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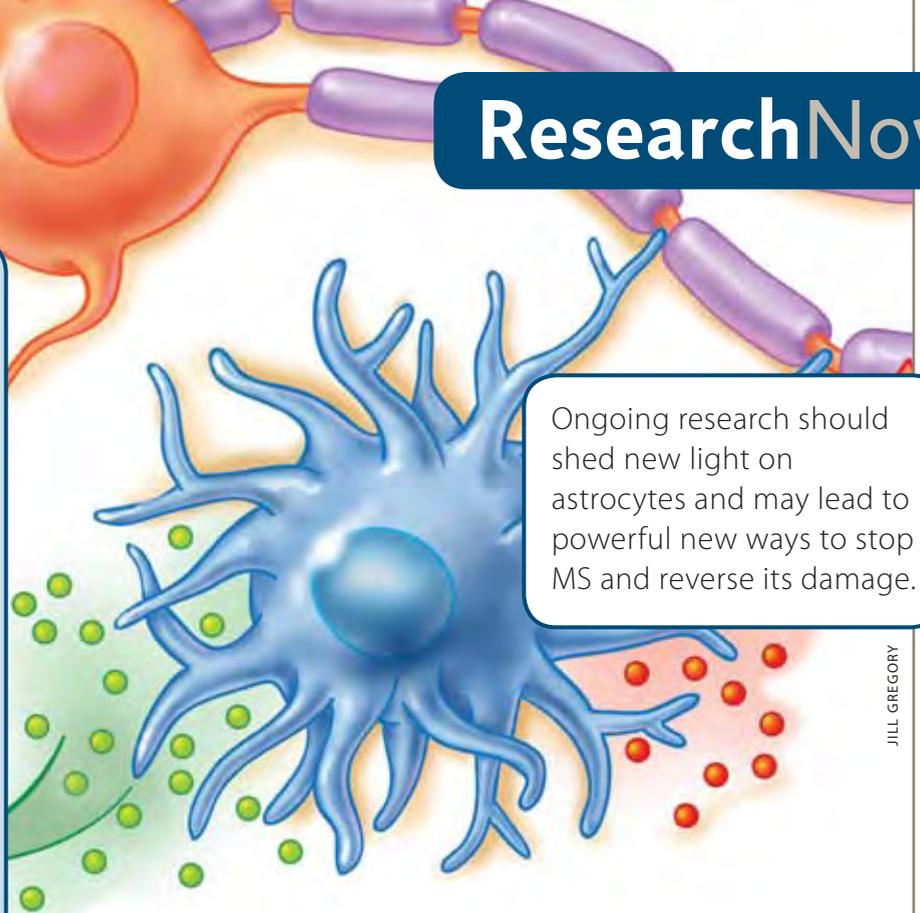
Sara Bernstein, Editor,
Research Now

Cathy Carlson, Senior
Director, Research
Information

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JILL GREGORY

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

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

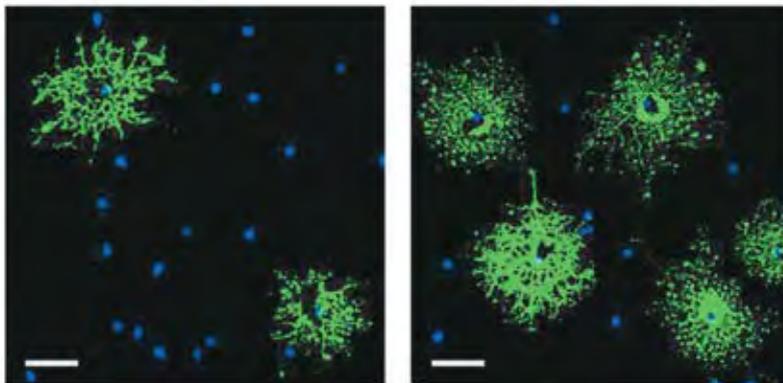


FIGURE 1. Mount Sinai researchers found that treating myelin-making oligodendrocytes with IL-11, a chemical produced by astrocytes, increased their survival and numbers in lab dishes (right panel)—courtesy of Dr. Gareth John

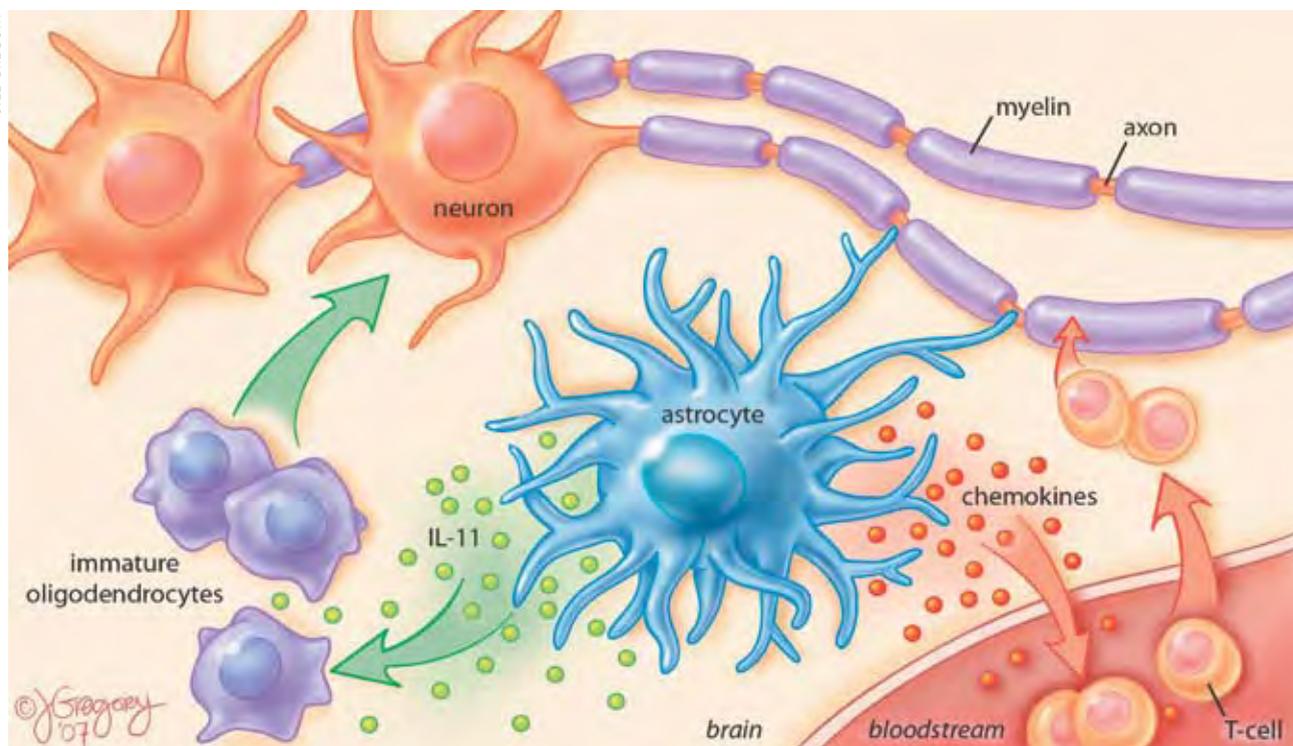
make myelin, the axonal insulation damaged in MS) to survive, mature, and form myelin. Figure 1 shows how treating oligodendrocytes isolated in test tubes with IL-11 enhanced their survival, numbers, and ability to form myelin. (**Journal of Neuroscience** 2006 Nov 22;26(47):12174–85)

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.