symposium featured more than 20 speakers from Italy, Australia, Japan and the United States and covered the latest news on PET and MRI

studies of Alzheimer's, beta-amyloid imaging, and biostatistics and informatics as applied to biomarker studies.

As the leader of WW-ADNI, 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 on a consistent basis throughout the year. By serving as a liaison for the exchange of information between researchers and pharmaceuti-

By serving as a liaison for the exchange of information between researchers and pharmaceutical companies, the Association plays a role in accelerating the pace of clinical trials.

cal companies, the Association plays a 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.

Alzheimer's Association Cerebrospinal Fluid (CSF) Quality Control Program

Launched in fall 2009, the Alzheimer's Association Cerebrospinal Fluid Quality Control Program brought together laboratories across the globe with the aim of standardizing the measurement of potential Alzheimer biomarkers in CSF.

More than 60 labs in North and South America, Asia, Australia and Europe are participating in the program.

Well-validated CSF biomarkers could be useful in aiding early detection of Alzheimer's and improving diagnostic accuracy.

Several studies, including studies involving data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), have shown that levels of biomarkers in CSF could be accurate predictors of which individuals will go on to develop Alzheimer's disease. Of particular interest are levels of beta-amyloid, phosphorylated tau and total tau.

Well-validated CSF biomarkers could be useful in aiding early detection of Alzheimer's and improving diagnostic accuracy. As scientists learn more about the relationship between well-validated CSF biomarkers and the underlying neurobiology of the disease, biomarkers will become useful tools in assessing the effect and effectiveness of drugs in clinical trials and in identifying asymptomatic people at risk for developing Alzheimer's.

The first of the two-part quality control program established consistent methods for performing the lumbar punctures required to collect CSF as well as consistent methods for collecting and processing CSF. The second part compared

biomarker measurements among participating labs, which received identical samples.

The quality control program and protocols were an outgrowth of discussions held at the Alzheimer's Association International Conference on Alzheimer's Disease 2009, which included input from ADNI representatives, biotechnology companies, pharmaceutical companies and CSF laboratories.

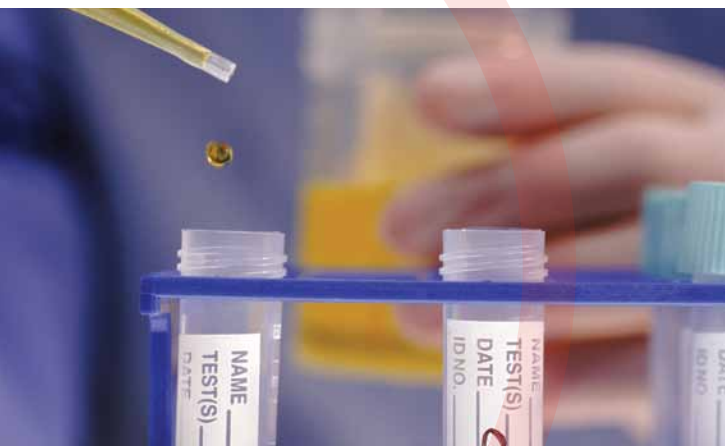
The Alzheimer's Association CSF Quality Control Program is made possible through the generous support of Dana and Dave Dornsife.



Research Roundtable

More than 100 researchers gathered in Washington, D.C., at the spring and fall meetings of the Alzheimer's Association Research Roundtable to discuss early diagnosis of Alzheimer's disease and the challenges and benefits of international clinical trials.

Begun in 2003 with four sponsors, the Research Roundtable has grown to include 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 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.

In a gathering that meeting co-chair Steven DeKosky, M.D., of the University of Virginia

described as bringing together the “dream team” of those in the field of Alzheimer's disease research, scientists at the spring Roundtable discussed the current criteria for Alzheimer diagnosis, which are nearly 25 years old, and whether the time had come to establish new criteria that take into account advances in Alzheimer research.

Richard Mohs, Ph.D., of Eli Lilly & Company noted that the current criteria had served the field well, but that much has been learned since 1984 about the neuropathology and epidemiology of Alzheimer's, as well as about biomarkers that might signal the presence of the disease in its earliest stages, when clinical symptoms have not yet developed. The question posed at the meeting, he explained, was whether these data are sufficient to warrant revision of the criteria for establishing a diagnosis of Alzheimer's.

The meeting brought the question into focus with discussions of the current status of Alzheimer's disease classification, improvements in cognitive and performance-based assessments, clinical presentation and risk assessment, structural and functional imaging assessments, and molecular imaging markers of Alzheimer's. David Knopman, M.D., of the Mayo Clinic observed that the current criteria are reasonably reliable and specific but do not detect Alzheimer's in its mildest forms and that if new criteria were developed, they should detect Alzheimer's across the continuum of the disease, from its earliest to its latest stages. In a statement echoed throughout the meeting, Dr. Knopman said that new criteria would need

to work for all stakeholders in the field, including clinicians, researchers and regulatory agencies.

The Alzheimer's Association and National Institute on Aging (part of the National Institutes of Health) moved forward on the recommendations resulting from the Roundtable and in 2009 formed three workgroups to propose revised criteria for preclinical Alzheimer's (Alzheimer's before the development of symptoms such as memory loss), mild cognitive impairment and Alzheimer's dementia.

Researchers reconvened in fall to learn about the challenges, benefits and ethical issues involved in conducting international Alzheimer's clinical trials. Several factors drive the need to conduct international clinical trials. Some sponsors of clinical trials and the clinical research organizations with which they partner to conduct clinical trials have found the United States to be saturated with clinical trials. As a result, they have difficulty finding the number and types of clinical trial participants required to conduct a study. For example, a trial may require that participants are "treatment-naïve," that is, have never taken a drug to treat Alzheimer's. These types of participants are typically easier found outside the United States.

Another driver is that trials conducted today tend to be longer and require more participants than the clinical trials that led to the development of the five drugs approved by the U.S. Food and Drug Administration (FDA) for the treatment of Alzheimer's. Cost is yet another factor in conducting clinical trials abroad. A clinical trial conducted in China, for example, can cost 20 percent that of conducting the same trial in the United States. In addition, participant recruitment numbers are often reached more quickly outside of the United States, and participant retention and compliance may be significantly increased in clinical trials conducted abroad.

However, with these benefits come implementation challenges and cultural complexities not present in U.S. clinical trials. A challenge that frequently surfaced during the Roundtable was the extended time required to get a trial up and running. While 48 days might be typical in the United States, start-up times can approach six months in Poland and Italy, four to eight months in Latin America, and even longer in some Asian countries. Speaker Michele Bronson, Ph.D., of Medivation, Inc., noted that in Latin America, Chile, Argentina and Brazil have the shortest start-up times, in that order, while in the European Union (EU), the fastest start-up times were in the United Kingdom, Belgium and the Netherlands.

In addition to the relative ease of recruiting sufficient numbers of clinical trial participants, potential costs savings, and potential gains in participant compliance and retention, conducting international trials enables study sponsors to provide evidence whether their experimental drugs are effective in a wide range of populations. Providing this evidence boosts the market potential of a new drug.

Jason Karlawish, M.D., of the University of Pennsylvania, asked attendees to consider the value of Alzheimer studies in sites being considered for clinical trials before proceeding with site selection. For example, Alzheimer studies may hold little value in low-income countries, where the leading cause of death is lower respiratory disease, shorter life spans mean that many people may not live long enough to develop Alzheimer's, and extended families with multiple caregivers lessen the burden of Alzheimer care. In this case, said Karlawish, it falls upon the clinical trial sponsor to explain why individuals should participate in a study that may hold little value to them.

Prevalence Conference

At the first Prevalence and Trends of AD and Other Age-Related Cognitive Disorders Conference, leaders in the epidemiology of Alzheimer's addressed the complex issues surrounding differences in prevalence numbers for Alzheimer's disease.

Jointly sponsored by the Alzheimer's Association and the National Institute on Aging, the conference drew nearly 100 attendees.

Diagnostic criteria used to define Alzheimer's and other dementias and challenges in applying those criteria were identified as important factors in varying estimates of prevalence (number of existing cases) and incidence (number of new cases) and were underscored in the conference.

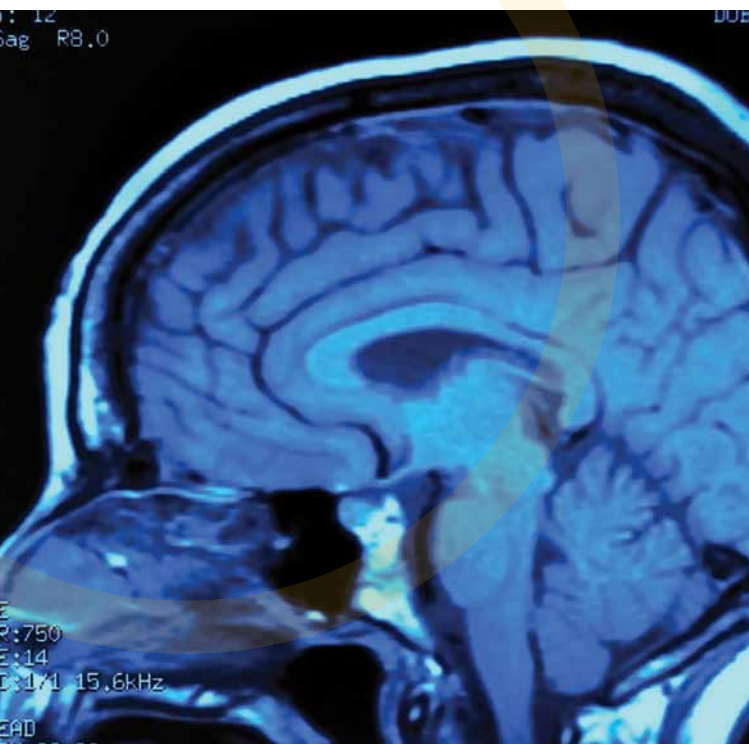
The conference also included discussions on assessing dementia in culturally diverse populations such as Mexican Americans and African-Americans and in the oldest old (those 85 and

older). Attendees examined numerous other factors that might contribute to differences in the reported prevalence and incidence of Alzheimer's, including the impact of culture and literacy on evaluating cognitive impairment and dementia.

Evening sessions provided data on estimating the global burden of dementia and a closer look at the sources of variability in U.S. prevalence estimates of dementia.

Changes in diagnostic criteria for Alzheimer's and other dementias and what that might mean for reports of Alzheimer prevalence were the subject of presentations and much discussion, as was the importance of understanding the spectrum of cognition from health to impairment. Evening sessions provided data on estimating the global burden of dementia and a closer look at the sources of variability in U.S. prevalence estimates of dementia.

Additional details about the presentations and discussions will appear in *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*.



Other Initiatives

In 2009, the Association's role in advancing Alzheimer science was also evident by the success of its bimonthly journal, *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*; increased visibility of its professional society, ISTAART; and progress of its Clinical Studies Initiative.

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

In 2009, *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* saw a nearly 120 percent increase in citations to the journal and more than a 65 percent increase in online article requests compared with 2008. Page views of the peer-reviewed journal were consistently higher for each month in 2009 compared with 2008. These data were gathered by ScienceDirect, the world's largest electronic collection of science, technology and medicine information, and the leading online access point for users including those at colleges, universities, and other institutions.

That researchers are increasingly turning to the journal as a source of the latest developments in Alzheimer research was also reflected in 2008, when the journal was 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.

Completing its fifth year of publication in 2009, *Alzheimer's & Dementia* is distributed to members of the Association's International Society to Advance Alzheimer Research and Treatment, as well as other subscribers, and is available to Alzheimer researchers through academic and other institutions.

Featuring comprehensive review articles, research articles, short reports on clinical trials, peer commentaries, perspective pieces, and abstracts from international research meetings, *Alzheimer's & Dementia* aims to present new research and new thinking across diverse areas of investigation, from drug development to health economics and neuropsychiatry.



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 2007. By the close of 2009, ISTAART had nearly 1,500 members representing 63 countries.

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.

This unique professional society offers a variety of networking opportunities that facilitate interdisciplinary collaboration among members that may lay the groundwork for accelerating advances in the field. In addition to networking opportunities, ISTAART members receive a variety of other benefits, including reduced conference registration fees and a subscription to the Association journal *Alzheimer's & Dementia*.

The online career center enables members to browse new employment opportunities across the world by accessing job postings exclusive to the ISTAART site, as well as opportunities listed on popular career sites.

In November 2009, ISTAART announced its latest phase of benefits, including an online career center. The career center enables members to browse new employment opportunities across the world by accessing job postings exclusive to the ISTAART site, as well as opportunities listed on popular career sites. Resources available through the career center also include a content library with tips on topics such as interviewing and creating an effective resume;

career coaching with a trained expert; and an “ask an expert” feature. Access to the ISTAART career center is free to members. Non-members may access it for a nominal subscription fee.

Also in November, the ISTAART Advisory Council approved the establishment of its first Professional Interest Area (PIA): Neuroimaging and Technology. PIAs provide a forum for the exchange of information in specific areas of dementia research and care. Besides providing networking opportunities, each PIA organizes its own Featured Research Symposium at AAICAD.

ISTAART also launched a new Member Center on its Web site. The center gives members the ability to access member benefits, such as newsletters and codes for the career center and online publications; update contact information and view membership status; and review the member calendar of events and RSVP online. An online membership directory is under way to facilitate communication between members.

Clinical Studies Initiative

The Clinical Studies Initiative was formed in 2007 to find effective ways to mobilize and motivate individuals to participate in clinical studies and accelerate the rate of 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. 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.

In 2009, several activities and programs moved from the conceptual and planning stages toward implementation. This included the Alzheimer's Association TrialMatch® clinical studies matching service, which launched in July 2010. The program offers Internet- and phone-based searching for Alzheimer's clinical trials, as well as follow-up calls from the Alzheimer's Association Contact Center. Individuals complete a brief questionnaire on their diagnosis and treatment history and are matched to trials for which they are eligible and interested. The service is confidential and free for patients, families, physicians, researchers and trial sites.

Additionally, as part of the Clinical Studies Initiative, the Alzheimer's Association collaborated with several physician organizations, including the American Osteopathic Organization (AOA), the American Academy of Family Physicians (AAFP), the National Medical Association (NMA) and the National Hispanic Medical Association (NHMA). These organizations collectively represent more than 200,000 physicians. The Association will be working with these organizations to raise awareness of Alzheimer's, promote early detection and diagnosis, and highlight the urgent need for clinical study participants.

The results of these partnerships will include a variety of member and public communication vehicles (journals, newsletters, Web sites, continuing education sessions, annual meetings/conferences, white papers, consensus statements, etc.) to be used to deliver collaboratively created information and training on early detection of Alzheimer's/dementia and participation in clinical studies.

The Association is working closely with the chapters who were part of the Clinical Studies Initiative pilot to promote Clinical Studies Initiative projects and TrialMatch. Each of the chapters has been given an opportunity to apply for a \$10,000 grant to organize a menu of activities to educate the public and physicians about the urgent need for individuals to enroll in clinical studies.



