



National
Multiple Sclerosis
Society

Great Promise Seen for Cell Therapies for MS
-- Four-Day Stem Cell Research Summit Sets Next Steps

Introduction/Executive Summary

A four-day Stem Cell Research Summit convened by the National MS Society (USA) and the MS International Federation January 16-19, 2007 brought together leading stem cell and MS experts from around the world to explore the potential of all types of stem cell research for the treatment, prevention and cure of MS.

The Stem Cell Research Summit was organized at the recommendation of the National MS Society's Stem Cell Task Force, which met in 2005 to consider whether the Society should be taking actions to stimulate research in this area. Stem cells come from a variety of sources, and have varying degrees of "multipotency" – the ability to specialize into more than one kind of replacement cell.

Ms. Sarah Phillips, Chair of the MS International Federation described the unpredictable nature of MS, which she herself has struggled with for many years. MS is a chronic disease that attacks myelin in the brain and spinal cord, destroying this insulating material and also the wire-like nerve fibers or axons around which the myelin wraps. This tissue destruction results in impaired signals between the brain and the body.

While there are approved therapies that can reduce the immune attack in a proportion of patients, Ms. Phillips reminded attendees that there are no therapies that can stop the progression of MS or significantly restore neurological function.

In opening remarks, National MS Society President and CEO Joyce Nelson commented that while there has been a great deal of progress in MS research, "there are big questions still to be answered about multiple sclerosis and how we can speed the cure." She outlined the charge of the assembled experts: to map out research priorities and opportunities that will guide and propel MS research on a global scale.

How Do We Increase Tissue Repair in MS?

A segment of summit participants shared research results related to attempts to achieve nervous system repair in animal models through transplant therapy with many different types of cells, and on the use of stem cells for high-speed screening systems to identify new molecules that may target and stimulate tissue repair. Attendees pointed out that what is learned from stem cell studies may hold the key to finding ways to enhance the body's own repair mechanisms – a prospect that may be less invasive and more effective in the long run for treating the disease.

Other participants focused on the potential of various types of adult stem cells, including bone marrow cells and cells residing in the adult brain, to stop or to stimulate regeneration of tissues in MS. There were also presentations about the experimental treatment of other neurological disorders such as spinal cord injury and stroke.

The conference proved to be thought-provoking and exciting, stimulating debate on a host of issues surrounding the brain's intrinsic repair abilities and the potential and safety of transplanting a variety of cells to rescue nervous system tissues and stimulate recovery in MS.

Research Strategies Identified by Summit Participants

Outlined below are the strategic next steps recommended by the summit participants to help propel effective research in a deliberate and rational way to determine the potential of all types of stem cells for understanding and treating multiple sclerosis. The recommendations include:

- Develop tools to track in a non-invasive way the fate of transplanted cells, to see if they get to where they were needed, and to be able to detect them in places they don't belong;
- Develop sensitive, reliable methods of detecting success or failure of cell therapies;
- Do basic studies to understand how MS inflammation in the brain and spinal cord may interact in good and bad ways with transplanted cells;
- Develop consensus on guidelines that will help ensure that future clinical trials of cell therapies for MS are done safely and in ways that will yield definitive information about their success or failure;
- Develop better animal models of MS to enable better testing of cell-based therapies;
- Continue to support research using all types of stem cells because we don't know enough to determine which holds the most promise for treating MS;

- Gather as much data as possible on people with MS who have received cell-based therapies to see whether there are any lessons to be learned from these mostly uncontrolled treatments;
- Develop an international coalition to collect and bank adult brain tissues that have been surgically removed for other reasons and that may serve as sources of stem cells;
- The first proof-of-concept cell transplants to repair myelin may be better done in a disease such as transverse myelitis, in which the damaged area is discreet and it may be easier to detect a therapeutic effect.

Many participants stressed the importance of pursuing research in parallel and complementary areas: trying to stimulate the brain's own natural repair processes which appear to stall in MS; and exploring the feasibility of transplanting cells that may themselves repair and/or may jump-start nervous system repair processes.

Summarizing key take-home messages for participants of the Summit, William Hickey, MD (Dartmouth Medical School) noted that we actually have much, although by no means complete, information about stem cells of many types. "Are we at a tipping point where there is enough critical mass of information to seriously take steps needed to pursue cell-based therapies in MS? I think, based on what we've heard during this conference, the answer is yes."

Dr. Hickey noted that questionable and possibly unsafe cell-based therapies are proceeding in MS without sufficient safeguards. "We can either lead in the area of cell-based MS therapies or watch from the sidelines," he stated.

The National MS Society and MS International Federation have already begun discussions for the best ways to lead this exciting and promising work. Over the next weeks and months, we will take these recommendations and develop action steps for their implementation.

