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Pharmacological approaches to intervention in hypomyelinating and demyelinating white matter pathology

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Abstract

White matter disease afflicts both developing and mature central nervous systems. Both cell intrinsic and extrinsic dysregulation result in profound changes in cell survival, axonal metabolism and functional performance. Experimental models of developmental white matter (WM) injury and demyelination have not only delineated mechanisms of signaling and inflammation, but have also paved the way for the discovery of pharmacological approaches to intervention. These reagents have been shown to enhance protection of the mature oligodendrocyte cell, accelerate progenitor cell recruitment and/or differentiation, or attenuate pathological stimuli arising from the inflammatory response to injury. Here we highlight reports of studies in the CNS in which compounds, namely peptides, hormones, and small molecule agonists/antagonists, have been used in experimental animal models of demyelination and neonatal brain injury that affect aspects of excitotoxicity, oligodendrocyte development and survival, and progenitor cell function, and which have been demonstrated to attenuate damage and improve WM protection in experimental models of injury. The molecular targets of these agents include growth factor and neurotransmitter receptors, morphogens and their signaling components, nuclear receptors, as well as the processes of iron transport and actin binding. By surveying the current evidence in non-immune targets of both the immature and mature WM, we aim to better understand pharmacological approaches modulating endogenous oligodendroglia that show potential for success in the contexts of developmental and adult WM pathology.

Keywords

Oligodendrocytes; Brain injury; Adult; Neonatal; Remyelination; Regeneration; Repair; Development; Pharmaceutical

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1. INTRODUCTION

Oligodendrocytes have essential roles in the function of a healthy nervous system. They are, however, also among the most vulnerable of neural cell types in the CNS, and as a result, central myelin abnormalities are found in a wide variety of neurological disorders. White matter pathologies are found in many neurologic diseases, including genetic leukodystrophies (Costello et al., 2009), brain injury (Kinnunen et al., 2011), endocrine and metabolic abnormalities (Sievers et al., 2009; van der Werff et al., 2014), and psychiatric (Ladouceur et al., 2012) and neurodegenerative conditions (Mascalchi, 2005). These heterogeneous pathologies range from abnormal myelin structure to the virtual absence of myelin, and can arise directly from lack of myelin production or indirectly from damage to myelin. In white matter pathologies, insults such as oxidative stress, mechanical injury and inflammation ultimately lead to the degenerative loss of myelin (demyelination) or inadequate or abnormal formation of myelin (hypomyelination/dysmyelination). Primary mechanisms of myelin damage include destruction of the myelin sheath and oligodendrocyte (OL) death (Merrill and Scolding, 1999), failure of progenitor cell recruitment and/or differentiation during remyelination (Kremer et al., 2015; Shi et al., 2015), or in the case of neonates, delayed OPC maturation and defective ensheathment of myelinated axons (Jablonska et al., 2012; Ritter et al., 2013; Scafidi et al., 2014). As WM supports multiple axonal functions besides saltatory conduction, WM injury invariably leads to, or is associated with, devastating neurological disabilities, including motor and cognitive impairment.

In the adult CNS, approaches to intervention and protection against demyelination include attenuation of immune-mediated, excitotoxic and oxidative stress-mediated damage, as well as cell engraftment, direct protection of endogenous OLs and enhancement of repair by oligodendrocyte progenitor cells (OPCs). The success of cell replacement therapy is dictated by the lesion environment (Blakemore et al., 2002), so that an understanding of the multitude of factors in remyelination failure is needed not only for success of the graft, but also for stimulating repair by endogenous progenitor cells.

In the developing brain, perinatal WM damage, for which there is currently no cure, constitutes an important component of injury to the cerebrum that includes neurons and axons. Many of these insults occur in utero, as a consequence of preterm birth, or with complications of delivery (Silbereis et al., 2010). With improved antenatal care, the incidence of tissue degeneration from cystic lesions of the WM has declined, whereas the predominant lesion has now become more diffuse (Silbereis et al., 2010). As with the adult, the mechanisms which result in injury may also be excitotoxic, inflammatory and oxidative (Van Steenwinckel et al., 2014), and may either impact OLs directly, their synapses with axons (Shen et al., 2012), or other cells such as microglia (Kaur et al., 2012) and astrocytes (Deng et al., 2014).

This article aims to review pharmacological approaches to attenuate WM damage through efforts to promote remyelination in the adult, and reduce or prevent developmental delay in the neonate. Neuroprotection will not only help to preserve saltatory axonal conduction, but also aid in the maintenance of axonal metabolism and integrity, thus improving overall

connectivity. Interestingly, white matter integrity and connectivity are impacted in conditions besides primary demyelinating disease, such as psychiatric (Chew et al., 2013) and neurodegenerative disorders (Mascalchi, 2005). Since anti-psychotic and anti-depressant therapies have been found to additionally attenuate myelin damage, targeted approaches for promoting or preserving myelination in a wide variety of neurological conditions would be justified (Bartzokis, 2012). Many neurological diseases are strongly associated with inflammation. Not surprisingly, some therapeutic reagents which have been found to protect the OL cell from damage have been shown to possess immunomodulatory properties. However, as continuous oligodendrogenesis is now considered a central component of brain plasticity and remodeling throughout life (Young et al., 2013), we have chosen an emphasis on non-immune therapeutic targets employed to improve myelination and remyelination by endogenous OPCs. By reviewing reports of pharmacological intervention in experimental models of demyelination and hypomyelination/dysmyelination, we hope to identify overlapping mechanisms that show the potential to benefit neonatal and adult WM pathologies.

1.1 Animal models of WM damage

Experimental models of adult WM damage involve viral, chemical, and immune-mediated demyelination paradigms, as well as spinal cord injury. These systems are well described in laboratory rodents (Tanaka and Yoshida, 2014). Briefly, gliotoxic chemicals that are injected into the WM to generate localized lesions include ethidium bromide that kills OLs by intercalating into the minor groove of DNA, and lysolecithin/lysophosphatidylcholine (Hall, 1972) which specifically disrupts myelin sheaths. Cuprizone (bis-cyclohexanone-oxaldihydrazone), a copper chelator that causes OL apoptosis by impairing metabolic function and inhibiting cellular support of myelin, is administered via the diet. It causes diffuse demyelination that is most notable in, but not restricted to (Skripuletz et al., 2008), WM regions (Matsushima and Morell, 2001). Remyelination is initiated by resuming a cuprizone-free diet for 2 weeks. None of these toxin-based methods of demyelination mimics the dynamics and pathogenesis of human disease, but they are useful to understand many aspects of damage and remyelination, such as preferential vulnerability of myelin without significant axonal loss, properties of the cellular response in recovery, the biological factors regulating these processes, and therapeutic regimens that improve cellular repair. The focal lesion provides rapid (48hr) demyelination that is circumscribed, so that secondary inflammation (Hall, 1972; Miron et al., 2013) and directed progenitor recruitment may be studied, using the lesion as an endpoint destination (Jablonska et al., 2010). In addition, unilateral lesions allow internally controlled sampling (Aguirre et al., 2007). However practical considerations of consistency in lesion size and location, applicable to quantitative analysis by histological and biochemical methods, add to the technical demands of this approach. These models are most valuable to study cellular responses during remyelination after myelin loss and injury, but because they lack the autoimmune component of MS, cannot be considered ideal animal models of MS. The interested reader is referred to comprehensive chapters and articles that further discuss MS models (Croxford et al., 2011; Merrill, 2009; Ransohoff, 2012).

Diffuse demyelination is also observed in an immune-mediated model, experimental autoimmune encephalitis, or EAE. EAE has remained the most influential in our understanding of inflammatory demyelination (Robinson et al., 2014). EAE may be produced in both mice and rats, and can be generated by 1) passive immunization with WM tissue homogenate, or 2) immunization with MBP or MOG. A third method, the adoptive transfer of T cells isolated from myelin peptide primed animals, allows the selection or *in vitro* manipulation of T cells before transfer to naive recipients to produce EAE (Robinson et al., 2014). Another inflammatory model of demyelination utilizes viruses- Theiler's murine encephalomyelitis virus (TMEV), or neurotrophic variants of the mouse hepatitis virus (MHV) - that stimulate the activity of T cells to induce chronic demyelination (Lane and Buchmeier, 1997; Templeton and Perlman, 2007). Immune mediators secreted by T cells and macrophages/microglia have been suggested to contribute to virally-induced demyelination due to dysregulation or death of oligodendrocyte lineage cells (Marro et al., 2014). These models are often considered alongside autoimmune-based models such as EAE, as they are useful for the characterization of infectious events leading to CNS immune responses (Baker and Amor, 2015; Fazakerley and Walker, 2003). Although EAE is powerful and remains most commonly used MS model, it is recognized that its limitations for MS therapy (Constantinescu et al., 2011) stem from a dependence on the artificial induction of the immune response (Mecha et al., 2013), unreliable predictability of treatments, a spinal cord preference over brain lesions, difficulty in analyzing remyelination of stochastic lesions and inconsistency of clinical functional progression (Ransohoff, 2012). On the other hand, proponents of viral models of demyelination note an inside-out axon-first degeneration, the presence of brain demyelination and progressive disease with viral spread (Mecha et al., 2013). Given the heterogeneity of the disease, it is still useful to continue to identify disease-modifying treatments for MS with both of these demyelination models.

Spinal cord contusion injury as well as traumatic brain injury are associated with demyelination (Chao et al., 2012; McDonald and Belegu, 2006). Similarly, demyelination is also observed secondary to hypoxic-ischemic damage in stroke models (Mifsud et al., 2014; Skoff et al., 2001). The neonatal WM is particularly vulnerable to damage from oxidative stress- and inflammation-mediated brain injury in neurodevelopmental disease of the preterm infant (Silbereis et al., 2010). Cerebral white matter injury is a major form of brain injury found in survivors of premature birth (Volpe, 2009), which places these survivors at high risk of long-term neurological deficit (Hack et al., 2000; Wilson-Costello et al., 2005). Experimental white matter lesions are reproduced in the developing brain using ventricular hemorrhage (Chua et al., 2009; Ment et al., 2005; Ment et al., 2000; Vose et al., 2013), prenatal infection and inflammation, reviewed in (Chew et al., 2013), neonatal hypoxia-ischemia, or chronic hypoxia, reviewed in (Scafidi et al., 2009). Perinatal hypoxic-ischemia and chronic hypoxia in rodent models, may be distinct in mechanism (Busl and Greer, 2010), but together mimic many aspects of pathogenesis in the brain found in premature infants, which include apoptosis of neuronal and glial progenitors and an inflammatory response (Scafidi et al., 2009). Oligodendrocytes are more vulnerable than other glia to ischemia in culture, mimicked by glucose-oxygen deprivation (Lyons and Kettenmann, 1998). *In vivo*, oligodendrocytes are as vulnerable as neurons to ischemia (Pantoni et al., 1996). OL lineage cells are especially susceptible to oxidative stress from free radical

mediated injury (Fragoso et al., 2004). In addition, excitotoxicity is an important factor (Back and Rosenberg, 2014) in the death of pre-OL-stage cells *in vivo* from hypoxia-ischemia, leading to an inability of the lineage to progress to maturity (Back et al., 2001). In studies of experimental therapeutics, various perinatal animal models have been used to test the effect of growth factors on ameliorating WM damage. Expression changes for several growth factors including bFGF, EGF, IGF, and BDNF have been detected in hypoxic rodent models (Dieni and Rees, 2005; Scafidi et al., 2009) and several therapeutic strategies include administration of these and other growth factors.

Spontaneous repair in demyelinating disease occurs via re-activation of the process of OL development from neural stem cells, such as those from the subventricular regions of the brain, the SVZ, which gives rise to OL progenitor cells (OPCs). These OPCs, marked by the NG2 antigen and PDGFR α expression, proliferate and migrate to the lesion to differentiate into O4+ premyelinating OLs and then into mature myelinating O1+ OLs with elaborate processes and which express CC1/APC, 2'3'-cyclic nucleotide 3'-phosphodiesterase (CNP), proteolipid protein (PLP) and myelin basic protein (MBP), myelin associated glycoprotein (MAG). Expression of the transcription factor Olig2 extends from OPC through myelinating OL, allowing immunohistochemical analysis of overall changes in the oligodendroglial lineage during the course of injury and repair. In rodents, spontaneous remyelination is highly robust and efficient, proceeding to virtual completion in a few weeks (Armstrong et al., 2002; Blakemore, 1974; Ludwin, 1978). These experimental models are useful for testing pharmacological agents that potentially inhibit or enhance myelin repair. In human disease, inhibited, abortive or abnormal development of the OPC such as that in cerebral palsy (Back and Miller, 2014) and multiple sclerosis (Kipp et al., 2012b; Kuhlmann et al., 2008), is believed to contribute to the failure of repair and progression of pathology.

2. Strategies for improving protection and repair

2.1 Protecting the CNS from further damage

Pharmaceuticals which protect OLs from death were initially identified by their immunomodulatory or neuroprotective properties. Although many brain pathologies benefit from immunomodulation, complete inhibition of immune activation is detrimental, particularly in the neonate, as many aspects of cytokine function are inextricably associated with growth properties of progenitor cells. Synergy between immune cells and adult neural stem/progenitor cells has been shown to promote functional recovery from spinal cord injury (Ziv et al., 2006). Antenatal administration of the steroidal glucocorticoid dexamethasone to protect respiratory function is another case in point (see below). Other studies have shown that genetic ablation of the proinflammatory cytokine interleukin 1 beta (IL-1b) not only did not affect the severity of cuprizone-induced demyelination in the adult WM, but instead led to inadequate remyelination (Mason et al., 2001) because of an unexpected function of IL-1b in IGF-1 expression (Arnett et al., 2001; Mason et al., 2003). Interferon-gamma also possesses normal physiological function in supporting the growth of neural progenitor cells (Li et al., 2010). Immune modulation alone, which is currently the approach with many drugs for multiple sclerosis, has initially suffered from lack of specificity. Improvement has since been achieved with increased ability to specifically target the pathologic component of

the adaptive response, or efforts to increase immune tolerance to autoimmune epitopes (Getts et al., 2012). Studies with EAE have also shown that autoimmune tolerance is not completely effective against inhibiting disease progression (Pryce et al., 2005), supporting therapeutic strategies for combinatorial treatments in multiple sclerosis that target more than immune component alone.

Reagents such as minocycline (Fan et al., 2005), ethyl pyruvate (Wang et al., 2013) and even caffeine, as adenosine receptor modulators, have been shown to be protective against lipopolysaccharide- and hyperoxia- (Schmitz et al., 2014)-induced perinatal WM injury. Many anti-inflammatory agents have been effective in the perinatal brain (reviewed in Ofek-Shlomai (Ofek-Shlomai and Berger, 2014). These have also been effective against inflammation associated with adult traumatic brain injury (Abdel Baki et al., 2010; Moro and Sutton, 2010) and tissue damage from lipopolysaccharide (Brothers et al., 2010). These agents attenuated cell death and loss of O4+ and O1+ OLs, accompanied by suppression of inflammatory responses. However, minocycline was found to reduce remyelination in the cuprizone demyelination paradigm (Tanaka et al., 2013), because microglial-derived ciliary neurotrophic factor (CNTF), which promotes remyelination, was also suppressed. This further exemplifies the need for caution with some anti-inflammatory approaches.

Nitric oxide is an important regulator of cerebral blood flow (Toda et al., 2009) and inflammation (Blomgren and Hagberg, 2006). Inhaled nitric oxide is being considered as a therapeutic target in neonatal brain injury (Charriaut-Marlangue et al., 2013). Although not shown to be effective in directly promoting cellular regeneration, beneficial effects on neurological outcome in premature infants have been reported (Mestan et al., 2005; Walsh et al., 2010), including WM sparing (Pansiot et al., 2010; Pham et al., 2014) in rodent models of hyperoxia- (Schmitz et al., 2011) and glutamate-induced toxicity (Pansiot et al., 2010), indicating a primarily protective effect. However, due to concerns of side effects in both adults and neonates, the experimental data showing consistent benefit presently appears inadequate to support recommendation for clinical testing.

2.2 Repairing damage by exploiting the regenerative potential of progenitor cells

Cell grafts with stem cells and precursors are an important avenue for therapy in demyelinating disease (Karimi-Abdolrezaee et al., 2006), and neonatal stroke injury (van Velthoven et al., 2013), with the goal of cell replacement (Sher et al., 2008) and attenuation of damage. In the case of autoimmune demyelination, mesenchymal stem cell transplantation lowers self-reactivity, reducing damage primarily through bystander effects on the immune response (Payne et al., 2013), and not necessarily involving high efficiency cell regeneration or circuit restoration (Uccelli and Mancardi, 2010). However, intranasal mesenchymal stem cell delivery in perinatal hypoxia-ischemia has additionally been shown to improve regeneration and cortical rewiring (van Velthoven et al., 2012). This difference argues for a need to better understand neural cell interactions with the lesion environment (Laterza et al., 2013; Lisak et al., 2006). It is becoming more widely accepted that stem and progenitor cells provide immunomodulatory and neuroprotective benefits through the secretion of growth factors, chemokines, cytokines and stem cell regulators and guidance molecules, and the function of the stem cell secretome in therapeutic support and cellular

plasticity has been the subject of recent review articles (Cossetti et al., 2012; De Feo et al., 2012; Drago et al., 2013). Therapeutic potential using stem/progenitor cells can be further enhanced with genetic modification. Transplantation of human umbilical mesenchymal stromal cells, genetically modified to express neurotrophin-3 (NT-3, see Section 2.2.2 GROWTH FACTORS), promoted greater myelin sparing and functional recovery compared to unmodified cells in a rat spinal cord compression injury model (Shang et al., 2011).

Intercellular and autocrine signaling interactions form the underlying basis of repair mechanisms. While neurotrophic factors such as brain-derived neurotrophic factor (BDNF), have been tested as treatment for cell survival and axon growth in injury (Jain et al., 2011; Lopatina et al., 2011; Shu et al., 2013), there are relatively fewer reports of WM regeneration by pharmacological intervention, including growth factors, in adult and neonatal injury models. To address pharmacological treatment options in WM injury, we performed a survey of reports that describe pharmacological signaling modulators which have demonstrated effects in neonatal and adult models of WM injury. These studies, described in the sections below and summarized in Table 1, generally employed the delivery of pharmacological agents either through systemic administration or direct injection into brain tissue or ventricles using stereotaxic methods. To understand additional neuroprotective effects of each agent, we have also included in this summary, where applicable, reports of the same pharmacological agent in brain injury models in which the analysis of WM OLs was not the primary objective of the studies (Table 1).

2.2.1 Glutamate and purinergic receptor modulation—White matter pathology frequently involves the disruption of axons or axonal function, leading to excessive neurotransmitter signaling when axonal transport mechanisms are impaired (Bakiri et al., 2009). A variety of neurotransmitter receptors are expressed in oligodendrocytes and their progenitors (Butt, 2006; Butt et al., 2014). Adenosine, P2X7 and P2Y metabotropic receptors (Fields and Burnstock, 2006), NMDA (De Biase et al., 2011; Li et al., 2013a) and AMPA (Zonouzi et al., 2011) receptors are expressed on OPCs. Glutamate receptor activation is known to inhibit OPC proliferation and lineage progression in vitro (Gallo et al., 1996; Yuan et al., 1998) or induce cellular toxicity in OPCs (Liu et al., 2002). In injury models, excitotoxicity due to elevated glutamate or ATP causes structural and functional damage to WM. The sustained activation of ATP, AMPA, kainate and NMDA glutamate receptors causes OL death and myelin destruction through mitochondrial calcium influx (Matute, 2010; Tang and Xing, 2013). Oligodendroglia express P2X and P2Y purinergic receptors which serve as mediators of axo-oligodendroglial communication during myelination. However, EAE mechanisms involve ATP excitotoxicity, which can be mitigated by P2X7 receptor blockade (Matute et al., 2007). In addition to direct receptor-mediated death of OLs, the damage by ATP signaling through glial purinergic P2X and P2Y receptors involves neuroinflammatory cascades and subsequent exacerbation of degeneration (Matute et al., 2007). Intracerebral NMDA injection into the corpus callosum in the neonate generates WM lesions by excitotoxicity (Espinosa-Jeffrey et al., 2013). Perinatal injury and adult inflammatory demyelination models have been shown to benefit from blocking these receptors. NBQX, an AMPA receptor antagonist, was protective in neonatal mouse models of hypoxia/ischemia-mediated WM loss (Follett et al., 2004; Follett et al., 2000; Shen et al.,

2012) and in EAE demyelination (Kanwar et al., 2004; Pitt et al., 2000). Improved clinical score was observed in chronic EAE, using brilliant blue G to block P2X7 receptors (Matute et al., 2007). However in perinatal ischemia, P2X7 receptor expression was decreased, so that the potential benefit of brilliant blue G in this ischemia model is unclear (Wang et al., 2009). These studies thus indicate similar benefit in both age groups with NBQX, suggesting common mechanisms of WM damage involving AMPA receptor-mediated excitotoxicity.

2.2.2 GROWTH FACTORS

2.2.2.1 Epidermal growth factor (EGF): Therapeutic targets of EGF in adult WM brain injury models include the subventricular zone (SVZ), a region in the brain rich in multipotent adult stem cells that proliferate, differentiate and migrate. EGFR⁺ cells in the SVZ of adult mice reportedly correspond mostly to precursor cells (transit -amplifying C cells) with potential to differentiate into neuroblasts, astrocytes, and OLs (Doetsch et al., 2002). EGFR signaling has been found essential to promote OL development from the SVZ after demyelination (Aguirre and Gallo, 2007; Aguirre et al., 2007). Intranasal heparin binding EGF administered in an adult mouse model of lysolecithin-induced focal demyelination in the corpus callosum increased proliferation of SVZ cells and migration into the demyelinated corpus callosum. Additionally, EGF treatment increased the percentage of dividing astrocytes and OL lineage cells (BRDU⁺/GFAP⁺ and BRDU⁺ OLIG2⁺) in the demyelinated lesion compared to controls (Cantarella et al., 2008). Consistent with this finding, EGF treatment was found to increase CNPase⁺ cells derived from B1 cells (Type C precursors) in the SVZ and decrease lesion volume (Gonzalez-Perez et al., 2009).

Virally induced overexpression of EGFR in WM glial progenitors in post natal day 3 rats resulted in perpetual proliferation of OPCs but inhibition of OL maturation (Ivkovic et al., 2008). In contrast, intranasal heparin binding EGF treatment immediately after perinatal chronic hypoxia in mice (a model of very preterm brain injury) increased survival of OLs, NG2⁺ cell proliferation and differentiation to OL, as well as improved functional recovery (Scafidi et al., 2014). It has been demonstrated that EGF promotes WM oligodendrogenesis by inhibiting Notch activation in Olig2⁺ cells after hypoxia, relieving the hypoxia-induced inhibition of OL maturation (Scafidi et al., 2014).

