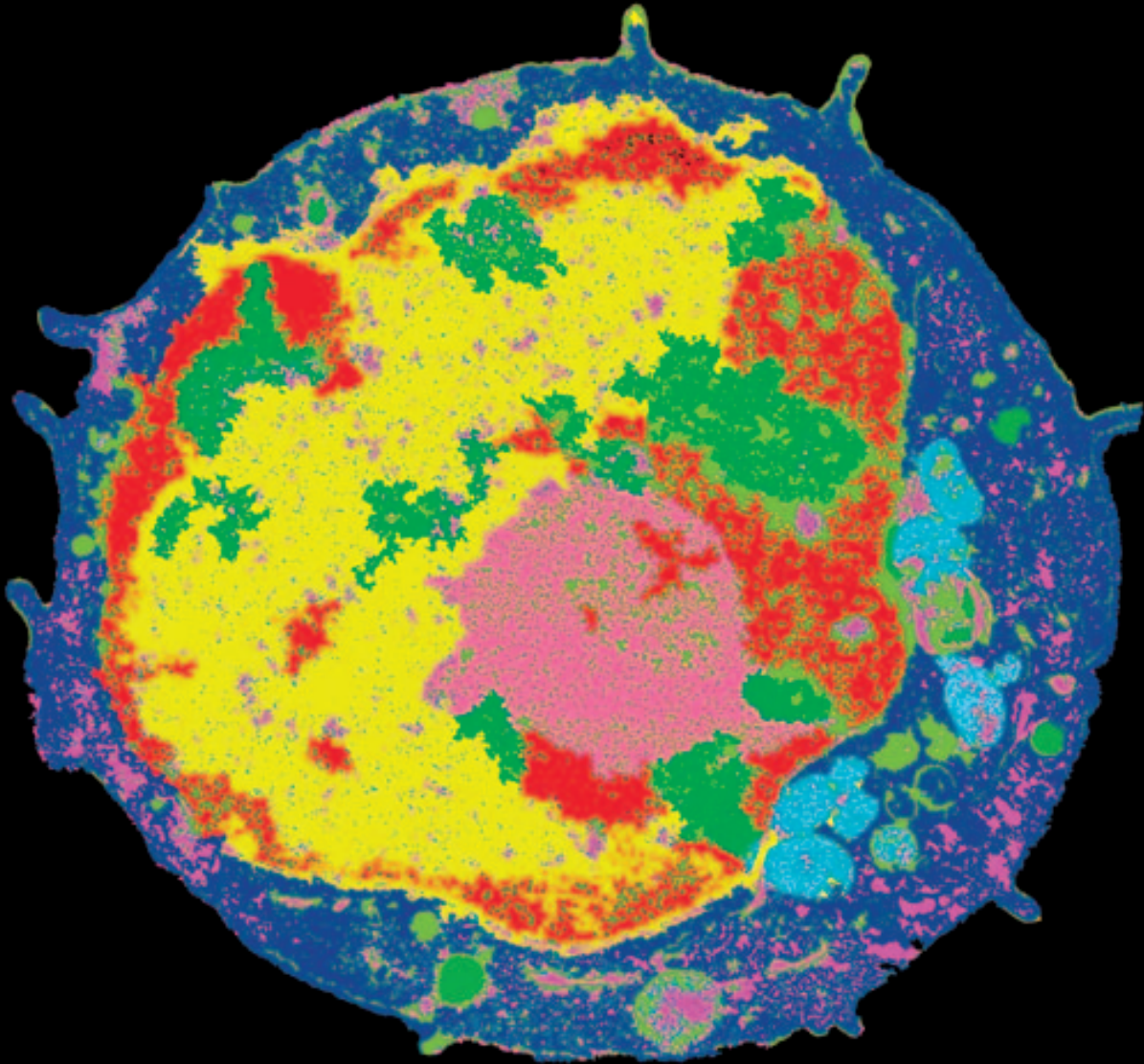


MS *in focus*

Issue 11 • 2008

● Stem cells and Remyelination in MS



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international federation

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Multiple Sclerosis International Federation (MSIF)

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- Communicate knowledge, experience and information about MS
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- Stimulate research into the understanding, treatment and cure of MS

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Cover image: Coloured transmission electron micrograph (TEM) of a section through a stem cell. Illustration copyright © DR GOPAL MURTI / SCIENCE PHOTO LIBRARY

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Letter from the Editor



There has been much controversy in the press recently about the pros and cons of stem cell research. Because the media plays such a prominent role in conveying reports on current advances, the debate about stem cells is often based on a lack of accurate and unbiased information.

Stories of miraculous recovery from MS are familiar to everyone. Stem cell therapies that are not exposed to scientific scrutiny and that prey on people's often desperate search for a cure, are dangerous and unethical.

Research "news" presents us with prospects that require us to improve our understanding of the latest direction the research is guiding us into, with each fact demanding further examination and scrutiny.

This issue of *MS in focus* on stem cells and remyelination in MS comes at a time when the MS community is full of hope and purpose, and some uncertainty as well. Understanding research involving stem cells is complicated. In this issue of *MS in focus* we have brought together leading scientists who present a comprehensible picture of what is known about stem cells at this time, and of where the efforts of scientists around the world are focused. Our hope is that the content of this issue will provide readers with a better understanding of how progress in research is bringing us closer to new therapeutic strategies for people with MS.

We hope this issue helps readers understand the immense effort involved in stem cell research, in terms of standards of excellence, scientific rigour, quality control, monitoring and reporting; standards that are indispensable if stem cell therapy is ever to become a real choice for helping people with MS.

On behalf of the Editorial Board, I would like to thank Dr Gianvito Martino for his assistance in bringing together the authors of issue 11 and for his help in ensuring that the content covers the most relevant issues in stem cell research in MS.

I look forward to receiving your comments.

Michele Messmer Uccelli, Editor

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We have provided a glossary on page 27 to help readers to understand this complex topic.

The next issue of *MS in focus* will be on Spasticity. Please send questions and letters to michele@aism.it or marked for the attention of Michele Messmer Uccelli at the Italian MS Society, Via Operai 40, Genoa, Italy 16149.

Editorial statement

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Stem cells: understanding

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Montreal Neurological Institute & Hospital,
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Multiple sclerosis (MS) is most frequently characterised by a relapsing remitting clinical course in which the affected individual develops one or more neurologic deficits which then resolve partially or completely over subsequent days or weeks. These relapses reflect the development of new lesions within the central nervous system (CNS) as visualised by magnetic resonance imaging (MRI). Such lesions, when examined in the laboratory, feature inflammation, myelin destruction, and a variable extent of injury to the underlying axons.

A further concern is that the persistent absence of myelin contributes to the ongoing loss of axons, the apparent basis for the progressive nature of MS in some cases. Persistent loss of myelin can make axons more vulnerable to repeated injury, induce axons to make compensatory changes in their properties (changes ion channel expression) that can result in further delayed insults to the axon and remove the supportive factors required for long-term axonal survival. This issue of *MS in focus* concentrates on whether stem cell treatment can repair or replace the damaged myelin as a means to restore effective electrical conduction in the CNS and thus result in the recovery of neurologic function.

What are stem cells and what do they do?

Stem cells, and certain types of “progenitor cells”, are classically defined as cells that are self-renewing (can divide and produce more of themselves) and that can differentiate into a mature cell type with the properties of cells that comprise specific organs. The initial stem cells are those which are the product of the first cell

divisions following ovum (egg) fertilisation, known as conception. Such cells have the capacity to differentiate into all the various cell types that comprise the body and are referred to as pluripotent stem cells.

During this process of differentiation, there are cells that still retain a capacity to self-renew but have more restrictive potential regarding differentiation; for example, they are more limited as to what cell types they may produce. The articles in this issue will discuss specific stem cell types. Stem cells that reside within the CNS and that can develop into neural cells are referred to as neural stem or progenitor cells. Some can produce all types of neural cells whereas others appear to be more restricted, including those that can only develop into myelin-forming cells (myelin or oligodendrocyte progenitor cells). Every cell in the body is created with specialised proteins, or receptors, and each cell has a specific combination of receptors. Scientists have used this biological uniqueness of stem cell receptors to tag or mark cells. As discussed in individual articles, these cell types can be identified by their expression of specific cell markers that correlate with their state of maturation and/or expression of gene products that regulate their responses to environmental signals.

Why might stem cells have a role in MS?

Histologic and MRI studies both indicate that remyelination can occur in MS lesions. The extent of such remyelination varies between lesions. There are a number of models of MS in animals in which the experimental demyelination induced by toxins or virus/immune mechanisms is subsequently almost completely repaired. In these models the

