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Research to stop MS, restore function and end MS forever



New hope for repairing myelin damage in MS

Stem cell therapies show early successes in lab models.

by Mary E. King, PhD

Stem cell therapies are receiving considerable attention as possible methods to repair nerve damage that occurs in progressive forms of multiple sclerosis. Dr. Jeffrey Cohen, director of the Experimental Therapeutics Program at the Cleveland Clinic, and Paul Tesar, PhD, assistant professor of genetics and genome sciences at Case Western Reserve School

of Medicine in Cleveland, are among many researchers advancing this field using several different approaches.

Why the intense interest? People with relapsing MS have a number of options for approved medications. These therapies target



COURTESY OF DR. JEFFREY COHEN

Dr. Jeffrey Cohen

myelin, a restorative step that would be particularly helpful to people in the progressive phase of MS. Although some cell-based therapies have entered early clinical trials in humans, including one by Dr. Cohen and his collaborators, so

far most of the research is being done in mice. the immune system, slowing damage to the myelin, the insulating substance that surrounds the nerve fibers and which is a major target for the attack in MS. However, these therapies do not directly repair damage that has already occurred, and they are not helpful for many who have progressive MS.

Stem cell therapy holds the promise of actually repairing

far most of the research is being done in mice.

Promoting repair

“The specific type of stem cell that we study is called a mesenchymal stem cell (MSC),” Dr. Cohen says of his team’s approach. “We isolate MSCs from the bone marrow of an adult and then multiply them in the lab,” so they can be tested in a clinical trial.

Purified MSCs are then injected into the same adult’s vein and travel through the bloodstream to the brain. What is most exciting, Dr. Cohen continues, is that “MSCs appear

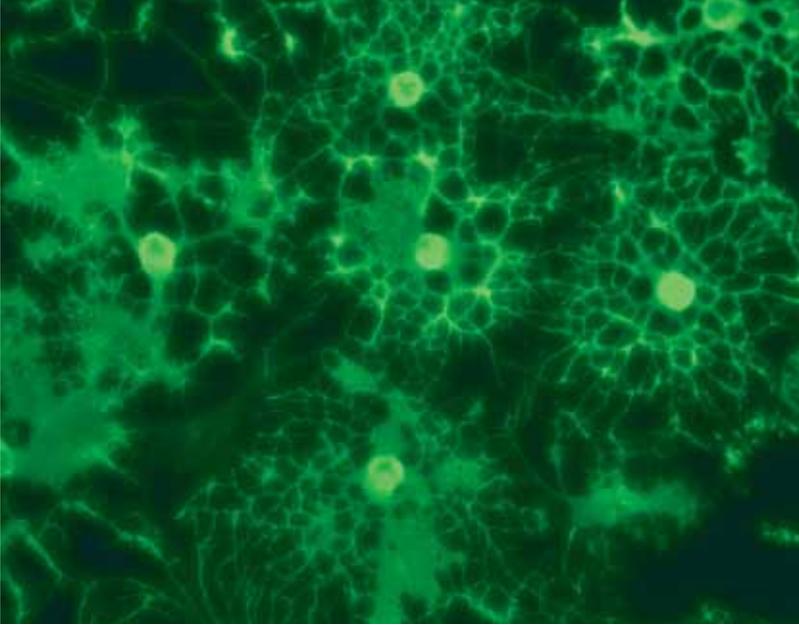
Update on progressive MS

Why do some people experience aggressive worsening of their multiple sclerosis and others experience a mild course? Right now, no one knows the answer. In its quest to unravel the mystery of MS progression, the Serial Unified Multicenter MS InvesTigation (SUMMIT) is generating much excitement.



Read the full story on **Momentum MagazineOnline.com**.

This international consortium is following 1,500 people with MS. The goal is to distinguish what causes the disease to progress more rapidly in some people versus others.



Myelin-repairing cells (oligodendrocytes, shown in green) were developed from mouse skin cells using newly simplified steps.

to seek out damaged areas and help promote myelin repair” in the brains of laboratory animals with experimental autoimmune encephalomyelitis (EAE), an MS-like disease. “We are hopeful that the same thing happens in people with MS.”

