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Strategies for Protecting Oligodendrocytes and Enhancing Remyelination in Multiple Sclerosis

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Abstract

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) characterized by encephalitogenic leukocyte infiltration and multifocal plaques of demyelination. Patients present with debilitating clinical sequelae including motor, sensory, and cognitive deficits. For the past 30 years, immune modulating treatments have entered the marketplace and continue to improve in limiting the frequency and severity of relapses, but no cure has been found and no drug has successfully stopped chronic progressive disease. Recent work focusing on the oligodendrocyte, the myelin-producing cell, has provided needed insight into the process of demyelination, the spontaneous ability of the CNS to regenerate, and the inevitable failure of remyelination. From this a number of promising molecular targets have been identified to protect oligodendrocytes and promote remyelination. Combining immunomodulatory therapy with strategies to protect oligodendrocytes from further degeneration and enhance remyelination presents a very real means to improve clinical outcome for chronic progressive patients in the near future. Here we lay out a combination therapy approach to treating MS and survey the current literature on promising drug candidates potentially capable of mediating oligodendrocyte protection and enhancing remyelination.

Myelin Is Necessary for Normal Central Nervous System Function

Electrical impulses conducted through the axonal segment of the neuron are essential for proper functioning of the central nervous system (CNS). Axonal conduction is integrally supported by sheaths of insulating membrane called myelin that are produced by glial cells termed oligodendrocytes. A single axon is wrapped with many segments of myelin often from multiple oligodendrocytes distributed along the length of the axon, and one oligodendrocyte can generate up to 40 myelin segments. Unlike the largely static morphology of a neuron, the oligodendrocyte is constantly generating new myelin and replacing segments in a form of ongoing myelin maintenance throughout adulthood (Lajtha *et al.*, 1977). In addition to supporting axonal conduction, oligodendrocytes have more recently been shown to promote the health of neurons by other mechanisms, specifically providing growth factor and structural support. Indeed there is compelling evidence that axonal survival is dependent on intact oligodendrocytes (Pohl *et al.*, 2011). It comes as no surprise then that oligodendrocyte deficiency and coincident demyelination can have devastating effects on a multitude of CNS functions. The prototypical demyelinating disease multiple sclerosis (MS) is characterized by multifocal lesions of demyelination in the brain

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and spinal cord ultimately presenting as progressive axonal loss and substantial neurological decline. Although the etiological origins of MS remain to be definitively explained – and as evidence suggests may not necessarily be restricted to any single mechanism – there is in most cases a definitive immunopathological component usually manifested as aberrant immune responses to host CNS cells and proteins.

Combining Therapeutic Strategies

There are three principal approaches to treating MS: 1) halting the pathologic immune response, 2) protecting the CNS from further damage, and 3) repairing the damage through the regeneration of new myelin sheaths, with the overarching goals being to restore conduction and prevent further axonal loss (Figure 1). Currently, all FDA-approved drugs for MS are exclusively immunomodulatory therapies. These drugs are relatively effective at preventing new demyelinated lesions from forming and significantly impeding relapsing-remitting disease progression, but are ineffective at preventing the transition to or advancement of progressive MS. At this chronic stage neurodegeneration becomes increasingly evident leading to the accumulation of irreversible clinical disability (Compston, 2006). At present approximately 50% of people affected by MS are at the progressive stage of the disease illustrating the critical need for developing additional therapeutic strategies to protect oligodendrocytes and bolster regeneration in combination with current immunotherapies.

