Protecting and repairing the brain

NOVEL THERAPEUTIC COMPOUNDS FOR MULTIPLE SCLEROSIS

Summary

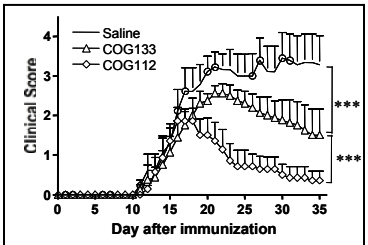
Apolipoprotein E (apoE) possesses anti-inflammatory, neuroprotective and cholesterol carrying activities. Cognosci Inc. has created a novel series of apoE-mimetic compounds that: a) inhibit macrophage activation, b) inhibit nitric oxide production, c) suppress proinflammatory cytokine release, d) inhibit lymphocyte proliferation, e) protect neurons from excitotoxic challenge and f) enhance rebuilding of myelin. These compounds effectively reduce clinical and biochemical signs of autoimmune disease in animal models of Multiple Sclerosis and Rheumatoid Arthritis. Using experimental autoimmune encephalomyelitis (EAE) as a model of Multiple Sclerosis, Cognosci compounds substantially reduce the clinical symptoms of EAE and promote disease remission in both relapsing remitting and progressive forms of EAE. In addition, histopathological analysis shows significant attenuation of spinal cord demyelination and dramatically reduced numbers of infiltrating peripheral cells. These data demonstrate that Cognosci's lead compounds effectively suppress inflammatory autoimmune disorders when applied in a therapeutic mode.

Multiple Sclerosis

This debilitating disease is characterized by loss of the myelin sheath that insulates the axons of nerves. Myelin loss results from immune recognition of myelin as an auto-antigen. Progressive destruction of the myelin sheath results in a loss of axonal signal conductance and eventually, to nerve degeneration. Of the two major forms of MS, relapsing-remitting MS and progressive MS, approved therapies only treat the relapsing-remitting form. This leaves progressive MS patients, about 15% of the entire patient population, with no therapeutic options. To make matters worse, while patients with relapsing-remitting disease do have several treatment options, only 30-40% of these patients experience a therapeutic benefit from current drugs. Each of the established drugs act to modulate the immune system, but have no demonstrated neuroprotective activity to maintain nerve viability. Recently, another drug was approved that slows myelin loss by preventing T-cell infiltration into the CNS. However, this new drug carries an increased risk of life-threatening infections that result from loss of T-cell movement. The limitations of existing drugs provide a significant opportunity for compounds that can inhibit myelin loss, prevent axonal degeneration and help to rebuild disease-damaged myelin sheaths.

Cognosci Compounds

Cognosci compounds (COG112 and COG133) show efficacy in animal models of both relapsing-remitting and progressive MS. The compounds available for licensing are small peptides of ten to thirty-four amino acids with potent *in vitro* and *in vivo* anti-inflammatory activity. The figure to the left shows the clinical course over time of a progressive form of MS in a mouse EAE model. Control animals that did not receive the Cognosci compounds experience higher clinical scores indicating a higher degree of clinical disability. Sick animals treated with Cognosci compounds starting on Day 15 showed a significant improvement in clinical scores with virtually complete recovery in the COG112 treatment group. Histopathological analysis of the spinal cords from these animals (see following page) revealed large demyelinated lesions with infiltrating T-cells in control animals, and a lack of significant lesions or infiltration in Cognosci compound treated animals.



Progressive EAE: Cognosci compounds promote the recovery of animals from clinical disability of progressive EAE when administered when animals first showed a Clinical Score ≥ 2. Animals were treated daily with COG133 or COG112 (1 mg/kg, i.p.) or normal saline.

COG133 treatment also demonstrated a significant clinical improvement in the PLP-induced EAE model of relapsing remitting MS, including complete remission of clinical signs in 25% of cases. COG133 treatment resulted in a longer average time between relapses, increasing from 12 days in placebo to 28 days in COG133 treated animals, resulting in 70% less time with disability.

Company Overview

- Privately held, founded in 2000
- Technology both in-licensed from Duke University and created at Cognosci
- Funded by >$8 M in NIH SBIR grants
- Strong IP portfolio - Two issued patents and many pending patents
- Currently employs 7 scientists

Multiple Sclerosis Disease Facts

- Neurodegenerative autoimmune disorder
- Progressive loss of nervous system function resulting in increasing disability
- Early age of onset (mid 30s)
- 2 million patients worldwide
- Highest prevalence in USA and Northern Europe

Current Market

- $4.8 Billion worldwide
- >$17,000 average annual wholesale cost
- Projected growth to >$10 Billion by 2015
- No approved treatment for Progressive MS
- 70% of patients do not respond to current treatments

Autoimmune Markets

- Rheumatoid arthritis $4 billion
- Inflammatory bowel disease $1+ billion
- Psoriasis ~$1 billion
- Lupus ~$1 billion