*Persistent loss of myelin
can make axons more
vulnerable to repeated injury.*

their role in treating MS

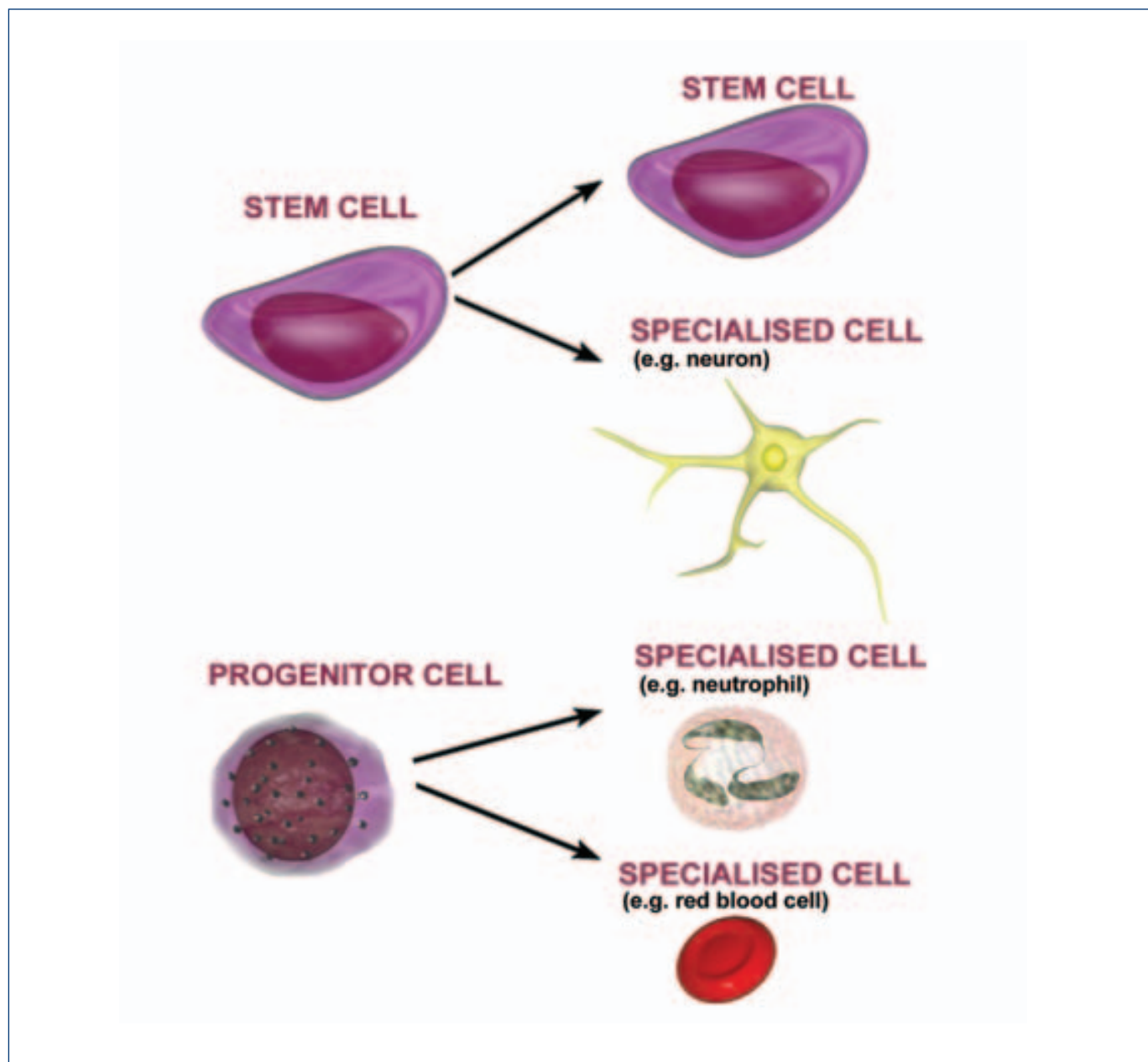
remyelination is carried out not by the cells (oligodendrocytes) which initially made the myelin but by immature progenitor cells or stem cells. These cells move to the site of injury (where demyelination has occurred) and develop into myelin-producing cells. Such cells can be identified in various sites in the adult human CNS including in regions surrounding MS lesions.

What do we need to know about stem cells in MS?

A central challenge for MS research is to define what limits the capacity of progenitor cells to repair the lesions in MS. Considerations include:

- numbers of progenitor cells available
- whether the progenitors that are present are in some way defective

Stem cells have the capacity to differentiate into all the various cell types that comprise the body.



- whether there are deficiencies in signals needed to recruit such cells to the lesions and to stimulate them to mature into myelin-forming cells or, conversely, whether actual signals in the CNS environment inhibit such responses from occurring. Is repair limited by the extent of damage to the underlying axons?

A theme of this edition of *MS in focus* is to outline the approaches that are being used to understand the make-up of progenitor or stem cells.

Translating stem cell biology into MS remyelination therapy

The current issue will present specific perspectives on the biology and potential clinical therapeutic use of an array of stem cell populations. Stem cell populations that are not normally present in the CNS must be delivered to the CNS (exogenous repair) and then induce them to directly participate

in the actual repair process. For stem cells residing within the CNS the potential exists to promote endogenous (within the body) repair, for example the use of biologic or pharmaceutical agents that can cross the blood brain barrier to amplify cell numbers and promote their development into useful myelin-producing cells.

The future for stem cell technology and MS

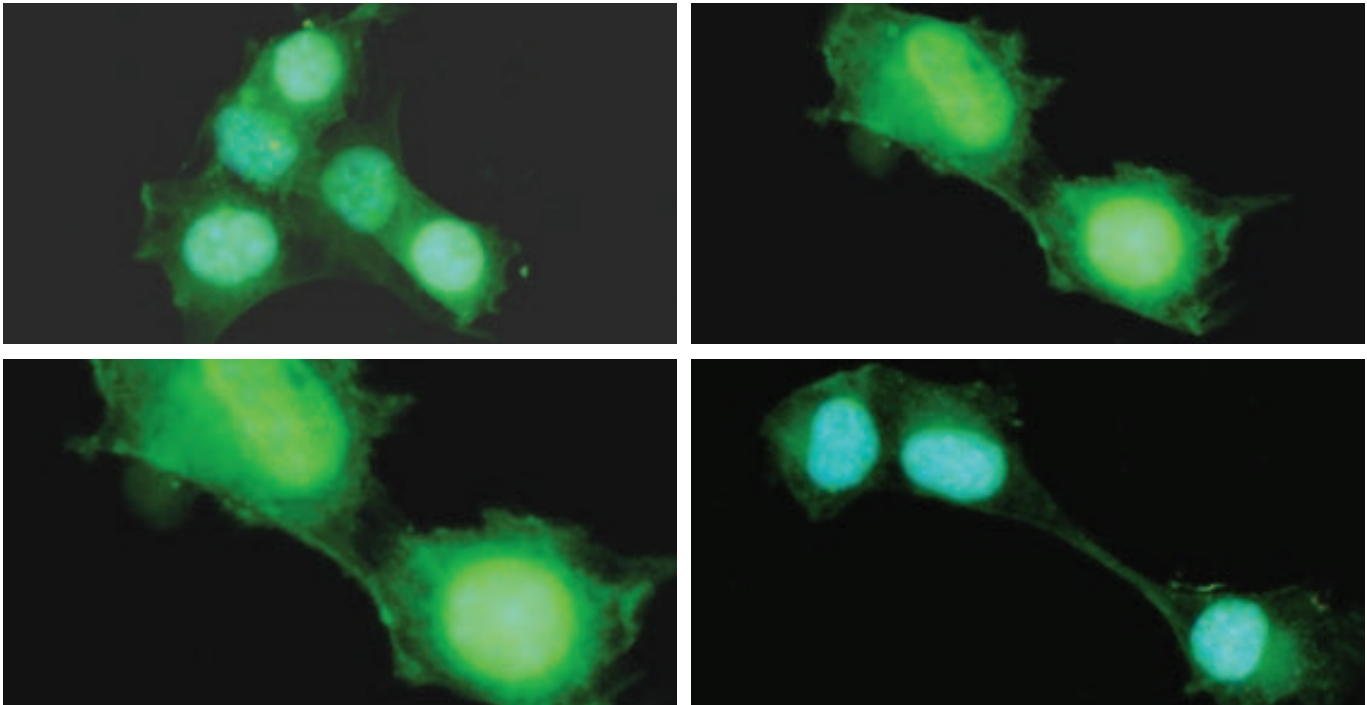
This issue of *MS in focus* will discuss how advances in understanding stem cell biology could lead us towards potentially using stem cell therapy for MS, specifically through combining insights into the pathological features of MS lesions, therapies to control the immune-mediated injury phase of MS, and MRI to dynamically monitor the MS disease process. The stronger the foundation of knowledge, the more likely it is that this “new biology” will translate into rational, safe and effective therapy.



Illustration copyright © Peter J. Darlington PhD, 2007

The challenge of repairing the CNS in MS.

Mesenchymal stem cells: promises and reality



Fluorescent murine mesenchymal stem cells in culture transfected (modified) with a green fluorescent protein.

Antonio Uccelli, MD, Neuroimmunology Unit, Department of Neurosciences, Ophthalmology and Genetics, University of Genoa, Genoa, Italy

Stem cells are heterogeneous cell populations, meaning they have various and different properties rather than being alike. They are often mistakenly considered capable of repairing almost every tissue, because of their capacity to differentiate into cells of every tissue type. Based on these expectations, stem cells have been proposed as a source of cells for tissue repair in different areas of regenerative medicine, including neurology.

T and B cells are elements of the body's immune system, also known as lymphocytes. Both types of

cells perform a role when the body is under attack: B cells produce antibodies and T cells mobilise other cells as part of the immune response. In MS the body orchestrates a faulty immune response. Autoreactive T and B cells in the CNS recognise the body's own myelin antigens as foreign bodies, attacking and destroying the myelin. Breakdown of myelin (demyelination) leads to impairment of nerve conduction and, in the long run, neuronal damage, the biological basis of irreversible disability. The ideal treatment for MS should therefore target the autoreactive cells, protect the assaulted CNS tissue and promote its repair.

Recent studies conducted in experimental autoimmune encephalomyelitis (EAE), the animal disease that resembles MS, have demonstrated that mesenchymal stem cells (MSCs) may be able to achieve some of these goals.

MSCs were first characterised in the bone marrow where they form cellular components in the blood through closely interacting with haematopoietic stem cells (HSCs). The natural pathway of MSCs is differentiation toward tissues such as bone, joint, fat, muscle and tendons, referred to as mesodermal tissues. Based on their natural tendency, MSCs might be better considered as multipotent precursor cells of mesodermal tissues, rather than true stem cells. However, under specific experimental conditions, MSCs have the ability to differentiate into other cell types including neural cells. More recently, studies have demonstrated that MSCs can affect many functions of cells of the immune system including activated T and B cells. In the presence of MSCs, lymphocytes and other immune cells do not increase in number and cannot produce the inflammatory cytokines – signallers of the faulty immune attack. Based on the capacity of MSCs to adjust the immune response and their apparent ability to differentiate into neural cells, MSCs were tested as treatment of EAE. Intravenous injection of MSCs in mice with EAE led to a striking improvement in the clinical course of the disease and reduced inflammation and demyelination. This beneficial effect was obtained when the mice were treated early after disease onset and was associated with moderating the T and B cell response against myelin antigens detected in the lymph nodes, suggesting the possibility that MSCs may be able to modulate the autoimmune attack against myelin. In contrast, clinical improvement was not seen in mice treated after the disease had reached the chronic phase. Injected MSCs could be detected inside the inflamed CNS, but without any significant evidence of them changing into neural cells. However, less axonal loss associated with an increased number of neurons in the inflamed

areas of the CNS was observed. A protective effect on neurons and other cell types exposed to inflammatory and other toxic threats has also been demonstrated in a controlled environment (*in vitro*) and in animal experiments, suggesting that MSCs could foster the survival of injured or dying cells in a living organism (*in vivo*).

As MS is a disease where neural degeneration follows CNS inflammation and demyelination, these results suggest MSCs could be a potential treatment for MS. However, there is no evidence so far that MSCs could become an effective therapy for patients with severe disability due to chronic and irreversible neural loss. In this situation it is not known whether MSCs, or any adult stem cell, could regenerate the complex neural network needed to recover from severe impairment. Current experimental evidence indicates that this possibility is, unfortunately, unlikely.

