World Journal of Neurology

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DOI: 10.5316/wjn.v5.i1.5

World J Neurol 2015 March 28; 5(1): 5-16
ISSN 2218-6212 (online)

REVIEW

Targeting remyelination treatment for multiple sclerosis

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Author contributions: All authors contributed to this work.
Conflict-of-interest: There is no conflict of interest on the part of any author of this manuscript.

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Received: September 28, 2014
Peer-review started: September 29, 2014
First decision: October 21, 2014
Revised: December 9, 2014
Accepted: December 18, 2014
Article in press: December 19, 2014
Published online: March 28, 2015

Abstract

Since disability in multiple sclerosis (MS) is a product of neurodegeneration and deficient remyelination, the ability to enhance neuroregeneration and myelin regeneration in MS is an enticing goal for MS drug development. In particular, remyelination treatments could promote return of neurological function and also prevent further axonal loss and neurodegeneration in MS due to trophic effects of myelin. The study of remyelination has advanced dramatically in the last several years such that a number of pathways inhibiting remyelination have been discovered, including those involving LINGO-1, Notch-1, hyaluronan, retinoid X receptor, and wnt/ß-catenin. Other approaches such as high throughput drug screening for remyelination drugs have caught fire, with identification of dozens of known drugs with oligodendrocyte maturation stimulatory effects. Several drugs identified through screens and other mechanisms are in the process of being further evaluated for remyelination in MS and MS models. We discuss the potential molecular targets and the variety of mechanisms towards drug identification and development in remyelination for MS.

Key words: Multiple sclerosis; Myelin; Remyelination; Oligodendrocyte; Repurposing; Treatment

Core tip: Over the last several years numerous remyelination pathways important to multiple sclerosis (MS) have been identified, including those of LINGO-1, hyaluronan, Notch-1, retinoid X receptor receptor, and wnt/ß-catenin. Newer discoveries include the pathways involving Chemokine (C-X-C Motif) ligand 12/C-X-C chemokine receptor type 4 and G protein-coupled receptor 17, and the involvement of Endothelin-1 in the Notch pathway. High-throughput screens have identified multiple antimuscarinic drugs with good remyelination. Also identified by screens, clemastine, with similar antimuscarinic but also antihistamine effects, may be useful in remyelination in MS. Drug repurposing, through screens or more serendipitously, has found that many drugs could enhance remyelination, including benztropine, clemastine, quetiapine, fasudil, olesoxime, and ibudilast, among others.

Nadeem M, Sklover L, Sloane JA. Targeting remyelination treatment for multiple sclerosis. *World J Neurol* 2015; 5(1): 5-16 Available from: URL: http://www.wjgnet.com/2218-6212/full/v5/i1/5.htm DOI: http://dx.doi.org/10.5316/wjn.v5.i1.5

INTRODUCTION

Multiple sclerosis (MS) is a debilitating disease of the central nervous system (CNS) that affects nearly 2.5

million people worldwide and is characterized by the predominant presentation in young women compared to men[1]. It manifests through an autoimmune inflammatory response which damages the protective myelin coating on axons, leading to disrupted neurological functioning[1]. Continued relapses can lead to irreversible damage within the CNS, driving clinical deterioration[2]. The MS spectrum ranges from 50%-85% of people initially diagnosed with MS beginning with the relapsing-remitting form of MS (RRMS); after approximately 10-20 years, most patients with RRMS transition to secondary progressive MS which is characterized by irreversible neurological decline[3]. MS takes a toll both physically and mentally within the patients, leading to a disease that requires management entailing high financial costs to both patients and health care systems.

The basis of neurological disability arises from neurodegeneration, defects in myelination, and continued inflammation[1]. Neurodegeneration develops over time in MS patients as a consequence of autoimmune inflammation and incomplete remyelination. Since myelin is attacked by autoimmune inflammation, damage can be primarily demyelination with axonal preservation, and this alone can cause neurological dysfunction unless repaired.

No drugs are currently in use to help prevent neurodegeneration or poor remyelination in MS. Drugs currently approved by the Food and Drug Administration (FDA) for MS treatment are immunomodulators/immunosuppressors that prevent or limit inflammation from occurring but do not directly repair damage already incurred on axons and myelin. Understanding that neurodegeneration and poor remyelination is the primary source of disability in MS, there is avoid in MS treatments aimed at remyelination in MS. This paper outlines the search for remyelination enhancing agents through drug repurposing and high throughput screens aimed at isolating an agent that removes the roadblocks to remyelination in the MS CNS.

NATURAL REMYELINATION IN MS

Remyelination can be a natural reparative mechanism in MS. Remyelination appears to require activation of oligodendrocyte progenitor cells (OPCs), recruitment of OPCs to lesions, and cellular differentiation of OPCS to become myelin-producing oligodendrocytes[4]. Remyelination occurs in the brains of some MS patients though not as complete as to allow for full return of normal function. In one post-mortem study, MS white matter lesions were 47% remyelinated on average and 22% of them were found to be fully remyelinated. This points to the existence of remyelination mechanisms even during late stages of disease[5]. However, this and other data indicate that remyelination is incomplete in the majority of cases.

