PERSPECTIVE

# Perspectives on neuroreparative therapies for treating multiple sclerosis

**A need to develop neuroreparative therapies for multiple sclerosis (MS):** MS is the most common neurological disease of young Caucasian adults. This disease is characterized by inflammatory demyelination of the central nervous system (CNS) and involves activation of key inflammatory cells of both the adaptive and innate immune systems, which target and destroy both myelin and oligodendrocytes (the myelin-forming glial cells in the CNS). Key pathological features of the disease include autoimmune inflammation, axonal degeneration and demyelination (myelin loss), latter of which can occur in both white matter and gray matter. The key cell type damaged in MS is oligodendrocytes, which produce the insulating myelin sheath surrounding many axons in the CNS. Myelin and oligodendrocytes have critical roles. Myelin is responsible for promoting rapid, saltatory conduction of action potentials throughout much of the CNS. When myelin is lost in diseases such as MS, saltatory conduction is disrupted and conduction block can ensue. Myelin also provides a physical barrier for axons and thus serves to abrogate axonally directed, immune attack. Oligodendrocytes can also provide key nutritive support to axons in the healthy, quiescent state, which is compromised when oligodendrocytes are targeted (Nave and Werner, 2014). There is an emerging consensus that the progressive disability that ultimately ensues for many patients with MS correlates with the degree of accumulative axonal degeneration. It is also apparent that the extent of demyelination, and the degree of oligodendrocyte targeting, are likely to be relevant factors that dictate outcomes. Whilst it is well identified that spontaneous remyelination occurs after a demyelinative insult, the degree of remyelination within MS lesions is variable; generally MS lesions remyelinate relatively efficiently early in disease; however, at later stages many lesions remain chronically demyelinated (Trapp and Nave, 2008). These chronically demyelinated lesions typically contain oligodendrocyte progenitor cells (OPCs) and premyelinating oligodendrocytes that have "stalled" in their differentiation (Franklin et al., 2012). These findings suggest remyelination is not limited by an absence of oligodendrocyte progenitors or their failure to generate oligodendrocytes, but a failure to differentiate into mature oligodendrocytes and to initiate new myelin formation.

Although the factors that inhibit remyelination in the context of MS are not fully understood, they most likely include a variety of inhibitory signals present within the lesion environment and an absence of positive signals (Franklin et al., 2012). Significant loss of axons and neurons occurs as a consequence of demyelination, which is believed to be a major determinant of the ultimate progression of MS and persistent neurological deficit (Trapp and Nave, 2008). Importantly, much of this axonal loss is thought to be secondary to the ongoing demyelination and failure of remyelination. However, available therapies for MS target the immune system to reduce the incidence of new lesion formation, but do not promote remyelination. This has led to substantial interest in developing neuroreparative therapies that directly enhance myelin repair and protect axons, to be used in conjunction with immunomodulatory therapies. However, this goal can only be rationally achieved via a better understanding of the nature of signals that regulate CNS myelination and identifying factors either promote or inhibit this process.

**Current molecular candidates to control remyelination:** Over the last two decades, a number of molecular candidates have been identified that appear, either directly or indirectly, to control myelination within the CNS. These factors include Lingo1 (Mi et al., 2005), brain-derived neurotrophic factor (BDNF) (Vondran et al., 2010; Xiao et al., 2010; Lundgaard et al., 2013), insulin-like growth factor-1 (Beck et al., 1995), members of the gp130 family of neuropoietic cytokines (Butzkueven et al., 2002) and neuregulin 1 type-III (Nave and Salzer, 2006; Lundgaard et al., 2013), fibroblast growth factors (Furusho et al., 2012). Although the extent to which these factors directly target oligodendrocytes, as opposed to exerting their effects on bystander lineages remains uncertain, a precise understanding of how these factors enhance CNS myelination has boosted the confidence of developing potential neuroreparative strategies for treating MS. Lingo1 and BDNF are two recent examples as developing pro-myelinating strategies. This is reflected by current clinical trials of neutralizing antibodies against the myelination inhibitor Lingo1 by Biogen Idec. Lingo1 is a negative regulator of neuronal survival, oligodendrocyte differentiation and myelination, axonal outgrowth and regeneration (Mi et al., 2005). Lingo1 is present on both neurons and oligodendrocytes. Blocking Lingo1 has been shown to enhance remyelination and axonal regeneration in animal models of central demyelination (Pepinsky et al., 2011). These studies have lead to the development of anti-Lingo1 antibodies to promote myelin repair and prevent axonal degeneration for clinical trials. These studies have provided important "*proof of principle*" evidence that targeting molecules expressed by oligodendrocytes and/or neurons in myelin lesion is a promising strategy to enhance myelin repair and restore nerve function to complement current immunotherapies in MS. Currently, anti-Lingo1 antibodies are under clinical trials for central demyelinating disorders such as MS. A recent published study has shown randomized phase I trials of anti-Lingo1 monoclonal antibody are safe and tolerable in both health volunteers and patients with MS (Tran et al., 2014), leading to phase II clinical trials for developing a potential anti-Lingo1 treatment in human MS. However, this approach targets one of many potential inhibitors present within the lesion environment, raising the question of whether identification of pro-myelination targets may be more effective.

