PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B

Phil. Trans. R. Soc. B (2008) **363**, 171–183
doi:10.1098/rstb.2006.2019
Published online 5 February 2007

Myelin repair: the role of stem and precursor cells in multiple sclerosis

Siddharthan Chandran[1,2,*], David Hunt[1,2], Alexis Joannides[1,2], Chao Zhao[1,3], Alastair Compston[1,2] and Robin J. M. Franklin[1,3]

[1]*Cambridge Centre for Brain Repair,* [2]*Department of Clinical Neurosciences, University of Cambridge, Robinson Way, Cambridge CB2 2PY, UK*
[3]*Department of Veterinary Medicine, University of Cambridge, Madingley Road, Cambridge CB3 0ES, UK*

Multiple sclerosis is the most common potential cause of neurological disability in young adults. The disease has two distinct clinical phases, each reflecting a dominant role for separate pathological processes: inflammation drives activity during the relapsing–remitting stage and axon degeneration represents the principal substrate of progressive disability. Recent advances in disease-modifying treatments target only the inflammatory process. They are ineffective in the progressive stage, leaving the science of disease progression unsolved. Here, the requirement is for strategies that promote remyelination and prevent axonal loss. Pathological and experimental studies suggest that these processes are tightly linked, and that remyelination or myelin repair will both restore structure and protect axons. This review considers the basic and clinical biology of remyelination and the potential contribution of stem and precursor cells to enhance and supplement spontaneous remyelination.

Keywords: multiple sclerosis; stem cells; precursor cells; neural repair; myelin; axonal injury

1. INTRODUCTION

Multiple sclerosis (MS) is the commonest cause of neurological disability in young adults with a prevalence of approximately 120 per 100 000 and a lifetime risk of 1 in 400 (Compston & Coles 2002). Although the cause of MS is unknown, it is well established that an interplay of genetic and environmental factors results in a multifocal and multiphasic disease defined histologically by inflammatory demyelination, axonal injury, astrocytosis and varying degrees of remyelination.

The clinical course in the majority of patients is initially characterized by episodes with complete recovery, followed by relapse with persistent deficits and finally secondary progression, a stage characterized by few, if any, discrete exacerbations. The natural history of MS reflects a dominant role for distinct but related pathological processes; thus, inflammation drives activity during the relapsing–remitting stage and axon degeneration becomes more prominent as disability accumulates and the disease starts slowly to progress. The occurrence of spontaneous remyelination has long been recognized, but is limited and seems ultimately to fail, resulting in progressive disability (Prineas & Connell 1979; Confavreux & Vukusic 2006*a*).

Comprehensive treatment strategies must therefore seek both to limit and repair the damage. At present, the modest achievements of disease-modifying treatments target only the inflammatory process and are ineffective in the progressive stage. While further advances in reducing relapse rates are expected, these will leave unsolved the clinical science of disease progression. Here, the requirement is for strategies that promote remyelination and prevent axonal loss. Pathological analyses and experimental studies suggest that these processes are tightly linked, and that remyelination will not only restore structure and nerve conduction, but also prove to be axon protective (Raine & Cross 1989; Kornek *et al.* 2000; Rodriguez 2003).

Remyelination is the reinvesting of new myelin around demyelinated axons. It will be argued that the fundamental importance of this process is due less to the restoration of saltatory conduction—welcome though it is—but mainly as the most rationale method for protecting axons and thus limiting clinical disability. There is thus a great need for strategies to promote remyelination. Debate around myelin repair can sometimes be reduced to an argument between endogenous and exogenous repair. However, this represents an oversimplification of processes that are not of themselves mutually exclusive. In this review, which addresses the basic and clinical biology of remyelination or myelin repair, we argue that stem cell-based insights can also contribute to the development of strategies that will both supplement and enhance spontaneous remyelination.

2. AXONAL INJURY AND IRREVERSIBLE DISABILITY IN MULTIPLE SCLEROSIS

Over the last decade, the emergence of increasingly sophisticated imaging techniques allied to detailed histological studies has catalysed a resurgence of interest in the contribution of axonal injury to MS. In some ways, this is a revisiting of an old story, given the reports of axonal pathology in early pathological

* Author for correspondence (sc222@cam.ac.uk).

One contribution of 14 to a Theme Issue 'Stem cells and brain repair'.

This journal is © 2007 The Royal Society

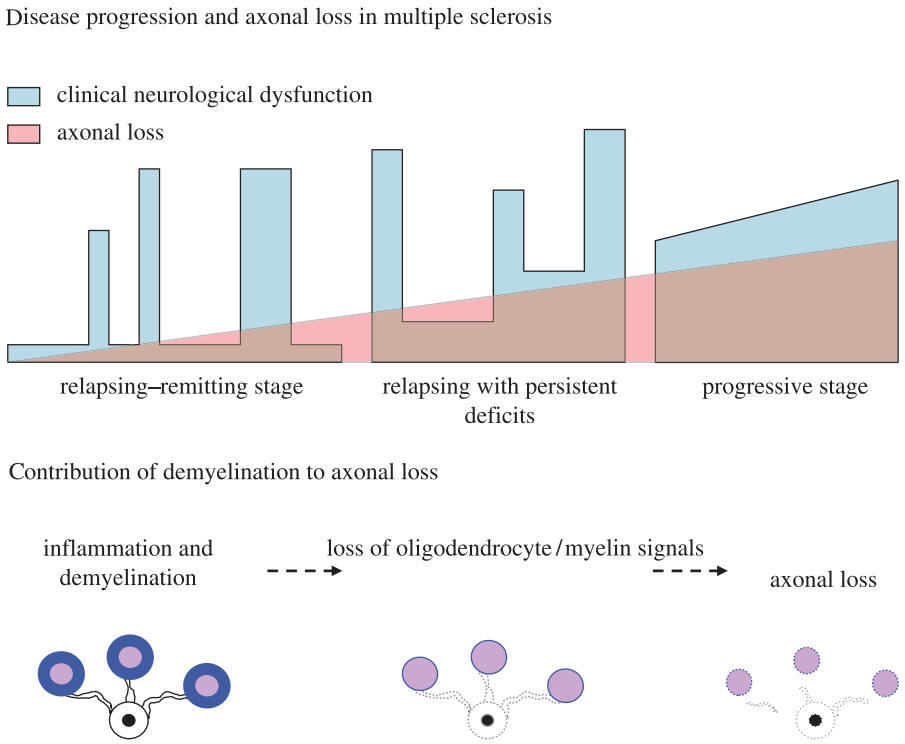

Figure 1. Demyelination, axonal loss and disease progression in MS. (*a*) The early stage of relapsing–remitting MS is characterized by transient neurological deficits that return to normal and pathology dominated by demyelination and focal inflammation. However, as the disease progresses, neurological dysfunction becomes fixed and accumulates. The pathological correlate of the progressive phase of the disease is axonal loss. (*b*) The early events of demyelination and inflammation are believed to contribute to axonal loss by numerous mechanisms, including loss of oligodendrocyte/myelin-derived trophic and structural support. The schematic diagram shows a single oligodendrocyte (black and white) myelinating three axons (axon: purple; myelin: blue). Early in the course of MS, the oligodendrocyte is damaged resulting in the demyelination of the axon. The loss of oligodendrocyte 'support' contributes and culminates in the axonal loss as found in progressive MS.

descriptions of the disease (Compston 2006). The focus on inflammation and demyelination had obscured the importance of axonal pathology as a key determinant of disability (De Stefano *et al.* 1998; Bjartmar *et al.* 2000).

Most patients develop progressive irreversible disability within 10–15 years of disease onset. Clinical, radiological and pathological evidence suggests that irreversible impairment and progressive disability result from exhausting a finite axonal reserve (Davie *et al.* 1995; De Stefano *et al.* 1998; Stevenson *et al.* 1998). Ferguson *et al.* (1997) and, subsequently, Trapp *et al.* (1998) provided quantitative evidence for axonal injury in both acute and chronic lesions. Together, these studies strongly suggest that axonal loss is the pathological substrate of progressive disability (figure 1*a*).

The precise mechanism, however, of axonal injury remains largely unknown. Acute axonal injury correlates with active inflammation (Trapp *et al.* 1998; Kornek *et al.* 2000; Kuhlmann *et al.* 2002). These observations have been extended by the demonstration of axonal injury in both non-inflammatory chronic lesions and normal-appearing white matter (Ferguson *et al.* 1997; Trapp *et al.* 1998; Bjartmar *et al.* 2000; Evangelou *et al.* 2000; Kornek *et al.* 2000; Lovas *et al.* 2000). These (and other) observations suggest that mechanisms that account for chronic axonal loss in MS are independent of inflammation. In turn, this raises the question of what is the interplay between the cardinal clinical features of MS, namely relapses and progression, and their pathological correlates, inflammation and axonal loss. The question remains unanswered despite considerable basic and clinical research activities. The answer(s) will also need to reconcile the weight of epidemiological evidence that argues for redundancy of the phenotypic distinction between relapsing–remitting and secondary progressive MS on reaching the stage of fixed moderate disability (Coles *et al.* 1999; Kremenchutzky *et al.* 1999; Confavreux *et al.* 2000; Confavreux *et al.* 2003; Confavreux & Vukusic 2006*b*; Kremenchutzky *et al.* 2006). Further discussion on the aetiopathogenesis of axonal injury in MS is outside the scope of this review, and the reader is referred to Compston *et al.* (2006).

3. REMYELINATION MATTERS: OLIGODENDROCYTE SIGNALS MAINTAIN AXONAL INTEGRITY

Experimental and pathological evidence supports the idea that myelin, in addition to enabling saltatory conduction, has a dynamic and vital role in maintaining axonal homeostasis and integrity; thus, chronically demyelinated axons—devoid of myelin-derived support, consequent on inflammation perhaps—are vulnerable to degeneration (figure 1*b*; Griffiths *et al.* 1998; Scherer 1999; Kornek *et al.* 2000). The influence of oligodendrocytes on axonal calibre and function is well described; oligodendrocytes myelinate axons, increase axonal stability and induce local accumulation and phosphorylation of neurofilaments within the axon (Colello *et al.* 1994; Sanchez *et al.* 1996; Witt & Brady 2000). Neuronal

function is further influenced by oligodendrocyte-derived soluble factors that induce sodium channel clustering, necessary for saltatory conduction, along axons and maintain this clustering even in the absence of direct axon–glial contact (Kaplan *et al.* 1997, 2001; Waxman 2001). Defined factors produced by cultured cells of the oligodendrocyte lineage also support neuronal survival and modulate axonal length by distinct intracellular mechanisms (Wilkins & Compston 2005; Wilkins *et al.* 2001, 2003).

Recent studies on experimental myelin mutant animals have further suggested a role for structural myelin proteins in the maintenance of axonal integrity. Griffiths and co-workers demonstrated a late axonopathy in the absence of inflammation and demyelination in proteolipid (PLP) mutant mice associated with a progressive motor disability. These observations have been extended by the finding in 2′,3′-cyclic nucleotide 3′-phosphodiesterase (CNPase) deficient mice of uncoupling between myelin assembly and axonal support compatible with the idea that oligodendrocyte dysfunction can result in a primary axonopathy (Lappe-Siefke *et al.* 2003). Along with the finding of axonal pathology in patients with a null mutation for PLP, these data suggest that myelin-derived signalling is necessary for the maintenance of axonal structure (Garbern *et al.* 2002). The function of such signals is unclear, although recent evidence implicates a role in enabling fast axonal transport (Pera *et al.* 2003; Edgar *et al.* 2004).

