Four Trials Investigate New Therapy Targets

Results of four research trials investigating new targets for therapies in Alzheimer’s disease, involve four compounds that target physical changes in the brain associated with the development and progression of Alzheimer’s disease. Two drugs are intended to reduce brain inflammation, one is thought to inhibit the production of an abnormal protein in the brain known as beta-amyloid, and the fourth promotes brain cell regeneration.

Microglial Modulator Reduces Inflammation and Improves Cognition in People with MCI

Inflammation in the brain has been implicated in the process and progression of Alzheimer’s disease. Microglia are cells that act as the first and main form of active immune defense in the brain and spinal cord where they must react quickly to decrease inflammation and protect sensitive tissues. It has been recently suggested that amyloid plaques in the brains of people with Alzheimer’s can stimulate microglia to produce compounds that cause brain cell damage. Thus, microglia have become a novel target for Alzheimer’s disease therapies.

This is one of the first studies indicating that this neuroinflammatory inhibitor may be able to improve cognition in people with MCI who carry the ApoE4 gene,” said Ross.

MK-8931 (BACE1 Inhibitor) Lowers Beta Amyloid in People with Mild to Moderate Alzheimer’s

The presence of beta-amyloid plaques in the brain is a well-known manifestation of Alzheimer’s disease. One hypothesis holds that the toxins produced by beta-amyloid initiate a cascade of events in the brain that cause Alzheimer’s, but it is still unclear to many whether the plaques are a cause or a result of the disease.

Academic and industry researchers have investigated a variety of approaches to slow or stop the production of beta-amyloid and/or clear it from the brain. Yet, to date, a combination of safety concerns and lack of effectiveness in slowing or stopping cognitive decline in people with Alzheimer’s has impacted all of these attempts. While this has led to further questions new approaches continue to be tested.

“This is the first demonstration of the lowering of beta-amyloid levels by a BACE1 inhibitor in people with Alzheimer’s disease,” said Mark S. Forman, M.D., Ph.D., working with his colleagues at Merck Research Laboratories. “We believe this candidate presents a unique opportunity to test the amyloid hypothesis.”

Allopregnanolone Regenerative Therapy Begins Phase 1 Trial

According to Roberta Brionton, Ph.D., of the University of Southern California, both aging and Alzheimer’s disease are characterized by a decline in the ability of the body (including the brain) to self-renew and repair, but the capacity for regeneration is retained, albeit at a decreased level. Allopregnanolone (also known as Allo) is a neurosteroid found in the brain and bloodstream. In previous studies, it has shown promise as a potential regenerative therapy to promote brain cell creation and improve cognitive function in older animals and animal models of Alzheimer’s disease.

Four Trials of New Therapy Targets continued from page 1

Brinton reported at AAIC on the design of a Phase 1 clinical trial of Allo in participants diagnosed with MCI due to Alzheimer’s and mild Alzheimer’s with doses administered once-per-week for 12 weeks to establish a safe and tolerated dose. Because Allo is naturally expressed in the brain and reaches relatively high levels during the third trimester of pregnancy, the scientists were able to advance beyond the time limits of a typical first-stage of safety testing.

Phase 3 Trial of Pioglitazone to Delay Onset of MCI in Cognitively Normal Elderly

International trials to delay onset of MCI due to Alzheimer’s disease are complex in design, requiring careful consideration of case definition, site characteristics, selection of primary outcome metrics, and methods to ensure appropriate cultural and psychometric validation. They require innovations to recruit the most appropriate study population, provide consistent MCI diagnoses across countries, and to ensure the credibility of their results.

Kathleen A. Welsh-Bohmer, Ph.D., of the Joseph and Kathleen Bryan Alzheimer’s Disease Research Center at Duke University Medical Center, and her colleagues at Zinfandel and Takeda Pharmaceuticals International, Inc., are currently initiating an international Phase 3 trial of low dose pioglitazone, a medication which at higher doses is approved for treatment of type 2 diabetes, as a therapy to delay onset of MCI due to Alzheimer’s. The trial will begin enrollment in 2013. In earlier human studies, treatment with pioglitazone was associated with decreased markers of brain inflammation.

