Promoting remyelination in multiple sclerosis: Current drugs and future prospects

David Kremer, Patrick Küry and Ranjan Dutta

Abstract: Myelin destruction due to inflammatory oligodendrocyte cell damage or death in conjunction with axonal degeneration are among the major histopathological hallmarks of multiple sclerosis (MS). The majority of available immunomodulatory medications for MS are approved for relapsing–remitting (RR) MS, for which they reduce relapse rate, MRI measures of inflammation, and the accumulation of disability. These medications are, however, of little benefit during progressive MS where axonal degeneration following demyelination outweighs inflammation. This has sparked great interest in the development of new remyelination therapies aimed at reversing the neurodegenerative damage observed in this disease. Remyelination as a result of oligodendrocyte production from oligodendrocyte precursor cells (OPCs) is considered a promising potential target for the treatment of all stages of MS. In this review we present an overview of a) approved medications (some of them FDA- and EMA-approved for other diseases) with a proposed role in regeneration, b) regenerative treatments under investigation in clinical trials, and c) promising future therapeutic approaches aiming specifically at facilitating endogenous repair.

Keywords: Multiple sclerosis, therapy, trials, remyelination

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Multiple sclerosis (MS)—a disease with remyelination failure

MS, first described by Jean-Martin Charcot almost 150 years ago, is a chronic inflammatory disease of the central nervous system (CNS). As tissue damage in MS was solely considered to be the result of an autoimmune inflammatory CNS process, it is hardly surprising that therapies developed over the course of the last 20 years have mainly focused on the immune system and, more specifically, on the modulation of immune cell behavior. Even though the currently available MS drugs are reliable, constantly improving, very effective in MS with relapses, and able to significantly reduce long-term disability in MS patients, they have only a limited effect on the progressive disease course without additional inflammatory relapses. As neuroarchitectural damage caused during disease relapses accumulates over time and results in increasing patient disability, it is critical to develop new therapies aiming at the regenerative mechanisms of MS pathogenesis.

Neurological disability during relapsing–remitting multiple sclerosis (RRMS) occurs in reversible episodes driven primarily by focal inflammatory demyelination, which destroys myelin, myelin-forming cells (oligodendrocytes), and axons. Untreated relapses usually last no more than a few months, after which the patient typically regains neurological function. Remyelination, accompanied by resolution of the inflammation and reorganization of axonal sodium channels on demyelinated axons, helps restore axonal conduction and contributes to the clinical recovery or remission. This remyelination during early disease is extensive in some MS patients but declines during the progressive disease course. During this progressive phase of the disease, where acute inflammatory relapses are scarce with increasing loss of neuronal function, exogenous stimulation of endogenous remyelination would potentially have the greatest impact.

Oligodendroglial precursor cells (OPCs) as a source for remyelination

Current research on the treatment of MS is directed at three major goals: preventing the development of new demyelinating lesions, protecting demyelinated axons from degeneration, and promoting remyelination. Phases of remyelination occur frequently during the RRMS disease course and are probably most relevant...
for clinical remission. The process of remyelination depends on the well-characterized population of OPCs, which are capable of differentiating into mature myelin-forming oligodendrocytes. OPCs, characterized by the surface expression of platelet-derived growth factor receptor α (PDGFRα) and sulfated proteoglycan NG2, are dispersed throughout the adult CNS and establish a network of stellate cells that covers most of the CNS parenchyma. These NG2/PDGFRα-positive cells remain as a major quiescent glial component of the adult mammalian CNS, providing a pool of progenitors that can later be tapped for repair of demyelinated axons.

In MS brains, OPCs can be recruited into lesions where they undergo differentiation, as evidenced by a spectrum of different morphologies of proteolipid protein (PLP)-positive cells. Eventually, these cells give rise to mature (re-)myelinating oligodendrocytes that repair demyelinated lesions where the resulting new myelin sheaths can be recognized by shorter internodes and thinner myelin. This capacity for myelin repair decreases over time, which is most likely due to failure of OPC differentiation by numerous inhibitory cues in MS lesions. These cues, therefore, represent interesting therapeutic targets for novel MS treatment strategies facilitating endogenous repair. However, the design of pharmacological approaches aiming at the neutralization of these stimuli is highly complex as evidenced, for instance, by the so-called Notch pathway. Notch-1, a highly conserved transmembrane receptor, first described in D. melanogaster, plays a role in a variety of developmental processes by controlling cell fate decisions.