It cannot be overstated that remyelination should lead to a host of benefits to the MS patient. Remyelination can strengthen function by reestablishing electrical communication between neurons and prevent further neurodegeneration through trophic support of neurons and axons[1]. Research targeting remyelination drug therapy requires an understanding of the reasons why natural remyelination eventually fails in patients with MS.

APPROACHES IN REMYELINATION DRUG DEVELOPMENT

The timeline for taking a drug from the laboratory to the consumer market is long and costly, creating a situation of diminishing returns and leading to the focus on the repurposing of existing, proven drugs. In general, novel drugs experience 1-6 years of preclinical development, 6-11 years of clinical trials, and then 0.6-2 years for FDA approval, for a total of 7.6-19 years. Sometimes drug development occurs rapidly, as was the case of natalizumab, first identified as a potential MS treatment in 1999[6] and winning FDA approval in 2004.

Drug repurposing (also referred to as repositioning or re-profiling) utilizes existing drugs for the treatment of a disease that was not the drug's original target. These drugs have already passed through pre-clinical and clinical stages of testing examining safety profiles and tolerability, which streamlines the process to finding treatments[7]. For example, metformin, a commonly prescribed drug for diabetes, may be suggested as a chemotherapeutic agent given its association with decreased mortality in cancer patients[8]. The antimalarial drug chloroquine may have important anticancer properties[9]. First introduced in 1957 for its antiemetic and sedative properties, thalidomide has since been repurposed for multiple myeloma treatment[10]. Interestingly, dimethylfumarate was originally in use since 1959 for psoriasis[11], was repurposed for MS treatment in 2004, went straight to phase 2 trials, and recently won FDA approval for MS treatment in 2013. Thus, while there was a long delay in repurposing dimethylfumarate, FDA approval of repurposed drugs like dimethy fumarate can occur relatively rapidly after selection for MS clinical trials.

This method of borrowing from both similar and dramatically different diseases' existing drugs creates an environment where the costly overhead of research and development and clinical trials can be eliminated. Drug repurposing can be implemented in searching for a remyelination-enhancing agent in MS even many years after they are brought to market for other applications. Since many candidate drugs already exist for repurposing, high throughput screens should be particularly amenable to drug discovery. Ultimately, repurposing provides a faster and more productive way to search for and isolate a viable remyelinating agent for MS.

Though more difficult, it may also be possible to devise novel drugs that attack specific pathways involved in remyelination in MS. High throughput screens could

Table 1 Known pathways affecting remyelination in multiple sclerosis

Pathway	Potential protein targets	Drugs	Ref.
Hyaluronan	TLR2	TLR2 Ab (OPN-305)	[28]
	Hyaluronidase	Vcpal	[28,30]
Notch-1	Notch-1	(pan) BMS-906024	[14,15,17,19]
	Jagged-1	-	[14]
	Endothelin-1	PD142,893, sitaxentan, ambrisentan, atrasentan, BQ-123, zibotentan, bosentan, macitentan, tezosentan	[17]
	γ-secretase	MW167, LY450139	[93]
Retinoid X receptor	RXR-γ	Bexarotene, IRX4204	[31]
Wnt/ß-catenin	ß-catenin	PKF118-744, CGP049090, PKF118-310, XTM000990, BC21, PKF115-584, PNU-74654	[21,22]
	Tankyrases 1-2	XAV939, IWR1, JW74, JW55	[57]
	GSK3ß	SB216763	[20]
LINGO-1	LINGO-1	Anti-LINGO-1 Ab	[23-25]
CXCL12/CXCR4	CXCR7	CCX771	[37,38]
	CXCR4	AMD3100	[37,38]
GPR17	GPR17	Unnamed	Omeros

TLR2: Toll-like-receptor 2; GPR17: G protein-coupled receptor 17; CXCL4: C-X-C chemokine receptor type 4; CXCL12: Chemokine (C-X-C Motif) ligand 12.

be designed around specific components of the identified pathway as a surrogate assay for remyelination. As described below, several pathways have been identified that control remyelination in MS and relevant animal models. With characterization of the molecular components of these pathways, it may be possible to design novel drugs or repurpose old drugs targeting these pathways to enhance remyelination in MS. In a review of the literature, both novel drug discovery and existing drug repurposing are being utilized in drug development in MS.

KNOWN REMYELINATION PATHWAYS IN MS

One of the most prominent issues with inhibited remyelination is that recruited progenitors fail to mature after they are recruited to the lesion site[12]. Multiple mechanisms are proposed for the blockade of OPC maturation, including pathways involving Notch-1, Wnt, LINGO-1, hyaluronan, and Retinoid X receptor (RXR) receptor (see Table 1). One of the first pathways to be identified was involving Notch-1, which responds to a broad array of ligands including Jagged1, Delta, Contactin, and Endothelin-1[13-17]. Originally increased Jagged1 expression was noted in reactive astrocytes stimulated with TGF-ß1[14]. Borders of acute MS lesions exhibited increased expression of Jagged1, Notch-1, and inhibitory basic helix-loop-helix protein, Hes5, suggesting the presence of active Jagged1/Notch-1 signaling.