2.2.2.2 Fibroblast growth factor (FGF): Basic fibroblast growth factor (FGF-2/bFGF) is up-regulated in spinal cord injury, corresponding to the time of active OPC proliferation (Tripathi and McTigue, 2008; Zai et al., 2005). bFGF in perinatal and adult models of CNS injury promotes proliferation of progenitor cells, but is known to inhibit terminal differentiation of OL in vivo. Intraventricular infusion with bFGF in postnatal day 3 rats after hypoxic ischemia increased cell division in the SVZ of Nestin⁺, NeuN⁺ and NG2⁺ cells (Jin-qiao et al., 2009). In adult rats, intracisternal injection of bFGF has been reported to improve axonal sprouting and functional recovery after cerebral infarction (Kawamata et al., 1997). Although FGF2 has been found to elongate OL processes, it was found to down regulate myelin protein in postmitotic mature OLs. In fact, bFGF delivered into cerebrospinal fluid disrupts developmental myelination in neonates, causing OPC accumulation and eventually demyelination in the adult (Butt and Dinsdale, 2005a, b;

Goddard et al., 2001). bFGF inhibits remyelination through FGFR1, as its genetic ablation in OPCs improves the generation of OLs as well as sensorimotor coordination in a chronic cuprizone demyelination model (Mierzwa et al., 2013; Zhou et al., 2012). Some of the pathological effects of high bFGF levels may be mediated by astrocytes and microglia, as raising bFGF in ventricular cerebrospinal fluid of neonatal rats led to astroglial and microglial reactivity (Goddard et al., 2002). Despite its properties of neuroprotection (Aguilar et al., 1993; Kirschner et al., 1995), based on its effects on glia, bFGF is considered a stem/progenitor cell activator whose downregulation benefits WM OL recovery.

2.2.2.3 Insulin-like growth factor: Insulin-like growth factor (IGF-1) regulates the survival (Ness et al., 2002; Ness et al., 2004), proliferation (Min et al., 2012) and differentiation of cells of the OL lineage through its activation of mammalian target of rapamycin (mTOR) in the PI3K/Akt pathway (Tyler et al., 2009). IGF-1 treatment has been shown to be beneficial in adult demyelinating models. IGF-1 overexpression in transgenic mice demyelinated with cuprizone were found to have increased OL cell survival and an increased remyelination rate (Mason et al., 2000). Intraventricular infusion of IGF-1 increased Olig2+CC1+ cells in the corpus callosum after cuprizone induced demyelination (Sabo et al., 2013). In contrast, injection of adenoviral vector to increase IGF-1 mRNA expression in a lysolethecine-induced demyelinated lesion in the spinal cord in 12 month aged rats did not promote remyelination, suggesting that the remyelinating cells responsible for IGF-1 improvements do not arise directly from the injury site (O'Leary et al., 2002).

Intravenous or subcutaneous IGF-1 treatment for acute EAE in rat, and chronic relapsing EAE in mouse improved clinical scores and decreased inflammatory lesions (Li et al., 1998; Liu et al., 1995). However, while subcutaneous IGF-1 treatment during the acute phase of EAE transiently improved clinical scores and myelination at early time points, treatment during the chronic phase had no effect on clinical scores or on remyelination (Cannella et al., 2000). Varied results may be attributed to the timing of treatment, the type of EAE model, and the presence of IGF binding proteins. While intraperitoneal injection of IGF-1 administered before symptom onset in an adoptive transfer murine model of EAE provided mild protection, IGF-1 combined with IGF binding protein 3 increased disease severity (Lovett-Racke et al., 1998). Although IGF-1 and IGF-1R have been found in OLs associated with plaques in multiple sclerosis, the presence of IGF binding proteins have also been detected, with potential to inhibit myelin synthesis and thwart therapeutic efforts (Wilczak et al., 2008). Additionally, IGF-1 may also impact astrocytic response to injury. Studies with astrocytes cultured from Beta Adrenergic Receptor (B2AR) knockout mice suggest that IGF-1 regulates B2AR dependent cAMP signaling and therefore in multiple sclerosis lesions, where a deficiency of B2AR has been observed, increasing the potential risk of IGF-mediated astrogliosis (Chesik et al., 2008).

IGF-1 has been found to promote OPC differentiation to mature OLs and subsequent OL survival in neonatal models. IGF-1 inhibition of caspase 3 and subsequent protection of neonatal rat pro-oligodendroblasts from glutamate-mediated apoptosis in vitro (Ness et al., 2004) has been substantiated in vivo. Intraventricular injections of IGF-1 in a neonatal rat hypoxia model (postnatal day 7) decreased caspase 3 and caspase 9 activation in the cerebral cortex associated with increased phosphorylated Akt and nuclear translocation of

phosphorylated GSK3B (Brywe et al., 2005). Furthermore, after hypoxia, IGF-1 increased OPC differentiation to mature OLs and inhibited caspase-3 to promote survival of OL lineage cells (Wood et al., 2007). IGF-1 treatment after hypoxia-ischemia has also been found to improve long-term memory and cognitive behavior (Zhong et al., 2009).

2.2.3 NEUROTROPHINS

2.2.3.1 Neurotrophin-3: Neurotrophin-3 (NT-3) activity, like IGF-1, has multiple effects on OL development. NT-3 promotes the survival and proliferation of OPCs, enhances OL differentiation (Barres et al., 1994b; Cohen et al., 1996; Kumar et al., 1998) and protects against glutamate excitotoxicity (Kavanaugh et al., 2000). NT-3 signals through high affinity TrkC receptors on oligodendroglial cells (Kumar and de Vellis, 1996). NT-3 initiates translation through ERK and PI3K/mTOR signaling and increases synthesis of MBP, MAG and MOG (Coelho et al., 2009). Additionally, NT-3 prevents oligodendrocyte apoptosis by a mechanism in which cAMP-response element binding protein (CREB) is phosphorylated to promote translocation of sphingosine kinase-1 to the cytoplasmic membrane to enhance activity of sphingosine-1-phosphate synthesis and the upregulation of Bcl-2 (Johnson et al., 2000; Saini et al., 2005; Saini et al., 2004). Oligodendrocytes lineage expression of sphingosine-1-phosphate receptor has been found to promote mature oligodendrocyte survival and progenitor cell process retraction (Jaillard et al., 2005). Implications for the therapeutic potential of regulating sphingosine-1-phosphate synthesis are demonstrated by efficacy of FTY720 (Fingolimod), which acts as an agonist for sphingosine-1-phosphate receptor once phosphorylated in-vivo and is used as a treatment in multiple sclerosis (Coelho et al., 2007). FTY720 has been found to protect oligodendrocyte progenitor cells from apoptosis via ERK1/2 and AKT pathways but inhibit oligodendrocyte differentiation, which however, could be overcome with concomitant NT-3 treatment to increase both oligodendrocyte survival and differentiation (Coelho et al., 2007). The sphingosine-1-phosphate dependent ability of NT-3 to inhibit apoptosis and yet the potential for NT-3 to abrogate FTY720 mediated inhibition of oligodendrocyte progenitor differentiation suggest either the distinction between FTY720 and SIP receptor signaling, or the importance of two distinct pathways by which NT-3 may promote both survival and differentiation of oligodendrocyte progenitor cells. In contrast, Fingolimod treatment in EAE mouse model activated the sonic hedgehog pathway and increased OPC proliferation and differentiation (Zhang et al., 2015). Sphingosine-1-phosphate activity has been implicated, not only in cross talk with NT-3, but also PDGF-AA (Coelho et al., 2010).

In the developing brain, neuropeptide Y was found to induce NT-3 in the neonatal cerebrum, accompanied by increased MBP expression (Hashimoto et al., 2011), but because NT-3 remains untested in neonatal brain injury, the role of NT-3 in neonatal OL protection and recovery is presently unknown.

Multiple strategies for NT-3 delivery in adult injury models: Early studies have shown that transplanting fibroblasts secreting neurotrophic factors, BDNF and NT-3 demonstrated success in increasing oligodendrocyte proliferation and myelination in spinal cord contusion rat model (McTigue et al., 1998), demonstrating the efficacy of neurotrophin administration in traumatic injury. Since then, more specific strategies, such as peptide injection, viral

expression and stem cell therapy have been used to deliver NT-3 to demyelinating lesions. NT-3 was included in a combinatorial intracranial treatment which showed benefit in cuprizone-induced demyelination in adult mice. PDGF-AA, NT-3 and IGF-1 may all signal through Akt/PKB to inhibit apoptosis while IGF-1, bFGF and PDGFA may also serve as a mitogen to stimulate proliferation of OL lineage cells (Kumar et al., 2007). Intracranial injection of PDGF-A, bFGF, IGF-1 and NT3 increased OL lineage proliferation and migration to demyelinated regions and increased myelination (Kumar et al., 2007).

NT-3 injected directly into the lysophosphatidylcholine-demyelinated corpus callosum of adult rats decreased lesion volume and increased MBP+ cell number at 15 days after injury, but not during the acute phase (day 3), and did not increase the number of GFAP+ cells (Jean et al., 2003), suggesting direct effect on the oligodendroglial lineage. An alternative strategy to deliver NT-3 peptide includes implantation of mesenchymal stem cells transfected with adenoviral vector to overexpress NT-3 in ethidium bromide-induced demyelinated rat spinal cord (Zhang et al., 2012). In contrast to peptide injection during the acute phase of a demyelinating spinal cord lesion (Jean et al., 2003), NT-3 expressing mesenchymal stem cells injected 3 days post-injury were found to improve functional recovery, and increase MBP expression and remyelination (Zhang et al., 2012).

Lentiviral delivery of NT-3 is another delivery strategy that has enhanced myelination and axon regeneration after spinal cord injury (Hou et al., 2012; Thomas et al., 2014). Different milieus established from various injury models and differences between species make direct comparison of treatment paradigms complicated. However, lentiviral delivery of NT-3 demonstrates efficacy in both acute and chronic phase of spinal cord injury, albeit in different models. Lentiviral delivery of NT-3 from support bridges 8 weeks after T9-T10 spinal cord injury in mice increased expression of nuclear Olig2+ in SOX2+ cells, (indicative of OL lineage), GFAP+ astrocytes, and yielded a 6 fold increase of myelinated axons extending into the middle of the bridge compared to controls, although Schwann cells contributed to the increased myelination of axons (Thomas et al., 2014). While this model demonstrates efficacy of using lentiviral expression of NT-3 during the acute phase of spinal cord injury, transplantation of lentiviral transduced neural progenitor cells secreting NT-3/D15A, a modified human NT-3 capable of activating TrkB and TrkC receptors, differentiated into astrocytes and oligodendrocytes and increased the volume of spared myelin during the chronic phase of a T9 compression spinal cord injury in rat when transplanted 6 weeks after injury (Kusano et al., 2010). Lentiviral transduction of bone marrow-derived neural stem cells is another therapeutic strategy combining the benefit of NSC transplant with NT-3 production, from a more easily accessible stem cell source. Bone marrow-derived neural stem cells transduced with NT-3 increased differentiation of oligodendrocytes and myelination, and decreased astrogliosis and inflammation when injected into a murine EAE model, compared to bone marrow-derived neural stem cells not expressing NT-3 (Yang et al., 2014).

In summary, NT-3 signaling, which activates ERK and PI3K/mTOR pathways, engages in crosstalk signaling with sphingosine-1-phosphate, and promotes oligodendrocyte survival, differentiation and potentially even immunomodulatory effects. Direct comparisons of NT-3 efficacy between injury models cannot be made due to intrinsic differences, but it is apparent

that the benefits of NT-3 delivery, particularly using transduction of NT-3 into neural stem cells, combines the benefits derived from NT-3 administration and neural stem cell transplant, promoting increases in myelination and decreased inflammation.

2.2.3.2 Brain-derived neurotrophic factor (BDNF): BDNF functions in the survival and development of neurons and glia in the CNS (Chao, 2003), operating primarily through region-specific expression of Trk receptors in oligodendroglia (Du et al., 2003). In the rat spinal cord, over 80% TrkB-expressing cells co-express CC1, indicating differentiated OLs. A small OPC pool also show TrkB immunoreactivity, suggesting a function in growth (Coulibaly et al., 2014). Ablation of the TrkB receptor in the oligodendroglial lineage disrupts myelination, and indirectly increases the density of OPCs (Wong et al., 2013). As BDNF promotes the growth of OPCs (Vondran et al., 2010) and enhances OL differentiation (Du et al., 2006), it is a strong therapeutic candidate for WM disease. Consistent with low levels of BDNF in relapsing-remitting multiple sclerosis (Azoulay et al., 2005), BDNF was found to be critical for WM maintenance in demyelination (VonDran et al., 2011). Interestingly, the anti-inflammatory agent being used in the treatment of multiple sclerosis, glatiramer acetate, not only has immunoregulatory properties, but also enhances the levels of BDNF in vivo (Aharoni et al., 2005). Fingolimod, a new oral drug for multiple sclerosis, was shown to attenuate neurotoxicity (Doi et al., 2013) and improves symptoms in models of neurodegenerative disorders (Fukumoto et al., 2014) and Rett syndrome (Deogracias et al., 2012). Its effects were associated with increased levels of BDNF (Deogracias et al., 2012; Doi et al., 2013). These studies indicated the likelihood that approaches to elevate endogenous BDNF would benefit WM pathology. In an elegant study, Fulmer et al found that BDNF levels could be stimulated with stereotaxic injections of the metabotropic glutamate receptor agonist trans-(1S,3R)-1-amino-1,3-cyclopentanedicarboxylic acid (ACPD) (Fulmer et al., 2014). The effect turned out to be mediated by metabotropic glutamate receptors in astrocytes, and not in oligodendrocytes. Injection of ACPD into the corpus callosum after 4 weeks of cuprizone intoxication in mice increased BDNF, MBP, and MAG within 6 hours. GFAP-directed genetic ablation of BDNF expression and coinjection of trkB-Fc abolished the beneficial effects of ACPD *in vivo*, indicating that astrocytic production of BDNF in response to ACPD enhances myelin recovery in chemical demyelination (Fulmer et al., 2014).

In neonatal injury, direct intracerebroventricular injection of BDNF protects neurons from caspase-mediated cell death in a neonatal hypoxic-ischemia rat model of cerebral palsy through the ERK1/2 pathway, and attenuates tissue loss and memory impairment (Almli et al., 2000; Han and Holtzman, 2000). Treatment with intraperitoneal humanin increased oligodendrogenesis and the levels of BDNF in a neonatal hypoxia-ischemia model, accompanied by axonal remyelination and reduced neurological deficit (Chen et al., 2014). Nuclear receptors, like thyroid hormone receptors, mediate protection by thyroxine. Thyroxine regulates developmental neurotrophin expression in the developing hippocampus (Luesse et al., 1998), and has proved to be protective against WMI through BDNF in the immature brain (Hung et al., 2013). BDNF-TrkB signaling that was attenuated following hypoxic ischemic injury at P7 was restored by 7,8-dihydroxyflavone, a new TrkB agonist that is permeable through the blood-brain barrier (Jang et al., 2010). T4, administered through i.p.

injections at P7, P9 and P11 decreased astrocytosis and microgliosis, protecting pre-oligodendrocytes from apoptosis (Hung et al., 2013). The protective effect of T4 on motor performance was inhibited by TrkB-Fc, blocking the activity of BDNF (Hung et al., 2013). The approach of ACPD awaits testing in neonatal WMI. Additionally, based on the above observations, it would be interesting to determine whether other non-peptide treatments found to mediate neuroprotection and functional improvement also regulate BDNF expression through signaling cross-talk in models of neonatal and adult WM disease.

2.2.4 NUCLEAR RECEPTOR LIGANDS

2.2.4.1 Thyroid Hormone: The ability of the liganded thyroid hormone receptor to interact with the MBP promoter to activate expression (Farsetti et al., 1991) and promote OL maturation (Fernandez et al., 2004b) has rendered it a viable therapeutic strategy for adult and neonatal WM damage. Thyroid hormone shows therapeutic potential in a range of adult demyelinating models. Triiodothyronine (T3) and its prohormone, thyroxine (T4) have been used as therapeutic agents in models of WM damage. While cuprizone induced an upregulation of thyroid hormone receptor (THR) alpha, but not THRB, T3 treatment preferentially increased expression of THRB, suggesting that THRB responds to T3, and is important in the remyelination process (Franco et al., 2008).

In a cuprizone-induced demyelination rat model, intranasal T3 treatment was found to increase MBP+ cells in the cerebral cortex (Silvestroff et al., 2012) and subcutaneous injection decreased the number of progenitor cells (Nestin+), increased the numbers of mature OL (O4+ and CC1+) cells and increased immunoreactivity for MBP+ and PLP+ in the corpus callosum (Franco et al., 2008). In another cuprizone study, T3 treatment restored SHH and Olig2 in the SVZ to control levels but did not change SHH expression in the corpus callosum suggesting the role for SVZ cell proliferation, migration and maturation in the remyelination process (Franco et al., 2008). T3 treatment in mice was also shown to improve clinical scores, decrease abnormal WM appearing in T-2 weighted images and myelin abnormalities, as well as increase the numbers of myelinated axons and proliferating OL progenitor cells in the recovery period, as long as 12 weeks after cuprizone withdrawal after chronic cuprizone demyelination for 12 weeks (Harsan et al., 2008).

Intraventricular hemorrhage, a cause of WM damage in premature infants was found to decrease an activator of Thyroid hormone, deiodinase 2, and increase an inactivator of thyroid hormone, deiodinase 3 (Vose et al., 2013). Intramuscular injection of T4, after glycerol-induced intraventricular hemorrhage in E29 rabbit pups was found to increase early OL lineage markers, Olig2 and Sox10 expression, increase OL proliferation and maturation as well as increase myelination and functional recovery (Vose et al., 2013). T4 treatment was also found to increase the density of myelinating OL in a small study using pre-term human infants (Vose et al., 2013). T4 administration at onset of symptoms in a chronic demyelinating EAE model of Lewis and DA rats increased PDGF-A R mRNA, RIP immunostaining and MBP RNA and protein expression in the spinal cord of both types of rats but only decreased the severity of relapse in Lewis, but not in DA rats (Fernandez et al., 2004a). Subcutaneous injection with T3 in DA rats with EAE, however, was found to improve clinical score along with nerve conduction, less myelin loss, and greater levels of

neurofilament (NF-200) immunoreactivity (Dell'Acqua et al., 2012). It is difficult to determine if the difference is due to variability inherent in the EAE model, or due to the form of thyroid hormone.

Because of the wide range of effects of thyroid hormone, concern that excess may cause adverse side effects has inspired a therapeutic strategy with a specific THRB1 agonist, GC1, in P7 mice, which increased the number of CC1+ cells, and protein expression of MBP, CNP, and MAG in the corpus callosum, occipital cortex and optic nerve (Baxi et al., 2014) but has not yet been tested in an injury model.

2.2.4.2 Retinoic acid: It is well established that retinoic acid, like thyroid hormone, promotes the differentiation of OL progenitor cells and MBP gene expression (Barres et al., 1994a; Laeng et al., 1994; Noll and Miller, 1994; Pombo et al., 1999). In addition, its promotion of glutathione synthesis and regulation of glutamate exchange indicates the capacity for protection from glutamate excitotoxicity (Crockett et al., 2011). These properties of retinoic acid suggest applicability in remyelination and repair in CNS injury. 9cis retinoic acid is an RXR ligand, while all trans retinoic acid activates RARs. 9-cis retinoic acid and all trans retinoic acid both reduce infarct size in ischemia models (Choi et al., 2009; Shen et al., 2009), and oral and subcutaneous administration of Am-80, a synthetic retinoid, increased expression of TrkB, the neurotrophin receptor and MBP, while reducing lesion cavity in a model of spinal cord injury (Takenaga et al., 2009). Retinoic acid receptor B activation inhibited Nogo receptor signaling and repression of LINGO resulting in increased neurite outgrowth in cerebellar cultures and in a model of axon regeneration (Puttagunta et al., 2011). CD2019, an RARbeta2 agonist, also increased neurite outgrowth and axonal regeneration in a model of spinal cord injury (Agudo et al., 2010). The RXRgamma agonist, 9cis retinoic acid, promoted OPC differentiation in vitro and increased the number of CC1+ OL cells and remyelinated axons in a focal demyelinating cerebellar lesion model in rats (Huang et al., 2011a).

2.2.4.3 Progesterone: Clinical evidence indicates a protective effect of sex steroids estrogens and progesterone in multiple sclerosis (Kipp et al., 2012a), that is also emerging from studies of a variety of CNS injury and disease models including demyelination (Deutsch et al., 2013). Progesterone promotes neurogenesis in the cerebral cortex and hippocampus (Brinton et al., 2008; Wang et al., 2005), and regulates OPC development and myelin formation in Schwann cells (Marin-Husstege et al., 2004; Schumacher et al., 2001). The neuroprotective effects of progesterone in ischemia and traumatic brain injury may in part be mediated by its anti-inflammatory properties (Habib et al., 2014; Lei et al., 2014) and ability to preserve mitochondrial function (Robertson and Saraswati, 2014) respectively. In addition to inhibiting inflammatory mediators, progesterone has been found to influence OL cell response to CNS injury. Pretreatment with progesterone improved clinical signs of EAE in mice, increased the number of mature OLs (CC1+), expression of myelin proteins PLP and MBP, myelination, and the density of precursor (NKx2.2+ and Olig1+) cells (Garay, 2012). Progesterone treatment also reduced the amount of demyelination caused by lysophosphatidylcholine in murine spinal cord, and increased both precursor (NG2+) and mature OL (CC1+) cells while decreasing macrophage/microglia cells markers (Ox-42+ and

CD11b+) (Garay et al., 2011). While progesterone treatment in demyelination models caused by chemical toxin and inflammatory mediators increased precursor cells, only chronic progesterone (treatment 21 days) after spinal cord injury in rats decreased NG2+ proliferation and increased CC1+BRDU+ cells indicating OL maturation. In contrast, acute progesterone treatment (3 days) increased NG2+ (OPC) proliferation, but also inhibited astrocyte and microglia/macrophage proliferation (Labombarda et al., 2011).

In neonatal hypoxia-ischemia, i.p. injections of progesterone given prior to hypoxia led to reduced neuronal apoptosis and brain damage (Li et al., 2014). The protective functions of progesterone in this model are diverse (Li et al., 2013b; Wang et al., 2014), and may involve activation of PI3K/Akt and inhibition of GSK-3 β (Li et al., 2014). The effects of progesterone on the function of OPCs in neonatal WM injury, however, remain to be described in future studies.

2.2.5 APO-TRANSFERRIN—As a nutrient factor important for myelination, the necessity of iron is well established, but its role in oligodendrocyte biology is not yet well understood. Transferrin is an iron transport protein that is expressed in developing oligodendroglial cells (Connor and Fine, 1987), and promotes the differentiation of OPCs, stimulating the expression of genes involved in myelinogenesis and OL membrane formation (Escobar Cabrera et al., 1994; Escobar Cabrera et al., 2000; Escobar Cabrera et al., 1997). These actions of apotransferrin have been shown to target the cytoskeleton, and involve tyrosine kinase, protein kinase C and A, and calcium-calmodulin kinase (Marta et al., 2002). The liganded transferrin receptor stimulates Fyn kinase and subsequent ERK1/2 phosphorylation, and receptor internalization activates Akt in cultured oligodendroglial cells (Perez et al., 2013), thus signaling through pathways important for myelin formation (Guardiola-Diaz et al., 2012; Ishii et al., 2012). Interestingly, it was recently found that thyroid hormone status determined transferrin expression in neonatal rats, i.e. hypothyroid rats showed decreased transferrin expression, with a less mature myelinating phenotype, while hyperthyroid animals showed upregulation of transferrin and myelination (Marziali et al., 2015). Apotransferrin administration was unable to rescue the hypothyroid state in this study (Marziali et al., 2015) but hypomyelination induced by thyroid deficiency was alleviated in an earlier study by intracranial injection of apo-transferrin at postnatal age 3 days (P3) (Badaracco et al., 2008). The difference in efficacy is not clear, and the answer may lie in the mechanism which regulates the contribution of transferrin to the effects of thyroid hormone. In euthyroid injury models, apotransferrin has been shown to be effective in mitigating WM damage. Intranasal apotransferrin treatment in a neonatal mouse model of hypoxia-ischemia decreased WM damage, reduced astrogliosis and increased both OPC proliferation and OL survival, and improved functional recovery (Guardia Clausi et al., 2012). The combination of transferrin and IGF-1 was effective in reducing NMDA-induced excitotoxic injury and enhancing regeneration in the neonatal brain (Espinosa-Jeffrey et al., 2013).