In the human CNS, Notch receptors on OPCs can be activated by Notch ligand Jagged1, an important factor during development and re-expressed by reactive astrocytes in MS lesions. This, in turn, leads to the activation of the inhibitory helix-loop-helix (HLH) transcription factors Hairy and enhancer of split 1 and 5 (Hes1 and Hes5) that inhibit oligodendroglial differentiation. At first glance, pharmacological inhibition of Notch-1 might thus seem like a promising therapeutic approach to overcome the endogenous OPC differentiation blockade. However, other studies have demonstrated that contactin, a Notch ligand expressed on the surface of demyelinated axons, stimulates remyelination through gamma-secretase-dependent nuclear translocation of the Notch intracellular domain (NICD). It therefore becomes clear why indiscriminate blockade of this receptor could be counterproductive and might not represent a viable therapeutic option to stimulate repair. The newly gained knowledge about the complex interplay of multiple molecules in MS lesions emphasizes the necessity of identifying mechanisms that specifically stimulate repair without interfering with other cellular processes, which is the first step for the development of any potential regenerative agent.

**Regenerative properties of United States Food and Drug Administration-approved drugs**

Current therapies used to treat MS patients act primarily by modulating or suppressing the immune system to reduce relapse rates and magnetic resonance imaging (MRI) measures of inflammation. Aside from clinical trials testing novel compounds specifically stimulating remyelination, research has also been focused on detecting additional regenerative properties of these existing drugs that might facilitate repair (see Table 1). Accordingly, an increasing number of FDA- and European Medicines Agency (EMA)-approved agents used in MS therapy and other diseases have been found to exert beneficial effects on resident CNS cells such as OPCs besides their primary immunomodulatory effects.

**Fingolimod**

Fingolimod, an S1P-receptor modulator, is primarily known for preventing egress of lymphocytes from lymph nodes. However, it also crosses the blood-brain barrier (BBB) and modulates resident CNS cells, including process outgrowth in immature oligodendrocytes via RhoA signaling. Fingolimod has also been reported to enhance remyelination upon lyssolecithin-induced demyelination of cerebellar slice cultures. However, it is largely unclear to what extent these observations might be due to fingolimod’s effect on CNS cell types aside from oligodendroglia. This concept is supported by experimental autoimmune encephalomyelitis (EAE) studies where fingolimod efficacy was lost in CNS mutants lacking S1P1 on glial fibrillary acidic protein (GFAP)-expressing astrocytes. Finally, fingolimod has been found to enhance BBB integrity by reducing the production of pro-inflammatory lipids in reactive astrocytes. It thus appears that several simultaneous effects mediated by different cell types constitute the overall beneficial effect of this agent within the CNS.

**Benztropine**

Recently, benztropine, an anticholinergic agent so far used to treat Parkinson’s disease (PD), was identified through a systematic compound screening as a facilitator of myelin regeneration while there seems to be no significant effect on the immune cell repertoire. In a cuprizone-induced non-inflammatory...
Table 1. Current and future therapies directed towards remyelination in MS.