Funded Research:

advancing the field and the careers of those who help shape it

The Alzheimer's Association is the world's largest private, nonprofit funder of Alzheimer research, having awarded more than \$279 million to 1,900-plus researchers since 1982.

Through its International Research Grant Program, the Association has helped advance broad fields of Alzheimer research—including early detection, prevention, and treatment—as well as the careers of the specific individuals who received funding.

In their own words, scientists Drs. Bruce Lamb, Jaya Padmanabhan, Sanjay Pimplikar, Cheryl Luis and Liqin Zhao describe the impact of being chosen Alzheimer's Association grant recipients.

Through its International Research Grant Program, the Association has helped advance broad fields of Alzheimer research.





Bruce T. Lamb, Ph.D.

Associate Staff, Lerner Research Institute, and Associate Professor, Cleveland Clinic Lerner College of Medicine, Cleveland, Ohio, recipient of a 2008 Investigator-Initiated Research Grant and 2005 Zenith Fellows Awards

Alzheimer's is a complex disease influenced by multiple genetic and environmental factors. A common denominator is the amyloid precursor protein (APP) and its byproduct, beta-amyloid, which seems to be involved in the initiation of the anatomical and functional changes of Alzheimer's. Beta-amyloid is a protein that goes on to accumulate into large clusters called plaques, one of the hallmarks of the disease. My laboratory uses complementary approaches to help unravel the complexities of Alzheimer's disease and identify factors that contribute to the disease and could be targeted by new drugs and therapies.

Through generous support from the Alzheimer's Association over the years, including both Investigator-Initiated Research Grants and a Zenith Award, my laboratory has 1) used novel animal models of Alzheimer's to examine the role of genetic and environmental factors that may trigger specific Alzheimer brain changes, 2) developed more complete animal models of the disease and 3) investigated therapies that might decrease the risk for Alzheimer's. These studies would not have been possible without the support of the Alzheimer's Association.

To identify genetic factors that may trigger brain changes, we have used groups of mice that have

been genetically engineered to carry different genes or combinations of genes associated with Alzheimer's. Mice with a mutant human Alzheimer's gene show a variety of brain changes, including increased APP and beta-amyloid production, development of plaques, activation of the immune system, behavioral abnormalities and abnormal neuronal changes called cell cycle events (CCEs). Depending on the genes they carry, some mice exhibited all, some, minimal or none of these changes. Employing a technique called genetic mapping, we have identified the location of several genes in these mice that influence both the production of beta-amyloid and its accumulation into plaques. Our current focus is identifying the specific genes involved in these events.

In addition to genetic factors, through support from the Alzheimer's Association we have initiated studies to examine the effects of specific environmental factors on the development of Alzheimer brain changes. In particular, we have focused on the effects of high-fat/high-cholesterol diets, as studies in humans have suggested that this may be a risk factor for the development of Alzheimer's.

Our studies have demonstrated that high-fat/high-cholesterol diets similar to those consumed by Western societies increase levels of beta-amyloid in some mouse models of Alzheimer's. The effect of a high-fat/high-cholesterol diet depends entirely on the genetic background of the mice, with some mice

being highly sensitive to the effects of diet, others completely resistant to the effects of diet and others falling somewhere in between. These studies suggest that the effects of an environmental risk factor for Alzheimer's depends on the genetic background of the mice. This has implications for 1) human studies examining the rates of Alzheimer's in different populations, 2) recommendations for specific diets to reduce Alzheimer's risk and 3) the development of therapies to counteract the effects of diet.

Finally, we have been examining whether common medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) have a beneficial effect in Alzheimer mouse models. Notably, we have found that NSAIDs including ibuprofen and naproxen can block inflammation and neuronal CCEs if given before the development of extensive Alzheimer brain changes. However, if NSAID treatments are begun later in disease progression, it does not reverse neuronal CCEs and other brain changes and

// My lab has been at the forefront of refining animal models of Alzheimer's. To build an animal model that most closely mimics what happens in humans with Alzheimer's, we have recently undertaken a study to introduce human Alzheimer genes into mice that have been genetically engineered to lack the mouse counterparts for these genes. This model should provide a better testing ground for new Alzheimer therapies. **//**

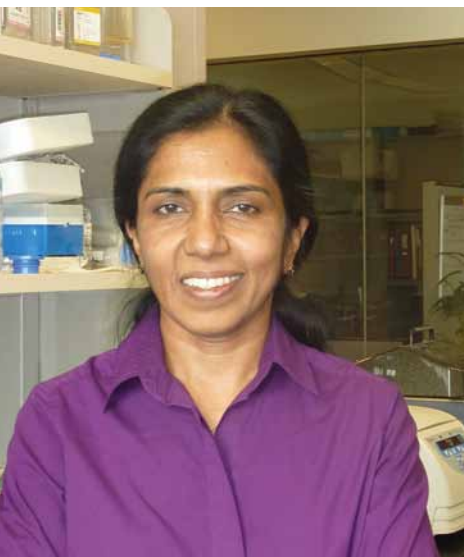
—Bruce T. Lamb, Ph.D.

My lab has been at the forefront of refining animal models of Alzheimer's. To build an animal model that most closely mimics what happens in humans with Alzheimer's, we have recently undertaken a study to introduce human Alzheimer genes into mice that have been genetically engineered to lack the mouse counterparts for these genes. This model should provide a better testing ground for new Alzheimer therapies.

One of the first surprises in this project came in a mouse whose own APP gene had been removed and replaced with a mutant human APP gene that causes Alzheimer's. Substituting the human APP gene actually lessened the brain changes of Alzheimer's. This suggests that the mouse APP gene contributes to the development of the brain changes in the transgenic mouse models of Alzheimer's.

has only a minimal effect on other signs of Alzheimer's exhibited by the mice.

These findings are consistent with studies in humans demonstrating that long-term use of NSAIDs for arthritis is associated with a decreased risk for Alzheimer's, while short-term clinical trials with NSAIDs in individuals diagnosed with Alzheimer's have proven largely unsuccessful. These results also suggest that NSAID treatments in humans may need to be initiated as a preventative measure, substantially before the development of extensive brain changes, to be successful.



Jaya Padmanabhan, Ph.D.

Assistant Professor of Molecular Medicine, Johnnie B. Byrd, Sr. Alzheimer's Center & Research Institute, University of South Florida, Tampa, recipient of a 2008 Investigator-Initiated Research Grant

I am grateful to the Alzheimer's Association for providing me with the first independent grant of my scientific career, an Investigator-Initiated Research Grant (IIRG), in 2008. I found out about this while we were traveling north, taking our daughter to a music camp in Vermont. My eyes welled with tears when I read the e-mail from the Association. The award came during a very hard time. The Byrd Alzheimer's Institute had just started, and the money situation was tight. This was when I found out that the Alzheimer's Association was going to fund our research. I am really thankful to this great organization for their timely help.

The major hallmarks of Alzheimer's disease are protein aggregates known as amyloid plaques and neurofibrillary tangles. Our laboratory is interested in understanding the molecular, cellular and biochemical changes in the brain that lead to plaques and tangles. Two proteins associated with plaques and tangles are beta-amyloid, a fragment of the amyloid precursor protein (APP), and tau. The grant from the Alzheimer's Association provides funding to help our laboratory examine the role of inflammatory proteins (proteins associated with inflammation) in Alzheimer's disease. Among these proteins are apolipoprotein E e4 (ApoE-e4),

alpha 1-antichymotrypsin (ACT), cytokines and complement factors. We are currently analyzing the significance of ACT in Alzheimer's disease.

ACT is present in abnormally high numbers in cells called astrocytes that surround plaques in the Alzheimer brain. Higher levels of ACT have been reported in cerebrospinal fluid from people with Alzheimer's, signifying that elevated levels of ACT could serve as a biomarker for early detection and diagnosis of Alzheimer's. Previous studies have shown that ACT helps individual beta-amyloid proteins stick together to form small clumps called oligomers. These clumps are much smaller than plaques and precede the development of plaques.

The combination of ACT and beta-amyloid seems to be more toxic to brain nerve cells tested in cell culture experiments than beta-amyloid itself, suggesting that this combination may have deleterious effects in brains as well as in brain cells. Other studies in mice that were genetically engineered to produce Alzheimer's and that produced excess ACT and APP showed that excess ACT accelerated the development of Alzheimer brain and behavioral changes. How ACT brings about these changes is not clearly understood. Beta-amyloid is generated when APP is clipped first by the enzyme beta-secretase and then by the enzyme gamma-secretase. Whether ACT affects these enzymes is currently being examined.

In addition to its effects on beta-amyloid, in cell culture studies of neurons from the cortex region of the brain, we found that ACT induces the protein tau to take on additional phosphate molecules (called phosphorylation). Purified ACT from human plasma was used for these studies. Neurons treated with the purified ACT showed a significant increase in phosphorylation at three particular sites on the tau protein that have been shown to be affected in Alzheimer's disease.

The second project in our laboratory is to determine the significance in Alzheimer's of proteins associated with cell division. These proteins are present in increased numbers in the Alzheimer brain. Neurons are non-dividing cells. Excess cell division proteins in the brain may disturb the normal function of neurons. Several investigators, we among them, have shown that inhibiting cell division in neurons grown in the lab protects them from degeneration and death. Results from several studies suggest

“We believe that a thorough knowledge of the molecular mechanisms involved in the development of Alzheimer's will help us generate novel therapies targeted toward neurodegenerative diseases, and funding from the Alzheimer's Association will help immensely in reaching this goal.”

—Jaya Padmanabhan, Ph.D.

Analysis of enzymes called kinases that are involved in tau phosphorylation showed that ACT increases the activity of the kinases ERK (extra-cellular signal-regulated protein kinase) and GSK-3 (glycogen synthase kinase 3). This suggests that one or both of these kinases may be involved in the tau phosphorylation that occurs with excess levels of ACT. This also implies that inhibiting the activity of these kinases may help prevent the changes in beta-amyloid and tau that are hallmarks of Alzheimer's. We hope to pinpoint the molecules involved in this process and use the information to develop drugs targeting these molecules, which may prove beneficial in treating the disease.

that Alzheimer's is like cancer, except that in cancer, cell division leads to an increase in cancer cells, while in Alzheimer's it leads to the degeneration and death of non-dividing neurons. By studying the differences and similarities between dividing cells and non-dividing neurons, we hope to gain information that will help us identify potential drug targets for Alzheimer's and cancer.

The IIRG from the Alzheimer's Association has helped advance both my research and my career. The grant helped me obtain a tenure-track faculty position in the Department of Molecular Medicine at the College of Medicine, University of South Florida, Tampa. I hope to do my best to help the scientific community find a cure or a way to prevent Alzheimer's disease.



Sanjay W. Pimplikar, Ph.D.

Associate Staff, Cleveland Clinic Foundation,
recipient of a 2008 Investigator-Initiated
Research Grant (IIRG), 2002 IIRG and 1995 Pilot
Research Grant

I entered the Alzheimer's disease research field more or less by accident.

Trained as a cell biologist, I was interested in studying how proteins on the outer membrane of a cell reached their correct destination inside a cell. I decided to use amyloid precursor protein (APP) as a marker protein to study this transport process. During these investigations we realized that when APP is clipped by the enzyme gamma-secretase, a fragment called AICD (for "APP intracellular domain") is able to enter the nucleus of the cell and change gene expression (some genes are "switched on" while others are "turned off"). Once I realized APP, a cell surface protein, could communicate with the nucleus of a cell in this fashion and that virtually nothing was known about AICD, I was hooked.

In the early years of AICD research, the attitude in the field oscillated between "AICD is inconsequential" to "AICD is not important." There is still some skepticism about its biological function and controversy about how it affects gene expression. However, the thinking in the field is now changing with the realization that AICD is conserved through evolution (meaning that it is identical in a range of species, from humans to mice) and interacts with several proteins that control communication inside the cell. A number of groups have started to make important contributions to our understanding of AICD biology and how it governs signaling inside cells.

Using genetic engineering techniques, we created mice that had elevated levels of AICD to study the effects of AICD overexpression. We were surprised to see the mice exhibit Alzheimer-like pathological features without increased levels of beta-amyloid or beta-amyloid plaques. Moreover, these features appear in a time-dependent fashion. Our transgenic mice start producing AICD at about 2 weeks. Abnormal activation of glycogen synthase kinase, a protein linked to the tau tangles of Alzheimer's, is seen at age 2 months. At age 3 to 4 months, the mice undergo an abnormal process in which phosphate is added to the tau protein. At this age, we also see abnormal, seizure-like electrical activity in the brain and changes in neuronal circuits, the 'wiring' of the brain that enables it to carry out various functions. Excess accumulation of insoluble tau and memory problems begin at 8 months, and neurons in the hippocampus of the mice start to die by 18 months. Thus, except for the development of beta-amyloid plaques (which are also found in non-demented individuals), the AICD transgenic mice seem to capture the essential pathological features of Alzheimer's.

We are now studying the underlying mechanisms that cause these pathological features, all of which occur in human Alzheimer's. Our latest findings suggest that inflammation in the brain is likely to be one of the pivotal events induced by AICD. We think that our observations in animals are applicable to human disease because we also find increased

amounts of AICD in the brains of people with Alzheimer's. If further studies confirm that AICD is a significant contributor to human Alzheimer's, we must change our thinking about the therapeutic strategies developed to fight Alzheimer's. Current clinical trials focused on reducing levels of beta-amyloid have met, at best, with limited success.

easy to convince others of ideas that run contrary to the prevailing dogma. In my view, the fact that the Association funded my previous and current studies on AICD demonstrates the Association's willingness to support innovative but risky ideas that more traditional agencies are reluctant to fund. Without the Association's support of my research

“Without the Association's support of my research program, I doubt that I would have pursued investigations of AICD. In fact, there is a good chance that without the Association's support I would not be doing Alzheimer research at all.”

—Sanjay W. Pimplikar, Ph.D.

Although a number of factors could account for this, the continued failure of amyloid-focused strategies should prompt us to seriously consider other, non-amyloid causes of the disease. I am organizing a symposium at the 2010 Annual Meeting of the Society for Neurosciences to discuss these alternative mechanisms.

I have been fortunate to receive significant funding from the Alzheimer's Association. It is not always

program, I doubt that I would have pursued investigations of AICD. In fact, there is a good chance that without the Association's support I would not be doing Alzheimer research at all.

I love interacting with the national as well as the local chapter of the Association. In the dark days of research when nothing seems to be going right, it is their commitment to the cause of fighting Alzheimer's that keeps me going.



Cheryl A. Luis, Ph.D.

Associate Clinic Director, the Roskamp Institute,
Sarasota, Florida, recipient of a 2009 New
Investigator Research Grant

The support of the Alzheimer's Association has allowed me to pursue an area of research that I refer to as the other major piece of the puzzle: cost-effective methods of earlier detection of Alzheimer's disease.

Science is moving closer to finding therapies that slow or stop the progression of Alzheimer's, but for these therapies to be truly beneficial, we must start treatment very early in the course of the disease. It makes little sense to halt the progression of the disease when an individual has already suffered considerable cognitive decline and functional impairment. My research at the Roskamp Institute has focused on developing practical methods for earlier detection of dementia.