Recognition of the importance of oligodendrocyte signals in maintaining axonal health and the awareness that axonal degeneration occurs by regulated processes independent of apoptosis provide a compelling biological argument that remyelination is an essential part of any therapeutic strategy for MS (Raff *et al.* 2002).

4. WHAT CELLS GIVE RISE TO REMYELINATING OLIGODENDROCYTES?

It is now generally agreed that most, if not all, remyelinating oligodendrocytes arise from a population of adult precursor cells. This view is based on several lines of experimental evidence. First, proliferating cells that are likely to be $NG2^+$ precursors, can be labelled either by injecting a LacZ expressing retrovirus into normal white matter or by labelling with tritiated thymidine or BrdU, give rise to labelled remyelinating oligodendrocytes following induction of demyelination (Carroll & Jennings 1994; Gensert & Goldman 1997; Horner *et al.* 2000; Watanabe *et al.* 2002). Second, precursors isolated from adult central nervous system (CNS) can remyelinate areas of demyelination following transplantation (Zhang *et al.* 1999; Windrem *et al.* 2002). Third, oligodendrocyte precursors cells (OPCs) identified with a range of markers that include the growth factor receptor PDGFRα (Redwine & Armstrong 1998; Di Bello *et al.* 1999; Sim *et al.* 2002*a*; Fancy *et al.* 2004), the proteoglycan NG2 (Levine & Reynolds 1999; Mason *et al.* 2000*a*,*b*; Watanabe *et al.* 2002) and the transcription factors MyT1, Nkx2.2, Olig1 and Olig2 (Sim *et al.* 2002*a*,*b*; Fancy *et al.* 2004; Watanabe *et al.* 2004) have patterns of expression that are consistent with being the source of new oligodendrocytes, although for few of these markers is there unequivocal evidence that the cells they label become the remyelinating oligodendrocytes. In most situations, these cells are a distinctive phenotype widely referred to as adult OPCs. These cells are the adult descendants of an extensively studied developmental precursor. In adult tissue, these cells have a characteristic multipolar morphology and express several markers, of which NG2 and PDGFRα are the most commonly used (Nishiyama *et al.* 1996; Dawson *et al.* 2000, 2003). Apart from their ability to contribute to repair processes, it seems probable that they fulfil a range of normal physiological functions. Whether OPCs express both markers in all circumstances and in all regions of the adult CNS is uncertain (Hampton *et al.* 2004); indeed, the extent to which this is a homogenous population of cells throughout the adult neuraxis is also unresolved. There is now clear evidence that oligodendrocytes can be generated via several distinct lineage pathways and therefore, from a developmental perspective, the progenitor phenotypes are diverse (Mallon *et al.* 2002; Liu & Rao 2004; Cai *et al.* 2005; Vallstedt *et al.* 2005). For example, two distinct populations can be described on the basis of expression of PDGFRα or DM20, an alternatively spliced isoform of the proteolipid protein gene (Spassky *et al.* 1998, 2000). The extent to which OPCs in the adult CNS retain an imprint of their developmental origin remains to be unequivocally determined. One possibility is that adult OPCs are a homogenous population of cells having a similar phenotype and responsiveness to environmental signals, despite their varied ontogeny. Alternatively, distinctive types of OPC may exist, either coexisting or being specific to a particular anatomical region. There is some evidence to suggest that this may be the case: in tissue culture, the markers O4 and A2B5 appear to identify distinct populations of adult forebrain OPCs that respond differently to a range and combination of growth factors (Mason & Goldman 2002). This is clearly an important issue to resolve, especially in adult human tissue, if growth factor-based strategies are to be used therapeutically to enhance endogenous remyelination in clinical disease. The evidence that cells other than OPCs contribute to remyelination is limited. Two studies have demonstrated that when demyelinating lesions are induced in the corpus callosum close to the subventricular zone (SVZ), then neural progenitor cells can be deflected away from their normal path towards the olfactory bulb and the lesion, where they can contribute to the generation of new oligodendrocytes during remyelination (Nait-Oumesmar *et al.* 1999; Picard-Riera *et al.* 2002; Menn *et al.* 2006). The component of the total remyelination attributable to SVZ-derived cells is uncertain but is likely to be small given the abundance and responsiveness of locally derived OPCs. A further uncertain issue is how close an area of demyelination must be in order for SVZ progenitors to respond. While it is clear that lesions within the adjacent corpus callosum can induce this response, it is improbable that white matter lesions remote from the SVZ in, for example, the spinal cord or brain stem white matter will do so, given that most remyelinating cells are recruited

from a narrow region surrounding a lesion (Franklin *et al.* 1997). In white matter regions remote from the SVZ, there is no clear evidence at present that cells other than OPCs contribute to remyelination.

5. DO ENDOGENOUS CNS STEM CELLS CONTRIBUTE TO REMYELINATION?

If one applies strict criteria to the definition of a stem cell (a multipotent cell, generally attached to a basal lamina, that divides slowly and is both self-renewing and able to give rise to rapidly proliferating progenitor cells by asymmetric division), then true stem cells within the adult mammalian CNS are rare, comprising the GFAP-expressing B cells of the SVZ and, perhaps, their hippocampal equivalents (Doetsch *et al.* 1999*a*,*b*; Sanai *et al.* 2004; Seri *et al.* 2004). Recent experimental evidence suggests that SVZ type B cells may contribute to remyelination (Menn *et al.* 2006). Thus, adult CNS stem cells make a small and anatomically restricted contribution to endogenous remyelination in the adult. This is similar to other regenerating tissues where proliferation of the stem cell population is scarcely affected by the sudden demand for new differentiated cells following injury. Instead, the transit-amplifying population of progenitors, which, unlike the stem cells from which they are generated, have the proliferative responsiveness to generate the new cells required to repair damaged tissue, takes up this demand. Should one regard the OPCs of the adult brain as being stem cells or progenitor cells? OPCs certainly exhibit some stem cell properties: they show multipotency, giving rise to oligodendrocytes, neurons and, at least *in vitro*, astrocytes (Ffrench-Constant & Raff 1986; Belachew *et al.* 2003; Kondo & Raff 2000; Nunes *et al.* 2003; Gaughwin *et al.* 2006), and have very high levels of telomerase activity allowing them to undergo many rounds of proliferation before becoming senescent (Tang *et al.* 2001). However, their rapid proliferation, symmetrical division (the daughter cells of OPC proliferation are still OPCs, regardless of whether they subsequently differentiate into oligodendrocytes or not) and absence of a distinct anatomical relationship with a basal lamina are more consistent with their being a transit-amplifying population and, in our view, they are more accurately designated as progenitors rather than stem cells. Indeed, a pertinent question to consider is how similar OPCs are to other multipotent neural progenitor cells within the adult CNS, and whether, perhaps, a generic term of neural progenitor should be more widely applied (Goldman 2003).

6. WHY DOES REMYELINATION FAIL?

Since the cells responsible for generating new oligodendrocytes are transit-amplifying progenitor cells, can their capacity to proliferate in response to injury become exhausted if repeatedly tested? This question has important implications for understanding why remyelination often fails and how easy it will be to mobilize OPCs therapeutically. The ability of adult OPCs to repopulate areas from which they are deficient appears to be very robust (Chari & Blakemore 2002). When the same area of CNS is exposed to several rounds of demyelination/remyelination, the number of OPCs is not reduced and the efficiency of remyelination is unimpaired by previous rounds of remyelination (Penderis *et al.* 2003*a*). This implies that a failure of remyelination is not due to an exhaustion of OPCs available to repopulate the demyelinated area and give rise to new oligodendrocytes. However, this appears only to be the case if sufficient time is left between demyelinating episodes to allow the OPC numbers to be replenished. OPC numbers do gradually diminish if an area of demyelination is exposed to a continuing demyelinating insult (Ludwin 1980; Mason *et al.* 2004). However, the interpretation of these long-term experiments in rodents is confounded by ageing, since this process alone can significantly impair the responsiveness of OPCs to demyelination (Sim *et al.* 2002*b*), partly due to changes in the signalling environment with ageing and, possibly, also due to intrinsic changes in the responsiveness of aged OPCs (Hinks & Franklin 2000; Decker *et al.* 2002; Chari *et al.* 2003). For a more detailed description of the many environmental factors regulating remyelination and how disturbances in their patterns of expression might contribute to remyelination failure see Franklin (2002).

7. PROMOTING ENDOGENOUS REMYELINATION

Since endogenous remyelination spontaneously occurs in MS, sometimes partially but on occasions completely, an obvious therapeutic approach is to promote this naturally occurring repair process in situations where it is inefficient or has failed (Dubois-Dalcq *et al.* 2005; Lubetzki *et al.* 2005). Improved understanding of the mechanism of endogenous remyelination and why it fails will enable the development of strategies to promote spontaneous remyelination, as outlined in figure 2. In truth, while this approach is generally regarded as the preferred long-term means of promoting remyelination, it is currently further away from clinical implementation than the exogenous or transplantation approach and experimental proofs-of-principle are few. The reasons for this are many, including matching the information gained from experimental models to the clinical analyses. A commonly used inflammatory-mediated animal model of MS is experimental autoimmune encephalitic (EAE), created by immunization against specific oligodendrocyte/myelin components. Several studies have reported enhancement of remyelination in EAE models following administration (often systemic) of specific compounds (Komoly *et al.* 1992; Cannella *et al.* 1998; Fernandez *et al.* 2004). However, the significance of these studies and their interpretation is unclear for reasons including difficulty in separating effects on reduction of demyelination versus promotion of remyelination and relevance to chronically demyelinated MS lesions (which often contain abundant quiescent oligodendrocyte lineage cells that fail to fully differentiate into remyelinating oligodendrocytes) for which remyelination enhancing therapies are required (Scolding *et al.* 1998; Wolswijk 1998; Chang *et al.* 2002).

Some of these difficulties can be overcome by using toxin models of demyelination. However, using these models, interventions that either inhibit remyelination or have no effect have proven much easier to achieve than those that promote remyelination

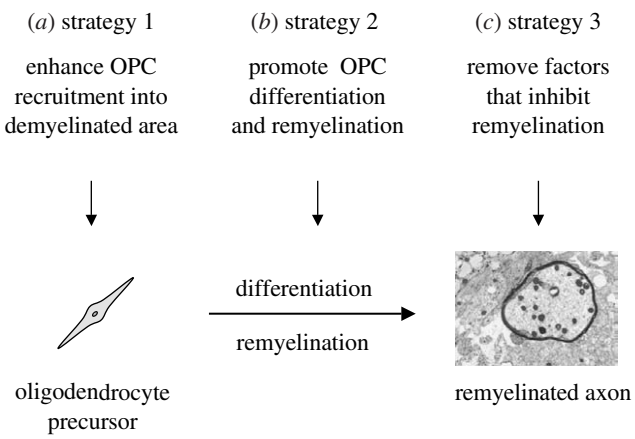

Figure 2. Strategies to promote endogenous remyelination. A schematic showing (*a*) recruitment of OPCs into the demyelinated MS lesion, (*b*) promotion of OPC differentiation, maturation, engagement and remyelination of axons, and (*c*) removal of inhibitory signals within the chronic demyelinated lesion that prevent successful remyelination. Electron micrograph demonstrating remyelination of a demyelinated adult axon by an oligodendrocyte progenitor cell (courtesy of S. Chandran and W. F. Blakemore).

