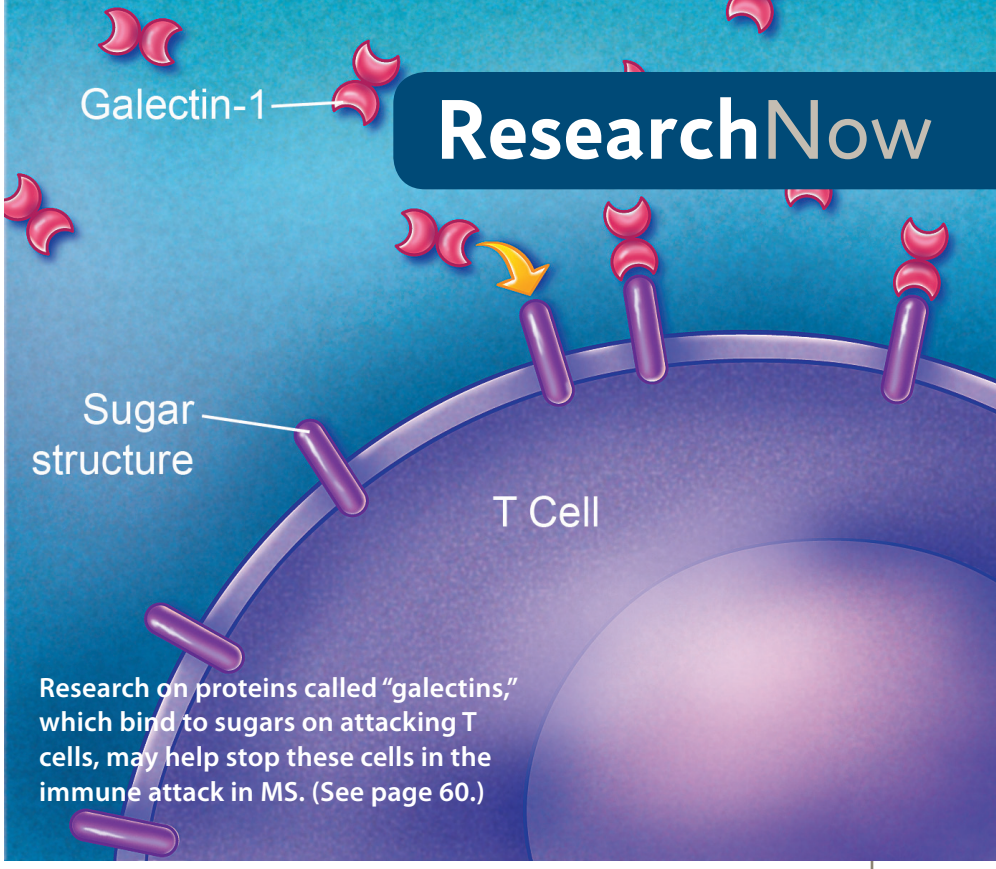

ResearchNow

Research on proteins called "galectins," which bind to sugars on attacking T cells, may help stop these cells in the immune attack in MS. (See page 60.)

JILL K. GREGORY

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

Sara Bernstein, Editor, **Research Now**

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INSIDE:

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Taking a fresh look at the immune attack in MS

by Sara Bernstein

- Researchers funded by the National MS Society are finding new possibilities for stopping MS immune attacks.
- New therapeutic strategies are evolving, thanks to better understanding of how attacks are triggered and carried out.

The main battleground for fighting disease activity in MS is the immune system, which launches attacks on the brain and spinal cord. Eight treatments currently are approved to modify MS, and each one addresses these attacks.

For example, Tysabri interferes with the movement of immune cells from the blood into the brain. Mitoxantrone broadly suppresses immune system activity. The latest therapies under investigation to treat MS aim at fine-tuning immune responses. For example,

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ocrelizumab binds to a molecule on immune B cells, eliminating them from the body. (See chart, page 59.)