The New Investigator Research Grant (NIRG) will allow further refinement of a screening approach that I and my colleagues have been studying for several years. This novel approach combines a cognitive test with studies of biomarkers in blood. Biomarkers are physical changes that indicate the presence of a disease or an elevated risk of developing a disease. In addition, this approach may prove useful in measuring the impact of potential new Alzheimer drugs.

Traditional cognitive tests of dementia severity such as the Mini-Mental State Exam (MMSE) are inadequate in detecting the early cognitive signs of the illness and mild cognitive impairment (MCI). MCI is a possible transitional state from normal cognition to Alzheimer's. One of the few cognitive tests that has been consistently effective in identifying those with MCI is the Montreal Cognitive Assessment (MoCA). It is more comprehensive than the MMSE in that it includes items assessing immediate and delayed memory, language fluency, visuospatial skill (the ability to understand and use symbols and maps, for example, and the brain's ability to translate visual signals into a correct impression of where objects are in space), abstract reasoning and divided attention (the ability to pay attention to more than one task at once, such as carrying on a conversation while preparing a meal).

The physical and functional changes of Alzheimer's are intimately linked to the abnormal accumulation of fragments of the amyloid precursor protein called beta-amyloid 1-40 and 1-42. Increased production and decreased removal of beta-amyloid is thought to precede the early symptoms of Alzheimer's, which typically include a decline in episodic memory, the ability to remember the people, places and events of episodes from one's past. As beta-amyloid accumulates, a cascade of inflammation, cognitive and behavioral decline and, ultimately, cell loss ensues.

We have been studying beta-amyloid in blood for its potential use as a marker of disease onset and progression because obtaining a blood sample is far more cost-effective and applicable for wide-scale use in routine healthcare settings than lumbar puncture and beta-amyloid imaging of the brain. Using a series of blood samples, we have shown that these markers in blood are less variable in

Furthermore, Alzheimer's is associated with increased levels of inflammation-causing proteins around beta-amyloid deposits in the brain. We have shown that a blood sample tested for the biomarkers beta-amyloid, inflammation-related proteins CD40 and CD40L, and Alzheimer's risk gene apolipoprotein E-e4 (ApoE-e4) has a high degree of accuracy in diagnosing Alzheimer's.

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— Cheryl A. Luis, Ph.D.

people with Alzheimer's than in healthy, nondemented individuals. We and others have also shown that levels of beta-amyloid in the blood are predictive of cognitive decline in healthy at-risk seniors and in individuals with MCI. In addition, in a group of individuals at high-risk for Alzheimer's whom we have been studying for several years, we have shown that beta-amyloid levels in blood are impacted by vascular disease.

Moreover, we have shown that beta-amyloid levels in blood are associated with the cognitive changes seen in Alzheimer's. In individuals with MCI or early Alzheimer's, higher levels of beta-amyloid 1-42 in blood are associated with poorer performance on episodic memory tests while higher levels of beta-amyloid 1-40 are correlated with impaired language fluency and processing speed, as well as impaired divided attention, which are indicators of disease progression.

Without funding from the Alzheimer's Association, I would not be able to move forward with this important line of investigation, which will examine how accurately the combined use of MoCA and blood tests of beta-amyloid, CD-40 and CD-40L, and APOE-e4 detect the presence or absence of Alzheimer's. We hope that further refinement of this screening method will lead to funding from the National Institutes of Health to take this approach into the primary care setting for further study.

Wide-scale, cost-effective methods for very early detection of Alzheimer's will allow us to start disease-modifying treatment early and hopefully prevent the significant loss of cognitive abilities currently experienced by people with Alzheimer's.



Liqin Zhao, Ph.D.

Research Assistant Professor of Pharmacology and Pharmaceutical Sciences, University of Southern California, Los Angeles, recipient of a 2005 New Investigator Research Grant

I often think about a very emotional conversation with a close friend regarding his 69-year-old father, who had just been diagnosed with early-stage Alzheimer's disease and had failed his driver's license exam. My friend was deeply hurt by the mean way in which his father communicated with him after failing the exam. "He is perfectly fine in all other areas, and I can't believe that he was so mean to me," my friend repeated, even after I had spent hours explaining to him how a human brain's structure and function can be altered by Alzheimer's and that these changes can affect the individual's judgment and the way they communicate and act.

Many months later, my friend was able to put these feelings behind him, but then was overwhelmed with emotion as he witnessed the disease slowly taking his father away from their family. While living in a nursing home over the next five years, his father continued to worsen until he could no longer recognize the people around him, even family members.

Those conversations with my friend solidified my passion for Alzheimer research and finding a cure so others would not experience the emotional struggles my friend had experienced. The

Alzheimer's Association opened a door to help turn my passion into reality. The New Investigator Research Grant (NIRG) from the Alzheimer's Association enabled me to pursue my own ideas and conduct the basic science research that has led to the discovery of a promising therapy for Alzheimer's. This novel therapy is being studied in a clinical trial funded by the National Institute on Aging (NIA).

Despite the attention given to Ronald Reagan, Charlton Heston, Sargent Shriver and other men who developed Alzheimer's, elderly women are still by far the principle victims of the disease, accounting for 68 percent of cases. Both basic science and clinical research suggest that ovarian estrogens may help prevent neurodegeneration in women. The loss of estrogen during menopause could be a risk factor for cognitive impairment and dementia such as Alzheimer's. Moreover, research suggests that timely initiation of an estrogen-containing hormone therapy (HT) could help prevent Alzheimer's and alleviate other estrogen deficiency-associated symptoms in menopausal and postmenopausal women. However, since current forms of HT may increase women's risk of breast cancer, stroke and blood clots, it's imperative that we develop an alternative HT that is both effective and safe.

Over the past decade, a group of plant-derived, non-steroidal estrogen-like compounds, known as phytoestrogens, have been found to have similar

functional activity to ovarian estrogens and have received enormous attention by both researchers and clinicians. This increased interest in phytoestrogens has been attributed in large part to the health-promoting effects suggested by epidemiological

American and 70 percent of European women. In addition, historically, breast and prostate cancer rates in Asia have been much lower than in Western countries. These positive observational findings, however, lack confirmation from well-controlled,

// In addition to its tremendous impact on my research, the NIRG award from the Alzheimer's Association has monumentally advanced my career as an independent Alzheimer researcher. I was appointed to a research faculty position soon after I received this honorable award, and the funded research has resulted in several peer-reviewed publications and two U.S. patent applications. No words can describe how grateful I am to the Alzheimer's Association for its instrumental role in making this happen. //

—Liqin Zhao, Ph.D.

studies of soy-based foods, which are rich in phytoestrogens and regularly consumed in Asian countries. For example, a number of epidemiological studies conducted in populations across the continents revealed a 2.5 times lower prevalence of Alzheimer's in Japan and China than in North America and Europe, where individuals consume less than 1 milligram of phytoestrogens per day compared with 20–80 milligrams per day in Asian individuals.

Moreover, epidemiological studies suggest that this difference in phytoestrogen intake may also contribute to differences in the incidence of other sex hormone-related disorders seen in Asian versus North America and European populations. In particular, recent statistics show that only 25 percent of Japanese and 18 percent of Chinese menopausal and postmenopausal women experience hot flashes compared with 85 percent of North

randomized clinical trials, which have produced inconsistent and inconclusive data.

Growing up in China and then living in the United States has given me a firsthand opportunity to appreciate the differences in the diets between these two distant parts of the world. Capitalizing upon such knowledge, I hypothesized that the discrepancies between observational studies focusing on soy-derived foods and interventional studies examining soy-derived extracts could have originated from the differences between the natural forms of soy foods and pharmacological preparations of soy extracts.

The bottom line is that soy foods and soy extracts are not the same. In recent years, many soy extract products have become available over the counter. Most of these are advertised as dietary supplements for use by women to lessen menopausal

symptoms such as hot flashes. However, these supplements are unregulated by the U.S. Food and Drug Administration, so their safety and efficacy are questionable.

The greatest problem is that the processing of soy extract products is not standardized. An analysis of a number of commercial soy extract supplements revealed an abundance of substances of unknown origin. Some of these substances may have been created through the extraction process. In this process, the organic solvents and high temperatures used may cause chemical reactions leading to the generation of substances not naturally present in soy. These substances could produce an undesirable effect, counteracting the favorable health-giving properties of other substances in the supplement.



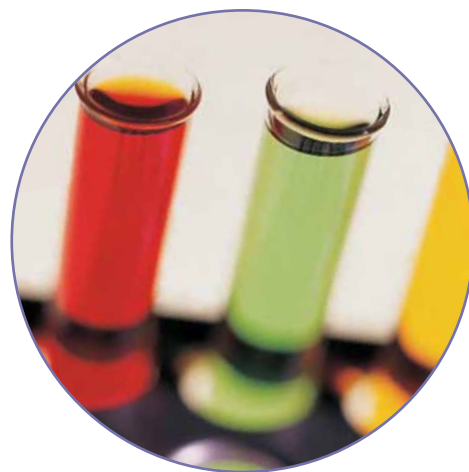
Funding from the Alzheimer's Association enabled me to test this hypothesis and attempt to develop a phytoestrogen formulation that is safe and effective. The research included screening a database of 25,000 phytoestrogens and resulted in the discovery of a formulation we've called phyto-beta-SERM that was found to be neuroprotective. A nine-month study of female mice engineered to develop Alzheimer's that were given the formulation provided additional support for the therapeutic potential of the formulation in slowing or reducing the cognitive decline and neurophysiological changes associated with Alzheimer's. In contrast, mice

receiving a commercial soy extract-containing diet did not show these improvements.

To my tremendous excitement, these benchside scientific discoveries have led to an NIA-funded, recently launched, first-in-humans pilot trial of phyto-beta-SERM. The trial evaluates the formulation's safety, its effect on hot flashes and cognition in menopausal and postmenopausal women and how it is absorbed, distributed, and metabolized (its pharmacokinetics) in the body. The trial consists of two studies to be completed in the next three years. The Phase I study is designed to determine the pharmacokinetics of the formulation and which doses are safe and well-tolerated. The Phase IIA study is a proof-of-concept study that will continue to examine safety and best dosages but also examine the formulation's effect on hot flashes and cognition. The success of these early stage human studies will lay important foundations for later stage, long-term efficacy studies in Alzheimer patients.

For many years, one of the largest unmet medical needs in the health of menopausal and postmenopausal women has been an estrogen therapy that is both effective and safe. I am hopeful that my research could lead to a breakthrough to fill the gap. The formulation may also help preserve cognitive function in men.

Perspectives in Alzheimer Science *timeline*



January

1

Brain “Exercises” as Dementia Therapy

In recent years, many games and exercises have been developed that aim to stimulate the brain and help prevent dementia. Researchers have analyzed data from numerous studies of such “cognitive training.” Their analysis found no clear evidence that cognitive training influenced cognitive loss. Current studies on this topic are small and inconclusive. The team recommends that future brain training research follows participants for a longer period and assesses the training’s effectiveness on a wider array of brain functions.

Alzheimer’s & Dementia: The Journal of the Alzheimer’s Association, January 2009;5(1):50–60.

Polyphenols in Red Wines May Reduce Alzheimer Pathology

Drinking red wine that contains cabernet sauvignon and muscadine grapes has been shown to significantly reduce the development of Alzheimer pathology and memory deterioration in mice by reducing amyloid accumulation in the brain. The study adds further support to the hypothesis that moderate consumption of red wines might facilitate disease-modifying interactions between polyphenolic compounds and beta-amyloid and suggests the possibility of developing a combination of dietary polyphenolic compounds for Alzheimer prevention and therapy.

Journal of Alzheimer’s Disease, January 2009;16(1):59–72.

Muscle-Building Protein Could Prevent Brain Cell Damage in Alzheimer’s

Collagen protein plays an essential role in building muscles and cartilage. Scientists discovered that a kind of collagen, called collagen VI, can protect brain cells from damage related to Alzheimer’s disease. Studying mice that were engineered to develop Alzheimer-like symptoms—as well as brain tissue from people who died of Alzheimer’s—the researchers observed that collagen VI levels were increased in a part of the brain called the dentate gyrus, which is vulnerable to Alzheimer damage. They then determined that collagen VI binds to beta-amyloid and may prevent toxic amyloid clumps called oligomers from harming brain cells. Future Alzheimer therapies may incorporate the potential protective effects of collagen VI.

Nature Neuroscience online (Print: February 2009;12(2):119–121.)

6

Genes Found that Increase Alzheimer Risk

Study results have revealed nine genes that may make people more likely to develop Alzheimer's disease. Researchers identified the genes by sequencing—or translating the genetic code—of thousands of gene variations from about 500 people with Alzheimer's and 500 healthy people. Discovering the genetic causes of Alzheimer's could lead to better methods of preventing it or diagnosing it at its earliest stages.

American Journal of Human Genetics, January 2009;84(1):35–43.

Imaging Technology Used to Detect Possible Early Signs of Dementia

Investigators have been using positron emission tomography (PET) imaging to search for two key protein clumps associated with Alzheimer's disease: beta-amyloid plaques and neurofibrillary tangles. The team injected 76 non-demented participants with FDDNP, a newly developed chemical that binds to plaques and tangles and can be detected on PET brain scans. According to the results, participants who showed high concentrations of FDDNP in their brains had other conditions that placed them at risk for Alzheimer's. Some had mild cognitive impairment (MCI), some had the Alzheimer-related APOE-e4 gene, and some had both MCI and APOE-e4. These results suggest that PET-FDDNP technology could prove a useful tool for early Alzheimer diagnosis.

Archives of General Psychiatry, January 2009;66(1):81–87.

7

Process of Nerve Cell Degeneration May Link Several Different Brain Diseases

Research results shed new light on how neurons die in Alzheimer's disease and other neurological disorders. The study, supported in part by the **Alzheimer's Association**, analyzed mice that lacked a neuronal protein called modifier of cell adhesion (MOCA). As the mice aged, protein clumps built up in their nerve cells' axons—the armlike extensions through which neurons communicate. This clumping led to axonal degeneration and eventual nerve cell death. In addition, the mice developed a motor coordination problem called ataxia. The researchers believe that this process may be involved in multiple brain diseases, including Alzheimer's, and could be targeted in a variety of disease therapies.

Journal of Neuroscience, January 7, 2009;29(1):118–130.

8

Antipsychotics Can Cause More Harm Than Good

Antipsychotic drugs have long been used to treat aggression and other mental problems related to Alzheimer's disease. However, a British study has found that these drugs may cause serious side effects. Elderly participants in the study were more likely to suffer stroke, chest infections and earlier death if they took antipsychotic drugs than if they took a placebo. Study researchers say that antipsychotic treatments are still useful for people with severe, dementia-related behavioral problems, but they do not recommend the drugs for most people with dementia.

Lancet Neurology online (Print: February 2009;8(2):151–157.)

Multiple Kinds of Statins May Help Prevent the Onset of Alzheimer's Disease

Researchers have found that people who take statins are 43 percent less likely to develop Alzheimer's than people who do not take these cholesterol-lowering drugs. The team used data from a large Dutch study assessing cognitive loss over time. Results showed that a variety of statins—including atorvastatin, simvastatin and pravastatin—had similar protective effects against Alzheimer's compared with a placebo. Moreover, the drugs were just as effective among people with the Alzheimer-related APOE-e4 gene as they were among people without the gene. These findings confirm earlier research on statins and could lead to statin-based Alzheimer therapies.