(O'Leary *et al.* 2002; Penderis *et al.* 2003*b*; Ibanez *et al.* 2004; Back *et al.* 2005). Moreover, systemically delivered agents, whose site and mode of action is generally unknown, have generally proved more effective than those delivered directly into areas of demyelination (O'Leary *et al.* 2002; Penderis *et al.* 2003*b*; Ibanez *et al.* 2004). Together, these various data point to a mechanism of remyelination that is both complex and highly redundant, whose failure results from perturbation of a network of factors; the 'dysregulation hypothesis' (Franklin 2002) and where single factors often fail to tip a multi-component process towards more efficient working. For example, growth factors, which are potent regulators of OPC biology, often function best in combination with other growth factors or by interaction with integrin-mediated signalling (Baron *et al.* 2002; Colognato *et al.* 2002). It is for this reason that single growth factor interventions are unlikely to work. Instead, effective pro-remyelinating factors are likely to be those that trigger cascades of signalling events leading to the creation of a multi-faceted pro-remyelination environment (and may not themselves be directly active of oligodendrocyte lineage cells) or are as yet unidentified non-redundant mediators of remyelination. In this regard, the role of 'stem cells' as potential cellular vehicles of 'factors' (see below) may be of interest.

An alternative strategy for promoting remyelination may be to overcome inhibitory factors in lesions preventing it from occurring (Charles *et al.* 2002; Back *et al.* 2005). Additional approaches, aside from the identification of non-redundant mediators of remyelination, are to explore empirical approaches, such as human monoclonal antibodies where binding to the oligodendrocyte surface enhances remyelination in several demyelination models (Pavelko *et al.* 1998; Warrington *et al.* 2000; Pirko *et al.* 2004). Another is to bypass redundant extrinsic signalling events and target transcription factor genes critical for the developmental differentiation of multipotent precursors into oligodendrocytes such as Olig1 (Arnett *et al.* 2004). Olig2 and Nkx2.2 are promising candidates since their expression increases in precursors responding to demyelination (Fancy *et al.* 2004).

8. REMYELINATION BY EXOGENOUS STEM/PRECURSOR CELLS

Considerable hope has been invested in the potential of stem cells as vehicles for neurological repair. In MS, expectation has been largely predicated on the potential of stem cells to yield unlimited numbers of defined myelinating cells. The emergence of methods to isolate and neuralize human embryonic stem cells in the last decade has fuelled that expectation. Successful remyelination has been achieved in a wide range of demyelinating models, using a variety of cell types. These have included embryonic- and adult-derived cells of the oligodendrocyte lineage, Schwann cells, olfactory ensheathing cells, and neural precursors (NPCs) and non-NPCs (figure 3; Blakemore & Crang 1988; Franklin & Blakemore 1997; Imaizumi *et al.* 1998*a*; Brustle *et al.* 1999; Keirstead *et al.* 1999; Zhang *et al.* 1999; Barnett *et al.* 2000; Kohama *et al.* 2001; Mitome *et al.* 2001; Akiyama *et al.* 2002).

Transplantation-mediated remyelination is effective. The question, however, is less 'does it work?' (it does), but rather 'are experimental predominantly rodent-based observations relevant to a multiphasic, multifocal disease with a variable natural history?' In order to address this question, it is helpful to consider the challenges and thus requirements of any putative pro-myelinating cell. At a minimum, the cell must survive and navigate the pathological host environment to encounter and successfully reinvest demyelinated axons with new myelin. The ability to migrate between lesions would be a welcome addition to the curriculum vitae of such a cell given the multifocal nature of the disease. Other requirements such as sufficient numbers, resistance to endogenous disease and immune rejection are discussed later.

The pathological environment, however, is not a fixed target, but variable and determined in part by the clinical phenotype and natural history of the disease. Recognition of four different patterns of demyelination in MS suggests that subtly different reparative treatments tailored for the distinct pathologies may be necessary (Lassmann *et al.* 2001). For example, primary progressive MS, characterized in general by less inflammation and earlier and more sustained axonal loss, may require a different approach to the more common relapse–remitting (RR) phenotype (Lucchinetti & Bruck 2004). Furthermore, the three distinct stages in the evolution of tissue injury attributable to MS—RR, relapsing with persistent deficits and secondary progressive—require different treatment strategies. Traditionally, it has been considered that remyelination strategies are best focussed upon chronic plaques—which are pathologically similar regardless of disease onset—characterized by demyelination, variable amounts of inflammation and gliosis (Lassmann *et al.* 1998). However, insights from animal models and pathological studies of MS lesions suggest that either earlier, and hence more acute, lesions represent better targets for transplantation-mediated

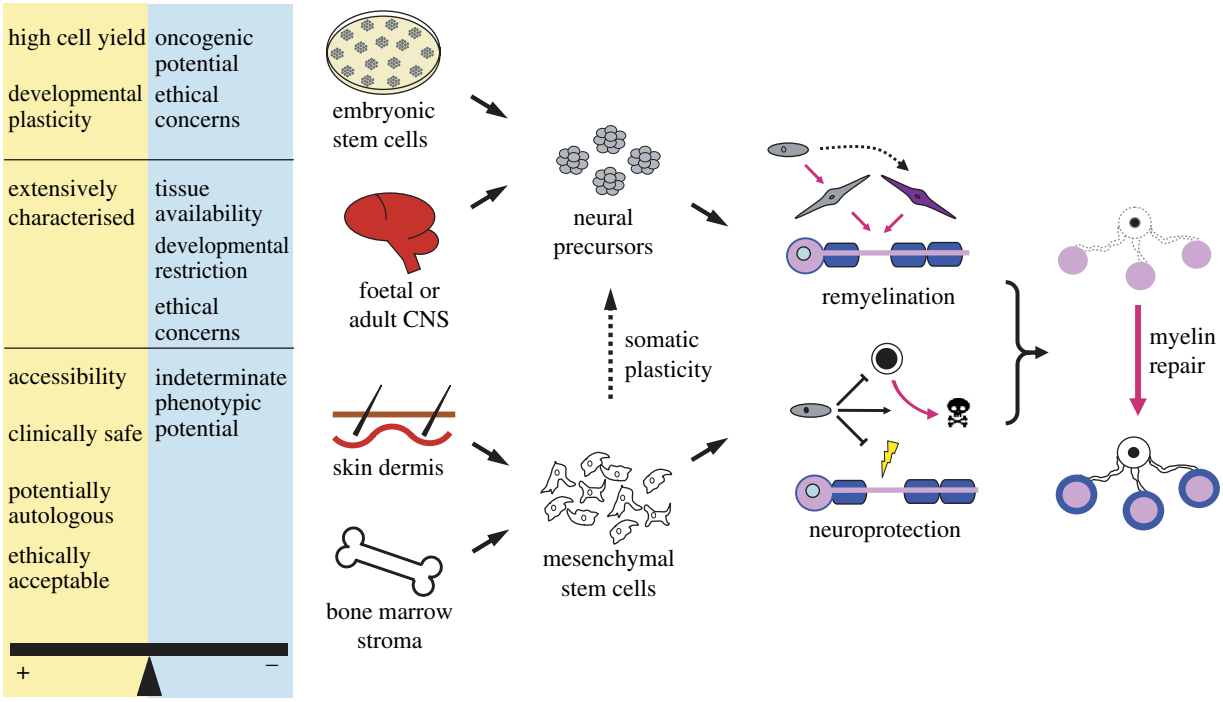

Figure 3. Promotion of myelin repair by exogenous cells. Cells may be derived from developmentally distinct stages: embryonic, foetal and adult. Two classes of cells have generated particular interest, each with their own benefits and drawbacks: NPCs and adult non-neural stem cells. NPCs may be generated by *ex vivo* manipulation from human embryonic stem cells, or directly from primary foetal or adult brain samples. Adult mesenchymal stem cells can be generated from readily accessible sources such as skin and bone marrow. Other cell types that are potentially capable of myelination include olfactory ensheathing cells and Schwann cells. Exogenous cells may promote remyelination directly or indirectly by differentiation into myelinating cells and/or promotion of endogenous remyelination. In addition, grafted cells can be neuroprotective by means independent of differentiation such as immune modulation and trophic support (see text for details).

myelin repair, or those chronic ones in which the environment has been altered to more closely resemble that of an acute remyelinating lesion are to be preferred (Hammarberg *et al.* 2000; Foote & Blakemore 2005; Kotter *et al.* 2005, 2006; Setzu *et al.* 2006). These studies provide evidence that inflammation can be beneficial to remyelination.

9. CHOICE OF EXOGENOUS STEM/PRECURSOR CELL

Although it is highly improbable that xenografts will ever be contemplated in clinical practice, comparatively few studies have examined the remyelination potential of human-derived cells. Recognition of inter-species difference in the behaviour of NPCs with respect to their capacity to generate oligodendrocytes caution the extent to which extrapolation from other systems can reliably be made to human disease; this emphasizes the need for improved understanding of human precursor cell biology (Chandran *et al.* 2004).

Olfactory ensheathing cells and Schwann cells are presently the only readily accessible and potentially autologous adult human cell populations with well-characterized myelinating potential. Olfactory ensheathing cells are specialized glial cells that are entering phase I clinical studies in spinal cord injury on account of their ability to promote and augment axon growth (Feron *et al.* 2005). These cells may also have a role in myelin repair, given their ability to remyelinate central demyelinated axons with a Schwann cell-like phenotype (Franklin *et al.* 1996; Imaizumi *et al.* 1998*b*; Barnett *et al.* 2000; Sasaki *et al.* 2004). Moreover, unlike Schwann cells, olfactory ensheathing cells appear to be able to migrate and more readily integrate into an astrocytic environment (Lakatos *et al.* 2000; Lakatos *et al.* 2003). This is a distinct advantage, given that astrocytic gliosis is prevalent in both acute and chronic MS lesions.