So what's next for tackling immune activity in MS? Researchers funded by the National MS Society are hot on the trail of new ideas for more specific and longer-lasting ways of stopping the immune attack in MS in its tracks.

A new look at triggers

Studying what turns on the immune attack in MS can offer new targets for turning it off.

Robert Clark, MD, and Frank Nichols, DDS, PhD (University of Connecticut Health Center), have studied how the immune attack launches in both MS and rheumatoid arthritis. They recently made an important discovery relevant to MS.

Each person has millions of harmless bacteria, known as "commensal" bacteria, living inside of them. Dr. Clark and his colleagues have found that these bacteria produce lipids—fatty substances—that increase the severity of EAE, an MS-like disease, in mice. Now they are looking at the precise molecular pathways by which these lipids affect EAE. They are also looking at how the lipids function in blood and brain tissue from people with MS. Results so far suggest that these lipids are present in unique patterns in people with MS, compared with people who don't have MS.

These results may provide the first direct evidence that these lipids play a role in triggering MS.

Dr. Clark's results may provide the first direct evidence that these lipids play a role in triggering MS, yielding new targets for slowing or preventing immune attacks. Also, measuring the lipids' presence in the blood may serve as a new test for MS disease activity.

Dr. Clark's work is part of a new approach to understanding how the normally friendly germs that live in our intestines, mouths and other areas of the body may profoundly influence immune activity and disease susceptibility.

Howard L. Weiner, MD (Harvard Medical School)—who earned the 2007 John Dystel Prize for MS Research for his contributions toward understanding the development of the immune attack in MS and translating these findings into MS treatments—is exploring this new frontier in immunology as well. Dr. Weiner recently earned a pilot research grant to test whether bacteria in the gut differ between people with MS and those without MS. Since these bacteria are known to influence the immune response, such differences may help explain why the immune response goes awry in MS.

Our bodies have a number of different cell types that interact to either turn on or off an immune response, such as inflammation. Some immune cells have "pathogen sensors" that recognize invaders, such as viruses or bacteria. This can cause the cells to launch an attack against the pathogen. The pathogen sensors on some immune cells may contribute to triggering the attack in MS.

Jenny Ting, PhD, and her colleagues at the University of North Carolina were among the teams that first described a family of specific pathogen sensors. Dr. Ting is a highly respected immunologist and microbiologist whose research has won awards from the American Society of Microbiology and is a National Institutes of Health Merit Awardee. With support from the Society, her team showed previously that one specific sensor was highly active during inflammation in mice with EAE.

Now her team is extending this work to study such sensors further. The results of this research should lead to better understanding of processes that trigger immune attacks in MS, and offer new targets for

What is the treatment under study?	How does it affect the immune attack in MS?	What is the status of these trials?
Helminth-induced immunomodulation therapy	Harmless parasitic worms that may stimulate protective immune response	In phase I trials for MS
Estriol	Pregnancy hormone that decreases inflammatory immune response	In phase II trials for MS
Abatacept	An antibody that blocks an early step in immune cell activation	In phase II trials for MS
Ocrelizumab (F. Hoffman La Roche, Ltd.)	A humanized antibody that binds to a molecule on the surface of select B cells and depletes them from the body	In phase III trials for MS
Daclizumab High Yield Process (DAC HYP, Biogen Idec)	A humanized antibody that suppresses T cells by blocking signals from an immune messenger protein	In phase III trials for MS
Lemtrada™ (alemtuzumab, Sanofi Aventis)	A humanized antibody that targets a protein on both T and B cells to shut down cell activity	Phase III trials showed benefit; company plans to seek regulatory approval from FDA in the first quarter of 2012
BG-12 (dimethyl fumarate, Biogen Idec)	A chemical compound that promotes cells that can regulate the immune response	Phase III trials showed benefit; company has applied to the FDA for approval for MS.
Aubagio™ (teriflunomide, Sanofi Aventis)	A compound that modulates responses of T cells within the immune system by impairing the genes that instruct these cells	Mixed results so far in two phase III trials out of 5 underway; FDA has accepted New Drug Application for review.

