Cognosci

Protecting and repairing the brain

NOVEL THERAPEUTIC COMPOUNDS FOR ALZHEIMER'S DISEASE

Summary

Apolipoprotein-E (apoE) possesses anti-inflammatory and neuroprotective activities. Cognosci Inc. has created a novel series of apoE-mimetic compounds that: a) suppress proinflammatory cytokine release, b) inhibit nitric oxide production, c) inhibit macrophage activation, d) inhibit lymphocyte proliferation and e) protect neurons from excitotoxic challenge. These compounds effectively reduce neuronal death as well as reducing inflammatory and histochemical signs of neurodegenerative disease in a transgenic animal model of Alzheimer's disease (AD).

Alzheimer's Disease

Alzheimer's disease currently affects over 4 million Americans and an estimated 10 million caregivers. As a progressive dementia, Alzheimer's begins with mild memory loss that typically progresses over 20 years to dramatic loss of most learning and memory abilities. Alzheimer's always results in the death of the patient. Of the currently approved therapeutics, none have been shown to modify the death outcome of Alzheimer's disease. Most current treatments are focused on preserving the neurotransmitter known as acetylcholine and these drugs offer temporary improvement in learning and memory behavior. However, the improvements are short lived, are generally mild, and do not address the underlying causes of the disease.

Research into the pathology underlying AD has shown three types of lesions in Alzheimer's brains: Amyloid Plaques composed of the Amyloid Beta Peptide, Cerebrovascular Amyloid composed of Amyloid Beta Peptide, and Neurofibrillary Tangles composed of hyperphosphorylated tau protein. Immunization strategies to reduce Amyloid Beta Peptide deposits in experimental animals have successfully inhibited memory loss, but initial clinical trials in humans have proven problematic. These early results strongly suggest that immunization strategies are not safe because immunization leads to severe brain inflammation and early deaths in human trials. However, given that brains of Alzheimer's patients display significant loss of healthy neurons in regions surrounding the Amyloid Plaques, the limited successes from immunization tests have supported efforts to develop alternative strategies that reduce Amyloid Beta Peptide and may prove of value to the Alzheimer's patient.

Cognosci Compounds

When evaluated in an Alzheimer's model where a transgenic Amyloid Peptide Precursor mouse is combined with a Traumatic Brain Injury technique to accelerate an Alzheimer's-like disease, Cognosci's compounds substantially reduced the deposition of Amyloid Beta Peptide (Figure 1). A reduction of Amyloid Beta Peptide deposition is associated with better behavioral performance in animal models of Alzheimer's disease.

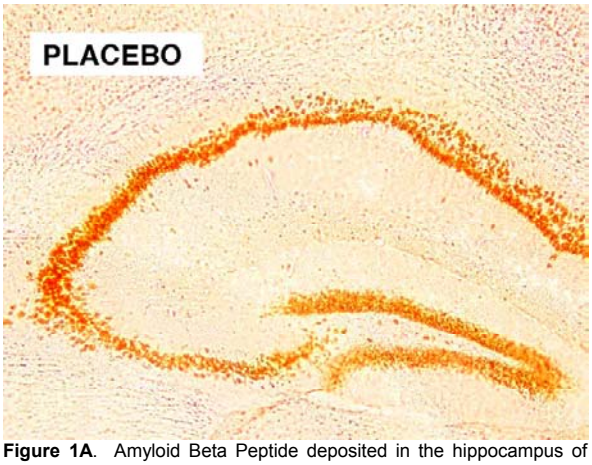

Figure 1A. Amyloid Beta Peptide deposited in the hippocampus of the brains of an accelerated mouse model of Alzheimer's disease treated with placebo for 7 days. Deposits visualized as a brown-orange stain.

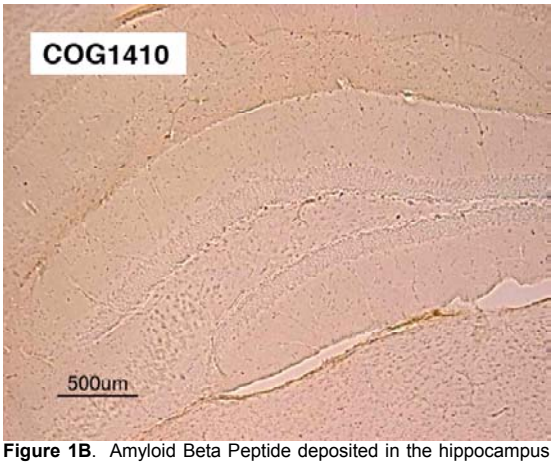

Figure 1B. Amyloid Beta Peptide deposited in the hippocampus of the brains of an accelerated mouse model of Alzheimer's disease treated with COG1410 for 7 days. Note the lack of amyloid beta peptide deposits.