MS tissue has been found to be iron-rich with deposits in gray matter and in the vicinity of lesions, but is low in iron in normal-appearing WM, and remaining low in remyelinated plaques (Hametner et al., 2013). Consistent with the notion of iron depletion in MS, apotransferrin has been found to be effective in adult models of demyelination. In a rat

lysolecithin demyelination model, apotransferrin injection increased MAG protein expression and remyelination, likely mediated by activating Notch (Aparicio et al., 2013). Apotransferrin also reduced damage from EAE, by decreasing T cell production of Interleukin-2 (Saksida et al., 2013), and accelerated remyelination after cuprizone withdrawal (Adamo et al., 2006). It is thought that the dysregulation of the ratio of free to bound iron, and its localization and intercellular shuttling impacts the balance between iron-mediated toxicity and iron-dependent remyelination. Therefore, iron shuttling proteins like transferrin are an important consideration for therapy (Stephenson et al., 2014).

2.2.6 MORPHOGENS—Tissue regeneration, like development, involves processes that shape tissue and organ formation. The signaling mechanisms which orchestrate morphogenesis during development are also important modulators of cell growth, survival, migration, maturation, and remodeling in WM pathology. The expression of many morphogenic signals, such as Sonic Hedgehog (SHH), Wnt/wingless, bone morphogenetic proteins (BMP), and Notch, have been shown to be regulated in animal models of WM injury, and their pharmacological modulation alters the course of WM damage.

2.2.6.1 Sonic Hedgehog: The Hedgehog family of secreted proteins comprises Sonic (SHH), Indian (IHH) and Desert (DHH). These ligands bind the Patched receptor and cause subsequent derepression of Smoothened, leading to the transduction of positive signals, such as activation of GLI transcription factors (Ingham and McMahon, 2001; Murone et al., 1999). Smoothened activity is modulated pharmacologically by the small molecule compounds cyclopamine, purmorphamine and Smoothened agonist (SAG). Since the initial discovery of Sonic Hedgehog, despite extensive characterization of its function as an inducer of ventral brain structures, OLs, and cerebellum (Kiecker and Lumsden, 2004; Lu et al., 2000), its role in regeneration in the adult brain is only beginning to be revealed. In the adult brain, Sonic Hedgehog maintains neural stem cells in their neurogenic zones (Machold et al., 2003), promotes precursor cell proliferation (Lai et al., 2003) and modulates the migration of precursors out of this zone (Angot et al., 2008). Sonic Hedgehog is induced following brain injury and in demyelination (Amankulor et al., 2009; Wang et al., 2008), and its inhibition by cyclopamine injected into the lateral ventricle aggravates ischemic brain damage (Ji et al., 2012). Numerous studies have shown significant benefit of enhancing Hedgehog signaling in brain injury models. Indeed, in addition to neural cell regeneration, Sonic Hedgehog promotes protection from ischemic damage by enhancing angiogenesis, providing resistance against oxidative stress (Huang et al., 2013), and maintaining immune quiescence by defending the integrity of the blood brain barrier (Alvarez et al., 2011). Injection of recombinant Sonic Hedgehog into demyelinated adult rat spinal cord increased the proliferation of neural precursor cells (Bambakidis et al., 2003). After spinal cord contusion, injection of SHH also increased cell proliferation of transplanted OPCs, protected WM and improved axonal conduction and spinal cord function (Bambakidis and Miller, 2004). In ischemic stroke, intrathecal administration of SHH improved behavioral function and stimulated neural precursor proliferation in the subventricular zone (Bambakidis and Onwuzulike, 2012). Consistent with these findings, in spinal cord injury, lentiviral expression of Sonic Hedgehog and NT-3 increased myelination by OLs and Schwann cells respectively (Thomas et al., 2014). The Smoothened agonist, purmorphamine, was found to

be neuroprotective in a model of ischemic brain injury (Chechneva et al., 2014). Sonic Hedgehog was both regenerative and neuroprotective in the lysolecithin focal demyelination paradigm, in which SHH or its peptide antagonist, Hedgehog interacting protein (Hhip) were expressed by adenovirus vectors (Ferent et al., 2013). In these latter studies, it is unknown whether canonical or non-canonical Hedgehog signaling was mediating each of the beneficial effects of Hedgehog, in regeneration or protection.

Glucocorticoids are commonly used pre- and postnatally to prevent or treat lung and cardiovascular disease, which are life-threatening conditions associated with preterm birth (Crowther et al., 2007; Miracle et al., 2008). However, the use of immunosuppressant steroids dexamethasone, or mineralocorticoids have been reported to show side effects as well as impaired neurodevelopment (Halliday et al., 2003). Animal studies have shown that glucocorticoids, especially repeated administration of dexamethasone, adversely affect myelination of the developing brain (Zia et al., 2014). Despite mixed reports of improvement in myelination in models of lipopolysaccharide-induced perinatal brain injury (Pang et al., 2012) it is now widely accepted that the risks of cerebellar and WM damage by glucocorticoids during critical periods of brain development may outweigh its benefits on immunosuppression. In addition to well-established cerebellar neuron changes by dexamethasone, recent studies have described degenerative, apoptotic, morphological changes in OPC, and loss of pre-OLs, leading to hypomyelination (Kim et al., 2013). In fact, high sublethal glucocorticoid/prenisolone dosing has been used as an animal model of perinatal cerebellar injury (Aden et al., 2008; Noguchi et al., 2011; Noguchi et al., 2008) that is relevant to cerebellar damage of the premature infant (Bodensteiner and Johnsen, 2005; Volpe, 2009).

Hedgehog signaling is critical for cerebellar development (Dahmane and Ruiz i Altaba, 1999; Wechsler-Reya and Scott, 1999). In the neonatal brain, systemic administration of the Smoothed analog (SAG) and transgenic Smoothed activation resulted in improved granule neuron generation and cerebellar granule neuron progenitor proliferation in a glucocorticoid injury model, in which chronic glucocorticoid treatment in the first postnatal week inhibits cerebellar growth (Heine et al., 2011). The antagonism of glucocorticoid effects was mediated by the induction of 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2) (Holmes et al., 2006) by Smoothed activation (Heine et al., 2011; Heine and Rowitch, 2009). It is, however presently unknown whether a similar approach with SAG would attenuate WM changes in the developing corpus callosum following perinatal hypoxic injury, although caution is warranted due to the documented effect of Hh in tumorigenesis (Gulino et al., 2007) and surprising decreased functional outcome in stem cell therapy for hypoxia-ischemia (van Velthoven et al., 2014).

2.2.6.2 Wnt signaling: Like Hedgehog, the Wnt signaling pathway comprises a family of secreted ligands which activate canonical and non-canonical signaling cascades to regulate diverse cellular functions in neural cell development. Canonical signaling is mediated by beta-catenin, while non-canonical Wnt signaling involves beta-catenin-independent pathways, such as planar cell polarity and ROR receptors (Gao and Chen, 2010; van Amerongen, 2012). Canonical Wnt signaling has been implicated in neurogenesis (Coyle-Rink et al., 2002) and neuronal cell survival. Injection of Bcl-2 expression plasmids into the

lateral ventricle increases stroke-induced striatal neurogenesis in adult brains by activation of beta-catenin signaling (Lei et al., 2012). However, the emerging roles for beta-catenin expression in OPCs in development and injury appear complex. Beta-catenin in OPCs mediates glial scarring and inhibition of axonal regeneration in traumatic brain injury (Rodriguez et al., 2014). Canonical Wnt/beta-catenin was previously identified as a signal which promotes stem and progenitor cell proliferation (Kalani et al., 2008) and which inhibits OPC development (Feigenson et al., 2009; Shimizu et al., 2005). Wnt inhibition with a tankyrase inhibitor XAV939 improved remyelination in focal WM injury as well as in neonatal cerebellar slices following hypoxia injury (Fancy et al., 2011), supporting an inhibitory function of beta-catenin in OPC maturation. In addition, elevated Wnt signaling was also found in neonatal WM injury (Fancy et al., 2014). Current studies indicate however, that the effect of canonical Wnt signaling in the development of the OL lineage is not as simple as previously thought. An unexpected, positive regulatory function in OPC formation as well as maturation was recently demonstrated *in vivo* by genetic ablation (Dai et al., 2014). Lithium chloride, which activates beta-catenin and which is already being used to treat neurological disease such as bipolar mood disorder (Chuang, 2004, 2005) based on its anti-apoptotic effects (Beural and Jope, 2006), was recently found to promote the expression of myelin genes in OLs in culture (Meffre et al., 2015). It should be noted that the effects of LiCl and beta-catenin (Meffre et al., 2014) on terminal OL differentiation are not identical, because of the specific involvement of Akt/CREB activation with lithium that overcomes the inhibitory effect of Wnt on terminal OPC differentiation (Azim and Butt, 2011). LiCl has been effective in promoting protection in EAE and remyelination of sciatic nerves (De Sarno et al., 2008; Makoukji et al., 2012).

There is also evidence for neuroprotective effects of Wnt/beta-catenin in the neonatal brain. Lithium chloride attenuated neuronal damage in neonatal hypoxia-ischemia (Shin et al., 2012) and was used to reverse glucocorticoid-induced apoptosis in the developing cerebellum (Cabrera et al., 2014). Given that neonatal WM injury was found to be associated with elevated Wnt signaling (Fancy et al., 2014), without further studies to examine its regenerative effects independent of its anti-inflammatory properties, it would be difficult to predict the outcome of pharmacological Wnt/beta-catenin modulation on OL development in neonatal brain injury.

2.2.6.3 Bone Morphogenetic Proteins (BMP): Bone morphogenetic proteins, originally identified for their function in bone growth, belong to the Transforming Growth factor-beta family of secreted proteins that direct patterning in multiple organ systems, including the specification of neuronal and glial cells in the early nervous system. Traumatic injury to the adult brain and spinal cord upregulates the expression of multiple BMP proteins and their antagonist Noggin (Hampton et al., 2007). Dysregulated expression of BMP Mausner-Fainberg, 2013 #3892] and its antagonists Noggin (Urshansky et al., 2011a) and Follistatin (Urshansky et al., 2011b) have also been reported in relapsing/remitting multiple sclerosis.

BMPs may have both neuroprotective and neuroregenerative properties (Cox et al., 2004; Yabe et al., 2002). Many studies have described the beneficial effects of exogenous treatment with BMP7/Osteogenic protein-1 (OP-1), by i.p. injection or intracerebral administration (Lin et al., 1999; Perides et al., 1995; Wang et al., 2001) in attenuating

damage after stroke/ischemia in animal models. Interestingly, 9-cis retinoic acid alleviates damage in a transient focal ischemia model through BMP7 (Shen et al., 2009). However, BMP4 and BMP7 elevation in demyelinated spinal cord lesions mediates the gliotic response of astrocytes (Fuller et al., 2007), a phenomenon associated with persistent demyelination (Anderson et al., 2008; Skripuletz et al., 2010) that is now known to inhibit OL differentiation (Nicolay et al., 2007; Wang et al., 2011). BMP4 is upregulated in lesions of the corpus callosum after cuprizone demyelination (Cate et al., 2010) and its inhibition by intraventricular infusion of Noggin during cuprizone challenge (Cate et al., 2010) or infusion of Chordin after lysolecithin demyelination increases the generation of Olig2+ oligodendroglia from the SVZ (Jablonska et al., 2010). In a model of ischemic brain injury, Noggin infusion not only decreased the glial scar, but was also shown to induce alternative activation of microglia, i.e. from M1 to M2, which demonstrates an additional function supportive of tissue repair and remodeling (Shin et al., 2014).

The treatment of developmental brain injury with recombinant Noggin has also produced positive results with regard to oligodendroglia. In intraventricular hemorrhage injury of the immature brain (Dummula et al., 2011) which leads to a loss of OLs through cell death and reduced proliferation and maturation of OPCs, intraventricular infusion of Noggin resulted in reduced gliosis, restoration of Olig2+ development and enhanced OPC maturation within the first two postnatal weeks. These effects of Noggin infusion in the adult and developing brain are further supported by the transgenic overexpression of Noggin in the observation of smaller infarct volumes, increased OPC response and motor recovery following ischemia (Samanta et al., 2010) and perinatal hypoxia-ischemia (Dizon et al., 2011). Consistent with the findings with recombinant Noggin in the adult (Cate et al., 2010), the increased population of Olig2+ cells in the Noggin transgenic mouse did not arise from proliferation but instead from nascent induction of precursor cells (Dizon et al., 2011).

2.2.6.4 Notch: Notch is an important developmental pathway for neural stem cell regulation, neural precursor fate determination, development and brain plasticity (Louvi and Artavanis-Tsakonas, 2006; Yoon and Gaiano, 2005). Notch signaling is initiated by the direct interaction of cell surface Notch receptors with cognate ligands, Jagged1,2, or Delta 1,3,4 expressed on adjacent cells. This causes the Notch receptor to undergo two proteolytic cleavage events, mediated sequentially by ADAM metalloprotease and gamma-secretase. The latter releases the intracellular Notch receptor Intracellular Domain (NICD) in the signal receiving cell, allowing NICD translocation to the nucleus where it activates target gene transcription with a coactivator CSL complex (Andersson et al., 2011). Notch signaling is activated with the gliogenic response of the adult subventricular zone to traumatic brain injury (Givogri et al., 2006), and abnormal Notch expression levels have been documented in disease, including Down's syndrome, Alzheimer's disease (Fischer et al., 2005; Veeraraghavalu et al., 2010) and multiple sclerosis (John et al., 2002). The Notch pathway inhibits OL differentiation (Wang et al., 1998), as well as myelination (Givogri et al., 2002), and despite the contribution of F3/contactin ligands which favor OL generation and maturation, the outcome of Notch1 ablation in OPCs results in premature OL differentiation, indicating a net inhibitory function (Genoud et al., 2002). Although Notch1 is expressed in ethidium-bromide-induced demyelinated lesions of the trigeminal tract (Stidworthy et al.,

2004), surprisingly the oligodendroglial-specific ablation of Notch showed that the rate of remyelination after cuprizone was not altered (Stidworthy et al., 2004), indicating that this was not the rate-determining step. Interestingly, other treatments which benefit remyelination, such as apotransferrin (Aparicio et al., 2013), instead activated Notch signaling during its promotion of remyelination, and the gamma secretase inhibitor DAPT abolished apotransferrin-induced pro-myelination effects. This indicates a positive regulatory role for Notch in remyelination in this focal demyelination paradigm using lyssolecithin.

Nonetheless, because of its widespread expression, Notch remains an important determinant in the outcome of WM pathology. Reactive astrocytes upregulate endothelin-1 in WM lesions, which activates Notch signaling via inducing Jagged1 (Hammond et al., 2014). Inhibiting endothelin-1 prevented Notch signaling and restored remyelination by OPCs (Hammond et al., 2014). An earlier study analyzed the effect of a pharmacologic inhibitor of gamma-secretase, MW167, that was administered by a post-immunization intraventricular injection in an EAE demyelination model (Jurynczyk et al., 2005). The rate of recovery assessed by clinical score was dependent on the dose of MW167, apparent within 3 days after treatment. This was accompanied by enhanced myelin repair based on histopathology with OL markers, reduced inflammatory response and significantly less nerve fiber damage (Wallerian degeneration), without remarkable glial scarring (Jurynczyk et al., 2005). The effect of MW167 on NICD levels, when analyzed in cultured OLs and ex vivo, confirmed the activity of MW167 against Notch activation. Notch signaling is critical to the function of immune cells, including the differentiation of T helper cells and the Th1 response. Pretreatment with the gamma secretase inhibitor LY-411575 reduced clinical symptoms in another study with EAE (Minter et al., 2005), where T helper polarization to Th1 subset was inhibited, along with Th1-mediated autoimmunity. The protective effect of Notch attenuation is not specific to OLs, as neuronal maturation in the hippocampus is also enhanced by intraventricular administration of the gamma-secretase inhibitor S2188 after ischemic injury (Oya et al., 2009).

In neonatal brain injury, recent evidence now implicates Notch in hypoxia-induced inflammatory damage (Yao et al., 2013). Pretreatment with i.p. injection of the gamma secretase inhibitor DAPT before hypoxia in P1 rats, prevented NICD expression in cerebral microglia and concomitant NF-kappaB activation. In primary cultured microglia, the induction of NICD is associated with NF-kappaB activation and the expression of cytokines, both NF-kB and cytokine expression were blocked with DAPT (Yao et al., 2013). Further studies will be needed to determine the effect of DAPT on attenuation of neural cell damage in this neonatal model.

2.2.7 Thymosin beta-4—Thymosin is a small thymus-derived, actin-binding peptide with wide-ranging pleiotropy in the repair of multiple tissue types (Goldstein et al., 2012; Treadwell et al., 2012). Its release by cells during injury reduces damage by limiting cell apoptosis and inflammation, in addition to controlling scar formation, promoting cell migration through binding of G-actin monomers, progenitor cell differentiation and subsequent angiogenesis and tissue remodeling in wound healing. It has been shown to be neuroprotective in a number of adult rodent injury models, including embolic stroke (Morris et al., 2010), traumatic brain contusion injury (Xiong et al., 2012a), and EAE demyelination

(Zhang et al., 2009). Thymosin beta-4, when administered intraperitoneally post-injury (Morris et al., 2010; Xiong et al., 2012a) or simultaneously with PLP-immunization during EAE (Zhang et al., 2009), showed improvement in clinical score in these models. At the cellular level, treatment with thymosin beta-4 stimulated OPC proliferation, and promoted their maturation to CNP⁺ OLs, as detected by BrdU labeling. This increase in oligodendrogenesis is observed not only in SVZ and WM, but also CA3 of the hippocampus. Thymosin beta-4 stimulates OPC development by modulating p38MAP kinase signaling (Chew et al., 2010; Fragoso et al., 2007; Haines et al., 2007; Santra et al., 2012), possibly mediated by its upregulation of microRNA-146a (Santra et al., 2014). Its efficacy in neonatal brain injury however remains unknown, but with promising evidence for clinical trials in the treatment of various wounds (Goldstein et al., 2012), findings from upcoming experiments applying thymosin beta-4 in developmental WM injury models will no doubt be eagerly awaited.

3. Conclusions and Closing comments

A diverse array of injury models produces WM damage in experimental rodents. Intrinsic differences in these models may impact the observed efficacy of the pharmacologic agents. The age of the experimental animals affects the level of inhibitory factors in WM and the proliferative response of the germinal zones that generate neural precursors that populate the WM, e.g. SVZ, thereby modulating remyelination and repair (McGinn et al., 2012; Shen et al., 2008; Tang et al., 2009). Furthermore, the delivery route and dosing regimen, as well as intrinsic differences amongst EAE models themselves are also a source of variability. Many pharmacological treatments which target the growth, survival and/or maturation of precursor cells and OPCs, such as EGF, IGF, BDNF, thyroid hormone and apotransferrin, show beneficial effects in both neonatal and adult brain injury and demyelination. The group of peptide factors, in particular, presents great promise. Much work has been done to evaluate the efficacy of IGF, EGF, and bFGF to treat WM damage, revealing potential, but also considerable barriers to effective treatment. Of these, IGF treatment in neonatal injury models provides one of the most consistent effects, by promoting oligodendrocyte differentiation and survival. Its action, however, is dependent on the activation and recruitment of endogenous cells migrating from germinal regions such as the subventricular zone to the injury site. The effect of EGF in demyelinating adult rodent models is also due in large part to proliferation and migration of multipotent adult stem cells from the subventricular zone to the site of injury. Similar to IGF, EGF administration has been shown to promote OL differentiation and survival in neonatal WM injury models. Although bFGF has neuroprotective effects, and promotes proliferation of progenitor and stem cells, its reported inhibition of terminal differentiation of oligodendrocytes with decreased remyelination in adult injury models, and disrupted myelination in neonatal models make bFGF a less favored WM therapeutic strategy.

NT-3 and BDNF stand out among peptide neurotrophins in consistently promoting oligodendrocyte differentiation and survival across various injury models. Potentially, temporal and spatial distribution of TrkC and TrkB receptors during development and injury, as well as the differential expression of the trophic factors, are critical for oligodendrocyte survival, differentiation and myelination. The importance of both trophic factors, whose

individual effects overlap, is evident from the numerous adult and neonatal injury models that benefit from NT-3 and BDNF treatment. It is possible that an additional advantage of neurotrophins arises in part from their ability to modulate the pathological effects of inflammation to provide neuroprotection (Jiang et al., 2011; Jiang et al., 2010; Yang et al., 2014). Furthermore, advances in delivery options through gene modifications and stem cell transplantation provide even more opportunities for these trophic factors to be incorporated into treatment paradigms in WM disease.

It is noticeable that few or no neonatal WM studies showing the effects of BDNF, NT-3, Thymosin beta-4 and RAR/RXR agonists have been reported, although the reasons for this are unclear. Risk of teratogenicity with retinoid derivatives may well have limited their use in developmental brain injury; nonetheless there is some discussion regarding potential therapeutic benefit for autism spectrum disorders (Ebstein et al., 2011), indicating ongoing interest in understanding the uterine conditions which alter isoform levels and balance in the fetus (Goldberg, 2011) and the sensitivity of the developing brain to retinoid effects which impact neural cell maturation and functional plasticity.

Although neonatal and adult pathologies are often considered in isolation, a relationship between neonatal events and adult risk should also be recognized. Neonatal exposure to dexamethasone increases susceptibility to autoimmune disease in the adult (Bakker et al., 2000). The long-term neurological outcome of the neonate is also determined by the extent of infant immaturity and multiple maternal influences (Knuesel et al., 2014) that often complicate therapeutic strategies. Increased understanding of the etiological bases of these WM pathologies will facilitate the search for safe, effective, and minimally invasive forms of intervention. Taken together, these studies indicate that pharmacological approaches with biofactors and small molecule modulators constitute a viable avenue for therapy that will require further investigation and due consideration together with other cell-based procedures, in order to provide favorable conditions for neuroprotection, immunomodulation and cellular regeneration.

