

**Research Now** is a quarterly feature of **Momentum**, produced by the Society's Research and Clinical Programs Department.

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## Investigating ion channels for MS symptoms, and even neuroprotection

by Sara Bernstein

**A**t this writing, Fampridine-SR (proposed name Amaya, from Acorda Therapeutics) has been recommended for approval to improve walking speed in MS by an advisory committee of the U.S. Food and Drug Administration. If approved it will be the first therapy approved specifically to treat a symptom in people with MS. But this drug also tops off years of preclinical research on “ion channels” and how blocking them may provide a strategy for treating

MS symptoms, or even protecting nerves from damage.

Ion channels (see illustration) are tiny pores that allow charged particles—for example, sodium, potassium and calcium ions—to pass in and out of a cell. These channels are made up of protein molecules that assemble to form a water-filled tunnel across the cell's protective membrane.

In nerve cells, ion channels work with extreme precision: Sodium channels open for a fraction of a second to allow just enough sodium in to trigger a nerve impulse. The impulse is then transmitted to the next cell, exactly the same way, and so on throughout the body. Potassium channels do the opposite and



**Stephen G. Waxman, MD, PhD (Yale University, New Haven, CT) was awarded the 2002 John Dystel Prize for MS Research by the National MS Society and the American Academy of Neurology for his groundbreaking findings on ion channels and MS.**



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act as a brake. Working together with sodium channels they regulate the impulse.

### **Does ion channel dysfunction play a role in MS?**

Missteps in the tightly run microcosm of ion channels can have dramatic effects on nerve cell function. Could such ion channel abnormalities contribute to MS? Stephen G. Waxman, MD, PhD (Yale University, New Haven, Conn.) was awarded the 2002 John Dystel Prize for MS Research by the National MS Society and the American Academy of Neurology for his groundbreaking findings on ion channels and MS.

Dr. Waxman demonstrated that the loss of myelin (the substance that surrounds nerve fibers and is a target of the immune attack in MS) exposes parts of nerve fibers that do not contain

enough sodium channels. This is important because it shows that the exposed, demyelinated part of the nerve fiber does not have the ability to produce nerve impulses. Dr. Waxman went on to show that, remarkably, the demyelinated nerve fiber can rebuild itself, acquiring enough sodium channels to conduct nerve impulses again. This “plasticity” contributes to remissions in MS. **Proceedings of the National Academy of Sciences (PNAS) USA** 2004;101:8168–8173

Dr. Waxman also showed that in MS the wrong type of sodium channels are produced in a part of the brain called the cerebellum (which controls coordination of movement), finding evidence that this can impair movement in MS. **PNAS USA** 2000;97:11598–602

### **Channel blockers to treat MS symptoms**

The work of Dr. Waxman and others led to development of treatments that might improve neurological function in MS by altering ion channel activity. Several channel blockers, such as phenytoin and carbamazepine, approved for other indications, are now used for MS pain.

Fampridine-SR is another such treatment—a sustained-release formula of 4-aminopyridine, which blocks potassium channels. When exposed by myelin damage, potassium ions leak out, causing the nerve impulse to “short circuit.” Fampridine-SR closes the exposed channels, and enables the nerve fiber to transmit nerve impulses again.

Early trials of this potassium-blocking approach in people with MS were supported by the Society, including a clinical trial by Christopher Bever, MD (University of Maryland, Baltimore). This trial used Fampridine’s chemical cousin, 3,4-diaminopyridine. In later clinical trials, a significantly greater proportion of people who responded to the therapy had a consistent improvement in walking speed compared to those who took a placebo.

### **The search for channel blockers to treat MS symptoms continues**

Investigators in France are seeking to determine whether 3,4-diaminopyridine can improve fatigue in 125 people with MS. Read more at [www.clinicaltrials.gov/ct2/show/NCT00190268](http://www.clinicaltrials.gov/ct2/show/NCT00190268). A phase II study is ongoing to determine whether oral nerispiridine—a potassium and sodium channel blocker—can improve walking speed in more than 300 people with all types of MS. The study is sponsored by Sanofi Aventis. Read more at: [www.clinicaltrials.gov/ct2/show/NCT00811902](http://www.clinicaltrials.gov/ct2/show/NCT00811902).

