

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

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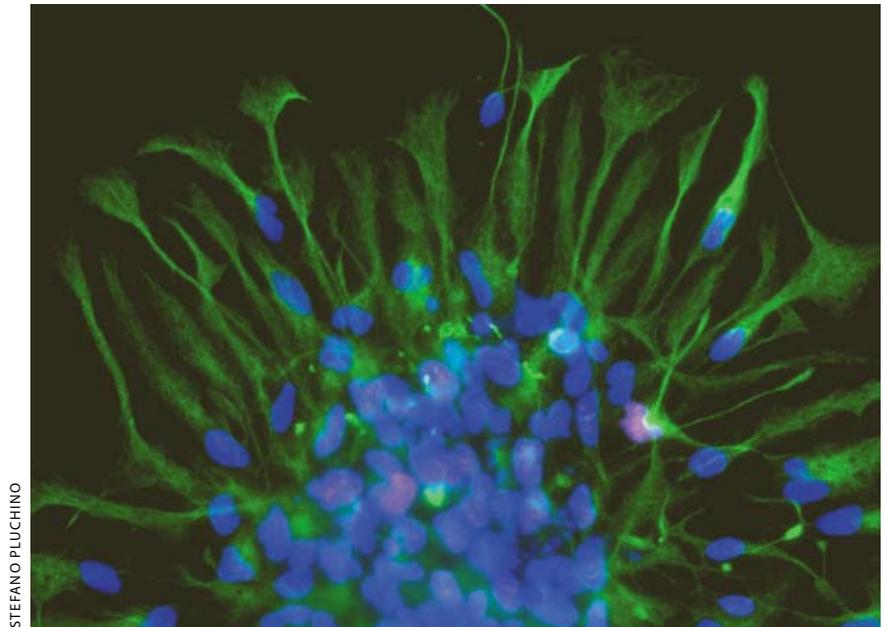
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STEFANO PLUCHINO

Cell therapy for MS

by Sara Bernstein

The Holy Grail of multiple sclerosis research is repairing damage to restore function. Although there are therapies that modify the course of the most common forms of MS, none has been proven to repair damage once it occurs. One strategy is the exciting frontier of cell transplantation or cell therapy. This approach may stimulate the brain's natural capacity for repair and may provide an outside source of replacement cells.

MS is not an easy target for

cell-based therapies though, because as a chronic disease it involves repeated assaults on brain and spinal cord tissues, and the damage occurs at many sites. For a cell therapy to work, the supply of cells would have to be vast, and the cells would probably have to be able to migrate to several areas concurrently. Ideally, new cells would be safeguarded from immune assaults that damaged the original tissue.

In May 2009 the MS societies of the United Kingdom and the United States held an international meeting in London to build

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consensus on clinical trials of all types of stem cell therapies in MS. The resulting guidelines for researchers and clinicians, slated to be published soon, should encourage consistency between studies and speed up the development of potential cell therapies.

Which cells?

Finding the best source of replacement cells and how to deliver them are just a few of the challenges being addressed by research teams around the world, including the four international teams collaborating as part of the National MS Society's Nervous System Repair and Protection initiative, launched through the Promise: 2010 campaign.

First let's distinguish these strategies from a similar-sounding procedure being investigated in MS. It is variously called "hematopoietic stem cell therapy," "bone marrow transplantation," and "autologous stem cell transplantation." This procedure aims to **reboot the immune system** by repopulating the body with new immune cells that will no longer attack the brain and spinal cord. There is no proof yet that it can "cure" a person with MS, but research is ongoing worldwide to determine whether it can halt progression or bring on remission of disease.

Here are just a few candidates under study for cell transplantation **to induce protection or repair** in MS.

Mastering mesenchymal stem cells

Adult mesenchymal (pronounced messENkimmul) stem cells are present in many tissues of the body, including the bone marrow and fat (adipose tissue). Dimitrios Karussis, MD, PhD, and colleagues (Hadassah-Hebrew University Hospital, Jerusalem) showed how they could protect the nervous system in mice with chronic EAE, an MS-like disease. In treated mice, 86% to 95% of nerve fibers were left intact, versus 45% in untreated controls. **Archives of Neurology** 2008;65:753–61

These and other preclinical results led Mark Freedman, MD (University of Ottawa), and Antonio Ucelli, MD (University of Genoa), to launch a unique effort to translate these findings to clinical trials. Realizing that initial studies each would involve very few people, in 2009 they invited investigators interested in mesenchymal research to share evidence and form a consensus on conducting clinical trials so that results of small studies could be compared.