Despite these concerns, the use of MSCs for the treatment of MS is possible and not some futuristic concept. Indeed, MSCs have been obtained for clinical purposes through bone biopsy or through aspirating fatty tissue. Although the long-term safety of injected MSCs is still unknown, they have been used to foster the development of blood cells (haematopoiesis) upon bone marrow transplantation from a non-compatible donor (a donor with a different blood type than the recipient) and as therapy for the treatment of a limited number of acute diseases including heart failure and graft-versus-host-disease (GVHD).

Thus, based on data from animals with EAE and clinical experience gained from other diseases, MSCs may represent a future therapy for the treatment of people with rapidly worsening MS, in whom currently available therapies are not effective. Future studies must verify MSCs' capacity to differentiate into neural cells *in vivo* and possibly the promotion of endogenous recovery by local neural precursor cells, which support axons and produce the myelin sheath, thus providing hope for tissue repair and regeneration.

Neural stem cells for myelin repair in MS

Gianvito Martino MD, Department of Neurology and Neurophysiology, San Raffaele Scientific Institute, Milan, Italy

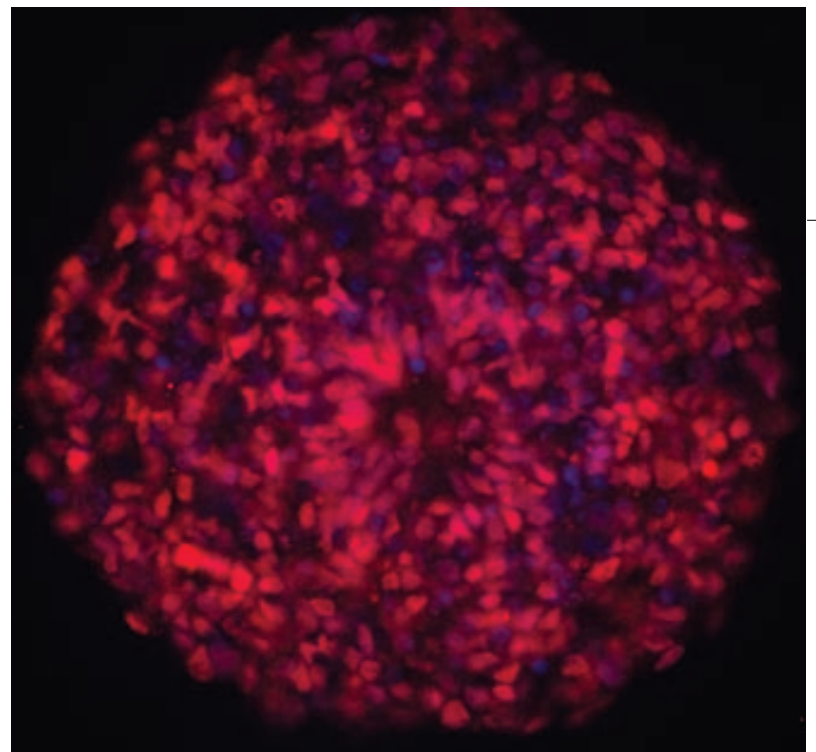
What are neural stem cells?

The very first indication of the existence of stem cells dates back to the end of the 19th century. At that time, scientists were able to hypothesise that stem cells were present in both embryos and in the blood. Nevertheless, the notion that stem cells were present in the mature brain was neglected until the early 1960s when new neurons generated from a population of dividing cells, thereafter named neural stem/progenitor cells (NPCs), were first observed. Further studies conducted through the early 1980s demonstrated that NPCs were self-renewing cells capable of giving rise to a limited number of multipotent cell types in a laboratory environment, owing to their capability to alter into the three main cell types of the nervous system: neurons, astrocytes and oligodendrocytes.

Since the identification of NPCs, protocols aimed at obtaining large numbers of NPCs *in vitro* have been successfully established. These harvesting protocols support the concept that these cells might represent a source of ready-to-use cells for transplantation purposes in virtually any CNS disorder including myelin disorders such as MS.

Neural stem cell therapy in MS – where are we and where are we headed?

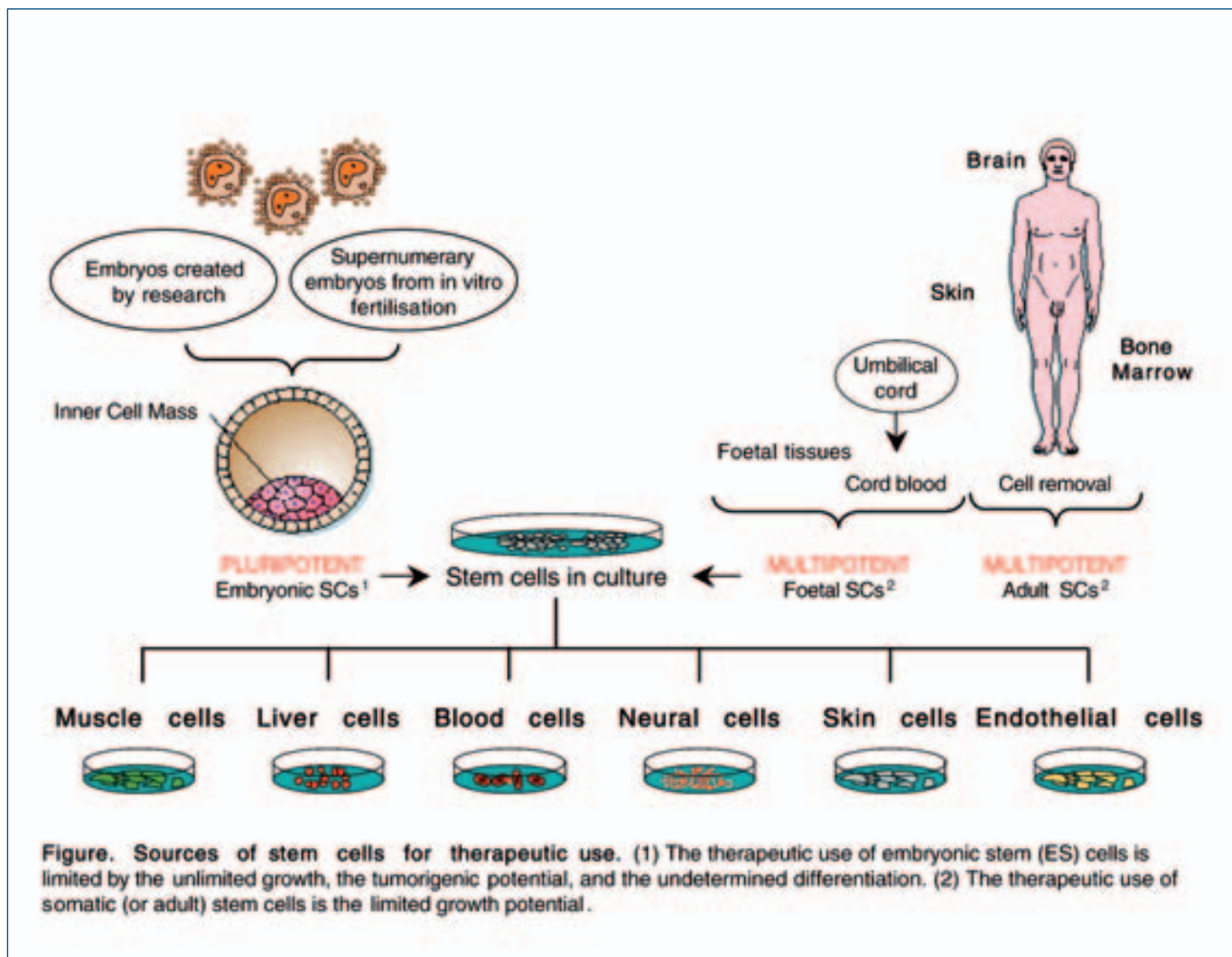
Encouraging preliminary results have been obtained by transplanting NPCs into rodents affected by EAE,



Neural progenitor cells might represent the ideal cell source for cell-based therapies in myelin disorders.

the experimental model of MS. However, there are still some issues we need to consider before any potential application of such therapies in people with MS:

- the ideal stem cell source for transplantation
- the route of cell administration
- the integration of the transplanted cells into the targeted tissue.



Since the identification of NPCs, protocols aimed at obtaining large numbers of NPCs in vitro have been established.

Stem cell source

Both embryonic stem cells (ES) and NPCs might represent the ideal cell source for cell-based therapies in myelin disorders. These cells are able to differentiate into myelin-forming cells and re-ensheath, *in vivo*, demyelinated nerves when transplanted in animals with EAE. But each of these potential sources has complications. Ethical issues are not the only cause for concern surrounding ES. Further studies have shown that the cells have a tendency to form tumours once transplanted. The use of NPCs is complicated by the difficulty in obtaining these cells for transplant to the person with MS without rejection. So far, the only available and reliable source of NPCs is from a human foetus but this renders the transplantation procedure difficult

because the recipient would need chronic immunosuppression, to avoid complications caused by the incompatibility between the donor's cells and the recipient's cells.

Route of cell administration

The route of cell administration represents another key issue for stem cell transplantation. While direct cell transplantation into lesions can be instrumental in CNS disorders characterised by a single, well-identifiable area of damage, such as in Parkinson's disease or a spinal cord injury, alternative approaches have to be established in a disease like MS where multiple areas of damage are a typical feature. Multiple cell injections into the brain are unrealistic. Some recent experiments have partially overcome this

latter limitation. In animal models of MS, it has been shown that NPCs may reach the most areas of myelin damage when injected intravenously (IV) or into the cerebrospinal fluid (IC) circulation.

Cell integration

Three steps are necessary to lead to a permanent restoration of nerve conduction. Transplanted NPCs should integrate into areas of myelin damage, differentiate into myelin-forming cells and re-ensheath the damaged nerves with newly formed myelin. NPCs can differentiate into myelin-forming cells once transplanted *in vivo*, but their capacity to reconstruct the actual complex brain architecture and to give rise to properly operating cells capable of long-lasting functional integration into the brain circuits still remains unproven.

On the other hand, recent data in animals with EAE suggests that NPCs may still be effective via therapeutic mechanisms. IV and IC injection of NPCs has been shown to prevent myelin damage by exerting a potent anti-inflammatory activity leading to the death of the blood-borne inflammatory cells invading the CNS and damaging the myelin sheath. This therapeutic effect – which prevents secondary neurodegeneration and irreversible neurological impairment – does not rely on NPCs' ability to differentiate into myelin-forming cells. The effect is exerted mainly by NPCs that have not differentiated. Actually, the study showed that less than 5-10 percent of the transplanted NPCs differentiated into myelin-forming cells in the rodents with EAE that benefited from cell transplantation.