Here are a few of many immune-modulating strategies under study in people with MS. Find more trials at nationalMSsociety.org/clinicaltrials. (Phase I—small early studies to determine safety; Phase II—studies in larger numbers of people that begin to determine effectiveness; Phase III—even larger, longer studies to better understand effectiveness and possible side effects.)

developing therapies to better turn off those attacks.

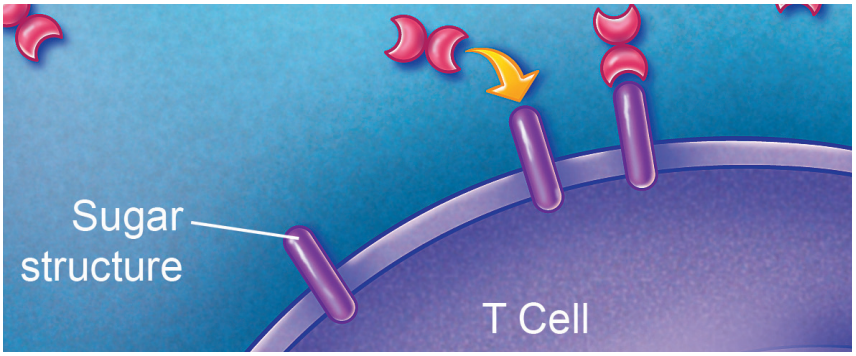
Taking on T cells

T cells have long been recognized as major players in immune attacks in MS, but new research is making inroads on how these cells are activated and how they can be suppressed.

Gabriel Rabinovich, PhD, exemplifies the global reach of the Society's research program. He is investigating emerging technology called glycomics at the Universidad de Buenos Aires, with Society funding. Glycomics investigates the ways that sugar structures in the body may influence biological processes.

Dr. Rabinovich and his colleagues recently demonstrated that galectin-1 (a protein that binds to sugars, which is found at sites of brain injury and inflammation) can selectively bind to and destroy aggressive T cells. They have observed that distinct groups of immune cells have different sugar structures on their surfaces, and these structures determine whether the sugars bind to galectin-1 or not. Now the researchers are studying how the surfaces of aggressive immune cells differ from those that can calm immune attacks.

Researchers are studying how the surfaces of aggressive immune cells differ from those that can calm immune attacks.



They aim to capitalize on this information to design therapies that will be tested in mice with EAE and in immune cells isolated from people with MS—important first steps before this novel approach can be tested in people.

Another novel approach is being taken by Society grantee Amy Lovett-Racke, PhD (Ohio State University), who has focused her research career on understanding how T cells operate in MS. Now she is delving into the genetic code that instructs T cells. Her team is studying recently discovered substances known as microRNAs (miRNAs), which regulate what proteins the cells produce.

The pathogen sensors on some immune cells may contribute to triggering the attack in MS.

They have found that miRNA levels are abnormal in T cells from people with MS, and also that this abnormality may affect development of important immune cells called T regs. T regs are "good guys"—they can dampen the activity of the bad, inflammatory T cells.

Now Dr. Lovett-Racke is investigating further the exact pathway by which this might happen. That understanding could provide a novel avenue for therapeutic intervention.

Research on the immune system already has yielded treatments that reduce MS disease activity. Pursuing novel avenues is sure to speed the development of more treatments that can stop the immune attack once and for all.

Sara Bernstein is manager, research information at the National MS Society and editor of Research Now.

In the pipeline for MS: Vitamin D supplementation

- A new clinical trial is studying whether vitamin D added to standard therapy with Copaxone reduces the frequency of MS relapses.

COURTESY OF THE MINNESOTA CHAPTER

Why use vitamin D to treat MS?

