

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.



Ongoing research should shed new light on astrocytes and may lead to powerful new ways to stop MS and reverse its damage.

JILL GREGORY

Astrocytes: good housekeepers or not for people with MS?

by Sara Bernstein

Star-shaped astrocytes are the most abundant cells in the central nervous system. These are the brain's "housekeepers," supporting the physical structure, providing nutrients for nerve cells, manipulating the blood-brain barrier that protects the brain, and even becoming involved in nerve impulse signaling. For years the role mainly ascribed to astrocytes in MS was the development of hardened scars after the immune attack caused damage, but recent research indicates that their role may, in fact, be more complex. It's becoming evident that these housekeepers are playing both sides of the

fence—they can incite the MS attack, and also may help repair its consequences.

Playing the villain

Astrocytes may get in on the action early in MS. Martin E. Dorf, PhD (Harvard Medical School, Boston), a researcher funded by the National MS Society, has shown that astrocytes actually amplify the immune attack in MS. Specifically, they act on immune messenger proteins called "chemokines" (pronounced KEE-moe-kines), which help recruit immune cells from the blood into the brain. His team is now trying to pinpoint a

therapeutic target in this process by screening for the genes that regulate how astrocytes produce chemokines. They have identified 19 genes and are studying them further. (**Molecular Cell** 2006 Nov 17;24(4):497–509)

Jaqueline Orian, PhD (La Trobe University, Bundoora, Australia), showed that in mice with EAE—an MS-like disease—astrocyte activity increased even when immune cells were barely infiltrating the brain. Furthermore, this increase in activity occurred in the same areas where there was damage to nerve fibers, the wire-like axons that transmit nerve signals. Axonal damage is believed to be associated with

long-term disability in MS. Dr. Orian is now testing these findings in several rodent models to determine whether there is a link between early changes to astrocytes and axonal injury. If so, it's possible that these cells present a therapeutic target for preventing MS progression. (**Glia** 2005 Aug 15;51(3):235–40)

My hero!

So astrocytes are bad guys... well, it's not that simple. Because these housekeepers play such a multifaceted role in the brain—with many positive results—it should come as no surprise that

their role in MS is also complex. With funding from the Society, Gareth John, VetMB, PhD, and colleagues (Mount Sinai School of Medicine, NY) were recently using microarray technology that can observe thousands of genes at once to determine which are “turned on” and which are “turned off” during repair in MS. They found that interleukin-11—a messenger protein produced by astrocytes—helps oligodendrocytes (the cells that

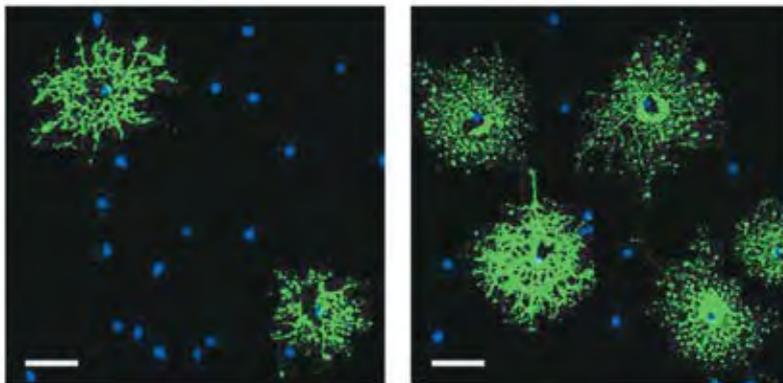


FIGURE 1. Mount Sinai researchers found that treating myelin-making oligodendrocytes with IL-11, a chemical produced by astrocytes, increased their survival and numbers in lab dishes (right panel)—courtesy of Dr. Gareth John

