

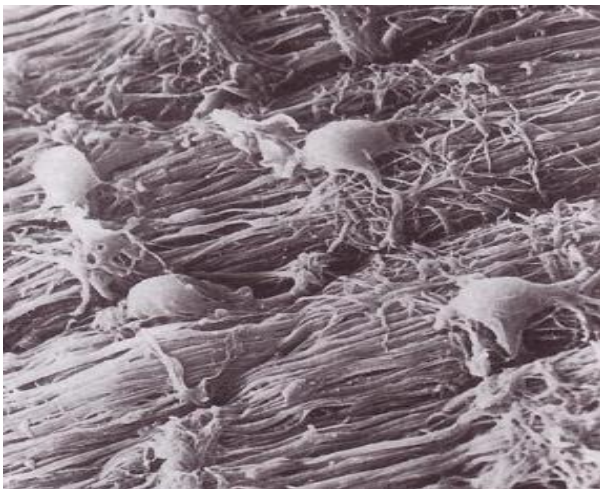
Status of Stem Cell Therapy for Multiple Sclerosis, November 2007.

This paper was commissioned by Regenecell Pty Ltd, to supplement the current anecdotal data on the treatment of MS with peer-reviewed published data relevant to umbilical cord stem cell therapy. For additional information, contact: info@regenecell.com.

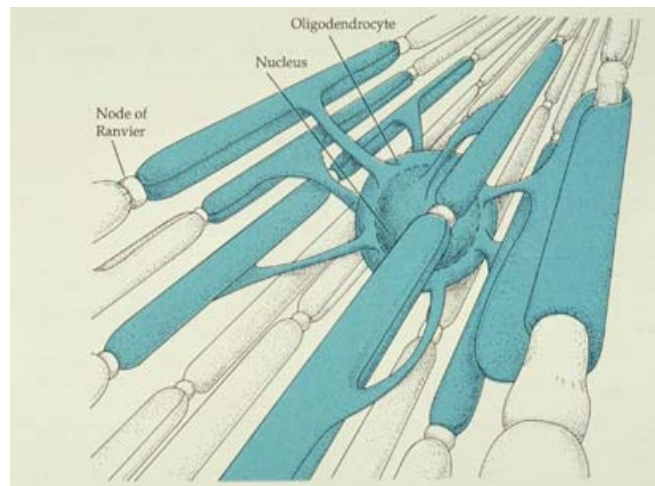
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About Multiple Sclerosis (MS)

Multiple Sclerosis, with an incidence of 100 in 100000 in the US and Europe, is by far the most frequent neurodegenerative disease ⁽¹⁾. MS is a chronic, demyelinating disease of the brain and spinal cord - collectively the central nervous system (CNS). **Demyelination** is a process of gradual destruction of the myelin sheath, that surrounds many of the axons of nerve cells (neurons), leading to axonal injury or loss and consequently severely impaired nerve signals. The disease is named for the multiple scleroses (scars or plaques) that are created on the myelinated axons. A repair mechanism - remyelination of the axons by cells known as **oligodendrocytes** - takes place in the early phases of disease but the reformed myelin sheaths are thinner and less effective. Repeated attacks lead to fewer effective remyelinations until a scar is built up on the damaged axon. The central nervous system should be able to recruit oligodendrocyte stem cells but something would seem to inhibit stem cells in the affected areas.



Electron micrograph showing branched oligodendrocytes with processes extending to several underlying axons



One oligodendrocyte wraps myelin around axons of several neurons

It is generally accepted that MS is an inflammatory autoimmune disease - whereby an individual's own immune response attacks the nervous system. Certain viruses, bacteria, stress and genetics have been implicated in disease manifestations. MS causes a variety of symptoms depending on where in the CNS the multiple lesions occur. Also, neurological deficits are progressively accumulated. In any individual there may be several complicating

factors affecting the unpredictable course of the disease - there may be times of dormancy or times when there is steady progression.

The disease is categorised by several subtypes:

Relapsing remitting MS: unpredictable relapses (attacks) followed by months to years of remission. Effects of attacks may either resolve or may be permanent.

Secondary progressive MS: characterised by neurologic decline between attacks without periods of remission. Most common type of MS and causes most disability.

Primary progressive MS: decline occurs continuously without clear attacks, no remission,

Progressive relapsing MS: steady neurologic decline from onset, patients suffer superimposed attacks. Least common

While MS does not currently have a cure, there are several treatments available for moderating the symptoms and for managing the various consequences of attacks. The currently approved treatments are aimed at returning function after an attack and preventing disability.

MS Treatment Objectives - the way forward: A Role for Stem Cells

During multiple relapses in the course of MS, oligodendrocytes and their progenitors are lost⁽²⁾ and the nervous system has only limited capacity to recover from this extensive neuronal or glial damage. This is partly due to the formation of barriers, known as "glial" scars, which are triggered by the body to protect the injured nerve tissue from further injury. This dense scar tissue throws up a blockade to foreign cells, including transplants meant to heal and regenerate (group at Harvard medical school). There is evidence, however, that the adult CNS retains populations of cells with stem cell-like properties that have extensive proliferative capacity⁽³⁾.

