

Research Now is a quarterly feature of **Momentum**, the national magazine of the National MS Society, and its content is produced and vetted by the Society's Research and Clinical Programs Department.

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The National MS Society is proud to be a source of information about MS. Our comments are based on professional advice, published experience and expert opinion, but do not represent individual therapeutic recommendation or prescription. For specific information and advice, consult your personal physician.

For news and added information, visit nationalmssociety.org/Research.

What researchers are doing for people with MS now

by Sara Bernstein

Imagine if something in the medicine cabinet could reliably alleviate MS fatigue, without keeping you awake all night. Or that speaking a few words could improve how you think. These dreams are shared by researchers who—working in parallel with those who are seeking the cause and cure—are trying to help people with this disease **now**, with interventions to improve the great variety of symptoms that can interfere with quality of life. Here is a small sample of ongoing research on just a few symptoms.

Fighting fatigue

Fatigue occurs in as many as 80% of people with MS, disturbing people's ability to function at home and work. It may be the most prominent symptom in people who might otherwise have minimal limitations.

Dean Wingerchuk, MD, FRCPC (Mayo Clinic, Scottsdale, AZ), and colleagues noticed that some people with MS reported less fatigue when using aspirin for other reasons. So they decided to study aspirin formally, giving

1,300 mg or an inactive placebo to 30 people with MS and fatigue.

The primary goal of the study was to determine if aspirin treatment would improve scores on the Modified Fatigue Impact Scale—a measuring tool in which patients report on how fatigue affects their physical, cognitive, and psychosocial functioning.



MFIS scores improved significantly in those taking aspirin. There were no serious adverse effects. (*Neurology* 2005 Apr 12;64[7]:1267–9)

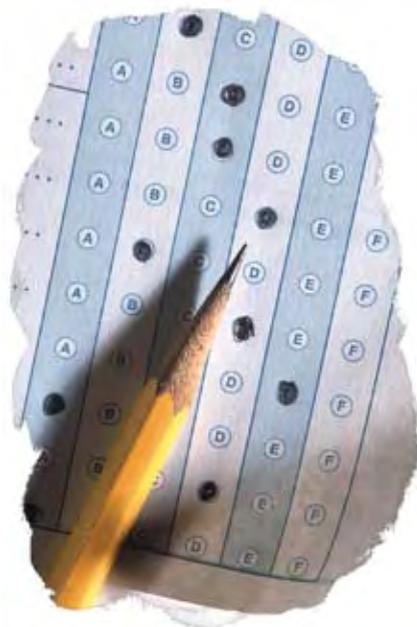
Based on these results, the National MS Society is now funding Dr. Wingerchuk to conduct a larger study at three sites, which is necessary to determine if aspirin indeed is safe and effective for MS-related fatigue. The team is giving aspirin or placebo to 135 people with MS-related fatigue.

Participants are completing questionnaires about the severity and impact of their fatigue, undergoing memory testing to assess cognitive fatigue, and are having blood taken to measure markers of inflammation. This further evaluation is necessary, particularly considering the risk of gastrointestinal bleeding that is possible with long-term aspirin use, even at low doses.

If this study is successful, it may add an important new option for treating MS-related fatigue.

Another approach to fighting MS fatigue could be “energy conservation strategies”—such as effort-saving devices, eliminating or delegating tiring tasks, and including rest periods every day. Virgil G. Mathiowetz, PhD (University of Minnesota, Minneapolis) investigated whether these strategies really help by evaluating a six-week course that teaches energy conservation. His study was funded by the National MS Society.

Dr. Mathiowetz’s team recruited 169 people to participate. Scales that measure fatigue were administered before and after the course—as well as before and after control periods during which no intervention occurred—to determine any changes. The course succeeded in significantly reducing the impact of fatigue on physical and social function, and in increasing vitality. (**Multiple Sclerosis** 2005 Oct;11[5]:592–601)



Dr. Mathiowetz followed people for one year after completing the course to see if the effects would last. Not only were the original results maintained, but they were improved upon, with the impact of fatigue on cognitive function being reduced significantly as well! (**International Journal of Rehabilitation Research** 2007 Dec;30[4]:305–13) Occupational therapists often recommend energy conservation strategies to people with MS and these results provide important evidence of how such strategies can succeed.

Minding cognitive function

Cognitive problems may be experienced by about half of all those with MS at some point in their disease, possibly affecting the ability to learn, remember, organize, plan and problem-solve—all critical parts of the activities of daily life. These prob-

lems are not related to physical function—a person with MS can have no physical limitations and yet experience significant cognitive impairment.

