In multiple sclerosis (MS), axons of the central nervous system lose their myelin sheaths, and there is also death of oligodendrocytes. Although some demyelinated axons rebuild their membranes so that they can conduct action potentials in the absence of myelin insulation, others do not; and loss of the myelin thus impairs impulse conduction either temporarily or permanently. Mounting evidence also suggests that loss of central myelin may have the secondary consequence of making axons more sensitive to damage or may, in itself, produce changes that impair axonal integrity, thereby leading to cumulative loss of axons that culminates in irreversible neurological deficits (Waxman, 2006). While a number of treatments such as the beta interferons (IFN-β) and glatirimer acetate (GA) are now available for the treatment of MS, and clinical studies using autologous haematopoietic stem cell transplantation (HSCT) and monoclonal antibody interventions in MS patients have shown profound suppression of inflammatory activity in many patients, these interventions were developed in the attempt to mute the immune attack on the nervous system in MS, and not with the goal of repairing demyelination. Thus, even if the immune assault on the nervous system in MS could be halted by a new immunomodulatory therapy and the subsequent cascade of tissue damage thereby stalled, hundreds of thousands of people harboring MS lesions would still be left with neurological deficits. It is therefore not surprising that myelin repair has become an area of major interest in MS research. Important progress in this respect has come from studies that have examined cell-based approaches to myelin repair. A critical issue for cell-based myelin repair is the choice of cell type for transplantation. The transplanted cell must be able to survive, migrate to demyelinated lesions, remyelinate axons and not be tumorigenic. Oligodendrocyte lineage cells, neural progenitor cells, post-natal Schwann cells, olfactory ensheathing cells and other cell types have been shown to be able to migrate and remyelinate demyelinated CNS after transplantation directly into experimentally demyelinated lesions (Radtke et al., 2007). Importantly, appropriate ion channel organization at nodal and paranodal axon regions is reestablished in central axons remyelinated by endogenous or transplanted cells, and impulse conduction is improved (Black et al., 2006; Sasaki et al., 2006; Eftekarpour et al., 2007). However, as pointed out by Woodhoo et al. in this issue of Brain, the scattered nature of MS lesions and the inability of transplanted cells to migrate through normal white matter currently limit the therapeutic potential of cell transplantation for MS. While transplanted myelin-forming cells in general demonstrate an ability to remyelinate and display some degree of migration within demyelinated or traumatic CNS injury lesions, poor survival and migration within normal white matter (which may be present between lesions in MS) may limit their repair capacity (Franklin and Blakemore, 1997). One approach to this challenge is suggested by the observation that, while oligodendrocyte precursor cells (OPCs) survive poorly and do not migrate in normal CNS white matter, focal X-irradiation of the spinal cord results in development of an environment permissive for extensive OPC migration (Franklin and Blakemore, 1997). However, the level of radiation required to enhance OPC migration is high and can itself lead to post-radiation necrosis or myelopathy several months later, thus rendering X-irradiation as an adjunct to cell therapy for MS impractical.

Transplanted Schwann cells derived from mature rats (Honmou et al., 1996) and from adult human nerves (Kohama et al., 2001) can remyelinate CNS axons and have been shown to improve conduction in demyelinated spinal cord lesions in the rat. There are substantial differences in the molecular makeup of oligodendrocyte and Schwann cell myelin. These differences may turn out to be clinically important since Schwann cell myelin is not affected in MS, and myelin formed by Schwann cells after transplantation to the CNS may not be a target for the destructive process in MS. However, the inability of post-natal Schwann cells to migrate extensively through normal white matter, or through astrocyte-rich environments such as glial scars, poses a serious limitation for the potential use of these cells for myelin repair in MS.

Woodhoo and colleagues (2007) present interesting data showing that Schwann cell precursors (SCPs) derived from embryonic day 14 (E14) rat nerves survive transplantation into normal CNS, migrate through normal white matter, integrate with host glia, and are capable of remyelinating axons even when the SCPs are transplanted at some distance from the focal demyelinating lesion. The myelin formed by the SCPs is a peripheral type, containing the peripheral myelin protein P0. Thus, the Woodhoo et al. (2007) study suggests that SCPs may overcome the
important obstacle of poor migration of transplanted cells
within MS lesions, while at the same time evading the
immune attack in MS.

The potential use of adult Schwann cells derived from
tissue biopsy for transplantation may have an advantage
over use of embryonically derived SCPs in that autologous
cell transplantation would avoid immune rejection. Yet, the
poor migratory properties of adult Schwann cells through
normal and gliotic white matter is extremely limiting. As
progress is made in determining the molecular and cellular
differences between SCPs and post-natal Schwann cells,
molecular clues may be derived that could guide the
engineering of adult Schwann cells, or other cell types, to
improve their migratory properties through normal and
gliotic white matter to repair damaged myelin. This might
allow autologous Schwann cells to be modified to improve
migration, while retaining their autologous immune status
to reduce cell rejection.

A step in this direction was taken by Lavdas et al. (2006)
who genetically modified Schwann cells to alter their
adhesive properties, by expressing on their surface the
polysialylated (PSA) form of the neural adhesion molecule
NCAM. PSA is associated with migration of oligodendro-
cyte precursors during development, but is down-regulated
in the adult brain except in areas of plasticity. Schwann cell
membranes express NCAM, but PSA expression has not
been described for developing Schwann cells. Lavdas et al.
(2006) demonstrated improved migratory potential in brain
of Schwann cells altered to express PSA. Given that
embryonic Schwann cells apparently do not express PSA-
NCAM, the enhanced migratory properties of SCPs as
compared to the post-natal Schwann cells reported by
Woodhoo et al. (2007) may reflect molecular specializations
independent of PSA-NCAM expression.

In this issue of Brain, Papastefanaki et al. (2007) report
that PSA-NCAM Schwann cells show improved integration
with astrocytes in vitro, and that transplantation of these
generically modified Schwann cells can lead to improved
remyelination, axonal regeneration, recruitment of endo-
genous myelinating cells and improved functional outcome
in a mouse spinal cord injury model. Thus, in principle,
modification of the adhesion properties of post-natal
Schwann cells may improve their ability to migrate through
astrocyte rich environments and to facilitate remyelination
by the modified Schwann cells as well as by recruitment of
endogenous cells.

A broader issue with regard to Schwann cells or their
precursors in repair of the demyelinated CNS in MS arises
from the potential consequences of introducing peripheral-
like myelin into the central nervous system. Unlike the
oligodendrocyte which forms multiple myelin segments
from a single relatively small cell, an individual Schwann
cell makes a single segment of myelin and occupies a
substantial volume, with a large, non-axonal cytoplasmic
and nuclear domain associated with each myelin segment.
It has been speculated that the phylogenetic selection for

References
Black JA, Waxman SG, Smith KJ. Remyelination of dorsal column axons
by endogenous Schwann cells restores the normal pattern of Nav1.6 and