The International Mesenchymal Stem Cell Transplantation Study Group's consensus report lays out their recommendations for study details such as inclusion/exclusion criteria, stem cell product, and measuring outcomes. "We hope that other researchers who are interested in pursuing MSCT as a potential treatment for MS will join in," they wrote. **Multiple Sclerosis** 2010 Jan 19

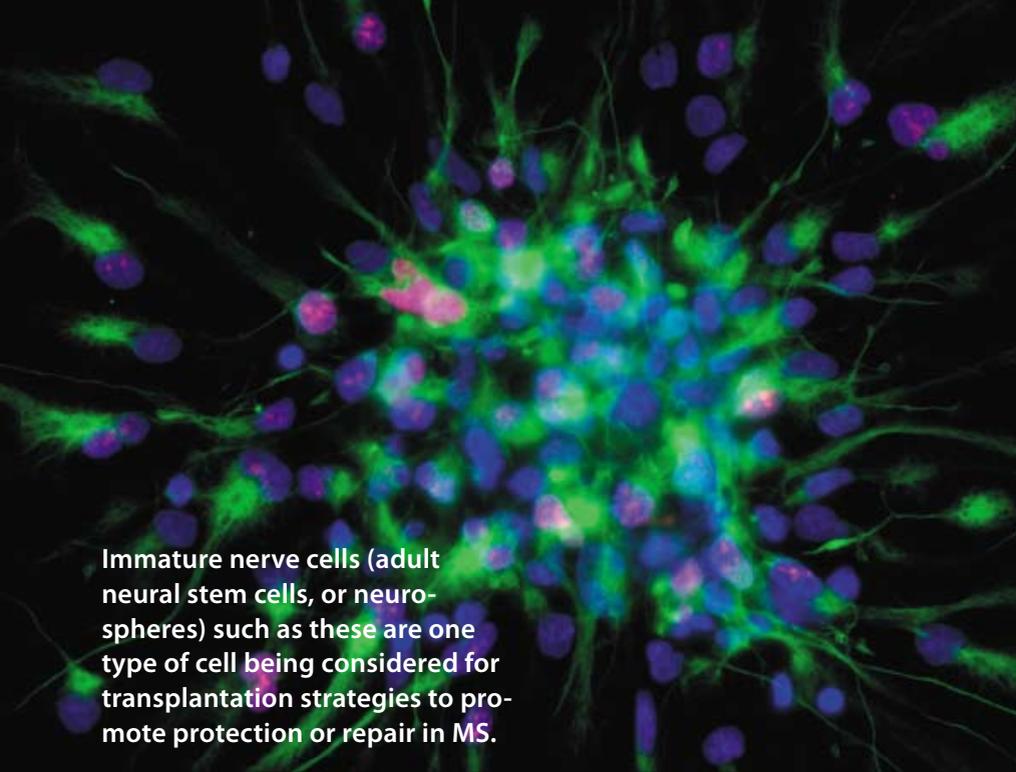
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As of this writing, at least five small clinical trials of mesenchymal stem cell transplantation are underway in people with MS; four are being conducted by members of the MSCT study group. More information is available on **clinicaltrials.gov**, and on our Web site at **nationalMSsociety.org/mescell**.

The promise of neurospheres

In 2003, Stefano Pluchino, MD, and Gianvito Martino, MD (San Raffaele Hospital, Milan) reported that immature nerve cells (adult mouse neural stem cells, or neurospheres) injected into the blood or brain cavities of mice with EAE could move throughout the brain and spinal cord to sites of tissue damage, promote repair of nerve-insulating myelin, decrease damage to nerve fibers, and reverse clinical disease. **Nature** 2003;422:688–694 Dr. Martino has since joined forces with the Nervous System Repair and Protection Initiative team based at the Universities of Cambridge and Edinburgh. He is investigating these immune mechanisms further, and is planning early clinical trials of neurosphere transplants in people with MS.

Jeffery Kocsis, PhD (Yale University) is a pioneer in the study of cell-based therapeutic strategies for MS. With funding from a Collaborative MS Research Center Award from the Society, his team investigated a novel source of neural stem cells in the adult



STEFANO PLUCHINO

Immature nerve cells (adult neural stem cells, or neurospheres) such as these are one type of cell being considered for transplantation strategies to promote protection or repair in MS.

brain—the olfactory bulb, which controls perception of odors. They isolated neural stem cells from the olfactory bulb of rats, and then introduced these cells into areas of myelin damage in the spinal cord of other rats. The cells survived, integrated into the areas of damage, and extensive myelin repair was observed. 2009; **PLoS one** 4(9):e7260 Research on this strategy continues.