Details about Summit presentations are highlighted in the following pages.

Summary of Conference Discussions

During the first session, **Leslie P. Weiner, MD** (University of Southern California) pointed out some things that have to be achieved to take stem cells from the laboratory to the clinic. These include the need for an abundant, renewable source of appropriate stem cells; proving they are safe and don't cause problems in humans; cells that can survive and continue to facilitate repair over a long period of time; the engineering of cells that can deliver growth factors or block repair inhibitors; and having ways to trace the cells and detect repair in a non-invasive fashion.

Jack Antel, MD (Montreal Neurological Institute) encouraged attendees to think about stem cells – both those natural “spare parts” cells that reside in the brain, and those that might be introduced from outside via transplantation – in terms of disease characteristics of multiple sclerosis. For example, research suggests that natural tissue repair does occur in MS, and it is important to explore why it sometimes succeeds and at other times fails. The reasons this occurs should, he suggested, propel repair efforts.

Models for Testing Stem Cell Therapies

There was extensive research data presented about what has been learned from the experimental treatment of animal models of MS and other neurological disorders such as spinal cord injury and stroke.

► Recent studies by several teams, including those by National MS Society-funded **Gianvito Martino, MD** (San Raffaele Scientific Institute) and **Tamir Ben-Hur, MD, PhD** (Hadassah University Medical Center) in treating different forms of the MS-like animal model EAE, suggest that under some circumstances transplanted cells may not only replace and repair myelin, but also stimulate natural repair and provide growth factors and anti-inflammatory molecules that protect nerve fibers and myelin-making cells from damage.

Dr. Martino, one of several attendees collaborating on teams supported through the National MS Society's [Promise: 2010 targeted initiative on nervous system repair and protection](#), and colleagues have stimulated myelin growth and functional recovery in mice and other lab animals with EAE by injecting adult neural stem cells intravenously. Depending on the timing of the injections, these cells reach inflammatory areas of the brain and spinal cord and help turn off the immune attack while turning on tissue regeneration. “The therapeutic effect is quite astonishing,” he commented.

► [Jeffery Kocsis, PhD](#) heads a National MS Society Collaborative MS Research Center at Yale University. He described cell transplant attempts to treat myelin loss in animal models using three types of cells: Schwann cells (which make myelin in the peripheral nervous system), olfactory ensheathing cells (which make myelin for scent-detecting nerve cells and bridge both the peripheral and central nervous systems) and bone marrow (“mesenchymal stem cells”). His group has reported varying degrees of success using different routes of delivery, such as direct cell transplantation into the brain and intravenous (into the vein) injections.

They have found that transplantation of olfactory ensheathing cells can cause diffuse myelin repair, and that they create tunnels through which nerve fibers can grow. His and other teams have also shown that transplants can protect other cells from damage, probably by releasing factors that support cell survival.

► **Douglas Kerr, MD, PhD** (Johns Hopkins University) and **Hans Keirstead, PhD** (University of California at Irvine) separately described successful attempts using transplantation with stem cells to achieve partial repair of spinal cord injury and myelin repair in lab rodents, making the case that these trials have potential implications for MS.

Dr. Kerr described a disorder called transverse myelitis (TM), which in some ways resembles MS but involves a single episode of myelin and nerve fiber loss in an isolated site along the spinal cord, rather than the repeated and more widespread damage experienced by people with MS. He suggested that it might be easier to test early cell transplant techniques in TM patients than in the more diffuse damage of MS.

► Another cell transplantation approach was described by **Steve Goldman, MD, PhD** (University of Rochester), a presenter who collaborates on two Society-supported [Promise: 2010 targeted initiative on nervous system repair and protection](#) teams. His lab extracted and purified oligodendrocyte progenitor cells (which have potential to mature into myelin-making cells) from brain tissues that had been surgically removed from individuals with epilepsy and transplanted them into the brains of mice that do not normally produce myelin. They were able to show extensive myelin growth and partial recovery of function in many of the mice.

Interestingly, Dr. Goldman found that when these progenitor cells are in the brain, they only mature into oligodendrocytes or astrocytes (support cells). However, when they are placed in lab dishes, they can become a third type

of cell, neural cells, suggesting that they are not as restricted as previously thought, and that they mature according to the dictates of their environment.

► **Evan Snyder, MD, PhD** (Burnham Institute for Medical Research) described intriguing and somewhat unexpected results from cell transplantation experiments in a variety of animal models for different neurological diseases. His team has found that transplanted stem cells act not only as replacement cells, but in many other ways promote recovery by providing chemical signals, contact support, and in other ways enhance the rescue, support, protection, and anti-inflammatory environment helpful to endogenous cells and tissues.