“Since this is an international trial with sites in the U.S., Europe, Australia, and Russia, it is vitally important that we apply standards that can be used and validated seamlessly around the world,” said Welsh-Bohmer. “This study is meant to operationalize the NIA/Alzheimer’s Association diagnostic criteria which represent new standards. The new procedures under development for this trial may serve as useful tools for application in other global trials to prevent the onset of symptomatic Alzheimer’s,” she added.

People with Early-Stage Mentor Medical Students continued from page 3

In the Buddy Program, medical students are paired with individuals with dementia and the “buddies” plan a year of regular meetings around mutually satisfying activities. These programs are improving medical student knowledge and familiarity with Alzheimer’s while also heightening sensitivity and empathy toward people with the disease.

Results of Phase 3 Trial of IVIG continued from page 5

Reactive oxygen species (ROS) are molecules that form as a natural byproduct of the normal metabolism of oxygen; they have important roles in communication between cells and keeping the body’s internal environment stable (homeostasis). However, during times of environmental stress, ROS levels can increase dramatically. This can cause significant damage to cells; it is known as oxidative stress. The scientists observed that IVIG pre-treatment (10 and 20mg/ml) provided significant protection to brain cells that were subsequently exposed to ROS. They also observed significant increase in cell viability in the neurons when they were treated with 10 and 20mg/ml doses of IVIG alone for four days.

“Our results suggest that IVIG treatments may make neurons less vulnerable to damage from reactive oxygen species,” Lahiri said. “Since preventing brain cell loss in Alzheimer’s is an important goal of therapy, our results suggest that IVIG may be beneficial for preserving and protecting neurons against oxidative damage.” This is particularly important because we know that beta amyloid deposits in the Alzheimer’s brain indirectly lead to the generation of ROS, including free radicals, that damage and destroy brain cells,” Lahiri added.

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It’s important to determine if memory loss or other signs you may be experiencing are a serious health concern. If you notice any of the 10 Warning Signs of Alzheimer’s, see your doctor.

1. Memory changes that disrupt daily life
2. Challenges in planning or solving problems
3. Difficulty completing familiar tasks—home, work or leisure
4. Confusion with time or place
5. Trouble understanding visual images, spatial relationships
6. New problems with words in speaking or writing
7. Misplacing things and losing the ability to retrace steps
8. Decreased or poor judgment
9. Withdrawal from work or social activities
10. Changes in mood and personality

Join thousands of members of the Alzheimer’s Early Detection Alliance.

Learn more about the 10 signs of Alzheimer’s disease and how you can support your employees and empower your customers.

Go to alz.org/aeda today, or call 800.272.3900.

The Alzheimer’s Association International Conference is the premier annual forum for presentation and discussion of the latest Alzheimer’s and dementia research.

Celebrating 25 years of progress while shaping the future of dementia science, AAIC 2013 brought together nearly 5,000 leading experts and researchers from 66 countries around the world, and featured more than 1,800 scientific presentations.
RESULTS OF PHASE 3 CLINICAL TRIAL OF IVIG

In May 2013, Baxter International announced topline results of the first Phase 3 clinical trial of IVIG as an add-on to established therapy in people with mild to moderate Alzheimer's disease, known as the Gamaglobulin Alzheimer's (GAP) Study. The drug did not meet either of its primary endpoints.

"The results tell us exactly why drugs, in particular those that are approved for one disease that are being tested for another, must go through the very thorough FDA approval process," said Mary Sano, Ph.D., Director of the Alzheimer's Disease and Research Center at Mount Sinai School of Medicine, Bronx, NY, and a member of the executive committee for the GAP Study. "The FDA process protects people from misguidedly using drugs that are not effective and may be very costly." Dr. Sano is a member of the Alzheimer's Association Medical and Scientific Advisory Council.

Updated Results from the GAP Phase 3 Trial of IVIG in Mild to Moderate Alzheimer's

In their topline announcement in May 2013, the GAP Study researchers reported that the results were negative on the main outcome measures, which were two well-established tests of cognition and daily functioning – the ADAS-Cog and ADCS-ADL. At the same time, they reported favorable cognitive changes in two pre-specified subgroups: people with Alzheimer's who carried the APOE-e4 Alzheimer's risk gene and those who were moderately impaired.