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Abbreviations

CNS	Central nervous system
WM	white matter
OPC	oligodendrocyte progenitor cell
OL	oligodendrocyte
SVZ	subventricular zone
EAE	experimental autoimmune encephalitis bromodeoxyuridine

BrdU	bromodeoxyuridine
i.p.	intraperitoneal
GFAP	glial fibrillary acidic protein
MBP	myelin basic protein
MAG	myelin associated glycoprotein
MOG	myelin oligodendrocyte glycoprotein
PLP	proteolipid protein
CNP	2',3'-cyclic nucleotide 3'-phosphodiesterase
APC	adenomatous polypolysis coli
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
NMDA	N-methyl-D-aspartic acid
NBQX	2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline-2,3-dione
PDGF	platelet derived growth factor
bFGF	basic fibroblast growth factor
NT-3	neurotrophin-3
BDNF	brain derived neurotrophic factor
IGF	insulin-like growth factor
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
RXR	retinoid X receptor
RAR	retinoic acid receptor
THR	thyroid hormone receptor
PKB	protein kinase B
MAP	mitogen-activated protein
SHH	kinase, Sonic Hedgehog
BMP	bone morphogenetic protein

REFERENCES

- Abdel Baki SG, Schwab B, Haber M, Fenton AA, Bergold PJ. Minocycline synergizes with N-acetylcysteine and improves cognition and memory following traumatic brain injury in rats. *PLoS One*. 2010; 5:e12490. [PubMed: 20824218]

- Adamo AM, Paez PM, Escobar Cabrera OE, Wolfson M, Franco PG, Pasquini JM, Soto EF. Remyelination after cuprizone-induced demyelination in the rat is stimulated by apotransferrin. *Exp Neurol*. 2006; 198:519–529. [PubMed: 16480980]
- Aden P, Goverud I, Liestol K, Loberg EM, Paulsen RE, Maehlen J, Lomo J. Low-potency glucocorticoid hydrocortisone has similar neurotoxic effects as high-potency glucocorticoid dexamethasone on neurons in the immature chicken cerebellum. *Brain Res*. 2008; 1236:39–48. [PubMed: 18706896]
- Agudo M, Yip P, Davies M, Bradbury E, Doherty P, McMahon S, Maden M, Corcoran JP. A retinoic acid receptor beta agonist (CD2019) overcomes inhibition of axonal outgrowth via phosphoinositide 3-kinase signalling in the injured adult spinal cord. *Neurobiol Dis*. 2010; 37:147–155. [PubMed: 19800972]
- Aguilar LC, Islas A, Rosique P, Hernandez B, Portillo E, Herrera JM, Cortes R, Cruz S, Alfaro F, Martin R, et al. Psychometric analysis in children with mental retardation due to perinatal hypoxia treated with fibroblast growth factor (FGF) and showing improvement in mental development. *J Intellect Disabil Res*. 1993; 37(Pt 6):507–520. [PubMed: 8123997]
- Aguirre A, Gallo V. Reduced EGFR signaling in progenitor cells of the adult subventricular zone attenuates oligodendrogenesis after demyelination. *Neuron Glia Biol*. 2007; 3:209–220. [PubMed: 18634612]
- Aguirre AA, Dupree JL, Mangin JM, Gallo V. A functional role for EGFR signalling in myelination and remyelination. *Nat Neurosci*. 2007; 10:990–1002. [PubMed: 17618276]
- Aharoni R, Eilam R, Domev H, Labunskay G, Sela M, Arnon R. The immunomodulator glatiramer acetate augments the expression of neurotrophic factors in brains of experimental autoimmune encephalomyelitis mice. *Proc Natl Acad Sci (USA)*. 2005; 102:19045–19050. [PubMed: 16365293]
- Almli CR, Levy TJ, Han BH, Shah AR, Gidday JM, Holtzman DM. BDNF protects against spatial memory deficits following neonatal hypoxia-ischemia. *Exp Neurol*. 2000; 166:99–114. [PubMed: 11031087]
- Alvarez JI, Dodelet-Devillers A, Kebir H, Ifergan I, Fabre PJ, Terouz S, Sabbagh M, Wosik K, Bourbonniere L, Bernard M, van Horssen J, de Vries HE, Charron F, Prat A. The Hedgehog pathway promotes blood-brain barrier integrity and CNS immune quiescence. *Science*. 2011; 334:1727. [PubMed: 22144466]
- Amankulor NM, Hambardzumyan D, Pyontek SM, Becher OJ, Joyce JA, Holland EC. Sonic hedgehog pathway activation is induced by acute brain injury and regulated by injury-related inflammation. *J Neurosci*. 2009; 29:10299–10308. [PubMed: 19692604]
- Anderson JM, Hampton DW, Patani R, Pryce G, Crowther RA, Reynolds R, Franklin RJ, Giovannoni G, Compston DA, Baker D, Spillantini MG, Chandran S. Abnormally phosphorylated tau is associated with neuronal and axonal loss in experimental autoimmune encephalomyelitis and multiple sclerosis. *Brain*. 2008; 131:1736–1748. [PubMed: 18567922]
- Andersson ER, Sandberg R, Lendahl U. Notch signaling: simplicity in design, versatility in function. *Development*. 2011; 138:3593–3612. [PubMed: 21828089]
- Angot E, Loulier K, Nguyen-Ba-Charvet KT, Gadeau A-O, Ruat M, Traiffort E. Chemoattractive activity of Sonic Hedgehog in the Adult Subventricular Zone modulates the number of Neural precursors reaching the Olfactory Bulb. *Stem Cells*. 2008; 26:2311–2320. [PubMed: 18617686]
- Aparicio E, Mathieu P, Luppi MP, Gubiani MFA, Adamo AM. The Notch signaling pathway: its role in focal CNS demyelination and apotransferring-induced remyelination. *J Neurochem*. 2013; 127:819–836. [PubMed: 24032544]
- Armstrong RC, Le TQ, Frost EE, Borke RC, Vana AC. Absence of fibroblast growth factor 2 promotes oligodendroglial repopulation of demyelinated white matter. *Journal of Neuroscience*. 2002; 22:8574–8585. [PubMed: 12351731]
- Arnett HA, Mason J, Marino M, Suzuki K, Matsushima GK. TNF α promotes proliferation of oligodendrocyte progenitors and remyelination. *Nature Neuroscience*. 2001; 4:1116–1122. [PubMed: 11600888]
- Azim K, Butt AM. GSK3 β negatively regulates oligodendrocyte differentiation and myelination in vivo. *Glia*. 2011; 59:540–553. [PubMed: 21319221]

- Azoulay D, Vachapova V, Shihman B, Miler A, Karni A. Lower brain-derived neurotrophic factor in serum of relapsing remitting MS: reversal by glatiramer acetate. *J Neuroimmunol.* 2005; 167:215–218. [PubMed: 16083971]
- Back SA, Luo NL, Borenstein NS, Levine JM, Volpe JJ, Kinney HC. Late oligodendrocyte progenitors coincide with the developmental window of vulnerability for human perinatal white matter injury. *J Neurosci.* 2001; 21:1302–1312. [PubMed: 11160401]
- Back SA, Miller SP. Brain injury in premature neonates: A primary cerebral dysmaturation disorder? *Ann Neurol.* 2014; 75:469–486. [PubMed: 24615937]
- Back SA, Rosenberg PA. Pathophysiology of glia in perinatal white matter injury. *Glia.* 2014; 62:1790–1815. [PubMed: 24687630]
- Badaracco ME, Ortiz EH, Soto EF, Connor J, Pasquini JM. Effect of transferrin on hypomyelination induced by iron deficiency. *J Neurosci Res.* 2008; 86:2663–2673. [PubMed: 18459135]
- Baker D, Amor S. Mouse models of Multiple Sclerosis: Lost in Translation? *Curr Pharm Des.* Mar 16.2015
- Bakiri Y, Burzomato V, Frugier G, Hamilton NB, Karadottir R, Attwell D. Glutamatergic signaling in the brain's white matter. *Neuroscience.* 2009; 158:266–274. [PubMed: 18314276]
- Bakker JM, Kavelaars A, Kamphuis PJ, Cobelens PM, van Vugt HH, van Bel F, Heijnen CJ. Neonatal dexamethasone treatment increases susceptibility to experimental autoimmune disease in adult rats. *J Immunol.* 2000; 165:5932–5937. [PubMed: 11067955]
- Bambakidis NC, Miller RH. Transplantation of oligodendrocyte precursors and sonic hedgehog results in improved function and white matter sparing in the spinal cords of adult rats after contusion. *Spine J.* 2004; 4:16–26. [PubMed: 14749190]
- Bambakidis NC, Onwuzulike K. Sonic Hedgehog signaling and potential therapeutic indications. *Vitam Horm.* 2012; 88:379–394. [PubMed: 22391313]
- Bambakidis NC, Wang RZ, Franic L, Miller RH. Sonic hedgehog-induced neural precursor proliferation after adult rodent spinal cord injury. *J Neurosurg.* 2003; 99:70–75. [PubMed: 12859063]
- Barres BA, Lazar MA, Raff MC. A novel role for thyroid hormone, glucocorticoids and retinoic acid in timing oligodendrocyte development. *Development.* 1994a; 120:1097–1108. [PubMed: 8026323]
- Barres BA, Raff MC, Gaese F, Bartke I, Dechant G, Barde YA. A crucial role for neurotrophin-3 in oligodendrocyte development. *Nature.* 1994b; 367:371–375. [PubMed: 8114937]
- Bartzokis G. Neuroglialpharmacology: Myelination as a shared mechanism of action of psychotropic treatments. *Neuropharmacology.* 2012; 62:2137–2153. [PubMed: 22306524]
- Baxi EG, Schott JT, Fairchild AN, Kirby LA, Karani R, Uapinyoying P, Pardo-Villamizar C, Rothstein JR, Bergles DE, Calabresi PA. A selective thyroid hormone beta receptor agonist enhances human and rodent oligodendrocyte differentiation. *Glia.* 2014; 62:1513–1529. [PubMed: 24863526]
- Beural E, Jope RS. The paradoxical pro- and anti-apoptotic actions of GSK3 in the intrinsic and extrinsic apoptosis signaling pathways. *Progress in Neurobiology.* 2006; 79:173–189. [PubMed: 16935409]
- Blakemore WF. Remyelination of the superior cerebellar peduncle in old mice following demyelination induced by cuprizone. *J Neurol Sci.* 1974; 22:121–126. [PubMed: 4830551]
- Blakemore WF, Chari DM, Gilson JM, Crang AJ. Modelling large areas of demyelination in the rat reveals the potential and possible limitations of transplanted glial cells for remyelination in the CNS. *Glia.* 2002; 38:155–168. [PubMed: 11948809]
- Blomgren K, Hagberg H. Free radicals, mitochondria, and hypoxia-ischemia in the developing brain. *Free Radic Biol Med.* 2006; 40:388–397. [PubMed: 16443153]
- Bodensteiner JB, Johnsen SD. Cerebellar injury in the extremely premature infant: newly recognized but relatively common outcome. *J Child Neurol.* 2005; 20:139–142. [PubMed: 15794181]
- Brinton RD, Thompson RF, Foy MR, Baudry M, Wang J, Finch CE, Morgan TE, Pike CJ, Mack WJ, Stanczyk FZ, Nilsen J. Progesterone receptors: form and function in brain. *Front Neuroendocrinol.* 2008; 29:313–339. [PubMed: 18374402]
- Brothers HM, Marchalant Y, Wenk GL. Caffeine attenuates lipopolysaccharide-induced neuroinflammation. *Neurosci lett.* 2010; 480:97–100. [PubMed: 20541589]

- Brywe KG, Mallard C, Gustavsson M, Hedtjarn M, Leverin AL, Wang X, Blomgren K, Isgaard J, Hagberg H. IGF-I neuroprotection in the immature brain after hypoxia-ischemia, involvement of Akt and GSK3beta? *Eur J Neurosci*. 2005; 21:1489–1502. [PubMed: 15845077]
- Busl KM, Greer DM. Hypoxic-ischemic brain injury: pathophysiology, neuropathology and mechanisms. *NeuroRehabilitation*. 2010; 26:5–13. [PubMed: 20130351]
- Butt AM. Neurotransmitter-mediated calcium signalling in oligodendrocyte physiology and pathology. *Glia*. 2006; 54:666–675. [PubMed: 17006895]
- Butt AM, Dinsdale J. Fibroblast growth factor 2 induces loss of adult oligodendrocytes and myelin in vivo. *Exp Neurol*. 2005a; 192:125–133. [PubMed: 15698626]
- Butt AM, Dinsdale J. Opposing actions of fibroblast growth factor-2 on early and late oligodendrocyte lineage cells in vivo. *J Neuroimmunol*. 2005b; 166:75–87. [PubMed: 16005082]
- Butt AM, Fern RF, Matute C. Neurotransmitter signaling in white matter. *Glia*. 2014; 62:1762–1779. [PubMed: 24753049]
- Cabrera O, Dougherty J, Singh S, Swiney BS, Farber NB, Noguchi KK. Lithium protects against glucocorticoid induced neural progenitor cell apoptosis in the developing cerebellum. *Brain Res*. 2014; 1545:54–63. [PubMed: 24361977]
- Cannella B, Pitt D, Capello E, Raine CS. Insulin-like growth factor-1 fails to enhance central nervous system myelin repair during autoimmune demyelination. *American Journal of Pathology*. 2000; 157:933–943. [PubMed: 10980132]
- Cantarella C, Cayre M, Magalon K, Durbec P. Intranasal HB-EGF administration favors adult SVZ cell mobilization to demyelinated lesions in mouse corpus callosum. *Dev Neurobiol*. 2008; 68:223–236. [PubMed: 18000828]
- Cate HS, Sabo JK, Merlo D, Kemper D, Aumann TD, Robinson J, Merson TD, Emery B, Perreau VM, Kilpatrick TJ. Modulation of bone morphogenic protein signalling alters numbers of astrocytes and oligodendroglia in the subventricular zone during cuprizone-induced demyelination. *J Neurochem*. 2010; 115:11–22. [PubMed: 20193041]
- Chao MV. Neurotrophins and their receptors: a convergence point for many signalling pathways. *Nat Rev Neurosci*. 2003; 4:299–309. [PubMed: 12671646]
- Chao PK, Lu KT, Jhu JY, Wo YY, Huang TC, Ro LS, Yang YL. Indomethacin protects rats from neuronal damage induced by traumatic brain injury and suppresses hippocampal IL-1beta release through the inhibition of Nogo-A expression. *J Neuroinflammation*. 2012; 9:121. [PubMed: 22676811]
- Charriaut-Marlangue C, Bonnin P, Pham H, Loron G, Leger PL, Gressens P, Renolleau S, Baud O. Nitric oxide signaling in the brain: a new target for inhaled nitric oxide? *Ann Neurol*. 2013; 73:442–448. [PubMed: 23495069]
- Chechneva OV, Mayrhofer F, Daugherty DJ, Krishnamurty RG, Bannerman P, Pleasure DE, Deng W. A Smoothed receptor agonist is neuroprotective and promotes regeneration after ischemic brain injury. *Cell Death and Disease*. 2014; 5:e148.
- Chen J, Sun M, Zhang X, Miao Z, Chua BH, Hamdy RC, Zhang QG, Liu CF, Xu X. Increased oligodendrogenesis by humanin promotes axonal remyelination and neurological recovery in hypoxic/ischemic brains. *Hippocampus*. 2014
- Chesik D, Wilczak N, De Keyser J. IGF-1 regulates cAMP levels in astrocytes through a beta2-adrenergic receptor-dependant mechanism. *Int J Med Sci*. 2008; 5:240–243. [PubMed: 18690292]
- Chew LJ, Coley W, Cheng Y, Gallo V. Mechanisms of regulation of oligodendrocyte development by p38 mitogen-activated protein kinase. *J Neurosci*. 2010; 30:11011–11027. [PubMed: 20720108]
- Chew LJ, Fusar-Poli P, Schmitz T. Oligodendroglial alterations and the role of microglia in white matter injury: relevance to schizophrenia. *Developmental Neuroscience*. 2013; 35:102–129. [PubMed: 23446060]
- Choi BK, Kim JH, Jung JS, Lee YS, Han ME, Baek SY, Kim BS, Kim JB, Oh SO. Reduction of ischemia-induced cerebral injury by all-trans-retinoic acid. *Exp Brain Res*. 2009; 193:581–589. [PubMed: 19050858]
- Chua CO, Chahboune H, Braun A, Dummula K, Chua CE, Yu J, Ungvari Z, Sherbany AA, Hyder F, Ballabh P. Consequences of intraventricular hemorrhage in a rabbit pup model. *Stroke*. 2009; 40:3369–3377. [PubMed: 19661479]

- Chuang DM. Neuroprotective and neurotrophic actions of the mood stabilizer lithium: can it be used to treat neurodegenerative diseases? *Crit Rev Neurobiol.* 2004; 16:83–90. [PubMed: 15581403]
- Chuang DM. The antiapoptotic actions of mood stabilizers: molecular mechanisms and therapeutic potentials. *Ann N Y Acad Sci.* 2005; 1053:195–204. [PubMed: 16179524]
- Coelho RP, Payne SG, Bittman R, Spiegel S, Sato-Bigbee C. The immunomodulator FTY720 has a direct cytoprotective effect in oligodendrocyte progenitors. *J Pharmacol Exp Ther.* 2007; 323:626–635. [PubMed: 17726159]
- Coelho RP, Saini HS, Sato-Bigbee C. Sphingosine-1-phosphate and oligodendrocytes: from cell development to the treatment of multiple sclerosis. *Prostaglandins Other Lipid Mediat.* 2010; 91:139–144. [PubMed: 19808013]
- Coelho RP, Yuelling LM, Fuss B, Sato-Bigbee C. Neurotrophin-3 targets the translational initiation machinery in oligodendrocytes. *Glia.* 2009; 57:1754–1764. [PubMed: 19455580]
- Cohen RI, Marmur R, Norton WT, Mehler MF, Kessler JA. Nerve growth factor and neurotrophin-3 differentially regulate the proliferation and survival of developing rat brain oligodendrocytes. *J Neurosci.* 1996; 16:6433–6442. [PubMed: 8815922]
- Connor JR, Fine RE. Development of transferrin-positive oligodendrocytes in the rat CNS. *J Neurosci Res.* 1987; 17:51–59. [PubMed: 3573080]
- Constantinescu CS, Farooqi N, O'Brien K, Gran B. Experimental autoimmune encephalomyelitis (EAE) as a model for multiple sclerosis (MS). *Br J Pharmacol.* 2011; 164:1079–1106.
- Cossetti C, Alfaro-Cervello C, Donega M, Tyzack G, Pluchino S. New perspectives of tissue remodelling with neural stem and progenitor cell-based therapies. *Cell Tissue Res.* 2012; 349:321–329. [PubMed: 22322425]
- Costello DJ, Eichler AF, Eichler FS. Leukodystrophies: Classification, Diagnosis and treatment. *The Neurologist.* 2009; 15:319–328. [PubMed: 19901710]
- Coulibaly AP, Deer MR, Isaacson LG. Distribution and phenotype of TrkB oligodendrocyte lineage cells in the adult rat spinal cord. *Brain Res.* 2014; 1582:21–33. [PubMed: 25072185]
- Cox S, Harvey BK, Sanchez JF, Wang JY, Wang Y. Mediation of BMP7 neuroprotection by MAPK and PKC IN rat primary cortical cultures. *Brain Res.* 2004; 1010:55–61. [PubMed: 15126117]
- Coyle-Rink J, Del Valle L, Sweet T, Khalili K, Amini S. Developmental expression of Wnt signaling factors in mouse brain. *Cancer Biology and Therapy.* 2002; 1:640–645. [PubMed: 12642687]
- Crockett S, Clarke M, Reeves S, Sims B. Cystine glutamate exchanger upregulation by retinoic acid induces neuroprotection in neural stem cells. *NeuroReport.* 2011; 22:598–602. [PubMed: 21716153]
- Crowther CA, Doyle LW, Haslam RR, Hiller JE, Harding JE, Robinson JS, Group AS. Outcomes at 2 years of age after repeat doses of antenatal corticosteroids. *N Engl J Med.* 2007; 357:1179–1189. [PubMed: 17881750]
- Croxford AL, Kurschus FC, Waisman A. Mouse models for multiple sclerosis: Historical facts and future implications. *Biochimica et Biophysica Acta.* 2011; 1812:177–183. [PubMed: 20600870]
- Dahmane N, Ruiz i Altaba A. Sonic hedgehog regulates the growth and patterning of the cerebellum. *Development.* 1999; 126:3089–3100. [PubMed: 10375501]
- Dai ZM, Sun S, Wang C, Huang H, Hu X, Zhang Z, Lu QR, Qiu M. Stage-specific regulation of oligodendrocyte development by Wnt/beta-catenin signaling. *J Neurosci.* 2014; 34:8467–8473. [PubMed: 24948802]
- De Biase LM, Kang SH, Baxi EG, Fukaya M, Pucak ML, Mishina M, Calabresi PA, Bergles DE. NMDA receptor signaling in oligodendrocyte progenitors is not required for oligodendrogenesis and myelination. *J Neurosci.* 2011; 31:12650–12662. [PubMed: 21880926]
- De Feo D, Merlini A, Laterza C, Martino G. Neural stem cell transplantation in central nervous system disorders: from cell replacement to neuroprotection. *Curr Opin Neurol.* 2012; 25:322–333. [PubMed: 22547103]
- De Sarno P, Axtell RC, Raman C, Roth KA, Alessi DR, R.S. J. Lithium prevents and ameliorates experimental autoimmune encephalomyelitis. *J Immunol.* 2008; 181:338–345. [PubMed: 18566399]
- Dell'Acqua ML, Lorenzini L, D'Intino G, Sivilia S, Pasqualetti P, Panetta V, Paradisi M, Filippi MM, Baiguera C, Pizzi M, Giardino L, Rossini PM, Calza L. Functional and molecular evidence of

- myelin- and neuroprotection by thyroid hormone administration in experimental allergic encephalomyelitis. *Neuropathol Appl Neurobiol.* 2012; 38:454–470. [PubMed: 22007951]
- Deng YY, Xie D, Fang M, ZHu G, Chen C, Zeng H, Kaur C. Astrocyte-derived proinflammatory cytokines induce hypomyelination in the periventricular white matter in the Hypoxic Neonatal brain. *PLoS One.* 2014; 9:e87420. [PubMed: 24498101]
- Deogracias R, Yazdani M, Dekkers MP, Guy J, Ionescu MC, Vogt KE, Barde YA. Fingolimod, a sphingosine-1 phosphate receptor modulator, increases BDNF levels and improves symptoms of a mouse model of Rett syndrome. *Proc Natl Acad Sci U S A.* 2012; 109:14230–14235. [PubMed: 22891354]
- Deutsch ER, Espinoza TR, Atif F, Woodall E, Kaylor J, Wright DW. Progesterone's role in neuroprotection, a review of the evidence. *Brain Res.* 2013; 1530:82–105. [PubMed: 23872219]
- Dieni S, Rees S. BDNF and TrkB protein expression is altered in the fetal hippocampus but not cerebellum after chronic prenatal compromise. *Exp Neurol.* 2005; 192:265–273. [PubMed: 15755544]
- Dizon ML, Maa T, Kessler JA. The bone morphogenetic protein antagonist noggin protects white matter after perinatal hypoxia-ischemia. *Neurobiol Dis.* 2011; 42:318–326. [PubMed: 21310236]
- Doetsch F, Petreanu L, Caille I, Garcia-Verdugo JM, Alvarez-Buylla A. EGF converts transit-amplifying neurogenic precursors in the adult brain into multipotent stem cells. *Neuron.* 2002; 36:1021–1034. [PubMed: 12495619]
- Doi Y, Takeuchi H, Horiuchi H, Hanyu T, Kawanokuchi J, Jin S, Parajuli B, Sonobe Y, Mizuno T, Suzumura A. Fingolimod phosphate attenuates oligomeric amyloid beta-induced neurotoxicity via increased brain-derived neurotrophic factor expression in neurons. *PLoS One.* 2013; 8:e61988. [PubMed: 23593505]
- Drago D, Cossetti C, Iraci N, Gaude E, Musco G, Bachi A, Pluchino S. The stem cell secretome and its role in brain repair. *Biochimie.* 2013; 95:2271–2285. [PubMed: 23827856]
- Du Y, Fischer TZ, Lee LN, Lercher LD, Dreyfus CF. Regionally specific effects of BDNF on oligodendrocytes. *Developmental Neuroscience.* 2003; 25:116–126. [PubMed: 12966210]
- Du Y, Lercher LD, Zhou R, Dreyfus CF. Mitogen-activated protein kinase pathway mediates effects of brain-derived neurotrophic factor on differentiation of basal forebrain oligodendrocytes. *J Neurosci Res.* 2006; 84:1692–1702. [PubMed: 17044032]
- Dummula K, Vinukonda G, Chu P, Xing Y, Hu F, Mailk S, Csiszar A, Chua C, Mouton P, Kayton RJ, Brumberg JC, Bansal R, Ballabh P. Bone morphogenetic protein inhibition promotes neurological recovery after intraventricular hemorrhage. *J Neurosci.* 2011; 31:12068–12082. [PubMed: 21865450]
- Ebstein RP, Mankuta D, Yirmiya N, Malavasi F. Are retinoids potential therapeutic agents in disorders of social cognition including autism? *FEBS Letters.* 2011; 585:1529–1536. [PubMed: 21557943]
- Escobar Cabrera OE, Bongarzone ER, Soto EF, Pasquini JM. Single intracerebral injection of apotransferrin in young rats induces increased myelination. *Developmental Neuroscience.* 1994; 16:248–254. [PubMed: 7768203]
- Escobar Cabrera OE, Bongiovanni G, Hallak M, Soto EF, Pasquini JM. The cytoskeletal components of the myelin fraction are affected by a single intracranial injection of apotransferrin in young rats. *Neurochem Res.* 2000; 25:669–676. [PubMed: 10905629]
- Escobar Cabrera OE, Zakin MM, Soto EF, Pasquini JM. Single intracranial injection of apotransferrin in young rats increases the expression of specific myelin protein mRNA. *J Neurosci Res.* 1997; 47:603–608. [PubMed: 9089208]
- Espinosa-Jeffrey A, Barajas SA, Arrazola AR, Taniguchi A, Zhao PM, Bokhoor P, Holley SM, Dejarne DP, Chu B, Cepeda C, Levine MS, Gressens P, Feria-Velasco A, de Vellis J. White matter loss in a mouse model of periventricular leukomalacia is rescued by trophic factors. *Brain Sci.* 2013; 3:1461–1482. [PubMed: 24961618]
- Fan L, Pang Y, Lin S, Tien LT, Ma T, Rhodes PG, Cai Z. Minocycline reduces lipopolysaccharide-induced neurological dysfunction and brain injury in the neonatal rat. *J Neurosci Res.* 2005; 82:72–82.