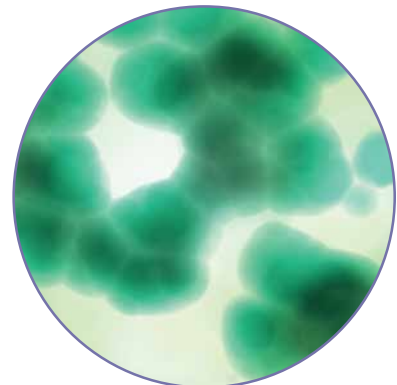
Journal of Neurology, Neurosurgery and Psychiatry, January 2009;80(1):13–17.

11

Gene Variant Boosts Alzheimer Risk

Investigators have found that women who inherit two copies of a gene variant possess a greater risk of developing Alzheimer's disease. Because this gene—a variant of the PCDH11X gene—occurs on the X chromosome, only women can inherit two copies. Women have two X chromosomes, while men have an X and a Y chromosome. However, even inheriting one copy of the gene has been shown to increase Alzheimer risk slightly. Normal PCDH11X genes encode a protein that promotes cell development and cell-to-cell communication in the central nervous system. According to the researchers, variant PCDH11X might be involved with presenilins, proteins linked to inherited forms of Alzheimer's. Further research could lead to novel methods of Alzheimer prevention or early diagnosis.

Nature Genetics online (Print: February 2009;41(2):192–198.)



12

Diabetes Treatment Linked to Brain Injury Patterns in Dementia

Individuals with dementia and diabetes who receive treatment for diabetes appear to suffer a different pattern of brain injuries than people with dementia and diabetes who do not receive treatment. Scientists have found that those who received treatment for diabetes had more damage to brain blood vessels and less damage caused by beta-amyloid and toxic oxygen molecules than those who did not receive treatment. Brain injury patterns among those with dementia but no diabetes were similar to those of people with dementia and untreated diabetes. If confirmed by future research, these findings could help scientists understand the causes of dementia and develop more precise therapies for this subpopulation of people with dementia.

Archives of Neurology online (Print: March 2009;66(3):315–322.)

15

Caffeine May Reduce Dementia Risk

People who drink coffee during midlife may decrease their risk of Alzheimer's by as much as 65 percent, Finnish researchers suggest. The researchers acquired their results after a long-term study of middle-aged participants who drank varying daily amounts of coffee. They found that the individuals who drank "moderate" amounts of coffee—3–5 cups per day—were least likely to develop dementia. These results, however, are preliminary and need to be confirmed by larger studies. The exact relationship between caffeine consumption and brain health remains unclear.

Journal of Alzheimer's Disease, January 2009;16(1):85–91.

20

Lifestyle Choices Could Prevent the Onset of Dementia

People who lead socially active lives with limited stress may reduce their risk of Alzheimer's disease. Researchers conducting a six-year study of more than 500 elderly participants with varying lifestyles found that the people who were both outgoing and calm were half as likely to develop dementia as those with only one of these positive lifestyle characteristics.

Neurology, January 20, 2009;72(3):253–259.

22

Verbal Abuse Common Among Caregiver Relatives of People with Dementia

After questioning more than 200 family caregivers of people with dementia, researchers found that more than half committed some form of verbal abuse toward the person in their care. Such abuse often consisted of harsh yelling, though some caregivers admitted to making verbal threats. Caregiver abuse usually occurs after the person with dementia has become aggressive or difficult to handle. The researchers hope their study's results will focus more attention on improving dementia care in the home, as well as in clinics and hospitals.

British Medical Journal, January 22, 2009;338:b155.

28

Developing Midlife Diabetes Boosts Alzheimer Risk

As part of an ongoing study of twins, Swedish researchers found that participants who developed diabetes before age 65 had more than double the risk of developing Alzheimer's disease as those who did not develop diabetes. These results suggest that many of the lifestyle choices that increase one's chances of getting diabetes, including overeating and lack of exercise, may also be risk factors for dementia. The team's study was supported, in part, by the **Alzheimer's Association**.

Diabetes, January 2009;58(1):71–77.

Nicotinic Receptor Is a Potential Therapeutic Target for Alzheimer's

Researchers have found that nicotinic receptors in the basal forebrain, the part of the brain responsible for memory and learning, are highly sensitive to blockage by low levels of beta-amyloid, and that small aggregates of beta-amyloid had this same blocking effect. The researchers hypothesize that as beta-amyloid begins to increase, it first blocks acetylcholine signaling at the nicotinic receptors, possibly triggering neurodegeneration.

Journal of Neuroscience, January 28, 2009;29(4):918–929.

February

1

Mediterranean Diet May Delay the Progression of Alzheimer's

A study testing the effects of a "Mediterranean" diet—one high in fish, olive oil and vegetables—on nearly 2,000 people with mild cognitive impairment (MCI) or no cognitive problems found that, among the participants with MCI, those on the diet were less likely to develop Alzheimer's disease than those not on the diet. Moreover, cognitively normal people on the diet were less likely than those not on the diet to suffer memory problems. These results suggest that a healthy diet, may help lower one's risk of dementia.

Archives of Neurology, February 2009;66(2):216–225.

3

Education May Not Affect the Rate of Mental Decline in Old Age

Contradicting earlier research, a large study found that education does not slow the rate of cognitive decline in the elderly. However, educated older people were shown to have higher than normal levels of cognition when they began to lose their mental faculties. Thus, the time it took for them to become mentally incapable of independent living was also longer than typical. The investigators followed more than 6,000 people for up to 14 years, conducting at least three mental assessments for each one. Their results highlight the potential importance of education in delaying advanced Alzheimer's disease. Such delays could save millions of dollars in medical costs.

Neurology, February 3, 2009;72(5):460–465.

6

Atrophy in Certain Brain Regions May Predict Alzheimer's

People with certain patterns of brain damage on MRI scans may be particularly susceptible to Alzheimer's disease. In a study of more than 300 participants, most of whom had mild cognitive impairment, researchers found that certain individuals showed considerable brain atrophy in regions called the medial and lateral temporal lobes and the frontal lobes. These people suffered dramatic declines in cognitive function and brain health one year later, declines that may lead to an Alzheimer diagnosis. The research sheds new light on what Alzheimer's may "look like" before clinical symptoms appear. Such efforts could lead to earlier and more targeted Alzheimer interventions.

Radiology online (Print: April 2009;251(1):195–205.)

8

Naturally Produced Brain Protein Reverses Alzheimer Progression in Animals

Brain-derived neurotrophic factor (BDNF), a protein that occurs naturally in the brain, has been shown to halt the progression of Alzheimer's disease in rats, mice and monkeys. When the animals were treated with BDNF, they showed improved brain cell function—including cell-to-cell communication—and improved cognitive ability compared with animals that did not receive treatment. These positive effects occurred even though BDNF did not slow beta-amyloid accumulation in the animals' brains. The researchers, whose work was supported in part by the **Alzheimer's Association**, hope that BDNF might be used in tandem with amyloid-reducing techniques to provide a more potent, multi-pronged Alzheimer therapy.

Nature Medicine online (Print: March 2009;15(3):331–337.)

10

Study Tests the Driving Ability of People with Alzheimer's

Scientists describe the results of a study identifying factors that may indicate when a person with Alzheimer's disease should stop driving. Researchers tested the driving ability of 40 individuals with early Alzheimer's and 115 cognitively normal older people. On average, the drivers with Alzheimer's made 42 errors, compared with 33 for the nondemented drivers. Many of the errors made by those with Alzheimer's involved swerving or other lane violations. Subsequent cognitive testing found that the drivers who made the most mistakes had suffered the steepest declines in visual and motor skills. These results may contribute to accurate, physician-administered exams to gauge whether Alzheimer's disease has made a person unsafe behind the wheel.

Neurology, February 10, 2009;72(6):521–527.

11

The Body's Immune System May Help Reduce Protein Build-Up in Alzheimer's

The innate immune system is an ancient self-defense mechanism that fights off microbial invaders in the body. Using a treatment to stimulate this system, scientists have dramatically reduced beta-amyloid levels in mice engineered to develop Alzheimer-like symptoms. The treatment involves immune system molecules called toll-like 9 receptors. These results, along with the findings of other studies, show that beta-amyloid “vaccination” therapies may prove an effective option for people suffering with Alzheimer's.

Journal of Neuroscience, February 11, 2009;29(6):1846–1854.

12

Dementia Risk Could Increase After Exposure to Second-Hand Smoke

According to a British study, high amounts of second-hand smoke may cause cognitive loss and put people at risk for Alzheimer's and other forms of dementia. The study assessed more than 4,800 people, finding that participants with the most second-hand smoke exposure were about 44 percent more likely to experience cognitive impairment than people with less smoke exposure. These results confirm findings of earlier research and highlight a potential new benefit of smoke-free homes and public places.

British Medical Journal, February 12, 2009;338:b462.

Two Antibodies in the Blood May Predict Alzheimer Severity

Scientists have found that levels of two antibodies in the blood directly correspond to levels of brain inflammation in Alzheimer's disease. These antibodies attack molecules that proliferate in Alzheimer's: the protein fragment beta-amyloid and the protein RAGE (receptor for advanced glycation endproducts). Beta-amyloid and RAGE may work together to hinder cell-to-cell communication in the demented brain. Further testing of these antibodies could lead to an effective Alzheimer blood test.

Journal of Gerontology: Medical Sciences, February 2009;64A(2):264–271.

19

A Mechanism Used in Early Brain Development Might Contribute to Alzheimer's

During embryonic development of the brain and spinal cord, a “pruning” mechanism is used to destroy excess nerve cells. Researchers have found that a protein fragment called N-APP is involved in this mechanism and may play a role in Alzheimer's disease. N-APP is clipped from APP, the same molecule from which the dementia-related beta-amyloid fragment is cut. During Alzheimer's disease, N-APP may “highjack” the embryonic pruning mechanism in order to kill vital adult nerve cells. The researchers have found that, in laboratory studies of embryonic cells, they can block the pruning mechanism. They are now testing their procedure in adult neurons. If successful, this procedure could lead to a novel Alzheimer therapy.

Nature, February 19, 2009;457(7232):981–989.

26

Prion Proteins Assist Beta-Amyloid in Causing Alzheimer Brain Damage

The protein fragment beta-amyloid is suspected of causing brain cell damage and death in Alzheimer's disease. In cell culture studies, researchers have found that this damage may occur after prion proteins bind to beta-amyloid molecules. Prions are best known to cause such neurological disorders as Creutzfeldt-Jakob disease and mad cow disease. This research indicates a role for prions in Alzheimer's disease as well.

Nature, February 26, 2009;457(7233):1128–1132.

27

Beta-Amyloid Plaques Linked to Damaged Astrocytes in Alzheimer's Disease

Astrocytes are cells that occur throughout the brain and assist neurons in conducting brain functions. Using sophisticated imaging techniques, researchers studied the effects of Alzheimer's disease on astrocytes in mouse brains and found that beta-amyloid plaques, a key hallmark of Alzheimer's, may cause astrocytes throughout the brain to develop higher than normal calcium levels. Abnormal regulation of calcium levels is another feature of Alzheimer's. This finding shows that plaques have more widespread effects on the brain than previously believed, causing damage to both neurons and astrocytes.

Science, February 27, 2009;323(5918):1211–1215.



March

1

Cardiovascular Risk Factors in Older Women May Increase Alzheimer Risk

Having a combination of risk factors for heart disease, including high blood pressure, obesity and high levels of bad (LDL) cholesterol, is known as the metabolic syndrome. Investigators recently analyzed data from a large group of older women to determine whether having the metabolic syndrome affected their risk of cognitive impairment. The results showed that cognitive decline occurred in about 7 percent of women with the syndrome, but only about 4 percent of women without the syndrome. These findings suggest that avoiding risk factors for heart disease could also reduce one's chances of developing dementia.

Archives of Neurology, March 2009;66(3):324–328.

Dementia Risk for the Obese Increased in Mid-Life, Decreased in Late Life

Researchers report that obesity has different effects on cognitive loss during middle age and old age. Among middle-aged study participants, obese people had a greater than average risk of developing dementia. Among the elderly, however, underweight people had the greatest dementia risk, while the obese had a lower than average risk. These findings suggest that dementia prevention strategies should be tailored to different age groups.

Archives of Neurology, March 2009;66(3):336–342.

High Cholesterol and Diabetes Hasten Decline in People With Alzheimer's

According to researchers, people with Alzheimer's disease tend to suffer faster than normal rates of cognitive decline if they also have diabetes or high levels of total cholesterol or bad (LDL) cholesterol. These findings suggest a strong association between Alzheimer progression and risk factors for cardiovascular disease.

Archives of Neurology, March 2009;66(3):343–348.

Accurate Alzheimer Biomarkers May Exist in CSF

Many researchers have been searching for accurate biomarkers, or molecular indicators, of Alzheimer's disease. In one such effort, Finnish investigators studied more than 100 participants with Alzheimer's and other brain disorders. They focused on levels of beta-amyloid and tau in the cerebrospinal fluid (CSF) surrounding the brain. Results showed that when levels of CSF beta-amyloid became low and CSF tau became high, corresponding increases occurred in the development of beta-amyloid plaques and tau-based neurofibrillary tangles—two Alzheimer hallmarks in the brain. This finding suggests that CSF amyloid and tau can be used to detect the onset and progression of dementia.

Archives of Neurology, March 2009;66(3):382–389.

Alzheimer's Disease May Destroy the Brain's "Helper" Cells

Astrocytes are helper cells in the brain, and they play a vital role in maintaining the synaptic channels through which brain cells communicate. One research group studying astrocytes in mice that were engineered to develop Alzheimer-like symptoms found that the astrocytes near beta-amyloid plaques grew in size, possibly to protect the affected nerve cells. But astrocytes farther away from the plaques appeared to shrink and die. These results contradict earlier studies that found astrocytes becoming inflamed throughout the Alzheimer brain and may influence future studies of inflammation and Alzheimer's disease.

Cell Death & Differentiation, March 2009;16(3):378–385.

12

Anesthesia Linked to Protein Tangles in Alzheimer's

Neurofibrillary tangles, a key hallmark of the Alzheimer brain, are produced after tau protein becomes abnormally modified. In two studies with mice, researchers found that anesthesia promotes this abnormal modification of tau. Moreover, the modification occurs at sites where tau tangles usually form in Alzheimer's disease. This finding suggests a mechanism by which anesthesia can boost dementia risk.

Journal of Alzheimer's Disease, March 2009;16(3):619–626, and
The *FASEB Journal* online (Print: August 2009;23(8):2595–2604.)

Procedures Reduce Agitation Among People with Dementia

Researchers are working to improve the care of people with dementia who live in residential care facilities. One study assessed the effectiveness of two care procedures: person-centered care and dementia-care mapping. Both procedures devote more individual attention to residents in order to ameliorate such behaviors as agitation, screaming and pacing. The results of this study found that the procedures reduced agitation levels among residents. However, neither procedure was shown to improve other aspects of resident well-being or quality of life.