Research on vitamin D began with a simple observation: that MS occurs less often in regions of the world where exposure to sunlight—which contributes to the body's production of vitamin D—is high. Could it be that exposure to sunlight or levels of vitamin D in the blood are important environmental factors that combine with genetics to determine MS risk or severity? Subsequent studies in lab mice showed that vitamin D can reduce the effects of EAE, an MS-like disease; epidemiologic studies (studies of who gets MS) have backed them up, clearly linking decreased vitamin D levels to increased MS risk or severity. This growing evidence suggests it is time to test whether vitamin D supplements can provide benefits to people who have MS.

What does the research show so far?

In a small safety study, Paul O'Connor, MD, and Jodie Burton, MD (St. Michael's Hospital, Toronto) and their colleagues examined the effects of administering increasing doses of vitamin D3. A group of 25 people with MS were given 4,000 to 40,000 international units (IU) per day for a year, while 24 people with MS in a control group were limited to 600 IU, the maximum amount the Institute of Medicine recommends to avoid adverse effects, such as excessive blood calcium levels. Calcium levels remained within normal limits in this small study, demonstrating that people with MS can tolerate higher levels of the vitamin. The relapse rate was reduced more in the treatment group, but this finding did not reach statistical significance (**Neurology** 2010;74:1852). In the same study, the team also found that immune T cells involved in MS attacks were calmed in those who achieved high blood levels of vitamin D (**The Journal of Clinical Endocrinology and Metabolism** 2011;96:2826).

What is being tested in a new clinical trial?

Ellen Mowry, MD, MCR (Johns Hopkins University) is funded by the Society to conduct a controlled clinical trial to determine whether high-dose vitamin D added to standard therapy with Copaxone reduces the frequency of relapses in people with MS. In this trial, 172 people who have MS will start daily Copaxone and will then be randomly assigned to take either 600 IU or 5,000 IU of vitamin D daily. During the two years of the study, information about relapse frequency, disability, MRI scans and other measures of MS activity will be collected from each group.

This study will provide important evidence to show whether vitamin D supplements are a safe and effective addition to standard MS therapies. Read more about this study at **clinicaltrials.gov/ct2/show/NCT01490502**.

Priorities for funding MS research

by Timothy Coetzee, PhD

Many people are aware that the Society's Strategic Response to MS includes a commitment to fund more research on progressive MS. For years we've been supporting research to stop MS, restore function and end MS forever. Much of this research applies to all types of MS. With that foundation laid, we have new opportunities to speed work on progressive MS.

"Progressive MS" means different things. For example:

- There's the relatively rare type of progressive MS that does not wax and wane (relapse/remit) but rather worsens from onset (primary-progressive MS).
- There's the more common type of slow worsening after a person has experienced a course of relapsing-remitting MS, when relapses subside or are infrequent (secondary-progressive MS).
- There's the silent progression of tissue injury that is often detected using MRI even when a person isn't experiencing worsening symptoms.
- And sometimes progressive MS refers to a person with severe disabilities.

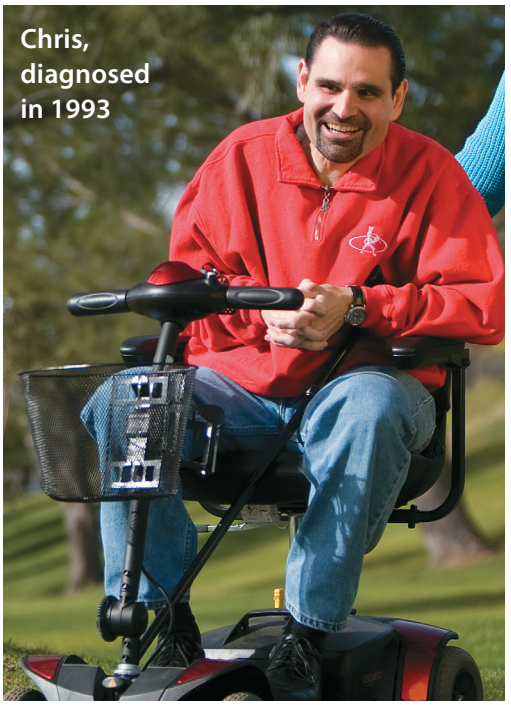
Recently our scientific advisers convened to begin shaping research priorities in progressive MS. They agreed that for us to develop better treatments for every type of MS progression, we need a better understanding of the underlying mechanisms that drive it.

