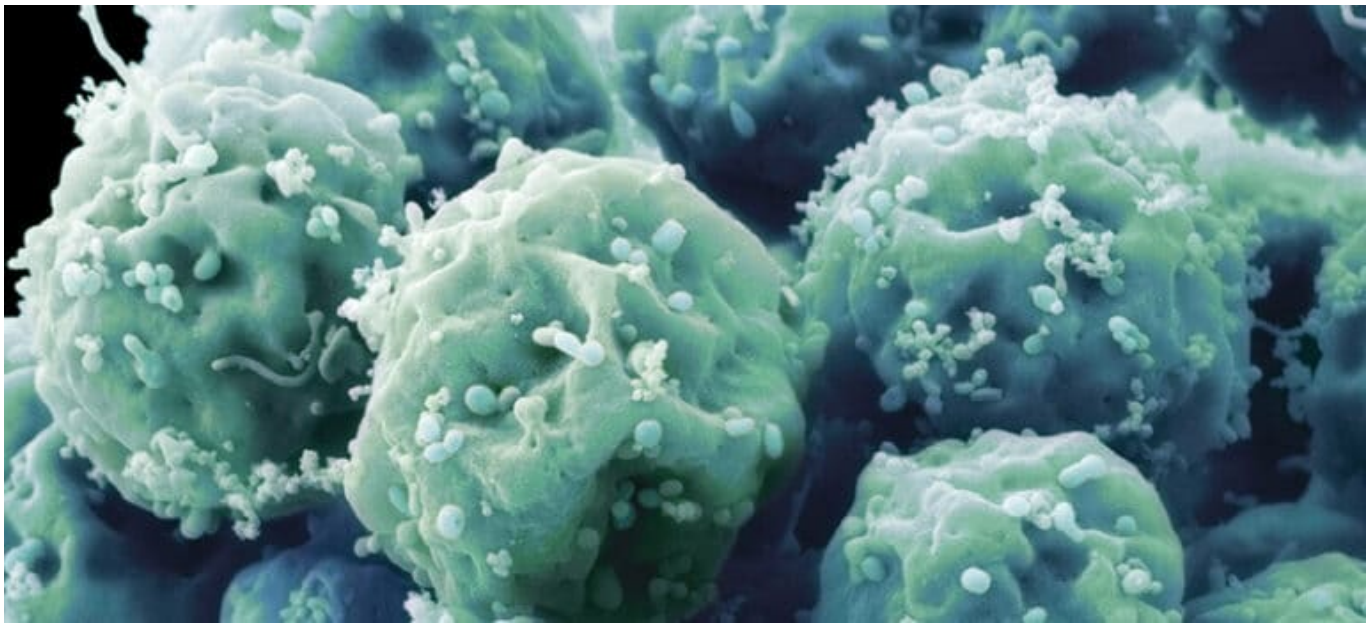
Stem cells: What we know



Exciting field offers promises—and risks.

by Mary E. King, PhD

Scan the mainstream media for health-related stories these days, and you're likely to see headlines like the following:

"Stem cells for arthritis,"
"The latest in the heart stem cell debate,"
"Stem cells for personalized pain management,"
and, yes, "Stem cell therapy—hope for MS."

But this topic is much more complicated than a short news video or story can cover adequately.

With so much in the news, many people with multiple sclerosis are wondering why they can't access a treatment that seems to be revolutionary. The truth is that presently, there are no FDA-approved stem cell therapies for MS. The National MS Society is currently supporting 12 research projects exploring various types of stem cells, including cells derived from human bone marrow, fat and skin, and has supported 68 stem cell studies over the past 10 years to ensure that the potential is thoroughly explored and understood. We want to share some of what has been learned from leading investigators to help you unravel this exciting, yet complex, research.

Stem cell basics
Stem cells take their name from "Stammzelle," a word created by a German biologist in the late 1800s to describe cells in early development from which he believed all other cells must

stem. Today we know that stem cells have two very important abilities: They are cells that can divide to make unlimited copies of themselves and, under the right conditions, they can change ("differentiate") into the specialized cells that make up our tissues and organs. Stem cells can be isolated from many different tissues in the body, not just those from embryos.