In view of the need for scale, human NPCs represent the most plausible source of exogenous central myelinating cells. NPCs can be readily derived from embryonic stem cells and the foetal and adult CNS (figure 3). There are merits and disadvantages associated with selecting any human-derived material. NPCs and cells of more restricted glial and neuronal potential are found in the adult brain. Aside from the degree of phenotypic potential of adult glial progenitors, contingent on environment, it is clear that (viewed collectively) the adult human brain contains a range of NPCs (Kukekov *et al.* 1999; Arsenijevic *et al.* 2001; Palmer *et al.* 2001; Nunes *et al.* 2003; Sanai *et al.* 2004). Regardless of origin, the requirement to direct human precursors to the early oligodendrocyte lineage—necessary for remyelination—*ex vivo* presents a considerable challenge (Smith & Blakemore 2000). For example, foetal NPCs, although readily propagated, cannot be systematically directed to a myelinating phenotype (Murray & Dubois-Dalcq 1997; Quinn *et al.* 1999; Zhang *et al.* 2000; Chandran *et al.* 2004). Cell surface-based selection methods provide one approach directly to isolate human white matter precursor(s) that possesses remyelinating potential (Roy *et al.* 1999; Windrem *et al.* 2002, 2004). Although valuable as an experimental resource, limited availability of foetal and adult human material constrains any widespread clinical application. Furthermore, in

addition to there being a limited supply stream, the inability to standardize and predict or define sample(s) in terms of age, region and co-morbidity (for adult biopsy-derived specimens) precludes ready comparison between samples and increases the 'noise' of any resulting data. By contrast, human embryonic stem cells offer an alternative means to generate potentially unlimited numbers of defined NPCs and enriched populations of functional oligodendrocytes (Carpenter *et al.* 2001; Reubinoff *et al.* 2001; Zhang *et al.* 2001; Keirstead *et al.* 2005; Nistor *et al.* 2005). Notwithstanding advances in isolation, propagation of human embryonic stem (hES) cells and neuralization protocols that bring closer the prospect of clinical grade hES-derived NPCs, much remains to be determined with respect to the long-term efficacy of hES-derived precursors (Klimanskaya *et al.* 2005; Joannides *et al.* 2006; Ludwig *et al.* 2006). To date, no long-term studies have demonstrated stable functional integration of hES-derived neural derivatives. Indeed, concerns regarding potential oncogenic complications of hES-derived material have catalysed the study of alternative sources of human NPCs.

10. NON-NEURAL STEM CELLS

Until recently, somatic stem cells were regarded as restricted to regeneration of their tissue of origin. Recent observations have raised the concept of more widespread phenotypic potential of adult somatic stem cells, despite additional explanations for some of the earlier experimental observations (Terada *et al.* 2002; Ying *et al.* 2002). Several lines of evidence focused largely around bone marrow and mesenchymal derivatives (figure 3) suggest that somatic stem cells derived from non-neural tissue may be capable of generating NPCs (Jiang *et al.* 2002, 2003; Clarke & Frisen 2001; Toma *et al.* 2001; Joannides *et al.* 2004). These studies find some support from opportunistic observations on the brains of females receiving bone marrow transplants from males indicating transdifferentiation rather than fusion as a potential explanation (Weimann *et al.* 2003; Cogle *et al.* 2004; Crain *et al.* 2005). The prospect of an ethically acceptable, readily accessible and potentially autologous source of NPCs is clearly very attractive. However, despite the evidence of remyelination by adult bone marrow-derived cells, there remains a large amount of basic characterization and improved understanding of the mechanism of 'somatic stem cell plasticity' to be gained before adult non-neural stem cells can be reasonably contemplated as a reliable source of myelinating cells (Akiyama *et al.* 2002; Takahashi & Yamanaka 2006). Additional properties of adult stem cells may, however, offer a more immediate and plausible role in remyelination and neuroprotective therapies.

11. CAN CELLULAR THERAPIES PROMOTE NEUROPROTECTION INDEPENDENT OF DIFFERENTIATION?

Cellular therapies for MS have until recently been viewed as a cell-replacement strategy to be targeted at site-specific repair. However, recognition of the potential utility of NPCs outside of directed differentiation offers additional therapeutic opportunities. The demonstration that intravenous administration of stem cells leads to delivery throughout the inflammatory neuraxis resulting in axonal protection and functional improvement is of considerable interest (Pluchino *et al.* 2003, 2005; Zappia *et al.* 2005). Specifically, increasing evidence suggests that stem cell-based therapies may be neuroprotective in models of multifocal inflammatory disease, independent of directed differentiation. These studies highlight the immune-modulatory effects of stem cells. Inflammation is not only central to disease pathogenesis, but is also likely to be necessary for optimum remyelination (see below), and the idea that cellular immune-modulation may blunt the former and promote the latter is intriguing. Two cell types have demonstrated efficacy: rodent NPCs (neonatal and adult) and adult mesenchymal stem cells (MSCs; Einstein *et al.* 2003; Pluchino *et al.* 2005; Zappia *et al.* 2005). Pluchino *et al.* (2003, 2005) have shown that systemically delivered undifferentiated adult NPCs into EAE mice can, contingent on the microenvironment, either differentiate into myelinating cells or, where inflammation predominates, exert a neuroprotective effect by inducing selective apoptotic death of Th1 cells. Expression of integrin and G-protein-coupled receptors permits circulating NPCs to be recruited to the CNS using adhesion and chemokine-mediated homing mechanisms analogous to those used by activated lymphocytes. In this regard, the expression of chemokine receptors by NPCs and MSCs is of interest (Tran *et al.* 2004; Dar *et al.* 2005; Honczarenko *et al.* 2005; Pluchino *et al.* 2005; Sordi *et al.* 2005). The mechanism of neuroprotection is uncertain, but evidence is provided suggesting that this is mediated, at least in part, by selective NPC-mediated T-cell death. Importantly, in the chronic recurrent EAE model, NPCs resulted in functional improvement and reduced axonal loss (Pluchino *et al.* 2005). A further study has demonstrated that peripheral delivery of human bone marrow-derived MSCs also promote functional recovery in EAE mice (Zhang *et al.* 2005). It remains to be determined whether MSCs also produce trophic factors that have previously been shown to promote axonal health, thus offering a further mechanism of neuroprotection (Wilkins *et al.* 2003).

The multifocal nature of MS has long been a conceptual barrier to stem cell-based therapies. However, the ability of precursors, delivered systemically or by the intrathecal route, to cross the blood–brain barrier and then exhibit migratory behaviour within the pathological brain suggests that the dilemma of how best to deliver and distribute a novel cellular therapy may not be problematic (Ben Hur *et al.* 2003; Pluchino *et al.* 2003). In addition to the idea of stem cells behaving as cellular immune-modulators, their demonstrated migratory and 'homing' effects additionally raise the prospect of using neural stem cells as cellular delivery vehicles. Proofs of concept studies in animal models have exploited the innate tropism of stem cells to target therapy to pathological lesions (Aboody *et al.* 2000; Benedetti *et al.* 2000). The molecular basis of homing is uncertain; however, inflammation appears to be a regulator of tropism through the action of various cytokines acting through receptors including CCR2,

CCR3, CCR5 and CXCR4 that are expressed in EAE and MS brains (Kennedy *et al.* 1998; Simpson *et al.* 2000; Tran *et al.* 2004; Honczarenko *et al.* 2005; Pluchino *et al.* 2005).

12. CONCLUSION

The Holy Grail in MS research is to deliver therapies that limit and repair damage. Despite significant advances in disease-modification treatments, strategies that enable repair remain elusive. This in part reflects the absence of consensus for the cause and mechanism of disease progression. At the heart of this question lies the role and interrelationship of inflammation and axonal loss. A parallel though ultimately convergent question is how can axonal loss, the pathological correlate of disability, be limited? The intuitive view that remyelination is protective of axons in MS is supported by considerable although largely indirect evidence. Remyelination as a neuroprotective therapy thus appears a reasonable hypothesis. Although therapeutic success will most probably require details of the pathological process that limit remyelination to be further understood, an increasing body of evidence provides grounds for cautious optimism that stem cell-based therapies offer realistic prospects for myelin repair over the next decade.

REFERENCES

Aboody, K. S. *et al.* 2000 Neural stem cells display extensive tropism for pathology in adult brain: evidence from intracranial gliomas. *Proc. Natl Acad. Sci. USA* **97**, 12 846–12 851. (doi:10.1073/pnas.97.23.12846)

Akiyama, Y., Radtke, C. & Kocsis, J. D. 2002 Remyelination of the rat spinal cord by transplantation of identified bone marrow stromal cells. *J. Neurosci.* **22**, 6623–6630.

Arnett, H. A. *et al.* 2004 bHLH transcription factor Olig1 is required to repair demyelinated lesions in the CNS. *Science* **306**, 2111–2115. (doi:10.1126/science.1103709)

Arsenijevic, Y., Villemure, J. G., Brunet, J. F., Bloch, J. J., Deglon, N., Kostic, C., Zurn, A. & Aebischer, P. 2001 Isolation of multipotent neural precursors residing in the cortex of the adult human brain. *Exp. Neurol.* **170**, 48–62. (doi:10.1006/exnr.2001.7691)

Back, S. A. *et al.* 2005 Hyaluronan accumulates in demyelinated lesions and inhibits oligodendrocyte progenitor maturation. *Nat. Med.* **11**, 966–972.

Barnett, S. C. *et al.* 2000 Identification of a human olfactory ensheathing cell that can effect transplant-mediated remyelination of demyelinated CNS axons. *Brain* **123**, 1581–1588. (doi:10.1093/brain/123.8.1581)

Baron, W., Shattil, S. J. & Ffrench-Constant, C. 2002 The oligodendrocyte precursor mitogen PDGF stimulates proliferation by activation of alpha(v)beta3 integrins. *EMBO J.* **21**, 1957–1966. (doi:10.1093/emboj/21.8.1957)

Belachew, S., Chittajallu, R., Aguirre, A. A., Yuan, X., Kirby, M., Anderson, S. & Gallo, V. 2003 Postnatal NG2 proteoglycan-expressing progenitor cells are intrinsically multipotent and generate functional neurons. *J. Cell Biol.* **161**, 169–186. (doi:10.1083/jcb.200210110)

Ben Hur, T., Einstein, O., Mizrachi-Kol, R., Ben Menachem, O., Reinhartz, E., Karussis, D. & Abramsky, O. 2003 Transplanted multipotential neural precursor cells migrate into the inflamed white matter in response to experimental autoimmune encephalomyelitis. *Glia* **41**, 73–80. (doi:10.1002/glia.10159)

Benedetti, S. *et al.* 2000 Gene therapy of experimental brain tumors using neural progenitor cells. *Nat. Med.* **6**, 447–450. (doi:10.1038/74710)

Bjartmar, C., Kidd, G., Mork, S., Rudick, R. & Trapp, B. D. 2000 Neurological disability correlates with spinal cord axonal loss and reduced *N*-acetyl aspartate in chronic multiple sclerosis patients. *Ann. Neurol.* **48**, 893–901. (doi:10.1002/1531-8249(200012)48:6<893::AID-ANA10>3.0.CO;2-B)

Blakemore, W. F. & Crang, A. J. 1988 Extensive oligodendrocyte remyelination following injection of cultured central nervous system cells into demyelinating lesions in adult central nervous system. *Dev. Neurosci.* **10**, 1–11.