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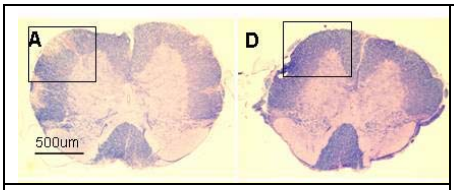
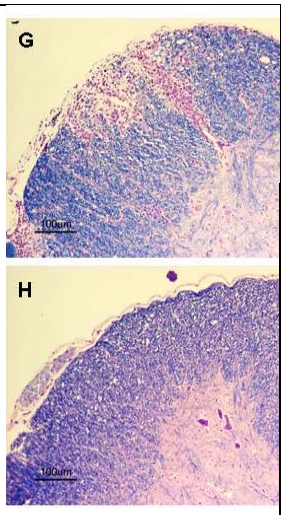
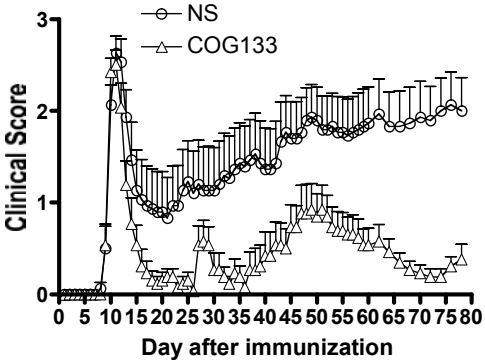




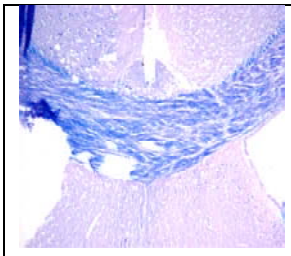
200×

Histopathological Analysis: COG133 prevented spinal cord demyelination in MOG-induced EAE mice. The animals were sacrificed 30 days after MOG immunization, the whole spinal cord was dissected out and 5-μm –thick sections were made from cervical segments of COG133-treated animals (D, H) and Normal Saline treated ones (A, G). These sections were stained with Luxol fast blue (for myelin, stained in blue) and then counterstained with eosin (showing peripheral infiltrates, in purple). Picture G is the magnifying of inset A and H for inset D.

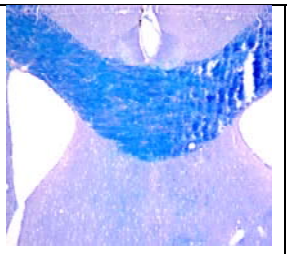


Relapsing remitting EAE: COG133 promotes the recovery of animals from clinical disability of relapsing remitting EAE with therapeutic treatment when animals first showed a Clinical Score ≥ 2. Daily treatments with COG133 or placebo (NS).

The activity of the Cognosci compounds derives from suppression of inflammation, protection of neurons from glutamate excitotoxicity and oxidative stress (see Laskowitz *et al.* 2001 and Aono *et al*. 2003 for *in vitro* studies). These activities are retained *in vivo* (see Lynch *et al*. 2003) in both peripheral tissues (see left panel below) and in the CNS. In the brain, we have demonstrated a reduction in cytokine levels and cytokine expression, as monitored through real-timePCR, that is due to the presence of the compound. These compounds also protect neurons from NMDA excitotoxicity. Pharmacokinetic analysis has shown that 1-3% of the injected compound can be isolated in an intact form in perfused brain tissue.



Loss of Myelin: Cuprizone treatment reduces Luxol Fast Blue stained myelin in the corpus collosum of the brain of placebo treated animals.



Restoration of Myelin: Cuprizone followed by COG112 treatment greatly restores myelin levels that stain with Luxol Fast Blue.

Cognosci compounds display neurorestorative activities in a cuprizone model of demyelination. Loss of myelin is prominent in the brains of MS patients and in mice treated with cuprizone. Following cuprizone treatment, animals are allowed to recover while being treated with placebo (left panel) or with COG112 (right panel). Brain slices are stained with Luxol Fast Blue to visualize the amount of myelin in the corpus collosum in the center of the brain. As shown in the figures, the amount of blue-staining myelin is significantly greater in the COG112 treated animals then in the placebo treated animals. This result suggests an additional reparative activity of COG112 in whole animals.

Strategic Opportunity

Cognosci's lead compounds are multi-dimensional inhibitors of Multiple Sclerosis–disease activities that:

- Reduce cytokine expression – suppresses recruitment and activation of additional immune cells,
- Reduce nitric oxide production – suppresses sodium channel-related axonal degeneration,
- Protects against excitotoxic injury – preserves axons and oligodendrocytes,
- Cross the blood brain barrier – suppresses activation of microglia and astrocytes.
- Inhibit T-cell proliferation – suppresses number of activated T-cells and infiltration into the CNS,
- Enhance rebuilding of new myelin – stimulates oligodendrocyte proliferation and differentiation.

Lead compounds with demonstrated efficacy in therapeutic treatment of progressive and relapsing remitting forms of MS in murine EAE models 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 Multiple Sclerosis.

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