Making the myelin makers

Although myelin-making cells—oligodendrocytes—are lost in MS, research indicates that the capacity for repair exists in people with the disease, but fails for some unknown reason. The Society is funding some of the best minds in cell transplantation to tackle this problem, and several are studying how to take advantage of immature oligodendrocytes—known as oligodendrocyte precursor cells (OPCs).

Steven A. Goldman, MD, PhD (University of Rochester

Medical Center), is among the leaders focusing on the potential of cell therapy to treat MS. His team showed that transplanting OPCs into mice that normally make no myelin results in almost complete restoration of their previously lost neurological function. **Cell Stem Cell** 2008;2:553–65 This Society-funded project was supported in full by gifts from the Charles and Margery Barancik Foundation and the Alan Buegeleisen Research Fund. Now they are exploring these findings in other mouse models, including a model that resembles progressive MS. Dr. Goldman also is working with Ian D. Duncan, BVMS, PhD, FRCPath (University of Wisconsin, Madison), whose Repair initiative team is investigating novel methods of encouraging and tracking OPCs in novel animal models and exploring other sources of replacement cells.

Thomas Lane, PhD (University of California, Irvine) is lead-

ing a new Collaborative MS Research Center focusing on cell therapy. He has been funded to study messenger chemicals, called chemokines, for clues to stopping the influx of damaging immune cells in MS, but now is looking at them as possible vehicles for allowing the migration of OPCs into sites needing repair.

These studies require major sources of cells, which is the focus of team member Hans Keirstead, PhD, who has extensive expertise in generating stem cell lines.

Another potential source of myelin-making cells is in the body's periphery. "Schwann cells" are very good at repairing myelin lost from nerves in the arms or legs, but do not normally cross into the central nervous system. Anne Baron-Van Evercooren, PhD, and colleagues at INSERM in Paris, as well as other teams, have found that altering gene activity in Schwann cells could enhance their migration to lesion sites and promote their repair activities in the central nervous system of mice. **Brain** 2010;133:406–420

Fast-paced field

These studies are just a small sample of research going on around the world on cell therapy for MS. Cell therapy is truly an exciting strategy that brings much promise for restoring function in people with MS.



Following MS research down every path

Recent MS research findings have led scientists down a variety of paths—some well-trodden, and other in totally new directions. In trying to find the cause and more effective treatments for a disease as complex and unpredictable as MS, the National MS Society is steadfast in its commitment to pursue all promising avenues of research that can lead to improved treatments and, ultimately, a cure. It is important for researchers to think outside the box, and many of the intriguing opportunities detailed below represent that kind of thinking.

Verifying venous problems

CCSVI exploded onto the MS research scene in 2009. Paolo Zamboni, MD (University of Ferrara, Italy) reported evidence

of slowed and obstructed blood flow in the veins draining the brain and spinal cord in 65 people with different types of MS, compared with 235 controls. His team called this venous obstruction “chronic cerebrospinal venous insufficiency,” or CCSVI. **Journal of Neurology Neurosurgery & Psychiatry** 2009; 80:392–399

This novel concept warrants further, more extensive and controlled study. The Society responded to this need quickly by distributing a special request for research applications, and collaborating with sister societies around the world to convene an international panel of experts to conduct an expedited review of applications received. Funded research should start in July 2010.

To get the quickest and most reliable results about benefits and risks of any surgical procedure that might attempt to address blood flow in or out of the brain, it is important that surgery initially be performed only as part of controlled trials, especially since there have been anecdotal reports of surgical attempts to treat CCSVI in people with MS resulting in severe adverse events, including one reported death. Find CCSVI updates at nationalMSSociety.org/ccsvi.

Let the “sunshine vitamin” in

Healthy living with MS includes eating well; some people even take vitamins. But one of these vitamins—vitamin D—may actually play a crucial role in MS.