Lancet Neurology online (Print: April 2009;8(4):317–325.)

13

APP Variant Causes Alzheimer's Disease in Some People and Prevents It in Others

Scientists report on their discovery of a rare gene variant for amyloid precursor protein (APP) in an Italian family. Members of this family who inherited two copies the gene developed dementia early in life, while members who inherited only one copy were protected against the disease. The researchers produced laboratory cells that expressed this variant gene to measure the cells' production of toxic beta-amyloid from APP. Results showed that the cells with two copies of the gene produced extensive clumps of beta-amyloid. Cells with only one copy produced far less beta-amyloid, even less than cells that lacked the gene.

Science, March 13, 2009;323(5920):1473–1477.

17

MRI Technology Predicts Alzheimer Risk

Researchers have found that damage to the hippocampus can predict the risk of a cognitively normal person developing Alzheimer's disease. The team administered magnetic resonance imaging (MRI) scans over time to a group of elderly participants with no cognitive loss. Results showed that those whose hippocampuses were shrinking fastest had an Alzheimer risk two to four times greater than average. The investigators believe that brain cell loss in the hippocampus could be an effective biomarker for early Alzheimer diagnosis.

Neurology, March 17, 2009;72(11):999–1007.

Study Assesses the Ability of CSF Molecules to Predict Alzheimer's

Another study has found that cerebrospinal fluid (CSF) levels of beta-amyloid and tau may prove useful as Alzheimer biomarkers. The researchers showed that people with high levels of CSF tau tended to have increased brain cell degeneration. People with low CSF beta-amyloid tended to have more beta-amyloid clumping in the brain. The team also found that people with two copies of the APOE-e4 gene, a known risk factor for Alzheimer's, had particularly low concentrations of CSF beta-amyloid, indicating increased beta-amyloid accumulation in the brain.

Annals of Neurology online (Print: April 2009;65(4):403–413.)

23

Abnormal Tau and Beta-Amyloid May Work Together to Hinder Cell Function in Alzheimer's

Researchers have discovered a mechanism by which nerve cells become dysfunctional in Alzheimer's disease. Toxic clumps of beta-amyloid and tau molecules activate enzymes that prevent the transport of vital proteins from one part of a cell to another. These activities also hinder communication between brain cells and eventually lead to brain cell death. Understanding how such Alzheimer processes work may lead to more effective disease therapies.

Proceedings of the National Academy of Sciences online (Print: April 7, 2009;106(14):5907–5912.)



April

1

MRI Can Detect Alzheimer-Related Shrinkages in the Brain

People with mild cognitive impairment (MCI) who go on to develop Alzheimer's typically develop physical changes in the brain before the first cognitive symptoms of the disease appear. These changes include shrinking of the hippocampus and other dementia-affected brain areas. Investigators report that they have developed a computer-based technology called volumetric magnetic resonance imaging (MRI) that can accurately detect shrinkages in the hippocampus, amygdala and temporal horn regions. The team used volumetric MRI to measure the brain volumes of 269 people with MCI. They found that those with smaller hippocampus and amygdala volumes performed poorly on subsequent cognitive tests. Scientists suspect that early changes in brain volume may be biomarkers in detecting conversion from MCI to Alzheimer's disease.

Alzheimer Disease & Associated Disorders, April/June 2009;23(2):139–145.

3

Scientists Reveal a Key Alzheimer Protein in Mitochondria

Researchers have discovered a mechanism by which beta-amyloid may hinder cell-to-cell communication in the Alzheimer brain. In cell culture studies, the team found that small beta-amyloid clumps increase levels of a toxic oxygen molecule called nitric oxide. This molecule, in turn, chemically alters a protein in mitochondria called Drp1. Mitochondria are cellular structures that use oxygen and nutrients to provide energy for a cell. When Drp1 becomes altered, it causes mitochondria to break apart, damaging the tiny channels through which brain cells send and receive messages. Ultimately, this damage causes brain cells to die. If further research validates these results, Drp1 could prove an important target for Alzheimer therapies.

Science, April 3, 2009;324(5923):102–105.

8

Young Adults With an Alzheimer Gene Show Abnormal MRI Brain Activity

The gene variant APOE-e4 puts people at greater risk for developing Alzheimer's disease. According to researchers, young adults with APOE-e4 were shown to have abnormally increased brain activity on MRI scans. This activity occurred in the hippocampus, one of the first brain regions affected by Alzheimer's. Such findings suggest that Alzheimer-related changes may begin decades before clinical symptoms occur, but much additional research is needed.

Proceedings of the National Academy of Sciences online (Print: April 28, 2009;106(17):7209–7214.)

Proteins, Cholesterol and Calcium Interact to Kill Aging Neurons in Alzheimer's

As brain cells age, they become more susceptible to processes associated with Alzheimer's disease. In cell culture studies, researchers found that older neurons can develop high levels of both calcium and cholesterol. Abnormal cholesterol levels can make brain cells more vulnerable to damage by toxic beta-amyloid, a key suspect in Alzheimer's. Such damage includes the production of the toxic tau protein. Moreover, high calcium levels can put brain cells under stress and cause cell death. The researchers found that by removing cholesterol, they could prevent some of the damage caused by beta-amyloid. This study suggests that Alzheimer's disease involves complex relationships between beta-amyloid, tau, calcium and cholesterol and that effective therapies will need to target multiple systems. *Journal of Neuroscience*, April 8, 2009;29(14):4640–4651.

14

Statins May Not Decrease the Risk of Dementia

Scientists reviewing two large studies of the role that statin drugs may play in people at risk for Alzheimer's disease found that two statins—simvastatin and pravastatin—had no significant effect in lowering Alzheimer risk. Participants in the studies who took statins showed no better results on cognitive tests than participants who took a placebo. These findings contradict the results of other studies that support the role of statins in Alzheimer treatment. *Cochrane Database of Systematic Reviews*, April 2009;2:CD003160.

Tube Feeding Not Recommended for People with Late-Stage Dementia

Hospitals often use enteral feeding, or tube feeding, for people in advanced stages of Alzheimer's disease and other dementias, but an analysis of several studies suggests that this may cause more harm than good. The analysis found that tube feeding may lead to pneumonia, dangerous abdominal disorders and increased aggressive behavior. Other evidence suggests that withholding food may not cause pain in people with advanced dementia. These findings highlight the need for further research into how people with dementia are treated near the end of life. *Cochrane Database of Systematic Reviews*, April 2009;2:CD007209.

15

Dementia Risk Increases in Diabetics with Low Blood Sugar Attacks

People with type 2 diabetes can experience dangerously low blood sugar levels, often as a result of taking medication that overproduces insulin in the body. Researchers report that these hypoglycemic attacks can increase the risk of dementia in the elderly. Using data from thousands of older diabetics, researchers found that one hypoglycemic attack can increase dementia risk by 26 percent. Two or three attacks increase the risk by 115 percent and 160 percent, respectively. These results suggest that aggressive insulin treatment can be harmful for the elderly. Whenever possible, diabetics' blood sugar levels should be controlled with diet and exercise. *Journal of the American Medical Association*, April 15, 2009;301(15):1565–1572.

Blocking Beta-Amyloid Production at the Right Time May Delay Alzheimer's

Researchers have found that by suppressing beta-amyloid production for a short time, they may significantly delay the onset of Alzheimer's disease and other dementias. Using mice engineered to develop beta-amyloid, the team injected some of the mice with amyloid antibodies for six months. After the treatment was stopped, the animals began producing beta-amyloid again—but their overall amyloid levels never reached those of the mice that had not been treated. The researchers believe that such short-term amyloid suppression, if administered early in life, could delay the onset of amyloid-related diseases in both mice and humans.

Journal of Neuroscience, April 15, 2009;29(15):4964–4971.

16

Brain Diseases are Associated With Specific Nerve Cell Pathways

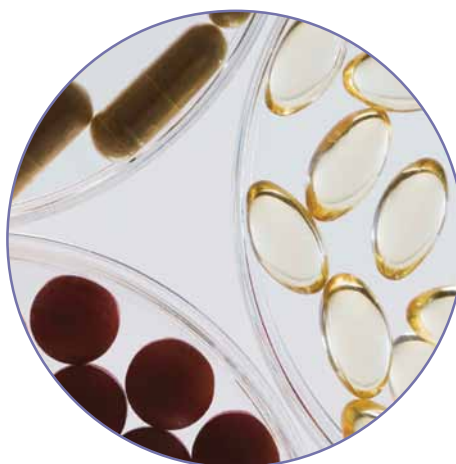
Using sophisticated imaging methods, scientists have found that different brain disorders—including Alzheimer's disease and frontotemporal dementia—spread along different “neural networks.” These networks are pathways that connect nerve cells in various parts of the brain. Normally, neurons use the pathways to communicate with one another and produce healthy proteins. But in diseased brains, the pathways can be “hijacked” to create molecules that harm brain cells. In Alzheimer's disease, such molecules include toxic forms of the protein fragment beta-amyloid and the protein tau. The results of this study could lead to better, more targeted methods of treating brain disease.

Neuron, April 16, 2009;62(1):42–52.

Abnormal Calcium Regulation May Be Related to Cell Death in Alzheimer's Disease

Researchers have identified a mechanism by which beta-amyloid can cause abnormal calcium levels in brain cells, a key feature of Alzheimer's disease. In cell culture studies, beta-amyloid was found to create pores in the neuronal membranes—enabling calcium ions to build up in the cells and damage cellular functions. These results contradict earlier research that found membrane thinning to be responsible for higher calcium levels in Alzheimer cells. The study team, funded in part by the **Alzheimer's Association**, hopes their work may lead to more effective ways of slowing Alzheimer progression.

Neurotoxicity Research online (Print: July 2009;16(1):1–13.)



A Natural Survival Mechanism Could Help Prevent Alzheimer's Disease

When oxygen levels become low in the body, cells protect themselves with a mechanism called the hypoxic response. This response is “turned off” after adequate oxygen levels are restored. In a study involving worms, researchers found that by keeping the worms’ hypoxic response “on”—even when oxygen levels were normal—they could extend the animals’ lives by about 30 percent. These worms were engineered to lack a protein called VHL-1, which normally destroys another protein that regulates hypoxic response. Worms that lacked VHL-1 also remained healthy in old age and developed few of the clumps of toxic proteins associated with neurodegenerative diseases of aging such as Alzheimer’s and Huntington’s disease. The researchers believe that similar hypoxic response treatments may be useful in preventing dementia in humans. Their work was supported in part by the

Alzheimer’s Association.

Science online (Print: May 29, 2009;324(5931):1196–1198.)

22

Molecules May Destroy Toxic Beta-Amyloid in Alzheimer's Disease

In a cell culture study of neurons, researchers found two chemicals—called Ia1 and Ia2—that boost by 700 percent and 400 percent, respectively, the activity of insulin-degrading enzyme (IDE), which breaks down beta-amyloid in the brain. These results could spur further research into the effectiveness of IDE treatments for human Alzheimer’s disease.

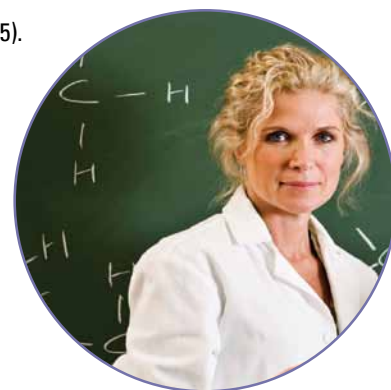
PLoS ONE, April 22, 2009;4(4):e5274.

27

A Protein Thought to Promote Alzheimer's Disease Could Have Protective Abilities

Researchers report the results of a study involving mice engineered to develop beta-amyloid but lack the protein p75, which normally regulates the growth and programmed death of nerve cells. Earlier research found that, in Alzheimer’s disease, p75 may bind to beta-amyloid and cause abnormal brain cell death. Researchers expected that the genetically engineered mice would be protected from the toxic effects of amyloid-p75 interactions. Instead, the animals developed abnormally formed nerves outside the brain, nerves that made their hearts and other organs more vulnerable to stress. Most of the mice died at a young age—around three weeks. These results indicate that p75 can help maintain the structure of the nervous system against beta-amyloid damage. Future studies of p75 could lead to novel treatments that take advantage the molecule’s protective abilities.

Proceedings of the National Academy of Sciences online (Print: May 12, 2009;106(19):7870–7875).



May

1

CSF Proteins and Alzheimer Risk

Researchers report study results showing that among people with very mild Alzheimer's disease who were followed for more than three years, those with the lowest levels of beta-amyloid and highest levels of tau in cerebrospinal fluid (CSF) suffered the steepest cognitive declines. Changes in the beta-amyloid and tau proteins are hallmarks of Alzheimer's. These findings support the role of protein levels of CSF as potential predictors of disease progression.

Archives of Neurology, May 2009;66(5):638–645.

5

Cognitive Loss Accelerates After an Episode of Delirium

Delirium, or a severe episode of mental confusion, often affects older hospitalized individuals. In assessments of data from hospitalized people with Alzheimer's disease, a research team found that delirium episodes can double or even triple a person's rate of cognitive decline. The team believes that such episodes can be prevented in hospitals. Study author Tamara Fong, M.D., recommends that hospitals try to "orient the patient to his or her surroundings, to allow for as much uninterrupted sleep as possible by not waking patients ... at night, and to get patients out of bed and walking as soon as their medical condition allows." This study was funded in part by the **Alzheimer's Association**.

Neurology, May 5, 2009;72(18):1570–1575.

11

Prescription Drugs for Alzheimer's Disease Can Cause Harmful Side Effects

In a study of people with Alzheimer's, Canadian researchers found an increased risk of health problems in those taking cholinesterase inhibitors. Researches analyzed information from healthcare databases that included more than 19,000 people with dementia who were taking cholinesterase inhibitors and more than 61,000 people nondemented individuals who were not taking these medications. They found that those taking cholinesterase inhibitors had a 100 percent increased risk of fainting, 69 percent increased the risk of a dangerously slowed heart rate, 49 percent increased risk of needing a pacemaker and 18 percent increased risk of hip fractures. Researchers urge physicians to examine the risks and benefits of cholinesterase inhibitors before prescribing them and to be especially careful in monitoring the health of patients on this medication.

Archives of Internal Medicine, May 11, 2009;169(9):867–873.

18

Risk Factors for Dementia Revealed by New Assessment Tool

Researchers have developed a diagnostic tool aimed at predicting dementia. This “risk index” tool assesses various disease risk factors. Some of the factors are well known, including old age and poor scores on cognitive tests. Other, novel factors were identified by the research team, which studied 480 people who progressed from cognitive health to dementia over six years. The novel factors include being underweight, not drinking alcohol and being slow at performing dexterous physical tasks. The researchers found that their risk index correctly identified 88 percent of study participants who developed dementia. Further testing of the index could lead to an effective, and relatively inexpensive, method of detecting those at increased risk of dementia.

Neurology online (Print: July 21, 2009;73(3):173–179.)