However, followup *in vivo* work was initially more contradictory, with conditional deletion of Notch-1 in PLP+ oligodendrocytes having no effect on remyelination in the cuprizone model of demyelination/remyelination[18]. Because PLP+ oligodendrocytes may be too far along in maturation to respond to Notch-1 signaling, conditional deletion of Notch-1 in CNP+ oligodendrocytes was performed, and this did in fact show precocious oligodendrocyte maturation[19]. Similarly, conditional deletion of Notch-1 in Olig2 oligodendrocytes also promoted premature oligodendrocyte maturation[19]. Remyelination was more extensive after lysolecithin demyelination in these mice as well. More recently, Endothelin-1 expression by astrocytes appears to limit oligodendrocyte through Notch-1 signaling in animal models of remyelination[17]. However, contactin is increased in MS lesions and induces myelin-associated glycoprotein (MAG) upregulation after Notch-1 stimulation[15], suggesting different opposing effects of Notch-1 on oligodendrocyte maturation. If the inhibitory effect of Notch-1 can be better characterized, there may be an opportunity to target this pathway to enhance remyelination in MS, as inhibitors to Notch, Endothelin-1 and gamma-secretase exist and have been studied in humans for other conditions (Table 1).

The canonical wnt signaling pathway has also been identified for remyelination purposes[20-22]. Although the developmental role of the wnt pathway in oligodendrocyte maturation has been known for some time, the involvement of the wnt pathway was more recently uncovered in a mouse lysolecithin injection model by in situ screens of 1040 transcription factors[21]. Three additional murine multiple sclerosis models were used to confirm the role of the wnt pathway in remyelination, including lysolecithin injection, cuprizone intoxication, and ethidium bromide injection models. TCF4 a major transcription factor involved in wnt signaling, is expressed in OPCs in demyelinated lesions. A transgenic mouse expressing dominant negative TCF4 exhibited normal OPC development but grossly impaired oligodendrocyte maturation[22]. Dominant active ß-catenin in Olg2+ cells showed decreased mature oligodendrocytes in spite of normal oligodendrocyte numbers, as well as evidence of reduced myelination in development[21]. Olig1+ specific knockout of ß-catenin also induced premature oligodendrocyte development[22]. Since Wnt pathway activation and protein expression was observed in MS lesions[21], it remains possible that the wnt pathway controls remyelination in MS.

There are multiple drugs identified that target

wnt and ß-catenin and can be assessed for effects on remyelination *in vivo*. Other targets in the wnt/ß-catenin cascade, including disheveled, axin, and porcupine, could be involved in limited OPC maturation. There are many small molecular weight drugs in clinical trials or approved for human use that modulate the functions of these proteins and wnt signaling as well, including sulindac (disheveled), bosutinib (Src kinase inhibitor) and imatinib (tyrosine kinase inhibitor) (Table 1).

Leucine rich repeat and Ig domain containing 1 (or LINGO-1) has also been shown to limit oligodendrocyte maturation and remyelination[23-25]. Upregulation and downregulation of LINGO-1 expression restricts and enhances features of oligodendrocyte maturation *in vitro*[23-25]. Functional blockade of LINGO-1 through blocking antibodies or dominant negative LINGO-1 enhances myelin sheet formation, induction of MBP expression, and myelination *in vitro*[23-25]. The repressive effect of LINGO-1 appears to work through downstream activation of a rho kinase (ROCK)[25]. *In vivo* overexpression of LINGO-1 reduces cord myelination[26]. Conversely, LINGO-1 KO mice show increased myelination in development and oligodendrocyte cultures contain an increased percentage of mature oligodendrocytes[25]. Antibody blockade of LINGO-1 enhances remyelination in EAE when given after peak disease activity, indicating an effect on remyelination processes rather than immune functions most likely[23]. Remyelination is also enhanced by anti-LINGO-1 antibody treatment in other models, including the lysophosphatidylcholine injection and cuprizone models[24]. Clearly, there is great potential for anti-LINGO-1 treatment in MS and phase 1 clinical trials are now underway (NCT01052506 and NCT01244139) (Table 1).

The glycosaminoglycan hyaluronan (HA) also inhibits OPC maturation[27,28]. Our group found that HA blocked OPC maturation in a dose-dependent manner[28]. Because specific Toll-Like-Receptor 2 (TLR2) agonists blocked OPC maturation, HA was suspected to act through TLR2 on oligodendrocytes. This suspicion was confirmed when TLR2-blocking antibodies ablated the effects of HA on OPC maturation. The downstream signaling of TLR2 was also implicated when small molecular weight inhibitors of MyD88 and IRAK1/4 also ablated the effects of HA *in vitro*. When lysolecithin and HA were injected into TLR2-null mice, enhanced remyelination occurred compared to wild-type mice. These findings indicate that HA acts on TLR2 to inhibit OPC maturation.

Our work further implicated hyaluronidase in the hyaluronan pathway. Our group suspected that high molecular weight (HMW) HA must be converted to low molecular weight (LMW) HA in order to act on TLR2, since both LMW and HMW HA block OPC maturation though only LMW is known to stimulate TLR2[28,29]. Only complete degradation of HMW HA by both hyaluronidase and ß-glucuronidase neutralized the effects of HA on OPCs by completely degrading all sources of HA. Ascorbate 6-hexadecanoate (Vcpal), a hyaluronidase inhibitor, cultured with OPCs and HMW HA allowed OPC maturation to proceed normally by limiting the conversion of HMW HA to LMW HA[28]. This effect of Vcpal was confirmed *in vivo*[30]. Based on these exciting findings, hyaluronidase inhibition should be further evaluated for remyelination effects in MS (Table 1).