Brustle, O., Jones, K. N., Learish, R. D., Karram, K., Choudhary, K., Wiestler, O. D., Duncan, I. D. & McKay, R. D. 1999 Embryonic stem cell-derived glial precursors: a source of myelinating transplants. *Science* **285**, 754–756. (doi:10.1126/science.285.5428.754)

Cai, J., Qi, Y., Hu, X., Tan, M., Liu, Z., Zhang, J., Li, Q., Sander, M. & Qiu, M. 2005 Generation of oligodendrocyte precursor cells from mouse dorsal spinal cord independent of Nkx6 regulation and Shh signaling. *Neuron* **45**, 41–53. (doi:10.1016/j.neuron.2004.12.028)

Cannella, B., Hoban, C. J., Gao, Y. L., Garcia-Arenas, R., Lawson, D., Marchionni, M., Gwynne, D. & Raine, C. S. 1998 The neuregulin, glial growth factor 2, diminishes autoimmune demyelination and enhances remyelination in a chronic relapsing model for multiple sclerosis. *Proc. Natl Acad. Sci. USA* **95**, 10 100–10 105. (doi:10.1073/pnas.95.17.10100)

Carpenter, M. K., Inokuma, M. S., Denham, J., Mujtaba, T., Chiu, C. P. & Rao, M. S. 2001 Enrichment of neurons and neural precursors from human embryonic stem cells. *Exp. Neurol.* **172**, 383–397. (doi:10.1006/exnr.2001.7832)

Carroll, W. M. & Jennings, A. R. 1994 Early recruitment of oligodendrocyte precursors in CNS demyelination. *Brain* **117**, 563–578.

Chandran, S., Compston, A., Janauiax, E., Gilson, J., Blakemore, W. F. & vendsen, C. 2004 Differential generation of oligodendrocytes from human and rodent embryonic spinal cord neural precursors. *Glia* **47**, 314–324. (doi:10.1002/glia.20011)

Chang, A., Tourtellotte, W. W., Rudick, R. & Trapp, B. D. 2002 Premyelinating oligodendrocytes in chronic lesions of multiple sclerosis. *N. Engl. J. Med.* **346**, 165–173. (doi:10.1056/NEJMoa010994)

Chari, D. M. & Blakemore, W. F. 2002 Efficient recolonisation of progenitor-depleted areas of the CNS by adult oligodendrocyte progenitor cells. *Glia* **37**, 307–313. (doi:10.1002/glia.10038)

Chari, D. M., Crang, A. J. & Blakemore, W. F. 2003 Decline in rate of colonization of oligodendrocyte progenitor cell (OPC)-depleted tissue by adult OPCs with age. *J. Neuropathol. Exp. Neurol.* **62**, 908–916.

Charles, P., Reynolds, R., Seilhean, D., Rougon, G., Aigrot, M. S., Niezgoda, A., Zalc, B. & Lubetzki, C. 2002 Re-expression of PSA-NCAM by demyelinated axons: an inhibitor of remyelination in multiple sclerosis? *Brain* **125**, 1972–1979. (doi:10.1093/brain/awf216)

Clarke, D. & Frisen, J. 2001 Differentiation potential of adult stem cells. *Curr. Opin. Genet. Dev.* **11**, 575–580. (doi:10.1016/S0959-437X(00)00235-5)

Cogle, C. R., Yachnis, A. T., Laywell, E. D., Zander, D. S., Wingard, J. R., Steindler, D. A. & Scott, E. W. 2004 Bone marrow transdifferentiation in brain after transplantation: a retrospective study. *Lancet* **363**, 1432–1437. (doi:10.1016/S0140-6736(04)16102-3)

Colello, R. J., Pott, U. & Schwab, M. E. 1994 The role of oligodendrocytes and myelin on axon maturation in the developing rat retinofugal pathway. *J. Neurosci.* **14**, 2594–2605.

Coles, A. J., Wing, M. G., Molyneux, P., Paolillo, A., Davie, C. M., Hale, G., Miller, D., Waldmann, H. & Compston, A. 1999 Monoclonal antibody treatment exposes three mechanisms underlying the clinical course of multiple sclerosis. *Ann. Neurol.* **46**, 296–304. (doi:10.1002/1531-8249(199909)46:3<296::AID-ANA4>3.0.CO;2-)

Colognato, H., Baron, W., Avellana-Adalid, V., Relvas, J. B., Baron-Van Evercooren, A., Georges-Labouesse, E. & Ffrench-Constant, C. 2002 CNS integrins switch growth factor signalling to promote target-dependent survival. *Nat. Cell Biol.* **4**, 833–841. (doi:10.1038/ncb865)

Compston, A. & Coles, A. 2002 Multiple sclerosis. *Lancet* **359**, 1221–1231. (doi:10.1016/S0140-6736(02)08220-X)

Compston, A. 2006 In *McAlpine's multiple sclerosis* (ed. A. Compston *et al.*), 4th edn. London, UK: Churchill Livingstone.

Confavreux, C. & Vukusic, S. 2006*a* Accumulation of irreversible disability in multiple sclerosis: from epidemiology to treatment. *Clin. Neurol. Neurosurg.* **108**, 327–332. (doi:10.1016/j.clineuro.2005.11.018)

Confavreux, C. & Vukusic, S. 2006*b* Natural history of multiple sclerosis: a unifying concept. *Brain* **129**, 606–616. (doi:10.1093/brain/awl007)

Confavreux, C., Vukusic, S., Moreau, T. & Adeleine, P. 2000 Relapses and progression of disability in multiple sclerosis. *N. Engl. J. Med.* **343**, 1430–1438. (doi:10.1056/NEJM200011163432001)

Confavreux, C., Vukusic, S. & Adeleine, P. 2003 Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. *Brain* **126**, 770–782. (doi:10.1093/brain/awg081)

Crain, B. J., Tran, S. D. & Mezey, E. 2005 Transplanted human bone marrow cells generate new brain cells. *J. Neurol. Sci.* **233**, 121–123. (doi:10.1016/j.jns.2005.03.017)

Dar, A. *et al.* 2005 Chemokine receptor CXCR4-dependent internalization and resecretion of functional chemokine SDF-1 by bone marrow endothelial and stromal cells. *Nat. Immunol.* **6**, 1038–1046. (doi:10.1038/ni1251)

Davie, C. A., Barker, G. J., Webb, S., Tofts, P. S., Thompson, A. J., Harding, A. E., McDonald, W. I. & Miller, D. H. 1995 Persistent functional deficit in multiple sclerosis and autosomal dominant cerebellar ataxia is associated with axon loss. *Brain* **118**, 1583–1592.

Dawson, M. R., Levine, J. M. & Reynolds, R. 2000 NG2-expressing cells in the central nervous system: are they oligodendroglial progenitors? *J. Neurosci. Res.* **61**, 471–479. (doi:10.1002/1097-4547(20000901)61:5<471::AID-JNR1>3.0.CO;2-N)

Dawson, M. R., Polito, A., Levine, J. M. & Reynolds, R. 2003 NG2-expressing glial progenitor cells: an abundant and widespread population of cycling cells in the adult rat CNS. *Mol. Cell Neurosci.* **24**, 476–488. (doi:10.1016/S1044-7431(03)00210-0)

De Stefano, N., Matthews, P. M., Fu, L., Narayanan, S., Stanley, J., Francis, G. S., Antel, J. P. & Arnold, D. L. 1998 Axonal damage correlates with disability in patients with relapsing-remitting multiple sclerosis. Results of a longitudinal magnetic resonance spectroscopy study. *Brain* **121**, 1469–1477. (doi:10.1093/brain/121.8.1469)

Decker, L., Picard-Riera, N., Lachapelle, F. & Baron-Van Evercooren, A. 2002 Growth factor treatment promotes mobilization of young but not aged adult subventricular zone precursors in response to demyelination. *J. Neurosci. Res.* **69**, 763–771. (doi:10.1002/jnr.10411)

Di Bello, I. C., Dawson, M. R., Levine, J. M. & Reynolds, R. 1999 Generation of oligodendroglial progenitors in acute inflammatory demyelinating lesions of the rat brain stem is associated with demyelination rather than inflammation. *J. Neurocytol.* **28**, 365–381. (doi:10.1023/A:1007069815302)

Doetsch, F., Caille, I., Lim, D. A., Garcia-Verdugo, J. M. & Alvarez-Buylla, A. 1999*a* Subventricular zone astrocytes are neural stem cells in the adult mammalian brain. *Cell* **97**, 703–716. (doi:10.1016/S0092-8674(00)80783-7)

Doetsch, F., Garcia-Verdugo, J. M. & Alvarez-Buylla, A. 1999*b* Regeneration of a germinal layer in the adult mammalian brain. *Proc. Natl Acad. Sci. USA* **96**, 11 619–11 624. (doi:10.1073/pnas.96.20.11619)

Dubois-Dalcq, M., Ffrench-Constant, C. & Franklin, R. J. 2005 Enhancing central nervous system remyelination in multiple sclerosis. *Neuron* **48**, 9–12. (doi:10.1016/j.neuron.2005.09.004)

Edgar, J. M. *et al.* 2004 Oligodendroglial modulation of fast axonal transport in a mouse model of hereditary spastic paraplegia. *J. Cell Biol.* **166**, 121–131. (doi:10.1083/jcb.200312012)

Einstein, O., Karussis, D., Grigoriadis, N., Mizrachi-Kol, R., Reinhartz, E., Abramsky, O. & Ben Hur, T. 2003 Intraventricular transplantation of neural precursor cell spheres attenuates acute experimental allergic encephalomyelitis. *Mol. Cell Neurosci.* **24**, 1074–1082. (doi:10.1016/j.mcn.2003.08.009)

Evangelou, N., Esiri, M. M., Smith, S., Palace, J. & Matthews, P. M. 2000 Quantitative pathological evidence for axonal loss in normal appearing white matter in multiple sclerosis. *Ann. Neurol.* **47**, 391–395. (doi:10.1002/1531-8249(200003)47:3<391::AID-ANA20>3.0.CO;2-J)

Fancy, S. P., Zhao, C. & Franklin, R. J. 2004 Increased expression of Nkx2.2 and Olig2 identifies reactive oligodendrocyte progenitor cells responding to demyelination in the adult CNS. *Mol. Cell Neurosci.* **27**, 247–254.

Ferguson, B., Matyszak, M. K., Esiri, M. M. & Perry, V. H. 1997 Axonal damage in acute multiple sclerosis lesions. *Brain* **120**, 393–399. (doi:10.1093/brain/120.3.393)

Fernandez, M., Giuliani, A., Pirondi, S., D'Intino, G., Giardino, L., Aloe, L., Levi-Montalcini, R. & Calza, L. 2004 Thyroid hormone administration enhances remyelination in chronic demyelinating inflammatory disease. *Proc. Natl Acad. Sci. USA* **101**, 16 363–16 368. (doi:10.1073/pnas.0407262101)

Feron, F., Perry, C., Cochrane, J., Licina, P., Nowitzke, A., Urquhart, S., Geraghty, T. & Mackay-Sim, A. 2005 Autologous olfactory ensheathing cell transplantation in human spinal cord injury. *Brain* **128**, 2951–2960. (doi:10.1093/brain/awh657)

Ffrench-Constant, C. & Raff, M. C. 1986 The oligodendrocyte-type-2 astrocyte cell lineage is specialized for myelination. *Nature* **323**, 335–338. (doi:10.1038/323335a0)

Foote, A. K. & Blakemore, W. F. 2005 Inflammation stimulates remyelination in areas of chronic demyelination. *Brain* **128**, 528–539. (doi:10.1093/brain/awh417)

Franklin, R. J. 2002 Why does remyelination fail in multiple sclerosis? *Nat. Rev. Neurosci.* **3**, 705–714. (doi:10.1038/nrn917)

Franklin, R. J. & Blakemore, W. F. 1997 Transplanting oligodendrocyte progenitors into the adult CNS. *J. Anat.* **190**, 23–33. (doi:10.1046/j.1469-7580.1997.19010023.x)