Immune Modulation

The ten existing disease-modifying treatments for MS target the immune compartment (Derwenskus, 2011). Early approaches aimed to limit activation of pathologic immune cells and were relatively nonspecific in their scope. Early drugs – interferon-beta (Avonex, Rebif, Betaseron, Extavia) and glatiramer acetate (Copaxone), a synthetic copolymer, are both administered subcutaneously to suppress multiple cell types including antigen presenting cells and T_H1 and T_H17 helper subsets cells and shift the immune system towards a regulatory phenotype (Lalive *et al.*, 2011). Mitoxantrone (Novatrone), a synthetic antineoplastic drug, induces apoptosis in highly proliferative cells and suppresses macrophages, B cells, and T_H cells (Derwenskus, 2011). Recent work in autoimmunity has sought to refine the therapeutic approach in new ways, more specifically targeting the pathologic immune compartment without compromising the entire arm of the adaptive immune response thus minimizing side effects and any risks of opportunistic infection. Two current therapies limit T cell migration: fingolimod (Gilenya) constrains T cell migration from lymph nodes, whereas natalizumab (Tysabri) blocks T cell infiltration across the blood-brain barrier into the CNS. Other drugs such as dimethyl fumarate (Tecfidera) have been purported to have neuroprotective effects by modulating oxidative stress in addition to immunomodulatory effects. We also recently published the favorable results in both MS animal model studies (Getts *et al.*, 2013; 2011) and in a phase I clinical trial that induces antigen-specific immune tolerance to myelin epitopes without excessively compromising the adaptive immune system (Lutterotti *et al.*, 2013). Nine MS patients who were off-treatment for standard therapies received a single infusion of autologous peripheral blood mononuclear cells chemically coupled with seven myelin peptides (MOG_{1-20}, MOG_{35-55}, MBP_{13-32}, MBP_{83-99}, $MBP_{111-129}$, $MBP_{146-170}$, and $PLP_{139-154}$). Administration of antigen-coupled cells was feasible and well tolerated, and patients receiving the higher doses ($>1 \times 10^9$) had a decrease in antigen-specific T cell responses after peptide-coupled cell therapy. We are hopeful this approach may fill a critical need of antigen-specificity for immunomodulatory therapies.

Oligodendrocyte Protective Therapies

The majority of drugs under investigation to protect oligodendrocytes from apoptosis were first discovered for their immunomodulatory or neuroprotective capabilities in other capacities. In the context of MS, it is often poorly understood whether the beneficial effects are due to immune modulation, neuroprotection, or both. Indeed uncoupling these effects is particularly difficult as CNS degeneration is so intimately associated with inflammation. In light of a combination therapeutic approach, drugs that protect oligodendrocytes from apoptosis are likely to be most effective when used in combination with systemic immune modulation whether in cases of acute or chronic inflammation. Current data highlight the importance of proper timing in CNS-protective drug treatments as some prove to be most efficacious in early relapsing-remitting disease associated with deleterious inflammation. In this vein neuroprotective drugs may be unnecessary once immune tolerance has been established, particularly if tolerance can be induced early in disease and proves to have long-lasting effects.

Anti-apoptotic drugs

Minocycline, the most lipophilic of the broad-spectrum tetracycline antibiotics, is commonly used for its potent systemic antibacterial and immunomodulatory actions (Kloppenburg *et al.*, 1996). Its ability to penetrate the CNS and modulate local inflammatory responses however makes it an attractive drug for neurological disorders (Kim and Suh, 2009). Minocycline was shown to be effective in attenuating experimental autoimmune encephalomyelitis (EAE), an immune-mediated rodent model that bears many semblances to MS, both prophylactically and therapeutically (Brundula *et al.*, 2002; Popovic *et al.*, 2002). It is difficult to attribute the therapeutic success of minocycline to either immunomodulation or anti-apoptotic oligodendrocyte effects and it may likely be due to both. Minocycline has a long half-life and is safe for long-term use (Klein and Cunha, 1995), making it an ideal add-on treatment for MS. It has been tested in MS patients in three separate clinical trials in combination with current FDA-approved MS therapies and alone (Luccarini *et al.*, 2008; Metz *et al.*, 2009; 2004; Ruggieri *et al.*, 2008). There were modest positive results (Metz *et al.*, 2004) leading to a current clinical trial recruiting for earlier stage in disease when significant inflammation is present.

Caspases, a family of cysteine proteases whose activity is essential for apoptosis, are known to be up-regulated in the CNS during acute EAE disease (Das *et al.*, 2008). Treatment of EAE with FK506, a caspase inhibitor, reduced the level of demyelination (Gold *et al.*, 2004). FK506 reduction of oligodendrocyte apoptosis has also been verified in the mouse spinal cord injury (SCI) model and *in vitro* suggesting that caspase inhibition protects oligodendrocytes from apoptosis (Craighead *et al.*, 1999; Nottingham *et al.*, 2002). However, given that FK506 is also a potent immunosuppressant commonly used to regulate transplant rejection (Liu *et al.*, 1991) and that caspase-mediated apoptosis is a necessary process in anti-tumor immunity (van de Loosdrecht *et al.*, 1993), the use of this drug and other caspase inhibitors for long-term MS treatment is not desirable.