## Channel blockers for neuroprotection

Dr. Waxman's research has shown even more potent ramifications for the role of ion channel dysfunction in MS, by demonstrating a strong association between sodium channel abnormalities and nerve fiber damage in mice with the MS-like disorder EAE. **Brain** 2004;127:294–303

Nerve fiber damage contributes to the progression of disability in MS. So, can channel blockers protect nerve cells, and possibly prevent MS progression? Dr. Waxman administered phenytoin to mice with EAE, which protected nerve fibers from damage for up to 180 days. **Brain** 2006;129:3196–208

Ion channels are composed of several subunits. Lori Isom, PhD (University of Michigan, Ann Arbor), is exploring whether targeting subunits of a channel can help to develop better blockers. In her current Society-funded project, Dr. Isom's team has focused on the "beta 2" subunit; mice lacking the gene that instructs the building of this subunit had significant decreases in nerve fiber loss and degeneration during the course of EAE.

**Molecular and Cellular Neuroscience** 2009;40:143–55 They are currently examining how to "knock down" the activity of this gene in the spinal cord using experimental gene therapy.

In 2009, disappointing results were reported in a study testing the neuroprotective effects of a

channel blocker in people with MS. Raj Kapoor, MD, (National Hospital for Neurology and Neurosurgery, Queen Square, London) and colleagues studied the epilepsy drug lamotrigine in 120 people with secondary-progressive MS. The primary goal of the trial was to determine whether this drug (which may block sodium channels) could slow or stop the loss of brain tissue volume. The results suggested that tissue volume actually **decreased**, although the fact that decreases were recovered when treatment was stopped suggested that volume loss may have been related to the drug's strong anti-inflammatory nature. Surprisingly, participants taking lamotrigine improved in walking speed, although the study was not designed specifically to measure this as a primary outcome. **European Committee for Treatment and Research in MS 2009** (Abstract #135)

The neuroprotective potential of lamotrigine is still under study in combination with interferon beta-1a, in a Swiss study of nearly 90 people with MS. Read more at [www.clinicaltrials.gov/ct2/show/NCT00917839](http://www.clinicaltrials.gov/ct2/show/NCT00917839).

The Society is funding another effort to explore neuroprotective effects in a drug that blocks sodium channels and is approved to treat ALS (Lou Gehrig's disease). Emmanuelle Waubant, MD, PhD, and investigators at the University of California, San Francisco, are study-

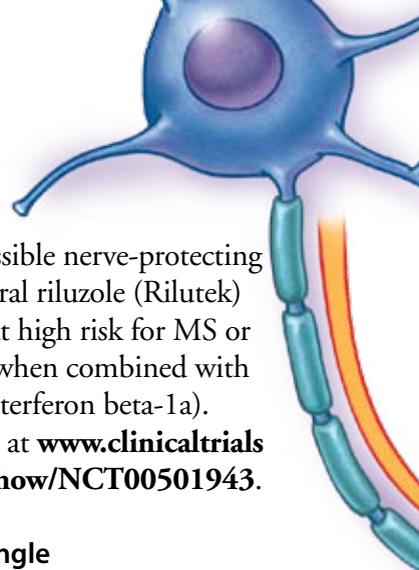
ing the possible nerve-protecting effects of oral riluzole (Rilutek) in people at high risk for MS or early MS, when combined with Avonex (interferon beta-1a). Read more at [www.clinicaltrials.gov/ct2/show/NCT00501943](http://www.clinicaltrials.gov/ct2/show/NCT00501943).

## Another angle

K. George Chandy, MD, PhD (University of California, Irvine) has taken another view of how ion channels contribute to MS. He and colleagues are focusing on ion channels on the surface of immune T cells, thought to lead the immune-system attack against the nervous system. Ion channels on T cells control the influx of charged particles and allow T cells to become activated. In research supported by the Society, Dr. Chandy's team successfully prevented and treated EAE in rats by blocking "Kv1.3," a specific T cell channel through which ions enter the cell.

Dr. Chandy's team formed a company, Airmid Incorporated, to develop Kv1.3 blockers as a strategy for MS and similar diseases. Kineta, Inc. acquired this portfolio in July 2009, and according to its Web site, plans to bring an MS drug to clinical trials in 2010.

Although the true potential of ion channel blockers to help people with MS has not yet been reached, this strategy carries potential for stopping symptoms, restoring function and even protecting against nervous system damage in people with MS.



## Bigger, better, faster, more—high-tech research in MS

**W**e have big goals for MS research—stop the disease, restore function and end the disease forever. These days, big goals in biomedical research demand the best that high technology has to offer. Here are just a few examples of how investigators funded by the National MS Society and others are reaching to the cutting edge and beyond.

### A marriage of data and biology

Sergio E. Baranzini, PhD (University of California, San Francisco), was chosen for the Society's prestigious Harry Weaver Neuroscience award this year because he is a young investigator with potential to make great contributions to MS research. He is a world-class expert in "systems biology" and is now applying this approach to MS.