Retinoid X receptor gamma (RXR-γ) has been implicated as a positive regulator in CNS remyelination[31]. RXR-γ is a nuclear receptor that dimerizes with other receptors, including retinoic acid receptors, thyroid hormone receptors, vitamin D receptors, and peroxisome proliferator activator receptors to regulate cell differentiation, proliferation, and apoptosis[32]. In MS, RXR-γ expression increases in the nuclear component of OPCs in active lesion borders but is lowered in chronic inactive lesions, suggesting RXR-γ plays a positive role in remyelination. RXR-γ is also strongly upregulated after demyelination from lysolecithin injection. Knockdown of RXR-γ expression in OPCs promotes simple undifferentiated cellular morphology compared to controls. *In vitro* testing of RXR-selective antagonists (HX531 and PA452) with OPCs reduced MBP expression. In contrast, 9-*cis*-retinoic acid, an RXR activator, increased the number of MBP+ membrane sheets in culture. *In vivo* testing showed an increased level of CC1+ differentiated oligodendrocytes and thicker myelin sheaths after 9-*cis*-retinoic acid treatment[31].

In mouse models of Alzheimer's disease, the RXR agonist bexarotene improved cognitive functioning and decreased amyloid-β plaque burden[33]. Bexarotene also has positive effects in shizophrenia[34] and cutaneous T cell lymphoma[35]. Though bexarotene nonspecifically acts on all retinoid X receptors, testing in MS patients can confirm whether bexarotene may be successful in promoting remyelination in MS. Other RXR agonists including IRX4204 may be immediately useful in clinical trials of remyelination in MS, although more preclinical work needs to be performed (Table 1)[36].

Recently, certain chemokines have been identified that modulate remyelination, although effects on inflammation are likely also involved. CXCL12 promotes remyelination by acting on the receptor CXCR4 on OPCs. The recently discovered scavenge receptor for CXCL12, CXCR7 limits the availability of CXCL12 to act on CXCR4[37]. During demyelination in cuprizone-fed animals, both receptors and CXCL12 were elevated above levels in control animals[38-41]. During remyelination phase, CXCR7 expression returns to normal while CXCR4 and CXCL12 remain elevated. CXCR7 appears to regulate the availability of extracellular CXCL12. When CCX771, a CXCR7 antagonist, was given to animals during weeks three to six (remyelination phase) of a six week cuprizone-infused diet, levels of CXCL12 and ligand activated CXCR4 were elevated in the corpus callosum. Once mice were allowed to remyelinate after cessation of the cuprizone and CCX771, mice showed significantly increased numbers of GST-pi+ (mature oligodendrocyte marker) cells and increased myelin oligodendroglial

glycoprotein (MOG) expression and myelin staining. The improvement was shown to occur through CXCR4 activation by CXCL12 when a CXCR4 antagonist blocked remyelination. Increased remyelination also correlated with CXCR4 phosphorylation[38]. In EAE, CCX771 also lead to significant decrease in peak severity of disease. The antagonist ultimately preserved axonal integrity as found through diffusion tensor imaging[37]. Antagonism of CXCR4 increased disease activity while antagonism of CXCR7 significantly decreased disease severity in the mice model of experimental autoimmune neuritis based on clinical scores[41]. Thus, treatments that either enhance CXCR4 stimulation or block CXCR7 may be useful in enhancing remyelination in MS (Table 1).

The Uracil nucleotide/cysteinyl leukotriene receptor [(also known as the G-protein coupled receptor 17 (GPR17)] is known to be involved with OPC differentiation and is activated by uracil-nucleotides (UDP-sugars) and cysteinyl-leukotrienes LTC4 and LTD4[42,43]. GPR17 mRNA levels peak in conjunction with rising MBP levels in maturing OPC cultures. In morphologically mature oligodendrocytes, GPR17 expression then decreases to very low levels. Since UDP-glucose increased the number MBP expressing cells and GPR17 expression is highest in OPCs, it was initially thought that GPR17 plays a stimulatory role in the early stages of differentiation[44]. Complicating its role in oligodendrocyte biology, GPR17 also appears to play a role in OPC migration as GPR17 antagonist prevented migration[45].

Though scientists are convinced that GPR17 activation could enhance therapy for demyelinating diseases, the role of GPR17 in remyelination is accompanied by much debate because GPR17 expression and activation is also thought to arrest progenitors in a premature state. GPR17 overexpressing transgenic mice showed significant reduction in MBP and PLP1 expression. Prolonged overexpression in the transgenic mice resulted in differentiation arrest or apoptotic cell death compared to WT animals[46]. These *in vivo* data countered understanding that GPR17 plays a positive role in OPC maturation and instead supported the idea that GPR17 arrests CNS cells at a pre-myelination stage. However, efforts towards creating a safe and effective GPR17 antagonist were put into motion once the GPR17 activator MDL29951 inhibited oligodendrocyte maturation in culture[47]. As part of its G-protein coupled receptors (GPCR) program, the biopharmaceutical company Omeros significantly increased mean clinical scores using GPR17 antagonists in EAE animals. Identification and evaluation of GPR17 modulators in multiple remyelination models is needed to fully evaluate for remyelinating effects (Table 1).