MS researchers wondered why MS occurs less often in regions of the world where exposure to sunlight is high. Colleen Hayes, PhD (University of Wisconsin-Madison) and colleagues first suggested that vitamin D, which is made by cells in the skin in response to sunlight, may suppress the immune response involved in MS. The Society has funded some of Dr. Hayes’s extensive research in this area, including recent findings that showed how vitamin D protected female mice (but, curiously, not males) from developing EAE (an MS-like disease). **The Journal of Immunology** 2009;183:3672–81

Startling clinical findings on vitamin D were published this

year by Ellen Mowry, MD, a Sylvia Lawry Physician Fellow (University of California, San Francisco) who is developing expertise in MS clinical trials. Dr. Mowry worked with two pediatric centers funded through the Society's Promise: 2010 campaign to review records of vitamin D levels in children and adolescents diagnosed with MS, and to determine any association with relapse rates. Every 10 nanogram per milliliter increase in blood vitamin D level was associated with a 34% decrease in the rate of subsequent relapses. **Annals of Neurology**, accepted January 20, 2010

There are still questions about whether addressing vitamin D deficiency might affect the course of MS, and it's not clear how much supplementation might be effective, yet safe. Excessive intake of vitamin D can have toxic effects on the body, such as kidney damage, so we need to get it right.

Christopher Eckstein, MD—another Lawry Fellow (Johns Hopkins University, Baltimore)—has designed a study to investigate the effects of different doses and forms of vitamin D on immune activity in people with MS. And after a small pilot study conducted in Canada, at least one clinical trial is in the planning stages to determine whether supplementation can impact MS symptoms. These are the kinds of nuts-and-bolts studies that are necessary if vitamin D supplementation is to become a part of managing MS.

Red, red wine

A major unmet need in MS treatment is some way of protecting nerve cells from damage in the brain and spinal cord. One unusual strategy that the Society is funding involves resveratrol, a natural substance found in red wine.

Resveratrol has shown benefit in animal models of neurological disorders such as stroke, so the Society funded Ikuo Tsunoda, MD, PhD (University of Utah, Salt Lake City) with a pilot research award to determine if it could protect nerve cells from damage in animal models of MS. He reported that treated mice had reduced mortality compared with untreated mice, a finding that the researchers say might be attributed to nerve protection.

(**World Congress of MS 2008**, Abstract #P212)

Now the Society is funding Kenneth Shindler, MD, PhD (University of Pennsylvania, Philadelphia) to hash out this issue with a full research grant. He is conducting a series of tests to determine how resveratrol protects nerve cells in mice that have relapsing or progressive forms of EAE. The resveratrol used in this study has been used in clinical trials involving other conditions, so this work could lead relatively quickly to MS trials.

These are just a few examples of our efforts to take into consideration the variety of paths that might lead to the end of MS. Read more at **nationalMSSociety.org/research**.

"Since my first MS symptoms appeared, I've seen the decline of the Soviet Union, the disintegration of the Columbia space shuttle, the execution of Saddam Hussein, and the collapse of the stock market. But in the midst of these dramatic events, I've seen the explosive growth of MS research breakthroughs and significant improvements in diagnostic techniques. Gone are the days of doctors telling patients to quit work and avoid exercise. Patients no longer hear, "There's nothing we can do." There are now medications that are effective in slowing the progress of the disease. Stem cell research and spinal cord injury research have provided clues to the MS mystery, and there are many MS drugs in the pipeline queuing up for future testing. This gives me great hope that a cure is coming in my lifetime."

Joan Wheeler, excerpt from "A Short in the Cord," from **Voices of Multiple Sclerosis, The Healing Companion: Stories for Courage, Comfort and Strength** © 2010 by Joan Wheeler, reprinted with permission of Joan Wheeler and LaChance Publishing, LLC, **lchancepublishing.com**.

Targeting MS pain

Pain is a common symptom of MS—acute pain, such as a stabbing pain in the face, and chronic pain, such as “pins and needles.” People with MS are not alone—according to the American Pain Society, pain symptoms result in \$100 billion in medical bills and lost workdays each year.

Congress declared 2001–2011 the Decade of Pain Control and Research. Let’s look at this decade in the field of MS.

The scope of pain in MS

Dawn Ehde, MD, and colleagues (University of Washington, Seattle) sought answers to basic

questions about how pain affects people with MS by reviewing surveys mailed to 180 people with MS. Among this group, 66% reported pain symptoms, with 40.7% reporting constant pain during the previous four weeks. People reported pain in an average of over six areas of the body. **Multiple Sclerosis** 2006;12:629–38

Led by Travis L. Osborne, PhD, this team then investigated psychosocial factors that might affect pain (e.g., alarming thoughts about pain, social support) in 125 of these responders. Psychosocial factors significantly

contributed to people’s report of pain intensity. The group suggests that addressing pain from a purely biomedical standpoint is not enough. A biopsychosocial approach—including, for example, cognitive-behavioral therapy to address alarming thoughts about pain—would better serve people with MS.