<table>
<thead>
<tr>
<th>Drug</th>
<th>General mode of action</th>
<th>Relevance for remyelination</th>
<th>Clinical status</th>
<th>Current trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fingolimod</td>
<td>Prevents lymphocytic egress from lymph nodes by downregulating lymphocytic S1P1 receptors</td>
<td>Modulates process outgrowth in immature oligodendrocytes, enhances remyelination in experimental MS models and reduces brain atrophy in RRMS patients (ClinicalTrials.gov identifiers: NCT00289978 and NCT00355134)</td>
<td>Approved for the treatment of RRMS by the FDA in 2010 and the EMA in 2011</td>
<td>Currently no trials explicitly investigating its potential to enhance remyelination are underway</td>
</tr>
<tr>
<td>Benztropine</td>
<td>Anticholinergic molecule inhibiting parasympathetic nerve activation</td>
<td>Increases remyelination in toxic demyelination and decreases the clinical severity of EAE via muscarinic receptors; possibly also stimulates OPC differentiation by blocking Notch signaling</td>
<td>Approved for treatment of Parkinson’s disease (PD) and dystonia</td>
<td>Currently the initiation of a clinical trial for efficacy in MS is being considered.</td>
</tr>
<tr>
<td>Quetiapine fumarate</td>
<td>Antagonist at the D2, 5-HT2A, H1, alpha 1 and 5-HT1A receptors exerting an antipsychotic effect</td>
<td>May stimulate proliferation and maturation of oligodendrocytes and increases antioxidant defenses.</td>
<td>Approved for use in schizophrenia, bipolar disorder and as an add-on antidepressant medication</td>
<td>Phase I study to determine safety and tolerability in MS patients (ClinicalTrials.gov identifier: NCT02087631)</td>
</tr>
<tr>
<td>BIIB033</td>
<td>Antibody against leucine-rich repeat and Ig domain-containing Nogo receptor-interacting protein (LINGO-1) modulating RhoA signaling</td>
<td>Neutralization of LINGO-1 enhances myelin sheath formation and myelination and reduces severity of EAE</td>
<td>Not approved yet</td>
<td>Phase II studies for efficacy in MS as an add-on to therapy for interferon β-1a (ClinicalTrials.gov identifier: NCT01864148) and optic neuritis (ClinicalTrials.gov identifier: NCT01721161)</td>
</tr>
<tr>
<td>rHigM22</td>
<td>Recombinant human antibody potentially binding to vitronectin/fibronectin receptor αvβ3</td>
<td>Promotes the synthesis of new myelin in animal models</td>
<td>Not approved yet</td>
<td>Phase I study in MS patients (ClinicalTrials.gov identifier: NCT01803867)</td>
</tr>
<tr>
<td>GNbAC1</td>
<td>Humanized antibody, directed against the proinflammatory envelope protein (ENV) of multiple sclerosis-associated retrovirus (MSRV)</td>
<td>Targets ENV to promote OPC differentiation by reduction of nitrosative stress</td>
<td>Not approved yet</td>
<td>Phase IIa study was successfully concluded (ClinicalTrials.gov identifier: NCT01639300); proof-of-concept phase IIb study will follow in 2015</td>
</tr>
<tr>
<td>IRX4204</td>
<td>Small-molecule IRX4204 activates retinoic acid receptor gamma (RXR-γ), which is involved in remyelination</td>
<td>Enhances oligodendrogial differentiation</td>
<td>Not approved yet</td>
<td>Clinical trials are currently in the planning stage.</td>
</tr>
</tbody>
</table>

(Continued)
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<td>Olexosime</td>
<td>Cholesterol-like small-molecule compound binding to two components of the mitochondrial permeability transition pore (PTP)</td>
<td>Increases number of mature rodent oligodendroglial cells in animal model</td>
<td>Not approved yet</td>
<td>Phase I clinical trial evaluating olexosome as an add-on therapy for interferon beta in patients with stable RRMS (ClinicalTrials.gov identifier: NCT01808885)</td>
</tr>
</tbody>
</table>
| Quercetin   | Flavonoid molecule acting as: 1. An inhibitor of intramembranous γ-secretase and, 2. A disruptor of beta-catenin binding to transcription factor 4 (TCF-4) | 1. γ-secretase inhibitors interfere with canonical Notch signaling, which leads to enhanced remyelination  

2. binding of beta-catenin to TCF-4 was shown to delay myelin repair | Not approved yet                          | None of the γ-secretase compounds have yet been evaluated in CNS remyelination               |
| GSK239512   | Small-molecule histamine H3 receptor antagonist so far studied in the context of Alzheimer’s disease | H3 receptor antagonists enhance remyelination in the cuprizone model | Not approved yet                          | Phase II study assessing whether GSK239512 can promote remyelination as an add-on therapy in patients receiving glatiramer acetate or interferon β-1a (ClinicalTrials.gov identifier: NCT01772199) |
| Clemastine  | Antihistamine/anticholinergic compound blocking histamine H1 receptor                   | Acts as an enhancer of OPC differentiation                                                   | Not approved yet                          | Phase II study investigating the potential of clemastine as a remyelinating agent in RRMS patients (ClinicalTrials.gov identifier: NCT02040298)          |
| VX15/2503   | Humanized IgG4 anti-semaphorin 4D (SEMA4D) antibody interfering with SEMA4D/Plexin B1 interactions | Blockade of this pathway ameliorates EAE, increases OPC differentiation and restores BBB breakdown | Not approved yet                          | Phase I study investigating the safety of VX15/2503 (ClinicalTrials.gov identifier: NCT01764737)                                           |