A drug under study for its possible ability to protect nerve tissue may also improve cognitive function in people with MS. Hannelore Ehrenreich, MD, DVM (Max Planck Institute of Experimental Medicine, Gottingen, Germany) and colleagues reported results from a small, uncontrolled study of a laboratory-produced version of erythropoietin, a naturally-occurring hormone used to treat anemia.

They administered the drug to eight people with chronic, progressive (secondary-progressive) MS and followed them for 48 weeks. Five people took a high dose of the intravenous drug, along with two control patients who had Parkinson’s disease, and three received a low dose.

Although this was primarily a safety study, with no adverse events reported, the investigators found that cognitive function improved and improvements persisted for three to six months after treatment. The low-dose and control groups did not improve. (**Brain** 2007 Oct;130[Pt 10]:2577–88)

This is not the first evidence of this capability—erythropoietin has improved cognitive function in rodent models of neurological and psychiatric disorders, and in people with schizophre-

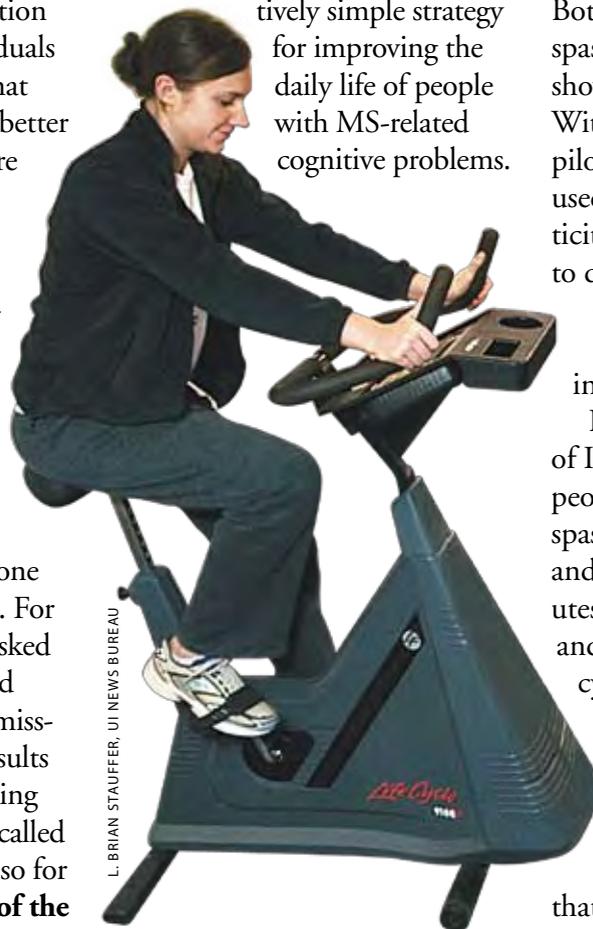
nia. (**Journal of Renal Nutrition** 2008 Jan;18[1]:146–53) Further research will determine the safety and effectiveness of this drug for protecting nervous tissue in MS as well as improving cognitive function.

Memory impairment in MS may be related to difficulty in learning new information. Yael Goverover, PhD (New York University, New York, NY), and colleagues tested a method of “self-generation” with funding from the National MS Society. The self-generation strategy suggests that individuals remember items or words that they generate or “make up” better than if the items or words are just provided to them.

Twenty people with MS and mild cognitive impairments and 18 controls without MS were asked to complete two cooking tasks and two financial management tasks. One task was carried out with all instructions provided, and in the other task, participants generated one key word in the instructions. For example, a participant was asked to “beat together _____” and would have to generate the missing item, “two eggs.” The results showed that tasks learned using self-generated words were recalled and performed better, more so for the cooking tasks. (**Journal of the International Neuropsychological Society** 2005;11[S1]:49)

Now Dr. Goverover is extending these studies with further

funding from the National MS Society. Her team is studying 78 people with MS—26 with mild cognitive impairments, 26 with moderate to severe cognitive impairments, and 26 with no cognitive impairments. Participants are completing a variety of tasks using provided and self-generated instructions, and the ability to remember these instructions will be tested 30 minutes and one week after the tasks are completed. The results may yield important information on a relatively simple strategy for improving the daily life of people with MS-related cognitive problems.



