



NOVEL THERAPEUTIC COMPOUNDS FOR TRAUMATIC BRAIN INJURY

Traumatic Brain Injury

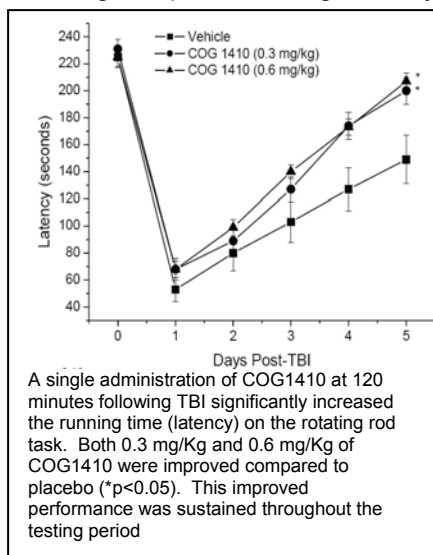
Traumatic brain injury (TBI) affects 1.4 million Americans at a cost of \$60 billion annually. Due to the brains' limited ability to self-repair, survivors are left with persistent motor and cognitive deficits that substantially reduce their quality of life. The dramatic impairment of learning and memory skills typically results in a low level of employment with attendant financial problems. Following TBI, neurons die acutely due to trauma and lack of blood flow, however, even greater neuronal damage occurs hours and days following the traumatic insult due to uncontrolled brain inflammation. The time dependent progression of damage presents a window of opportunity to inhibit ischemic injury and control inflammation thereby improving clinical outcome. Despite increased understanding of the pathophysiology of TBI, there are still no drug treatments that improve important functional outcomes like the restoration of the learning and memory losses that follow TBI.

Cognosci's Therapeutic Approach

Apolipoprotein E (apoE) is the primary apolipoprotein synthesized in the brain in response to injury where it modulates several components of the neuroinflammatory cascade triggered by TBI. Cognosci Inc. has created a novel series of apoE-mimetic compounds (COG133 and COG1410) that function by multiple mechanisms relevant to the pathogenesis of TBI. Using clinically relevant models of both open and closed head TBI, we have demonstrated that a single intravenous administration of Cognosci compounds following TBI significantly improved motor and cognitive function. The compounds available for licensing are small peptides ranging from twelve to seventeen amino acids with potent *in vitro* and *in vivo* antioxidant, anti-inflammatory, neuroprotective, and neurotrophic activity.

Preclinical Efficacy of COG compounds

We have used multiple models of TBI that replicate the cortical brain contusion, diffuse neuronal injury and death of vulnerable nerve cells seen in the clinical setting of blunt head trauma. The figure below demonstrates that mice treated intravenously with COG1410 at 120 minutes following TBI performed significantly better on tests of vestibulomotor function (ability to maintain balance and run on a rotating rod) than those treated with placebo. At 5 days following injury, COG1410 treated animals are performing at 90% of their preinjury level, while the placebo treated animals never reach this level even with extended days of testing. In addition, none of the COG1410 treated animals died after the TBI.



Although TBI-induced motor dysfunction improves following rehabilitative therapy, TBI-induced learning and memory impairments only slightly improve with therapy so that these cognitive impairments continue and result in a substantial negative impact on quality of life. Thus, any successful therapy for TBI needs to address and improve learning and memory, brain-based activities that depend upon healthy neurons. As demonstrated in the figure on the back page, treatment with COG1410 at 120 min following TBI significantly reduced the number of injured and dying neurons in the hippocampus of brain injured mice (Panels B and D) compared to those that received the placebo (Panels A and C). Consistent with this

neuroprotection demonstrated in the hippocampus, treatment with COG1410 significantly improved performance in the Morris water maze task, a task used to assess hippocampus-dependent long-term spatial memory in which rodents use an array of extra-maze cues to locate a hidden escape platform that is submerged below the water surface.

Company Overview

- Privately held, founded in 2000
- **Technology both in-licensed from Duke University and created at Cognosci**
- Funded by >\$7.5 M in NIH SBIR grants
- Strong IP portfolio - One issued patent and many pending patents
- Currently employs 7 scientists

Traumatic Brain Injury Facts

- Neurons die acutely from trauma and lack of blood supply
- Most neuronal damage occurs days later providing a window for therapeutic intervention