With funding from the U.S. Department of Defense, Dr. Cohen is now conducting an early stage clinical trial (called “phase 1”) to test the safety and feasibility of using MSCs in people with MS. The study enrolled a total of 24 people. Final results are expected in early 2014 (**Journal of the Neurological Sciences** 2013; Jan 4). If the results are positive, Dr. Cohen hopes to initiate a larger, phase 2 trial to determine the effectiveness of MSC transplantation.

To facilitate the potential of this study, the National MS Society awarded a pilot grant to Dr. Cohen to help refine procedures for expanding patients’ MSCs for injection and to see whether MSCs from

people with MS differ from MSCs from people without MS.

As Dr. Cohen explains, “This is a very complicated undertaking; [stem cell therapy] is not like a drug, where you know exactly what you are giving to a patient. Stem cells are very dynamic, and they can change their function depending on where they find themselves. However, [if this approach works], it does offer a new strategy to repair damage in the progressive stage of MS.”

Direct repair

Dr. Tesar uses a different type of stem cell and a different approach in attempts to directly repair myelin. He explains, “The cell type we are most excited about as a cellular therapeutic is the oligodendrocyte progenitor cell (OPC).” When injected into the brain in animal models, these cells directly myelinate damaged nerve fibers.

Recent advances by Dr. Tesar and other investigators involve taking skin cells and converting them into OPCs in the

What are stem cells?

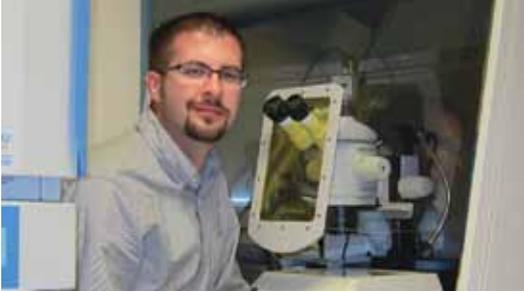
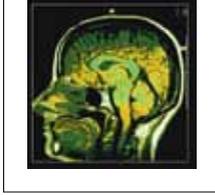
Stem cells possess two key qualities: They divide and replicate when they are grown in the laboratory, and they have the potential to turn into a specialized cell, such as a brain or blood cell.

Mesenchymal stem cells (MSCs) can be isolated from many tissues. When injected into the bloodstream, they migrate directly into damaged or inflamed tissues, including the brain. MSCs do not directly repair the myelin that is damaged by the immune attack that occurs in MS. Instead, they seem to release chemicals that stimulate the natural repair processes of damaged tissue.

Oligodendrocyte progenitor cells (OPCs) develop into cells that do the actual job of repairing the myelin damage. However, because OPCs cannot move from the bloodstream into the brain across what is known as the “blood-brain barrier,” these cells probably will need to be injected directly into the brain.

laboratory. This procedure could potentially enable scientists to take a tiny piece of skin from an individual with MS, grow the skin cells in the lab, convert them to OPCs, and then inject the OPCs into the person’s brain to repair the damage that has occurred in MS (**Nature Biotechnology** 2013; 31:426).

The National MS Society has



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Dr. Paul Tesar hopes animal studies that start with skin cells to repair myelin eventually lead to new treatments for humans.

current investments of more than \$3 million to explore the potential of stem cell therapies.

One team, led by Dr. Steven Goldman at the University of Rochester, recently reported success transplanting stem cells derived from human skin into the brains of mice. The cells developed into myelin-making cells that formed new myelin quickly and efficiently. Dr. Goldman and his collaborators have leveraged \$12.1 million in funding from New York State Stem Cell Science for clinical trials of stem cell strategies.

While Dr. Tesar's research is not yet ready for a clinical trial—additional questions about how OPCs behave long-term in animal models must be answered before they can be tested in humans—he is enthusiastic about its possibilities. “Cell transplantation is a completely

new field for diseases of the brain. We are hoping that this type of research will change how we treat MS.” ■

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Read more about Dr. Steven Goldman's stem cell therapy study at nationalMSsociety.org/skincellstudy.