Cardiovascular drugs

Statins are a commonly-used class of drugs that lower cholesterol levels (Alberts, 1988). Besides the ability to reduce atherosclerosis, statins have been shown to have a plethora of anti-inflammatory and neuroprotective effects in the CNS (Garcia, 2005). In a SCI model accompanied by demyelination, researchers found that atorvastatin treatment reduced oligodendrocyte apoptosis and demyelination resulting in a significant improvement in locomotor activity (Pannu *et al.*, 2005). The mechanism was largely attributed to anti-inflammatory effects, reduced inflammatory cytokines, and improved blood-brain barrier

integrity; however, it has also been suggested that atorvastatin inhibited apoptosis (Dery *et al.*, 2009; Pannu *et al.*, 2005). Atorvastatin was shown to produce a T_H2 helper cell bias and ameliorate clinical disease in EAE (Youssef *et al.*, 2002) and was first investigated for its effects in MS in combination with interferon-beta and minocycline. The results revealed beneficial effects yet minimally above interferon-beta or minocycline alone (Luccarini *et al.*, 2008; Paul *et al.*, 2008). A recent phase 2 clinical trial of atorvastatin for clinically isolated syndrome (CIS) reported a significant decrease in the number of new lesions in patients who began treatment shortly after they experienced their first episode of neurological symptoms (Waubant *et al.*, 2012).

Amiloride, a pyrazine-carbonyl-guanidine originally discovered for its ability to block epithelial sodium channels, is approved for the treatment of hypertension and congestive heart failure. Amiloride has been shown to block other ion channels and exchangers, including acid-sensing ion channel 1 (ASIC1) that is expressed on oligodendrocytes (Feldman *et al.*, 2008) and is up-regulated by oligodendrocytes in MS and EAE lesions (Vergo *et al.*, 2011). Amiloride treatment during EAE reduced disease severity (Friese *et al.*, 2007; Vergo *et al.*, 2011) and these effects were shown to be CNS-protective, reducing tissue acidosis, rather than immunomodulatory (Friese *et al.*, 2007). Thus amiloride is a promising oligodendrocyte protective drug that is currently being tested in a phase II clinical trial for MS.

Cannabinoids

Cannabinoids (CB) are a family of compounds, originating from the plant *Cannabis sativa*, known for numerous effects on the CNS and immune systems (Zajicek and Apostu, 2011). These effects are mediated by cannabinoid receptors, CB1 and CB2, with restricted expression patterns; whereas CB1 exerts psychotropic effects in the CNS, CB2 receptors are expressed by immune and glial cells and exert immunomodulatory effects (Arevalo-Martin *et al.*, 2008; Galiegue *et al.*, 1995). In EAE, CB1 activation in neurons and CB2 activation in $CD4^+$ T cells have both been shown to ameliorate disease (Croxford and Miller, 2004; Croxford *et al.*, 2008; Maresz *et al.*, 2007). Cannabinoids may also induce neuroprotective effects in oligodendrocytes and oligodendrocyte progenitor cells (OPCs) which both express CB2 (Molina-Holgado *et al.*, 2002). Cannabidiol was shown to protect OPCs from cytokine-mediated apoptosis by attenuating ER stress (Mecha *et al.*, 2012). Additionally WIN55,212-2, a synthetic cannabinoid, stimulated OPC proliferation as well as survival *in vivo* (Solbrig *et al.*, 2010), and there is evidence that cannabinoids can enhance remyelination by promoting oligodendrocyte maturation (Gomez *et al.*, 2010; 2011). Thus cannabinoids may be a unique means to stimulate neuroprotection as well as regeneration. Several clinical trials of MS patients treated with cannabinoids found significant decreases in neurological symptoms and pain (Zajicek and Apostu, 2011). Currently the cannabinoid oral spray nabiximols is available in Canada and parts of Europe, but has yet to be approved in the U.S.