Other factors also play a role in remyelination and may inhibit oligodendrocyte maturation. Chondroitin sulphate proteoglycans (CSPGs) that exist on the surface of terminally differentiated oligodendrocytes inhibit growth responses using the Rho/ROCK/LIMK cascade[48]. Klotho expression in brain decreases with age and enhances oligodendrocyte maturation as well as cognitive benefits[49]. Axonal damage can also result in the accumulation of myelin-associated inhibitors or myelin debris that inhibits OPC differentiation[50,51]. Efficient phagocytic removal of myelin debris is required for remyelination to occur[50,52]. The extent of overlap among these mechanisms is still unclear. Furthermore, drugs that modulate these additional pathways could be discovered through high throughput screens, such as with Klotho[53].

HIGH THROUGHPUT SCREENS FOR REMYELINATION INDUCING DRUGS

High throughput screening is a rapid method for identifying drugs that may be useful in treating disease. One of the difficulties in remyelination research is what screens would be useful for screening and modeling aspects of remyelination. Initial screens using zebrafish were complicated by multiple effects of drugs on OPC proliferation (olig2 counts) as well as maturation (MBP expression)[54]. With this screen several drugs were identified that increase OPC proliferation but none that enhanced maturation. Since OPC maturation is essential for remyelination and may be blocked in MS, high throughput screens utilizing OPC cultures examining markers of maturation has been identified as a more streamlined method of identifying drugs. Several drugs have been discovered using this approach recently, including benztropine[55] (Table 2).

Through use of an OPC maturation screen, benztropine was found to be a potent inducer of differentiation based on the expression of MBP and MOG *in vitro*[55]. Benztropine is a muscarinic receptor antagonist used for the treatment of Parkinson's disease and readily crosses the blood brain barrier (BBB). Cells expressed the highest level of MBP after treatment given at an immature state suggesting that the compound acts most effectively on the cells at an early stage of differentiation. In cuprizone induced demyelination and in EAE experiments, benztropine improved clinical outcomes and myelin content indicating enhancement of remyelination rather than immune effect[55].

However, benztropine is associated with dose-dependent side effects including tachycardia, paralytic ileus and urinary retention[55,56]. Although benztropine may need to be dosed at unsafe levels to be effective in MS remyelination, clinical trials in MS patients could help determine whether a safe dosage effective in promoting remyelination does indeed exist.

Based on the findings that oligodendrocytes can myelinate paraformaldehyde fixed axons as well as electron-spun nanofibers, micropillar arrays were fabricated to assess myelination drugs in a high throughput format[57] (Table 2). OPCs bound to micropillars and matured into oligodendrocytes that wrapped the micropillars. Similar to the work of Deshmukh *et al*[55], this group found a cluster of antimuscarinic compounds including benztropine that enhanced oligodendrocyte

Table 2 Drug classes identified in remyelination screens

Drug class	Compounds	Ref.
Adrenergic agonist	Methoxamine, nerepinephrine, tolaxoline, salmeterol	[55]
Dopamine antagonists	Opipramol, flupentixol, fluphenazine, trifluoperazine, perphenazine, quetiapine	[55,57]
Dopamine uptake inhibitor/dopamine agents	Vanoxerine, GBR12935, methyldopa	[55]
Histamine antagonists	Clemastine, doxylamine, clemizole	[55,57]
Adrenergic antagonist	Opipramol, trifluoperazine, Cgp-26505, tolazoline, quetiapine	[55,57]
Anticholinergics/cholinesterase reactivators	Homatropine, clemastine, benztropine, disopyramide, trospium, diacetyl-monoxime, tiotropium, oxybutynin, atropine, ipratropium, hyosamine, atropine, methy atropine, octatropine, glycpyrrolate, carbetapentane, piperildolate, bevonium, propiverine, dicyclomine, mepenzolate, trihexylphenidyl	[55,57]
Phosphodiesterase inhibitor	8-bromo cyclic GMP, IBMX, enprofylline, enoximone, rolipram	[55]
PPAR agonist	GW-1929	[55]
Ion channel blockers	Gabapentin, 8-aminobenzoic acid, disopyramide, oubain	[55]
Serotonin modulators	Brl-15572, paroxetine, clemizole, quetiapine	[55,57]
Glutamate receptor antagonist	UPF-523, l-aminodan-1,5-dicarboxylic acid	[55]
Beta-catenin inhibitor	XAV939	[55]
Retinoic acid receptor agonist	Retinoids, AM580	[55,94]
Thyroid hormone receptor agonist	T3	[55,57]
COX-2 inhibitors	Niflumic acid, flunixin	[55]
HMG-CoA reductase Inhibitor	Mevastatin, simvastatin	[55]
Rho kinase inhibitor	Ml-7, Ml-9, fasudil	[55,63,94]
Antifungal/antibacterial	Ketoconazole	[55]
Cathartic/emetic	Emetine	[55]
Opioid antagonists	Levallorphan	[55]
Glucocorticoids	Dexamethasone, hydrocortisone, budesonide, flunisolide	[94]
EGF/ErbB2 inhibitor	PD174265	[94]

PPAR: Peroxisome proliferator activator receptor. COX-2: Cyclooxygenase-2; HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A; EGF: Epidermal growth factor.

maturation and wrapping. Clemastine, an antihistamine compound with antimuscarinic properties, and quetiapine, an atypical antipsychotic, were also identified.