BDNF has been identified as a positive regulator of CNS myelination both *in vitro* and *in vivo* (Vondran et al., 2010; Xiao et al., 2010) and it exerts its promyelinating effect *via* activating its TrkB receptors (Xiao et al., 2010). Importantly, BDNF has been found to improve both clinical outcomes and increases nervous system repair in two separate animal models of central demyelination (Makar et al., 2009; Fulmer et al., 2014). However, the utility of BDNF for therapeutic purposes is complex, as it exhibits pharmacokinetic behavior that is sub-optimal. BDNF has a relatively short half-life in the circulation, there is no strong evidence that it can readily cross the blood-brain barrier, and it has complex receptor interactions signaling through two distinct receptors: TrkB and $p75^{NTR}$ (Chao, 2003). Although there is an active search for alternative delivery strategies to overcome some of these problems, the advantages of developing small molecule mimetics of BDNF that targets TrkB are evident: small molecules can be modified to penetrate freely into the brain parenchyma, can be designed for oral administration, and can exhibit selective receptor activation. Currently there are peptide and non-peptide small molecules that have recently been developed as TrkB agonists. TDP6 is a small molecule peptide memetic of BDNF that has been shown to enhance oligodendrocyte myelination *via* TrkB *in vitro* (Wong et al., 2014). LM22A4 and Dihydroxyflavone are two non-peptide small molecule TrkB agonists that have been studied in a number of distinct neurological disease models (Massa et al., 2010; Simmons et al., 2013; Zeng et al., 2013), For example, LM22A4 reduces motor impairment and neuropathology in mouse models of Huntington's disease

(Simmons et al., 2013). However, none of these TrkB agonists have yet been studied in the context of myelination. The next would be to identify if these TrkB agonists enhance remyelination and exert a protective influence in animal models of CNS demyelination.

**Animal models of CNS demyelination:** Potential and limitation: The difficulty of identifying factors with selective remyelinating potential is compounded by the composite and complex pathology generated in some commonly used animal models of central demyelinating diseases. The most commonly used animal model for studying MS is experimental autoimmune encephalomyelitis (EAE), a T-cell mediated inflammatory demyelinating model. Of note, EAE can be induced in a variety of species including a number of susceptible mouse strains by either the systemic injection of myelin antigens or by the passive administration of autoreactive T cells (Gold et al., 2000). The exact pathology of the resultant disease differs between species and induction method, but uniformly involves inflammatory demyelination, often without a clear-cut remyelinative phase (Gold et al., 2000). On the other hand, toxin induced models of demyelination, in particular those generated by either the injection of lysolecithin, ethidium bromide or the consumption of the copper chelatorcuprizone, induce a selective oligodendrocytopathy and enable a more focused interrogation of remyelinative potential (Skripuletz et al., 2011). As no one animal model faithfully mimics all aspects of MS, the therapeutic potential of future candidate factors or approaches in promoting remyelination should be investigated in separate models of central demyelination in the context of MS.

**Neuroreparation and future directions:** Future work is still required to identify molecules and signals that directly control myelin repair. It is likely that these molecules are not acting in isolation, but rather part of a larger signaling network. Understanding the interactions between these various molecules will also decipher the precise balance between pro-myelination and anti-myelination. Precisely determining their underlying mechanisms is crucial to identify molecular targets with greater selectivity for remyelination in order to avoid off-target effect possibly compromising therapeutic potential. Emerging neuroreparative approaches that selectively target the nervous system and enhance myelin repair may one day allow for acute or post-acute treatment strategies to reverse damage inflicted by MS attacks. We hope and believe for a future in which treatment for MS will come to consist of combination immunomodulatory and neuroreparative strategies. Neuroreparative therapies remain under investigation, but are likely to become important complementary elements of MS therapy in the future.

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## References

Beck KD, Powell-Braxton L, Widmer HR, Valverde J, Hefti F (1995) Igf1 gene disruption results in reduced brain size, CNS hypomyelination, and loss of hippocampal granule and striatal parvalbumin-containing neurons. Neuron 14:717-730.

Butzkueven H, Zhang JG, Soilu-Hanninen M, Hochrein H, Chionh F, Shipham KA, Emery B, Turnley AM, Petratos S, Ernst M, Bartlett PF, Kilpatrick TJ (2002) LIF receptor signaling limits immune-mediated demyelination by enhancing oligodendrocyte survival. Nat Med 8:613-619.

Chao MV (2003) Neurotrophins and their receptors: a convergence point for many signalling pathways. Nat Rev Neurosci 4:299-309.