MS: multiple sclerosis; RRMS: relapsing–remitting multiple sclerosis; FDA: United States Food and Drug Administration; EMA: European Medicines Agency; CNS: central nervous system; BBB: blood-brain barrier; Ig: immunoglobulin; EAE: experimental autoimmune encephalomyelitis; OPCs: oligodendrocyte precursor cells.
myelin and the surface of oligodendrocytes. Even though the exact molecular mechanisms underlying the observed effects are thus far unknown, mechanistically, vitronectin/fibronectin receptor αvβ3 has been identified as a potential rHlgM22 target that—upon binding to the Src family kinase (SFK) Lyn—mediates proliferation and oligodendroglial survival via a reduction of caspase-3 and caspase-9 cleavage. These results have prompted a phase I clinical trial investigating the tolerability of intravenous infusion of rHlgM22 in MS patients (ClinicalTrials.gov identifier: NCT01803867).

Emerging regenerative therapies

**Leucine-rich repeat and immunoglobulin (Ig) domain-containing Nogo receptor-interacting protein (LINGO-1)**

One of the drug trials currently fueling high expectations in the field of MS research and treatment involves an antibody directed against LINGO-1. This transmembrane protein is expressed exclusively in the CNS, where it appears to associate with p75 and NogoR1 to modulate RhoA signaling in non-neuronal cells. Specific loss of LINGO-1 in vitro as well as in vivo enhances myelin sheath formation and myelination with an increased percentage of mature oligodendrocytes. Application of specific anti-LINGO-1 antibodies strongly reduces severity of EAE at all stages of the disease. Currently, an anti-LINGO-1 antibody, BIIB033, is in phase 3 trials in MS (ClinicalTrials.gov identifier: NCT01864148) and optic neuritis (ClinicalTrials.gov identifier: NCT01721161).

**Human monoclonal IgM antibody 22 (rHlgM22)**

The recombinant human autoantibody, rHlgM22, accumulates in CNS lesions and promotes the synthesis of new myelin in animal models by binding to myelin and the surface of oligodendrocytes. Even though the exact molecular mechanisms underlying the observed effects are thus far unknown, mechanistically, vitronectin/fibronectin receptor αvβ3 has been identified as a potential rHlgM22 target that—upon binding to the Src family kinase (SFK) Lyn—mediates proliferation and oligodendroglial survival via a reduction of caspase-3 and caspase-9 cleavage. These results have prompted a phase I clinical trial investigating the tolerability of intravenous infusion of rHlgM22 in MS patients (ClinicalTrials.gov identifier: NCT01803867).

**GNbAC1**

A recently developed humanized antibody GNbAC1, directed against the envelope protein (ENV) of multiple sclerosis-associated retrovirus (MSRV), a member of the HERV-W family of endogenous retroviruses, is another promising candidate that might potentially affect remyelination capacity. Although the majority of HERVs are silenced through epigenetic control, certain environmental factors such as viruses lead to dysregulated expression in susceptible cells. (Re)activation and expression of HERV-W in humans may result in the secretion of extracellular viral particles that can be detected in the serum and the cerebrospinal fluid of MS patients. Recently it was also demonstrated that the ENV protein is present in close proximity to OPCs in normal-appearing white matter (NAWM) in the brain of MS patients and that it is capable of directly interfering with OPC differentiation via an activation of Toll-like receptor 4 (TLR4). In a recent study, it was now shown that GNbAC1, a novel anti-ENV IgG4 antibody, can neutralize this effect rescuing myelin gene expression in OPCs. GNbAC1 apparently also exerts a protective effect on OPCs, which makes it a potential new therapeutic tool for the promotion of CNS remyelination in MS. Of note, a recent phase IIa study found that GNbAC1 was well tolerated by MS patients; (ClinicalTrials.gov identifier: NCT01639300) and a follow-up phase IIb trial investigating its efficacy in MS is scheduled to start in 2015.