Systems biology has only recently become possible. Using a combination of new techniques including rapid genome analysis (the entire collection of an individual's genes), data banks of information about gene and protein sequences and sophisticated computer programs to analyze massive amounts of information, Dr. Baranzini and his team can evaluate how networks of many factors interact.

As part of his project, Dr. Baranzini is conducting a full genome analysis of a pair of

identical twins. One twin has MS, while the other does not. Because identical twins start life with identical sets of genes, this analysis should reveal the alterations in gene structure related to the development of MS that may have been influenced by the environment.

The results could improve our understanding of MS and reveal new targets for the development of treatments.

### Imaging the genetics of MS

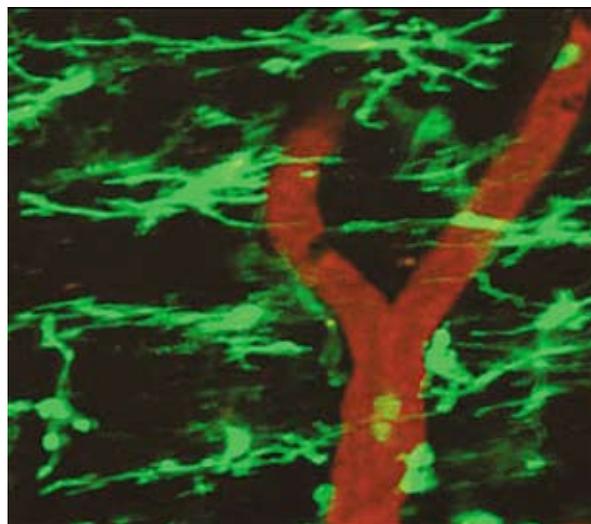
Heather A. Wishart, PhD (Dartmouth Medical School), started her career as an award-winning scholar who studied psychology. Now she is launching a unique study where genetics and imaging information will be linked with participants' levels of physical and cognitive impairment. This groundbreaking study is geared

to understanding why MS varies so greatly among individuals.

With support from the Department of Defense, Dr. Wishart is using advanced magnetic resonance imaging techniques—including high-resolution scans and diffusion imaging (which measures the flow of water particles) to map details of nerve tissue damage. Next, her team will screen the entire genome of these individuals, looking for differences and focusing on genes involved in nerve growth factors that may facilitate nervous system repair.

Piggy-backing on these high-tech approaches with the help of Society funding, she will then search for linkages to the results from series of tests measuring the physical and cognitive impairment of her study participants.

This ambitious study should enable Dr. Wishart's team to determine how the extent and location of nerve damage (revealed by imaging), and genetic



DIMITRIOS DAVALOS

**Nervous system immune cells (green) extend processes towards the blood vessels (red) in myelin-covered areas in the spinal cord; such images are possible using two-photon microscopy, a technique that uses fluorescence to image living tissue.**

## Big goals in biomedical research demand the best that high technology has to offer.

variations (revealed by the whole genome studies) relate to physical impairments and cognitive disability. This new knowledge could form the basis for methods to predict the course of MS and tailor treatments for individuals.

### Seeking clarity in the spinal cord

Katerina Akassoglou, PhD (University of California at San Francisco) is a pioneer in nervous system research known for her efforts to understand the effects of blood proteins such as fibrinogen. She reported that blocking a segment of the fibrinogen protein reduced MS-like disease in mice. She received the Presidential Early Career Award for Scientists and Engineers for her research, the highest honor bestowed by the United States government on scientists and engineers beginning independent careers.

Dr. Akassoglou also integrates novel technology into her studies. She uses two-photon microscopy, a technique that uses fluorescence to image living tissue. Until now, two-photon microscopy has been applied highly successfully to studies of the brain, but not the spinal cord. For one thing, says Dr. Akassoglou, the proximity of the heart to the spinal column results in interference caused by the heartbeat and breathing movements.

With Society funding, Dr. Akassoglou's team, which

includes Dimitrios Davalos, PhD, a postdoctoral fellow funded by the Society, has developed a way to adapt two-photon microscopy to get live images of myelinated areas by exposing only a very small area of the spinal cord of an anesthetized mouse. The technique allowed them to see cells in action. They were able to watch immune cells interacting with nervous system cells and blood cells. This technique should allow researchers to visualize the immune attack launched on the spinal cord in MS. **Journal of Neuroscience Methods** 2008;169:1-7

### Capturing a viral culprit

John Kriesel, MD (University of Utah), uses genetics to "capture" viruses that cause disease. His team reported on findings linking a gene to cold sores in 2008. Now, with funding from a Society Pilot Research Award, Dr. Kriesel is using genetics technology to identify a possible viral trigger of MS.