- Fancy SP, Harrington EP, Baranzini SE, Silbereis JC, Shiow LR, Yuen TJ, Huang EJ, Lomvardas, Rowitch D. Parallel states of pathological Wnt signaling in neonatal brain injury and colon cancer. *Nat Neurosci*. 2014
- Fancy SP, Harrington EP, Yuen TJ, Silbereis JC, Zhao C, Baranzini SE, Bruce CC, Otero JJ, Huang EJ, Nusse R, Franklin RJM, Rowitch DH. Axin2 as regulatory and therapeutic target in newborn brain injury and remyelination. *Nat Neurosci*. 2011; 14:1009–1016. [PubMed: 21706018]
- Farsetti A, Mitsuhashi T, Desvergne B, Robbins J, Nikodem VM. Molecular basis of thyroid hormone regulation of myelin basic protein gene expression in rodent brain. *J Biol Chem*. 1991; 266:23226–23232. [PubMed: 1720778]
- Fazakerley JK, Walker R. Virus demyelination. *J Neurovirol*. 2003; 9:148–164. [PubMed: 12707846]
- Feigenson K, Reid M, See J, Crenshaw E. B. r. Grinspan JB. Wnt signaling is sufficient to perturb oligodendrocyte maturation. *Mol Cell Neurosci*. 2009; 42:255–265. [PubMed: 19619658]
- Ferent J, Zimmer C, Durbec P, Ruat M, Traiffort E. Sonic hedgehog signaling is a positive oligodendrocyte regulator during demyelination. *J Neurosci*. 2013; 33:1759–1772. [PubMed: 23365216]
- Fernandez M, Giuliani A, Pirondi S, D'Intino G, Giardino L, Aloe L, Levi-Montalcini R, Calza L. Thyroid hormone administration enhances remyelination in chronic demyelinating inflammatory disease. *Proc Natl Acad Sci U S A*. 2004a; 101:16363–16368. [PubMed: 15534218]
- Fernandez M, Pirondi S, Manservigi M, Giardino L, Calza L. Thyroid hormone participates in the regulation of neural stem cells and oligodendrocyte precursor cells in the central nervous system of adult rat. *Eur J Neurosci*. 2004b; 20:2059–2070. [PubMed: 15450085]
- Fields RD, Burnstock G. Purinergic signaling in neuron-glia interactions. *Nat Rev Neurosci*. 2006; 7:423–436. [PubMed: 16715052]
- Fischer DF, van Dijk R, Sluijs JA, Nair SM, Racchi M, Levelt CN, van Leeuwen FW, Hol EM. Activation of the Notch pathway in Down syndrome: cross-talk of Notch and APP. *FASEB J*. 2005; 19:1451–1458. [PubMed: 16126912]
- Follett PL, Deng W, Dai W, Talos DM, Massillon LJ, Rosenberg PA, Volpe JJ, Jensen FE. Glutamate receptor-mediated oligodendrocyte toxicity in periventricular leukomalacia: a protective role for topiramate. *J Neurosci*. 2004; 24:4412–4420. [PubMed: 15128855]
- Follett PL, Rosenberg PA, Volpe JJ, Jensen FE. NBQX attenuates excitotoxic injury in developing white matter. *J Neurosci*. 2000; 20:9235–9241. [PubMed: 11125001]
- Fragoso G, Haines JD, Roberston J, Pedraza L, Mushynski WE, Almazan G. p38 mitogen-activated protein kinase is required for central nervous system myelination. *Glia*. 2007; 55:1531–1541. [PubMed: 17729284]
- Fragoso G, Martinez-Bermudez A, Lui H-N, Khorchid A, Chemtob S, Mushynski W, Almazan G. Developmental differences in H2O2-induced oligodendrocyte cell death: role of glutathione, mitogen-activated protein kinases and caspase 3. *J Neurochem*. 2004; 90:392–404. [PubMed: 15228596]
- Franco PG, Silvestroff L, Soto EF, Pasquini JM. Thyroid hormones promote differentiation of oligodendrocyte progenitor cells and improve remyelination after cuprizone-induced demyelination. *Exp Neurol*. 2008; 212:458–467. [PubMed: 18572165]
- Fukumoto K, Mizoguchi H, Takeuchi H, Horiuchi H, Kawanokuchi J, Jin S, Mizuno T, Suzumura A. Fingolimod increases brain-derived neurotrophic factor levels and ameliorates amyloid beta-induced memory impairment. *Behav Brain Res*. 2014; 268:88–93. [PubMed: 24713151]
- Fuller ML, Dechant AK, Rothstein B, Caprariello A, Wang R, Hall AK, Miller RH. Bone morphogenetic proteins promote gliosis in demyelinating spinal cord lesions. *Annals of Neurology*. 2007; 62:288–300. [PubMed: 17696121]
- Fulmer CG, VonDran MW, Stillman AA, Huang Y, Hempstead BL, Dreyfus CF. Astrocyte-derived BDNF supports myelin protein synthesis after cuprizone-induced demyelination. *J Neurosci*. 2014; 34:8186–8196. [PubMed: 24920623]
- Gallo V, Zhou JM, McBain CJ, Wright P, Knutson PL, Armstrong RC. Oligodendrocyte progenitor cell proliferation and lineage progression are regulated by glutamate receptor-mediated K⁺ channel block. *Journal of Neuroscience*. 1996; 16:2659–2670. [PubMed: 8786442]

- Gao C, Chen YG. Dishevelled: the hub of Wnt signaling. *Cell Signal*. 2010; 22:717–727. [PubMed: 20006983]
- Garay. Progesterone down-regulates spinal cord inflammatory mediators and increases myelination in experimental autoimmune encephalomyelitis. *Neuroscience*. 2012; 226:40–50. [PubMed: 23000619]
- Garay L, Tungler V, Deniselle MC, Lima A, Roig P, De Nicola AF. Progesterone attenuates demyelination and microglial reaction in the lyssolecithin-injured spinal cord. *Neuroscience*. 2011; 192:588–597. [PubMed: 21736923]
- Genoud S, Lappe-Siefke C, Goebbels S, Radtke F, Aguet M, Scherer SS, Suter U, Nave KA, Mantei N. Notch1 control of oligodendrocyte differentiation in the spinal cord. *J Cell Biol*. 2002; 158:709–718. [PubMed: 12186854]
- Getts DR, Martin AJ, McCarthy DP, Terry RL, Hunter ZN, Yap WT, Getts MT, Pleiss M, Luo X, King NJ, Shea LD, Miller SD. Microparticles bearing encephalitogenic peptides induce T-cell tolerance and ameliorate experimental autoimmune encephalomyelitis. *Nat Biotechnol*. 2012; 30:1217–1224. [PubMed: 23159881]
- Givogri MI, Costa RM, Schonmann V, Silva AJ, Campagnoni AT, Bongarzone ER. Central nervous system myelination in mice with deficient expression of Notch1 receptor. *Journal of Neuroscience Research*. 2002; 67:309–320. [PubMed: 11813235]
- Givogri MI, de Planell M, Galbiati F, Superchi D, Gritti A, Vescovi A, de Vellis J, Bongarzone ER. Notch signaling in astrocytes and neuroblasts of the adult subventricular zone in health and after cortical injury. *Developmental Neuroscience*. 2006; 28:81–91. [PubMed: 16508306]
- Goddard DR, Berry M, Kirvell SL, Butt AM. Fibroblast growth factor-2 inhibits myelin production by oligodendrocytes in vivo. *Mol Cell Neurosci*. 2001; 18:557–569. [PubMed: 11922145]
- Goddard DR, Berry M, Kirvell SL, Butt AM. Fibroblast growth factor-2 induces astroglial and microglial reactivity in vivo. *J Anat*. 2002; 200:57–67. [PubMed: 11833655]
- Goldberg JS. Monitoring maternal Beta carotene and retinol consumption may decrease the incidence of neurodevelopmental disorders in offspring. *Clin Med Insights Reprod Health*. 2011; 6:1–8. [PubMed: 24453512]
- Goldstein AL, Hannappel E, Sosne G, Kleinman HK. Thymosin beta4: a multi-functional regenerative peptide. Basic properties and clinical applications. *Expert Opin Biol Ther*. 2012; 12:37–51. [PubMed: 22074294]
- Gonzalez-Perez O, Romero-Rodriguez R, Soriano-Navarro M, Garcia-Verdugo JM, Alvarez-Buylla A. Epidermal growth factor induces the progeny of subventricular zone type B cells to migrate and differentiate into oligodendrocytes. *Stem Cells*. 2009; 27:2032–2043. [PubMed: 19544429]
- Guardia Clausi M, Paez PM, Campagnoni AT, Pasquini LA, Pasquini JM. Intranasal administration of aTf protects and repairs the neonatal white matter after a cerebral hypoxic-ischemic event. *Glia*. 2012; 60:1540–1554. [PubMed: 22736466]
- Guardiola-Diaz HM, Ishii A, Bansal R. ERK1/2 MAPK and mTOR signaling sequentially regulates progression through distinct stages of oligodendrocyte differentiation. *Glia*. 2012; 60:476–486. [PubMed: 22144101]
- Gulino A, Di Marcotullio L, Ferretti E, De Smaele E, Screpanti I. Hedgehog signaling pathway in neural development and disease. *Psychoneuroendocrinology*. 2007; 32(Suppl 1):S52–56. [PubMed: 17619088]
- Habib P, Slowik A, Zendedel A, Johann S, Dang J, Beyer C. Regulation of hypoxia-induced inflammatory responses and M1-M2 phenotype switch of primary rat microglia by sex steroids. *J Mol Neurosci*. 2014; 52:277–285. [PubMed: 24163150]
- Hack M, Wilson-Costello D, Friedmand H, Taylor GH, Schluchter M, Fanaroff AA. Neurodevelopment and predictors of outcomes of children with birth weights of less than 1000g. *Arch Pediatr Adolesc Med*. 2000; 154:725–731. [PubMed: 10891026]
- Haines JD, Fragoso G, Hossain S, Mushynski WE, Almazan G. p38 Mitogen-activated protein kinase regulates myelination. *Journal of Molecular Neuroscience*. 2007; 35:23–33. [PubMed: 17994198]
- Hall SM. The effect of injections of lysophosphatidyl choline into white matter of the adult mouse spinal cord. *J Cell Sci*. 1972; 10:535–546. [PubMed: 5018033]

- Halliday HL, Ehrenkranz RA, Doyle LW. Early postnatal (<96 hours) corticosteroids for preventing chronic lung disease in preterm infants. *Cochrane Database Syst Rev*. 2003;CD001146. [PubMed: 12535402]
- Hametner S, Wimmer I, Haider L, Pfeifenbring S, Bruck W, Lassmann H. Iron and neurodegeneration in the multiple sclerosis brain. *Ann Neurol*. 2013; 74:848–861. [PubMed: 23868451]
- Hammond TR, Gadea A, Dupree J, Kerninon C, Nait-Oumesmar B, Aguirre A, Gallo V. Astrocyte-derived endothelin-1 inhibits remyelination through notch activation. *Neuron*. 2014; 81:588–602. [PubMed: 24507193]
- Hampton DW, Asher RA, Kondo T, Steeves JD, Ramer MS, Fawcett JW. A potential role for bone morphogenetic protein signaling in glial cell fate determination following adult central nervous system injury in vivo. *European Journal of Neuroscience*. 2007; 26:3024–3035. [PubMed: 18028109]
- Han BH, Holtzman DM. BDNF protects the neonatal brain from hypoxic-ischemic injury in vivo via the ERK pathway. *J Neurosci*. 2000; 20:5775–5781. [PubMed: 10908618]
- Harsan LA, Steibel J, Zaremba A, Agin A, Sapin R, Poulet P, Guignard B, Parizel N, Grucker D, Boehm N, Miller RH, Ghandour MS. Recovery from chronic demyelination by thyroid hormone therapy: myelinogenesis induction and assessment by diffusion tensor magnetic resonance imaging. *J Neurosci*. 2008; 28:14189–14201. [PubMed: 19109501]
- Hashimoto R, Udagawa J, Kagohashi Y, Matsumoto A, Hatta T, Otani H. Direct and indirect effects of neuropeptide Y and neurotrophin 3 on myelination in the neonatal brains. *Brain Res*. 2011; 1373:55–66. [PubMed: 21167823]
- Heine VM, Griveau A, Chapin C, Ballard PL, Chen JK, Rowitch DH. A small-molecule smoothened agonist prevents glucocorticoid-induced neonatal cerebellar injury. *Sci Transl Med*. 2011; 3:105ra104.
- Heine VM, Rowitch DH. Hedgehog signaling has a protective effect in glucocorticoid-induced mouse neonatal brain injury through an 11betaHSD2-dependent mechanism. *Journal of Clinical Investigation*. 2009; 119:267–277. [PubMed: 19164857]
- Holmes MC, Sangra M, French KL, Whittle IR, Paterson J, Mullins JJ, Seckl JR. 11beta-Hydroxysteroid dehydrogenase type 2 protects the neonatal cerebellum from deleterious effects of glucocorticoids. *Neuroscience*. 2006; 137:865–873. [PubMed: 16289840]
- Hou S, Nicholson L, van Niekerk E, Motsch M, Blesch A. Dependence of regenerated sensory axons on continuous neurotrophin-3 delivery. *J Neurosci*. 2012; 32:13206–13220. [PubMed: 22993437]
- Huang JK, Jarjour AA, Ffrench-Constant C, Franklin RJ. Retinoid X receptors as a potential avenue for regenerative medicine in multiple sclerosis. *Expert Rev Neurother*. 2011a; 11:467–468. [PubMed: 21469916]
- Huang JK, Jarjour AA, Nait Oumesmar B, Kerninon C, Williams A, Krezel W, Kagechika H, Bauer J, Zhao C, Baron-Van Evercooren A, Chambon P, Ffrench-Constant C, Franklin RJ. Retinoid X receptor gamma signaling accelerates CNS remyelination. *Nat Neurosci*. 2011b; 14:45–53. [PubMed: 21131950]
- Huang SS, Cheng H, Tang CM, Nien MW, Huang YS, Lee IH, Yin JH, Kuo TB, Yang CC, Tsai SK, Yang DI. Anti-oxidative, anti-apoptotic, and pro-angiogenic effects mediate functional improvement by sonic hedgehog against focal cerebral ischemia in rats. *Exp Neurol*. 2013; 247:680–688. [PubMed: 23499832]
- Hung PL, Huang CC, Huang HM, Tu DG, Chang YC. Thyroxine treatment protects against white matter injury in the immature brain via brain-derived neurotrophic factor. *Stroke*. 2013; 44:2275–2283. [PubMed: 23715956]
- Ingham PW, McMahon AP. Hedgehog signaling in animal development: paradigms and principles. *Genes and Development*. 2001; 15:3059–3087. [PubMed: 11731473]
- Ishii A, Fyffe-Maricich SL, Furusho M, Miller RH, Bansal R. ERK1/ERK2 MAPK Signaling is Required to Increase Myelin Thickness Independent of Oligodendrocyte Differentiation and Initiation of Myelination. *J Neurosci*. 2012; 32:8855–8864. [PubMed: 22745486]
- Ivkovic S, Canoll P, Goldman JE. Constitutive EGFR signaling in oligodendrocyte progenitors leads to diffuse hyperplasia in postnatal white matter. *J Neurosci*. 2008; 28:914–922. [PubMed: 18216199]

- Jablonska B, Aguirre A, Raymond M, Szabo G, Kitabatake Y, Sailor KA, Ming GL, Song H, Gallo V. Chordin-induced lineage plasticity of adult SVZ neuroblasts after demyelination. *Nat Neurosci*. 2010; 13:541–550. [PubMed: 20418875]
- Jablonska B, Scafidi J, Aguirre A, Vaccarino F, Nguyen V, Borok E, Horvath TL, Rowitch DH, Gallo V. Oligodendrocyte regeneration after neonatal hypoxia requires FoxO1-mediated p27Kip1 expression. *J Neurosci*. 2012; 32:14775–14793. [PubMed: 23077062]
- Jaillard C, Harrison S, Stankoff B, Aigrot MS, Calver AR, Duddy G, Walsh FS, Pangalos MN, Arimura N, Kaibuchi K, Zalc B, Lubetzki C. Edg8/SIP5: An oligodendroglial receptor with dual function on process retraction and cell survival. *J Neurosci*. 2005; 25:1459–1469. [PubMed: 15703400]
- Jain A, McKeon RJ, Brady-Kalnay SM, Bellamkonda RV. Sustained delivery of activated Rho GTPases and BDNF promotes axon growth in CSPG-rich regions following spinal cord injury. *PLoS One*. 2011; 6:e16135. [PubMed: 21283639]
- Jang SW, Liu X, Yepes M, Shepherd KR, Miller GW, Liu Y, Wilson WD, Xiao G, Blanchi B, Sun YE, Ye K. A selective TrkB agonist with potent neurotrophic activities by 7,8-dihydroxyflavone. *Proc Natl Acad Sci U S A*. 2010; 107:2687–2692. [PubMed: 20133810]
- Jean I, Lavialle C, Barthelaix-Poupard A, Fressinaud C. Neurotrophin-3 specifically increases mature oligodendrocyte population and enhances remyelination after chemical demyelination of adult rat CNS. *Brain Res*. 2003; 972:110–118. [PubMed: 12711083]
- Ji H, Miao J, Zhang X, Du Y, Liu H, Li S, Li L. Inhibition of sonic hedgehog signaling aggravates brain damage associated with the down-regulation of Gli1, Ptch1 and SOD1 expression in acute ischemic stroke. *Neurosci Lett*. 2012; 506:1–6. [PubMed: 22133807]
- Jiang Y, Wei N, Lu T, Zhu J, Xu G, Liu X. Intranasal brain-derived neurotrophic factor protects brain from ischemic insult via modulating local inflammation in rats. *Neuroscience*. 2011; 172:398–405. [PubMed: 21034794]
- Jiang Y, Wei N, Zhu J, Lu T, Chen Z, Xu G, Liu X. Effects of brain-derived neurotrophic factor on local inflammation in experimental stroke of rat. *Mediators Inflamm*. 2010; 2010:372423. [PubMed: 21490702]
- Jin-qiao S, Bin S, Wen-hao Z, Yi Y. Basic fibroblast growth factor stimulates the proliferation and differentiation of neural stem cells in neonatal rats after ischemic brain injury. *Brain Development*. 2009; 31:331–340. [PubMed: 18657919]
- John GR, Shankar SL, Safit-Zagardo B, Massimi A, Lee SC, Raine CS, Brosnan CF. Multiple sclerosis: Re-expression of a developmental pathway that restricts oligodendrocyte maturation. *Nature Medicine*. 2002; 8:1115–1121.
- Johnson JR, Chu AK, Sato-Bigbee C. Possible role of CREB in the stimulation of oligodendrocyte precursor cell proliferation by neurotrophin-3. *J Neurochem*. 2000; 74:1409–1417. [PubMed: 10737596]
- Jurynczyk M, Jurewicz A, Bielecki B, Raine CS, Selmaj K. Inhibition of Notch signaling enhances tissue repair in an animal model of multiple sclerosis. *Journal of Neuroimmunology*. 2005; 170:3–10. [PubMed: 16290267]
- Kalani MY, Cheshier SH, Cord BJ, Bababeygy SR, Vogel H, Weissman IL, Palmer TD, Nusse R. Wnt-mediated self-renewal of neural stem/progenitor cells. *Proc Natl Acad Sci (USA)*. 2008; 105:16970–16975. [PubMed: 18957545]
- Kanwar JR, Kanwar RK, Krissansen GW. Simultaneous neuroprotection and blockade of inflammation reverses autoimmune encephalomyelitis. *Brain*. 2004; 127:1313–1331. [PubMed: 15130951]
- Karimi-Abdolrezaee S, Eftekharpour E, Wang J, Morshead CM, Fehlings MG. Delayed transplantation of adult neural precursor cells promotes remyelination and functional neurological recovery after spinal cord injury. *J Neurosci*. 2006; 26:3377–3389. [PubMed: 16571744]
- Kaur C, Rathnasamy G, Ling EA. Roles of activated microglia in hypoxia induced neuroinflammation in the developing brain and the retina. *J Neuroimmune Pharmacol*. 2012
- Kavanaugh B, Beesley J, Itoh T, Itoh A, Grinspan J, Pleasure D. Neurotrophin-3 (NT-3) diminishes susceptibility of the oligodendroglial lineage to AMPA glutamate receptor-mediated excitotoxicity. *J Neurosci Res*. 2000; 60:725–732. [PubMed: 10861784]