Franklin, R. J., Gilson, J. M., Franceschini, I. A. & Barnett, S. C. 1996 Schwann cell-like myelination following transplantation of an olfactory bulb-ensheathing cell line into areas of demyelination in the adult CNS. *Glia* **17**, 217–224. (doi:10.1002/(SICI)1098-1136(199607)17:3<217::AID-GLIA4>3.0.CO;2-Y)

Franklin, R. J., Gilson, J. M. & Blakemore, W. F. 1997 Local recruitment of remyelinating cells in the repair of demyelination in the central nervous system. *J. Neurosci. Res.*

50, 337–344. (doi:10.1002/(SICI)1097-4547(19971015)50:2<337::AID-JNR21>3.0.CO;2-3)

Garbern, J. Y. *et al.* 2002 Patients lacking the major CNS myelin protein, proteolipid protein 1, develop length-dependent axonal degeneration in the absence of demyelination and inflammation. *Brain* **125**, 551–561. (doi:10.1093/brain/awf043)

Gaughwin, P. M., Caldwell, M. A., Anderson, J. M., Schwiening, C. J., Fawcett, J. W., Compston, D. A. & Chandran, S. 2006 Astrocytes promote neurogenesis from oligodendrocyte precursor cells. *Eur. J. Neurosci.* **23**, 945–956. (doi:10.1111/j.1460-9568.2006.04625.x)

Gensert, J. M. & Goldman, J. E. 1997 Endogenous progenitors remyelinate demyelinated axons in the adult CNS. *Neuron* **19**, 197–203. (doi:10.1016/S0896-6273(00)80359-1)

Goldman, S. 2003 Glia as neural progenitor cells. *Trends Neurosci.* **26**, 590–596. (doi:10.1016/j.tins.2003.09.011)

Griffiths, I. *et al.* 1998 Axonal swellings and degeneration in mice lacking the major proteolipid of myelin. *Science* **280**, 1610–1613. (doi:10.1126/science.280.5369.1610)

Hammarberg, H. *et al.* 2000 Neuroprotection by encephalomyelitis: rescue of mechanically injured neurons and neurotrophin production by CNS-infiltrating T and natural killer cells. *J. Neurosci.* **20**, 5283–5291.

Hampton, D. W., Rhodes, K. E., Zhao, C., Franklin, R. J. & Fawcett, J. W. 2004 The responses of oligodendrocyte precursor cells, astrocytes and microglia to a cortical stab injury, in the brain. *Neuroscience* **127**, 813–820. (doi:10.1016/j.neuroscience.2004.05.028)

Hinks, G. L. & Franklin, R. J. 2000 Delayed changes in growth factor gene expression during slow remyelination in the CNS of aged rats. *Mol. Cell Neurosci.* **16**, 542–556. (doi:10.1006/mcne.2000.0897)

Honczarenko, M., Le, Y., Swierkowski, M., Ghiran, I., Glodek, A. & Silberstein, L. E. 2005 Human bone marrow stromal cells express a distinct set of biologically functional chemokine receptors. *Stem Cells* **24**, 1030–1041. (doi:10.1634/stemcells.2005-0319)

Horner, P. J., Power, A. E., Kempermann, G., Kuhn, H. G., Palmer, T. D., Winkler, J., Thal, L. J. & Gage, F. H. 2000 Proliferation and differentiation of progenitor cells throughout the intact adult rat spinal cord. *J. Neurosci.* **20**, 2218–2228.

Ibanez, C., Shields, S. A., El Etr, M., Baulieu, E. E., Schumacher, M. & Franklin, R. J. 2004 Systemic progesterone administration results in a partial reversal of the age-associated decline in CNS remyelination following toxin-induced demyelination in male rats. *Neuropathol. Appl. Neurobiol.* **30**, 80–89. (doi:10.1046/j.0305-1846.2003.00515.x)

Imaizumi, T., Lankford, K. L., Waxman, S. G., Greer, C. A. & Kocsis, J. D. 1998*a* Transplanted olfactory ensheathing cells remyelinate and enhance axonal conduction in the demyelinated dorsal columns of the rat spinal cord. *J. Neurosci.* **18**, 6176–6185.

Imaizumi, T., Lankford, K. L., Waxman, S. G., Greer, C. A. & Kocsis, J. D. 1998*b* Transplanted olfactory ensheathing cells remyelinate and enhance axonal conduction in the demyelinated dorsal columns of the rat spinal cord. *J. Neurosci.* **18**, 6176–6185.

Jiang, Y. *et al.* 2002 Pluripotency of mesenchymal stem cells derived from adult marrow. *Nature* **418**, 41–49. (doi:10.1038/nature00870)

Jiang, Y., Henderson, D., Blackstad, M., Chen, A., Miller, R. F. & Verfaillie, C. M. 2003 Neuroectodermal differentiation from mouse multipotent adult progenitor cells. *Proc. Natl Acad. Sci. USA* **100**, 11 854–11 860. (doi:10.1073/pnas.1834196100)

Joannides, A. *et al.* 2006 A scaleable and defined system for generating neural stem cells from human embryonic stem cells. *Stem cells* (Epub ahead of print).

Joannides, A., Gaughwin, P., Schwiening, C., Majed, H., Sterling, J., Compston, A. & Chandran, S. 2004 Efficient generation of neural precursors from adult human skin: astrocytes promote neurogenesis from skin-derived stem cells. *Lancet* **364**, 172–178. (doi:10.1016/S0140-6736(04)16630-0)

Kaplan, M. R., Meyer-Franke, A., Lambert, S., Bennett, V., Duncan, I. D., Levinson, S. R. & Barres, B. A. 1997 Induction of sodium channel clustering by oligodendrocytes. *Nature* **386**, 724–728. (doi:10.1038/386724a0)

Kaplan, M. R., Cho, M. H., Ullian, E. M., Isom, L. L., Levinson, S. R. & Barres, B. A. 2001 Differential control of clustering of the sodium channels Na(v)1.2 and Na(v)1.6 at developing CNS nodes of Ranvier. *Neuron* **30**, 105–119. (doi:10.1016/S0896-6273(01)00266-5)

Keirstead, H. S., Ben-Hur, T., Rogister, B., O'Leary, M. T., Dubois-Dalcq, M. & Blakemore, W. F. 1999 Polysialylated neural cell adhesion molecule-positive CNS precursors generate both oligodendrocytes and Schwann cells to remyelinate the CNS after transplantation. *J. Neurosci.* **19**, 7529–7536.

Keirstead, H. S., Nistor, G., Bernal, G., Totoiu, M., Cloutier, F., Sharp, K. & Steward, O. 2005 Human embryonic stem cell-derived oligodendrocyte progenitor cell transplants remyelinate and restore locomotion after spinal cord injury. *J. Neurosci.* **25**, 4694–4705. (doi:10.1523/JNEUROSCI.0311-05.2005)

Kennedy, K. J., Strieter, R. M., Kunkel, S. L., Lukacs, N. W. & Karpus, W. J. 1998 Acute and relapsing experimental autoimmune encephalomyelitis are regulated by differential expression of the CC chemokines macrophage inflammatory protein-1alpha and monocyte chemotactic protein-1. *J. Neuroimmunol.* **92**, 98–108. (doi:10.1016/S0165-5728(98)00187-8)

Klimanskaya, I., Chung, Y., Meisner, L., Johnson, J., West, M. D. & Lanza, R. 2005 Human embryonic stem cells derived without feeder cells. *Lancet* **365**, 1636–1641. (doi:10.1016/S0140-6736(05)66473-2)

Kohama, I., Lankford, K. L., Preiningerova, J., White, F. A., Vollmer, T. L. & Kocsis, J. D. 2001 Transplantation of cryopreserved adult human Schwann cells enhances axonal conduction in demyelinated spinal cord. *J. Neurosci.* **21**, 944–950.

Komoly, S., Hudson, L. D., Webster, H. D. & Bondy, C. A. 1992 Insulin-like growth factor I gene expression is induced in astrocytes during experimental demyelination. *Proc. Natl Acad. Sci. USA* **89**, 1894–1898. (doi:10.1073/pnas.89.5.1894)

Kondo, T. & Raff, M. 2000 Oligodendrocyte precursor cells reprogrammed to become multipotential CNS stem cells. *Science* **289**, 1754–1757. (doi:10.1126/science.289.5485.1754)

Kornek, B., Storch, M. K., Weissert, R., Wallstroem, E., Stefferl, A., Olsson, T., Linington, C., Schmidbauer, M. & Lassmann, H. 2000 Multiple sclerosis and chronic autoimmune encephalomyelitis: a comparative quantitative study of axonal injury in active, inactive, and remyelinated lesions. *Am. J. Pathol.* **157**, 267–276.

Kotter, M. R., Zhao, C., van Rooijen, N. & Franklin, R. J. 2005 Macrophage-depletion induced impairment of experimental CNS remyelination is associated with a reduced oligodendrocyte progenitor cell response and altered growth factor expression. *Neurobiol. Dis.* **18**, 166–175. (doi:10.1016/j.nbd.2004.09.019)

Kotter, M. R., Li, W.-W., Chao, Z. & Franklin, R. J. M. 2006 Myelin impairs CNS remyelination by inhibiting oligodendrocyte percursor cell differentiation. *J. Neurosci.* **26**, 328–332.

Kremenchutzky, M., Cottrell, D., Rice, G., Hader, W., Baskerville, J., Koopman, W. & Ebers, G. C. 1999 The natural history of multiple sclerosis: a geographically based study. 7. Progressive-relapsing and relapsing-progressive multiple sclerosis: a re-evaluation. *Brain* **122**, 1941–1950. (doi:10.1093/brain/122.10.1941)

Kremenchutzky, M., Rice, M., Baskerville, J., Wingerchuk, D. & Ebers, G. 2006 The natural history of multiple sclerosis: a geographically based study 9: observations on the progressive phase of the disease. *Brain* **129**, 584–594.