Acute Brain Injury Market

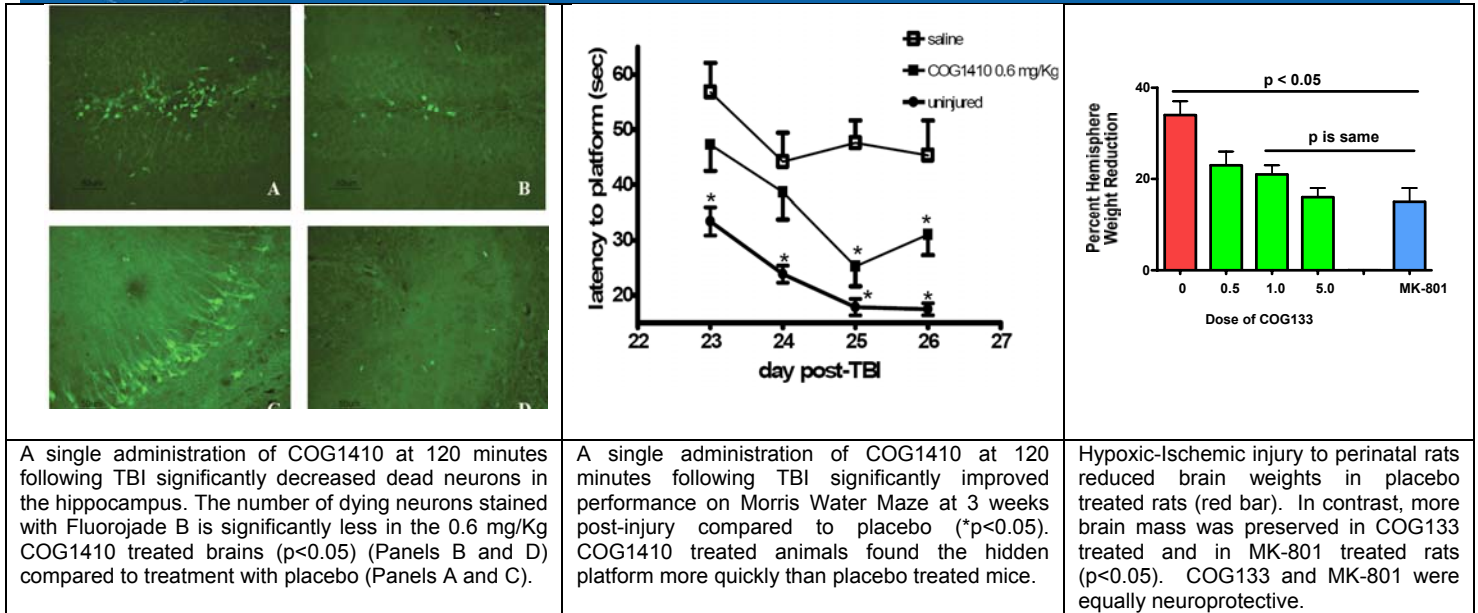
- Excellent commercial prospects: >\$3 B for Traumatic Brain Injury
- No FDA approved treatments for TBI
- Eligible for FDA's Orphan status
- Demonstration of neuroprotection will open new markets for:
 - Stroke >\$2 B
 - Subarachnoid Hemorrhage \$500 M
 - Dementia associated with Coronary Bypass > \$1B

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We have also demonstrated the neuroprotective properties of Cognosci compounds in several other clinically relevant models of neurological disorders including Multiple Sclerosis, where treatment with COG133 decreased clinical scores and increased the number of mice that achieved remission compared to mice that received vehicle (Li et al., 2006). We demonstrated the neuroprotective effects of intrathecal administration of COG133 in a perinatal rat model of hypoxic-ischemic injury (HIE; McAdoo et al., 2005). In addition, we demonstrated that COG1410 administration following subarachnoid hemorrhage resulted in a dramatic reduction in mortality, vasospasm, cerebral edema, and functional deficits compared to vehicle treated mice (Gao et al., 2006). The ability of COG1410 to reduce cerebral edema is particularly relevant as this represents a significant source of neurological morbidity in the clinical setting following TBI, as well as in neurodegenerative diseases such as Alzheimer's Disease and Multiple Sclerosis. These studies show that Cognosci's lead compounds effectively improve functional behaviors and reduce neuronal cell loss following a variety of neurological insults when applied after the brain injury.

Strategic Opportunity

Cognosci's lead compounds are multi-dimensional inhibitors of the brain inflammation and injury associated with Traumatic Brain Injury, Stroke and Subarachnoid Hemorrhage that:

- Reduce cytokines and free radicals associated with brain inflammation
- Protect against excitotoxic injury – neuroprotection preserves brain cells from injury
- Cross the blood brain barrier – suppress activation of microglia and astrocytes
- When given following trauma, significantly improves short term motor function
- When given following trauma, significantly improves long term learning and memory functions

Cognosci currently seeks a strategic partner for completion of preclinical testing, clinical trials, and commercialization of these novel drugs for acute traumatic and ischemic brain injuries.

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