Remyelination Enhancing Therapies

The third component to a combinatorial therapeutic approach for MS is to enhance regeneration in the absence of the pathologic immune response and primary CNS damage. Early regenerative efforts focused on exogenous cell sources transplanted into the demyelinated CNS to form new myelin sheaths. Characterization of the robust nature of spontaneous remyelination, the process whereby demyelinated axons are ensheathed by new myelin membrane to functionally restore compromised axonal conduction, has refocused efforts towards promoting endogenous repair. Here we review exogenous cell therapies, current understanding on the nature of remyelination, and recent encouraging data employing endogenous remyelinating strategies.

Cell transplantation strategies

Brain OPCs can efficiently myelinate denuded axons when transplanted into a demyelinated lesion forming the basis for decades of cell transplantation research for MS (Duncan *et al.*, 2008; Franklin and Ffrench-Constant, 2010). Promising cellular sources have included adult OPCs, Schwann cells, olfactory ensheathing cells, multipotent mesenchymal and hematopoietic progenitors from bone marrow, and adult and embryonic neural stem cells (Einstein *et al.*, 2003; Huang and Franklin, 2012; Pluchino *et al.*, 2003; Uccelli *et al.*, 2011). To date, these approaches have raised more concerns rather than viable cellular therapies. Confounds include limited availability of source cells, limited migration of transplanted cells in models with multifocal sites of injury, immune rejection of transplanted cells, potential tumorigenesis, and determination of optimal route of administration for maximal delivery into the CNS (Chu *et al.*, 2004; Miron *et al.*, 2011). Finally the viability of cellular transplantation therapies for chronic progressive MS proves problematic in that transplanted OPCs are less likely to regenerate myelin in chronically demyelinated lesions than in the acutely demyelinated environment (Franklin, 2002). Migration and differentiation of transplanted progenitors in the EAE model directly corresponds to the peak of inflammation, and it may be the decrease in inflammation and thus pro-regenerative stimuli that underlie the failure in chronic demyelinated lesions (Foote and Blakemore, 2005; Setzu *et al.*, 2006). An additional concern exists in that transplanted OPCs and newly generated myelin sheaths are subject to the same immune-mediated injury that resulted in the initial demyelinating insult (Blakemore *et al.*, 2002).

Cellular therapy has lately taken an interesting turn in that many cell types under investigation are now thought to influence the injury environment through immunomodulation or trophic support to promote endogenous remyelination and neuroprotection, rather than direct cell replacement (Freedman *et al.*, 2010; Munoz *et al.*, 2005; Reynolds and Rietze, 2005; Robinson *et al.*, 2011). Neural stem cells and bone marrow-derived mesenchymal stem/stromal cells (MSCs) have both been shown to act through anti-inflammatory mechanisms in animal models of demyelination and are purported to act through distinct immunomodulatory mechanisms (Pluchino and Martino, 2008; Uccelli *et al.*, 2008). Recently a phase IIa clinical trial of intravenously infused MSCs into patients with secondary progressive MS was completed. Despite pre-clinical data suggesting MSCs do not engraft long-term in the CNS, patients exhibited improved CNS structure, function, and physiology (Connick *et al.*, 2012).

True cellular replacement therapies may be best suited for treating developmental dysmyelination disorders such as the leukodystrophies, where the unrelenting immunological attack and exhaustion of transplanted cells is not an issue, as opposed to MS (Windrem *et al.*, 2002; 2008). Replacement strategies have recently been bolstered by the demonstration of direct induction of OPCs from embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) (Czepiel *et al.*, 2011; Hu *et al.*, 2009; Liu *et al.*, 2011; Najm *et al.*, 2013; 2011). Induced OPCs can be rapidly expanded in culture and in two recent studies have been shown to functionally restore myelin in animal models of congenital hypomyelination (Wang *et al.*, 2013; Yang *et al.*, 2013).

Remyelination naturally follows demyelinating insult and disease

Generation of new myelin in the MS demyelinated lesion has been extensively documented by neuropathologic data (Prineas *et al.*, 1984). Perhaps not surprisingly, clinical remissions or recovery from relapses in MS are correlated with remyelination in the lesions, both older lesions with diminished inflammatory activity and in new lesions with ongoing inflammation (Prineas *et al.*, 1993; Raine and Wu, 1993). Indeed remyelination seems to be limited not by the acute, hostile inflammatory environment, but instead gradually dissipates

over time (Sim *et al.*, 2002). In addition to the restoration of conduction, multiple mechanisms have been associated with clinical remissions including the resolution of inflammation, sparing of neural and oligodendroglial cells, and the functional reorganization of myelin components (Mahad *et al.*, 2008). Once a patient transitions to progressive MS, there is a strong correlation between the failure to remyelinate and axonal loss, and both show steady progression (Kornek *et al.*, 2000).