The Ebers effect

Canadian researcher awarded 2013 John Dystel Prize for MS Research.

by Elinor Nauen

Doctors and medical researchers are often compared to detectives, tracking down clues—not to solve a crime but to make a diagnosis and suggest treatment. Professor George C. Ebers, MD, of the University of Oxford in London, is one such detective, investigating the case of multiple sclerosis. He has made extensive contributions to understanding the disease, shedding new light on factors such as genes that contribute to susceptibility to MS, as well as other factors that influence who eventually gets MS.

For this work, Dr. Ebers was awarded this year's John Dystel Prize for MS Research. The \$15,000 prize, given jointly by the National MS Society and the American Academy of Neurology, has been awarded since 1995 in honor of John Dystel, a young lawyer—and one-time patient of Dr. Ebers—whose career and life were cut short by progressive MS. The prize is given to a scientist who has made significant, wide-ranging and exciting contributions to the understanding, treatment or prevention of MS.

Science sleuth

Dr. Ebers followed clues to tease out the link between sunlight and MS. “In 1987, in **The New England Journal of Medicine**, I said the geography of MS had to be determined by climate or diet or both,” he says. “Vitamin D was attractive because it was sourced via both climate and diet.” His continuing investigation throughout the subsequent decades has clarified the connection.

The biggest clue to the vitamin D and MS correlation, Dr. Ebers says, “was that the risk of MS was determined very strongly by where you live. We knew that if English, Welsh or Irish people moved to South Africa or Australia, their risk for MS would go down 80 percent. But studies of families, adoptees, stepchildren and half-siblings raised together and apart all exonerated the effect of family and household conditions. Risk appeared to be determined by the place, acting at a broad population level, in much the same way as a local virus.”

Dr. Ebers sifted through the evidence. “For 3 million years humans were naked on the plains of Africa, and



Dr. George Ebers examines clues for information about the causes of MS.

plenty of vitamin D was made in the skin from sunlight.” As humans migrated northward, they became deficient in vitamin D, which led to evolutionary changes toward lighter skin. “The frequency of MS increases with distance from the equator,” he

continues, “suggesting that one risk factor may be vitamin D, which is only synthesized in the body when sunlight is of sufficient strength.”

Take Scotland, for one example. Unlike countries with year-round sunshine—and fewer cases of MS—Scotland has too little sunlight for people to make adequate amounts of vitamin D. The typical Scot shows evidence of vitamin D deficiency having influenced his or her appearance: The light skin, reddish hair and freckling are all genetic adaptations aimed at maximizing vitamin D production in the skin. The Scots’ diet used to contain higher levels of vitamin D, but in the 50 years since their diet changed, MS levels in Scotland have tripled. There are some exceptions to this latitude effect, but they seem to still correlate with low vitamin D levels.

The genetic component

Even if it turns out that sunlight/vitamin D level does determine the geography of MS, it is not the only environmental factor, Dr. Ebers notes. Smoking, virus infection and early-life hygiene all influence disease susceptibility within the context of genetic factors. “Indeed, we showed several ways in which vitamin D interacts with the genetics,” he explains. “The old argument about genes versus environment has been settled: It is both, and they interact.”

Other research found that both the main genes and a number of the small genes that predispose a person to MS are regulated by vitamin D. Dr. Ebers’ group discovered that people who have a genetic deficiency of an enzyme called 1,25-alpha-hydroxylase, which converts vitamin D

to the active form, were more likely to develop MS.

Dr. Ebers previously practiced at the London (Ontario) Health Sciences Centre, where he conceived and initiated the Canadian Collaborative Project on Genetic Susceptibility to MS. This project comprises data and DNA on some 30,000 people with MS and their families.

For 25 years, starting in the early 1980s, Dr. Ebers also followed about a thousand people with MS in Canada. These people had received no treatment for 20 years or more, in most cases because disease-modifying treatments were not yet available. “It’s important to understand the disease course without treatment,” he notes, in order to compare the long-term effects of treatment, given the short-term nature of clinical trials. These studies of the “natural history” of MS have also led to important insights, such as understanding the average number of MS relapses a person may experience; the predictive value of the early course of MS; and the features of primary-progressive MS.