Kuhlmann, T., Lingfeld, G., Bitsch, A., Schuchardt, J. & Bruck, W. 2002 Acute axonal damage in multiple sclerosis is most extensive in early disease stages and decreases over time. *Brain* **125**, 2202–2212. (doi:10.1093/brain/awf235)

Kukekov, V. G., Laywell, E. D., Suslov, O., Davies, K., Scheffler, B., Thomas, L. B., O'Brien, T. F., Kusakabe, M. & Steindler, D. A. 1999 Multipotent stem/progenitor cells with similar properties arise from two neurogenic regions of adult human brain. *Exp. Neurol.* **156**, 333–344. (doi:10.1006/exnr.1999.7028)

Lakatos, A., Franklin, R. J. & Barnett, S. C. 2000 Olfactory ensheathing cells and Schwann cells differ in their *in vitro* interactions with astrocytes. *Glia* **32**, 214–225. (doi:10.1002/1098-1136(200012)32:3<214::AID-GLIA20>3.0.CO;2-7)

Lakatos, A., Barnett, S. C. & Franklin, R. J. 2003 Olfactory ensheathing cells induce less host astrocyte response and chondroitin sulphate proteoglycan expression than Schwann cells following transplantation into adult CNS white matter. *Exp. Neurol.* **184**, 237–246. (doi:10.1016/S0014-4886(03)00270-X)

Lappe-Siefke, C., Goebbels, S., Gravel, M., Nicksch, E., Lee, J., Braun, P. E., Griffiths, I. R. & Nave, K. A. 2003 Disruption of Cnp1 uncouples oligodendroglial functions in axonal support and myelination. *Nat. Genet.* **33**, 366–374. (doi:10.1038/ng1095)

Lassmann, H., Raine, C. S., Antel, J. & Prineas, J. W. 1998 Immunopathology of multiple sclerosis: report on an international meeting held at the Institute of Neurology of the University of Vienna. *J. Neuroimmunol.* **86**, 213–217. (doi:10.1016/S0165-5728(98)00031-9)

Lassmann, H., Bruck, W. & Lucchinetti, C. 2001 Heterogeneity of multiple sclerosis pathogenesis: implications for diagnosis and therapy. *Trends Mol. Med.* **7**, 115–121. (doi:10.1016/S1471-4914(00)01909-2)

Levine, J. M. & Reynolds, R. 1999 Activation and proliferation of endogenous oligodendrocyte precursor cells during ethidium bromide-induced demyelination. *Exp. Neurol.* **160**, 333–347. (doi:10.1006/exnr.1999.7224)

Liu, Y. & Rao, M. S. 2004 Glial progenitors in the CNS and possible lineage relationships among them. *Biol. Cell* **96**, 279–290. (doi:10.1016/j.biolcel.2004.02.001)

Lovas, G., Szilagyi, N., Majtenyi, K., Palkovits, M. & Komoly, S. 2000 Axonal changes in chronic demyelinated cervical spinal cord plaques. *Brain* **123**, 308–317. (doi:10.1093/brain/123.2.308)

Lubetzki, C., Williams, A. & Stankoff, B. 2005 Promoting repair in multiple sclerosis: problems and prospects. *Curr. Opin. Neurol.* **18**, 237–244. (doi:10.1097/01.wco.0000169739.83793.e0)

Lucchinetti, C. & Bruck, W. 2004 The pathology of primary progressive multiple sclerosis. *Mult. Scler.* **10**, S23–S30. (doi:10.1191/1352458504ms1027oa)

Ludwig, T. E. *et al.* 2006 Derivation of human embryonic stem cells in defined conditions. *Nat. Biotechnol.* **24**, 185–187. (doi:10.1038/nbt1177)

Ludwin, S. K. 1980 Chronic demyelination inhibits remyelination in the central nervous system. An analysis of contributing factors. *Lab Invest.* **43**, 382–387.

Mallon, B. S., Shick, H. E., Kidd, G. J. & Macklin, W. B. 2002 Proteolipid promoter activity distinguishes two populations of NG2-positive cells throughout neonatal cortical development. *J. Neurosci.* **22**, 876–885.

Mason, J. L. & Goldman, J. E. 2002 A2B5+ and O4+ Cycling progenitors in the adult forebrain white matter respond differentially to PDGF-AA, FGF-2, and IGF-1. *Mol. Cell Neurosci.* **20**, 30–42. (doi:10.1006/mcne.2002.1114)

Mason, J. L., Jones, J. J., Taniike, M., Morell, P., Suzuki, K. & Matsushima, G. K. 2000*a* Mature oligodendrocyte apoptosis precedes IGF-1 production and oligodendrocyte progenitor accumulation and differentiation during demyelination/remyelination. *J. Neurosci. Res.* **61**, 251–262. (doi:10.1002/1097-4547(20000801)61:3<251::AID-JNR3>3.0.CO;2-W)

Mason, J. L., Ye, P., Suzuki, K., D'Ercole, A. J. & Matsushima, G. K. 2000*b* Insulin-like growth factor-1 inhibits mature oligodendrocyte apoptosis during primary demyelination. *J. Neurosci.* **20**, 5703–5708.

Mason, J. L., Toews, A., Hostettler, J. D., Morell, P., Suzuki, K., Goldman, J. E. & Matsushima, G. K. 2004 Oligodendrocytes and progenitors become progressively depleted within chronically demyelinated lesions. *Am. J. Pathol.* **164**, 1673–1682.

Menn, B., Garcia-Verdugo, J. M., Yaschine, C., Gonzalez-Perez, O., Rowitch, D. & Alvarez-Buylla, A. 2006 Origin of oligodendrocytes in the subventricular zone of the adult brain. *J. Neurosci* **26**, 7907–7918.

Mitome, M., Low, H. P., van den, P. A., Nunnari, J. J., Wolf, M. K., Billings-Gagliardi, S. & Schwartz, W. J. 2001 Towards the reconstruction of central nervous system white matter using neural precursor cells. *Brain* **124**, 2147–2161. (doi:10.1093/brain/124.11.2147)

Murray, K. & Dubois-Dalcq, M. 1997 Emergence of oligodendrocytes from human neural spheres. *J. Neurosci. Res.* **50**, 146–156. (doi:10.1002/(SICI)1097-4547(19971015)50:2<146::AID-JNR4>3.0.CO;2-F)

Nait-Oumesmar, B., Decker, L., Lachapelle, F., Avellana-Adalid, V., Bachelin, C. & Van Evercooren, A. B. 1999 Progenitor cells of the adult mouse subventricular zone proliferate, migrate and differentiate into oligodendrocytes after demyelination. *Eur. J. Neurosci.* **11**, 4357–4366. (doi:10.1046/j.1460-9568.1999.00873.x)

Nishiyama, A., Lin, X. H., Giese, N., Heldin, C. H. & Stallcup, W. B. 1996 Co-localization of NG2 proteoglycan and PDGF alpha-receptor on O2A progenitor cells in the developing rat brain. *J. Neurosci. Res.* **43**, 299–314. (doi:10.1002/(SICI)1097-4547(19960201)43:3<299::AID-JNR5>3.0.CO;2-E)

Nistor, G. I., Totoiu, M. O., Haque, N., Carpenter, M. K. & Keirstead, H. S. 2005 Human embryonic stem cells differentiate into oligodendrocytes in high purity and myelinate after spinal cord transplantation. *Glia* **49**, 385–396. (doi:10.1002/glia.20127)

Nunes, M. C., Roy, N. S., Keyoung, H. M., Goodman, R. R., McKhann, G., Jiang, L., Kang, J., Nedergaard, M. & Goldman, S. A. 2003 Identification and isolation of multipotential neural progenitor cells from the subcortical white matter of the adult human brain. *Nat. Med.* **9**, 439–447. (doi:10.1038/nm837)

O'Leary, M. T., Hinks, G. L., Charlton, H. M. & Franklin, R. J. 2002 Increasing local levels of IGF-I mRNA expression using adenoviral vectors does not alter oligodendrocyte remyelination in the CNS of aged rats. *Mol. Cell Neurosci.* **19**, 32–42. (doi:10.1006/mcne.2001.1062)

Palmer, T. D., Schwartz, P. H., Taupin, P., Kaspar, B., Stein, S. A. & Gage, F. H. 2001 Cell culture. Progenitor cells from human brain after death. *Nature* **411**, 42–43. (doi:10.1038/35075141)

Pavelko, K. D., van Engelen, B. G. & Rodriguez, M. 1998 Acceleration in the rate of CNS remyelination in lysolecithin-induced demyelination. *J. Neurosci.* **18**, 2498–2505.

Penderis, J., Shields, S. A. & Franklin, R. J. 2003*a* Impaired remyelination and depletion of oligodendrocyte progenitors does not occur following repeated episodes of focal demyelination in the rat central nervous system. *Brain* **126**, 1382–1391. (doi:10.1093/brain/awg126)

Penderis, J., Woodruff, R. H., Lakatos, A., Li, W. W., Dunning, M. D., Zhao, C., Marchionni, M. & Franklin, R. J. 2003*b* Increasing local levels of neuregulin (glial growth factor-2) by direct infusion into areas of demyelination does not alter remyelination in the rat CNS. *Eur. J. Neurosci.* **18**, 2253–2264. (doi:10.1046/j.1460-9568.2003.02969.x)

Pera, E. M., Ikeda, A., Eivers, E. & De Robertis, E. M. 2003 Integration of IGF, FGF, and anti-BMP signals via Smad1 phosphorylation in neural induction. *Genes Dev.* **17**, 3023–3028. (doi:10.1101/gad.1153603)

Picard-Riera, N., Decker, L., Delarasse, C., Goude, K., Nait-Oumesmar, B., Liblau, R., Pham-Dinh, D. & Evercooren, A. B. 2002 Experimental autoimmune encephalomyelitis mobilizes neural progenitors from the subventricular zone to undergo oligodendrogenesis in adult mice. *Proc. Natl Acad. Sci. USA* **99**, 13 211–13 216. (doi:10.1073/pnas.192314199)

Pirko, I. *et al.* 2004 A human antibody that promotes remyelination enters the CNS and decreases lesion load as detected by T2-weighted spinal cord MRI in a virus-induced murine model of MS. *FASEB J.* **18**, 1577–1579.

Pluchino, S. *et al.* 2003 Injection of adult neurospheres induces recovery in a chronic model of multiple sclerosis. *Nature* **422**, 688–694. (doi:10.1038/nature01552)

Pluchino, S. *et al.* 2005 Neurosphere-derived multipotent precursors promote neuroprotection by an immunomodulatory mechanism. *Nature* **436**, 266–271. (doi:10.1038/nature03889)

Prineas, J. W. & Connell, F. 1979 Remyelination in multiple sclerosis. *Ann. Neurol.* **5**, 22–31. (doi:10.1002/ana.410050105)

Quinn, S. M., Walters, W. M., Vescovi, A. L. & Whittemore, S. R. 1999 Lineage restriction of neuroepithelial precursor cells from fetal human spinal cord. *J. Neurosci. Res.* **57**, 590–602. (doi:10.1002/(SICI)1097-4547(19990901)57:5<590::AID-JNR2>3.0.CO;2-X)

Raff, M. C., Whitmore, A. V. & Finn, J. T. 2002 Axonal self-destruction and neurodegeneration. *Science* **296**, 868–871. (doi:10.1126/science.1068613)

Raine, C. S. & Cross, A. H. 1989 Axonal dystrophy as a consequence of long-term demyelination. *Lab Invest.* **60**, 714–725.

Redwine, J. M. & Armstrong, R. C. 1998 *In vivo* proliferation of oligodendrocyte progenitors expressing PDGFalphaR during early remyelination. *J. Neurobiol.* **37**, 413–428. (doi:10.1002/(SICI)1097-4695(19981115)37:3<413::AID-NEU7>3.0.CO;2-8)

Reubinoff, B. E., Itsykson, P., Turetsky, T., Pera, M. F., Reinhartz, E., Itzik, A. & Ben-Hur, T. 2001 Neural progenitors from human embryonic stem cells. *Nat. Biotechnol.* **19**, 1134–1140. (doi:10.1038/nbt1201-1134)

Rodriguez, M. 2003 A function of myelin is to protect axons from subsequent injury: implications for deficits in multiple sclerosis. *Brain* **126**, 751–752. (doi:10.1093/brain/awg070)

Roy, N. S., Wang, S., Harrison-Restelli, C., Benraiss, A., Fraser, R. A., Gravel, M., Braun, P. E. & Goldman, S. A. 1999 Identification, isolation, and promoter-defined separation of mitotic oligodendrocyte progenitor cells from the adult human subcortical white matter. *J. Neurosci.* **19**, 9986–9995.