How scientists are using stem cells to understand MS

Since NPCs residing in the adult brain are considered to be self-renewing, multipotent cells capable of repairing brain lesions, it is not clear why such cells fail to promote stable remyelination in MS spontaneously over time. Preliminary experimental and human studies in

MS indicate that the inflammatory process leading to myelin damage might also cause selective damage to endogenous NPCs, or NPCs already present in the organism itself. The most striking evidence supporting this hypothesis is that the vast majority of brain lesions irreversibly progressing in MS are located within the periventricular area, the very same area where NPCs accumulate during adulthood. Thus, NPC damage can be, at least in part, responsible for the failure of remyelination in people with MS. Understanding the interactions between cells and how the interactions are regulated might lead to therapeutic strategies aimed at re-establishing NPCs' capacity to spontaneously regenerate in MS.

Safe and controlled development will have a profound impact.

The future of stem cell research

Before conducting small, phase I, safety trials using NPCs in MS, the scientific community would need to agree on important preliminaries such as:

- the establishment of common patient enrolment criteria and outcome measures (to compare results, etc)
- the establishment of a common registry of transplanted patients
- the development of reproducible and traceable procedures for stem cell production (source of the cells, traceability of the donor, etc).

The future of this research also depends upon the development of biomarkers, which are molecules that allow for the detection and isolation of a particular cell type, and of MRI techniques aimed at assessing efficacy/toxicity of transplanted cells. Although it will take years before neural stem cell therapy will become a routine therapy in MS, its safe and controlled development will certainly have a profound impact on the therapeutic options for this disease.

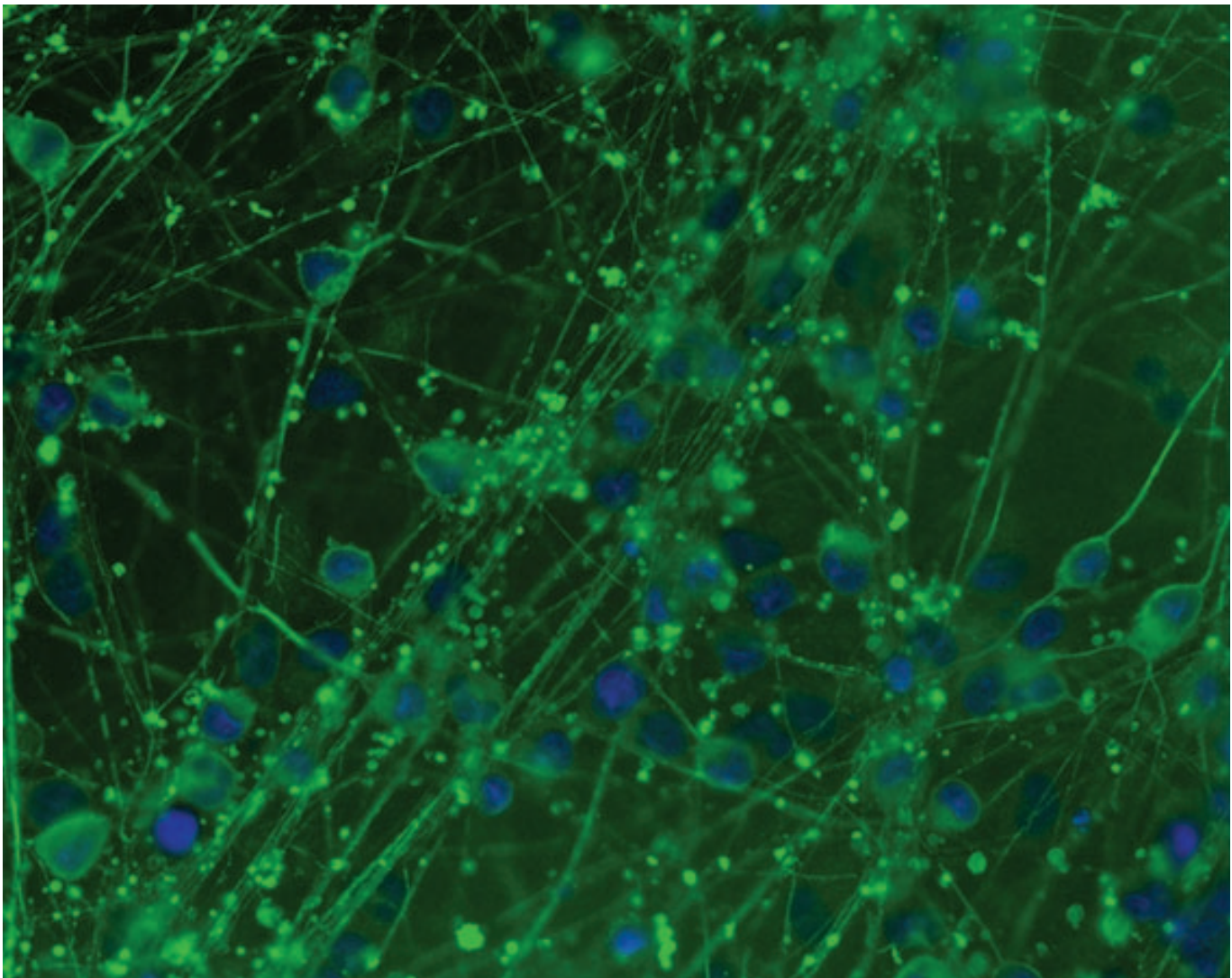
Human embryo

an experimental and therapeutic resource?

Siddharthan Chandran, MRCP, PhD, Department of Clinical Neurosciences,
Centre for Brain Repair, University of Cambridge, Cambridge, UK

The last decade has witnessed an unprecedented explosion of interest in stem cells in general and human embryonic stem (ES) cells in particular. It

has excited at turns both hope and fear in a wide range of groups, from the familiar stakeholders through to policy makers and ethicists.



ES cells can generate a virtually unlimited supply of nerve cells (above) as an experimental and drug discovery tool.

Conic stem cells:

ES – the ultimate repair kit?

Most stem cells are restricted to making cells that belong to their tissue of origin. For example, nerve stem cells will make nerve cells. Human embryonic stem cells (ES) can make all the cell types (over 200) that make up an individual. The twin property of being self-renewing and pluripotent (unrestricted specialisation) means that ES may prove to be the ultimate body repair kit.

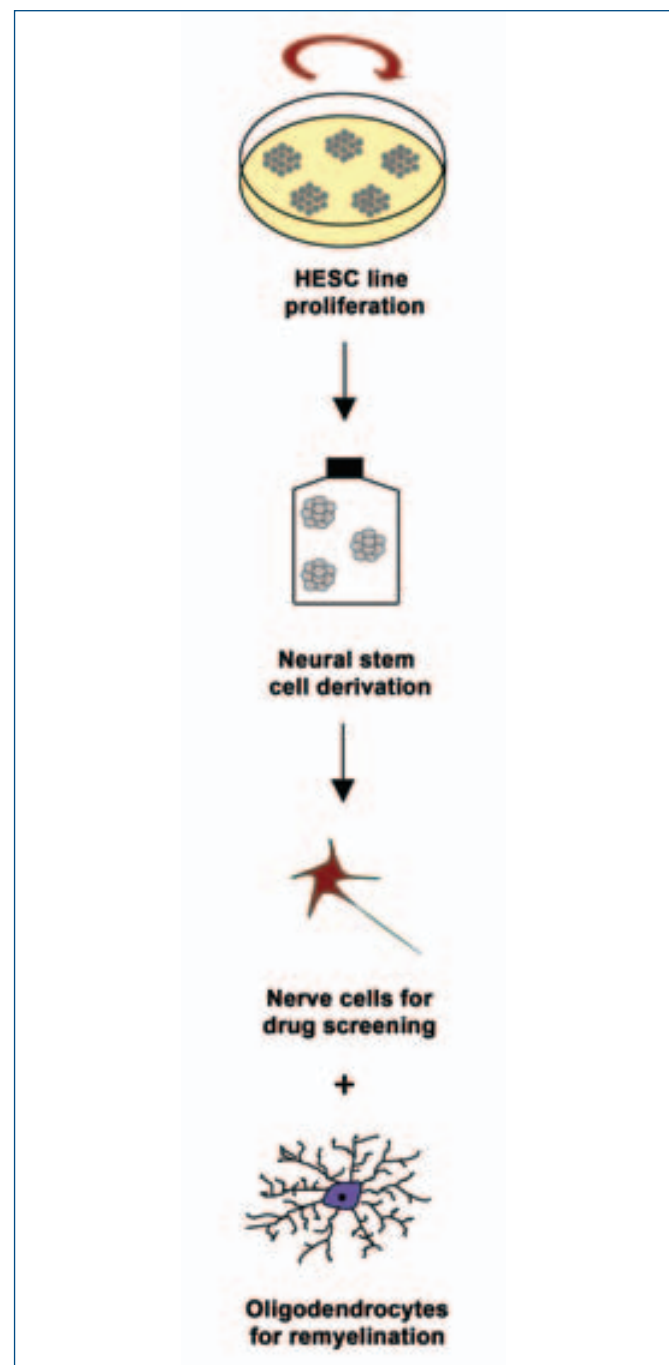
Where are they from?

ES are stem cells removed from embryos (four to five days old) obtained from fertility clinics. These embryos were fertilised outside the body (*in vitro*) and are donated for research under informed consent. The removed cells are then grown on a layer of feeder cells in the presence of specialised medium-containing nutrients (cell culture). Over time the ES will proliferate and out-grow the starting dish and be reseeded onto several further dishes. The process will eventually result in the generation of many millions of ES, all from just a few starting ES.

How can ES help scientists understand MS?

MS treatments have two aims: to prevent and to repair damage. Despite important advances in treatments (disease-modifying medications) that reduce relapse rate and some emerging evidence that early treatment may limit disability, no meaningful therapies are available to prevent or repair fixed disability.

Therapy development requires an improved understanding of the nature of disease



Until the advent of ES the possibility of widespread study of human cells was simply not possible.

evolution and the failure of recovery. Currently we use many animal-based systems to learn about MS. Although immensely valuable, there remains a great need to be able to study human cells. Until the advent of ES the possibility of widespread study of human cells was simply not possible.

Stem cells could enable remyelination by acting as a cellular reservoir.

An invaluable research resource for MS researchers would be access to unlimited numbers of human nerve cells and oligodendrocytes. ES make this feasible. In order to fulfil this possibility, scientists have first to understand the process or signals that direct an ES to become a nerve stem cell and then a nerve cell or oligodendrocyte. Much research focuses on this and borrows heavily on insights gained from studies of developing animals. Once understood, these chemical signals can be applied under controlled conditions to drive ES to become nerve stem cells, neurons or oligodendrocyte cells exclusively.