Some types of stem cells have the ability to develop into any type of cell in the body, while others can only become certain types of specialized cells. In MS, much of the stem cell research focuses on creating specialized cells that have the potential to fix an immune system that is mistakenly attacking myelin, or to repair damage to myelin to restore nerve signaling.

There are four main categories of stem cells that may have applications for MS:

Tissue-specific stem cells. Sometimes called "adult" stem cells—referring to the stage of growth of the cell, not the person or organism that hosts them—these are found in some tissues or organs, including the heart, lungs, skin, brain, sperm and eggs. While these cells can differentiate, they are limited to a few types of specialization, depending on where the tissue-specific cell originates. Those found in the brain, for example, can become neurons, astrocytes or oligodendrocytes. Neurons are cells that process and transmit information through electrical and chemical signals in the nervous system. Oligodendrocytes are cells in the brain and spinal cord that conduct many support and cleanup activities to improve brain function. Astrocytes create the nerve-protecting myelin sheath that is damaged by the immune attack in MS.

Embryonic stem cells. Probably the most well-known and most controversial type of stem cell is derived from a blastocyte, a ball of 150 to 200 cells that forms at the very beginning of embryo development. Under the right laboratory conditions, embryonic stem cells all have the ability to become any type of cell, so they are referred to as pluripotent stem cells.

Induced pluripotent stem cells (iPSC). In 2007, scientists figured out how to program skin cells and other cells to transform—in a sense, to move backward in time, so they could become pluripotent, much like embryonic stem cells. This means investigators now have a powerful research tool, a way to make the rough equivalent of human embryonic stem cells from skin and other cells without using embryos. These iPSC, like embryonic stem cells, have the capacity to become other kinds of cells (including brain cells) under the right conditions in the laboratory.

Mesenchymal stem cells (MSC). A fourth type of stem cell is commonly isolated from bone marrow, blood or fat cells. MSC have broader abilities, under the right laboratory conditions, to become cells normally found in very different types of tissue, such as bone, cartilage or fat. In some experimental circumstances, MSC also appear to be able to modify immune functions.

Stem cells in MS research

The entire field of stem cell research in MS is rapidly expanding in many different directions. Here are just a few of the promising new avenues and results.

1. Trying to reboot the immune system.
This method aims to use a **hematopoietic stem cell transplant (HSCT)** to replace cells in the bone marrow that give rise to circulating immune cells in the blood, in an effort to slow or stop MS.

Bone marrow, a spongy tissue deep inside some of our bones like the hip and thigh, contains special types of tissue-specific stem cells called **hematopoietic stem cells**. These stem cells differentiate to become key parts of our blood—red cells, platelets and white (immune) blood cells, all of which are continuously released into our bloodstream. A small number of the stem cells are also released into the bloodstream.

Stem cell clinics: What you need to know

As stem cell research progresses, people worldwide have become excited about the potential applications of stem cell therapy for treating MS and other disorders, and stem cell therapy clinics in the United States and around the world have proliferated.

However, despite claims, none of the clinics so far have provided medical evidence that their treatments work or are safe. In the field of MS, many experts have expressed concerns about these clinics.

In addition to the lack of clinical evidence of success, experts are concerned that in many countries, stem cell clinics are not held to strict sanitary guidelines and are allowed to operate without oversight related to the safety of their procedures. Also, the sources of the stem cells they use are not always made clear, nor are the procedures they use to derive the stem cells or ensure they are free from infectious agents. Find additional information on stem stem cell clinics and stem cell safety.

HSCT has been used successfully to treat diseases originating in bone marrow cells, like leukemia. Because immune cells form in bone marrow, HSCT research expanded to other diseases that involve problems with immune function, including MS. Many different approaches to HSCT have been developed. Some involve a milder form of immunosuppressive medication that leads to only a partial destruction (called **nonablative** treatment) of bone marrow, while others use stronger medications and completely wipe out the bone marrow (**ablative**). In both cases, stem cells are intravenously returned to the individual to reconstitute the bone marrow in an effort to “reboot” the immune system. In MS, the primary goal is to stop the attack on myelin.