University of Illinois researchers are studying the use of cycling to alleviate spasticity. Participant Ashley Hayes.

Addressing muscle trouble

Spasticity may be as mild as the feeling of tightness of muscles or may be so severe as to produce painful, uncontrollable spasms, usually in the legs. Although there are prescription medications that can treat spasticity, they often cause unwanted side effects.

Robert Motl, PhD, found that an electrical reading from muscles, called the H-reflex, was higher in persons with MS than in others without the disease. Both intense exercise and anti-spasticity medications have been shown to reduce the H-reflex. With funding from a Society pilot research award, Dr. Motl used clinical measures of spasticity and tests of the H-reflex to determine whether sessions of exercise with a stationary bike could relieve spasticity in MS.

His team at the University of Illinois collected data in 27 people with MS and leg muscle spasticity before and 10, 30, and 60 minutes after 20 minutes of leg cycling and before and after a control exercise. The cycling resulted in prolonged reductions in H-reflex and spasticity scores. (**Neuroscience Letters** 2006 Oct 9;406(3):289–92)

The team also has found that combining cycling and anti-spastic medications in six people with MS showed positive results. (**International Journal of Neuroscience** 2007

Jul;117[7]:895–901, **Archives of Physical Medicine & Rehabilitation**, in press)

Proponents of the use of marijuana (cannabis) or its derivatives in MS have suggested that it may help reduce spasticity, although it has been difficult for researchers to obtain objective data of its effectiveness. Mark Agius, MD, and colleagues (University of California, Davis) are conducting a well-designed, placebo-controlled study to test the safety and effectiveness of inhaled cannabis and of oral tetrahydrocannabinol, a cannabis derivative, for the treatment of spasticity in 60 persons who have MS and spasticity.

The team has developed novel instruments to objectively test muscle tone and other measures of spasticity and is using them to compare these experimental therapies with inactive placebo.

In addition to funding this important study, the National MS Society is seeking to find the “bottom line” on cannabis treatments for MS symptoms such as spasticity and pain. A task force gathered by the Society recently released an expert opinion paper on the use of marijuana for MS. For more details on this effort, see page 18.

Driving away depression

Depression in its various forms is common during the course of multiple sclerosis—from feeling down for a few hours on a given day to severe clinical depression

that may last for several months. David C. Mohr, PhD (Northwestern University, Chicago, IL) is studying ways to identify depression earlier in people with MS and treat it more effectively.

Dr. Mohr recently published findings on both these goals. In one study, his team attempted to simplify the diagnosis of depression by administering this simple two-question screen to 260 people with MS: During the past two weeks, have you often been bothered by feeling down, depressed, or hopeless? During the past two weeks, have you often been bothered by having little interest or pleasure in doing things?

The results were correlated with a standard diagnostic method. This simple screen, using even just one question, correctly identified 66 of 67 people with a major depressive disorder, and correctly ascertained that 167 of 193 people did not have such a disorder. (**Multiple Sclerosis** 2007 Mar;13[2]:215–9)

As far as treating depression, Dr. Mohr has reported on a technique that could especially help people with MS and mobility issues—telephone-administered psychotherapy. In a group of 127 people with MS and depression, participants showed significant improvements in mood during 16 weeks of two types of phone therapy. Cognitive-behavioral therapy (a structured therapy that teaches skills aimed at changing thoughts and behaviors that lead

to depression) showed significantly greater improvements than a less structured therapy called supportive emotion-focused therapy (a therapy that encourages discussion of difficult feelings).

There were significant, lasting improvements in both groups even 12 months following the end of treatment, and the dropout rates were significantly lower than those reported in studies of face-to-face psychotherapies for depression. (**Archives of General Psychiatry** 2005;62:1007–1014)

Dr. Mohr’s team then showed that participants in both groups showed significant reductions in disability and fatigue (more so in the cognitive-behavioral group), which were related to the reductions in depression. So treating depression in people with MS—even via phone—may even improve their battle with the disease itself. (**Health Psychology** 2007 Sep;26[5]:554–63)

The symptoms of MS are varied and unpredictable. As the search for cause and cure continue, so does the search for interventions to help people with MS address these challenges now.