If unlimited numbers of human nerve and oligodendrocyte cells were available, important questions could be addressed. For example, knowing more about the chemical signals between nerve cells and oligodendrocytes and how this language is disrupted in MS. Such knowledge may lead to therapies to restore the correct cellular dialogue in people with MS, thus promoting repair. The pharmaceutical industry is particularly interested in ES for this reason. An ample supply of human cells would provide a unique opportunity to test and discover new drugs.

Is there a role for cells made from ES to be used in MS?

It is incontrovertible that ES can generate a virtually unlimited supply of nerve cells as an experimental and drug discovery tool. It is less

certain that ES have a role in cell-based therapies.

The damaged nervous system in people with MS can self-repair. Endogenous repair occurs when oligodendrocyte cells lay down new insulation around damaged nerves and thus effectively provide a protective “plaster” known as remyelination. Unfortunately in MS such repair is limited and inadequate. Stem cells could enable remyelination by either acting as a cellular reservoir of supportive factors that limit damage and/or enable endogenous remyelination. In addition, stem cell-derived cells, specifically oligodendrocytes, may be used to directly repair areas of injury. Animal models of MS support such an idea. However, given the fact that MS lesions can appear in diverse locations within the CNS, the method of administering such remyelinating cells has been a conceptual obstacle. Recent findings do provide some hope that intravenous delivery of nerve stem cells will allow distribution of cells to widespread areas of injury, an idea known as “homing”. However, there remain important issues to be overcome before stem cells can be considered for clinical trial. These include the development of clinically compatible ES and methods to ensure the exclusion of “contaminant” ES from “therapeutic” nerve stem cell preparations.

The method of administering remyelinating cells has been a conceptual obstacle.

Conclusion

The science of ES is rapidly growing. The provision of unlimited numbers of human nerve cells for experimental study will accelerate our understanding and thus development of new therapies for MS. Together this provides the basis for cautious optimism that meaningful therapies can emerge from ES.

Haematopoietic stem cell therapy:

can we repair the immune system in MS?

Paolo A Muraro, MD, Department of Cellular and Molecular Neuroscience, Imperial College, London, UK

Haematopoietic stem cells (HSCs) are the “seeds” of the cells that constitute our blood and immune system. In adult humans, the home of these progenitor cells is the bone marrow, a complex soft tissue that occupies hollow spaces inside bones, particularly large, flat bones. Throughout the span of our life, a large number of HSCs continuously differentiate in order to fill up the blood and lymphoid organs with mature cells and replace the cells that reach the end of their useful life or are otherwise eliminated or lost. Thus, HSCs are essential for our development and survival. In addition, HSCs’ ability to repopulate the blood and immune system is an extremely useful property to treat certain disorders. In fact, infusion of HSCs can “rescue” the subject from a failure of the bone marrow that may result from marrow disorders or exposure to radiation therapy or chemotherapy, by generating a progeny of new healthy cells. In experiments, a single HSC has repopulated the blood of a mouse that received an otherwise lethal dose of nuclear radiation!

HSCs in the clinic: haematopoietic stem cell transplantation

Today, haematologists routinely utilise HSC infusion in a procedure called haematopoietic stem cell transplantation (HSCT) to promote the



New and healthy immune cells from HSCs would be “resetting the immunological clock”.

recovery of blood cell numbers in people who received high doses of immunosuppressive radiation therapy or chemotherapy. Normally, HSCs are obtained either by direct aspiration of the bone marrow from the hip bones or through mobilisation of the progenitor cells into the peripheral blood. Administration of a blood cell growth factor that stimulates production and the

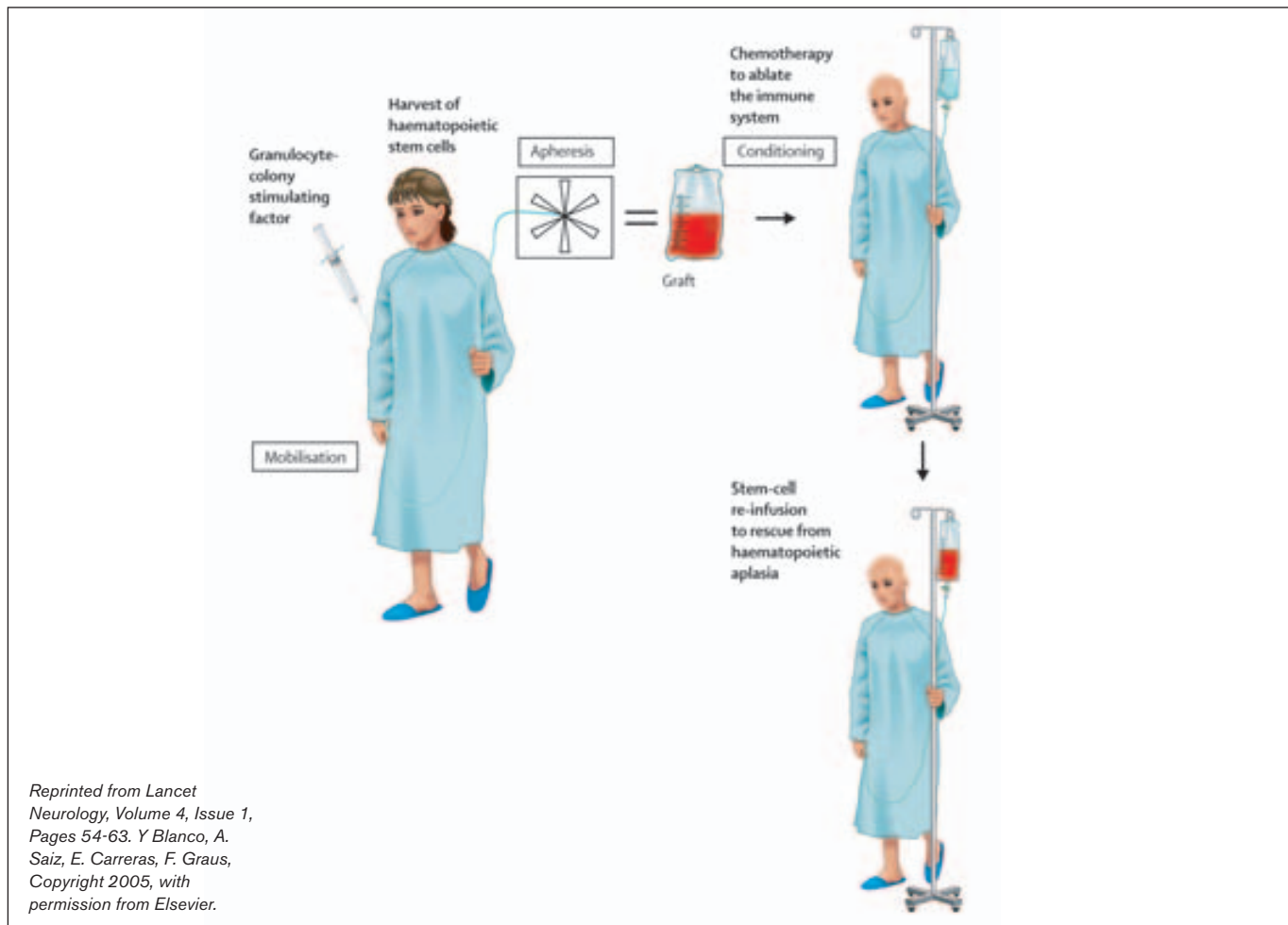


Fig. 1 – HSCs can be obtained from the same individual and preserved for reinfusion.

release of stem cells induces HSCs to move out of the bone marrow and into the bloodstream. Blood is drawn from the patient into a cell separator machine, which collects the mobilised HSCs together with white cells in a process called leukapheresis. HSCs can subsequently be purified by selecting cells bearing the marker CD34, which they specifically express on the cell membrane. Umbilical cord blood is also rich in HSCs and has been utilised for haematopoietic transplants for cancer, particularly in children who did not have a matching bone marrow donor. The HSCs can be obtained from the same patient and preserved for re-infusion after the chemotherapy; this procedure is named autologous haematopoietic stem cell transplantation (Fig. 1). Alternatively, a genetically “matching” donor can be identified among the person’s relatives or through a bone marrow or cord blood donors’ registry; the transplantation of

HSCs from another individual is termed allogeneic transplantation. Allogeneic and autologous HSCT have different indications and both are used extensively for treating cancers of the blood, of the lymphoid organs and of the bone marrow. Indeed, transplantation of HSCs has been a life-saving treatment for tens of thousands of people affected by leukaemia, lymphoma, myeloma and other malignancies.

HCST for “immune repair”

Clinical studies investigating the potential usefulness of HSCT in MS and other immune-mediated disorders were initiated, following the observation of those people with an autoimmune disease who, after developing cancer, were treated with HSCT and experienced a remission of the autoimmune disorder. These trials have been limited to autologous HSCT since allogeneic

transplantation has a higher risk of side-effects and serious complications.

How does autologous HSCT work in MS?

The lesions in MS are infiltrated by blood-originating immune cells including T and B lymphocytes that seem to attack and injure myelin-producing cells. We do not know what causes this attack but the process almost certainly involves a dysfunction of the immune system. The goal of HSCT in MS is to purge the existing immune system with immunosuppressive chemotherapy and regenerate a pool of new and healthy immune cells originating from HSCs. The idea has been ingeniously termed as the “resetting of the immunological clock”. This means that in principle the mature cells of the immune system, and amongst them the cells that attack the brain, can be eliminated and replaced by new, harmless cells. Recent studies have proven that this “resetting” of the immune system actually occurs and that the thymus, the organ where haematopoietic progenitor cells mature into T lymphocytes, is reactivated after HSCT giving rise to large numbers of new T cells, possibly including “regulatory” T cells that suppress autoimmune attacks.

What can HSCT do for people with MS?

At the time of writing, more than 350 people with MS have undergone autologous haematopoietic stem cell transplantation. Although no randomised controlled studies rigorously assessing the efficacy have yet been completed, an analysis of the reported results provides some indication on what this treatment can and cannot do at the present time. Firstly, HSCT generally has shown beneficial suppressive effects on inflammation and development of new plaques as detected by MRI. In the overall majority of treated individuals there was a stabilisation of the pre-existing neurological disability. Although in principle HSCs can transform into any cell lineage, including neural or myelin-producing

cells, we do not know whether HSCs can directly help repair the neural structures that have already been damaged by MS. The clinical studies found that those who had a higher and chronically established degree of disability prior to HSCT frequently continued to worsen post-therapy. This observation suggests that those individuals suffered from a type or stage of neural deterioration that was not (or no longer) caused by the typical inflammation that HSCT could not reverse or even arrest, in spite of its powerful effects on the immune system. Therefore, clinical trials are now seeking to recruit earlier in the disease course, patients with very active forms of MS who failed to respond to other immune treatments, in order to determine if HSCT can prevent them from worsening.