Overwhelming evidence from the past 20 years suggests that new myelin in the MS lesion is synthesized by OPCs rather than the previously myelinating oligodendrocyte (Franklin and Ffrench-Constant, 2008; Keirstead and Blakemore, 1997). OPCs are cells randomly distributed throughout the CNS that are proliferative, motile, and capable of differentiating into oligodendrocytes and forming functional myelin sheaths. OPCs have been identified in the adult human brain comprising 5-8% of glial cells. Their function is presumably for normal myelin turnover as well as remyelination in response to injury (Jones *et al.*, 2003). Current thinking posits that a complex series of coordinated steps is necessary for OPC "activation" and effective remyelination (Franklin and Kotter, 2008). Parenchymal OPCs migrate to sites of demyelination and undergo a vigorous proliferation to repopulate cells lost in the lesion (Gensert and Goldman, 1997; Lucchinetti *et al.*, 1999). Next OPCs differentiate, a process characterized by down-regulation of OPC markers and up-regulation of markers associated with mature oligodendrocytes, coincident with exit from the cell cycle, a loss of motility, and an increasingly complex arborization (Crockett *et al.*, 2005). In possessing all the cellular machinery for myelin formation, the final step involves axon contact and wrapping.

The pivotal question then is: why does remyelination fail? Therapeutic strategies have to date sought to stimulate all facets of OPC activation, though currently promoting OPC differentiation is the most prevalent approach. OPCs can be detected in chronic MS lesions suggesting that remyelination failure is not solely due to exhaustion of the progenitor pool or the breakdown of migration but rather may be primarily a dysregulation of OPC differentiation and axon ensheathment (Kuhlmann *et al.*, 2008). As we elucidate the molecular underpinnings of the failure of remyelination and the activation of OPCs, several promising antibodies directed against CNS targets and pharmacological targets have been identified to promote OPC maturation and/or remyelination.

Antibody-based strategies to promote remyelination

Recombinant antibodies—LINGO-1 is a recently discovered leucine-rich repeat protein that is expressed in the CNS and functions as a negative regulator of OPC differentiation (Mi *et al.*, 2005). Human antibodies generated against LINGO-1 were shown to block signaling in cultured OPCs and stimulate OPC differentiation and function in myelinating co-cultures. In animal models of demyelination, anti-LINGO-1 purportedly promotes remyelination by creating a hospitable environment for OPC activation (Mi *et al.*, 2009). Early stage clinical trials are currently underway (Rudick *et al.*, 2008). Restricted expression of the target protein in the CNS makes anti-LINGO-1 a particularly attractive target minimizing the chance of non-neural tissue complications (Mi *et al.*, 2008); however, delivering the antibody in sufficient concentrations to the CNS may prove problematic.

A recombinant human IgM, termed rHIgM22, was identified from screens of antibodies for oligodendrocyte binding and remyelination promotion and has been shown to very effectively stimulate remyelination in an animal model of demyelination (Warrington *et al.*, 2000; 2007). Mechanistic studies indicate that rHIgM22 drives OPC proliferation in conjunction with other glial-derived factors by inhibiting apoptotic signaling in OPCs (Watzlawik *et al.*, 2010; 2013). rHIgM22 is currently the only antibody-based approach targeted to promote OPC proliferation.

Naturally occurring antibodies—Naturally occurring autoantibodies represent another promising source for antibody-based therapy to promote remyelination. Myelin- and oligodendrocyte-reactive autoantibodies have been identified from serum, CSF, and CNS tissue from MS patients and have been shown to promote remyelination in animal models of demyelination (Bieber *et al.*, 2002; Miller *et al.*, 1996). The antigenic targets have in some cases been identified as demonstrated by description of anti-myelin basic protein (MBP) antibodies that promote CNS remyelination (Rodriguez *et al.*, 1996). The observation that remyelination-promoting oligodendrocyte-specific antibodies are polyreactive, binding to both extracellular and intracellular antigens, argues against a direct activation mechanism via specific cell surface receptor. Instead IgM binding to damaged oligodendrocytes via the common μ-heavy chain has been hypothesized to enhance debris clearance by scavenger macrophages and microglia thus indirectly enhancing remyelination (Asakura *et al.*, 1998).