As Dr. Bruce Bebo, executive vice president of research for the Society, points out, however:

“Published data suggest that this approach is most likely to work in people who have aggressive relapsing-remitting MS (RRMS). In contrast, there is a lack of good evidence that this approach will work in progressive MS. This might be because progressive MS is driven more by degeneration of nerve cells and fibers than by inflammation.”

One recently published clinical trial of HSCT in MS made international headlines. Drs. Mark Freedman and Harold Atkins, along with colleagues from The Ottawa Hospital and the University of Ottawa, conducted a phase 2 clinical trial in which they isolated stem cells originating in the bone marrow from the blood of 24 people with early, aggressive, relapsing MS. The individuals then received ablative treatment, followed by HSCT. Twenty-three of the participants had no clinical relapses and did not develop new brain lesions during their four- to 13-year follow-up, eliminating the need for additional MS medications. Seventy percent of the participants had a complete halt in disease progression, and 40 percent had some sustained improvement of symptoms such as vision loss, muscle weakness or balance issues. However, one person died from the procedure. These results were published in the June 9 issue of **The Lancet**.

“While these are very exciting results, it is important to emphasize that this was a small study in only 24 people who had very early and very aggressive disease. They had no other options for treatment,” says Dr. Freedman. All of the study participants had previously experienced disease progression despite having been treated with available MS disease-modifying therapies for at least a year, and they had very poor prognoses. Additional clinical trials are needed to identify the optimal approach and to clarify which individuals are the best candidates, Dr. Freedman adds.

“This is a very risky, very complex procedure” that should only be performed at highly specialized centers that have expertise both in HSCT and in the management of MS, and that have a very good track record for safety both during and after the transplant, Dr. Freedman emphasizes. He encourages individuals with questions about HSCT to talk with an experienced MS neurologist about whether they are appropriate candidates for this type of clinical trial.

Dr. Richard Burt, chief of the Division of Immunotherapy at Northwestern University’s Feinberg School of Medicine in Chicago, is testing HSCT in a randomized clinical trial of people with RRMS for whom first-line therapy was unsuccessful. His team’s approach does not ablate the bone marrow, but does “knock down” the immune system. The trial is enrolling only individuals with RRMS because the goal is to stop MS while it is in a primarily inflammatory stage. Repeated inflammatory attacks on myelin and nerve fibers are characteristic of active RRMS, but not as common in primary or secondary progressive MS. Dr. Burt has reported early data suggesting this approach may reverse disability and improve quality of life in these carefully selected individuals.

Dr. Bebo also stresses that there are many risks in HSCT, especially for developing dangerous, life-threatening infections when the first step—bone marrow ablation—destroys

the immune system. People who have undergone HSCT for any reason, including in research trials for MS, have also developed autoimmune thyroid diseases, he states, for reasons that aren't completely understood. The risk of developing other, more serious autoimmune diseases is also higher.

Dr. Bebo adds, "The findings from these preliminary trials are quite promising, but we need larger, placebo-controlled trials so we can clarify the benefits and risks and determine who is most likely to be the best candidate for this treatment." There is still insufficient evidence for how the HSCT approach compares to treatment with the more powerful disease-modifying therapies currently approved for MS.

2. Stem cells to promote repair.
Another aim of research in MS is to figure out how to use stem cells as tools to aid in the repair of damage that has already occurred to myelin. Here, the long-term goal is to isolate stem cells and convert them into specialized cells, then introduce the specialized cells back into the bloodstream or directly into the spinal fluid to stimulate repair of MS damage. It's still not known which, if any, stem cells may be valuable for promoting myelin repair, so research is ongoing using several different approaches. Researchers are also working on figuring out **how** transplanted cells may promote repair, with the goal of finding alternative approaches to stimulating the body's own repair cells.