Studies combining clinical and laboratory research can help make HSCT safer and more effective.

Current difficulties and hope through research

The main difficulty in clinical studies of HSCT for MS is the issue of treatment-related risks. Fatal complications have resulted from HSCT and while these occurrences have been decreasing owing to improved knowledge and technology, life-threatening side-effects can still occur. Another challenge is identifying early those who are affected by a severe form of MS and fail to respond to other treatments. It can be reasonable to consider the option of an intensive therapeutic intervention for these people, such as “immune repair” through HSCT. Treatment with HSCT should preferably be received through participation in a qualified clinical trial. Studies combining clinical and laboratory research can help make HSCT safer and more effective and can teach us how changes in the immune system can control the development and course of MS.

Remyelination, the next treatment target for MS?

Robin J.M. Franklin, Professor of Neuroscience and Director of the UK MS Society Cambridge Centre for Myelin Repair, University of Cambridge, Cambridge, UK

What is remyelination?

The nervous system works because nerve fibres (axons) convey information between nerve cells (neurons) by way of electrical impulses. Their ability to do so is greatly enhanced by an insulating sheath that wraps around the nerve fibre. This sheath is made by a substance called myelin and in the CNS – the brain and spinal cord – myelin is made by a cell called the oligodendrocyte. In MS the oligodendrocyte and the myelin sheath it makes are a major target of the disease process. Loss of oligodendrocytes leads to loss of myelin sheaths from around axons – a process called demyelination. The immediate consequence of demyelination is that the axons become considerably less efficient at conducting impulses. However, demyelination may be followed by a spontaneous regenerative or healing process in which new myelin sheaths are restored to the axons. This process is called remyelination or myelin repair, although this term suggests that damaged myelin gets patched up – which is not really what happens – and enables the axons to resume efficient impulse conduction.

Why is remyelination important?

Remyelination is the normal response to demyelination and was first shown to occur in MS many years ago. More recent studies have

shown that in some patients, remyelination can be very widespread and extensive. However, for reasons that are currently far from clear and are likely to be multiple, remyelination is sometimes incomplete or fails altogether. This means that axons remain permanently demyelinated; a serious situation since in this state they become very vulnerable to death themselves. A view widely held by MS researchers is that the progressive loss of chronically demyelinated axons accounts for the progressive and largely untreatable deterioration experienced by nearly all MS patients. Preventing axonal loss is therefore a major therapeutic objective which, it is hoped, will allow treatment of stages of the disease for which none currently exist, and that will slow down or even arrest deterioration. Since myelin appears to be important for maintaining the health of the axons, many experts in the field believe that the therapeutic promotion of remyelination in situations where it has failed may represent one of the most effective ways of preventing axon loss. Preventing axonal loss is sometimes called neuroprotection.

How might remyelination be enhanced?

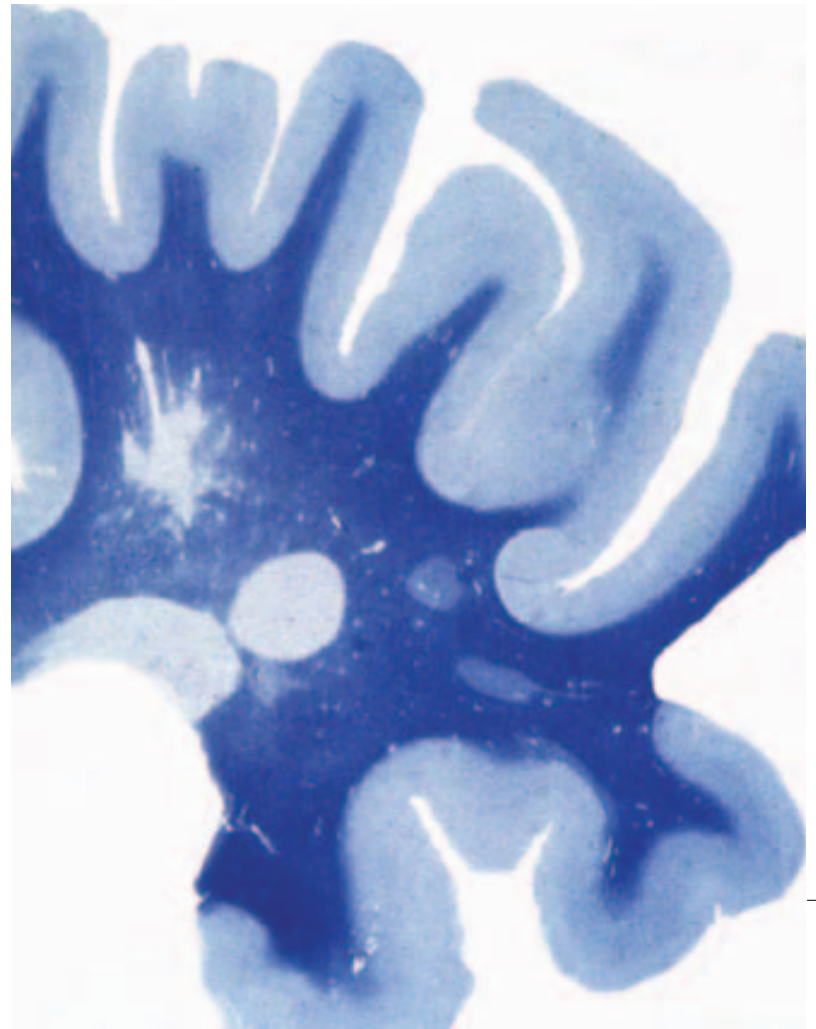
Since remyelination can occur as a spontaneous response to demyelination, one approach to its therapeutic enhancement is to persuade the

body's own remyelination mechanisms not to give up but to work more effectively. This is sometimes called the endogenous approach. Another approach is based on the argument that because endogenous healing has failed it needs some external help, which can be provided in the form of transplanted cells that are able to make new myelin. This is sometimes called the exogenous or cell therapy approach and is currently viewed by some as being more appropriate for rare genetic diseases of myelin rather than MS. A third, combined approach also exists in which transplanted (exogenous) cells are used to enhance endogenous remyelination. This approach is still in its infancy, but certainly has much potential. Recent experimental evidence suggests the remarkable possibility that transplanted cells, easily delivered into the blood stream, not only encourage endogenous repair but are especially effective at preventing damage occurring in the first instance by damping down the damaging inflammatory response that characterises acute MS episodes (relapses).

An attraction of the endogenous approach is that it may be amenable to drug-based treatments. In order for this to be developed it is necessary to know why remyelination fails so that the faulty aspects can be identified and corrected. However, in order to do this it is important to understand how remyelination works. By analogy, it is very difficult to mend a broken car engine if you have no comprehension of the engine's internal workings.

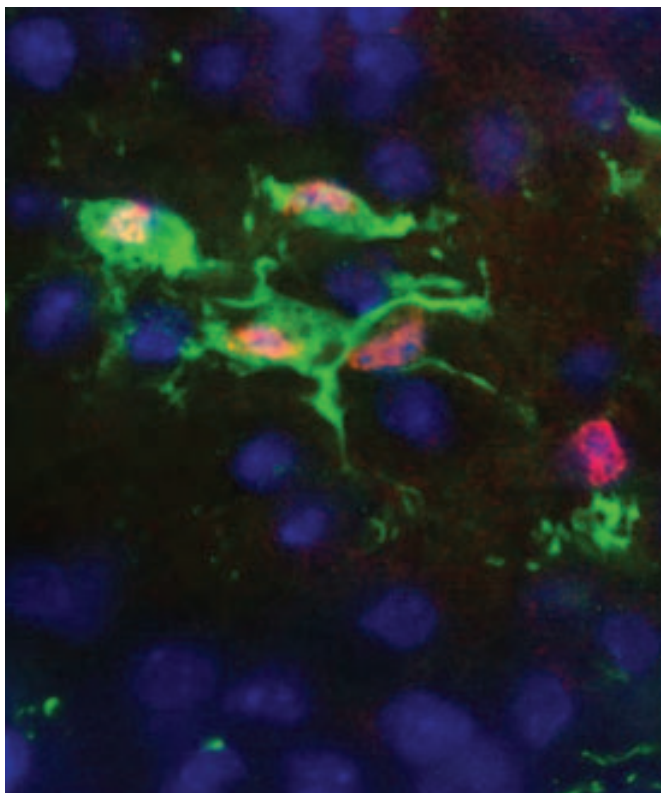
How does remyelination work?

Remyelination is mediated by a population of stem cells that are abundantly distributed throughout the entire adult CNS. These cells are often referred to as oligodendrocyte precursor cells or OPCs. When demyelination occurs, all the OPCs in the vicinity are stirred into action. This event is called activation and involves the cells increasing their responsiveness to factors generated by



A section from the brain of a person with MS. Within the dark blue staining region (white matter) the pale (white) areas are demyelination - the pale blue areas are remyelination.

demyelination that make them move around and make copies of themselves. Very quickly the area of demyelination is filled up with OPCs, a process called recruitment. The next step is for these cells to become replacement oligodendrocytes that make new myelin sheaths around the demyelinated axons. This process is called differentiation. Thus, remyelination is the result of a two-stage process of OPC recruitment and differentiation. Over the last few years scientists have been busy identifying the multitude of factors involved in OPC recruitment and differentiation. Some of these are environmental factors to which the OPCs are exposed; others are factors within the



Adult stem precursor cells (above) give rise to new myelinating cells in remyelination.

OPCs that allow them to make the appropriate responses to environmental factors. While much has been learnt it is apparent that there is still a great deal more to be understood. The number of factors is very large and most work in complex networks, making the process an immensely complicated one to understand completely.

Why does remyelination fail?

In theory, remyelination might fail because of a failure of either OPC recruitment or differentiation, which would determine whether remyelination therapies were to be based on the provision of recruitment or differentiation factors. Differentiation seems to be the more complicated of the two processes, and therefore the one most likely to go wrong. It is therefore of little surprise that recent evidence shows that a common cause of remyelination failure in MS patients is not an absence of OPCs (these are often present in abundance) but due to the OPCs failing to differentiate into remyelinating oligodendrocytes.

At what stage is remyelination research?