**Quetiapine fumarate**

Quetiapine, an atypical antipsychotic drug administered in the form of a fumarate salt, has been reported to stimulate the differentiation of neural progenitors into oligodendrocytes via extracellular signal-related kinases, to increase the synthesis of myelin basic protein (MBP) thereby increasing oligodendroglial maturation, and to prevent toxic demyelination in C57BL/6 mice by cuprizone following chronic administration. These studies in rodents have raised the question if similar effects might be observed in MS patients, and currently there is a phase I study underway to determine this compound’s safety and tolerability in MS patients (ClinicalTrials.gov identifier: NCT02087631). Of note, quetiapine fumarate is chemically similar to the compound dimethyl fumarate, which was approved for the treatment of RRMS in 2013. However, while it has been established that dimethyl fumarate exerts neuroprotective effects in neuroinflammation via the NF-E2-related factor 2.
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(Nr2) antioxidant pathway,39 effects on remyelination have so far not been studied.

**Histamine receptor antagonists GSK239512 and clemastine**

H3 receptor antagonists such as GSK239512 have been identified as promoters of OPC differentiation in a compound screening using an in vitro differentiation assay based on myelin basic protein (MBP) expression analysis. Further investigations revealed that histamine receptors are found in demyelinated MS lesions,40 and that histamine receptor antagonists can enhance remyelination in a cuprizone model. Lack of histamine receptors was also demonstrated to increase the resistance to EAE in mice where these receptors are thought to modulate T cell responses, cytokine production, BBB permeability, and regulatory T cell (Treg) activity.41 Currently, a phase II study is underway assessing whether GSK239512, so far studied in the context of Alzheimer’s disease (AD), can promote remyelination as an add-on therapy in patients receiving glatiramer acetate or interferon β-1a. The primary outcome will be measured using the recovery of the magnetization transfer ratio in actively inflamed brain lesions (ClinicalTrials.gov identifier: NCT01772199).

Independently from the study above, another antihistaminergic compound is currently under investigation for its potential use as a remyelinating agent. Histamine receptor 1 antagonist clemastine was originally identified via a high-throughput screening as an enhancer of OPC differentiation42 and a corresponding phase II clinical trial is currently underway using visually evoked potentials (VEPs) and magnetic resonance tomography (MRT) as readouts for remyelination in the visual CNS pathways of RRMS patients (ClinicalTrials.gov Identifier: NCT02040298).

**VX15/2503**

Semaphorin 4D (CD100) inhibits OPC differentiation,43 induces oligodendroglial process collapse,44 and disrupts endothelial tight junctions via its receptor Plexin B1, suggesting a role for BBB breakdown.45 Recent data demonstrated that an antibody interfering with SEMA4D/PLXNB1 interaction ameliorates EAE, increases OPC differentiation, and improves cognitive function.46 These observations are being followed up through an ongoing phase I study investigating the safety of VX15/2503, a humanized form of the previously used anti-SEMA4D IgG4 antibody (ClinicalTrials.gov identifier: NCT01764737).

**What’s in the therapeutic pipeline? New regenerative agents**

**IRX4204**

In a transcriptional profiling approach investigating spontaneous remyelination following focal demyelination of the rat CNS, it was discovered that retinoic acid receptor gamma (RXR-γ) was upregulated during remyelination.37 RXR-γ was also found to be expressed by activated OPCs in the active borders of MS lesions. In the same study, knockdown of RXR-γ by siRNA or RXR-specific antagonists inhibited oligodendrocyte differentiation in vitro, resulting in decreased myelin gene expression and simpler cell morphology. However, following experimental demyelination in RXR-γ knockout mice, OPCs showed only delayed differentiation into mature oligodendrocytes as demonstrated by a transient reduction of CC1+ mature oligodendrocytes in lesions while, at 30 days post-lesion, there was no significant difference between knockouts and controls. In an in vitro approach, administration of 9-cis-retinoic acid, an isomer of the vitamin A-derived all-trans retinoic acid and known ligand for RXR to aged rats after demyelination caused an increase in the number of remyelinated axons.47 There is thus strong evidence that, even though other endogenous mechanisms might compensate for failing or missing RXR signaling, this receptor plays a role in remyelination and CNS regeneration. A recently presented study also suggests the potential of a specific RXR-γ agonist named IRX4204 to stimulate OPC differentiation.48 As the molecule has already been studied in prostate cancer patients without serious adverse effects, an open-label phase II clinical trial of IRX4204 in taxane-resistant, castration-resistant metastatic prostate cancer (CRPC) is currently in preparation.49