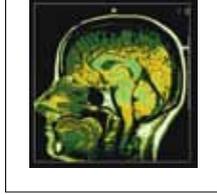
D is for determination

Dr. Ebers thinks it eventually may be possible to prevent MS by adding vitamin D to foods to increase people’s intake of the vitamin. “Unexpectedly, there are hints that vitamin D may help people who already have the disease, as small studies show some MS improvement in people with MS taking high doses of vitamin D,” he says, “but there is much more work needed to substantiate this.”

Some research suggests the possibility that vitamin D supplements taken during pregnancy and the early years may reduce the risk of a child developing MS later on. “In fact, if you do supplement with vitamin D, it may change the risk for your children or grandchildren,” he says, “and there is good evidence for effects from exposure in previous generations, which ramps up the stakes in any decision about supplementing on a large scale.” Similar efforts, such as folic acid supplementation to reduce certain severe birth defects, have been successful.

Dr. Ebers says he has been interested in MS ever since he was a neurology resident at Cornell University in the 1970s. Thirty-five years later, “I’m still at it,” he says. And although he hasn’t broken the case entirely, “we’ve covered a lot of ground,” he says. “There’s lots of progress!” ■

Elinor Nauen is a health writer based in New York City.



Become an informed MS consumer

Learn to sort the science from the sales pitches, and make informed decisions.

by Timothy Coetzee, PhD



If you Google “MS research,” you’ll get an avalanche of hits. How do you determine which information to trust—especially about experimental treatments, such as stem cell therapy? Here are a few ways I check the reliability of MS research news.

Reading into research

When I hear about a new claim, I start asking questions:

- > **What is the source?** Is it coming from a well-established, prestigious medical journal, such as *The New England Journal of Medicine*, or is it a press release from a manufacturer, meaning that the information is probably not independently vetted?
- > **Is the news related to treating lab animals or people with actual MS?** Many things that work in mice don’t succeed in people.
- > **How many people were involved in the study being reported?** Ten? Five hundred? More is better, if properly done.

- > **Was it a controlled trial?** This means the study compared two groups and used the practice of “blinding”—in which neither the participants nor the researchers knew who received the placebo and who received the treatment being studied—to block any potential biases of the researchers.



Download a PDF report on Stem Cell Therapies in MS at nationalMSsociety.org/stemcelltherapies.

> **Are claims backed up by clinical trials instead of personal testimonials?** MS is different for everyone, so it’s better to draw conclusions from large study groups rather than from individual anecdotes.

> **Does the treatment claim to be a cure for many different disorders?** If so, I’m skeptical. In addition, I sometimes see phrases on websites that can be tip-offs that a treatment may not be a good choice. For example, “This is the cure.” If a cure had been discovered, it would have been reported worldwide by credible news agencies. Or, “Please pay in advance.” As with most purchases, a reputable company delivers a product at the time of payment.

Thinking about stem cell therapies

Research in stem cells holds great promise (see story on p. 46), but getting cell therapies outside of rigorously designed clinical trials can be risky and of unproven value. Being a smart consumer is imperative in an era when stem cell therapy is being promoted by clinics worldwide.

I get suspicious when something is touted as safe simply because it’s “natural.” Think of how many “natural” muscle-building or weight-loss pills have been found harmful, such as ephedra, a plant that is now banned in the U.S. because of the severe gastrointestinal and psychiatric side effects it caused.

Likewise, just because a treatment involves a person’s own cells, it doesn’t mean it is safe: As soon as cells leave your body, they may become contaminated with bacteria or viruses if improperly handled. Injecting cells also may damage the tissue into which they are injected. Until this and other issues are overcome, stem cell treatments remain risky. The FDA has established standards for development of stem cell therapies and so far, none have been approved for use in MS.

More than 10 million people seek information on the Society’s website (nationalMSsociety.org) each year. We work hard to ensure this information is accurate and comprehensive so that people have the information needed to make informed decisions. ■

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