19

Low Weight and Weight Loss Could Make the Elderly More Susceptible to Alzheimer's

In a study of about 2,000 older Japanese Americans, researchers found that thinner people were 79 percent more likely than heavier people to develop dementia. Moreover, individuals who had lost extensive weight—or who had lost weight quickly—were more likely to develop dementia than those whose weight had remained stable. These results suggest that being underweight is a Alzheimer risk factor in the elderly.

Neurology, May 19, 2009;72(20):1741–1746.

23

Novel Mechanism May Underlie the Creation of Abnormal Tau in Alzheimer's

Investigators share results of a study showing how the addition of a single phosphate molecule to a particular amino acid may be responsible for creating the harmful tau tangles of Alzheimer's. Tau protein normally plays a crucial role in maintaining the structural framework and transport systems within nerve cells. The protein is modified when phosphate molecules are added to it. In Alzheimer's disease, however, too many phosphate molecules are added to tau, causing the protein to become abnormally modified and no longer able to carry out its helpful functions. The researchers suggest that the addition of a single phosphate to the Ser202 amino acid in tau is the principal culprit responsible for the tau tangles of Alzheimer's. Future Alzheimer therapies could target the enzyme responsible for depositing this phosphate on Ser202.

Journal of Biological Chemistry, May 2009;284(20):13422–13433.

25

Computer-Based MRI Technology Could Better Predict Early Alzheimer's

Using an imaging software package, researchers have compared MRI scans from 216 people with Alzheimer's disease, mild cognitive impairment (MCI) or no cognitive loss. They analyzed changes in three brain areas that are affected early in Alzheimer's: the hippocampus, entorhinal cortex and supramarginal gyrus. This technique correctly distinguished people with Alzheimer's disease from people with MCI 95 percent of the time. When distinguishing people with Alzheimer's from cognitively normal people, the program achieved 100 percent accuracy. These encouraging results show the potential value of automated imaging technology in Alzheimer diagnosis.

Brain online (Print: August 2009;132(8):2048–2057.)

27

Vitamin D is Linked to Brain Health

In an analysis of several vitamin D studies, researchers find that people with low levels of vitamin D in blood are more likely to develop heart disease, diabetes, osteoporosis and tooth loss, conditions that are risk factors for dementia. In addition, low vitamin D levels may make the brain more susceptible to inflammation, which has been associated with Alzheimer's disease. Given this evidence, the researchers suggest that more studies be conducted to reveal the mechanisms underlying vitamin D's role in brain health. They also recommend that older people at risk for dementia have their vitamin D levels checked by a physician and take supplements if necessary.

Journal of Alzheimer's Disease, May 2009;17(1):151–159.

June

1

Older Whites and African-Americans with Cognitive Loss Have Similar Survival Rates

A study of 1,700 older adults, about half of whom were white and half African-American, finds that people with mild cognitive impairment were 50 percent more likely to die over 10 years than cognitively healthy people. Participants with Alzheimer's were nearly three times more likely to die over that period than healthy participants. These dementia-related increases in risk of death did not differ significantly between whites and African-Americans.

Archives of Neurology, June 2009;66(6):767–772.

2

Alzheimer Risk Might Increase, Not Diminish, After Anti-Inflammatory Treatment

A study evaluating the effectiveness of non-steroidal anti-inflammatory drugs (NSAIDs) in nearly 3,000 older participants with minimal cognitive problems showed that participants on heavy NSAID treatment were 66 percent more likely to develop Alzheimer's than people taking little or no NSAIDs. The researchers noted that in earlier NSAID trials, participants tended to be younger and healthier—a fact that might have accounted for the trials' positive results.

Neurology, June 2, 2009;72(22):1899–1905.

8

New Blood Analysis Method Could Detect Alzheimer's Disease

Using a light-based analytical technique called near-infrared (NIR) spectroscopy, researchers studied blood samples of healthy people and people with Alzheimer's disease. Specifically, the team measured blood levels of oxidative stress, or damage caused by toxic oxygen molecules. This technique distinguished people who had Alzheimer's from those who did not with 80 percent accuracy. The researchers believe NIR spectroscopy may also detect whether certain people with mild cognitive impairment are likely to develop Alzheimer's.

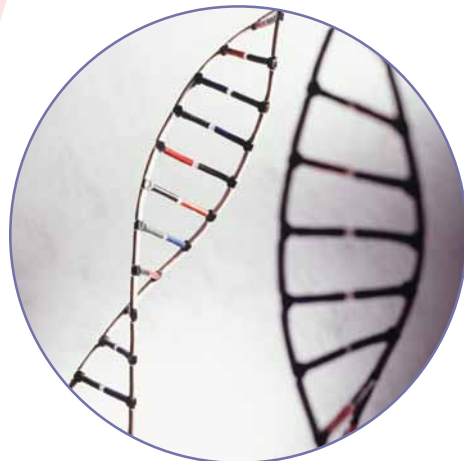
Journal of Alzheimer's Disease, June 8, 2009;17(2):391–397.

9

Novel Cognitive Test for Alzheimer's May Supplant Standard Tests

British researchers have developed a short, easy-to-use cognitive test for detecting early Alzheimer's disease. Known as "test your memory" (TYM), the assessment was administered to about 680 individuals who were cognitively normal or had mild Alzheimer's or mild cognitive impairment. The participants also underwent other memory tests, including the Mini-Mental State Examination (MMSE). Results showed that TYM correctly identified 93 percent of participants with Alzheimer's, compared with 52 percent for the MMSE. These results suggest that TYM might prove a good alternative to standard cognitive tests.

British Medical Journal, June 9, 2009;338:b2030.



10

APP Promotes Brain Health

Amyloid Precursor Protein (APP) is the parent molecule of beta-amyloid, a key suspect in Alzheimer's disease. Yet the protein may also help facilitate cell-to-cell communication in the brain. In cell culture studies of neurons, researchers found that APP stabilized the synapse channels through which brain cells communicate. Moreover, APP worked with a protein called reelin to promote the development of axons and dendrites, armlike extensions of neurons from which cells send chemical messages. Maintaining levels of "good" APP in the brain may be an important strategy for ensuring cognitive health.

Journal of Neuroscience, June 10, 2009;29(23):7459–7473.

14

Human Blood Stem Cell Growth Factor Reverses Alzheimer Symptoms in Mice

Granulocyte-colony stimulating factor (GCSF)—a human growth factor that stimulates blood stem cells to proliferate in bone marrow—significantly reduced levels of beta-amyloid in the brains of mice genetically engineered to develop Alzheimer's, increased the production of new neurons and promoted nerve cell connections. The growth factor could eventually be a powerful new therapy for Alzheimer's disease.

Neuroscience online (Print: September 29, 2009;163(1):55–72.)

16

Inflammation May Not Lead to Alzheimer's

Investigators report results of a study that contradict the long-held theory that beta-amyloid causes microglia—a group of helper cells in the brain—to become inflamed during Alzheimer's disease. The researchers devised a chemical that binds to microglia in Alzheimer brain tissue, making the cells easier to see under a microscope. Analysis of this tissue found that the microglia were not inflamed, but instead had begun to degenerate. This may affect future studies addressing the connection between brain inflammation and Alzheimer's.

Acta Neuropathologica online (Print: October 2009;118(4):475–485.)

Donepezil and Depression in MCI

Researchers report results of a study examining whether the Alzheimer drug donepezil delays the onset of Alzheimer's disease in people with mild cognitive impairment (MCI) and depression. Previous studies have shown that those with MCI and depression may be more likely to develop Alzheimer's disease than those with MCI alone. The researchers reported that after more than two years, 14 percent of the people on donepezil had developed Alzheimer's, compared with 29 percent of people receiving a placebo. These findings suggest that donepezil may prove useful in slowing dementia progression among individuals with MCI and depression. The study was supported in part by the **Alzheimer's Association**.

Neurology, June 16, 2009;72(24):2115–2121.

19

An Alzheimer's Disease Profile May Exist in CSF

Investigators report that among people with minimal memory impairment, having a “cerebrospinal fluid AD profile” increased one’s risk of severe cognitive decline 27-fold. This profile includes low levels of the protein beta-amyloid and high levels of the protein tau. This profile can be detected long before Alzheimer symptoms appear, which may help physicians identify people who should receive preventive treatments for Alzheimer’s disease, once such treatments are available.

Lancet Neurology online (Print: July 2009;8(7):619–627.)

28

Statins Can Lessen Brain Cell Damage and Cognitive Loss in Dementia

In studies with mice, researchers found that cholesterol-lowering statin drugs can protect brain cells from the effects of Alzheimer’s disease. One such effect, called excitotoxicity, overexcites nerve cells and causes them to die. Using a kind of statin called lovastatin, researchers prevented the death of mouse neurons that they had artificially overstimulated. This treatment also prevented cognitive loss in the animals. If proven effective in human clinical studies, statins may become a therapeutic option for Alzheimer’s.

Journal of Alzheimer’s Disease, June 2009;17(2):327–336.

29

Beta-Amyloid May Cause Brain Blood Flow Problems in Alzheimer’s

Beta-amyloid may play a role in restricting blood flow in the brain, a hallmark of Alzheimer’s disease, say researchers. In cell culture studies, scientists found that beta-amyloid increases the expression of a protein called endothelin converting enzyme-2 (ECE-2). This enzyme produces the protein endothelin-1, which constricts blood vessels and decreases blood flow. Drugs have already been produced to combat endothelin-1, which has been implicated in high blood pressure. Such drugs might be given new uses as Alzheimer therapies.

American Journal of Pathology online (Print: July 2009;175(1):262–270.)

Closeness of Caregiver-Care Recipient Relationship Can Impact Disease Progression

Slower cognitive and functional decline occurs in people with Alzheimer’s disease who have a close relationship with their caregivers. This is especially true when the caregiver is a spouse, researchers found in a 6-month study.

Journal of Gerontology: Psychological Sciences and Social Sciences online (Print: September 2009;64B(5):560–568.)

July

1

Anti-Inflammatory Drug Prevents Malfunction Linked to Beta-Amyloid Accumulation

Scientists report that in mouse studies, indomethacin—a nonsteroidal anti-inflammatory drug—prevented inflammation from turning off a molecular mechanism called the lipoprotein receptor-related protein (LRP) pump that allows beta-amyloid to exit the brain. When LRP malfunctioned, toxic levels of amyloid protein accumulated in the brains of study mice. This suggests that anti-inflammatory therapies may have a role in Alzheimer treatments.

Journal of Alzheimer's Disease, July 2009;17(3):553–570.

2

Marriage and Cohabitation Lower Dementia Risk

A study of marital status and dementia risk reveals that people who live alone have twice the risk of developing dementia and Alzheimer's disease in later life as people who are married or cohabiting. Individuals who are widowed or divorced in midlife have three times the risk of developing dementia.

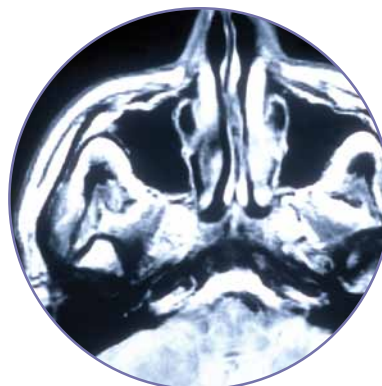
British Medical Journal, July 2009;339(7712):b2462.

5

MiRNA-145 May Protect Against Vascular Disease and Decrease Alzheimer Risk

Researchers report that a ribonucleic acid (RNA) molecule called miRNA-145 may have a role in vascular disease and Alzheimer's. The study suggests that miRNA-145 may limit the growth of vascular muscle cells that cause narrowing of arteries and can lead to vascular disease. The study also revealed that miRNA-145 encourages the expression of the protein myocardin. Myocardin activates genes that may influence the rate at which the brain can remove amyloid-beta. This finding could explain why myocardin occurs in higher levels in Alzheimer's disease. Delivering miRNA-145 into vessel walls may normalize levels of myocardin and counter its negative effects.

Nature online (Print: August 6, 2009;460:705–710.)



6

Antibodies Could Hold Promise in Preventing Alzheimer's

Investigators share results of a study suggesting that antibodies in blood could play a role in preventing or slowing the progression of Alzheimer's disease. Researchers studied blood samples from more than 250 individuals aged 21–89 with and without Alzheimer's. In both groups, they found antibodies targeting many forms and aggregation-states of beta-amyloid, which is toxic to neurons in the brain. The researcher also revealed that overall levels of these antibodies decline with age and with advancing stages of Alzheimer's. The findings suggest that therapies that increase antibody levels may have a role in preventing Alzheimer's.

Proceedings of the National Academy of Sciences online (Print: July 2009;106(29):12145–12150.)

Two Studies Support Benefits of Caffeine in Mouse Models of Alzheimer's

Large quantities of caffeine reversed memory impairment in mice genetically engineered to exhibit the symptoms of Alzheimer's disease, report researchers. Mice were given the equivalent of five cups of coffee a day. Additionally, caffeine reduced abnormal levels of beta-amyloid by nearly 50 percent. Caffeine appears to restore memory by reducing enzymes needed to produce beta-amyloid. It may also suppress inflammatory changes in the brain that lead to an overabundance of beta-amyloid. More research is needed to determine if caffeine has a role in treating Alzheimer's in humans.

Journal of Alzheimer's Disease, July 2009;17(3):661–680 and 681–697.

8

Language Abilities in 20s Could Predict Alzheimer Risk

Women with more sophisticated language abilities in their 20s had a lower risk of developing Alzheimer's disease later in life, according to scientists. This was true despite the fact that these women, who had no symptoms of Alzheimer's, had evidence of Alzheimer brain changes on autopsy. Scientists reported that their brains had larger, more functional neurons, which might compensate for the beta-amyloid plaques and tau tangles that are hallmarks of Alzheimer's. These results lend support to the "cognitive reserve" hypothesis that suggests that greater years of education in early life helps the brain find alternative routes of neuron-to-neuron communication when the neurons originally used die because of Alzheimer's.

Neurology online (Print: September 2009;73(9):665–673.)

Nicotinic Receptor May Help Trigger Alzheimer's Disease

Researchers report that the combination of beta-amyloid and the nicotinic receptor alpha-7 may exacerbate Alzheimer's symptoms. Eliminating alpha-7 seems to cancel out beta-amyloid's harmful effects. The findings suggest that therapies that block the function of the alpha-7 receptor or beta-amyloid's access to it may be beneficial in Alzheimer's.

The Journal of Neuroscience, July 8, 2009;29(27):8805–8815.

12

Omega-3 Supplement Fails to Slow Alzheimer's

Findings from an 18-month study showed that taking supplements of the omega-3 fatty acid docosahexaenoic acid (DHA) did not slow cognitive decline in individuals with mild-to-moderate Alzheimer's disease, said researchers. However, a six-month study conducted by makers of a DHA supplement found that DHA helped restore some mental acuity in individuals without Alzheimer's. Additional research is needed to determine if DHA has a role in treating or preventing Alzheimer's.

Alzheimer's Association International Conference on Alzheimer's Disease

PTSD Increases Dementia Risk

Veterans aged 55 years or older who experienced post-traumatic stress disorder (PTSD) develop dementia at a higher rate than those without PTSD, say researchers. Those with PTSD developed dementia at a rate of 10.6 percent over seven years compared with 6.6 percent for veterans without PTSD. The research suggests that physicians should be especially alert to the potential signs of dementia in this population.