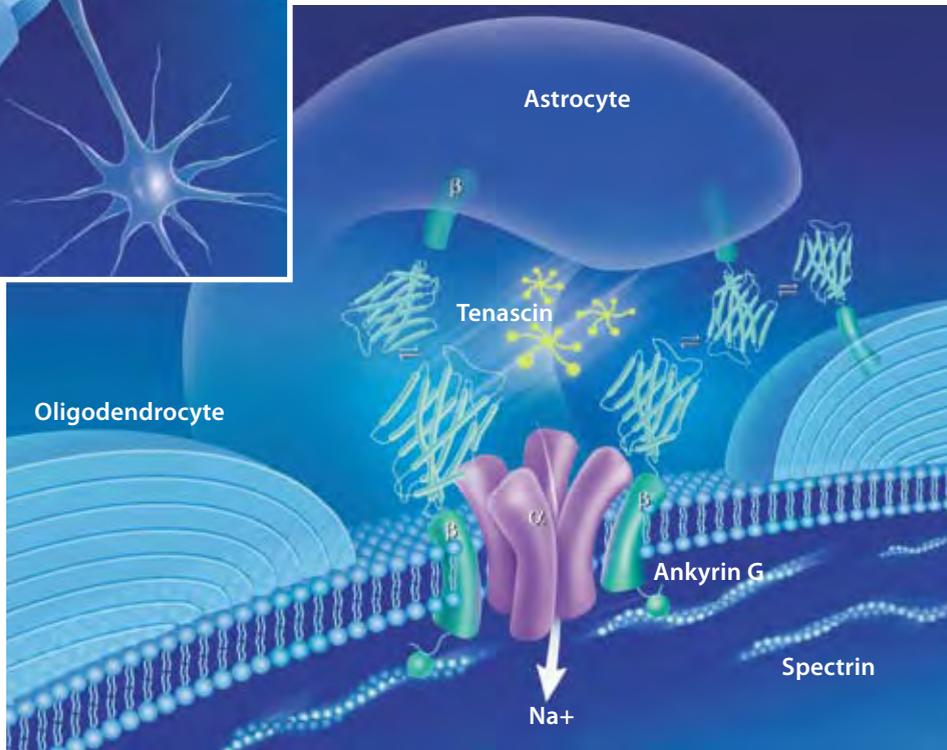
For more information about MS symptom management: **nationalmssociety/symptoms**

Henze, T. What is new in symptom management? **International MS Journal**. 2007 Mar;14(1):22–7.

Davis, Winston, “A More Livable Life Now” **InsideMS**. June–July 2006. Volume 25, Issue 3.



Limiting the tiny channels (shown here) by which sodium (Na⁺) passes through nerve cells may be key to protecting these cells in MS (see text).



LORI L. ISOM, PH.D., AND MICHIGAN PRODUCTIONS, UNIVERSITY OF MICHIGAN

MS research for the first time. Ultimately, they are using this knowledge to develop ways to enhance mitochondrial function and hopefully protect nerve fibers from injury. They'll also be able to rapidly test such therapies in rodent models and then in early clinical trials in people with MS. This is a talent-packed collaboration that we are pleased to count among our Collaborative MS Research Centers.

Our peer reviewers rank research proposals according to their scientific excellence and

their relevance to MS. This year's most highly-ranked project was submitted by Daniel Goldberg-Zimring, PhD (Harvard Medical School, Boston), an investigator who is new to the National MS Society. He's looking at various imaging technologies to determine how we can observe—in people at high risk for MS—those changes that predict which people will indeed develop MS. This winning study is crucial as more treatments are approved for preventing the progression to clinically definite MS. Because of its ranking, this grant was dubbed this year's Stephen C. Reingold Award, in honor of my predecessor here at the MS Society.

Repairing nervous system damage is the goal of Gianvito Martino, MD (San Raffaele

New explorations launched

by John R. Richert, MD

The selection of new research grants for funding is an exciting event for us at the National MS Society. The grant applications are reviewed by our volunteer peer reviewers and recommended for funding. The men and women who are starting their new projects this spring and summer—61 in all—epitomize the possibilities of MS research today.

Take the new Collaborative MS Research Center being launched by Dennis Bourdette, MD (Oregon Health Sciences University), which pursues a novel direction in MS research—the role of mito-

chondria in nerve fiber damage. Preliminary research has revealed that mitochondria—the energy factories of cells—play a key role in calcium balance within nerve fibers. It is known that abnormal calcium levels are toxic to nerves. Thus, this research may be key to preventing the progressive disability that occurs due to the gradual loss of nerve fibers in MS.