The challenge for current medical therapies appears to be remyelinating chronically demyelinated axons. Two distinct approaches can be considered to promote myelin repair; in one the endogenous myelin repair processes are stimulated through the delivery of growth factors, and in the second the repair process are augmented through the delivery of exogenous cells with myelination potential. Also, the effective treatment of MS requires modulation of the immune system, since demyelination is associated with specific immunological activation⁽⁴⁾.

Karussis and kassis (sept 2007) described how different stem cells migrate to areas of white matter lesions (plaques) and have the potential to support local neurogenesis and rebuilding of the affected myelin – believed to be achieved by support of the resident CNS stem cells and by differentiation of the transplanted cells into neurons and myelin-producing oligodendrocytes. These stem cells were also shown to possess immunomodulating properties,

Several types of stem cells (discussed later in this article) having the capacity for promoting myelin repair, as well as modulating the immune response, are potential candidates for MS therapy.

Stem cell transplantation for treating MS: current developments (as at 2007)

Many inflammatory diseases are diffuse and widespread. However, intravenous injection has been demonstrated as an appropriate means of diffuse delivery of stem cells with the possibility of targeting; the problem for distribution to other tissues or organs still needs evaluation^(1,5).

Neural stem cells: Many different cell types, including neural stem cells and precursors, have been suggested as candidate cells for therapy. There are however complexities in obtaining neural stem cells from the adult CNS. A group from the University of California, San Francisco published their findings in *The Scientist* (July 2007) cautioning against the notion that neural stem cells can generate any type of neuron. This group predict difficulties in using adult neural stem cells to treat neurological disease, although it remains possible that scientists could manipulate neural stem cells in vitro to make them more flexible.

Bone marrow stem cells: As early as the year 2000 adult bone marrow cells were shown to have the capacity to differentiate to oligodendroglial cells indicating their potential for treating demyelinating diseases ⁽⁶⁾. At the same time, a phase II trial using autologous bone marrow stem cell transplantation to treat 85 patients for progressive MS was conducted in 20 European centers. Neurological improvement was seen in 21% of patients; confirmed progression-free survival was seen in 74% of patients at 3 years; disease progression occurred in 20%. Additionally, it was reported that autologous haematopoietic stem cell transplantation can regenerate a tolerant immune system and is a potentially effective rescue therapy in a subset of patients with aggressive forms of MS refractory to approved immunomodulatory and immunosuppressive agents ⁽⁷⁾. Cassiani-Ingoni and fellow investigators, suggest that bone marrow transplantation can suppress inflammatory disease in a majority of MS patients, but retards clinical progression only in patients treated in the early stages of the disease ⁽⁸⁾.

Mesenchymal stem cells (MSCs): [Mesenchymal cells are non-haematopoietic stem cells derived from marrow or umbilical cord, the more appropriate terminology is multipotent stromal cell yet MSC still persists in the literature] Emerging evidence suggests that mesenchymal stem cells may have the capacity to generate cells with the characteristics of neurons and glia and consequently promote repair in the injured CNS. How mesenchymal stem cells affect functional recovery in the damaged adult CNS is not well understood. Possibly the transplanted multipotent cells migrate to the injury sites, proliferate, and then differentiate into the appropriate neural cells that then effect repair. Although mesenchymal stem cells have a high survival and migration potential, the proportion that can be directed towards a neural fate appears to be relatively small. It may be that MSCs, through the release of soluble signals in areas of injury, have a direct influence on the endogenous neural stem cells to promote repair through neuro- and oligodendrogenesis ⁽³⁾.

Mesenchymal cells can also exert immunomodulatory effects by inducing suppression of the autoimmune myelin-targeting lymphocytes. MSCs harvested from bone marrow can be obtained from the donor patient him/herself, thereby reducing the risk for developing malignancies. It has been mooted that these cells offer significant practical advantages over other types of stem cells ^(5,9).

CD34+ cells: CD34+ cells are multipotent haematopoietic stem cell found in bone marrow and umbilical cord blood. These stem cells are reportedly capable of transforming into neuroprotective glia and myelin-producing oligodendrocytes ⁽¹⁰⁾. A proposed advantage of umbilical cord CD34+ stem cell transplantation is that, when administered without additional medications and powerful immune suppressants, virtually no side effects are evident ⁽¹⁰⁾.

Stem Cell Therapy – cause for optimism

Significant advances have been made in researching the therapeutic potential of stem cells for neurodegenerative diseases and there are already several facilities offering stem cell treatments! Transplanting cells into focal MS lesions may be the ultimate therapeutic approach, and clinical trials may be the way to determine whether exogenous stem cells are

able to survive, differentiate and myelinate axons in plaques⁽²⁾. While the current number of stem cell-based clinical trials for demyelinating diseases is limited, this is likely to increase significantly in the next few years⁽⁴⁾.

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