Alzheimer's Association International Conference on Alzheimer's Disease

Study Gives New Understanding on Successful Clinical Study Recruitment

Partnering with local physicians, working with local clinics and conducting educational seminars and health fairs are the most effective tools in recruiting people for Alzheimer clinical studies, according to researchers. Patient registries and Internet recruiting are much less successful recruitment strategies. Among African-Americans, the most powerful incentives for participating in clinical research were having a relative with the disease, receiving monetary compensation and interacting with underrepresented study personnel during the recruitment process.

Alzheimer's Association International Conference on Alzheimer's Disease

13

Some ACE Inhibitors May Lessen Cognitive Decline

Data from the long-term Cardiovascular Health Study reveals that participants who took ACE (angiotensin-converting enzyme) inhibitors that crossed the blood-brain barrier had 65 percent less cognitive decline per year than participants who took other blood pressure medications. ACE inhibitors that did not cross the blood-brain barrier increased one's risk of dementia, and the people taking them were more likely to develop difficulty performing daily activities. The study was funded in part by the **Alzheimer's Association**.

Archives of Internal Medicine, July 13, 2009;169(13):1195–1202.

14

ADNI Studies Identify Predictors of Alzheimer Risk

Data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) continue to shed light on Alzheimer risk, say researchers. In a study of older people without memory or thinking problems, researchers found that those with the fastest rate of growth of white matter hyperintensities, or small areas of brain damage, were more likely to later develop permanent thinking problems that in many cases led to dementia. In a second study, researchers found that participants with low scores on a memory recall test and low glucose metabolism in certain areas of the brain (detected by positron emission tomography [PET]), had a 15-fold greater risk of developing Alzheimer's than those with higher memory scores and brain glucose metabolism.

Neurology, July 14, 2009;73(2):120–125 and *Alzheimer's Association International Conference on Alzheimer's Disease*

Controlling High Blood Pressure Through Diet May Reduce Cognitive Decline

Researchers report that individuals with high blood pressure, a potential risk factor for Alzheimer's, who adhered to the Dietary Approaches to Stop Hypertension diet had higher scores of cognitive function at the beginning of the study and over time. The results suggest that a diet of whole grains, vegetables, low-fat dairy foods and nuts may offer cognitive benefits in late life.

Alzheimer's Association International Conference on Alzheimer's Disease

Two Studies Find Being Active in Late Life May Slow Cognitive Decline

Researchers studying the physical activity and cognitive function of older adults in their 70s for over seven years report that those who were sedentary throughout the study had the lowest levels of cognitive function at the beginning of the study and experienced the fastest rate of cognitive decline. Those whose physical activity declined during the study period experienced a faster rate of cognitive decline than those with consistent activity levels. The good news is that sedentary elders who began aerobic exercise programs during the study experienced improvements in cognitive function, especially in their ability to process complex information quickly. In another study, researchers found that long-term strenuous activity may increase the risk of cognitive impairment in recently postmenopausal women. On the other hand, moderate long-term physical activity may improve late-life cognition.

Alzheimer's Association International Conference on Alzheimer's Disease

Potential Predictive Gene for Alzheimer's Discovered

Scientists shared results of a study in which inheriting the long-repeat version of the Tomm40 gene, in addition to the e3 form of the apolipoprotein E (APOE) gene, was associated with an increased risk of developing Alzheimer's and an increased risk of developing it at an earlier age. Individuals in the study carrying both genes developed Alzheimer's an average of seven years earlier—at about age 70—than individuals who inherited the APOE-e3 gene but not the Tomm40 gene. If this association is confirmed in larger studies, the presence of both genes could prove a tool for identifying those at increased risk of Alzheimer's.

Alzheimer's Association International Conference on Alzheimer's Disease

Detailed X-Ray Imaging May Help Detect Early Alzheimer's Disease

Individual beta-amyloid plaques can be seen in a mouse-brain model using diffraction-enhanced imaging (DEI), report researchers. DEI uses extremely bright X-ray beams that show not only bone, but also soft tissue in a way not possible using standard X-rays. Researchers say this is the first study to test DEI's ability to show the beta-amyloid plaques that are a hallmark feature of Alzheimer's disease. They hope to further develop this imaging tool so that it can be used to determine the presence of beta-amyloid plaques in humans.

NeuroImage, July 15, 2009;46(4):908–914.

Moderate Alcohol Consumption Lowers Dementia Risk

Investigators report that people who consume 8 to 14 alcoholic drinks per week had a 37 percent lower of developing dementia, while those who consumed more than 14 drinks per week had twice the normal risk of developing dementia. The research supports findings from other studies that suggest moderate alcohol consumption confers a lower risk of dementia.

Alzheimer's Association International Conference on Alzheimer's Disease

Blocking Endothelin-1 May Offer Benefit in Treating Alzheimer's

The enzyme endothelin converting enzyme-2 (ECE-2) may constrict blood vessels and reduce blood flow in the brain, potentially contributing to Alzheimer disease, according to researchers. This finding suggests that ECE-2-blocking drugs, already approved for treating other diseases, may be a potential treatment for Alzheimer's disease.

American Journal of Pathology, July 2009;175(1):262–270.

15

PMX205 Improves Memory Loss in Mice

Mice genetically engineered to exhibit Alzheimer symptoms ("transgenic" mice) that were treated with the drug PMX205 performed almost as well as normal mice on learning and memory tests, report scientists. In addition, treated mice had fewer Alzheimer's lesions and inflammatory immune cells than untreated transgenic mice. PMX205 prevented inflamed immune cells from clustering in brain regions with amyloid plaques. This inflammation causes brain cell damage and worsens the disease. These findings suggest that PMX205 may have potential in slowing or treating Alzheimer's.

Journal of Immunology, July 15, 2009;183(2):1375–1383.

Valproate Shows No Benefit in Treating Alzheimer-Related Neuropsychiatric Symptoms

Valproate, an anticonvulsant medication, does not prevent or delay the emergence of agitation or psychosis in Alzheimer's patients, say researchers, who compared groups who received valproate or a placebo. There were also no differences between valproate and placebo in tests of behavior, cognition or global functional status.

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16

Alzheimer Risk Knowledge Is Not Associated with Increased Distress

Results of the REVEAL (Risk Evaluation and Education for Alzheimer's Disease) study, the first to analyze the psychological effects of disclosing information about one's genetic risk of developing Alzheimer's, demonstrated that no significant short-term psychological distress occurred when test results were revealed. Those who learned they carried the APOE-e4 gene variant, which is associated with an increased risk of developing Alzheimer's, did not experience significantly greater anxiety, depression or test-related distress than non-carriers. The results provide potentially helpful information for individuals considering undergoing testing for the APOE-e4 gene, which, while increasing one's risk of Alzheimer's, does not guarantee that individuals will develop the disease.

New England Journal of Medicine, July 16, 2009;361:245-254

APOE-e4 Carriers Have Significantly Higher Risk of Alzheimer's

Having one copy of the gene variant apolipoprotein E-e4 (APOE-e4) results in a 29 percent lifetime risk of developing Alzheimer's disease, report researchers. Study participants without the gene had a 9 percent lifetime risk. Compared with non-carriers, those with the APOE-e4 gene also had earlier memory impairment—developing impairment as young as in their 50s. Those with two copies of APOE-e4 gene are at even great risk of developing Alzheimer's.

The New England Journal of Medicine, July 16, 2009;361:255-263.

21

Immunotherapy Could Offer Protection Against Alzheimer's Disease

Study results show that people who received immunotherapy in the form of intravenous immunoglobulin (IVIg) had a 42 percent lower risk of developing Alzheimer's disease over four years than those who did not receive IVIg. Researchers studied the medical records of 847 people who received IVIg treatments for other conditions as well as the records of nearly 85,000 people who did not receive IVIg. IVIg, which pumps good antibodies into the bloodstream, is being studied on a larger scale to determine whether it may be an effective treatment for Alzheimer's.

Neurology, July 2009;73:180-185.

22

BDNF Replacement a Potential Therapy for Alzheimer's

Research suggests that large amyloid-beta oligomers (clusters of beta-amyloid that precede plaque formation) are responsible for the decrease in brain-derived neurotrophic factor (BDNF) levels in mouse models of Alzheimer's disease and that replacing BDNF could be a potential treatment for the disease.

Journal of Neuroscience, July 22, 2009;29(29):9321-9329

Inhibiting RTN3 Aggregation May Help Treat Alzheimer's

The protein reticulon 3 (RTN3) has been shown to hamper the accumulation of the Alzheimer protein beta-amyloid by inhibiting the enzyme beta-secretase that is essential for beta-amyloid development. But researchers report that in mice genetically engineered to develop Alzheimer symptoms, RTN3's positive effects only occur if it does not aggregate and distort neurons. Researchers suspect that blocking RTN3 aggregation could be a potential treatment for Alzheimer's. This study was funded in part by the **Alzheimer's Association**.

Journal of Neuroscience, July 22, 2009;29(29):9163–9173.

CSF Biomarkers Show Promise in Predicting Conversion from MCI to Alzheimer's

A multicenter clinical trial shows that levels of beta-amyloid, total tau and phosphorylated tau in cerebrospinal fluid (CSF) have a high degree of accuracy in predicting which individuals with mild cognitive impairment will go on to develop Alzheimer's disease. While the results are a significant step forward in detecting who will develop Alzheimer's, further research is needed before the biomarkers can be used by physicians as a tool for early detection.

Journal of the American Medical Association, July 22, 2009;302:385–393.

24

Neuronal Stem Cells Restore Memory Loss in Alzheimer Mice

Researchers report that administering neuronal stem cells to mice with symptoms of advanced Alzheimer's resulted in significant improvements in memory tests. The stem cells did not replace lost neurons or reduce the amount of beta-amyloid plaques and tau tangles, but instead increased the production of brain-derived neurotrophic factor (BDNF), which in turn increased the number of synapses in the hippocampus of the brain. BDNF levels are decreased in the hippocampus and cortex of people with Alzheimer's. The findings lend support to the use of stem cells as a potential therapy for the disease.

Proceedings of the National Academy of Sciences online (Print: August 11, 2009;106(32):3594–13599.)

August

1

For People with Cognitive Loss, Pictures Enhance Memory Better than Words

Researchers report the results of a study testing the ability of people with mild cognitive impairment or no cognitive loss to recognize subjects in pictures and words. During the testing, researchers monitored participants' brain activity. Results showed that memory-related activity in the brain was similar for both groups when looking at pictures. When listening to words, however, the people with MCI showed less brain activity than cognitively normal people. Further research is needed to determine why people with memory loss respond better to pictures than to words. The researchers hope to use these findings to develop interventions to help people with memory problems.

Neuropsychologia, August 2009;47(10):2044–2055.

11

Enzyme's Benefit Could Offer New Direction for Alzheimer Treatment

The enzyme superoxide dismutase (SOD-2) reduces levels of superoxide (reactive oxygen) in cells and improves cognitive function in mice genetically engineered to exhibit signs of Alzheimer's, report researchers. The study, funded in part by the **Alzheimer's Association**, links superoxide to the disabling effects of Alzheimer's and suggests that SOD-2 may have a beneficial effect in treating Alzheimer's.

Proceedings of the National Academy of Sciences, August 11, 2009;106(32):13576–13581.

12

Eating a Mediterranean Diet and Being Physically Active Lowers Alzheimer's Risk

Scientists report that study participants who consumed a Mediterranean diet—consisting of olive oil, red wine, fish and fresh produce—and were the most physically active had a 60 percent lower risk of developing Alzheimer's disease than those who didn't follow the diet or exercise. This is the first study to look at the benefits of the Mediterranean diet and exercise combined.

Journal of the American Medical Association, August 12, 2009;302:627–637.

Formal Education Could Be Protective Against Alzheimer's

Researchers report that education diminishes the impact of Alzheimer's disease on cognitive function even if brain volume loss has already occurred. This research supports the theory that those with more formal years of education have a "cognitive reserve," or resilience against the brain damage of Alzheimer's.

Journal of Alzheimer's Disease, August 2009;17(4):855–862.

High Intake of Fruit and Vegetables Linked to Better Cognitive Performance

Researchers studying the impact of diet on cognitive function find that healthy people aged 45 to 102 who consumed 400 grams of fruits and vegetables daily had higher antioxidant levels, less evidence of free radical damage and better cognitive performance than those consuming less than 100 grams of fruits and vegetables. This finding supports other data suggesting that modifying lifestyle factors such as diet may decrease one's risk of cognitive impairment.

Journal of Alzheimer's Disease, August 2009;17(4):921-927.

24

People With High Blood Pressure Have Increased Alzheimer Risk

A study of nearly 20,000 people over age 45 shows that for each 10-point increase in diastolic blood pressure, a person's likelihood of developing memory problems increases 7 percent. A rise in diastolic blood pressure can cause arterial walls in the brain to thicken more quickly than normal, potentially causing reduced blood flow and tissue death. The results of this study strengthen the belief that modifying lifestyle factors such as blood pressure may help reduce one's risk of cognitive dysfunction.

Neurology, August 2009;73:589-595.

MRI Finds Brain Hyperactivity Might Compensate for Disease-Related Deterioration

Using functional magnetic resonance imaging (fMRI) to monitor the brain activity of cognitively normal individuals, scientists find that those with a family history of Alzheimer's disease or genetic markers of the disease had increased activation in certain areas of the brain when asked to recall people's names. This hyperactivity may indicate that these brain areas must work harder to compensate for very early brain changes caused by Alzheimer's.

Neurology, August 2009;73:612-620.

Keeping the Brain Active May Help Delay Onset of Dementia

Researchers report that staying mentally active may help delay the onset of dementia. They interviewed almost 500 healthy people in their late 70s to find out how many cognitive activities (reading, crossword puzzles, card games, group discussions, or playing music) they participated in and for how many days a week. Among individuals who went on to develop dementia, those with the highest activity level (about 11 activities a week) developed dementia an average of 15.5 months later than those with the lowest activity level (four activity days per week). The finding supports others that suggest that staying mentally active may impact cognitive decline.

Neurology, August 2009;73:356-361.

High Cholesterol in 40s More Than Doubles Risk of Late-Life Dementia

A 40-year study of nearly 10,000 men and women reveals that having high cholesterol in one's 40s increases the risk of developing Alzheimer's disease later in life by 66 percent. The study also showed that even moderately elevated cholesterol levels raise dementia risk. These data lend support to the idea that modifiable lifestyle factors such as diet and exercise may influence cognitive health.

Dementia and Geriatric Cognitive Disorders, August 2009;28(1):70-74.

September

3

RanBP9 Protein Increased in Alzheimer Brains, Offers a Potential Drug Target

Researchers find that the N60 fragment of the protein RanBP9 increases the production of the amyloid precursor protein (APP), which is present in great amounts in the Alzheimer brain. Targeting RanBP9 expression and/or the N60 fragment may lead to novel strategies to combat Alzheimer's disease.

The Journal of the Federation of American Societies for Experimental Biology, September 2010;24:119–127.