At AAIC 2013, Norman Relkin, M.D., Ph.D., of Weill Cornell Medical College and the Cornell Memory Disorders Program and lead investigator of the GAP study, reported additional analyses including cognitive and biomarker tests. Biomarker analyses demonstrated that antibodies from the treatment reached the central nervous system. The researchers found:

- A statistically significant dose dependent reduction in plasma beta-amyloid 42 levels (but not beta-amyloid 40) was observed in IVIG treated patients relative to placebo.
- Statistically significant, dose dependent increases in anti-oligomer and anti-fibril antibodies in the CSF or plasma occurred in IVIG-treated patients relative to placebo.
- A reduction in brain fibrillar amyloid (as measured by PET scan using florbetapir) was seen in patients who received IVIG at the 400mg/kg/2wk dose.
- No effect in tau and phosphorylated tau levels in spinal fluid.

Baxter studies of IVIG in mild to moderate Alzheimer's disease were discontinued after the announcement of topline results in May.

APOE-e4 is one of three naturally occurring forms of the APOE gene; the others are APOE-e2 and APOE-e3. Everyone inherits a copy of some form of APOE from each parent. Those who inherit one copy of APOE-e4 have an increased risk of developing Alzheimer's disease. Those who inherit two copies have an even higher risk, but not a certainty. Risk genes increase the likelihood of developing a disease, but do not guarantee it will happen. Researchers have found several genes that increase the risk of Alzheimer's. APOE-e4 is the first Alzheimer's risk gene identified and remains the gene with the strongest impact on risk. Despite the negative results of the Phase 3 IVIG trial and because of the successes of IVIG in animal models of Alzheimer's and early stage trials in people, researchers continue to pursue how IVIG may work in the brain to inform ongoing Alzheimer's therapy research.

IVIG Reduces Tau Pathology in a Mouse Model of Alzheimer's Disease

"IVIG may help clear brain amyloid to prevent amyloid plaque buildup, but the poor results so far of clinical trials targeting amyloid raise the possibility that IVIG acts in a different way. Therefore, we tested whether IVIG might target the other characteristic lesion of the Alzheimer's brain, the neurofibrillary tangle," said Scott Counts, Ph.D., of Rush University Medical Center, Chicago. "Our preliminary data suggest that IVIG may reduce Alzheimer's-like tangle pathology and increase neuroprotective gene expression in a mouse model of Alzheimer's disease," Counts said.

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IVIG May Make Neurons Less Vulnerable to Damage from Reactive Oxygen Species

In an effort to uncover the mechanism(s) by which IVIG might provide benefit, Debomoy Lahiri, Ph.D., of the Indiana University School of Medicine and colleagues recently showed that treatment of degenerating rat brain cells with IVIG in a test tube protected the structure of the cells and enabled them to survive longer. They hypothesized that IVIG treatment might also preserve and protect human brain cells.

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Most Kinds of Cancer Associated with Decreased Risk of Alzheimer's

A study of the health records of 3.5 million U.S. veterans indicated that most kinds of cancer are associated with a significantly decreased risk of Alzheimer's disease. Results suggested that chemotherapy treatment for almost all of those cancers conferred an additional decrease in Alzheimer's risk. The researchers found no association between cancer history and reduced risk of any other typical age-related health outcome; in fact, most cancer survivors were found to be at increased risk for non-Alzheimer's dementia. The scientists concluded that the findings indicate that the protective relationship between most cancers and Alzheimer's disease is not explained simply by increased mortality among cancer patients. More research is needed to determine the cause(s) of the reduced risk and therefore identify potential new therapeutic avenues for Alzheimer's.

Diabetes Drug Associated with Reduced Risk of Dementia

Type 2 diabetes may double the risk of dementia. However, in a study of nearly 15,000 type 2 diabetes patients age 55 and older, patients who started on metformin, an insulin sensitizer, had a significantly reduced risk of developing dementia compared with patients who started other standard diabetes therapies. Trials are currently under way to evaluate metformin as a potential therapy for dementia and mild cognitive impairment.

Older Age at Retirement is Associated with a Reduced Risk of Dementia

An analysis of health and insurance records of more than 429,000 self-employed workers in France found that retirement at older age is associated with a reduced risk of dementia, with a lower risk for each added year of working longer. The researchers suggested that professional activity may contribute to higher levels of intellectual stimulation and mental engagement which may be protective against dementia, though more research is needed in this area.