Because remyelination appears to be failing at the differentiation stage, at least in a proportion of damaged areas in a proportion of patients, many scientists are currently focusing on how differentiation works and how it might be promoted. There are two possible explanations for differentiation failure and either or both of which may be possible: differentiation may fail because of an absence of factors to enhance it or the presence of factors that inhibit it. Several possibilities for both explanations are being investigated. These studies usually take the form of laboratory-based studies, using various animal models and cell cultures, and studies of post-mortem tissue from MS patients, which is becoming increasingly widely available thanks to the setting up of specific MS brain banks. An excellent example is the one funded by the UK MS Society based at Imperial College in London. The results obtained from the two types of studies mutually inform each other – the post-mortem tissue pointing the way to the laboratory studies and the laboratory study giving clues as to what one might expect to find in post-mortem material. This work is progressing on many fronts via an increasing number of researchers and research groupings.

Although patient-based studies are currently in progress to establish ways in which enhanced remyelination can be monitored and assessed in patients, remyelination research is still at present an essentially laboratory-based endeavour. This is inevitable considering the complexities of the problem and it is worth remembering that there are very few currently available treatments to enhance regenerative process for any tissue in the body, let alone the CNS. Nevertheless, scientists and clinicians involved are optimistic that in the future the availability of remyelination therapies will have a significant impact on the treatment of MS, given the pace and momentum that this important area of research has acquired in recent years.

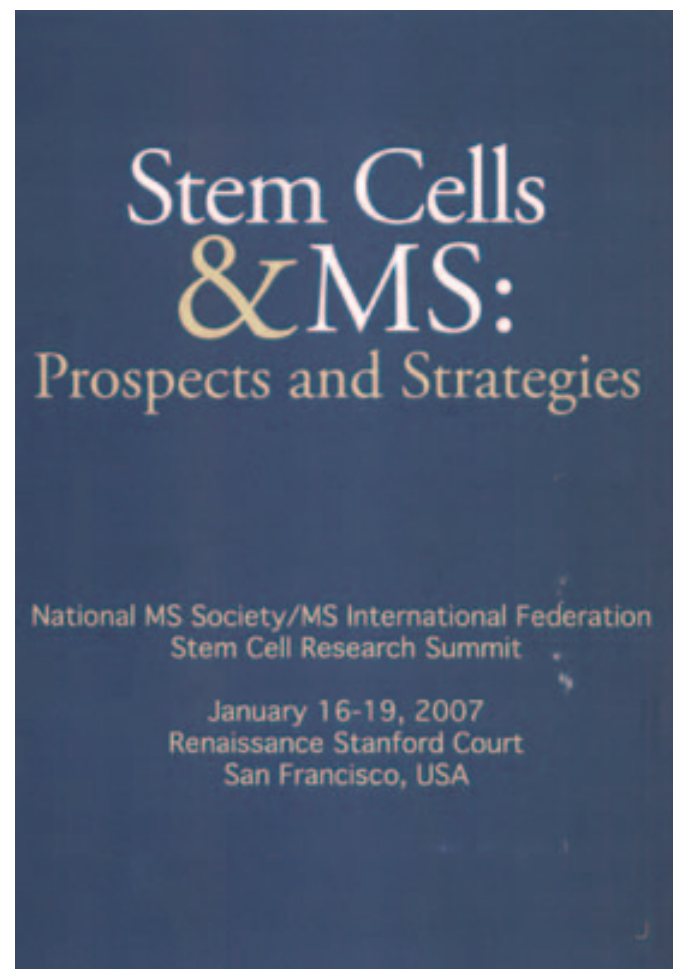
Building a policy on stem cells in MS

Cathy Carlson, Senior Director, Research Information,
National MS Society (NMSS), USA

In 2005, the Stem Cell Research Task Force of the National MS Society (USA) met with stem cell researchers, legal and regulatory experts, bioethicists, and other voluntary health agencies. The task force found that research with all types of stem cells held great promise, potential, and hope for people affected by MS, and that there was a high likelihood that this research would improve our understanding of the disease process and lead to new pathways for therapeutic intervention. Members recommended that the Society be more publicly active to ensure that this research could move

The task force found that research with all types of stem cells held great promise, potential, and hope for people affected by MS.

forward. The Society approved the recommendations and asked chapter volunteers and staff leadership to voice concerns, but little opposition was raised. "We did lose a few key volunteers whose counsel we valued highly by taking a more public profile on embryonic stem cell research, ... however, we would not remain true to our mission if we continued to stay silent on this promising area of research," noted John R. Richert, MD, Executive Vice President of Research and Clinical Programs of the National MS Society (USA).



Programme cover from the Stem Cell Research Summit, convened by the National MS Society (NMSS) and the MS International Federation (MSIF) on January 16-19, 2007. It brought together leading stem cell and MS experts from around the world to explore the potential of all types of stem cells for the treatment, prevention and cure of MS.

Recommendations from the National MS Society Stem Cell Research Task Force

Among its recommendations were that the Society should:

- Continue to be open to funding stem cell research, including human embryonic stem cells.
- Support somatic cell nuclear transfer (“therapeutic cloning”: implanting a person’s DNA into an unfertilised egg to grow stem cells that could be used to treat that person’s medical condition) for biomedical research, but oppose its use for reproductive purposes.
- Publicly advocate for policies conducive to embryonic stem cell research, and clearly articulate the Society’s position.
- Respect the beliefs of those who may oppose the Society’s stance, but not permit such beliefs to limit its research or advocacy activities.

- Establish an Ethical, Legal & Social Implications Committee to review Society policies periodically and serve as a forum for addressing public comments.
- Sponsor a scientific workshop on stem cell research in MS.

Steps to consider in developing a stem cell policy

What steps might other MS societies take to develop a stem cell policy? Here are a few recommendations, based on the NMSS’s experience:

- Cooperate with research centres in your country, provide them with any support they need.
- Know the political climate of your country in terms of human embryonic stem cell research.
- Through letters received or a survey, understand where the majority of your constituents and supporters stand on stem cell research (providing information about its promise for people with MS may help pave the way for a positive response).
- Consider steps you might take to propel this research. Is it to advocate for policy changes, to join a coalition working for change, to fund stem cell research? For each of the possible steps, have your leadership weigh the possible risks (such as losing key supporters) and benefits (such as moving research forward for people with MS).
- Once you have arrived at a position, invest time in educating your constituents about the issue and communicating your position clearly and consistently to them.
- Let your mission drive your actions.

Photo ©2007 Jessica Brandt Liffland



John R. Richert, MD welcomed Stem Cell Summit participants and asked for their help in setting research priorities.

Details about Summit presentations can be found on the NMSS’s website:

www.nationalMSSociety.org/stemcell

Your questions answered

Dr Gianvito Martino answers questions here based on evidence concerning autologous haematopoietic stem cell transplantation, the only type of stem cell therapy currently available in people with MS.

Q. Would I be able to choose which stem cells to use for ethical reasons?

A. Presently, the only stem cell therapy available is that based on autologous haematopoietic stem cell transplantation. Other possible stem cells (mesenchymal, neural, etc.) are still far from being used routinely in the clinic. Thus, at this time there is no possibility to choose.

Q. Is stem cell therapy a “one-time” treatment or can it be an ongoing programme?

A. So far autologous haematopoietic stem cell transplantation has been performed as a “one-time” treatment for patients with MS. It cannot be excluded that in the future whatever type of stem cell therapy used will require repeated or multiple treatments.

Q. Would stem cells help me even if my MRI results show no new lesions?

A. Currently there are no consistent data showing that autologous haematopoietic stem cell transplantation can be effective when no signs of ongoing inflammation are present. On the other hand, it appears that the more inflammatory the disease, the better the outcome after transplantation.

Q. Where do embryonic stem cells come from? Can they be created or must they come from a living organism?



A. Presently, human embryonic stem cells (ES) come only from early stage human embryos (those used for *in vitro* fertilisation) or from therapeutic cloning. In mice the possibility of obtaining ES from mature cells (for example skin cells) is possible, thus avoiding the use of “living organisms”. Very recently it has been shown that a procedure called “somatic cell programming” is also possible using human adult tissues. In November 2007, Shinya Yamanaka of Kyoto University in Japan reported making pluripotent (ES-like) cells – cells that can turn into any of the roughly 220 cell types in the body – by using retroviruses to carry three key genes into human skin cells. Although this can be considered as a major advancement in ES research, it is a general belief that much more work needs to be done before translating such advances into clinical practice.

Interview: Dr Pablo Villoslada

Can you please tell us a bit about yourself and your work?

I am a neurologist working at the Multiple Sclerosis Centre at the University of Navarra in Pamplona, Spain. I trained in Barcelona and San Francisco, California, and my focus has always been on MS. At the MS Centre we are trying to understand the pathogenesis of MS, including undertaking biological studies to understand the disease and hope to use this information to find biomarkers and MS therapies.

Do many of your patients ask you about stem cell research and MS?

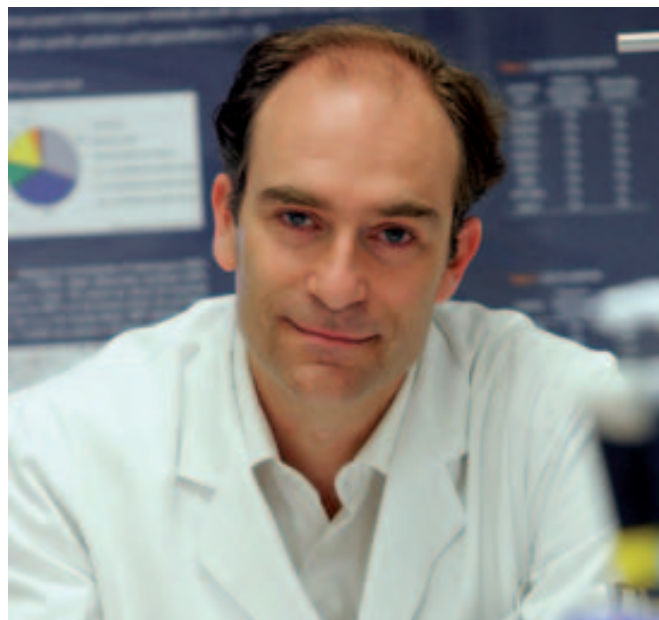
More than 30 percent of my patients ask about stem cell therapy, especially those with a high level of disability. More people ask now than they used to due to stories in the press of people having therapy, but there has always been an interest. Many people see stem cells as a way to renew their body – a bit like doing up a house – and are interested, even if they normally do not like the idea of taking drugs.

What questions do they ask?

The main question they ask is: “What about stem cell therapy for me?”, but many are not aware of the scientific complexity of this subject. They have often read or heard about someone else having success with it and want it for themselves. They are not usually concerned about safety or how much it will cost but would probably have many more questions if the therapy was possible for them!