- Kawamata T, Dietrich WD, Schallert T, Gotts JE, Cocke RR, Benowitz LI, Finklestein SP. Intracisternal basic fibroblast growth factor enhances functional recovery and up-regulates the expression of a molecular marker of neuronal sprouting following focal cerebral infarction. *Proc Natl Acad Sci U S A*. 1997; 94:8179–8184. [PubMed: 9223335]
- Kiecker C, Lumsden A. Hedgehog signaling from the ZLI regulates diencephalic regional identity. *Nat Neurosci*. 2004; 7:1242–1249. [PubMed: 15494730]
- Kim JW, Kim YJ, Chang YP. Administration of dexamethasone to neonatal rats induces hypomyelination and changes in the morphology of oligodendrocyte precursors. *Comp Med*. 2013; 63:48–54. [PubMed: 23561937]
- Kinnunen KM, Greenwood R, Powell JH, Leech R, Hawkins PC, Bonnelle V, Patel MC, Counsell SJ, Sharp DJ. White matter damage and cognitive impairment after traumatic brain injury. *Brain*. 2011; 134:449–463. [PubMed: 21193486]
- Kipp M, Amor S, Krauth R, Beyer C. Multiple sclerosis: neuroprotective alliance of estrogen-progesterone and gender. *Front Neuroendocrinol*. 2012a; 33:1–16. [PubMed: 22289667]
- Kipp M, Victor M, Martino G, Franklin RJ. Endogenous remyelination: findings in human studies. *CNS Neurol Disord Drug Targets*. 2012b; 11:598–609. [PubMed: 22583436]
- Kirschner PB, Henshaw R, Weise J, Trubetskoy V, Finklestein S, Schulz JB, Beal MF. Basic fibroblast growth factor protects against excitotoxicity and chemical hypoxia in both neonatal and adult rats. *J Cereb Blood Flow Metab*. 1995; 15:619–623. [PubMed: 7790410]
- Knuesel I, Chicha L, Britschgi M, Schobel SA, Bodmer M, Hellings JA, Toovey S, Prinssen EP. Maternal immune activation and abnormal brain development across CNS disorders. *Nat Rev Neurol*. 2014; 10:643–660. [PubMed: 25311587]
- Kremer D, Kury P, Dutta R. Promoting remyelination in multiple sclerosis: current drugs and future prospects. *Mult Scler*. 2015; 21:541–549. [PubMed: 25623245]
- Kuhlmann T, Miron V, Cuo Q, Wegner C, Antel J, Bruck W. Differentiation block of oligodendroglial progenitor cells as a cause for remyelination failure in chronic multiple sclerosis. *Brain*. 2008; 131:1749–1758. [PubMed: 18515322]
- Kumar S, Biancotti JC, Yamaguchi M, de Vellis J. Combination of growth factors enhances remyelination in a cuprizone-induced demyelination mouse model. *Neurochemical Research*. 2007; 32:783–797. [PubMed: 17186374]
- Kumar S, de Vellis J. Neurotrophin activates signal transduction in oligodendroglial cells: expression of functional TrkC receptor isoforms. *J Neurosci Res*. 1996; 44:490–498. [PubMed: 8776670]
- Kumar S, Kahn MA, Dinh L, de Vellis J. NT-3-mediated TrkC receptor activation promotes proliferation and cell survival of rodent progenitor oligodendrocyte cells in vitro and in vivo. *J Neurosci Res*. 1998; 54:754–765. [PubMed: 9856859]
- Kusano K, Enomoto M, Hirai T, Tsoulfas P, Sotome S, Shinomiya K, Okawa A. Transplanted neural progenitor cells expressing mutant NT3 promote myelination and partial hindlimb recovery in the chronic phase after spinal cord injury. *Biochem Biophys Res Commun*. 2010; 393:812–817. [PubMed: 20171177]
- Labombarda F, Gonzalez S, Lima A, Roig P, Guennoun R, Schumacher M, De Nicola AF. Progesterone attenuates astro- and microgliosis and enhances oligodendrocyte differentiation following spinal cord injury. *Exp Neurol*. 2011; 231:135–146. [PubMed: 21704617]
- Ladouceur CD, Peper JS, Crone EA, Dahl RE. White matter development in adolescence: the influence of puberty and implications for affective disorders. *Dev Cogn Neurosci*. 2012; 2:36–54. [PubMed: 22247751]
- Laeng P, Decimo D, Pettmann B, Janet T, Labourdette G. Retinoic acid regulates the development of oligodendrocyte precursor cells in vitro. *J Neurosci Res*. 1994; 39:613–633. [PubMed: 7897699]
- Lai K, Kaspar BK, Gage FH, Schaffer DV. Sonic hedgehog regulates adult neural progenitor proliferation in vitro and in vivo. *Nat Neurosci*. 2003; 6:21–27. [PubMed: 12469128]
- Lane TE, Buchmeier MJ. Murine coronavirus infection: a paradigm for virus-induced demyelinating disease. *Trends Microbiol*. 1997; 5:9–14. [PubMed: 9025229]
- Laterza C, Merlini A, De Feo D, Ruffini F, Menon R, Onorati M, Fredrickx E, Muzio L, Lombardo A, Comi G, Quattrini A, Taveggia C, Farina C, Cattaneo E, Martino G. iPSC-derived neural

precursors exert a neuroprotective role in immune-mediated demyelination via the secretion of LIF. *Nat Commun.* 2013; 4:2597. [PubMed: 24169527]

- Lei B, Mace B, Dawson HN, Warner DS, Laskowitz DT, James ML. Anti-inflammatory effects of progesterone in lipopolysaccharide-stimulated BV-2 microglia. *PLoS One.* 2014; 9:e103969. [PubMed: 25080336]
- Lei ZN, Liu F, Zhang LM, Huang YL, Sun FY. Bcl-2 increases stroke-induced striatal neurogenesis in adult brains by inhibiting BMP-4 function via activation of beta-catenin signaling. *Neurochem Int.* 2012; 61:34–42. [PubMed: 22521772]
- Li C, Xiao L, Liu X, Yang W, Shen W, Hu C, Yang G, He C. A functional role of NMDA receptor in regulating the differentiation of oligodendrocyte precursor cells and remyelination. *Glia.* 2013a; 61:732–749. [PubMed: 23440860]
- Li L, Walker TL, Zhang Y, Mackay EW, Bartlett PF. Endogenous interferon gamma directly regulates neural precursors in the non-inflammatory brain. *J Neurosci.* 2010; 30:9038–3050. [PubMed: 20610738]
- Li W, Quigley L, Yao DL, Hudson LD, Brenner M, Zhang BJ, Brocke S, McFarland HF, Webster HD. Chronic relapsing experimental autoimmune encephalomyelitis: effects of insulin-like growth factor-I treatment on clinical deficits, lesion severity, glial responses, and blood brain barrier defects. *J Neuropathol Exp Neurol.* 1998; 57:426–438. [PubMed: 9596413]
- Li X, Han H, Hou R, Wei L, Wang G, Li C, Li D. Progesterone treatment before experimental hypoxia-ischemia enhances the expression of glucose transporter proteins GLUT1 and GLUT3 in neonatal rats. *Neurosci Bull.* 2013b; 29:287–294. [PubMed: 23307114]
- Li X, Zhang J, Chai S, Wang X. Progesterone alleviates hypoxic-ischemic brain injury via the Akt/GSK-3beta signaling pathway. *Exp Ther Med.* 2014; 8:1241–1246. [PubMed: 25187832]
- Lin S, Fan LW, Pang Y, Rhodes PG, Mitchell HJ, Cai Z. IGF-1 protects oligodendrocyte progenitor cells and improves neurological functions following cerebral hypoxia-ischemia in the neonatal rat. *Brain Res.* 2005; 1063:15–26. [PubMed: 16259966]
- Lin S, Fan LW, Rhodes PG, Cai Z. Intranasal administration of IGF-1 attenuates hypoxic-ischemic brain injury in neonatal rats. *Exp Neurol.* 2009; 217:361–370. [PubMed: 19332057]
- Lin SZ, Hoffer BJ, Kaplan P, Wang Y. Osteogenic protein-1 protects against cerebral infarction induced by MCA ligation in adult rats. *Stroke.* 1999; 30:126–133. [PubMed: 9880400]
- Lisak RP, Bealmeier B, Nedelkoska L, Benjamins JA. Secretory products of central nervous system glial cells induce Schwann cell proliferation and protect from cytokine-mediated death. *J Neurosci Res.* 2006; 83:1425–1431. [PubMed: 16583376]
- Liu HN, Giasson BI, Mushynski WE, Almazan G. AMPA receptor-mediated toxicity in oligodendrocyte progenitors involves free radical generation and activation of JNK, calpain and caspase 3. *J Neurochem.* 2002; 82:398–409. [PubMed: 12124441]
- Liu X, Yao DL, Webster H. Insulin-like growth factor I treatment reduces clinical deficits and lesion severity in acute demyelinating experimental autoimmune encephalomyelitis. *Mult Scler.* 1995; 1:2–9. [PubMed: 9345463]
- Lopatina T, Kalinina N, Karagyaur M, Stambolsky D, Rubina K, Revischin A, Pavlova G, Parfyonova Y, Tkachuk V. Adipose-derived stem cells stimulate regeneration of peripheral nerves: BDNF secreted by these cells promotes nerve healing and axon growth de novo. *PLoS One.* 2011; 6:e17899. [PubMed: 21423756]
- Louvi A, Artavanis-Tsakonas S. Notch signalling in vertebrate neural development. *Nat Rev Neurosci.* 2006; 7:93–102. [PubMed: 16429119]
- Lovett-Racke AE, Bittner P, Cross AH, Carlino JA, Racke MK. Regulation of experimental autoimmune encephalomyelitis with insulin-like growth factor (IGF-1) and IGF-1/IGF-binding protein-3 complex (IGF-1/IGFBP3). *Journal of Clinical Investigation.* 1998; 101:1797–1804. [PubMed: 9541512]
- Lu QR, Yuk D-I, Alberta JA, Zhu Z, Pawlitzky I, Chan J, McMahon AP, Stiles CD, Rowitch DH. Sonic Hedgehog-regulated oligodendrocyte lineage genes encoding bHLH proteins in the mammalian central nervous system. *Neuron.* 2000; 25:317–329. [PubMed: 10719888]
- Ludwin SK. Central nervous system demyelination and remyelination in the mouse: an ultrastructural study of cuprizone toxicity. *Lab Invest.* 1978; 39:597–612. [PubMed: 739762]

- Luesse HG, Roskoden T, Linke R, Otten U, Heese K, Schwegler H. Modulation of mRNA expression of the neurotrophins of the nerve growth factor family and their receptors in the septum and hippocampus of rats after transient postnatal thyroxine treatment. I. Expression of nerve growth factor, brain-derived neurotrophic factor, neurotrophin-3, and neurotrophin 4 mRNA. *Exp Brain Res*. 1998; 119:1–8. [PubMed: 9521530]
- Lyons SA, Kettenmann H. Oligodendrocytes and microglia are selectively vulnerable to combined hypoxia and hypoglycemia injury in vitro. *J Cereb Blood Flow Metab*. 1998; 18:521–530. [PubMed: 9591844]
- Machold R, Hayashi S, Rutlin M, Muzumdar MD, Nery S, Corbin JG, Gritli-Linde A, Dellovade T, Porter JA, Rubin LL, Dudek H, McMahon AP, Fishell G. Sonic hedgehog is required for progenitor cell maintenance in telencephalic stem cell niches. *Neuron*. 2003; 39:937–950. [PubMed: 12971894]
- Makoukji J, Belle M, Meffre D, Stassart R, Grenier J, Shackleford G, Fledrich R, Fonte C, Branchu J, Goulard M, de Waele C, Charbonnier F, Sereda MW, Baulieu EE, Schumacher M, Bernard S, Massaad C. Lithium enhances remyelination of peripheral nerves. *Proc Natl Acad Sci (USA)*. 2012; 109:3973–3978. [PubMed: 22355115]
- Manning SM, Talos DM, Zhou C, Selip DB, Park HK, Park CJ, Volpe JJ, Jensen FE. NMDA receptor blockade with memantine attenuates white matter injury in a rat model of periventricular leukomalacia. *J Neurosci*. 2008; 28:6670–6678. [PubMed: 18579741]
- Marin-Husstege M, Muggironi M, Raban D, Skoff RP, Casaccia-Bonnel P. Oligodendrocyte progenitor proliferation and maturation is differentially regulated by male and female sex steroid hormones. *Developmental Neuroscience*. 2004; 26:245–254. [PubMed: 15711064]
- Marro BS, Blanc CA, J.F. L, Cahalan MD, Lane TE. Promoting remyelination: utilizing a viral model of demyelination to assess cell-based therapies. *Expert Rev Neurother*. 2014; 14:1169–1179. [PubMed: 25245576]
- Marta CB, Davio C, Pasquini LA, Soto EF, Pasquini JM. Molecular mechanisms involved in the actions of apotransferrin upon the central nervous system: Role of the cytoskeleton and of second messengers. *J Neurosci Res*. 2002; 69:488–496. [PubMed: 12210842]
- Marziali LN, Garcia CI, Pasquini JM. Transferrin and thyroid hormone converge in the control of myelinogenesis. *Exp Neurol*. 2015; 265:129–141. [PubMed: 25595122]
- Mascalchi, M. Neurodegenerative diseases with associated white matter pathology.. In: Filippi, MM.; De Stefano, N.; Dousset, V.; McGowan, JC., editors. *MR Imaging in White matter diseases of the brain and spinal cord*. Springer Berlin Heidelberg; 2005. p. 377–388.
- Mason JL, Suzuki K, Chaplin DD, Matsushima GK. Interleukin-1 β promotes repair of the CNS. *J Neurosci*. 2001; 21:7046–7052. [PubMed: 11549714]
- Mason JL, Xuan S, Dragatsis I, Efstratiadis A, Goldman JE. Insulin-like growth factor (IGF) signaling through type 1 IGF receptor plays an important role in remyelination. *J Neurosci*. 2003; 23:7710–7718. [PubMed: 12930811]
- Mason JL, Ye P, Suzuki K, D'Ercole AJ, Matsushima GK. Insulin-like growth factor-1 inhibits mature oligodendrocyte apoptosis during primary demyelination. *J Neurosci*. 2000; 20:5703–5708. [PubMed: 10908609]
- Matsushima GK, Morell P. The neurotoxicant, cuprizone, as a model to study demyelination and remyelination in the central nervous system. *Brain Pathology*. 2001; 11:107–116. [PubMed: 11145196]
- Matute C. Calcium dyshomeostasis in white matter pathology. *Cell Calcium*. 2010; 47:150–157. [PubMed: 20036774]
- Matute C, Torre I, Perez-Cerda F, Perez-Samartin A, Alberdi E, Etxebarria E, Arranz AM, Ravid R, Rodriguez-Antiguedad A, Sanchez-Gomez M, Domercq M. P2X(7) receptor blockade prevents ATP excitotoxicity in oligodendrocytes and ameliorates experimental autoimmune encephalomyelitis. *J Neurosci*. 2007; 27:9525–9533. [PubMed: 17728465]
- McDonald JW, Belegu V. Demyelination and remyelination after spinal cord injury. *J Neurotrauma*. 2006; 23:345–359. [PubMed: 16629621]

- McGinn MJ, Colello RJ, Sun D. Age-related proteomic changes in the subventricular zone and their association with neural stem/progenitor cell proliferation. *J Neurosci Res.* 2012; 90:1159–1168. [PubMed: 22344963]
- McTigue DM, Harner PJ, Stokes BT, Gage FH. Neurotrophin-3 and brain derived neurotrophic factor induce oligodendrocyte proliferation and myelination of regenerating axons in the contused adult rat spinal cord. *J Neurosci.* 1998; 18:5354–5365. [PubMed: 9651218]
- Mecha M, Carrillo-Salinas FJ, Mestre L, Feliu A, Guaza C. Viral models of multiple sclerosis: Neurodegeneration and demyelination in mice infected with Theiler's virus. *Progress in Neurobiology* 101. 2013; 102:46–64.
- Meffre D, Grenier J, Bernard S, Courtin F, Dudev T, Shackleford G, Jafarian-Tehrani M, Massaad C. Wnt and lithium: a common destiny in the therapy of nervous system pathologies? *Cell Mol Life Sci.* 2014; 71:1123–1148. [PubMed: 23749084]
- Meffre D, Massaad C, Grenier J. Lithium chloride stimulates PLP and MBP expression in oligodendrocytes via Wnt/beta-catenin and Akt/CREB pathways. *Neuroscience.* 2015; 284:962–971. [PubMed: 25451297]
- Ment LR, Allan WC, Makuch RW, Vohr B. Grade 3 to 4 intraventricular hemorrhage and Bayley scores predict outcome. *Pediatrics.* 2005; 116:1597–1598. author reply 1598. [PubMed: 16322189]
- Ment LR, Vohr B, Allan W, Westerveld M, Sparrow SS, Schneider KC, Katz KH, Duncan CC, Makuch RW. Outcome of children in the indomethacin intraventricular hemorrhage prevention trial. *Pediatrics.* 2000; 105:485–491. [PubMed: 10699097]
- Merrill JE. In vitro and in vivo pharmacological models to assess demyelination and remyelination. *Neuropsychopharmacology.* 2009; 34
- Merrill JE, Scolding NJ. Mechanisms of damage to myelin and oligodendrocytes and their relevance to disease. *Neuropathol Appl Neurobiol.* 1999; 25:435–458. [PubMed: 10632895]
- Mestan KK, Marks JD, Hecox K, Huo D, Schreiber MD. Neurodevelopmental outcomes of premature infants treated with inhaled nitric oxide. *N Engl J Med.* 2005; 353:23–32. [PubMed: 16000353]
- Mi S, Hu B, Hahm K, Luo Y, Kam Hui ES, Yuan Q, Wong WM, Wang L, Su H, Chu TH, Guo J, Zhang W, So KF, Pepinsky B, Shao Z, Graff C, Garber E, Jung V, Wu EX, Wu W. LINGO-1 antagonist promotes spinal cord remyelination and axonal integrity in MOG-induced experimental autoimmune encephalomyelitis. *Nature Medicine.* 2007; 13:1228–1233.
- Mierzwa AJ, Zhou YX, Hibbits N, Vana AC, Armstrong RC. FGF2 and FGFR1 signaling regulate functional recovery following cuprizone demyelination. *Neurosci Lett.* 2013; 548:280–285. [PubMed: 23684572]
- Mifsud G, Zammit C, Muscat R, Di Giovanni G, Valentino M. Oligodendrocyte pathophysiology and treatment strategies in cerebral ischemia. *CNS Neurosci Ther.* 2014; 20:603–612. [PubMed: 24703424]
- Min J, Singh S, Fitzgerald-Bocarsly P, Wood TL. Insulin-like growth factor I regulates G2/M progression through mammalian target of rapamycin signaling in oligodendrocyte progenitors. *Glia.* 2012; 60:1684–1695. [PubMed: 22836368]
- Minter LM, Turley DM, Das P, Shin HM, Joshi I, Lawlor RG, Cho OH, Palaga T, Gottipati S, Telfer JC, Kostura L, Fauq AH, Simpson K, Such KA, Miele L, Golde TE, Miller SD, Osborne BA. Inhibitors of gamma-secretase block in vivo and in vitro T helper type 1 polarization by preventing Notch upregulation of Tbx21. *Nat Immunol.* 2005; 6:680–688. [PubMed: 15991363]
- Miracle X, Di Renzo GC, Stark A, Fanaroff A, Carbonell-Estrany X, Saling E, Coordinators Of World Association of Perinatal Medicine Prematurity Working, G. Guideline for the use of antenatal corticosteroids for fetal maturation. *J Perinat Med.* 2008; 36:191–196. [PubMed: 18576926]
- Miron VE, Boyd A, Zhao JW, Yuen TJ, Ruckh JM, Shadrach JL, van Wijngaarden P, Wagers AJ, Williams A, Franklin RJ, French-Constant C. M2 microglia and macrophages drive oligodendrocyte differentiation during CNS remyelination. *Nat Neurosci.* 2013; 16:1211–1218. [PubMed: 23872599]
- Moro N, Sutton RL. Beneficial effects of sodium or ethyl pyruvate after traumatic brain injury in the rat. *Exp Neurol.* 2010; 225:391–401. [PubMed: 20670624]

- Morris DC, Chopp M, Zhang L, Lu M, Zhang ZG. Thymosin beta4 improves functional neurological outcome in a rat model of embolic stroke. *Neuroscience*. 2010; 169:674–682. [PubMed: 20627173]
- Murone M, Rosenthal A, De Sauvage FJ. Sonic hedgehog signaling by the patched-smoothed receptor complex. *Current Biology*. 1999; 9:76–84. [PubMed: 10021362]
- Ness JK, Mitchell NE, Wood TL. IGF-I and NT-3 signaling pathways in developing oligodendrocytes: differential regulation and activation of receptors and the downstream effector Akt. *Developmental Neuroscience*. 2002; 24:437–445. [PubMed: 12666655]
- Ness JK, Scaduto RCJ, Wood TL. IGF-1 prevents glutamate-mediated bax translocation and cytochrome C release in O4+ oligodendrocyte progenitors. *Glia*. 2004; 46:183–194. [PubMed: 15042585]
- Nicolay DJ, Doucette JR, Nazarali AJ. Transcriptional control of Oligodendrogenesis. *Glia*. 2007; 55:1287–1299. [PubMed: 17647291]
- Noguchi KK, Lau K, Smith DJ, Swiney BS, Farber NB. Glucocorticoid receptor stimulation and the regulation of neonatal cerebellar neural progenitor cell apoptosis. *Neurobiol Dis*. 2011; 43:356–363. [PubMed: 21530661]
- Noguchi KK, Walls KC, Wozniak DF, Olney JW, Roth KA, Farber NB. Acute neonatal glucocorticoid exposure produces selective and rapid cerebellar neural progenitor cell apoptotic death. *Cell Death Differ*. 2008; 15:1582–1592. [PubMed: 18600230]
- Noll E, Miller RH. Regulation of oligodendrocyte differentiation: a role for retinoic acid in the spinal cord. *Development*. 1994; 120:649–660. [PubMed: 8162861]
- O'Leary MT, Hinks GL, Charlton HM, Franklin RJ. 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*. 2002; 19:32–42. [PubMed: 11817896]
- Ofek-Shlomai N, Berger I. Inflammatory injury to the neonatal brain - what can we do? *Front Pediatr*. 2014; 2:30. [PubMed: 24783185]
- Oya S, Yoshikawa G, Takai K, Tanaka JI, Higashiyama S, Saito N, Kirino T, Kawahara N. Attenuation of Notch signaling promotes the differentiation of neural progenitors into neurons in the hippocampal CA1 region after ischemic injury. *Neuroscience*. 2009; 158:683–692. [PubMed: 19017538]
- Pang Y, Fan L-W, Zheng B, Campbell LR, Cai Z, Rhodes PG. Dexamethasone and betamethasone protect against LPS-induced brain damage in the neonatal rats. *Pediatr Res*. 2012; 71:552–558. [PubMed: 22314662]
- Pansiot J, Loron G, Olivier P, Fontaine R, Charriaut-Marlangue C, Mercier JC, Gressens P, Baud O. Neuroprotective effect of inhaled nitric oxide on excitotoxic-induced brain damage in neonatal rat. *PLoS One*. 2010; 5:e10916. [PubMed: 20532231]
- Pantoni L, Garcia JH, Gutierrez JA. Cerebral white matter is highly vulnerable to ischemia. *Stroke*. 1996; 27:1641–1646. discussion 1647. [PubMed: 8784142]
- Payne NL, Sun G, McDonald C, Layton D, Moussa L, Emerson-Webber A, Veron N, Siatskas C, Herszfeld D, Price J, Bernard CC. Distinct immunomodulatory and migratory mechanisms underpin the therapeutic potential of human mesenchymal stem cells in autoimmune demyelination. *Cell Transplant*. 2013; 22:1409–1425. [PubMed: 23057962]
- Perez MJ, Fernandez N, Pasquini JM. Oligodendrocyte differentiation and signaling after transferrin internalization: a mechanism of action. *Exp Neurol*. 2013; 248:262–274. [PubMed: 23797152]
- Perides G, Jensen FE, Edgecomb P, Rueger DC, Charness ME. Neuroprotective effect of human osteogenic protein-1 in a rat model of cerebral hypoxia/ischemia. *Neurosci Lett*. 1995; 187:21–24. [PubMed: 7617293]
- Pham H, Vottier G, Pansiot J, Duong -Q,S, Bollen B, Dalous J, Gallego J, Mercier JC, Dinh-Xuan AT, Bonnin P, Charriaut-Marlangue C, Baud O. Inhaled NO prevents hyperoxia-induced white matter damage in neonatal rats. *Exp Neurol*. 2014; 252:114–123. [PubMed: 24322053]
- Pitt D, Werner P, Raine CS. Glutamate excitotoxicity in a model of multiple sclerosis. *Nature Medicine*. 2000; 6:67–70.

