Elan's scientific approach to treating Alzheimer's disease (AD) focuses on the beta amyloid hypothesis, as it is believed that blocking the generation of beta amyloid in the brain or enhancing the clearance of beta amyloid will result in the successful treatment of AD patients. The beta amyloid hypothesis asserts that beta amyloid is involved in the formation of the plaque that causes the disruption of thinking that is the hallmark of AD. This hypothesis is also the leading approach to development of therapeutic treatments that may fundamentally alter the progression of the disease, and evidence suggests that clearance of beta amyloid may lead to improved function in AD patients.

Beta amyloid, also known as Abeta, is actually a small part of a larger protein called the amyloid precursor protein, or APP. Beta amyloid is formed when certain enzymes called secretases clip (or cleave) APP. Elan scientists are investigating three key therapeutic approaches that target the production of beta amyloid: 1) amyloid immunotherapy, in collaboration with Wyeth; 2) inhibiting beta secretase; and 3) inhibiting gamma secretase.

Research in Beta Amyloid Immunotherapy

Beta amyloid immunotherapy is the treatment of Alzheimer's disease by inducing or enhancing the body's own immune response in order to clear beta amyloid from the brain. Active immunization stimulates the body's own immune system to manufacture anti beta amyloid antibodies that may attach to amyloid and clear it from the brain. This, in turn, appears to reduce the build up of beta amyloid in the brain tissue of patients.

Through a monoclonal antibody approach (passive immunization), synthetically engineered antibodies directed at beta amyloid are injected into the bloodstream and are thought to help reverse beta amyloid accumulation.

Elan and Wyeth Research in Amyloid Immunotherapy

AN-1792

AN-1792 is a synthetic form of the beta amyloid peptide. Scientists have theorized that immunotherapy with the beta amyloid peptide might stimulate an immune response against the peptide that would, in turn, elicit clearance of beta amyloid peptide and plaques in the brains of those affected by Alzheimer's disease (active immunization).

Elan initiated a Phase I study of AN-1792 in 2000. In 2001, Elan in collaboration with Wyeth, initiated a Phase IIa study of AN-1792. Dosing in the Phase IIa study was halted after signs and symptoms consistent with encephalitis were reported in four patients; however, both trials provided key findings that support the beta amyloid immunotherapy approach.

Phase I:
The Phase I trial was designed to assess safety, tolerability and immunogenicity (antibody response to the study medication) of various doses of AN-1792. The trial also helped to identify doses and regimens to study in the larger Phase IIa clinical trial.

Key Findings:

- AN-1792 elicits an anti beta amyloid antibody response in patients with mild to moderate Alzheimer's Disease.
- In this small safety study, as anticipated, no positive outcomes were observed in three exploratory efficacy measures; however, positive responses were reported for activities of daily living.
- After encephalitis was reported in the Phase IIa study, an autopsy analysis of a Phase I study patient who died from a pulmonary embolism indicated evidence of encephalitis.

Phase IIa:
The Phase IIa study was designed to evaluate the clinical impact of eliciting an immune response (formation of antibodies) to the beta amyloid peptide in patients with mild to moderate Alzheimer’s disease. The evaluation included standard clinical assessments of cognition as well as the assessment of surrogate markers of Alzheimer’s disease.

Key Findings:

- Evidence of beta amyloid plaque clearance was observed in four autopsy cases that have been examined from the Phase I and IIa AN-1792 trials. The observed plaque clearance mirrors those findings seen by numerous laboratories investigating beta amyloid immunotherapy in animal models of Alzheimer’s disease. Memory, attention and concentration improved at 12 months in anti beta amyloid antibody responders,
according to a composite neuropsychological performance measure. (In this interrupted trial, primary cognitive endpoints did not demonstrate improvement in those treated with AN-1792.)

- Levels of tau protein (a marker known to be elevated in AD) in cerebrospinal fluid (CSF) were lower in anti beta amyloid antibody responders.
- Brain volume was lower in anti beta amyloid antibody responders as measured by magnetic resonance imaging (MRI).

Elan and Wyeth continue to evaluate the data from AN-1792, which suggest that the biological effects of the immunotherapy approach may warrant further study.

**AAB-001**

Elan and Wyeth are continuing to pursue beta amyloid immunotherapy for mild to moderate Alzheimer's disease in a Phase II study of a humanized monoclonal antibody, AAB-001. This therapeutic antibody, which binds to and clears beta amyloid peptide, is designed to provide antibodies to beta amyloid directly to the patient, rather than requiring the patient to mount their own individual response. It is believed that this approach may eliminate the need for the patient to mount an immune response to beta amyloid.

Animal studies have shown that this approach is equally effective in clearing beta amyloid from the brain as traditional active immunization methods. By providing such a "passive immunization" approach for treatment of Alzheimer's disease, it is believed that the benefits demonstrated with AN-1792 will be retained, while the safety concerns will be greatly reduced or eliminated due to the absence of stimulation of the patient's immune response to beta amyloid.

**ACC-001**

Elan and Wyeth are also developing ACC-001, a novel beta amyloid-related active immunization approach now in Phase I clinical trials. This approach is intended to induce a highly specific antibody response to beta amyloid. The goal is to clear beta amyloid while minimizing side effects such as inflammation of the central nervous system.

**Elan’s Secretase Inhibitor Research**

Beta and gamma secretases are proteases (enzymes that break down other proteins) that appear to clip the amyloid precursor protein (APP), resulting in the formation of beta amyloid. This is significant because if the "clipping" of APP could be prevented, the pathology of Alzheimer’s disease may be changed. As a result of these discoveries, Elan has developed and is pursuing advanced discovery programs focused on identifying and developing small molecule inhibitors of beta and gamma secretases. Elan has been at the forefront of research in this area.

**Beta Secretase**

Beta secretase is believed to initiate the first step in the formation of beta amyloid, the precursor to plaque development in the brain.

Elan has been an industry leader in beta secretase research for more than 10 years. Our finding published in Nature in 1999 concerning the role beta secretase plays in beta amyloid production is considered a landmark discovery. Today, Elan continues to be at the center of understanding the complexities of beta secretase and advancing potential disease-modifying agents that inhibit its role in Alzheimer’s disease pathology. This program is in the preclinical discovery phase.

**Gamma Secretase**

Gamma Secretase is an unusual multi-protein complex that is thought to play a significant role in the formation of beta amyloid.

Elan has played a critical leadership role in the increased awareness of how gamma secretase may affect AD pathology. Elan’s finding, published in 2001, that functional gamma secretase inhibitors appear to reduce beta amyloid levels in the brain was an important step in this area of AD research. Elan’s gamma secretase research is currently in the preclinical discovery phase.

**A Retrospective and Key Publications**

For brief descriptions of key publications by Elan scientists and Elan-sponsored research teams, from 1992 to 2002, please click here

Learn more about Elan and its work from the 10th International Conference on Alzheimer’s Disease and Related Disorders, Madrid, July 15 - 20, 2006