► **William Blakemore, ScD** (University of Cambridge) and **Ian Duncan, BVMS, PhD** (University of Wisconsin-Madison) described studies with specific animal models that have provided valuable data about types of transplant cells that might be used to replace myelin damaged by MS. Dr. Blakemore showed that immature myelin-making cells can behave quite differently in the brain versus when they are in culture dishes. He and others commented that to propel myelin repair by transplanted cells, there needs to be active inflammation.

► **Dr. Duncan**, one of several presenters who are leading or collaborating on teams supported through the National MS Society's [Promise: 2010 targeted initiative on nervous system repair and protection](#), explained that various animal models, such as those with a mutation that makes them unable to produce myelin, can help investigators test modes of cell delivery, to visualize cell movement toward sites of injury, and to detect myelin repair and restoration of function before testing cell-based therapies in people.

► As **Celia Witten, MD, PhD** (U.S. Food and Drug Administration) pointed out, such studies in animal models, and as much as can be learned about mechanisms of action of cell-based therapies, are needed to show as well as possible that a proposed cell therapy will be safe in the people for whom it is intended, and also to better understand what the cells might do once they get in the body.

► One spinal cord injury expert attending was **Scott Whittemore, PhD** (Kentucky Spinal Cord Injury Research Center, University of Louisville). Spinal cord injury usually does not just damage nerve fibers, but also can cause myelin damage, leaving the axons that have been stripped of their protective coatings open to further injury. This kind of damage has some similarities to what is seen in MS.

His team has implanted various types of stem cells into the spinal cords of rodents, and found that they can sometimes generate scar-producing astrocytes, rather than the myelin-producing oligodendrocytes desired. Culturing the cells in a broth of specific growth factors can drive them more favorably toward repair, but he cautioned that for myelin repair strategies, “Stems cells are only one piece of a very complicated puzzle.”

► Reporting from his experience treating of experimental models of stroke with bone marrow mesenchymal cells, **Michael Chopp, PhD** (Henry Ford Health Sciences Center) suggested that these transplants do not directly cause any cell replacement or repair, but rather jump-start the brain’s recovery mechanisms in dramatic ways through their communication with brain cells and stimulation of molecular growth factors and the “spare part” adult stem cells residing there.

There is ongoing debate about the ability of transplanted cells to replace damaged cells versus improve the milieu to influence recovery. Research is underway to discover the array of molecules that are secreted by transplanted cells of various types and ones they in turn may stimulate in other cells within the brain.

Small Clinical Studies

► In light of their apparent ability to influence a wide range of events in the brain, **Neil Scolding, PhD** (University of Bristol) announced the start of a new, very small transplant study involving 5 individuals with multiple sclerosis to test the feasibility and safety of injecting the individuals’ own bone marrow cells intravenously. Many questions were asked by audience members in terms of how much will be learned from this trial and whether it was premature. Dr. Scolding pointed out that some questions can only be answered by doing clinical studies involving individuals with MS.

► One real-life application of stem cell therapy taking place right now is a brand new clinical trial of stem cell injections to treat a progressive, nerve-degenerating disease in children called Batten disease, which causes profound degeneration of brain cells. **Ann Tsukamoto, PhD** (StemCells, Inc.) described some of the extensive testing of the injected neural stem cells which had to take place to satisfy FDA guidelines. Ultimately their work led to a small safety trial involving six patients, with the first receiving the injections in November 2006.

In terms of the potential application of this treatment to people with MS, participants highlighted many questions that would need to be answered about their safety and potential effectiveness. To name one, it is not clear what would happen to these cells in the inflammatory environment of an MS central nervous system. Nevertheless, this Batten disease clinical trial is interesting as the first application of human stem cell therapy to a disease affecting the central nervous system.

► **Alan Mackay-Sim, PhD** (Griffith University, Australia) described a small clinical trial to treat spinal cord injury, in which a form of these olfactory ensheathing cells have been removed from a person's nostril, grown to large numbers in tissue culture, and injected into their spinal cords. Results of this three-year study may be available later in 2007.

New Frontiers for Drug Discovery

► National MS Society-funded investigator **Wendy B. Macklin, PhD** (Cleveland Clinic) presented results of ongoing studies that use mouse neural stem cells (capable of producing different types of brain cells) in lab dishes to screen small molecules for their repair potential. Out of 14,000 compounds screened in a matter of months, 13 appeared to drive the unspecialized cells toward becoming myelin-making cells.

Of those, three still seem promising after further investigations. Dr. Macklin explained that they are testing the promising compounds in a variety of ways to determine if they have potential for stimulating repair pertinent to MS damage.