- Pombo PM, Baretino D, Ibarrola N, Vega S, Rodriguez-Pena A. Stimulation of the myelin basic protein gene expression by 9-cis-retinoic acid and thyroid hormone: activation in the context of its native promoter. *Brain Res Mol Brain Res*. 1999; 64:92–100. [PubMed: 9889331]
- Pryce G, O'Neill JK, Croxford JL, Amor S, Hankey DJ, East E, Giovannoni G, Baker D. Autoimmune tolerance eliminates relapses but fails to halt progression in a model of multiple sclerosis. *J Neuroimmunol*. 2005; 165:41–52. [PubMed: 15939483]
- Puttagunta R, Schmandke A, Floriddia E, Gaub P, Fomin N, Ghyselinck NB, Di Giovanni S. RA-RAR-beta counteracts myelin-dependent inhibition of neurite outgrowth via Lingo-1 repression. *J Cell Biol*. 2011; 193:1147–1156. [PubMed: 21690307]
- Ransohoff RM. Animal models of multiple sclerosis: the good, the bad and the bottom line. *Nat Neurosci*. 2012; 15:1074–1077. [PubMed: 22837037]
- Ritter J, Schmitz T, Chew L, Buhner C, Wiebke M, Zonouzi M, Gallo V. Neonatal hyperoxia exposure disrupts axon-oligodendrocyte integrity in the subcortical white matter. *J Neurosci*. 2013; 33:8990–9002. [PubMed: 23699510]
- Robertson CL, Saraswati M. Progesterone protects mitochondrial function in a rat model of pediatric traumatic brain injury. *J Bioenerg Biomembr*. 2014
- Robinson AP, Harp CT, Noronha A, Miller SD. The experimental autoimmune encephalomyelitis (EAE) model of MS: utility for understanding disease pathophysiology and treatment. *Hand Clin Neurol*. 2014; 122:173–178.
- Rodriguez JP, Coulter M, Miotke J, Meyer RL, Takemaru K, Levine JM. Abrogation of beta-Catenin Signaling in Oligodendrocyte Precursor Cells Reduces Glial Scarring and Promotes Axon Regeneration after CNS Injury. *J Neurosci*. 2014; 34:10285–10297. [PubMed: 25080590]
- Sabo JK, Aumann TD, Kilpatrick TJ, Cate HS. Investigation of sequential growth factor delivery during cuprizone challenge in mice aimed to enhance oligodendroglialogenesis and myelin repair. *PLoS One*. 2013; 8:e63415. [PubMed: 23650566]
- Sabo JK, Aumann TD, Merlo D, Kilpatrick TJ, Cate HS. Remyelination is altered by bone morphogenic protein signaling in demyelinated lesions. *J Neurosci*. 2011; 31:4504–4510. [PubMed: 21430151]
- Saini HS, Coelho RP, Goparaju SK, Jolly PS, Maceyka M, Spiegel S, Sato-Bigbee C. Novel role of sphingosine kinase 1 as a mediator of neurotrophin-3 action in oligodendrocyte progenitors. *J Neurochem*. 2005; 95:1298–1310. [PubMed: 16313513]
- Saini HS, Gorse KM, Boxer LM, Sato-Bigbee C. Neurotrophin-3 and a CREB-mediated signaling pathway regulate Bcl-2 expression in oligodendrocyte progenitor cells. *J Neurochem*. 2004; 89:951–961. [PubMed: 15140194]
- Saksida T, Miljkovic D, Timotijevic G, Stojanovic I, Mijatovic S, Fagone P, Mangano K, Mammana S, Farina C, Ascione E, Maiello V, Nicoletti F, Stosic-Grujicic S. Apotransferrin inhibits interleukin-2 expression and protects mice from experimental autoimmune encephalomyelitis. *J Neuroimmunol*. 2013; 262:72–78. [PubMed: 23890777]
- Samanta J, Alden T, Gobeske K, Kan L, Kessler JA. Noggin protects against ischemic brain injury in rodents. *Stroke*. 2010; 41:357–362. [PubMed: 20019326]
- Santra M, Chopp M, Zhang ZG, Lu M, Santra S, Nalani A, Santra S, Morris DC. Thymosin beta 4 mediates oligodendrocyte differentiation by upregulating p38 MAPK. *Glia*. 2012; 60:1826–1838. [PubMed: 23073962]
- Santra M, Zhang ZG, Yang J, Santra S, Chopp M, Morris DC. Thymosin beta-4 upregulation of microRNA-146a promotes oligodendrocyte differentiation and suppression of the Toll-like proinflammatory pathway. *J Biol Chem*. 2014
- Scafidi J, Fagel DM, Ment LR, Vaccarino FM. Modelling premature brain injury and recovery. *Int J Dev Neurosci*. 2009; 27:863–871. [PubMed: 19482072]
- Scafidi J, Hammond TR, Scafidi S, Ritter J, Jablonska B, Roncal M, Szigeti-Buck K, Coman D, Huang Y, McCarter RJ Jr. Hyder F, Horvath TL, Gallo V. Intranasal epidermal growth factor treatment rescues neonatal brain injury. *Nature*. 2014; 506:230–234. [PubMed: 24390343]
- Schmitz T, Krabbe G, Weikert G, Scheuer T, Matheus F, Wang Y, Mueller S, Kettenmann H, Matyash V, Buhner C, Endesfelder S. Minocycline protects the immature white matter against hyperoxia. *Exp Neurol*. 2014; 254:153–165. [PubMed: 24491957]

- Schmitz T, Ritter J, Mueller S, Felderhoff-Mueser U, Chew LJ, Gallo V. Cellular changes underlying hyperoxia-induced delay of white matter development. *Journal of Neuroscience*. 2011; 31:4327–4344. [PubMed: 21411673]
- Schumacher M, Guennoun R, Mercier G, Desarnaud F, Lacor P, Benavides J, Ferzaz B, Robert F, Baulieu EE. Progesterone synthesis and myelin formation in peripheral nerves. *Brain Res Brain Res Rev*. 2001; 37:343–359. [PubMed: 11744099]
- Shang AJ, Hong SQ, Xu Q, Wang HY, Yang Y, Wang ZF, Xu BN, Jiang XD, Xu RX. NT-3-secreting human umbilical cord mesenchymal stromal cell transplantation for the treatment of acute spinal cord injury in rats. *Brain Res*. 2011; 1391:102–113. [PubMed: 21420392]
- Shen H, Luo Y, Kuo CC, Deng X, Chang CF, Harvey BK, Hoffer BJ, Wang Y. 9-Cis-retinoic acid reduces ischemic brain injury in rodents via bone morphogenetic protein. *J Neurosci Res*. 2009; 87:545–555. [PubMed: 18803283]
- Shen S, Sandoval J, Swiss VA, Li J, Dupree J, Franklin RJ, Casaccia-Bonnett P. Age-dependent epigenetic control of differentiation inhibitors is critical for remyelination efficiency. *Nature Neuroscience*. 2008; 11:1024–1034. [PubMed: 19160500]
- Shen Y, Liu XB, Pleasure DE, Deng W. Axon-glia synapses are highly vulnerable to white matter injury in the developing brain. *J Neurosci Res*. 2012; 90:105–121. [PubMed: 21812016]
- Sher F, Balasubramaniyan V, Boddeke E, Copray S. Oligodendrocyte differentiation and implantation: new insights for remyelinating cell therapy. *Curr Opin Neurol*. 2008; 21:607–614. [PubMed: 18769257]
- Shi H, Hu X, Leak RK, Shi Y, An C, Suenaga J, Chen J, Gao Y. Demyelination as a rational therapeutic target for ischemic or traumatic brain injury. *Exp Neurol*. 2015; 2015
- Shimizu T, Kagawa T, Wada T, Muroyama Y, Takada S, Ikenaka K. Wnt signaling controls the timing of oligodendrocyte development in the spinal cord. *Developmental Biology*. 2005; 282:397–410. [PubMed: 15950605]
- Shin JA, Lim SM, Jeong SI, Kang JL, Park EM. Noggin improves ischemic brain tissue repair and promotes alternative activation of microglia in mice. *Brain Behav Immun*. 2014; 40:143–154. [PubMed: 24704569]
- Shin WJ, Gwak M, Baek CH, Kim KS, Park PH. Neuroprotective effects of lithium treatment following hypoxic-ischemic brain injury in neonatal rats. *Childs Nerv Syst*. 2012; 28:191–198. [PubMed: 22094358]
- Shu X, Zhang Y, Xu H, Kang K, Cai D. Brain-derived neurotrophic factor inhibits glucose intolerance after cerebral ischemia. *Neural Regen Res*. 2013; 8:2370–2378. [PubMed: 25206547]
- Sievers C, Samann PG, Dose T, Dimopoulou C, Spieler D, Roemmler J, Schopohl J, Mueller M, Schneider HJ, Czisch M, Pfister H, Stalla GK. Macroscopic brain architecture changes and white matter pathology in acromegaly: a clinicoradiological study. *Pituitary*. 2009; 12:177–185. [PubMed: 18836838]
- Silbereis JC, Huang EJ, Back SA, Rowitch DH. Towards improved animal models of neonatal white matter injury associated with cerebral palsy. *Disease models and Mechanisms*. 2010; 3:678–688. [PubMed: 21030421]
- Silvestroff L, Bartucci S, Pasquini J, Franco P. Cuprizone-induced demyelination in the rat cerebral cortex and thyroid hormone effects on cortical remyelination. *Exp Neurol*. 2012; 235:357–367. [PubMed: 22421533]
- Skoff RP, Bessert DA, Barks JD, Song D, Cerghet M, Silverstein FS. Hypoxic-ischemic injury results in acute disruption of myelin gene expression and death of oligodendroglial precursors in neonatal mice. *Int J Dev Neurosci*. 2001; 19:197–208. [PubMed: 11255033]
- Skripuletz T, Bussmann JH, Gudi V, Koutsoudaki PN, Pul R, Moharreh-Khiabani D, Lindner M, Stangel M. Cerebellar cortical demyelination in the murine cuprizone model. *Brain Pathology*. 2010; 20:301–312. [PubMed: 19371354]
- Skripuletz T, Linder M, Kotsiari A, Garde N, Fokuhl J, Linsmeier F, Trebst C, Stangel M. Cortical demyelination is prominent in the murine cuprizone model and is strain-dependent. *American Journal of Pathology*. 2008; 172:1053–1061. [PubMed: 18349131]

- Stephenson E, Nathoo N, Mahjoub Y, Dunn JF, Yong VW. Iron in multiple sclerosis: roles in neurodegeneration and repair. *Nature Reviews Neurology*. 2014; 10:459–468. [PubMed: 25002107]
- Stidworthy MF, Genoud S, Li W-W, Leone DP, Mantei N, Suter U, Franklin RJM. Notch1 and Jagged1 are expressed after CNS demyelination, but are not a major rate-determining factor during remyelination. *Brain*. 2004; 127:1928–1941. [PubMed: 15289265]
- Takenaga M, Ohta Y, Tokura Y, Hamaguchi A, Shudo K, Okano H, Igarashi R. The effect of Am-80, a synthetic retinoid, on spinal cord injury-induced motor dysfunction in rats. *Biol Pharm Bull*. 2009; 32:225–231. [PubMed: 19182380]
- Tanaka T, Murakami K, Bando Y, Yoshida S. Minocycline reduces remyelination by suppressing ciliary neurotrophic factor expression after cuprizone-induced demyelination. *J Neurochem*. 2013; 127:259–270. [PubMed: 23647102]
- Tanaka T, Yoshida S. Mechanisms of remyelination: recent insight from experimental models. *Biomol Concepts*. 2014; 5:289–298. [PubMed: 25372760]
- Tang H, Wang Y, Xie L, Mao X, Won SJ, Galvan V, Jin K. Effect of neural precursor proliferation level on neurogenesis in rat brain during aging and after focal ischemia. *Neurobiol Aging*. 2009; 30:299–308. [PubMed: 17644223]
- Tang XJ, Xing F. Calcium-permeable AMPA receptors in neonatal hypoxic-ischemic encephalopathy (Review). *Biomed Rep*. 2013; 1:828–832. [PubMed: 24649036]
- Templeton SP, Perlman S. Pathogenesis of acute and chronic central nervous system infection with variants of mouse hepatitis virus, strain JHM. *Immunol Res*. 2007; 39:160–172. [PubMed: 17917063]
- Thomas AM, Seidlits SK, Goodman AG, Kukushliev TV, Hassani DM, Cummings BJ, Anderson AJ, Shea LD. Sonic hedgehog and neurotrophin-3 increase oligodendrocyte numbers and myelination after spinal cord injury. *Integr Biol (Camb)*. 2014; 6:694–705. [PubMed: 24873988]
- Toda N, Ayajiki K, Okamura T. Cerebral blood flow regulation by nitric oxide: recent advances. *Pharmacol Rev*. 2009; 61:62–97. [PubMed: 19293146]
- Treadwell T, Kleinman HK, Crockford D, Hardy MA, Guarnera GT, Goldstein AL. The regenerative peptide thymosin beta4 accelerates the rate of dermal healing in preclinical animal models and in patients. *Ann N Y Acad Sci*. 2012; 1270:37–44. [PubMed: 23050815]
- Tripathi RB, McTigue DM. Chronically increased ciliary neurotrophic factor and fibroblast growth factor-2 expression after spinal contusion in rats. *J Comp Neurol*. 2008; 510:129–144. [PubMed: 18615534]
- Tyler WA, Gangoli N, Gokina P, Kim HA, Covey M, Levison SW, Wood TL. Activation of the mammalian target of rapamycin (mTOR) is essential for oligodendrocyte differentiation. *J Neuroscience*. 2009; 29:6367–6378. [PubMed: 19439614]
- Uccelli A, Mancardi G. Stem cell transplantation in multiple sclerosis. *Curr Opin Neurol*. 2010; 23:218–225. [PubMed: 20375893]
- Urshansky N, Mausner-Fainberg K, Auriel E, Regev K, Bornstein NM, Karni A. Reduced production of noggin by immune cells of patients with relapsing-remitting multiple sclerosis. *J Neuroimmunol*. 2011a; 232:171–178. [PubMed: 21111488]
- Urshansky N, Mausner-Fainberg K, Auriel E, Regev K, Karni A. Low and dysregulated production of follistatin in immune cells of relapsing-remitting multiple sclerosis patients. *J Neuroimmunol*. 2011b; 238:96–103. [PubMed: 21880375]
- van Amerongen R. Alternative Wnt pathways and receptors. *Cold Spring Harb Perspect Biol*. 2012; 4
- van der Werff SJA, Andela CD, Pannekoek JN, Meijer OC, Van Buchem MA, Rombouts SARB, van der Mast RC, Biermasz NR, Pereira AM, van der Wee NJA. Widespread reduction of white matter integrity in patients with long-term remission of Cushing's disease. *NeuroImage: Clinical*. 2014; 4:659–667. [PubMed: 24936417]
- Van Steenwinckel J, Schang AL, Sigaut S, Chhor V, Degos V, Hagberg H, Baud O, Fleiss B, Gressens P. Brain damage of the preterm infant: new insights into the role of inflammation. *Biochem Soc Trans*. 2014; 42:557–563. [PubMed: 24646278]

- van Velthoven CT, Braccioli L, Willemsen HL, Kavelaars A, Heijnen CJ. Therapeutic potential of genetically modified mesenchymal stem cells after neonatal hypoxic-ischemic brain damage. *Mol Ther*. 2014; 22:645–654. [PubMed: 24172866]
- van Velthoven CT, Sheldon RA, Kavelaars A, Derugin N, Vexler ZS, Willemsen HL, Maas M, Heijnen CJ, Ferriero DM. Mesenchymal stem cell transplantation attenuates brain injury after neonatal stroke. *Stroke*. 2013; 44:1426–1432. [PubMed: 23539530]
- van Velthoven CT, van de Looij Y, Kavelaars A, Zijlstra J, van Bel F, Huppi PS, Sizonenko S, Heijnen CJ. Mesenchymal stem cells restore cortical rewiring after neonatal ischemia in mice. *Ann Neurol*. 2012; 71:785–796. [PubMed: 22718545]
- Veeraraghavalu K, Choi SH, Zhang X, Sisodia SS. Presenilin 1 mutants impair the self-renewal and differentiation of adult murine subventricular zone-neuronal progenitors via cell-autonomous mechanisms involving notch signaling. *J Neurosci*. 2010; 30:6903–6915. [PubMed: 20484632]
- Volpe JJ. Cerebellum of the premature infant: rapidly developing, vulnerable, clinically important. *J Child Neurol*. 2009; 24:1085–1104. [PubMed: 19745085]
- Vondran MW, Clinton-Luke P, Honeywell JZ, Dreyfus CF. BDNF+/- mice exhibit deficits in oligodendrocyte lineage cells of the basal forebrain. *Glia*. 2010; 58:848–856. [PubMed: 20091777]
- VonDran MW, Singh H, Honeywell JZ, Dreyfus CF. Levels of BDNF impact oligodendrocyte lineage cells following a cuprizone lesion. *J Neurosci*. 2011; 31:14182–14190. [PubMed: 21976503]
- Vose LR, Vinukonda G, Jo S, Miry O, Diamond D, Korumilli R, Arshad A, Zia MT, Hu F, Kayton RJ, La Gamma EF, Bansal R, Bianco AC, Ballabh P. Treatment with thyroxine restores myelination and clinical recovery after intraventricular hemorrhage. *J Neurosci*. 2013; 33:17232–17246. [PubMed: 24174657]
- Walsh MC, Hibbs AM, Martin CR, Cnaan A, Keller RL, Vittinghoff E, Martin RJ, Truog WE, Ballard PL, Zadell A, Wadlinger SR, Coburn CE, Ballard RA. Two-year neurodevelopmental outcomes of ventilated preterm infants treated with inhaled nitric oxide. *Journal of Pediatrics*. 2010; 156:556–561. e551. [PubMed: 20138299]
- Wang JM, Johnston PB, Ball BG, Brinton RD. The neurosteroid allopregnanolone promotes proliferation of rodent and human neural progenitor cells and regulates cell-cycle gene and protein expression. *J Neurosci*. 2005; 25:4706–4718. [PubMed: 15888646]
- Wang LY, Cai WQ, Chen PH, Deng QY, Zhao CM. Downregulation of P2X7 receptor expression in rat oligodendrocyte precursor cells after hypoxia ischemia. *Glia*. 2009; 57:307–319. [PubMed: 18942747]
- Wang S, Sdrulla AD, diSibio G, Bush G, Nofziger D, Hicks C, Weinmaster G, Barres BA. Notch Receptor activation inhibits oligodendrocyte differentiation. *Neuron*. 1998; 21:63–75. [PubMed: 9697852]
- Wang X, Zhang J, Si D, Shi R, Dong W, Wang F, Wang L, Li X. Progesterone inhibits the expression of cyclooxygenase-2 and interleukin-1 β in neonatal rats with hypoxic ischemic brain damage. *Int J Neurosci*. 2014; 124:42–48. [PubMed: 23786480]
- Wang Y, Chang CF, Morales M, Chou J, Chen HL, Chiang YH, Lin SZ, Cadet JL, Deng X, Wang JY, Chen SY, Kaplan PL, Hoffer BJ. Bone morphogenetic protein-6 reduces ischemia-induced brain damage in rats. *Stroke*. 2001; 32:2170–2178. [PubMed: 11546913]
- Wang Y, Cheng X, He Q, Zheng Y, Kim DH, Whittemore SR, Cao QL. Astrocytes from the contused spinal cord inhibit oligodendrocyte differentiation of adult oligodendrocyte precursor cells by increasing the expression of bone morphogenetic proteins. *J Neurosci*. 2011; 31:6053–6058. [PubMed: 21508230]
- Wang Y, Imitola J, Rasmussen S, O'Connor KC, Khoury SJ. Paradoxical dysregulation of the neural stem cell pathway Sonic hedgehog-Gli1 in autoimmune encephalomyelitis and multiple sclerosis. *Ann Neurol*. 2008; 64:417–427. [PubMed: 18991353]
- Wang Y, Yin P, Huang S, Wang J, Sun R. Ethyl pyruvate protects against lipopolysaccharide-induced white matter injury in the developing rat brain. *Int J Dev Neurosci*. 2013; 31:181–188. [PubMed: 23280059]
- Wechsler-Reya RJ, Scott MP. Control of neuronal precursor proliferation in the cerebellum by Sonic Hedgehog. *Neuron*. 1999; 22:103–114. [PubMed: 10027293]