Researchers continue to push the envelope when it comes to stem-cell therapies for MS. Some are looking into ways to transform stem cells "harvested" from people with MS into specialized cells that then could be re-injected to reverse the damage.

Dr. Saud Sadiq of the Tisch MS Research Center of New York has transplanted stem cells derived from bone marrow into people with progressive forms of MS. His laboratory created a specialized form of MSC, called MSC-neural progenitor cells, which can become certain types

of brain cells. Following positive results in mouse studies, Dr. Sadiq and his colleagues conducted a phase 1 clinical trial in 20 individuals with relatively stable progressive MS. Preliminary results, presented at the April 2016 meeting of the American Academy of Neurology, indicate some improvement in Expanded Disability Status Scale (EDSS) scores, upper extremity function and bladder function. Headache and fever were the most frequent side effects. Once the phase 1 trial is completed, Dr. Sadiq plans to advance this treatment to a larger phase 2 trial to further evaluate safety and efficacy.

Dr. Jeffrey Cohen of the Cleveland Clinic's Mellen Center for Multiple Sclerosis Treatment and Research conducted a phase 1 study to test whether infusing an individual's own mesenchymal stem cells could inhibit immune mechanisms and boost conditions that foster natural tissue repair in people with relapsing forms of MS. No serious safety concerns were reported, and he is planning a phase 2 trial to continue this research.

Dr. Marius Wernig of Stanford University is collaborating with Dr. David Rowitch of the University of California at San Francisco to devise new ways to generate oligodendrocyte precursor cells (OPCs) from human skin cells. OPCs are cells that become oligodendrocytes, the type of brain cell that makes myelin. They hope to do this either directly (that is, convert skin cells to OPCs) or in two steps, by first creating iPSCs from the skin cells and then converting those to OPCs.

While Dr. Wernig's stem cell research is at a more basic, preclinical stage, the hope is to someday take skin cells from a person with MS using a simple skin biopsy. The cells would be converted into oligodendrocytes and returned to that individual to repair damaged neurons without risking rejection as foreign cells. "In mice, OPCs transplant well when injected into the brain," Dr. Wernig explains. "They grow, make more copies of themselves and migrate very well throughout the brain. That's the hope in the human brain." However, he cautions that for MS, this approach would have to be combined with a treatment that modulates the immune system, because of the presumed immune attacks that would occur against newly formed myelin. Dr. Wernig is funded by the National MS Society with support from the National Stem Cell Foundation and the Donald C. McGraw Foundation.

Other researchers, such as Dr. Steven Goldman of the University of Rochester, are investigating more ways to transform stem cells "harvested" from people with MS into specialized cells that then could be re-injected to reverse the damage. Dr. Goldman is developing a collaborative network of scientists to focus on stem cell–derived approaches to generating OPCs for potential therapy for progressive forms of MS.

3. Stem cells for other MS research

Stem cells can also be a valuable tool for basic research to better understand the disease. Dr. Valentina Fossati, of The New York Stem Cell Foundation Research Institute, is a young researcher who turned her attention to MS when she developed the disease herself. Dr. Fossati received a National MS Society Pilot Research Award to create better model systems to improve basic research in MS. "Myelination is a complex, fascinating, dynamic process,

and there are likely some human-specific features," she says, pointing to failures in human trials of therapies for MS that appeared successful in mouse models.

Dr. Fossati has developed a unique way to take human skin cells, create iPSC, convert those into oligodendrocytes and, she hopes, use the oligodendrocytes as a better model for studying myelination in MS and evaluating potential MS stem cell therapies. Dr. Fossati wants to expand this approach to other brain cell types, such as neurons and astrocytes. A goal is to develop different types of cells from skin cells taken from people with various types and stages of MS. Dr. Fossati wants to grow these various cell types in individual cell culture dishes in the laboratory. She hopes this approach will enable researchers to test different therapeutic approaches in the different types and stages of the disease. "I think we are in the middle of a clear revolution in the MS field," she adds.

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Learn more about potential stem cell treatments for MS.