6

Discovery of Two Gene Variants Advances Understanding of Alzheimer Risk

Researchers pooling 16,000 DNA samples from European and U.S. databases discover that two gene variants—CLU (ApoJ/clusterin, located on chromosome 8) and PICALM (phosphatidylinositol-binding clathrin assembly protein, located on chromosome 11)—are associated with increased Alzheimer risk. Thirteen other potential gene variants were identified and warrant further study.

Nature Genetics online (Print: December 2009;41(12):1308-1312.)

Drug in a Family of Cancer Compounds Improves Memory in Mice

Researchers report that using a drug from a family of compounds now used to treat cancer resulted in improved memory in mice genetically engineered to develop Alzheimer's. Administering the drug, a histone deacetylase inhibitor, improved memory performance to the level found in normal mice. More research is needed to determine if the drug would have the same effect in humans.

Journal of Alzheimer's Disease, September 2009;18(1):131–139.

21

Individualized Immunotherapy for Alzheimer's Could Be on the Horizon

Research on a vaccine for Alzheimer's has revealed that the brain triggers a natural immune response when beta-amyloid is introduced. How the body responds to beta-amyloid depends on key genes of the immune system. This study, partially funded by the **Alzheimer's Association**, helps lay the groundwork for developing an individually based immunotherapeutic approach to Alzheimer's disease, since different populations will respond differently to a vaccine based on their genetic backgrounds.

Journal of Immunology, September 2009;183:3522–3530.

22

Even Mild Infections Hasten Decline With Alzheimer's

Temporary illness or conditions that can trigger inflammation in the body, such as a respiratory infection or a bruise, are associated with an increased rate of memory loss in people with Alzheimer's disease, report researchers. The reason may be that people with Alzheimer's can have high levels of tumor necrosis factor- α (TNF- α)—a protein associated with inflammation—in their blood. Individuals who had high levels of TNF- α or chronic inflammatory illness at the beginning of the study had 10 times the rate of memory decline as those who did not.

Neurology, September 2009;73:768–774.

Phone-Based Cognitive Assessments Could Be Effective

Study results show that telephone and in-person cognitive assessments in elderly individuals were comparable in effectiveness, suggesting that telephone assessment may be a useful, cost-effective and time-efficient alternative to in-person assessment of cognition in the elderly. Greater use of telephone assessments could provide cognitive evaluations to a wider range of people, including those who live in rural areas or at great distances from medical centers.

International Journal of Geriatric Psychiatry, September 2009; 25(5):531–539.

24

Lack of Sleep May Contribute to Alzheimer's

Researchers monitoring beta-amyloid levels in the brains of mice report that sleep deprivation boosted beta-amyloid levels and were associated with increased plaque formation. Although the research is preliminary, the possible link between sleep deprivation and Alzheimer's raises the prospect of possible treatments that target sleep-related pathways in the brain.

Science online (Print: November 13, 2009;326(5955):1005–1007.)

29

Decreased Heart Rate Associated with Use of Cholinesterase Inhibitors

After analyzing medical information from 1.4 million people aged 67 and older, researchers report that people who recently started on cholinesterase inhibitors for Alzheimer's were nearly twice as likely to be hospitalized with bradycardia, or slowed heart rate, as other individuals. The study highlights the potential adverse effect of cholinesterase inhibitors on heart rate, and researchers urge professionals to reassess the benefits of continuing cholinesterase inhibitor therapy in people who develop bradycardia while taking these drugs.

PLoS Medicine, September 2009;6(9):e1000157.

30

NFL Study Shows Players Have Increased Dementia Risk

A study commissioned by the National Football League (NFL) shows that former NFL players ages 30–49 were diagnosed with Alzheimer’s and related memory-related disease at a rate 19 times that of the general population. The results support the link between head injury and increased dementia risk, however, additional research is needed to better understand dementia risk in these former athletes.

National Football League

Inhibiting Hsp70 a Novel Path in the Development of Alzheimer Therapies

Researchers report that inhibiting the protein Hsp70 clears the tau tangles of Alzheimer’s in mouse studies. Their goal is to develop an Hsp-70 inhibitor that will prove safe and effective in humans.

This study was partially funded by the **Alzheimer’s Association**.

Journal of Neuroscience, September 2009;29:12079–12088.

October

6

PP5 Enzyme May Protect Against Beta-Amyloid Toxicity

The enzyme protein phosphatase 5, or PP5, may protect neurons from cell death caused by reactive oxygen species such as free radicals that are linked to beta-amyloid, report researchers. In cell culture studies, they found that overexpression of PP5 prevented neuronal death by stopping harmful processes that occur with the generation of reactive oxygen species. The excess beta-amyloid production of Alzheimer’s has been associated with increased generation of reactive oxygen species. The finding could mean that PP5 may be protective against other health issues caused by reactive oxygen species, such as stroke and heart attack.

Journal of Neurochemistry, October 2009;111(2):391–402.



Decline in Cognitive Skills, Not Memory Loss, May Be First Clue to Alzheimer's

Researchers report that loss of cognitive skills such as visuospatial abilities—being aware of one's surroundings and how objects relate to each other in space—may be an early symptom of Alzheimer's disease, occurring even before memory loss. The study reveals that a sharp decline in visuospatial abilities may be seen three years before clinical diagnosis of Alzheimer's disease, and that a sharp decline in overall cognitive ability occurred two years before diagnosis. Verbal and working memory declined one year before diagnosis. The findings suggest that evaluation of visuospatial abilities may be especially important in early detection of Alzheimer's disease.

Archives of Neurology, October 2009;66:1254–1259.

12

Higher Beta-Amyloid Levels in Plasma Are Associated with Cognitive Decline

Study results show that people who have high ratios of beta-amyloid 1-40 to beta-amyloid 1-42 in plasma in midlife and who experience an increase in these ratios 10 years later are at greater risk for cognitive decline later in life than individuals without elevated ratios. If confirmed in other studies, this ratio could serve as a biomarker for Alzheimer's and help identify Alzheimer risk before symptoms develop.

Archives of Neurology, October 2009;66(10):1247–1253.

16

Activation of Microglia Removes Beta-Amyloid Plaques in Mice

Researchers report that when microglia, the brain's immune cells, are activated by the protein interleukin-6, they eliminated beta-amyloid plaques instead of causing or worsening them. This study, conducted in mice genetically engineered to develop Alzheimer's, could lead to the development of Alzheimer's disease treatments that manipulate the brain's immune response.

The Federation of American Societies for Experimental Biology Journal online (Print: February 2010;24(2):548–559.)

November

10

Greater Muscle Strength Associated with Less Risk of Alzheimer's

Older people who have greater muscle strength are less likely to develop Alzheimer's disease, report researchers. Their study results further support the connection between physical health and cognitive function. Researchers studied 970 people over age 54 and found that those who were in the top 10 percent for muscle strength were 61 percent less likely to develop Alzheimer's than the weakest 10 percent. Stronger people also showed a slower decline in mental abilities over time.

Archives of Neurology, November 2009;66:1339–1344.

Ability to Multitask May Differentiate Depression from Alzheimer's

Study results show that a person's ability to multitask may be a distinguishing factor between early Alzheimer's disease and depression, which can have common symptoms. Researchers found that, compared with depressed people and healthy, non-depressed individuals, people with Alzheimer's performed significantly worse when given multiple tasks to perform, despite being given allowances for memory deficits.

Journal of Neurology, November 2009;256:1860–1868.

11

Dementia Risk Elevated After Multiple Strokes

Researchers report that the number of strokes experienced are tied to dementia risk. People who had a recurrence of stroke were three times more likely to develop dementia within a few months than those who had one stroke. The finding suggests that physicians be especially alert to the signs of dementia in patients with a history of multiple strokes.

The Lancet Neurology, November 2009;8(11):1006–1018.

17

Protein Attempts to Repair Alzheimer Brain Damage

Researchers report that the protein Vimentin, which is released from neurons in the brain when the neurons' dendrites and synapses degenerate in Alzheimer's, attempts to repair the brain damage caused by Alzheimer's. A similar damage-response mechanism has been seen after traumatic brain injury, suggesting that therapeutic agents could be developed to enhance repair both for sudden brain trauma and progressive neurodegenerative diseases. This study was partially funded by the **Alzheimer's Association**.

Brain Research, November 17, 2009;1298:194–207.

18

Down Syndrome Study Could Shed Light on Alzheimer's Disease

Boosting norepinephrine signaling in the brains of mice genetically engineered to develop symptoms of Down syndrome improves their cognitive function, report scientists. Norepinephrine is a neurotransmitter that nerve cells use to communicate. If intervention occurred at an early age in children with Down syndrome, it could lead to an improvement in cognitive abilities. Most individuals with Down syndrome ultimately develop Alzheimer's disease, and results of this study could shed light on methods to improve cognitive function in Alzheimer's as well. This study was partially funded by the **Alzheimer's Association**.

Science Translational Medicine, November 18, 2009;1(7):7–17.

20

MRI Technique Aids in Early Detection, Tracking Alzheimer's Progression

Scientists describe how, using magnetic resonance imaging (MRI), they were able to measure atrophy in very precise areas of the brain. These sub-regional brain volume measurements outperformed other measures used for tracking Alzheimer severity, including tests of overall brain atrophy and some common cognitive tests for the disease. Brain atrophy in some areas is a particularly sensitive measure of the early stages of Alzheimer's. Measurements of these areas could aid in early detection of the disease.

Proceedings of the National Academy of Sciences online (Print: December 8, 2009;106(49):20954–20959.)

22

Beta-Amyloid Helps Maintain Normal Brain Function, Study Reports

Research results show that beta-amyloid plays an important role in maintaining the day-to-day function of the brain. Removing beta-amyloid from the brain, which is the goal of many Alzheimer drugs being developed, can impair neuronal function, say researchers. In cell culture and mouse studies, researchers found that an optimal amount of beta-amyloid is needed for healthy neuronal function and that the smallest imbalance in beta-amyloid production impairs neuron-to-neuron communication. Study findings highlight the importance of examining multiple potential causes of Alzheimer's disease, not just beta-amyloid.

Nature Neuroscience, November 2009;12:1567–1576.

Imaging Technique Shows Healthy APOE-e4 Carriers Have Same Brain Changes as People with Alzheimer's

Using automated neuroimaging analysis techniques, researchers find that cognitively healthy older people with the APOE-e4 Alzheimer risk gene had reduced cognitive performance and decreased brain volume in the hippocampus and amygdala (regions important for memory processing) compared with people without the APOE-e4 gene. These brain changes are also found in people with Alzheimer's and suggest that these cognitively normal individuals may already be experiencing the early, presymptomatic stages of the disease.

Journal of Alzheimer's Disease, November 2009;18(3):553–564.

December

11

Reducing the IGF-1 Signaling Pathway Slows Aging, May Delay Alzheimer's

Researchers report that altering the IGF-1 (insulin-like growth factor 1) signaling pathway, which is known to slow aging in mice, also improved animals' ability to function on various cognitive tests. When IGF-1 activity was cut in half, mice lived up to 35 percent longer. Although the long-lived mice tended not to show any of the cognitive or behavioral impairments typical of people with Alzheimer's, their brains were riddled with highly compacted beta-amyloid plaques. This suggests that beta-amyloid plaques may not be key players in Alzheimer's disease.

Cell, December 11, 2009;139:1157–1169.

14

Beta-Amyloid Raises Alzheimer Risk in People without Cognitive Problems

Two studies show that cognitively healthy people with high levels of beta-amyloid deposits in the brain have a greater risk of developing Alzheimer's, as well as a greater risk of decreasing brain volume and cognitive decline. The findings suggest that beta-amyloid accumulation may be a sign of Alzheimer's disease even before symptoms have developed.

Archives of Neurology, December 2009;66:1469–1481.

16

High Leptin Level Linked to Lower Risk of Alzheimer's Disease

A study of 200 older individuals shows that those with high levels of leptin, a natural hormone produced by fat cells, had a decreased likelihood of developing Alzheimer's. Individuals who are obese typically have low levels of leptin. This finding supports previous research connecting Alzheimer's risk and obesity.

Journal of the American Medical Association, December 16, 2009;302:2565–2572.

23

Ginkgo Biloba Does Not Improve Memory

Ginkgo biloba, an extract from the ginkgo tree, failed to improve memory and prevent cognitive decline in cognitively normal older people and older people with mild cognitive impairment, report researchers. The Ginkgo Evaluation of Memory study, conducted at six medical centers and involving more than 3,000 people between ages 72 and 96 for seven years, was larger than all previous ginkgo studies combined. Study results published in 2008 found that ginkgo was not effective in preventing Alzheimer's dementia or dementia overall, while this study examined whether ginkgo had any effect on cognitive decline, specifically memory, visual-spatial construction, language, attention, psychomotor speed and executive function.

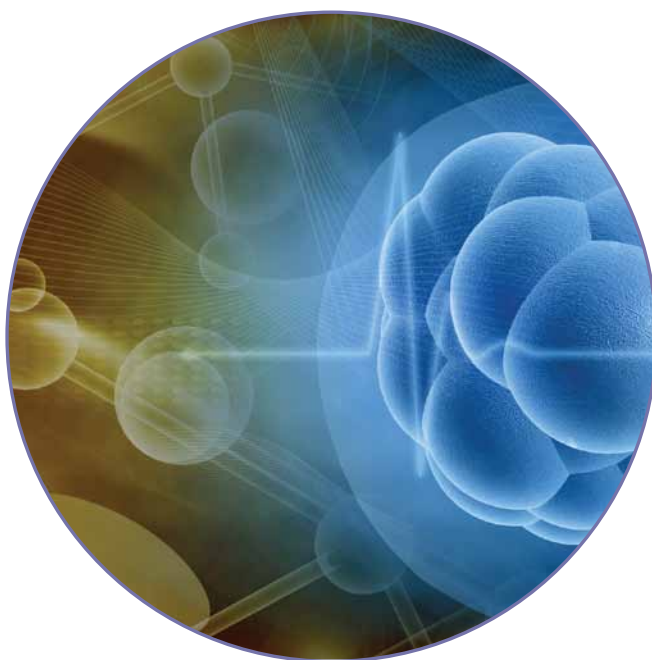
Journal of the American Medical Association, December 23/30, 2009;302(24):2663–2670.

27

Overproduction of Beta-Amyloid Decreases Neuronal Plasticity

Researchers report that overproduction of the Alzheimer protein beta-amyloid decreases the ability of brain cells' dendrites to grow and change—referred to as “plasticity”—which in turn decreases the transmission of information throughout the brain cell. This weakens the individual brain cell or neuron, as well as circuits of neuron-to-neuron communication that are essential to learning and memory. These findings provide new insight into beta-amyloid's potential role in Alzheimer's.

Nature Neuroscience online (Print: February 2010;13(2):190-196.)Volume:





The Alzheimer's Association is the leading voluntary health organization in Alzheimer care, support and research. Our mission is to eliminate Alzheimer's disease through the advancement of research; to provide and enhance care and support for all affected; and to reduce the risk of dementia through the promotion of brain health.

Our vision is a world without Alzheimer's disease.

For information and support,
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