NOVEL THERAPEUTIC COMPOUNDS FOR SUBARACHNOID HEMORRHAGE

Subarachnoid Hemorrhage
Subarachnoid hemorrhage due to aneurysm rupture (aSAH) affects approximately 50,000 Americans annually. Unlike ischemic stroke, SAH tends to affect younger patients without traditional vascular risk factors. Due to the limited ability of the brain to self-repair, greater than 50% of all 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 SAH, neurons die acutely due to trauma and lack of blood flow; however, even greater neuronal damage may occur in the first several weeks following aneurysm rupture due to vasospasm and delayed cerebral ischemia. This provides a unique opportunity to initiate prophylactic neuroprotective therapy in a controlled environment prior to the onset of secondary injury. The time dependent progression of damage presents a window of opportunity to inflammation and vasospasm, thereby reducing ischemic injury and improving clinical outcome. At present, nimodipine is the only approved drug for patients with SAH, and has established a defined regulatory pathway for FDA approval. Even with this treatment, however, there is still significant neurological morbidity and mortality associated with SAH, which represents a compelling unmet clinical need.

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 SAH. Cognosci has created a novel series of apoE-mimetic compounds (COG133 and COG1410) that function by multiple mechanisms relevant to the pathogenesis of SAH. Using clinically relevant models of SAH, we have demonstrated that intravenous administration of Cognosci compounds following SAH 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 tested the efficacy of COG 1410 in multiple models of SAH that replicate the acute brain injury due to intracranial bleeding and delayed cerebral ischemia following vasospasm. The figure below demonstrates that mice treated intravenously with COG1410 showed reduced mortality following SAH. In a clinically relevant treatment paradigm, animals were treated with COG1410 intravenously after SAH and treatment was continued at 12-hour intervals for three days after injury. Administration of COG1410 resulted in reduced vessel narrowing associated due to post-SAH vasospasm relative to animals treated with placebo (MCA diameter 98.1 ± 30.6 µM in peptide group versus 70.5 ± 37.2 µM in placebo group; p < 0.05), as shown on the following page. Animals treated with COG1410 also performed significantly better on tests of vestibulomotor function (the ability to maintain balance and run on a rotating rod) than those treated with placebo. At 3 days following injury, COG1410 treated animals performed at 90% of their pre-injury level, while placebo treated animals never reached this level even with extended days of testing (Gao et al., 2006). These dramatic effects of COG 1410 have since been replicated in an independent rabbit model (unpublished), and in conjunction with nimodipine, as would be used in the current clinical standard of care (Mesial et al., 2006).
Cognosci’s lead compounds are multi-dimensional inhibitors of brain inflammation and injury associated with Subarachnoid Hemorrhage, Stroke, and Traumatic Brain Injury that:

- Reduce cytokine expression and production of free radicals associated with brain inflammation
- Protect against excitotoxic injury to preserve brain cells from ischemic injury
- Cross the blood brain barrier to suppress activation of microglia and astrocytes and protect neurons
- Reduce cerebral edema and vasospasm associated with subarachnoid hemorrhage

We have previously demonstrated the ability of COG1410 to reduce cerebral edema and neuroinflammation (Lynch et al., 2005) and cerebral ischemia (Aono et al., 2003), two mechanisms of cellular injury that play a central role following SAH. These protective mechanisms are also important in a number other neurological diseases. Cognosci has also demonstrated the neuroprotective properties of Cognosci compounds in several other clinically relevant models of neurological disorders including Multiple Sclerosis. Treatment of an MS model with COG133 decreased clinical scores and increased the number of mice that achieved remission from clinical disease compared to mice that received placebo (Li et al., 2006). We also demonstrated the neuroprotective effects of intrathecal administration of COG133 in a perinatal rat model of hypoxic-ischemic injury (McAdoo et al., 2005). The ability of COG1410 to reduce cerebral edema and prevent ischemic brain injury is particularly relevant as this represents a significant source of neurological morbidity in the clinical setting following SAH. 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**

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