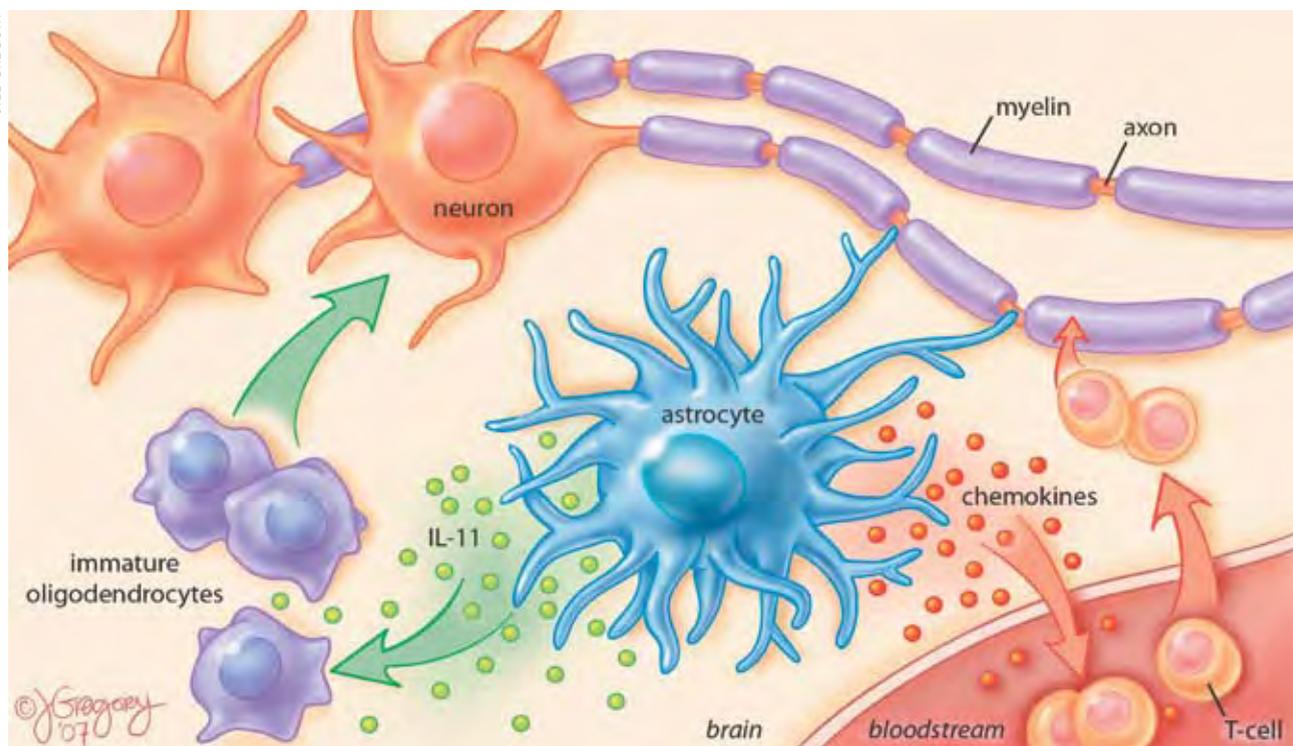
make myelin, the axonal insulation damaged in MS) to survive, mature, and form myelin. Figure 1 shows how treating oligodendrocytes isolated in test tubes with IL-11 enhanced their survival, numbers, and ability to form myelin. (**Journal of Neuroscience** 2006 Nov 22;26(47):12174–85)

Now Dr. John's team is taking these studies further. Postdoctoral fellow Yueting Zhang, PhD, is examining how increasing and decreasing interleukin-11 signals affects the development of EAE in mice. The team is studying tissue samples obtained from people with MS to confirm the connection between interleukin-11 and myelin formation, and to determine whether interleukin-11 is associated with myelin repair as well. This research

could identify a target for stimulating tissue repair in MS.

Studying the positive role of astrocytes in MS is also a goal of a National MS Society Collaborative MS Research Cen-

ter Award to Rhonda Voskuhl, MD (University of California, Los Angeles). Her collaborator Michael Sofroniew, MD, PhD, has developed a mouse model in which removing astrocytes from the spinal cord causes many more nerve cells to be lost than in control mice whose astrocytes are intact. Dr. Voskuhl's team induced EAE in this model, resulting in a more rapid onset, more acute disease, and increased axonal loss. These findings are strong evidence that astrocytes play a protective role in MS. (Abstract #S46.002, AAN 2007)



Phase III drug targets astrocytes

The goal of this research, of course, is to find targets for MS treatments that will either decrease the negative aspects of astrocytes or play up their positive features. Recent research indicates that one drug already in phase III clinical trials in people with MS may, in fact, do the latter.

Fingolimod (also known as FTY720, by Novartis Pharmaceuticals Corp.) binds to a docking site (sphingosine-1-phosphate receptor, or S1P receptor) on immune cells that cause nervous system damage in MS. The drug appears to induce immune cells to remain in lymph nodes, where they can do little harm, preventing them from migrating into the brain and spinal cord. It turns out that S1Ps also are found in the brain, and Florian Muller-
shausen, PhD (Novartis Institute

for Biomedical Research), and colleagues recently reported that astrocytes are the major cell type responding to fingolimod in the brain. (*Journal of Neurochemistry* 2007 May 4; [Epub ahead of print]) Fingolimod may be inducing astrocytes to promote nerve and myelin-making cell survival—more research is necessary to say for sure.