MS is thought to occur when people whose genes make them susceptible encounter something in their environment that triggers an immune attack. But no single viral or bacterial trigger has yet been identified.

Dr. Kriesel's team is applying "subtractive sequencing" to brain specimens taken from 12 people who had MS in their lifetimes and

12 controls who did not have MS. Subtractive sequencing allows detection of millions of different RNA molecules in a single specimen. RNA, or ribonucleic acid, is the chemical that delivers the instructions from a gene to a cell. All living things, including viruses, make RNA. In subtractive sequencing, human RNA is "subtracted" out from the millions of RNAs in a human tissue specimen, detected, leaving thousands of non-human, possibly disease-causing RNAs. This pilot study will help determine whether this technique will be fruitful for identifying infectious triggers of MS.

The men and women who are exploring the underpinnings of MS continue to apply the best of new technology to move us closer to the great goal of ending this disease forever.

In the Fall 2009 issue, we ran a story called "Dangerous foe or tiny protector? Understanding microglia" and failed to cite pioneering work by Society-funded researcher Dr. Ian D. Duncan and team, who in a series of papers showed the impacts of the antibiotic minocycline on microglia and its potential promise as a therapeutic approach for MS. We regret the inadvertent omission.

## Glimmers of hope for people with progressive MS

by John R. Richert, MD

Last fall's publication of results from a large-scale clinical trial of the drug rituximab (Rituxan, Genentech and Biogen Idec) brought glimmers of hope to prospects for treating progressive MS—even though, for the most part, the drug failed its primary objective of slowing disease progression in people with the primary-progressive form of MS.

The trial was designed to explore both the primary end point of disease progression, and also some other endpoints, and to analyze effects in several specific subgroups. What the trial found was telling.

Those on Rituxan therapy had significantly smaller increases in the volume of their brain lesions after 96 weeks. Analyses of subgroups showed that disease progression was significantly delayed in those who were less than 51 years of age and in those whose pre-treatment MRIs showed signs of active (gadolinium-enhanced) brain lesions. These enhanced lesions are indicative of active inflammation.

There's been ongoing debate about the extent to which inflammation plays a role in primary-progressive MS. These results offer new evidence that a possibly substantial subgroup of

younger people with primary-progressive MS may benefit from anti-inflammatory therapy.

There are other clinical trials planned or in progress focusing on progressive MS. One is a large-scale trial of oral fingolimod from Novartis. They also offer hope that a specific therapy for progressive MS may be forthcoming at last.

Other projects of particular relevance include efforts to protect nervous system tissues (called neuroprotection) and studies aimed at reversing damage and restoring function. Restoring function can range all the way from research into rehabilitation techniques to experimental stem cell therapies.

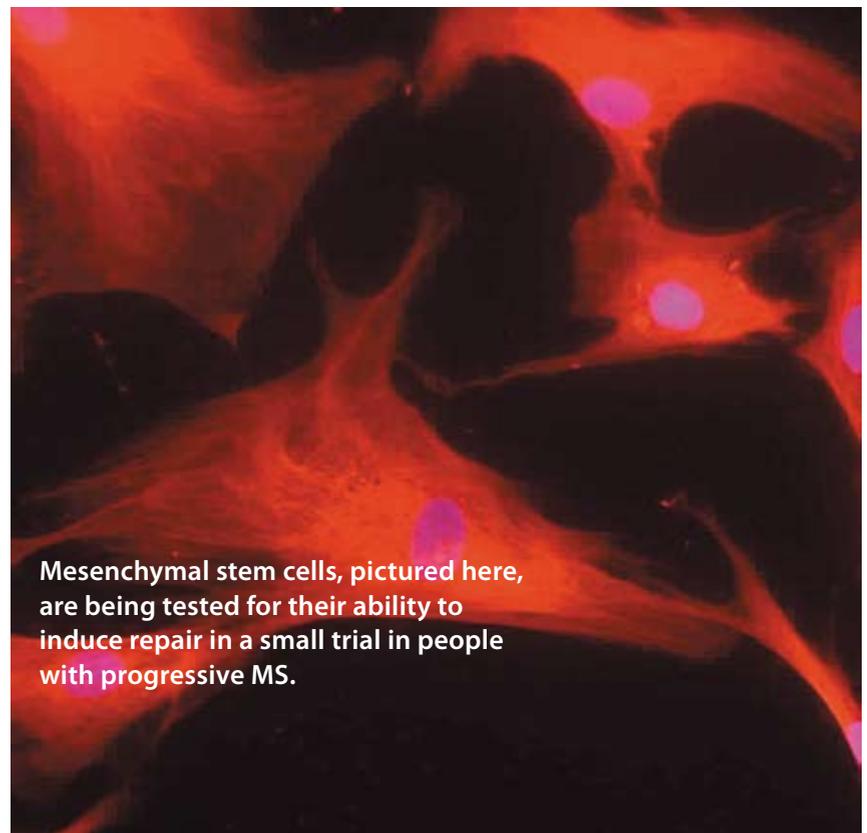
You'll read about one approach to restoring function in this issue of Research Now. (See "Investigating ion channels for MS symptoms, and even neuroprotection" on page 61.)