Company Overview

- Privately held, founded in 2000
- **Technology both in-licensed from Duke University and created at Cognosci**
- Funded by >$7 M in NIH SBIR grants
- Strong IP portfolio - Issued patent and pending patents on compositions, formulatons and use
- Currently employs 7 scientists

Alzheimer's Disease Facts

- Neurodegenerative and Fatal Disease
- Progressive learning and memory loss
- Late stages require around the clock care
- Late age of onset (mid 60s to 70s)
- 4 million patients in United States
- Equally affects all populations worldwide

Current Market

- $2.9 Billion worldwide
- Projected growth to >$6 Billion by 2015
- No disease modifying treatment
- Patients that respond to current treatments respond for a short time, but then catch up to untreated counterparts

Chronic Neurodegenerative Markets

- Parkinsons $3 billion
- Multiple Sclerosis ~$5 billion
- ALS ~$1 billion

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Brains of Alzheimer's patients display significant loss of healthy neurons, particularly those neurons surrounding the Amyloid Plaques. Cognosci studies using Fluorojade-B stain that identifies dying and dead neurons revealed that treatment with COG1410 significantly reduced dysfunctional and dead neurons when compared to placebo in the accelerated AD/Traumatic Brain Injury model (Figure 2A and 2B). Inflammation is another mechanism that has been implicated in the pathology of AD and activation of microglia, the main inflammatory cell in the brain, is significantly reduced in COG1410 treated brains (Figure 3). These data demonstrate that Cognosci's lead compounds effectively suppress Amyloid Beta Peptide deposition and reduce neuronal loss when applied in a therapeutic mode.

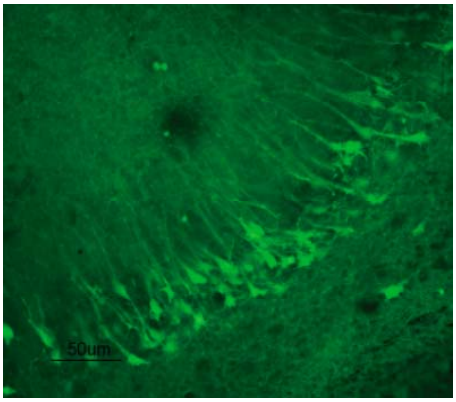

Figure 2A. Fluorjade-B stained dysfunctional neurons in the hippocampus of the brains of an accelerated mouse model of Alzheimer's disease treated with placebo for 7 days. Dead or dying neurons are labeled bright green by the Fluorojade-B stain.

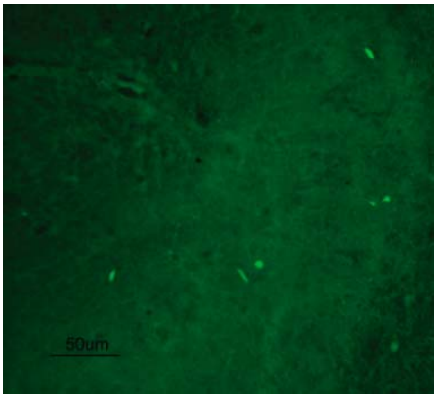

Figure 2B. Fluorjade B stained dysfunctional neurons in the hippocampus of the brains of an accelerated mouse model of Alzheimer's disease treated with COG1410.

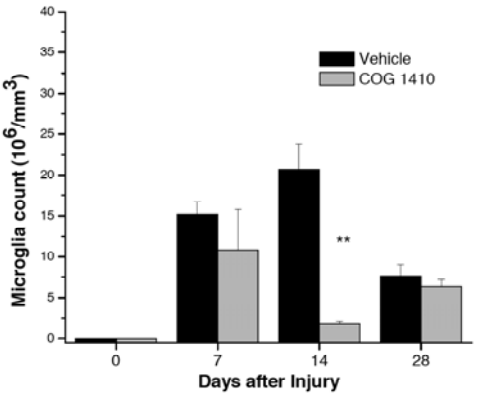

Figure 3. COG1410 treatment reduces activated microglia staining with F4/80 antibodies in the brains of our accelerated mouse model of Alzheimer's disease.

Apolipoprotein-E and Alzheimer's Disease

Humans are the only animal known to express multiple isoforms of the apolipoprotein-E protein. The most common isoforms known as apolipoprotein-E2, apolipoprotein-E3 and apolipoprotein-E4, have been linked to susceptibility to Alzheimer's Disease. Although it does not directly cause Alzheimer's, about 16% of the general population expresses the apolipoprotein-E4 isoform and this percentage increases to about 45% in the persons who are afflicted with Alzheimer's disease. Patients that express apolipoprotein-E4 also experience an earlier onset of dementia, approximately 10 years earlier than patients that carry the other apoE alleles. Alzheimer's patients that express apolipoprotein-E4 also display more Amyloid Plaques, more Cerebrovascular Amyloid, and more Neurofibrillary Tangles than their apolipoprotein-E3 counterparts. This finding suggests that apolipoprotein-E3 may reduce the amount of brain lesions and delay the age-of-onset in the Alzheimer's patient and indicates that supplementation with an apoE mimetic may provide a therapeutic strategy to effectively treat the underlying pathology of AD. As we have shown above, COG1410 effectively reduced Amyloid Beta Peptide deposition without the use of immunization strategies and without their unwanted side-effects.

Strategic Opportunity

Cognosci's lead compounds are multi-dimensional inhibitors of Alzheimer's disease activities that:

- Reduce inflammation – suppresses microglial activation and production of cytokines in the brain,
- Inhibits Amyloid Beta Peptide deposition – reduces neurotoxicity and protects neurons,
- Crosses the blood brain barrier – suppresses activation of microglia and astrocytes and provides neuroprotection.

Lead compounds with demonstrated efficacy in therapeutic treatment of an animal model of Alzheimer's disease are now available for licensing. Cognosci currently seeks a strategic partner for completion of preclinical testing, clinical trials, and commercialization of these drugs for the treatment of Alzheimer's Disease.