Myelin Repair Foundation

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The Myelin Repair Foundation and National Institutes of Health
Initiate Clinical Studies of Guanabenz for Treatment of Multiple Sclerosis

Guanabenz shown to diminish myelin damage and oligodendrocyte loss in animal models of MS

SARATOGA, Calif. – [April 30, 2015] – The Myelin Repair Foundation (MRF), in partnership with the National Institutes of Health (NIH), announced today that patients are now being enrolled in a clinical trial conducted to study guanabenz, an FDA-approved drug to treat high blood pressure that was identified by MRF-funded researchers as a potential therapeutic to reduce loss of myelin, in multiple sclerosis (MS) patients. If successful, guanabenz (formerly called MRF-008) could be the first MS treatment to focus on protecting myelin from damage, which is the hallmark of MS, rather than on suppressing the immune system – as all currently available MS treatments do.

The trial, a collaboration between the MRF and the National Institute of Neurological Disorders and Stroke at the National Institutes of Health (NIH) Clinical Center, is being led by NIH Investigators Dr. Irene Cortese, M.D., and Dr. Daniel Reich, M.D., Ph.D.

Myelin is the membrane sheath that surrounds and protects nerve fibers (axons) in the central nervous system, allowing for the quick and effective transmission of signals through the brain and spinal cord. In MS patients, the immune system damages myelin and the cells that produce and maintain it (oligodendrocytes). As the disease progresses, severe myelin degeneration is accompanied by axonal loss and neurodegeneration, all of which can profoundly disrupt signaling in the central nervous system – leading to the array of symptoms that characterize MS. Because loss of myelin correlates with neurodegeneration, new therapies that are designed to protect myelin or promote remyelination would be categorized as neuroprotective. MS is a chronic neurodegenerative disease, the most common disabling neurological disease of young adults, affecting 2.3 million people worldwide. The cause of MS is unknown.

Guanabenz and Protection

In a *Nature Communications* paper published on March 13, 2015, MRF-funded researchers reported that guanabenz prevents myelin loss and alleviates clinical symptoms of MS in animal models by prolonging an innate mechanism that is activated in response to stressors such as inflammation. When this protective response is disrupted or overloaded – by the chronic inflammation seen in MS, for example – oligodendrocyte cell death and demyelination are significantly enhanced. Treatment with guanabenz strengthens this stress-response mechanism and helps protect oligodendrocytes from cell death. These findings point to promising avenues for the development of new therapeutics against MS.

“Guanabenz appears to enhance the cell’s own protective machinery to diminish the loss of myelin,” said senior study author Brian Popko, Ph.D., Jack Miller Professor of Neurological Disorders at the University of Chicago and a member of the Myelin Repair Foundation’s Research Consortium. “While there have been many efforts to stimulate remyelination, this now represents a unique protective approach. You don’t have to repair the myelin if you don’t lose it in the first place.”

The MRF has supported Dr. Popko’s research on the effects of inflammation on oligodendrocyte health and myelin production for over 10 years. In addition to Dr. Popko’s team at the University of Chicago, MRF-funded researchers at Northwestern University in Chicago, Case-Western Reserve University in Cleveland, and scientists at the MRF’s Translational Medicine Center in Sunnyvale, CA, made key contributions to the guanabenz publication.

The MRF’s clinical advisory board reviewed the preclinical data and encouraged the MRF to advance guanabenz into clinical testing. The drug’s protective efficacy and ability to alleviate myelin loss, coupled with its existing FDA approval and good safety profile, makes the clinical implications promising for MS patients, the advisory board concluded. However, before clinical studies could be initiated, the MRF had to identify a contract drug manufacturer to make clinical-grade guanabenz. Because guanabenz has been off the market for many years, it is no longer manufactured anywhere in the world.

“We are very pleased that guanabenz is now moving into studies in MS patients,” said Tassie Collins, Ph.D., Vice President of Translational Medicine at the Myelin Repair Foundation. “This is a promising therapeutic approach, but it might not have been able to move forward without MRF’s participation.” Because it is a generic drug, guanabenz would be an unlikely investment choice for pharmaceutical companies. And because it had to be custom-manufactured for the trial, most academic organizations would have been unable to resource it.

Clinical Trial Phase 1

Phase 1 clinical studies will be conducted to assess the safety and tolerability of the drug at varying doses in patients with MS. They will also identify an optimal dose for subsequent Phase 2 clinical studies. Though the safety profile of guanabenz as a treatment for hypertension is well established, the drug has not been tested in MS patients. The trial will employ a dose escalation strategy, gradually increasing the dosage to allow investigators to closely monitor patients as doses are increased.

Phase 1 test subjects will be patients with relapsing-remitting MS (RRMS) who are taking Copaxone, an FDA-approved anti-inflammatory treatment for MS. It is widely perceived by the MS clinical community that new MS therapeutics designed to protect or repair myelin will need to be coupled with drugs that prevent or reduce ongoing immune-mediated myelin destruction. Combination therapies that target multiple aspects of disease are standard in treating disorders such as cancer and HIV/AIDS, but a similar combinatorial treatment approach has not been available to MS patients because all currently available disease-modifying MS therapeutics act on a single aspect of the disease: suppressing the immune system.

Clinical Trial Phase 2: New Clinical Trial Design

In virtually all MS clinical trials, investigators track the number of new lesions in a patient's brain as determined by magnetic resonance imaging (MRI) as a measure of treatment efficacy. This quantitative measure is related to relapses: patients who develop new lesions are more likely to experience MS symptoms, such as blurred vision, difficulty moving or walking, or tingling or pain in various parts of the body.

But new lesions, important as they are, don't necessarily tell the full story. According to Dr. Reich, "MRI can also be used to look more carefully within the lesions, rather than simply to count them. This is important because the way individual lesions appear on MRI is related to the amount of damage to the brain at the spot where the lesion is located." Understanding the extent of tissue damage may provide a way to develop more precise endpoint measurements to assess whether – and how much – tissue protection and/or repair is occurring.

Dr. Reich's recent research has focused on identifying MRI measures that reflect tissue damage and repair. His team's work, published online on February 6, 2015, in *Multiple Sclerosis Journal* and supported by both NIH and the MRF, suggests that measuring changes to individual lesions over time will allow clinicians to assess lesion recovery. Therapeutics that protect and/or repair tissue would be expected to accelerate lesion recovery. Moreover, because MS patients typically have multiple lesions at any given time, studying each new lesion separately should allow clinical trials to be conducted using fewer patients, reducing the trial size and cost.

"Success of a trial design using this outcome measure would enable rapid and cost-effective screening of neuroprotective therapies," said Dr. Cortese. "This would definitively lead us into the next era of treatment strategies in MS, just as contrast-enhancing lesions did for disease-modifying immunomodulatory therapies in the 1990s."

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About the Myelin Repair Foundation

The Myelin Repair Foundation (MRF) is a Silicon Valley-based nonprofit research organization accelerating the development of therapeutics that repair myelin, the protective sheath surrounding nerves that is damaged in people with multiple sclerosis. The Foundation's Accelerated Research Collaboration™ model is bridging the gaps from academic research to FDA approval to significantly reduce the drug development timeline and bring the first myelin repair treatment for MS to patients as rapidly as possible. MRF is committed to demonstrating the applicability of its model to speed up the development of treatments for all diseases. For more information, please visit www.myelinrepair.org.

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