



the compassion to care, the leadership to conquer

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**MARKERS IN BLOOD AND SPINAL FLUID, AND A NEW IMAGING AGENT,  
SHOW PROMISE FOR EARLY DETECTION OF ALZHEIMER'S**

**Chicago, July 29, 2008** – 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. Four studies reported today at the Alzheimer's Association's 2008 International Conference on Alzheimer's Disease (ICAD 2008) in Chicago bring us closer to that goal of early detection by describing advances in biomarkers.

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 a therapeutic intervention.

It is widely believed that Alzheimer's disease brain changes, including amyloid plaques and neurofibrillary tangles, begin many years before symptoms are evident or there is significant death of brain cells. It is critical to identify affected individuals while they are still cognitively normal so that future disease modifying therapies can preserve normal function. The testing and eventual use of such therapies requires identification of affected and "at risk" individuals in order to steer them to clinical trials, and to direct and monitor therapy.

"Discovery of measurable markers that track with the presence of Alzheimer's pathology and that predict the development of cognitive decline in people who are still cognitively normal, known as 'antecedent biomarkers,' are especially needed," said William Thies, PhD, vice president of Medical and Scientific Relations at the Alzheimer's Association. "It is greatly preferable that these markers be easy to obtain, such as in samples of blood or urine, or through readily available imaging technologies, such as MRI and PET."

**Blood Test on White Blood Cells May Be Useful for Early Detection of Alzheimer's**

Healthy brain cells do not go through the process of division and replication (known as the "cell cycle") that is common in other cells in the body. However, in Alzheimer's disease, brain cells have demonstrated an abnormal tendency to prepare to re-enter this cell cycle, which may increase their likelihood of dying or directly cause their death.

The equivalent cell cycle defect is found in lymphocytes of people with Alzheimer's. Lymphocytes are white blood cells in the immune system that can easily be collected for testing by a simple blood draw. Professor Thomas Arendt, Director of the Paul Flechsig Institute, University of Leipzig, Germany, thought that this suggested a vehicle for detecting Alzheimer's.

In a study performed in the U.S. by GW Medical, the licensor of Arendt's technology, Arendt and colleagues measured the expression of CD-69 (a protein involved in white blood cell growth and

production) on multiple cell lines in people with probable Alzheimer's (n=32), healthy controls (n=30) and other dementias, chiefly Parkinson's disease dementia, (n=26).

Variations in levels of CD-69 enabled the researcher to clearly differentiate between Alzheimer's subjects and demented Parkinson's subjects. It was accurate 91 percent of the time when the diagnosis was Alzheimer's and 92 percent of the time when it was Parkinson's dementia. The assay correctly differentiated people with Alzheimer's from cognitively normal subjects 88 percent of the time when the diagnosis was Alzheimer's and 82 percent of the time when the person was cognitively normal.

In addition, Arendt found that the test results did not vary with dementia severity as measured by the Mini Mental State Exam.

"The lack of variation suggests that this test may be useful in the early stages of Alzheimer's," Arendt said. "A larger trial is underway with results expected by late summer 2008. If confirmed, it will give primary care physicians a better, more accurate and non-invasive test for Alzheimer's disease."

### **Spinal Fluid Marker Tracks Brain Amyloid, May Identify Alzheimer's Before Symptoms**

Some researchers believe that flaws in processes governing production, accumulation, or disposal of amyloid protein in the brain are the primary cause of Alzheimer's. A $\beta$ 42 is a particularly "sticky" variety of amyloid protein fragment that is more likely to aggregate into small clusters and eventually into the plaques that are considered one hallmark of the Alzheimer brain.

Anne M. Fagan, PhD, of the Washington University School of Medicine, St. Louis, MO, and colleagues previously demonstrated in a small group (n=24) that a low level of A $\beta$ 42 in cerebrospinal fluid (CSF) is an effective marker for determining the presence of amyloid in the brain as assessed by PET scans using a marker called Pittsburgh Compound B (PIB).

In a new study presented at ICAD 2008, Fagan reported on a much larger cohort (n=132; age 45-88 years, mean 65.7). This group included individuals who were non-demented plus those with very mild or mild dementia. Consistent with the prior study, the researchers observed a striking inverse relation between presence of amyloid in the brain and levels of A $\beta$ 42 in CSF.