Socioeconomic Factors May Explain Higher Alzheimer’s Risk in African Americans

In the United States, older African-Americans are about twice as likely to have Alzheimer's and other dementias as older whites. But in a study of 3,075 black and white elders who were free of dementia at the beginning of the study, the risk difference was no longer statistically significant after researchers adjusted for socioeconomic status, including education level, literacy, income, and financial adequacy. The authors urged that future studies investigating racial and ethnic dementia risk disparities should take a larger range of socioeconomic factors into account.

People with Early-Stage Alzheimer’s Mentor Medical Students

The number of doctors trained to effectively diagnose and treat people with Alzheimer's is woefully inadequate. According to the American Geriatrics Society there are currently approximately 7,500 certified geriatricians and fewer than 1,600 certified geriatric psychiatrists in the United States. It is projected that approximately 30 percent of the 65-plus patient population will need care by a geriatrician and that each geriatrician can care for a patient panel of 700 older adults. Based on these numbers approximately 17,000 geriatricians are needed now to care for about 12 million older Americans. Due to the projected increase in the number of older Americans it is estimated that approximately 30,000 geriatricians will be needed by 2030. To meet this need would require training approximately 1,200 geriatricians per year over the next 20 years. Few graduates of medical schools in the United States are pursuing advanced training in geriatrics. In 2010, a mere 75 residents in internal medicine or family medicine entered geriatric medicine fellowship programs. This is down from 112 in 2005.

A program developed by the Northwestern University Alzheimer's Disease Center in Chicago — and replicated now in Massachusetts, Missouri, and New Hampshire — provides opportunities for first-year medical students and persons diagnosed with early-stage Alzheimer’s to participate together in experiential learning programs.

Online Tests for Alzheimer's Do Not Measure Up

A panel of Canadian experts — including geriatricians, human-computer interaction specialists, neuropsychologists, and neuroethicists – reviewed 16 freely accessible online tests for Alzheimer's disease and found that the tests scored poorly on scales of overall scientific validity, reliability, and ethical factors. The experts found that most of the tests (12 of 16) scored "poor" or "very poor" for overall scientific validity and reliability, and concluded that these tests are not useful for the diagnosis of Alzheimer’s disease. All 16 tests scored "poor" or "very poor" on the evaluation criteria for ethical factors. Ethical issues included overly dense or absent confidentiality and privacy policies, failure to disclose commercial conflicts of interests, failure to meet the stated scope of the test, and failure to word the test outcomes in an appropriate and ethical manner.

No Evidence of Benefit in Population Screening for Dementia

UK researchers conducted a systematic review of studies that looked at population screening for dementia and compared outcomes with a routine pattern of care in the general population, among patients in general medical practice and among patients in community care. The researchers found no evidence of the effect of screening on patient outcomes including cognitive, mental and emotional health, social function and planning, and no indication of its added value compared to current practice. They suggest that policymakers should be very cautious about adopting population screening for dementia without any evidence of benefits or risks. The Alzheimer’s Association recommends that people see their doctor for a thorough evaluation at the earliest signs of memory problems or changes. For the 10 Warning Signs of Alzheimer's, visit www.alz.org.

Self-reported Changes in Memory May Be Earliest Clinical Markers of Alzheimer’s

Three studies supported increasing evidence that subjective cognitive decline (SCD) — the self-reported perception of memory or cognition problems — is a potentially valid early clinical marker of brain and cognitive changes that may indicate Alzheimer's disease.

One study cognitively normal older people showed a significant relationship between self-reported cognitive concerns and evidence of buildup of beta-amyloid protein, the main component of Alzheimer's brain "plaques," as revealed by PET scans.

Another study of nearly 4,000 nurses age 70 and older indicated that a subjective concern about memory could be a marker of subseuent decline in objectively measured memory especially among carriers of the ApoE4 gene, the strongest known genetic risk factor for Alzheimer’s.

In a third study, older adults underwent annual cognitive assessments for an average of 10 years. Subjects who reported a change in memory since their last assessment were almost twice as likely to be diagnosed with mild cognitive impairment or dementia during follow-up than those who did not report such a change.

In addition, an international group of Alzheimer's researchers announced the formation of the Subjective Cognitive Decline Initiative (SCD-I) to develop a new research framework for SCD with a focus on preclinical Alzheimer’s.

Potential Alzheimer’s Disease Risk Factors

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Alzheimer’s Association® CEO Harry Johns, with Director of Professional Education Amelia Schafer and Director of Family Services David Hoppe from Colorado Chapter at AAIC 2013.

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