Sanai, N. *et al.* 2004 Unique astrocyte ribbon in adult human brain contains neural stem cells but lacks chain migration. *Nature* **19**, 740–744. (doi:10.1038/nature02301)

Sanchez, I., Hassinger, L., Paskevich, P. A., Shine, H. D. & Nixon, R. A. 1996 Oligodendroglia regulate the regional expansion of axon caliber and local accumulation of neurofilaments during development independently of myelin formation. *J. Neurosci.* **16**, 5095–5105.

Sasaki, M., Lankford, K. L., Zemedkun, M. & Kocsis, J. D. 2004 Identified olfactory ensheathing cells transplanted into the transected dorsal funiculus bridge the lesion and form myelin. *J. Neurosci.* **24**, 8485–8493. (doi:10.1523/JNEUROSCI.1998-04.2004)

Scherer, S. 1999 Axonal pathology in demyelinating diseases. *Ann. Neurol.* **45**, 6–7. (doi:10.1002/1531-8249(199901)45:1<6::AID-ART3>3.0.CO;2-3)

Scolding, N., Franklin, R., Stevens, S., Heldin, C. H., Compston, A. & Newcombe, J. 1998 Oligodendrocyte progenitors are present in the normal adult human CNS and in the lesions of multiple sclerosis. *Brain* **121**, 2221–2228. (doi:10.1093/brain/121.12.2221)

Seri, B., Garcia-Verdugo, J. M., Collado-Morente, L., McEwen, B. S. & Alvarez-Buylla, A. 2004 Cell types, lineage, and architecture of the germinal zone in the adult dentate gyrus. *J. Comp. Neurol.* **478**, 359–378. (doi:10.1002/cne.20288)

Sim, F. J., Zhao, C., Li, W. W., Lakatos, A. & Franklin, R. J. 2002*a* Expression of the POU-domain transcription factors SCIP/Oct-6 and Brn-2 is associated with Schwann cell but not oligodendrocyte remyelination of the CNS. *Mol. Cell Neurosci.* **20**, 669–682. (doi:10.1006/mcne.2002.1145)

Sim, F. J., Zhao, C., Penderis, J. & Franklin, R. J. 2002*b* The age-related decrease in CNS remyelination efficiency is attributable to an impairment of both oligodendrocyte progenitor recruitment and differentiation. *J. Neurosci.* **22**, 2451–2459.

Simpson, J., Rezaie, P., Newcombe, J., Cuzner, M. L., Male, D. & Woodroofe, M. N. 2000 Expression of the beta-chemokine receptors CCR2, CCR3 and CCR5 in multiple sclerosis central nervous system tissue. *J. Neuroimmunol.* **108**, 192–200. (doi:10.1016/S0165-5728(00)00274-5)

Smith, P. M. & Blakemore, W. F. 2000 Porcine neural progenitors require commitment to the oligodendrocyte lineage prior to transplantation in order to achieve significant remyelination of demyelinated lesions in the adult CNS. *Eur. J. Neurosci.* **12**, 2414–2424. (doi:10.1046/j.1460-9568.2000.00137.x)

Sordi, V. *et al.* 2005 Bone marrow mesenchymal stem cells express a restricted set of functionally active chemokine receptors capable of promoting migration to pancreatic islets. *Blood* **106**, 419–427. (doi:10.1182/blood-2004-09-3507)

Spassky, N. *et al.* 1998 Multiple restricted origin of oligodendrocytes. *J. Neurosci.* **18**, 8331–8343.

Spassky, N., Olivier, C., Perez-Villegas, E., Goujet-Zalc, C., Martinez, S., Thomas, J. & Zalc, B. 2000 Single or multiple oligodendroglial lineages: a controversy. *Glia* **29**, 143–148. (doi:10.1002/(SICI)1098-1136(20000115)29:2<143::AID-GLIA7>3.0.CO;2-D)

Stevenson, V. L., Leary, S. M., Losseff, N. A., Parker, G. J., Barker, G. J., Husmani, Y., Miller, D. H. & Thompson, A. J. 1998 Spinal cord atrophy and disability in MS: a longitudinal study. *Neurology* **51**, 234–238.

Setzu, A., Lathia, J. D., Zhao, C., Wells, K. E., Rao, M. S., ffrench-Constant, C. & Franklin, R. J. M. 2006 Inflammation stimulates myelination by transplanted oligodendrocyte precursor cells. *Glia* **54**, 297–303.

Takahashi, K. & Yamanaka, S. 2006 Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* **126**, 663–676. (doi:10.1016/j.cell.2006.07.024)

Tang, D. G., Tokumoto, Y. M., Apperly, J. A., Lloyd, A. C. & Raff, M. C. 2001 Lack of replicative senescence in cultured rat oligodendrocyte precursor cells. *Science* **291**, 868–871. (doi:10.1126/science.1056780)

Terada, N. *et al.* 2002 Bone marrow cells adopt the phenotype of other cells by spontaneous cell fusion. *Nature* **416**, 542–545. (doi:10.1038/nature730)

Toma, J. G., Akhavan, M., Fernandes, K. J., Barnabe-Heider, F., Sadikot, A., Kaplan, D. R. & Miller, F. D. 2001 Isolation of multipotent adult stem cells from the dermis of mammalian skin. *Nat. Cell Biol.* **3**, 778–784. (doi:10.1038/ncb0901-778)

Tran, P. B., Ren, D., Veldhouse, T. J. & Miller, R. J. 2004 Chemokine receptors are expressed widely by embryonic and adult neural progenitor cells. *J. Neurosci. Res.* **76**, 20–34. (doi:10.1002/jnr.20001)

Trapp, B. D., Peterson, J., Ransohoff, R. M., Rudick, R., Mork, S. & Bo, L. 1998 Axonal transection in the lesions of multiple sclerosis. *N. Eng. J. Med.* **338**, 278–285. (doi:10.1056/NEJM199801293380502)

Vallstedt, A., Klos, J. M. & Ericson, J. 2005 Multiple dorsoventral origins of oligodendrocyte generation in the spinal cord and hindbrain. *Neuron* **45**, 55–67. (doi:10.1016/j.neuron.2004.12.026)

Warrington, A. E., Asakura, K., Bieber, A. J., Ciric, B., Keulen, V. V., Kaveri, S. V., Kyle, R. A., Pease, L. R. & Rodriguez, M. 2000 Human monoclonal antibodies reactive to oligodendrocytes promote remyelination in a model of multiple sclerosis. *Proc. Natl Acad. Sci. USA* **97**, 6820–6825. (doi:10.1073/pnas.97.12.6820)

Watanabe, M., Toyama, Y. & Nishiyama, A. 2002 Differentiation of proliferated NG2-positive glial progenitor cells in a remyelinating lesion. *J. Neurosci. Res.* **69**, 826–836. (doi:10.1002/jnr.10338)

Watanabe, M., Hadzic, T. & Nishiyama, A. 2004 Transient upregulation of Nkx2.2 expression in oligodendrocyte lineage cells during remyelination. *Glia* **46**, 311–322. (doi:10.1002/glia.20006)

Waxman, S. G. 2001 Acquired channelopathies in nerve injury and MS. *Neurology* **56**, 1621–1627.

Weimann, J. M., Charlton, C. A., Brazelton, T. R., Hackman, R. C. & Blau, H. M. 2003 Contribution of transplanted bone marrow cells to Purkinje neurons in human adult brains. *Proc. Natl Acad. Sci. USA* **100**, 2088–2093. (doi:10.1073/pnas.0337659100)

Wilkins, A. & Compston, A. 2005 Trophic factors attenuate nitric oxide mediated neuronal and axonal injury *in vitro*: roles and interactions of mitogen-activated protein kinase signalling pathways. *J. Neurochem.* **92**, 1487–1496. (doi:10.1111/j.1471-4159.2004.02981.x)

Wilkins, A., Chandran, S. & Compston, A. 2001 A role for oligodendrocyte-derived IGF-1 in trophic support of cortical neurons. *Glia* **36**, 48–57. (doi:10.1002/glia.1094)

Wilkins, A., Majed, H., Layfield, R., Compston, A. & Chandran, S. 2003 Oligodendrocytes promote neuronal survival and axonal length by distinct intracellular mechanisms: a novel role for oligodendrocyte-derived glial cell line-derived neurotrophic factor. *J. Neurosci.* **23**, 4967–4974.

Windrem, M. S., Roy, N. S., Wang, J., Nunes, M., Benraiss, A., Goodman, R., McKhann, G. M. & Goldman, S. A. 2002 Progenitor cells derived from the adult human subcortical white matter disperse and differentiate as oligodendrocytes within demyelinated lesions of the rat brain. *J. Neurosci. Res.* **69**, 966–975. (doi:10.1002/jnr.10397)

Windrem, M. S., Nunes, M. C., Rashbaum, W. K., Schwartz, T. H., Goodman, R. A., McKhann, G., Roy, N. S. & Goldman, S. A. 2004 Fetal and adult human oligodendrocyte progenitor cell isolates myelinate the congenitally dysmyelinated brain. *Nat. Med.* **10**, 93–97. (doi:10.1038/nm974)

Witt, A. & Brady, S. T. 2000 Unwrapping new layers of complexity in axon/glial relationships. *Glia* **29**, 112–117. (doi:10.1002/(SICI)1098-1136(20000115)29:2<112::AID-GLIA3>3.0.CO;2-Z)

Wolswijk, G. 1998 Chronic stage multiple sclerosis lesions contain a relatively quiescent population of oligodendrocyte precursor cells. *J. Neurosci.* **18**, 601–609.

Ying, Q. L., Nichols, J., Evans, E. P. & Smith, A. G. 2002 Changing potency by spontaneous fusion. *Nature* **416**, 545–548. (doi:10.1038/nature729)

Zappia, E. *et al.* 2005 Mesenchymal stem cells ameliorate experimental autoimmune encephalomyelitis inducing T-cell anergy. *Blood* **106**, 1755–1761. (doi:10.1182/blood-2005-04-1496)

Zhang, S. C., Ge, B. & Duncan, I. D. 1999 Adult brain retains the potential to generate oligodendroglial progenitors with extensive myelination capacity. *Proc. Natl Acad. Sci. USA* **96**, 4089–4094. (doi:10.1073/pnas.96.7.4089)

Zhang, J. *et al.* 2005 Human bone marrow stromal cell treatment improves neurological functional recovery in EAE mice. *Exp. Neurol.* **195**, 16–26. (doi:10.1016/j.expneurol.2005.03.018)

Zhang, S. C., Ge, B. & Duncan, I. D. 2000 Tracing human oligodendroglial development *in vitro*. *J. Neurosci. Res.* **59**, 421–429. (doi:10.1002/(SICI)1097-4547(20000201)59:3<421::AID-JNR17>3.0.CO;2-C)

Zhang, S. C., Wernig, M., Duncan, I. D., Brustle, O. & Thomson, J. A. 2001 *In vitro* differentiation of transplantable neural precursors from human embryonic stem cells. *Nat. Biotechnol.* **19**, 1129–1133. (doi:10.1038/nbt1201-1129)