Overall, those people with high amounts of brain amyloid (as indicated by PET scan images showing positive PIB-binding) had low CSF A $\beta$ 42 (36/37, 97%). Those with low levels of brain amyloid (negative PIB-binding) had high CSF A $\beta$ 42 (80/95, 84%). This was true regardless of cognitive status, indicating excellent sensitivity of CSF A $\beta$ 42 for identifying the presence of brain amyloid, according to the researchers.

In addition, they observed that three non-demented, low CSF A $\beta$ 42, PIB-positive study participants have subsequently received an Alzheimer's diagnosis suggesting that positive PIB and low CSF A $\beta$ 42 may be useful as markers of "preclinical Alzheimer's" (that is, Alzheimer's prior to visible symptoms).

"We found that CSF A $\beta$ 42 is an excellent marker for identifying the presence of amyloid in the brain, regardless of the person's cognitive status," Fagan said. "Our analyses also suggest that a decline in CSF A $\beta$ 42 may effectively identify non-demented individuals who are in the preclinical stage of Alzheimer's, even before they are PIB positive."

### **Brain Enzyme May Improve Alzheimer's Risk Assessment and Early Detection**

Researchers have previously found elevated  $\beta$ -secretase (BACE1) activity in the brains of patients with Alzheimer's compared to healthy individuals. BACE1 is one of two enzymes involved in the pathological

processing of amyloid precursor protein (APP) and the production of toxic A $\beta$  (beta amyloid, the main constituent of amyloid plaques in the brains of people with Alzheimer's).

Professor Harald Hampel, of Trinity College Dublin, Ireland and the University of Munich, Germany, Professor Yong Shen, of Sun Health Research Institute, USA, and colleagues investigated whether BACE1 assessed in cerebrospinal fluid (CSF) may be a feasible biomarker candidate for predicting Alzheimer's in people with mild cognitive impairment (MCI). MCI is a transition stage between the cognitive changes of normal aging and the more serious problems caused by Alzheimer's.

The research had two parts. In the first part, the scientists measured BACE1 levels in CSF in 80 people with Alzheimer's, 59 people with MCI, and 69 healthy elderly controls (HC) at two independent, international research centers. MCI subjects showed highly increased levels of BACE1 activity when compared to HC and people with Alzheimer's. BACE1 activity was significantly correlated with A $\beta$  level. A subsequent validation study replicated these initial findings in a new and independent set of 41 people with Alzheimer's, 46 with amnesic MCI and elderly HC.

In the second part, 47 MCI subjects were clinically followed up over two years to assess the predictive value of BACE1 in combination with other biomarker candidates for predicting the conversion from MCI to Alzheimer's. The additional candidates were abnormal brain proteins total tau and phosphorylated tau measured in CSF, and baseline performance on a large neuropsychological testing battery. Fifteen (15) MCI subjects converted to Alzheimer's after a mean follow-up interval of 2.3 years. Analysis showed that BACE1 protein levels and ApoE genotype (a genetic risk factor for Alzheimer's) were the strongest predictors of conversion to Alzheimer's, after controlling for age and gender. The classification accuracy was 78%, the sensitivity was 80%, and the specificity was 77% for the combined model.

“These important findings pave the way for further rigorous assessment of BACE1 as an effective and accurate clinical diagnostic tool, which could significantly improve risk assessment and early detection of Alzheimer's,” Hampel said. “We believe that BACE1 will be an excellent outcome biomarker to look at in ongoing clinical trials of anti-amyloid, disease modifying therapies. Furthermore, we are working on a blood-based diagnostic test for BACE1 as well.”

### **Improved Amyloid Imaging Agents for PET in Development**

A major recent advance in Alzheimer's is the ability to create images of amyloid in the brains of living people using positron emission tomography (PET) scanners. With PET, a radioactive compound, or tracer, is injected into the person to be scanned. The tracer attaches to a target substance in the body, in this case amyloid, which then “lights up” on the image captured by the scanner.