**Olesoxime**

Yet another potential candidate with promise for use as a remyelination therapy is olesoxime (cholest-4-en-3-one, oxime; TRO19622), a cholesterol-like small-molecule compound. Initially, olesoxime was discovered to play a role in promoting motor neuron survival in an animal model of amyotrophic lateral sclerosis (ALS).50 Mechanistically, this agent binds directly to two components of the mitochondrial permeability transition pore (PTP): the voltage-dependent anion channel and the translocator protein 18 kDa. This binding causes reduction in axonal degeneration and recovery of motor function. Unfortunately, following a successful phase I trial for ALS (ClinicalTrials.gov identifier: NCT00868166), a recently finished phase II–III trial failed to demonstrate any superiority of olesoxime treatment compared to controls.51 However, other research groups could
demonstrate that this agent also exerts a stimulatory effect on oligodendrogial differentiation in vitro and remyelination in models of demyelination. Following six days of olesoxime stimulation, the number of mature MBP-expressing rodent oligodendroglial cells was significantly increased in comparison to controls. In addition, in mice pretreated with oral olesoxime and subjected to lysolceithin-induced focal demyelination, there was a significant increase in the proportion of CC1+ mature oligodendrocytes one week post-lesion. Currently, there is an ongoing phase Ib clinical trial investigating the tolerance profile of olesoxime as an add-on therapy for interferon beta in patients with stable RRMS (ClinicalTrials.gov identifier: NCT01808885).

γ-secretase inhibitor quercetin
As described further above, it is well established that multiple molecular signaling cascades operate to inhibit OPC differentiation and remyelination of MS lesions. A number of small molecules aimed at targeting these endogenous inhibitory pathways are available and currently being tested in other diseases. For example, inhibiting oligodendroglial Notch signaling through γ-secretase has already been shown to significantly enhance clinical recovery and remyelination in a rodent EAE model. Although γ-secretase inhibitors such as LY450139 (semagacestat) have yielded disappointing results in several AD trials with the condition worsening in affected patients (ClinicalTrials.gov identifiers: NCT00810147 and NCT00890890), so far none of the γ-secretase compounds have yet been evaluated in MS. Besides the Notch pathway, Wnt signaling has also been shown to affect (re-)myelination by nuclear translocation of β-catenin, a process termed canonical Wnt signaling. In the nucleus, β-catenin binds to transcription factor 4 (TCF4), which, in turn, delays myelin repair. These experimental observations suggest the consideration of inhibitors of Wnt signaling as further potential therapeutic tools. However, there is the important therapeutic caveat that indiscriminate inhibition of Wnt is likely to interfere with both canonical and noncanonical Wnt signaling, which in turn regulate a multitude of different cell functions ranging from cell movements, via Rock and c-Jun N-terminal kinase (JNK), to early development. The most promising agent currently available for selective inhibition of canonical Wnt signaling may be the flavonoid quercetin, which has already been investigated in the context of colonic carcinoma and is found to strongly suppress the binding of Tcf complexes to specific DNA-binding sites and to disrupt the binding of beta-catenin to TCF-4. Quercetin could therefore provide a pharmacological approach allowing for highly selective therapeutic inhibition of Wnt signaling.

Conclusions
In the clinic, one of the most frequent questions MS patients ask neurologists is whether persistent deficits acquired during the disease course, such as ataxia, paresthesias or motor weakness, will ever improve. Even though the past two decades since the first introduction of the interferons in the early 1990s have seen incredible progress and innovations in MS therapy, neurologists still have little to offer in this setting. Regaining quality of life by improvement of acquired deficits in conjunction with effective prevention of disease relapses must be the goal of future therapeutic approaches. With an ever-increasing number of agents that have shown great promise in experimental animal models of demyelination, it is imperative to determine their potential use for future MS therapy. We believe that the time has come when research into regenerative aspects and therapies directed toward repair should be given the highest priority.

Search criteria
Online literature search for this review was performed with PubMed.com and scholar.google.com using parameters such as the respective drug or compound name in conjunction with the keywords “oligodendroglia,” “oligodendroglial precursor cell,” “myelin,” and “remyelination.” The clinical trials discussed in this review were checked for their current status on clinicaltrials.gov.

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Conflicts of interest
None declared.

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