Antibodies reactive to viral peptides, exogenous and endogenous, have also been identified for their ability to promote remyelination. Semliki Forest Virus (SFV) encephalomyelitis produces CNS inflammation and subsequent demyelination (Safavi *et al.*, 2011). Antibodies reactive to an SFV peptide were demonstrated to promote disease recovery, and when administered in EAE promote remyelination and clinical amelioration (Mokhtarian *et al.*, 2012). Another monoclonal antibody reactive against an envelope protein from the human endogenous retrovirus type W family was initially identified because the viral particles were isolated from brain tissue from MS patients (Curtin *et al.*, 2012; Perron *et al.*, 1997). The viral protein, named Multiple Sclerosis-Associated Retrovirus (MSRV), was found to potentiate inflammatory responses in a humanized mouse model (Firouzi *et al.*, 2003). The MSRV-reactive antibody, named GNbAC1, was shown to ameliorate EAE, and a phase I clinical trial was recently completed with favorable results (Curtin *et al.*, 2012). For both viral protein reactive antibodies, the direct oligodendroglial or CNS mechanism of action has yet to be identified.

Molecular and pharmacological strategies to promote remyelination

Wnt inhibitors—Wnt proteins are a family of signaling glycoproteins that promote accumulation and activation of the transcription factor beta-catenin. Beta-catenin signaling is a known regulator of embryonic neural development, cellular proliferation, and differentiation. In OPCs beta-catenin negatively regulates differentiation (Feigenson *et al.*, 2009) as an excess of beta-catenin in OPCs delays developmental myelination and remyelination during EAE (Fancy *et al.*, 2009; Ye *et al.*, 2009). XAV939, a small molecule inhibitor, enhances oligodendrocyte differentiation and remyelination by stabilizing Axin2, an intracellular target of Wnt transcriptional activation (Fancy *et al.*, 2011). Exploiting the function of Axin2 is likely to enhance remyelination in EAE and MS, but further research is needed.

Notch—Notch is a protein involved in cell fate decisions in the CNS as well as regulatory effects in the immune system (Jurynczyk and Selmaj, 2010). Notch has been detected in immature oligodendrocytes of MS lesions and following demyelination in mice (Stidworthy *et al.*, 2004). In addition, cultured human OPCs exposed to the Notch ligand Jagged failed to mature suggesting Notch may inhibit the differentiation of OPCs (John *et al.*, 2002). Indeed EAE mice treated with a γ-secretase inhibitor, MW167, which prevents Notch cleavage and signaling, demonstrated improved myelin repair and axonal survival (Jurynczyk *et al.*, 2005). γ-secretase inhibitors are under investigation for a number of CNS degenerative disorders. An oral formulation was recently tested in clinical trials for Alzheimer's disease, but yielded disappointing results. Nonetheless the agent is able to gain access to the CNS and was well tolerated and thus remains hopeful for MS trials (Fleisher *et al.*, 2008).

RXR agonists—Retinoid X receptor-γ (RXRγ), is a nuclear receptor that drives oligodendrocyte differentiation and myelin sheath formation by OPCs, and is the only positive regulator of OPC activation showing promising advanced results in studies (Huang *et al.*, 2011b). In MS tissues RXRγ is highly expressed in acute and remyelinating lesions compared to chronic inactive lesions (Huang *et al.*, 2011a). An RXR agonist was shown to improve remyelination in both an *ex vivo* cerebellar slice culture and EAE (Diab *et al.*, 2004). Additionally RXR agonists have been purported to enhance phagocytic activity and attenuate inflammation in the CNS by regulating macrophage activity suggesting RXR activation may exert dual functions in regulating inflammation and OPC differentiation in the injured CNS (Kotter *et al.*, 2006; Xu and Drew, 2006). Clinical trials evaluating RXR agonists for MS should be forthcoming. Indeed a licensed RXR agonist Targretin (bexarotene) is already in clinical use for the treatment of cutaneous T cell lymphoma (Ballanger *et al.*, 2010).