On the rehabilitation side

### On the rehabilitation side

A new project by Dr. Victor Mark, of the University of Alabama at Birmingham, is testing a type of physical therapy that has been successfully used in people recovering from stroke. "Constraint-Induced Movement therapy (CI therapy)" involves using a person's weaker arm to do skilled movements to promote increased use of that limb in daily life. Dr. Mark's clinical trial will randomly assign people with progressive MS either to CI therapy or to complementary and alternative treatment to provide new understanding of the potential of this approach.

One possible factor in causing



Mesenchymal stem cells, pictured here, are being tested for their ability to induce repair in a small trial in people with progressive MS.

FIGURE PROVIDED BY PROFESSOR NEIL SCOLDING, UNIVERSITY OF BRISTOL, UK.



**Here, an individual who experienced a stroke is practicing constraint-induced therapy, which encourages use of the weaker limb to promote its increased use. A team at University of Alabama Birmingham is testing this therapy in people with progressive MS.**

nervous system damage during the course of MS is a molecule called glutamate. It helps excite nerve cells, but too much of it may contribute to injury. With Society funding, Dr. Emmanuelle Waubant of the University of California, San Francisco, is conducting a clinical trial to see whether oral riluzole (a drug approved for treating ALS) can prevent the release of glutamate and, it is hoped, protect nerve fibers from damage in MS. Although this study involves people recently diagnosed with relapsing MS, its results will have implications for people with progressive MS as well.

Another neuroprotective agent being tested in relapsing forms of MS that may also impact people with progressive MS is the antibiotic minocycline. Trials are getting underway with the aim of stopping or slowing disease progression.

A key mission of the four international teams involved in the Society's Nervous System

Repair and Protection initiative (supported through the Promise: 2010 campaign) is to lay the groundwork for clinical trials to protect the nervous system and restore function. Now in their fifth year, these investigators have some trials that are already underway or in planning stages.

Team leader Dr. Gavin Giovannoni, of Queen Mary University of London in the UK, has been involved in a large multicenter study investigating whether the active compound in cannabis, called THC (tetrahydrocannabinol), is neuroprotective and can slow MS progression.

Two of the other repair teams are about to launch new, small-scale clinical trials with separate funding. One will investigate the safety of treatment with bone marrow (mesenchymal) stem cells; the other will attempt injections of neural stem cells. Both trials are fully enrolled and awaiting further funding and approvals.

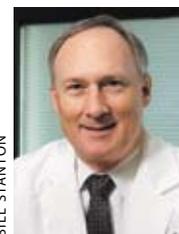
Despite these challenging economic times, we've just committed to funding four new Collaborative MS Centers, two of which are focusing on nervous system repair.

The Center led by Dr. Thomas Lane at the University of California at Irvine is exploring the potential of stem cells for stopping disease progression and restoring function. The new Center led by Dr. Moses Rodriguez at Mayo Clinic is zeroing in on molecular signals that might stimulate—or inhibit—repair processes in MS. His team is seeking clues to developing therapeutic strategies to promote repair.

All told, the Society has over \$40 million committed to new and ongoing projects focusing on approaches to repair damage or restore function. This is a high-priority investment, and it's beginning to pay off.

To read more about all of our Centers, go to [nationalMSSociety.org/research/research-we-fund/collab-research-centers/index.aspx](http://nationalMSSociety.org/research/research-we-fund/collab-research-centers/index.aspx).

To read more and view videos about living with progressive MS, go to [nationalMSSociety.org/living-with-multiple-sclerosis/progressive-ms/index.aspx](http://nationalMSSociety.org/living-with-multiple-sclerosis/progressive-ms/index.aspx). ■



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Dr. John Richert is executive vice president for the Society's Research & Clinical Programs.