Virtually every therapy that is approved for relapsing forms of MS has been tested, or is currently under testing, in people with progressive forms of the disease. Findings from these trials are driving some key research activities today.

We learned, for example, that a traditional measure of progression, called the EDSS, is not sensitive to changes over the short periods that are typical in clinical trials. We're already working to improve clinical measurements, imaging and other tools to detect changes in disability and nervous system integrity and more quickly determine whether a therapy for progressive MS is working.

We also learned that trials that combined people with different types of progression can be like "mixing apples and oranges" and possibly dilute potential treatment impacts. We're taking a harder look at the biological basis for MS categories like "secondary-progressive" and "primary-progressive"; these are mere descriptions of symptoms. We're tackling this in partnership with our European partners at ECTRIMS with the hope of making possible clinical trials that test therapies against specific processes underlying different types of disease activity.

We've got our work cut out for us, but it's a worthy challenge and efforts are already under way around the world to propel research that will make big strides for people with progressive MS.



Chris, diagnosed in 1993

Dr. Timothy Coetzee is chief research officer of the National MS Society.

In the news and on our website

STOP Lab test detects antibodies to virus that causes PML

A new laboratory test can detect antibodies to the JC virus and help determine a person's risk of developing PML, a severe brain infection that has emerged in some people who have taken Tysabri. The presence of antibodies indicates that a person has at some point been infected by or exposed to the virus, which can cause PML, but usually lies dormant. The U.S. Food and Drug Administration (FDA) has approved a change to the prescription label for Tysabri to indicate the availability of the lab test, which should enhance the ability of people with MS and their physicians to weigh the risks and benefits of this therapy.

END Does Epstein-Barr virus stimulate MS?

An international team has identified clues that may help explain how Epstein-Barr virus, which has been linked to MS, may contribute to the brain inflammation experienced by people who have MS. In active brain lesions (spots of disease activity) in people who have MS, the researchers found high levels of an inflammation-stimulating chemical (interferon alpha) that helps the body fight viruses, and immune B cells latently infected by Epstein-Barr virus, but without signs of active viral infection. The findings may point to a possible mechanism for how the virus might indirectly stimulate MS disease activity.

STOP Investigators recruiting for study of ocrelizumab in primary-progressive MS

Investigators worldwide are recruiting 630 people with primary-progressive MS to study the effectiveness of intravenous ocrelizumab (developed by Genentech) versus inactive placebo. This experimental therapy is also being tested in relapsing MS. The study is funded by F. Hoffmann-La Roche. Ocrelizumab depletes B cells, immune cells that play a role in the immune attack on the brain and spinal cord in MS. No treatment is currently approved to treat primary-progressive MS.

STOP Study focuses on Hispanics/Latinos who have MS

A new study funded by the Society provides insights into the disease and treatment of Latinos with MS. MS occurs less frequently among people with Hispanic backgrounds than among Caucasians, so there are few studies of Hispanics/Latinos with MS. The nationwide team used data from the North American Research Committee on Multiple Sclerosis registry, and conducted a telephone survey. Forty-four percent of the 99 Hispanics/Latinos in the study reported feelings that indicated depression; 61 percent were highly satisfied with their access to mental health care and 76 percent were highly satisfied with their access to MS care. This study is the first step toward meeting the needs of the Hispanic/Latino community with MS.

RESTORE Improving learning and memory in MS

Learning and memory improved in 16 people with MS with a technique that uses stories and imagery to cement learning. For the first time, this improvement was shown to be accompanied by increased activation in areas of the brain related to learning and memory. The study was funded by the Society's Mentor-Based Postdoctoral Fellowship in Rehabilitation Research, which recruits and trains talented clinician-scientists in rehabilitation research specific to MS. ■

Read more news and details of these stories at **nationalMSsociety.org/bulletins**.