- Wilczak N, Chesik D, Hoekstra D, De Keyser J. IGF binding protein alterations on periplaque oligodendrocytes in multiple sclerosis: implications for remyelination. *Neurochem Int.* 2008; 52:1431–1435. [PubMed: 18471934]
- Wilson-Costello D, Friedman H, Minich N, Fanaroff AA, Hack M. Improved survival rates with increased neurodevelopmental disability for extremely low birth weight infants in the 1990s. *Pediatrics.* 2005; 115:997–1003. [PubMed: 15805376]
- Wong AW, Xiao J, Kemper D, Kilpatrick TJ, Murray SS. Oligodendroglial expression of TrkB independently regulates myelination and progenitor cell proliferation. *J Neurosci.* 2013; 33:4947–4957. [PubMed: 23486965]
- Wood TL, Loladze V, Altieri S, Gangoli N, Levison SW, Brywe KG, Mallard C, Hagberg H. Delayed IGF-1 administration rescues oligodendrocyte progenitors from glutamate-induced cell death and hypoxic-ischemic brain damage. *Developmental Neuroscience.* 2007; 29:302–310. [PubMed: 17762198]
- Xiong Y, Mahmood A, Meng Y, Zhang Y, Zhang ZG, Morris DC, Chopp M. Neuroprotective and neurorestorative effects of thymosin beta4 treatment following experimental traumatic brain injury. *Ann N Y Acad Sci.* 2012a; 1270:51–58. [PubMed: 23050817]
- Xiong Y, Zhang Y, Mahmood A, Meng Y, Zhang ZG, Morris DC, Chopp M. Neuroprotective and neurorestorative effects of thymosin beta4 treatment initiated 6 hours after traumatic brain injury in rats. *J Neurosurg.* 2012b; 116:1081–1092. [PubMed: 22324420]
- Yabe T, Samuels I, Schwartz JP. Bone morphogenetic proteins BMP-6 and BMP-7 have differential effects on survival and neurite outgrowth of cerebellar granule cell neurons. *J Neurosci Res.* 2002; 68:161–168. [PubMed: 11948661]
- Yang J, Yan Y, Xia Y, Kang T, Li X, Ciric B, Xu H, Rostami A, Zhang G-X. Neurotrophin 3 transduction augments remyelinating and immunomodulatory capacity of neural stem cells. *Mol Ther.* 2014; 22:440–450. [PubMed: 24247929]
- Yao L, Kan EM, Kaur C, Dheen ST, Hao A, Lu J, Ling EA. Notch-1 signaling regulates microglia activation via NF-kappaB pathway after hypoxic exposure in vivo and in vitro. *PLoS One.* 2013; 8:e78439. [PubMed: 24223152]
- Yoon K, Gaiano N. Notch signaling in the mammalian central nervous system: insights from mouse mutants. *Nat Neurosci.* 2005; 8:709–715. [PubMed: 15917835]
- Young KM, Psachoulia K, Tripathi RB, Dunn SJ, Cossell L, Attwell D, Tohyama K, Richardson WD. Oligodendrocyte dynamics in the healthy adult CNS: evidence for myelin remodeling. *Neuron.* 2013; 77:873–885. [PubMed: 23473318]
- Yuan X, Eisen AM, McBain CJ, Gallo V. A role for glutamate and its receptors in the regulation of oligodendrocyte development in cerebellar tissue slices. *Development.* 1998; 125:2901–2914. [PubMed: 9655812]
- Zai LJ, Yoo S, Wrathall JR. Increased growth factor expression and cell proliferation after contusive spinal cord injury. *Brain Res.* 2005; 1052:147–155. [PubMed: 16005441]
- Zhang J, Zhang ZG, Li Y, Ding X, Shang X, Lu M, Elias SB, Chopp M. Fingolimod treatment promotes proliferation and differentiation of oligodendrocyte progenitor cells in mice with experimental autoimmune encephalomyelitis. *Neurobiol Dis.* 2015; 76:57–66. [PubMed: 25680941]
- Zhang J, Zhang ZG, Morris D, Li Y, Roberts C, Elias SB, Chopp M. Neurological functional recovery after thymosin beta4 treatment in mice with experimental auto encephalomyelitis. *Neuroscience.* 2009; 164:1887–1893. [PubMed: 19782721]
- Zhang YJ, Zhang W, Lin CG, Ding Y, Huang SF, Wu JL, Li Y, Dong H, Zeng YS. Neurotrophin-3 gene modified mesenchymal stem cells promote remyelination and functional recovery in the demyelinated spinal cord of rats. *J Neurol Sci.* 2012; 313:64–74. [PubMed: 21996274]
- Zhong J, Zhao L, Du Y, Wei G, Yao WG, Lee WH. Delayed IGF-1 treatment reduced long-term hypoxia-ischemia-induced brain damage and improved behavior recovery of immature rats. *Neurol Res.* 2009; 31:483–489. [PubMed: 19500451]
- Zhou YX, Pannu R, Le TQ, Armstrong RC. Fibroblast growth factor 1 (FGFR1) modulation regulates repair capacity of oligodendrocyte progenitor cells following chronic demyelination. *Neurobiol Dis.* 2012; 45:196–205. [PubMed: 21854849]

- Zia MT, Vinukonda G, Vose L, Bhimavarapu BB, Iacobas S, Pandey NK, Beall AM, Dohare P, LaGamma EF, Iacobas DA, Ballabh P. Postnatal glucocorticoid-induced hypomyelination, gliosis, and neurologic deficits are dose-dependent, preparation-specific, and reversible. *Exp Neurol*. 2014
- Ziv Y, Avidan H, Pluchino S, Martino G, Schwartz M. Synergy between immune cells and adult neural stem/progenitor cells promotes functional recovery from spinal cord injury. *Proc Natl Acad Sci U S A*. 2006; 103:13174–13179. [PubMed: 16938843]
- Zonouzi M, Renzi M, Farrant M, Cull-Candy SG. Bidirectional plasticity of calcium-permeable AMPA receptors in oligodendrocyte lineage cells. *Nat Neurosci*. 2011; 14:1430–1438. [PubMed: 21983683]

Highlights

- White matter damage occurs in a variety of perinatal and adult brain injuries
- Therapy exploits regenerative potential of endogenous progenitor cells
- Pharmacological agents attenuate tissue damage and enhance functional recovery
- Treatments provide benefit of cellular regeneration, maturation and neuroprotection

Table 1

Summary of studies showing effects of pharmacological intervention in neonatal brain injury, adult demyelination and ischemia models. In some cases, viral expression systems were included for comparison.

Drug name	Administration route	Model	Mechanism and outcome	Reference
Ion channels and Neurotransmitter receptors				
NBQX, AMPA receptor antagonist	Subcutaneous injections post-adoptive transfer	Adoptive transfer EAE	Amelioration of disease, increased OL survival, reduced axonal damage.	(Pitt et al., 2000)
NBQX, AMPA receptor antagonist	i.p. and intravenous injections in combination with integrin blockade	MOG EAE	No effect on lesion size, or inflammation.	(Kanwar et al., 2004)
NBQX	i.p. injections every 12 hr post lesion	Neonatal hypoxia-ischemia	Attenuates loss of myelin and death of OLs	(Follett et al., 2004; Follett et al., 2000; Shen et al., 2012)
Memantine, NMDA receptor antagonist	Post-injury i.p injections first at 1 hr post hypoxia then 3 more at 12 hr intervals	Neonatal hypoxia-ischemia	Attenuates loss of O1+ and MBP levels without affecting normal myelination	(Manning et al., 2008)
Brilliant Blue G, Periodate oATP, P2X7 antagonists	i.p. injection or pellets post immunization	Chronic MOG-EAE	Reduced demyelination assessed by MBP immunohistochemistry, improved axonal conduction	(Matute et al., 2007)
Growth factors				
bFGF2	Intraventricular infusion	Postnatal day 3 (P3) rat hypoxia-ischemia model	Proliferation (BRDU+) cells in SVZ with NG2, nestin, GFP and mostly NeuN colocalization	(Jin-qiao et al., 2009)
EGF	Infusion onto brain surface by mini-osmotic pumps for 7 days from time of lesion	Lysolecithin-induced focal demyelination in adult corpus callosum	Without injury, EGF induced adult neural precursors in SVZ to proliferate and migrate to striatum and corpus callosum, and differentiate to oligodendrocyte lineage and S100B+/GFAP+ cells in striatum, without neuronal differentiation. Demyelination injury +EGF increased precursor proliferation, migration and differentiation into OL at the lesion site	(Gonzalez-Perez et al., 2009)
EGF	Intranasal (heparin binding) EGF treatment in adult mouse beginning 1 day prior to lesion	Lysolecithin-induced focal demyelination in adult mouse corpus callosum	Adult SVZ cells proliferate and migrate to demyelinated corpus callosum. Increased total recruited cells and therefore increased OL cells	(Cantarella et al., 2008)
EGFR	Viral-induced over-expression	P3 rat pups	Proliferation of OPC; Maintain cells in an undifferentiated state – preventing maturation to OL.	(Ivkovic et al., 2008)
EGF	Intranasal (heparin binding) EGF immediately after injury	Chronic neonatal mouse hypoxia	Promoted OL survival, increased NG2+ OPC proliferation and inhibits	(Scafidi et al., 2014)

Drug name	Administration route	Model	Mechanism and outcome	Reference
			NOTCH to promote OPC differentiation to OPC to OL. Enhanced functional and recovery.	
IGF				
IGF-1	Spinal cord injection of non damaging dose of adenoviral vector to increase IGF-1 mRNA expression	Lyssolecithin induced focal demyelination in spinal cord in 12 month aged rat	Did not promote remyelination from OLs	(O'Leary et al., 2002)
Sequential delivery of growth factors: Noggin alone, IGF-1 alone or Sequential : BMP-4 with IGF or Noggin	Intraventricular infusion with osmotic pump during last 2 weeks of cuprizone	Cuprizone demyelination in adult mice	Combined BMP4+IGF or IGF alone increased OL in corpus callosum but not remyelinated axons. Noggin alone increased OLs and remyelination.	(Sabo et al., 2013)
IGF	Delivery via subcutaneous injection at different stages of EAE	Adoptive transfer EAE in adult mice	Treatment during acute phase transiently improved clinical score with only early apparent difference in myelination. Treatment during chronic phase had no effect on clinical score or on remyelination	(Cannella et al., 2000)
IGF-I	3 daily intraventricular injections after injury	P7 Neonatal rat hypoxia-ischemia	Increased phosphorylated Akt and GSK3B in the cerebral cortex Reduced lesion volume.	(Brywe et al., 2005)
IGF-I	intraventricular injection after injury once daily for 2 days	P7 Neonatal rat hypoxia-ischemia	Prevents caspase 3 activation and promotes differentiation to OLs that express MBP in in-vitro models Rescued loss of Olig2+ cells in WM	(Wood et al., 2007)
IGF-1	intraventricular injection (i.c.v.) after injury	P4 Neonatal hypoxia-ischemia	Decreased WM damage, O4+ death and increased myelination (MBP+ staining). Increased proliferation of SVZ cells and NG2+ and O4+ OPCs in WM and decreased GFAP+ cells. Improvements in functional recovery	(Lin et al., 2005)
IGF-1	Intranasal doses after injury	P7 Neonatal rat Hypoxia-ischemia	Akt activation; Decreased caspase 3 mediated apoptosis; Increased proliferation of neuronal and OPCs Reduced brain injury and Improved neurobehavioral outcomes	(Lin et al., 2009)
IGF-1	subcutaneous injection after hypoxia-ischemia	P7 Neonatal Hypoxia-ischemia	Prevents apoptosis, improved long-term memory and cognitive behavior	(Zhong et al., 2009)
Neurotrophic factors				
Neurotrophin-3 (NT-3)	NT-3 injection with LPC into corpus callosum in adult rat	Focal LPC demyelination model	56% decrease in demyelinated lesions 15 days after injury; increased MBP+ cells (no change to astrogliosis)	(Jean et al., 2003)

Drug name	Administration route	Model	Mechanism and outcome	Reference
NT-3-gene modified	Mesenchymal stem cells (adenoviral vector)	Ethidium bromine demyelination in rat spinal cord	Improved functional recovery, MBP and remyelination.	(Zhang et al., 2012)
BDNF	Intra-cerebroventricular administration before injury	P7 rat Hypoxia-ischemia injury	ERK- mediated inhibition of caspase 3 pathway in neurons	(Han and Holtzman, 2000)
BDNF released by trans- (1S,3R)-1-amino-1,3-cyclopentanedicarboxylic acid (ACPD)	Injection of ACPD into lesion	cuprizone demyelination in mice	Induced BDNF from astrocytes Increased MBP, MAG, and PLP within 6 hours of treatment, without a change in CC1+ cell number.	(Fulmer et al., 2014)
Combination	Intracranial injection of IGF, PDGF-AA, FGF2, NT-3 at cuprizone withdrawal	cuprizone demyelination mouse model	Akt/PKB inhibition of cytochrome c release OL lineage cell proliferation, migration to corpus callosum, and increased myelination.	(Kumar et al., 2007)
Nuclear receptors and hormones				
Thyroid hormone (T3)	Subcutaneous injection at cuprizone withdrawal	Rat cuprizone demyelination	Increased mature OLs, decreased progenitor cells and increased remyelination in the corpus callosum	(Franco et al., 2008)
Thyroid hormone (T3)	Intranasal thyroid hormone after cuprizone withdrawal	Rat cuprizone demyelination model	Increased MBP in the cortex	(Silvestroff et al., 2012)
Thyroid hormone (T4)	T4 administration at onset of symptoms	chronic demyelinating EAE in Lewis and DA rats with guinea pig spinal cord homogenate	Reduces relapse disease severity in Lewis rats only. Increased PDGF-A R mRNA in the spinal cord of both types of rats Increased RIP immunostaining and MBP RNA and protein expression.	(Fernandez et al., 2004a)
T3	Intraperitoneal injection at cuprizone withdrawal	Chronic Cuprizone demyelination in mice (12 weeks)	Improved radial diffusion tensor imaging (myelin abnormalities), improved clinical score, remyelination, and increased progenitor cell proliferation, (increased SHH+, Olig2+ cells and PSA-NCAM+) measured 12 weeks after cuprizone withdraw	(Harsan et al., 2008)
Thyroid hormone (T3)	Subcutaneous administration of T3	DA Rat EAE (guinea pig spinal cord homogenate)	Protection of myelin sheath and axon (neurofilament immunoreactivity, nerve conduction)	(Dell'Acqua et al., 2012)
Thyroid hormone (T4)	Intramuscular thyroxine injection in	Embryonic Day 29 rabbit pups with glycerol-induced Intraventricular hemorrhage	Converted to active T3 by deiodinases Increased OPC proliferation and maturation into OL; increased myelination and functional recovery	(Vose et al., 2013)
Retinoic Acid				
9-cis retinoic acid agonist	Intraperitoneal administration after lesion	Ethidium bromide induced cerebellar focal demyelination in aged rats	Agonist of the retinoid acid receptor increases myelination of axons	(Huang et al., 2011b)

Drug name	Administration route	Model	Mechanism and outcome	Reference
9-cis retinoic acid	Intracerebroventricular administration before injury	Transient focal ischemia by MCA ligation in adult	Reduced cerebral infarction and cell death. Increased locomotor activity, and attenuated neurological deficits.	(Shen et al., 2009)
All trans retinoic acid	i.p. injection with injury	Adult Cerebral ischemia	Reduced inflammation and size of cerebral infarct. Inhibition of COX-2 induction by ischemia	(Choi et al., 2009)
Am-80 synthetic retinoid	Oral- before injury, or subcutaneous administration after injury	Spinal cord injury	Reduced lesion cavity, increased MBP.	(Takenaga et al., 2009)
CD2019, RAR beta2 agonist	Infusion into lateral ventricle at time of injury	Spinal cord injury-dorsal column lesion	Activates PI3K signaling and stimulates spinal neurite outgrowth and motor recovery in spinal cord injury	(Agudo et al., 2010)
RA-RAR beta	Daily i.p. injections after spinal cord injury	Adult Dorsal column hemisection injury	Inhibition of Nogo receptor signaling/repression of LINGO RA/RARb inhibits Lingo-1 expression Promotes Neurite outgrowth and axonal regeneration	(Puttagunta et al., 2011)
Progesterone				
Progesterone	Subcutaneous progesterone implant Pre-treatment	Murine EAE	Immunomodulation; Independent effects on OPC proliferation and remyelination Improved clinical signs of EAE, increased expression of PLP, MBP, and number of NKx2.2+ and Olig1+ precursor and CC1+ OLs.	(Garay, 2012)
Progesterone	Subcutaneous Progesterone implant Pre-treatment	Lysophosphatidylcholine induced demyelination in adult murine spinal cord	Decreased demyelinated lesion; Increased NG2+ (OPC), and CC1+ (OL) cells and decreased Ox-42 and CD11b(macrophage/microglia)	(Garay et al., 2011)
Progesterone	Acute (3 d) Vs. Chronic (21 d) treatment after Spinal cord injury in rat	Adult spinal cord injury	Acute: Inhibited astrocytes and microglia/macrophage proliferation and increased NG2+ (OPC) proliferation Chronic: Decreased NG2+ proliferation and increased CC1+BRDU+ cells	(Labombarda et al., 2011)
Progesterone	Pre-injury i.p. injection	Neonatal rat hypoxia-ischemia	Reduced neuronal apoptosis, increased Phosphorylated Akt.	(Li et al., 2014)
Apo-transferrin				
Apo-transferrin	Daily i.p. injections post immunization	Adult murine EAE	Decrease IL-2 synthesis and secretion in myelin-specific T cells Ameliorated EAE	(Saksida et al., 2013)
Apotransferrin	Intraventricular injection 7 days after lysolecithin lesion	Focal demyelination with lysolecithin	Enhances remyelination through Notch activation. Study revealed positive	(Aparicio et al., 2013)

Drug name	Administration route	Model	Mechanism and outcome	Reference
Apo-transferrin	Intracranial injection at cuprizone withdrawal	Rat cuprizone demyelination	effect of gamma secretase on remyelination Accelerated OPC recruitment and maturation to speed up remyelination	(Adamo et al., 2006)
Apo-transferrin	Intranasal treatment 2 days after hypoxia-ischemia	Hypoxia-ischemia in neonatal mouse	Decreased WM damage and astrogliosis; increased OL survival, increased OPC proliferation in SVZ and CC and OPC differentiation ; functional recovery	(Guardia Clausi et al., 2012)
Apo-transferrin +IGF combination (TSC1)	Intraparenchymal brain injection together with NMDA or 3 days post injury	P4 neonatal NMDA excitotoxicity in mice	Attenuated myelin loss and death, reduced inward striatal inward currents and ventricle size (neuroprotection). Increased OPC proliferation and lineage progression	(Espinosa-Jeffrey et al., 2013)
Apo-transferrin	Intracranial injection at P3	Prenatal iron-deficient diet from E5	Iron deficiency decreased myelination MBP immunoreactivity increased after apotransferrin treatment	(Badaracco et al., 2008)
Morphogens				
Sonic Hedgehog				
SHH	Adenoviral vector	Focal demyelination with lysolecithin in adult mice	Increased OPCs and myelinating OLs, decreased astrogliosis and macrophage infiltration	(Feret et al., 2013)
SHH	Lentivirus Combined study with NT-3	Spinal cord injury	Decreased Sox2 and increased Olig2+ cells	(Thomas et al., 2014)
Purmorphamine Smoothened Agonist	i.v. injection 6hr post injury	Ischemic brain injury	Reduced infarct volume and apoptosis, increased neuroprotection, enhanced motor function, but did not increase the generation of new Olig2+ cells	(Chechneva et al., 2014)
SAG, Smoothened agonist	Daily i.p. injections	Mouse neonatal glucocorticoid injury to cerebellum	SAG traverses blood-brain barrier, does not affect lung maturation. Mouse cerebellar neuron precursors were protected against prednisolone toxicity. Side effects of tissue hyperplasia and reduced growth avoided with transient dose.	(Heine et al., 2011)
Wnt modulation				
Tankyrase inhibitor XAV939 (Wnt inhibition)	Injected with lysolecithin in vivo	Neonatal hypoxia injury and adult lysolecithin lesion in mouse	Increased Axin 1 and Axin 2 protein and increased phospho- β -catenin and β -catenin degradation, WNT pathway inhibition and increased OL differentiation Increased myelinated axons in ex vivo mouse cerebellar slice cultures after hypoxia injury and	(Fancy et al., 2011)

Drug name	Administration route	Model	Mechanism and outcome	Reference
Lithium chloride	Parenteral administration and Two i.p. injections post immunization	EAE model	lysophosphatidylcholine demyelination. In spinal cord lysophosphatidylcholine lesions, XAV939 increased differentiation of OLP recruited to injury site and thickened myelin sheath (not increase OL survival or diminish lesion formation)	(De Sarno et al., 2008)
Lithium chloride	Daily subcutaneous injection post - lesion	Rice-Vanucci P7 neonatal rat hypoxia-ischemia	Infarct reduced, morphological preservation noted with lithium.	(Shin et al., 2012)
BMP antagonist				
Noggin (BMP antagonist)	Intraventricular infusion for last 28 days of cuprizone	Cuprizone induced demyelination (6 weeks) in adult mouse corpus callosum	Increased density of Olig2+ oligodendroglia. Decreases GFAP+ astrocytes. Increased mature OLs, and remyelinated axons	(Cate et al., 2010) (Sabo et al., 2011)
Chordin (BMP antagonist)	Intraventricular infusion 2 days post lesion	Lysophosphatidylcholine demyelination in adult mice corpus callosum	Increased generation of MASH1+, Olig2+ OPCs and OL from SVZ-derived GAD65+ precursors	(Jablonska et al., 2010)
Noggin (BMP antagonist)	Intraventricular infusion post lesion at 24h	Intraventricular hemorrhage induced at E29 premature rabbit pups with i.p. 50% glycerol at 2h from E29 cesarian delivery	Restored Olig2 expression, overcomes arrested OL maturation, restored myelination of axons, reduced numbers of astrocyte	(Dummula et al., 2011)
Notch				
MW167, Gamma secretase inhibitor	Intraventricular injection 5days after first signs of symptoms	EAE	Improves myelin repair and survival	(Jurynczyk et al., 2005)
LY411575, Gamma secretase inhibitor	Multiple paradigms: Oral and i.p. injections pre-injury	EAE	Improves clinical score, inhibits Th1 polarization	(Minter et al., 2005)
DAPT, gamma secretase inhibitor	i.p. injection pre-injury	P1 neonatal rat hypoxia	Inhibited microglial activation assessed by MyD88 and TRAF6 expression	(Yao et al., 2013)
Others				
Anti-LINGO-1 antibody	Intrathecal delivery 3D after MOG induction	Rat MOG - EAE	Functional recovery, axonal integrity, myelin sheath formation after EAE.	(Mi et al., 2007)
Endothelin Receptor antagonist PD142,893	Post-lesion mini-osmotic pump infusion	Lysophosphatidylcholine lesion in adult mouse corpus callosum	Demyelination-induced Endothelin-1 increases astrocytic Jagged 1 which activates inhibitory Notch signaling in OPCs. PD142,893 improves remyelination.	(Hammond et al., 2014)
Thymosin beta-4	Post-injury or concurrent i.p. injections	Adult traumatic brain injury, stroke injury and EAE	Improved clinical score, reduced inflammation, increased oligodendrogenesis – increased OPCs and CNP + OLs	(Morris et al., 2010; Xiong et al., 2012a; Xiong et al., 2012b;

Drug name	Administration route	Model	Mechanism and outcome	Reference
				Zhang et al., 2009)

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