Through use of a DRG/oligodendrocyte coculture system, clemastine and benztropine were both shown to enhance myelin formation. After lysolecithin-induced demyelination, clemastine enhanced remyelination of cord lesions. Since clemastine is a safe over the counter drug (Tavist), clemastine is an exciting prospect for remyelination in MS. A phase 2 clinical trial has just begun (NCT02040298) and aims to study improvement in visual evoked potentials as well as myelin water volume and magnetization transfer ratios by MRI. Interestingly, GlaxoSmithKline is also conducting a phase 2 clinical trial (NCT01772199) largely in Europe that examines the effect of a histamine 3 receptor antagonist GSK239512 on remyelination in MS also through changes in magnetization transfer ratios. Further use of these high throughput screens may continue to identify additional targets beyond antimuscarinic (benztropine), antihistamine (clemastine), and antidopamine (quetiapine) pathways.

DRUGS IN SEARCH OF A MECHANISM

Another approach to generating drugs to help remyelinate MS brains has been a shotgun approach of generating, isolating, and identifying monoclonal antibodies with remyelinating effects. Beginning in 1987, the possibility was explored that monoclonal antibodies generated against myelin antigens might have a reparative and remyelinating effect. This work has continued to the present and has generated at least one viable antibody rHIgM22. However, a flaw in this approach is that mechanism of action is often hard to identify, as has been the case with rHIgM22.

In 2000, this line of work identified several human IgM antibodies, including rHIgM22, that enhance myelin formation from patients with Waldenstrom's macroglobinemia[58]. Once *in vivo* data confirmed its reparative properties, rHIgm22 became a very promising solution for impaired remyelination in MS because of its potency and safety. Virus-induced Theiler's murine encephalitis animals significantly reduced in clinical severity with rHIgM22 treatment at the smallest effective dose of 500 ng[59]. Volumetric measurements of spinal cord lesions revealed reduction in lesion size by 83% of all lesions. Biotinylated rHIgM22 was also able to pass the blood-brain-barrier in animals[60]. The half-life of rHIgM22 was determined to be 15.4 h and the antibody was cleared form the systems of animals within a short 48 h[61]. The short half-life and small effective dose of rHIgM22 amplified excitement for a drug with a low probability of causing adverse effects.

The mechanism through which rHIgM22 works is still unknown though *in vitro* data has identified key players working in conjunction with rHIgM22. rHIgM22 binds to the surface of oligodendrocytes though exactly what the antibody binds to is unknown[61]. In mature oligodendrocyte cultures, rHIgM22 highly co-localized with the αv integrin β3 and partially co-localized with integrin β1. Integrins are cell surface

Table 3 Repurposed drug potential for remyelination

Drug	Safety	BBB	*In vitro* effects	*In vivo* effects	MS trials	Mechanism
Quetiapine	+	+	+	+	NCT02087631	Atypical antipsychotic
Fasudil	+	NA	+	+		ROCK Inhibitor
Olesoxime	+	+	+	+	NCT01808885	Mitochondrial permeability transition pore modulator
Ibudilast	+	+	+	+	NCT01982942 NCT01910259	Phosphodiesterase PDE4 inhibitor
Simvastatin	+	+	+/-	+/-	NCT00647348	HMG-CoA reductase inhibitor
Lovastatin	+	+	+	+		HMG-CoA reductase inhibitor
Clemastine	+	+	+	+	NCT02040298	Antihistamine
IRX4204	NA	+	+	NA		Retinoid X receptor agonist
Bexarotene	+/-	+	-	-		Retinoid X receptor agonist
Benztropine	+/-	+	+	+		M1/M3 muscarinic receptor antagonist

BBB: Blood brain barrier; ROCK: Rho kinase; NA: Not available; MS: Multiple sclerosis; HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A.

proteins that are involved with signaling for cell migration and differentiation. rHIgM22 also blocked oligodendrocyte apoptosis in culture based on reduction of caspase 3 and caspase 9 cleavage. Decreased MBP and MOG expression *in vitro* clarified rHIgM22's primary mechanism, which is counterintuitive. rHIgM22 primarily provides protection from cell death while also delaying differentiation. The delayed differentiation is thought to occur through growth factor mediated inhibition that keeps cells in a proliferative state[61]. Finally, it was recently found that rIgM22 effects require PDGF to increase OPC proliferation[62]. While its *in vivo* data seem very promising, more work is required to establish mechanism of action for rIgM22. Results from the ongoing rHIgM22 phase 1 clinical trial will also begin in early 2015 (Acorda Therapeutics).

REPURPOSING DRUGS FOR REMYELINATION

Discovery of remyelination drugs may be rational by dissection of known pathways, may be through drug screens, but may also be through a more serendipitous pathway. We discuss here known drugs studied for other diseases or conditions that were also assessed for effects in remyelination or MS models. While there may be others, we will discuss fasudil, quetiapine, ibudilast, and olesoxime. Simvastatin and lovastatin are possibly also useful in remyelination although they may benefit MS outcomes through other mechanisms (Table 3).