Progesterone—Progesterone is a well-characterized steroid hormone involved in the female menstrual cycle and reproduction with immunomodulatory effects in several models of neurological diseases including EAE (Garay *et al.*, 2007; 2012). Additionally progesterone is known for neuroprotective effects and progesterone signaling in oligodendrocytes has been shown to promote remyelination. Mice with EAE treated with progesterone had decreased clinical severity and enhanced expression of transcription factors essential for oligodendrocyte differentiation, density of mature oligodendrocytes, and myelin protein transcripts (Garay *et al.*, 2012). Using a non-immune mediated animal model of demyelination researchers demonstrated that progesterone stimulated OPC proliferation and remyelination independent of immunomodulation (Garay *et al.*, 2011). It is common for pregnant MS patients with elevated levels of progesterone to experience fewer relapses, but they often relapse post-partum (Vukusic and Confavreux, 2006). A clinical trial in Europe is currently evaluating postpartum progesterone treatments to reduce the incidence of relapse.

Conclusions

The landscape for MS therapies is undergoing a rapid expansion as knowledge accumulates on how aberrant immune responses produce demyelinating injury and how the CNS is able to regenerate myelin. The early broad-based immunosuppressive drugs are giving way to targeted, antigen-specific approaches minimizing side effects and maximizing clinical benefit. At the same time decades of work suggest that immunomodulation alone will only go so far and that strategies to protect oligodendrocytes and promote remyelination should be considered in parallel, combinatorial therapeutic approaches. Many repurposed drugs are showing promise for protecting oligodendrocytes, and remyelination strategies focusing on antibodies and pharmacological targets have shifted the focus from cellular replacement to enhancing endogenous repair.

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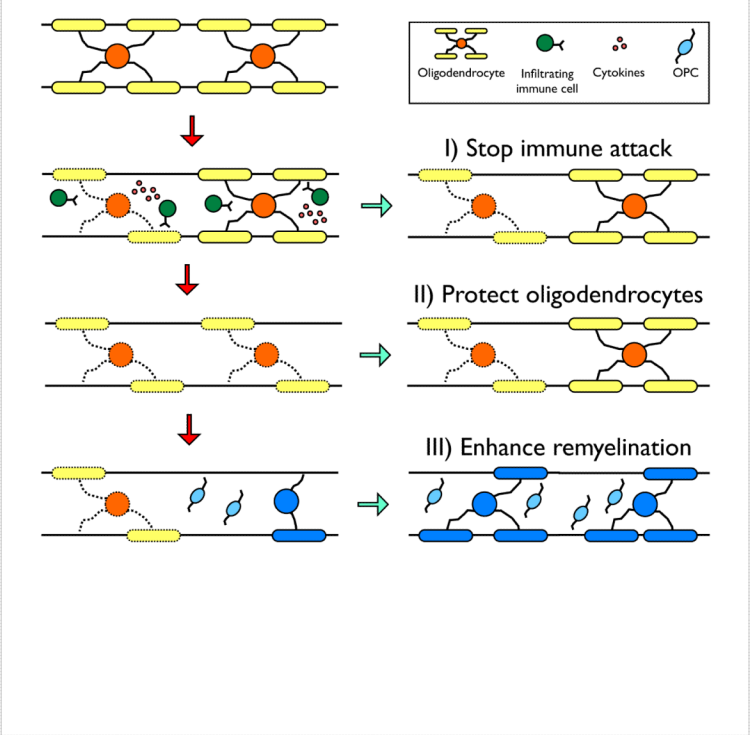

Figure 1.
Three therapeutic targets for combinatorial treatment strategies for multiple sclerosis. In the experimental autoimmune encephalomyelitis model of MS, CNS-infiltrating, autoreactive $CD4^+$ T cells secrete cytokines that activate resident and infiltrating inflammatory immune cells leading to oligodendrocyte damage. The release of myelin antigens perpetuates the inflammatory process and subsequent oligodendrocyte destruction. The CNS is capable of significant regeneration. Endogenous oligodendrocyte progenitor cells (OPCs) proliferate, migrate to sites of inflammation, and differentiate to synthesize new myelin sheaths. To improve clinical outcome of MS patients we present three principal approaches: 1) halt pathologic immunity ideally by inhibiting antigen-specific responses rather than employing generalized immunosuppression, 2) protect oligodendrocytes from further damage, and 3) enhance remyelination either by transplanted exogenous cells or promote repair via endogenous OPCs.