What types of information do you have to explain?

I usually explain and summarise the current state of research into stem cell therapy and MS and explain that the issues are more complex in neurological diseases than other types of disease. I also often have to point out that some of the centres where stem cell therapy has been done are not scientific, often very expensive and have serious safety concerns. But it can be frustrating for patients who feel they have no options, so we often also talk



Dr Pablo Villoslada.

about other current treatments that are working and may be more suitable.

What are the main concerns your patients have?

The main concern is whether they can have access to the therapy and whether it will help them recover their movement and ability, not just stop the progression of MS. Many hope it will give them their old bodies back. Some people also have concerns about the source of the cells.

Which other sources of information have they used?

Mostly news stories on television and in papers, as well as websites and speaking to other people with MS.

Do you suggest any sources to people who ask you about stem cell research?

I always suggest people contact their national MS society because they will have user-friendly information and be given neutral, unbiased opinions about all therapy options. I also specifically refer them to MSIF's website for more information: www.msif.org.

Stem cells online survey results

Stem cell treatment is a very high-profile topic in current MS research. Over 92 percent of the respondents to the questionnaire had MS and the interest was well reflected in the highest ever response – 886 – to any *MS in focus* online survey.

Awareness and the ethical question

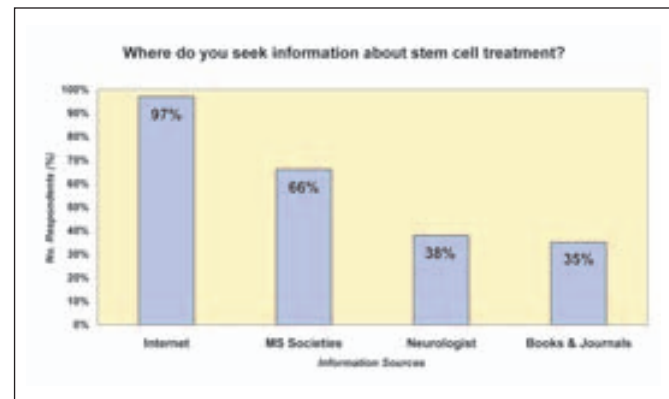
Only six percent (50 respondents) were unaware of different types of stem cells available and over 92 percent would consider having stem cell treatment, but many also wanted to know about risks and how safe it was, or what stage the research is currently at. Respondents were very specific about the kind of stem cells they found acceptable for treatment – many were uncomfortable with the concept of embryonic stem cells or against it altogether; however, it was seen by many as an ethical dilemma, but some would still proceed “if there was no alternative”.

Information sources

The Internet is a very popular source of information about stem cell research, with an overwhelming majority of 97 percent of respondents looking to the web for their information; two-thirds (66 percent) also went to MS Societies for more information. Interestingly, almost as many people looked to books and journals (35 percent) to research stem cells and MS as those who went directly to a neurologist (38 percent) for more information.

The future for stem cell research

In spite of 91 percent responding “yes” to the question: “Do you think that your national MS



Society should use funds for stem cell research?”, there were still many questions posed concerning stem cell treatment, ranging from what the risks would be, to what types of MS the treatment works on, and how invasive the treatment would be.

Conclusion

Overall awareness is very high but knowledge appears to be inconsistent in the field of stem cell research, with a high level of support from respondents about continuing with current research and finding out more about stem cell treatment overall. Many use the word “cure” in their comments; stem cell treatment is viewed positively by many as a future treatment or something they would definitely consider if their type of MS worsened. The general outlook and receptiveness for further research in this field is very positive.

Reviews



The Stem Cell Site

This site is part of the US government's official web portal, hosted by the National Institutes of Health, and can be

reached at <http://stemcells.nih.gov/info/basics>.

The Stem Cell Site will engage and inform visitors, with its crisp format and easy to follow index and navigation system. Topics include the unique properties of all stem cells, embryonic stem cells, adult stem cells, similarities and differences between embryonic and adult stem cells and potential uses of human stem cells. The site is comprehensive and helpful, including directions to other sources of information for the visitor. There is a glossary for most of the difficult words, but following the text may be difficult for those not already well-versed in biology.

The information is very extensive and comprehensive, with all relevant aspects addressed. Diagrams ("cartoons") are colourful and attractive, but require a good understanding of the terminology to interpret them comfortably (keep that glossary handy!). Most motivated, patient and diligent lay people will be able to follow the content and understand the concepts, but many will find it a challenge. Healthcare professionals should have a much easier time, since they already have the scientific foundation for this topic.

The Frequently Asked Questions link on the Home Page provides information in language more suitable for the general audience. On the Home Page, the *VII. Where can I get more information?* link provides access to the University of Wisconsin site, which is written in language more comfortable for the uninitiated:

www.news.wisc.edu/packages/stemcells/

Reviewed by Nancy Holland, Vice President, Clinical Programs, NMSS, USA.



A Health Handbook for Women with Disabilities

by Jane Maxwell, Julia Watts Belser and Darlena David

Copyright©2007 by Hesperian Foundation, February 2007, ISBN:

978-0-942364-50-7 paperback.

This book is written for the millions of women with disabilities around the world, including those with vision and hearing problems, difficulties walking, difficulties with speech, and those with learning impairments.

The book aims to help women better care for themselves and it will also assist family, friends, community health workers and caregivers who support women with disabilities.

There are 15 chapters, including mental health, taking care of your body, sexuality, family planning, caring for your baby, growing older with a disability, and support for caregivers.

The book offers very clear explanations related to the different themes and potential situations. It is written in a very straightforward way and this, together with the many illustrations, makes it very easy to read and understand.

In my opinion the book is very thorough and it considers all of the important aspects and information for women dealing with these conditions. I would highly recommend this book as an excellent introduction to anyone affected by or interested in these matters.

I enjoyed this book very much and I am sure that you will also find reading it both pleasurable and useful.

www.hesperian.org

Reviewed by Maria Marta Castro, PwMSIC member for Argentina.

Glossary of terms used

Astrocytes – also commonly called “neuroglia” or glia (Greek for glue), these are star-shaped non-neuronal cells in the brain: functions include the formation of the blood-brain barrier, providing nutrients to the nervous tissue, and playing a role in the repair and scarring process in the brain.

Axons – nerve fibres, projections of nerve cells, conducting electrical impulses away from the neuron’s cell body (soma).

Biomarker – a substance used as an indicator of a biologic state; a biomarker can be any kind of molecule indicating the existence (past or present) of living organisms.

Cytokines – a group of proteins and peptides used in organisms as signalling compounds.

Endogenous – inside of the body.

Exogenous – outside of the body.

Experimental Autoimmune

Encephalomyelitis (EAE) – animal model of the human central nervous system (CNS) demyelinating diseases, including MS.

Graft-versus-host disease – a common complication of bone marrow transplantation between genetically non-identical (allogeneic) individuals. The functional immune cells in the transplanted marrow recognise the recipient as

“foreign”, mounting an immunologic attack.

Haematopoiesis – the formation of blood cellular components; haematopoietic stem cells are the point of origin for all of the cellular components of cells.

Histology – anatomical study of the microscopic structure of animal and plant tissues; the microscopic study of tissues.

In vitro – within the glass; in a test tube; or performing an experiment in a controlled environment, outside of a living body.

In vivo – within the living; in a living organism.

Ion channel expression – ion channels are proteins that act as conductors, allowing water-loving ions to cross the oily lipid barrier of cell membranes into the watery cytoplasm of a cell. Once there, the ions enable basic physiological processes such as growth, reproduction and muscle contraction.

Mesenchymal – multipotent stem cells.

Multipotent – the ability of a cell to become several different types of cell; multipotent haematopoietic cells can become any type of cell in the blood system.

Oligodendrocytes – commonly called “neuroglia”, these are non-neuronal cells, whose main function is the myelination of axons in the central nervous system.

MS *in focus*



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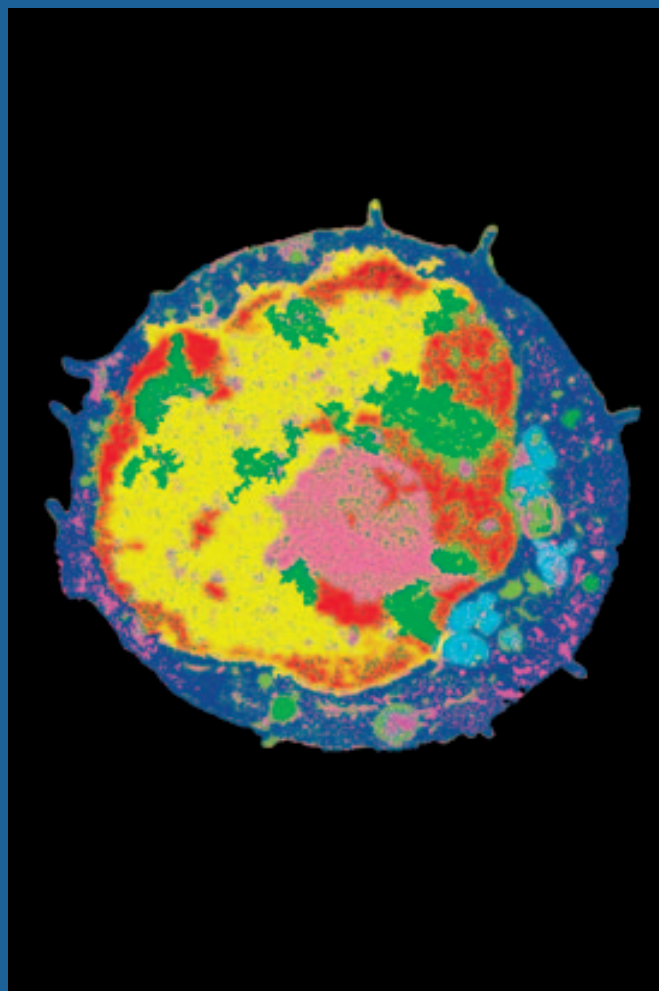
The Multiple Sclerosis International Federation produces **MS in focus** twice a year. With an international cross-cultural board, accessible language and free subscription, **MS in focus** is available to all those affected by MS worldwide. Go to www.msif.org/subscribe to sign up.

Previous issues are available in print or to download from our website:

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Merck Serono, a division of Merck KGaA, are specialists in innovative prescription pharmaceuticals with products available in over 150 countries worldwide. We have been active in the fight against MS for over a decade. Through pharmacogenomics, we

are active in research towards understanding the genetic basis of MS. Merck Serono has a long-term commitment to people with MS through constant research and discovery efforts as we look for new therapies and hopefully, one day, a cure.