And the winner is ...

How do we resolve these two faces of astrocytes in the development of MS? Writing a review of the topic, Anna Williams, MD, PhD (Western General Hospital, Edinburgh) and colleagues recommended that future research studies focus on “knockout models,” in which the proteins activated by astrocytes are deleted from rodent models. (*Glia* 2007 Oct;55(13):1300–12) This could

FIGURE 2. New research is revealing good and bad sides to these star-shaped housekeeping brain cells. The good: astrocytes may promote myelin repair by producing IL-11 to stimulate oligodendrocytes. The bad: they can amplify the immune attack by T cells by activating messenger “chemokines.”

be done specifically after myelin damage occurs, to find out the role of these cells during repair. Because myelin repair often occurs in the places where myelin is damaged, they add, it may not be surprising that one type of cell can be involved in both!

Ongoing research by these and other investigators should resolve the many questions remaining about astrocytes and may lead to powerful new approaches to stop MS or repair its damage.

Amy T. Waldman, MD: tracking children with MS

Amy T. Waldman, MD, brought her energetic style to the National MS Society years ago. “I started volunteering with the Society when I was 11,” she said. “My best friend was the daughter of the chapter president.”

Years later, Amy’s childhood experiences with the Society took root in a medical career. “I decided to go into pediatrics but I was fascinated by neurology, and so I combined the two,” she said. “At Children’s Hospital of Philadelphia, I recognized that pediatric MS was an underrepresented field. It was a great niche for me because of the time that I spent with people with MS through the Society.”

Children with MS have already benefited greatly from Amy’s passion and commit-

ment. She helped establish a pediatric MS clinic at CHOP and organized its first MS support group. Now she has received the MS Clinician Scientist Development Award, given jointly by the Society and the American Academy of Neurology to train promising young clinicians in MS clinical research. Her fellowship is funded in part by the Society’s Greater Delaware Valley Chapter.

Amy’s mentors are Laura J. Balcer, MD, MSCE, and Gihan Tennekoon, MD, who are exploring vision loss in people with MS and how it relates to other neurologic functions and quality of life. Amy is applying these studies to children.

“There are few ways to measure outcomes specifically in



Dr. Waldman

children with MS,” she said. “We need sensitive measures that can really monitor how children are doing over time, not just observe them.”

Since acute optic neuritis—inflammation of the optic nerve—is a common MS symptom in children, Amy’s team is using measurements of visual function, such as tests of low-contrast acuity (perception of light gray letters of progressively smaller size on a white background) and OCT (an eye test that measures the integrity of nerve fibers in the optic nerve). They are correlating these results with more common measures of functional abilities, and examining how clinical symptoms relate to quality of life for the children.

“This award has opened so many doors for me,” Amy said. “It’s given me ‘protected’ time to learn how to do proper research. Because of the award, I have established relationships with other scientists in the field. Most importantly, I have more time to focus on my patients and their families.”

Amy has dedicated her talents to the mission of the National MS Society for 20 years now. “Every time I go to an event, I think of how the Society is motivating everyone in the field to do a better job,” she said. “Just receiving this award makes me want to work harder, to be a scientist who can make a difference in the lives of children with MS.”

FRIENDS: Shimon Elimelech, a 17-year-old with MS, and Nicholas Brady, an 8-year-old with MS, at a family weekend sponsored by the Greater Delaware Valley Chapter. For more on Society programs for kids with MS, call 1-866-KIDS W MS.



NADIA PESTRAK

Fast Forward™: more treatments, faster

Picture a wide ribbon of smooth blacktop running through vast reaches of desert terrain. The road is teeming with fast-moving Formula One cars jockeying for position. Up ahead looms a gaping chasm in the road. Some of the cars may be able to jump the gap but without a bridge many will not finish the race.

“This is a good analogy to the road to new therapies, and we think we’ve found a way to help more cars jump the gap and cross the finish line,” said Dr. John Richert, Executive Vice President of Research and Clinical Programs. He’s referring to Fast Forward,™ the Society’s bold new initiative to speed the delivery of new treatments to people with MS.

“Our basic research funding has been doing an incredible job feeding the MS treatment pipeline,” he continued. “The problem comes when it’s time to take early lab findings and translate them into a clinical trial. Developing a therapy costs millions—and venture capitalists are not as adventurous as their name implies. We needed to find a way to bridge the funding gap and get more therapies into testing. That’s where Fast

Forward comes in,” he said.