Franklin RJ, ffrench-Constant C, Edgar JM, Smith KJ (2012) Neuroprotection and repair in multiple sclerosis. Nat Rev Neurol 8:624-634.

Fulmer CG, VonDran MW, Stillman AA, Huang Y, Hempstead BL, Dreyfus CF (2014) Astrocyte-derived BDNF supports myelin protein synthesis after cuprizone-induced demyelination. J Neurosci 34:8186-8196.

Furusho M, Dupree JL, Nave KA, Bansal R (2012) Fibroblast growth factor receptor signaling in oligodendrocytes regulates myelin sheath thickness. J Neurosci 32:6631-6641.

Gold R, Hartung HP, Toyka KV (2000) Animal models for autoimmune demyelinating disorders of the nervous system. Mol Med Today 6:88-91.

Lundgaard I, Luzhynskaya A, Stockley JH, Wang Z, Evans KA, Swire M, Volbracht K, Gautier HO, Franklin RJ, Charles FC, Attwell D, Karadottir RT (2013) Neuregulin and BDNF induce a switch to NMDA receptor-dependent myelination by oligodendrocytes. PLoS Biol 11:e1001743.

Makar TK, Bever CT, Singh IS, Royal W, Sahu SN, Sura TP, Sultana S, Sura KT, Patel N, Dhib-Jalbut S, Trisler D (2009) Brain-derived neurotrophic factor gene delivery in an animal model of multiple sclerosis using bone marrow stem cells as a vehicle. J Neuroimmunol 210:40-51.

Massa SM, Yang T, Xie Y, Shi J, Bilgen M, Joyce JN, Nehama D, Rajadas J, Longo FM (2010) Small molecule BDNF mimetics activate TrkB signaling and prevent neuronal degeneration in rodents. J Clin Invest 120:1774-1785.

Mi S, Miller RH, Lee X, Scott ML, Shulag-Morskaya S, Shao Z, Chang J, Thill G, Levesque M, Zhang M, Hession C, Sah D, Trapp B, He Z, Jung V, McCoy JM, Pepinsky RB (2005) LINGO-1 negatively regulates myelination by oligodendrocytes. Nat Neurosci 8:745-751.

Nave KA, Salzer JL (2006) Axonal regulation of myelination by neuregulin 1. Curr Opin Neurobiol 16:492-500.

Nave KA, Werner HB (2014) Myelination of the nervous system: mechanisms and functions. Ann Rev Cell Dev Biol 30:503-533.

Pepinsky RB, Shao Z, Ji B, Wang Q, Meng G, Walus L, Lee X, Hu Y, Graff C, Garber E, Meier W, Mi S (2011) Exposure levels of anti-LINGO-1 Li81 antibody in the central nervous system and dose-efficacy relationships in rat spinal cord remyelination models after systemic administration. J Pharmacol Exp Ther 339:519-529.

Simmons DA, Belichenko NP, Yang T, Condon C, Monbureau M, Shamloo M, Jing D, Massa SM, Longo FM (2013) A small molecule TrkB ligand reduces motor impairment and neuropathology in R6/2 and BACHD mouse models of Huntington's disease. J Neurosci 33:18712-18727.

Skripuletz T, Gudi V, Hackstette D, Stangel M (2011) De- and remyelination in the CNS white and grey matter induced by cuprizone: the old, the new, and the unexpected. Histol Histopathol 26:1585-1597.

Tran JQ, Rana J, Barkhof F, Melamed I, Gevorkyan H, Wattjes MP, de Jong R, Brosofsky K, Ray S, Xu L, Zhao J, Parr E, Cadavid D (2014) Randomized phase I trials of the safety/tolerability of anti-LINGO-1 monoclonal antibody BIIB033. Neurol Neuroimmunol Neuroinflamm 1:e18.

Trapp BD, Nave KA (2008) Multiple sclerosis: an immune or neurodegenerative disorder? Annu Rev Neurosci 31:247-269.

Vondran MW, Clinton-Luke P, Honeywell JZ, Dreyfus CF (2010) BDNF$^{+/-}$ mice exhibit deficits in oligodendrocyte lineage cells of the basal forebrain. Glia 58:848-856.

Wong AW, Giuffrida L, Wood R, Peckham H, Gonsalvez D, Murray SS, Hughes RA, Xiao J (2014) TDP6, a brain-derived neurotrophic factor-based trkB peptide mimetic, promotes oligodendrocyte myelination. Mol Cell Neurosci 63C:132-140.

Xiao J, Wong AW, Willingham MM, van den Buuse M, Kilpatrick TJ, Murray SS (2010) Brain-derived neurotrophic factor promotes central nervous system myelination via a direct effect upon oligodendrocytes. Neurosignals 18:186-202.

Zeng Y, Wang X, Wang Q, Liu S, Hu X, McClintock SM (2013) Small molecules activating TrkB receptor for treating a variety of CNS disorders. CNS Neurol Disord Drug Targets 12:1066-1077.