This research team includes scientists with expertise in clinical trials, magnetic resonance imaging, developing and investigating rodent models of MS, and in mitochondrial function; some are lending their expertise to

Scientific Institute, Milan, Italy). Dr. Martino's team broke new ground a few years ago when they showed that stem cells from adult brain tissue, when injected into the blood stream of mice with the MS-like disease EAE (experimental allergic encephalomyelitis), promoted repair of myelin, decreased damage to nerve fibers, and reversed clinical disease. In a new project Dr. Martino is tackling a major question in MS research: why does the brain's natural ability to repair itself fall short in people with MS? His team is focusing on what might be happening to the reservoirs of these neural stem cells in rodent models of MS.

Another new grant is focusing on **protecting** the nervous system from MS damage. A team led by Lori L. Isom, PhD (University of Michigan, Ann Arbor) is investigating tiny pores along the surface of nerve fibers, called sodium channels, which are responsible for nerve signal firing. (See illustration, page 71.) Her team is exploring a subunit that plays an important role in determining where, and how many, channels are present along the nerve fibers. When myelin is damaged in MS, more sodium channels are produced in the body's attempt to improve nerve conduction. This may make nerve fibers more vulnerable to injury. While drugs that block the sodium channel may be effective, they cause system-wide side effects. Dr. Isom is investi-

gating how to regulate the subunit to protect nerve fibers from injury. This novel study should inform the development of new drugs that block only a portion of the sodium channel to protect nerve fibers from damage.

Nurturing new researchers

This is just a sampling of the approximately 440 new and ongoing research projects that the Society is funding.

One of our top priorities is to ensure that there are young, bright scientists and physicians who are well trained and devoted to finding a cure for MS.

That's why our research fellowships are so important. It's always a pleasure to welcome a new group of fellows—these young men and women fuel the possibilities of MS research.

Take Christopher A. Severson, MD (Brigham and Women's Hospital, Boston), a new National MS Society-American Academy of Neurology Clinician Scientist Award winner. Dr. Severson is further investigating the exciting findings of the International Multiple Sclerosis Genetics Consortium, which identified two new genetic variations associated with MS. Dr. Severson is investigating the variation in the gene for "interleukin 2-receptor

alpha," to determine what may make people who carry it more susceptible to developing MS.

Another important training program is our Mentor-Based Rehabilitation Fellowship Program, designed to increase the quality and quantity of rehab research. Marcia Finlayson, PhD (University of Illinois at Chicago), who has made several key findings in the field, is one of two new recipients of this award. She is establishing a program to train researchers to conduct "self-management" research.

Self-management programs can teach people with MS to manage fatigue or provide strategies for dealing with cognitive changes. This is a sure way to help many people address the challenges of living with MS.

Speaking of fellows, we are quite proud to welcome seven new Sylvia Lawry Physician Fellows—the most ever approved in one year. This program trains young clinicians in the intricate and complex ways of planning and conducting MS clinical trials.

It's important for us to maintain this influx of new talent and make sure that they can eventually establish their own research programs to defeat this disease.

Dr. John Richert is executive vice president for our Research and Clinical Programs.



BILL STANTON

Dr. Nitin Karandikar: Pushing the boundaries of immunology

by Sara Bernstein

Immunology is big in MS research—so big that more than one-third of National MS Society grantees focus on the immune attack on the brain and spinal cord. Nitin Karandikar, MBBS, MD, PhD—a Harry Weaver Neuroscience Scholar of the Society—believes that MS immunology researchers need to push themselves farther. Pursuing a career as a physician-scientist from his hometown of Pune, India—to the laboratory of noted EAE/MS researcher Stephen Miller, PhD, in Chicago—and then to the University of Texas Southwestern Medical Center in Dallas, Dr. Karandikar exhibits the perseverance of which he speaks.

“We call MS an immune-related disease, we give patients immune system-based therapies, but we are not routinely looking at people’s immune systems,” he said. “Clinical testing of the immune response in MS patients has not kept up with our research knowledge of the immune attack in MS. I’d like to see such assays developed and used to help MS patients.”

Dr. Karandikar likes to think outside the box to solve research problems—bringing knowledge and technologies from other fields to the fore. “We have applied ‘flow cytometry’ technol-

ogy to traditional assays used in studying the immune response of people with MS,” he says. In flow cytometry, cells are passed through an instrument contain-

“We need to train the next generation of physicians and scientists, to expose young scientific minds to the issues faced by people with MS.”



Dr. Nitin Karandikar applies cutting-edge flow cytometry to MS research.

ing laser beams. Data about thousands of cells are acquired by a computer in seconds.