Many small pharmaceutical companies and small biotech companies have products in their pipelines of potential importance to MS but need funding to bring them through the early stages of clinical development. Fast Forward will provide funding that will allow them to demonstrate



The goal is to dramatically increase the number of drugs in the pipeline.

potential value in the treatment of MS. Furthermore, by bridging the gap between university-based research and drug development, Fast Forward connects people

with breakthrough ideas to people who can turn them into new therapies.

The core focus of Fast Forward is to:

- Increase the number of drugs in the development pipeline by connecting basic research to drug development.
- Increase the MS focus and speed with which these drugs are brought to clinical trial.
- Fund clinical trials of potential MS drugs.
- Expedite the repurposing of existing drugs used for other disorders to treat MS.

“Our science and business advisors will help us identify the most promising opportunities in research and industry,” said Timothy Coetzee, PhD, Executive Director of Fast Forward. “To move these opportunities forward, we plan to raise \$30 million over the next five years.”

The goal is to dramatically increase the number of potential drugs in the development pipeline, thereby increasing the probability of effective new treatments reaching the people who need them.

“Of course there are no guarantees,” commented Dr. Richert, “but progress can only occur through action, and I’m very excited that the Society has made this bold move.” To learn more, visit www.fastforward.org.

Targeted research: successes and new directions

by John R. Richert, MD

Two recent headlines drive home the idea that we're starting to reap the benefits of some targeted research initiatives the Society undertook as long as a decade ago. Over the last few months we've seen the startup of a new clinical trial involving the sex hormone estriol in women with MS and news that **two new gene variations** are associated with MS susceptibility (see page 74).

The **estriol trial** is a direct result of the Society's targeted initiative on gender differences in MS, and was made possible when the Southern California Chapter stepped up to the plate to raise the millions needed. The Society had also targeted MS genetics in the early 90s and funded many studies, including the establishment of a DNA bank that includes many MS families. This bank laid the groundwork and provided important research material for the recent genetics breakthrough.

It's tremendously heartening to be able to point to these successes as outcomes of deliberate commitments by Society leadership.

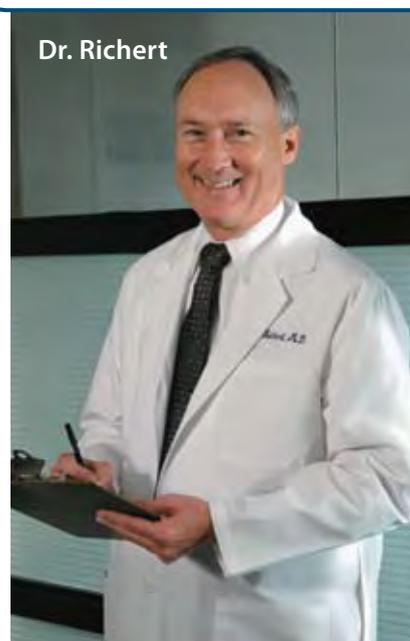
Current targets

The four research and care initiatives targeted through the Soci-

ety's **Promise: 2010** campaign include the Nervous System Repair partnerships, The MS Lesion Project, the Sonya Slifka Longitudinal MS Study, and the Pediatric MS Centers of Excellence. (Read more about these on our Web site at nationalsociety.org/Targeted.)

We won't know until further down the road what the total payoff will be from these targeted initiatives, but these projects are already beginning to bear fruit:

It's important to remember that no one knows from around which corner the next exciting breakthrough will come.



- new clinical trials in planning stages for nerve-protecting drugs and studies of cell transplantation (Nervous System Repair initiative);

- new evidence that MS may be more than one disease that requires different treatment approaches (MS Lesion Project);

- key data to influence legislators on matters such as access to therapies and other health-care and quality of life issues (Sonya Slifka Longitudinal MS Study);

- ground work for research on what triggers MS in young children, who may hold the key to the cause of MS in adults as well (Pediatric MS Centers of Excellence).

I'm pleased to introduce an additional new targeted initiative called **Fast Forward™** (See page 71). This is a creative approach to try to increase the number of potential drugs in the pipeline for treating MS. Funds will be used to help chaperone new agents through the difficult early stages of clinical testing. I'm really excited that the Society has taken this bold step, which you'll be hearing more about in the coming months.

Should all of our funding be targeted?

With recent successes in mind, some might ask whether the Society should target all of our research monies toward specific topics that seem to offer high potential. Funding agencies have

faced the question of targeted research since the beginning.

Seventy years ago the best minds of the day thought that MS was caused by blood clots and poor circulation. Thirty-five years ago many were convinced that measles virus triggered MS. If we had chosen to target all of our money on blood circulation or on measles virus, would we have six FDA-approved MS therapies today? Almost certainly not, as the Society ended up funding early investigator-initiated projects that played roles in the development of all of the currently approved drugs.