► Along a similar vein, **Sheng Ding, PhD** (Scripps Research Institute) has been using a "high-throughput" system to detect molecules that control the fate of stem cells and determine how specialized they become. They can use this system to study how these cells are influenced, and what molecules can influence them to become particular types of repair cells.

Identifying "Spare Parts" in the Brain and Other Sources

Several presenters discussed the presence of a variety of cells within or in proximity to the brain that appear capable of having potential for nerve and/or myelin repair. **Arturo Alvarez-Buylla, PhD** (University of California, San Francisco) described his team's elegant work in tracing classes of brain cells from their early development through their eventual fate as resident adult stem cells in the brain, some of which serve as spare

parts for the nerve cells and myelin-making cells (oligodendrocytes) of interest in the context of MS.

► National MS Society grantee **Paula Dore-Duffy, PhD** (Wayne State University) described her team's work with cells called pericytes, which wrap around blood vessels, including capillaries in the adult brain. These cells respond to injury by migrating to areas of damage, and her team has been investigating whether they have broad, stem cell-like capabilities for serving as regenerative cells in the brain.

► **Bruce D. Trapp, PhD**, who heads a National MS Society [Collaborative MS Research Center](#) at the Cleveland Clinic, reported on a previously undiscovered cell in the brain that occurs in increased numbers at the borders of MS brain lesions (sites of disease activity or damage). This cell shows characteristics of being a multipotent stem cell.

Under some conditions, the cell appears capable of transforming into at least three types of brain cells, including neurons, oligodendrocytes and astrocytes. Dr. Trapp's team is working to understand more about this cell, including its potential as a target for stimulating repair in MS.

► Research to understand and exploit the body's natural ability to repair itself using stem cells residing in the brain were described by **Anne Barron-van Evercooren, PhD** (INSERM) and others. Her team has examined natural repair cells, called endogenous stem cells, within MS lesions (sites of damage or disease activity) and within specific areas of the brain where they are known to reside. Contrary to prior suggestions, her team found that the MS disease process does not necessarily destroy endogenous stem cells in the subventricular zone of the brain. In fact, her research shows that new cells with potential for maturing into myelin-making oligodendrocytes proliferate within this zone in people with MS. Dr. Barron-van Evercooren and other presenters also showed that endogenous stem cells indeed travel to MS lesions as if to commence repair, but for reasons still unexplained, often fail to mature into myelin-producing cells.

► **Charles ffrench-Constant, MD, PhD** (Cambridge University), one of several presenters who are leading or collaborating on teams supported through the National MS Society's [Promise: 2010 targeted initiative on nervous system repair and protection](#), echoed these findings. He showed evidence that oligodendrocyte precursor cells can fail to complete the process of myelin repair in MS.

“This is a process we need to understand better if we are going to promote remyelination in MS,” he commented. Dr. ffrench-Constant outlined efforts to pinpoint factors that promote the wrapping of myelin sheaths around wire-like nerve fibers. One type of factor that appears necessary for myelination is a family of proteins called integrins, which are present on nerve fibers. Factors that either promote myelin growth like integrins, or others that may block inhibitors of repair, may serve as potential therapeutic targets in MS.

► **Irving Weissman, MD, PhD** (Stanford University's Institute of Stem Cell Biology and Regenerative Medicine) attempted to debunk some current claims by stating that blood stem cells derived from the bone marrow (hematopoietic stem cells) have not yet been proven capable of becoming nerve or other brain cells. As an expert in bone marrow transplantation, he suggested that lessons learned from this area of medicine can inform the more nascent field of nerve-related stem cell transplantation.

Dr. Weissman also made the point that the body “knows what to do with stem cells” -- such that in certain animal models and conditions, when fairly unspecialized brain stem cells are transplanted into the brain, they differentiate or specialize into several types of brain cells appropriate to their location.

► Among those presenting on embryonic stem cells were **Mahendra Rao, PhD** (Invitrogen Corporation) and **Su-Chun Zhang, MD, PhD** (University of Wisconsin-Madison). Dr. Rao pointed out that at present, adult stem cells are not sufficiently self-renewing and so they cannot multiply in adequate numbers to be practical for use in cell transplant therapies that may be attempted in the future. Investigators described the trial and error of teasing out ways to drive unspecialized stem cells into the more specialized cell types, such as nervous-system cells that would be needed to repair myelin or nerve cells damaged in MS. Progress has been made in defining and purifying the culture media -- the nutrient and growth factor-laced broth in which these cells thrive and self-renew, an important step if these or similar cells are to achieve standards for their clinical use.

Next Steps

As described in detail above, summit participants recommended research strategies and priorities that will help drive this work forward to determine its potential for understanding and treating MS. These priorities and opportunities should guide and propel MS research on a global scale.