Fasudil is ROCK inhibitor used for the treatment of vascular disease[63]. ROCK-II, the downstream effector of RhoA, phosphorylates molecules responsible for actin filament regulation[64]. Fyn-1 kinase acts on the GTPase RhoA which plays a role in oligodendrocyte morphology[65]. When OPCs were cultured with fasudil and myelin protein extracts inhibitory to oligodendrocyte differentiation, oligodendrocyte differentiation proceeded more rapidly[63]. In the presence of myelin protein extracts, neonatal rat OPCs showed decreased activation of Fyn-1 and increased levels of both GTP bound RhoA and activated ROCK-II[48]. siRNA mediated gene silencing or inhibitors of the RhoA- ROCK-II pathway induced OPC differentiation in the presence of inhibitory myelin debris[63]. It is also important to note that the ROCK inhibitors Y-27632, fasudil and dimethylfasudil increased neurite outgrowth dose-dependently in neurons cultured with CSPGs[48,66]. Thus, ROCK inhibitors including fasudil may benefit MS in that these treatments may induce more remyelination as well as axonal regrowth and neuroregeneration.

Another medication that should be evaluated for repurposing for MS remyelination is quetiapine, an atypical antipsychotic approved for the treatment of schizophrenia and acute bipolar disorder[67,68]. *In vitro* data shows that quetiapine facilitates oligodendrocyte lineage development[69]. The cuprizone animal model treated with quetiapine, though analyzed for locomotive and hyperactive indicators of schizophrenia, showed increased MBP expression positively correlated with length of time the drug was administered post-cuprizone recovery. Quetiapine increased the number of mature oligodendrocytes in treated animals compared to vehicle-treated controls suggesting quetiapine enhances both oligodendrocyte maturation and survival[70]. Apart from sedative effects, this drug has been generally well tolerated in patients with Parkinson's and Alzheimer's disease but clinical trials are needed to test safety, tolerability and efficacy in patients with MS[71,72]. A phase I/II trial is underway in Canada for this purpose (NCT02087631).

Ibudilast is an anti-inflammatory drug used in the treatment of asthma and stroke in Japan. Because of its anti-inflammatory effects, Ibudilast was first investigated for effects in EAE[73]. Prophylactic ibudilast treatment ameliorated severity of EAE but did not modify disease if given after disease onset. Mechanism of action appeared to be through limiting inflammatory infiltrate with mild suppression of T cell proliferation in regional lymph nodes. However, a phase 2 trial in relapsing remitting MS showed no beneficial effect of ibudilast both in terms of relapse rate and formation of new MRI lesions in a 12 mo interval[74]. A neuroprotective effect was postulated since a significant reduction in brain atrophy and in number of persistent T1 "black holes" was observed. No analysis was possible

to differentiate neuroprotective, neuroregenerative, or remyelinative effects.

More recent data also indicate rolipram, a PDE4 phosphodiesterase inhibitor like ibudilast, promotes OPC differentiation and remyelination *in vivo*[51]. Rolipram is postulated to negate effects of myelin protein extracts on inhibiting remyelination. Unfortunately, rolipram was ineffective and poorly tolerated in phase 2 relapsing remitting MS trials[75]. Since ibudilast is more potent than rolipram in PDE4 inhibition, there is hope that ibudilast will be more effective at more tolerable dosing. Several phase 2 trials are underway in MS patients, including a NeuroNext trial (NCT01982942) and the MS-SMART trial in England (NCT01910259) that will examine amiloride, rilozole, and ibudilast. Both trials will examine magnetization transfer ratio by MRI and this may detect effects on remyelination.

A HMG-CoA reductase inhibitor used for hypercholesterolemia, simvastatin has had mixed results in remyelination studies. Simvastatin promoted elaboration and extension of OPC and oligodendrocyte processes followed by process retraction days after. Longterm simvastatin treatment of OPCs worsened cell process elaboration. Cell process retraction could however be rescued by the addition of cholesterol[76]. Simvastatin use in cuprizone models of remyelination also raised concerns about deleterious effects of simvastatin on remyelination. After demyelination by cuprizone, animals treated with simvastatin exhibited significantly less remyelination compared to controls. Simvastatin treatment appeared to maintain OPCs in an immature state with no apparent effects on overall OPC numbers. Overall, simvastatin did not promote maturation and may have even been deleterious in the cuprizone model.

Cholesterol depletion as a consequence of using simvastatin could disrupt the functioning of lipid rafts that play a role in the remyelination process[77]. Simvastatin belongs to the group of lipophilic statins that are known to reduce levels of the lipid raft marker flotillin; decreased flotillin suggests that raft-associated proteins cannot access the membranes after statin treatment[78]. Because of promising anti-inflammatory response in EAE animals[79], simvastatin did however move towards clinical trials mainly in secondary progressive MS[80]. In a 2004 study, RRMS patients were given a daily 80 mg dose of simvastatin over the course of six months. MRI analysis concluded that Gadolinium-enhancing lesion volume shrank by an average of 41% after treatment[81]. A more recent secondary progressive study on simvastatin (MS-STAT; NCT00647348) showed for the first time a dramatic benefit in clinical and MRI outcomes[82]. The average brain atrophy rate significantly decreased in the simvastatin-treated group. Expanded Disability Severity Scale scores at 24 mo were also lower than placebo (average 5.93 *vs* 6.35)[82]. At present, it is not entirely clear the mechanism through which patients on simvastatin benefited, although anti-inflammatory effects are most likely.