Pain 2007;127:52-62

Pursuing new ways to stop pain

Investigators are exploring novel routes for stopping MS pain; the National MS Society’s Research Programs Advisory Committee recently noted that efforts to decrease MS symptoms are a research funding priority.

In 2005, Health Canada, the drug regulatory agency for Canada, approved the marijuana-derived drug Sativex (GW Pharmaceuticals) to treat MS-related pain. Sativex was reported to reduce central pain (induced by tissue damage in the brain/spinal cord) significantly more than inactive placebo in 66 people with MS. **Neurology** 2005;65: 812–819 Unlike most trials of new medications, however, investigators did not assess whether participants knew whether they were on study treatment or placebo, leading to some question about the results. Sativex, which is administered as a spray into the mouth, is not approved for use in the U.S.

Mark Jensen, PhD, and colleagues (University of Washington) conducted a pilot study



ALASDAIR NEVIN, UNIVERSITY OF ULSTER

Researchers funded by the National MS Society have studied whether reflexology—massaging areas on the feet that may correspond with benefit in different parts of the body—could reduce pain in people with MS.

combining self-hypnosis training and cognitive therapy for chronic pain management in 15 people with MS, with funding from the Society. Self-hypnosis involves learning how to enter a state of focused attention and then alter how one experiences pain, and making these changes “automatic.” In unpublished results, participants reported significant decreases in average daily pain and in the frequency of thoughts about pain. Dr. Jensen’s team is planning a larger study to better examine the benefits of self-hypnosis.

Andrea Lowe-Strong, PhD, and colleagues (University of Ulster, Northern Ireland) conducted a study to test the effects of reflexology—massaging areas on the feet that may correspond with benefit in different parts of the body—with funding from the Society. Dr. Lowe-Strong’s team randomly assigned 73 people with MS to receive reflexology or “sham” foot massages for 10 weeks. **Both** groups experienced a 50% decrease in pain measured by a clinical scale, along with significant decreases in other symptoms, such as fatigue and depression. Decreases were maintained for up to 12 weeks after completing treatment. The researchers suggest that improvement in the sham group might be due to the possibility that reflexology points were affected by the nonspecific massage, or to a placebo effect. **Multiple Sclerosis** 2009;15:1329–38

Where pain comes from

Stephen G. Waxman, MD, PhD (Yale University), broke new ground in MS pain research, showing the role of abnormalities in sodium channels (tiny pores along the axon that are essential for nerve conduction). This research led to the use of channel blockers (such as phenytoin and carbamazepine) approved for other indications to treat MS pain.

Matthew Rasband, PhD (Baylor College of Medicine, Houston), is continuing in Dr. Waxman’s footsteps, with funding from a Harry Weaver Neuroscience Award from the Society. He is identifying proteins that direct the organization of ion channels, and how alterations in these proteins might contribute to disorganization of channels, and nerve pain. Such studies might yield new treatment strategies more specific to MS pain.

Researchers also are investigating how pain evolves during the immune attack that damages the brain and spinal cord in MS. Camille J. Olechowski, Bradley Kerr, PhD, and colleagues (University of Alberta, Edmonton) studied “allodynia” in mice with MS-like EAE. Allodynia is neuropathic pain that occurs in response to a stimulus that should not cause pain. These mice developed strong allodynia responses to mild cold and light touch. The responses were associated with significant immune system activity in the area of the

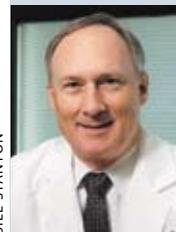
spinal cord where sensory information is received, including an influx of T cells, and increased activity of brain cells (astrocytes, microglia, macrophages) that play a role in the immune attack. **Pain** 2009;141:156–64 The team is investigating immune mechanisms further to develop treatments for neuropathic pain.

This decade has brought us a better understanding of MS-related pain. People with MS and pain should discuss with their doctors options that can help reduce this troublesome symptom. Read more at nationalMSSociety.org/symptoms. ■

John Richert, MD

After five years of leading Research & Clinical Programs at the National MS Society, Dr. Richert has stepped down, returning to one of his first loves, the development of new therapies for MS. This time he will work in partnership with the research program of a major pharmaceutical firm. Please join the Society staff in heartfelt thanks for his many contributions and our wishes for the success of

his newest endeavors on behalf of everyone affected by MS.



BILL STANTON