Until we know precisely what causes MS and how to cure it, in my view it would be foolish to sink all of our precious dollars into targeted areas. Research is full of twists, turns, dead-ends, and serendipitous discoveries. It's important to remember that no one knows from around which corner the next exciting breakthrough will come.

When we have a very specific question in mind that is not being adequately addressed already, it makes sense to send out a request for proposals and have the most qualified investigators compete for funding to answer that question. That is how we make funding decisions on "targeted" projects. But it also makes good sense to invite investigators to tell us their best ideas and compete for funding of those studies as well. Most times

the best ideas are initiated by the investigators themselves and are what commonly drive the field forward most dramatically.

So yes, it's vital that we target good leads that may not otherwise be tracked down. But it's also vital that we let individual creativity, and sometimes serendipity, play a hand, and continue funding investigator-initiated basic research that advances our knowledge about MS biology and that keeps the doors open to unexpected, and sometimes high-

risk, ideas and discoveries.

I'm certain that our scientific advisors will continue to help us identify new opportunities to target under-explored, high-potential areas that are deserving of special attention. At the same time, I'm confident that our continued funding of high-quality, investigator-initiated research ideas will help propel us faster to a world free of MS.

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



What does research cost?

\$70,000 will buy lab supplies, including reagents, tissue cultures, serum, test tubes, and assorted test kits for a 3-year research project

\$45,000 will cover salary and benefits of a lab technician for one year

\$10,000 will buy one year's supply of monoclonal and other lab antibodies needed to study disease activity

\$5,000 will buy one year's supply of dishes, growth media, staining agents, and other supplies for tissue culture experiments

\$2,500 will buy about 35 hours of MS research activity

\$2,000 will buy a year's worth of X-ray film and developing for protein analysis and blotting

\$1,000 will buy 20 hours of use of laser microsection equipment to prepare slides for the microscope

\$600 will buy one MRI needed for research purposes

\$250 will buy automated DNA sequencing of 10 samples

In the news and on our Web site

● **Early sun exposure associated with reduced risk of MS**

Researchers report that sun exposure during childhood was associated with a reduced risk of MS in a study of 79 pairs of twins in which one twin had MS. This study, from investigators at Keck School of Medicine, Los Angeles, adds to a growing body of evidence suggesting that sun exposure may be protective against MS.

● **Clinical trial of sex hormone estriol recruiting women with MS**

In the first effort of its kind in MS, a team of investigators at seven medical centers has begun a two-year, controlled clinical trial of the hormone estriol added to standard therapy to treat MS in 130 women with relapsing-remitting MS. This clinical trial could lay the groundwork for a larger, definitive trial that could lead to a new treatment option for women with MS.

This study is being funded by the National MS Society in partnership with the Society's Southern California chapter and the NIH. Women with relapsing-remitting MS interested in the possibility of participating should consult with their physicians or contact one of the medical centers listed on our Web site.

● **International collaborators identify new genetic risk factors for MS**

The International Multiple Sclerosis Genetics Consortium has identified two new genetic variations associated with MS, completing the largest replicated whole genome scan for MS to date. In addition, two independent collaborating groups published papers confirming one of

Read more news and details of these stories on our Web site: www.nationalmssociety.org/Bulletins.



these gene variations. The findings point to potential mechanisms underlying the disease and present possible new targets for designing better therapies to stop the immune attack in MS. The Society and Harvard jointly raised \$3.63 million to fund this study, all of the data from which are being made available publicly to spur future research.

● **Possible target of immune attack in MS and new therapeutic approach identified**

A new study by National MS Society-supported researchers

suggests a small protein normally produced by cells to protect against injury may itself be the target of the multiple sclerosis immune attack. Researchers from Stanford University and other institutions report that administering the protein alpha B-crystallin to mice with a similar disease countered the effect, opening the door to a potential new therapeutic approach for MS.

● **Betaseron "BENEFIT" follow-up study results published**

A published study shows for the first time that early treatment can slow the rate at which disability progresses in individuals who have had a first event suggestive of MS but who have not yet been diagnosed. The study is a follow-up to the completed, two-year BENEFIT study, in which treatment with Betaseron® (interferon beta-1b) was shown to delay the onset of clinically definite MS in people at high-risk for the disease compared with people who did not receive treatment. In the three-year follow-up study, both groups are now receiving Betaseron, and the study is assessing the impact of early treatment versus delayed treatment on progression.

The first years' results of the ongoing follow-up study, funded by Bayer Schering Pharma, were reported by an international group of investigators in August. ■