The results already have broken new ground. “The majority of researchers believe that CD4+ T cells are the main immune cells involved in the MS attack,” Karandikar said. “We showed that CD8+ T cells have tremendous involvement.” (*Blood* 2004; 103:4222–4231) His team has also used flow cytometry to show that treatment with Copaxone (glatiramer acetate, Teva Pharmaceuti-

cal Industries, Ltd.) increased CD8+ responses in people with MS and that these responses served to **suppress** the immune attack. (*JCI* 2002;109:641–9; *Journal of Immunology* 2006;176:7119–29)

Dr. Karandikar believes that studying approved MS treatments is crucial to moving us closer to a world free of the disease. “If we don’t dissect the mechanism of therapies that are already approved to treat MS, we will never know what is working and why,” he said.

Dr. Karandikar speaks humbly of how the Weaver award has helped to establish him in MS research. “This award has been critical to my career,” he said. “It is a prestigious honor that makes other funding agencies and peer reviewers take notice. The salary support relieves you of other worries, so you can do what you came into the field to do.”

Dr. Karandikar loves to train young researchers, and the feeling is mutual, judging from several “Outstanding Teacher” awards that he has won. In particular, he is excited to bring these young scientists into the MS fold, and is currently mentoring Vinodh Pillai, MBBS, PhD, a postdoctoral fellow of the Society, along with seven other trainees. “We need to train the next generation of physicians and scientists, to expose young scientific minds to the issues faced by people with MS,” he said.

In the news and on our Web site

● **Study: One course of Rituximab reduced MS disease activity for 48 weeks**

Researchers report that one course of the IV drug rituximab (Rituxan, Genentech and Biogen Idec) reduced disease activity and relapses for 48 weeks in people with relapsing-remitting MS. Rituximab depletes immune B cells, which may play a role in the immune attack on brain and spinal cord tissues in MS. The clinical trial was supported by Biogen Idec and Genentech.

Read the details on our Website: nationalmssociety.org/Bulletins.

Larger and longer-term studies are needed to confirm the drug's safety and effectiveness.

● **Tysabri in the news**

Data from the two large-scale clinical trials of Tysabri (natalizumab, Biogen Idec and Elan Pharmaceuticals) that led to its approval show that, in addition to reducing MS relapses and slowing the rate of disability accumulation, the drug significantly improved health-related quality of life in people with relapsing-remitting MS who were on active therapy. Quality of life measures include a person's general well-being and physical, social and psychological functioning, and they are not often part of outcomes

measured in clinical trials involving people with MS.

In other Tysabri news, an FDA-mandated label change includes a new warning about the possibility of significant liver injury in people being treated with the drug. According to the label, Tysabri should be discontinued in patients with jaundice or other evidence, such as laboratory evidence, of significant liver injury. This warning is similar to that related to the beta interferons. Also, physicians in Boston reported two cases of melanoma (skin cancer) that developed in women in their practice who were administered Tysabri to treat their MS. It cannot be confirmed from these reports that Tysabri caused them.

"This drug is relatively new to the market, and as experience grows we are bound to learn more about its benefits as well as possible adverse events," said Dr. John Richert, executive vice president of research and clinical programs at the National MS Society.

● **Genetic differences may predict response to interferon treatment**

Researchers have found differences in genetic material between people who respond to interferon beta treatment and those who don't, in a study of 287 people with relapsing-remitting MS. These results, if confirmed by larger studies and explored further, are an important step toward

using genetic information to predict who will respond to specific therapies for MS.

● **High-tech study may offer clues to future treatments**

Researchers at Stanford University, the University of Connecticut and other institutions report having uncovered hundreds of proteins that may be active at different stages of MS by conducting high-tech analyses of MS brain lesions. To validate the approach, they narrowed in on two of the proteins and blocked their activity using existing drugs in mouse models of MS and were able to improve symptoms. The study was funded by the National MS Society and National Institutes of Health. ■

Recently Posted Studies Enrolling People with MS

- Five U.S. Sites Enrolling to Evaluate Effects of Tysabri on Vaccination
- Single-Dose Experimental IV Drug "RTL1000" Recruiting MS Patients at Five Sites Nationwide
- Clinical Trial of Investigational, Once-Daily Oral FTY720 Recruiting Participants with MS across the U.S.

For more information on these and other studies, visit nationalmssociety.org/ClinicalTrials.