In research reported at ICAD 2008, Michael J. Pontecorvo, PhD, of Avid Radiopharmaceuticals, Philadelphia, PA, and colleagues reported the development of a novel 18F-labeled PET amyloid imaging agent, 18F-AV-45, that may eventually provide a practical approach for routine brain imaging for Alzheimer's

PET scanners are relatively common – they are available in most hospitals – yet one of the challenges to more widespread use of PET imaging in Alzheimer's is that the radioactivity of the first amyloid-imaging tracer, called 11C-PIB or Pittsburgh Compound B, is relatively short-lived. With this agent, based on radioactive carbon, half of the radioactivity is lost every 20 minutes. This means that it must be manufactured onsite, a process that requires a cyclotron (a type of particle accelerator), which is rarely found in community hospitals. This limitation has prompted a search for longer-lived tracers, such as 18F-labeled agents, based on radioactive fluorine, which would be suitable for regional production and wider community use.

In the study, three 18F-labeled compounds were evaluated in 42 cognitively healthy elderly volunteers and 39 individuals with Alzheimer's. Each participant received a single intravenous injection of one of the compounds followed by PET imaging.

People with Alzheimer's showed retention of all three tracers in brain areas expected to be high in amyloid. In contrast, cognitively healthy volunteers showed rapid removal of the tracers, with minimal retention in the brain. Two individuals diagnosed with Alzheimer's had a pattern of tracer uptake similar to healthy volunteers. Chart notes for both suggested unusual presentations – prominent Parkinsonism in one case and slowly progressive dementia in the other.

While the three compounds were similar in pattern and amount of tracer retention, they differed in how they were processed by the body in ways that favored one compound, 18F-AV-45. For example, 18F-AV-45 showed rapid uptake and steady levels were maintained in the brain between 50 and 90 minutes post injection. This allowed high quality images to be obtained from PET imaging beginning 50 minutes after 18F-AV-45 administration, with minimal inconvenience or delay for the patient or the imaging center, according to the researchers.

“18F-AV-45 is being used as a research tool today, but it has the potential to aid in the diagnosis and early detection of Alzheimer's in a community setting and may be a useful biomarker for the development and monitoring of novel amyloid reducing therapies,” Pontecorvo said. “On the basis of the findings we reported today, Phase II trials with 18F-AV-45 have been initiated.”

#### **About the Alzheimer's Association**

The Alzheimer's Association is the leading voluntary health organization in Alzheimer's research, care and support. Our mission is to eliminate Alzheimer's disease through the advancement of research, provide and enhance care and support for all affected, and reduce the risk of dementia through the promotion of brain health. Our vision is a world without Alzheimer's. For more information, visit [www.alz.org](http://www.alz.org).

#### **About ICAD**

The Alzheimer's Association 2008 International Conference on Alzheimer's Disease (ICAD 2008) is the largest gathering of Alzheimer researchers in history. At ICAD 2008, more than 5,000 researchers will share groundbreaking information and resources on the cause, diagnosis, treatment and prevention of Alzheimer's and related disorders. As a part of the Association's research program, ICAD serves as a catalyst for generating new knowledge about dementia and fostering a vital, collegial research community.

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- Thomas Arendt. “Diagnosis Of Alzheimer's Disease Using Peripheral Blood Lymphocyte Expression Of CD-69 Following A Mitogenic Stimulus.” (Funders: National Institutes of Health, GW Medical, Provista Life Sciences)
- Anne M. Fagan. “Update on the relationship between in vivo amyloid imaging with 11C-PIB and CSF A $\beta$ 42.” (Funders: : National Institute on Aging, Dana Foundation, Anonymous Foundation, Charles and Joanne Knight Alzheimer's Initiative)
- Harald Hampel. “Alteration of beta secretase (BACE1) functional candidate biomarkers in subjects with mild cognitive impairment and Alzheimer's disease.” (Funders: Science Foundation Ireland, Federal Ministry of Education and Research (Germany), Alzheimer's Association)
- Michael J. Pontecorvo. “Development of 18F-AV-45, a novel 18F-labeled A $\beta$  amyloid imaging agent.” (Funders: Avid Radiopharmaceuticals)