Another blood-brain barrier permeable lipophilic statin, lovastatin may also be considered for MS clinical trial testing. In EAE animals treated with lovastatin, MBP, proteolipid protein (PLP), MOG, and MAG expression increased compared to EAE controls though expression did not match the healthy controls[83]. Lovastatin also reduced gadolinium-enhancing lesion load in MS patients, suggesting an anti-inflammatory effect[84]. Although there is some controversy about effects on myelin formation, the statin class of drugs may provide neurologists with orally deliverable agents for secondary progressive MS and possibly for remyelination.

Olesoxime has just recently been shown to prevent progressive loss of motor function in individuals with spinal muscular atrophy and could also be considered for the treatment of MS. Olesoxime has shown promise by increasing the area of myelinated axons in mouse forebrain slice cultures by approximately 40%[85]. In the same study, healthy new born and adult mice fed olesoxime had increased numbers of oligodendrocytes in the corpus callosum along with increased numbers of myelinated axons in the region. Myelin sheath thickness increased during neonatal development when animals were treated with olesoxime. Mice were also put on a cuprizone diet to test the effects of olesoxime on the demyelination and remyelination phases in animals. At peak demyelination, treated groups had higher MBP and NF (neurofilament) content. When animals were evaluated two weeks after peak demyelination, analysis showed that proliferation was promoted during remyelination based on increased Olig2+ cell counts; a two-fold increase in myelinated axons compared to vehicle-treated animals was found as well. Animals pretreated with olesoxime food pellets were injected with lysolecithin to induce focal demyelination; in this model, expression of differentiation protein markers did not differ between the treated and untreated group though CC1+ mature oligodendrocytes were higher in number in the pretreated group. MRI analysis of the lysolecithin/olesoxime pretreated animals showed attenuation, though insignificant, of lesions in the treated group. Olesoxime is currently undergoing a phase 1b trial in MS patients as add-on therapy to the immunosuppressant interferon-beta (MSREPAIR; NCT01808885) and diffusion tensor imaging and magnetization transfer ratio will be performed to assess remyelination.

Two other drugs, minocycline and rolipram were to date unsuccessful in MS trials. Minocycline is a tetracycline antibiotic that easily crosses the blood–brain barrier and has been used to treat a variety of infections for years[86]. In a cuprizone-fed animal model, minocycline inhibited microglial activation that suppressed expression of ciliary neurotrophic transcription factor. However, the drug also decreased the number of CC1+ mature oligodendrocytes in animals[87]. In clinical trials with Rebif, minocycline use was associated with increased brain atrophy and progression and the trial was halted. Minocycline use with glatiramer showed no benefit over glatiramer alone

in MS patients as well[88].

Rolipram was originally tested for treatment of depression though not tolerated well in clinical trials. Nausea was reported as the main side effect which limited its clinical application[89,90]. When considered as a treatment option for MS, rolipram showed a dose dependent increase in MBP+ oligodendrocytes *in vitro*. After rolipram treatment, lysolecithin injected animals showed increased MAG, CNPase, and MBP expression[91]. Myelin sheaths in ethidium bromide injected animals were found to be thicker when analyzed fourteen days after lesion[51]. Positive *in vitro* and *in vivo* results propelled rolipram to a phase I/II clinical trial in a small group of MS patients. The measurement of contrast-enhancing lesions (CELs) from MRI results indicated that brain inflammatory activity actually increased with rolipram treatment. The total number of CELs per patient per month significantly increased in the treatment group. Adverse events significantly increased and exacerbations generally increased with treatment[75]. Though originally promising, rolipram dosing may not be high enough for remyelination to occur in humans. Nevertheless, rolipram may be worthy of further research efforts since both rolipram and ibudilast are phosphodiesterase inhibitors and appear to enhance remyelination in animal models.

Clearly several extant drugs could potentially be repurposed for remyelination in MS. One issue cogently raised by others in relation to the MS-STAT trial[92], is the difficulty that exists in performing required phase 3 clinical trials to validate these drugs for remyelination in MS. The patents of many of the drugs named here have expired so pharmaceutical companies are expected to have limited interest in financing expensive trials. Since no trial has actually produced positive data showing evidence of remyelination in MS, the risk is also especially high to any trial studying remyelination. Alternative funding mechanisms do not exist since NIH and other governmental agencies have no established mechanism through which a large-scale expensive trial can be performed. Furthermore, medical insurance companies may not pay for treatments only characterized by limited phase 2 trials utilizing approximately 100 patients. It remains to be seen how best to fund phase 3 trials of this sort but it is likely trials of newer and more patentable drugs will lead the way first.

CONCLUSION

Remyelination therapeutics is an emerging and exciting field in MS drug development. While it is important to remember sustained neurological deficits in MS are clearly related to both neurodegeneration as well as impaired myelination, remyelination-enhancing treatments may improve patients' function and quality of life in spite of their restricted effects. Several remyelination pathways important to MS have been identified, including those of LINGO-1, hyaluronan, Notch-1, RXR receptor, and wnt/ß-catenin. Other newer discoveries include the pathways involving CXCL12/CXCR4 and GPR17, and the involvement of Endothelin-1 in the Notch pathway. A number of known drugs with effects on these pathways can be evaluated for remyelination enhancing effects in MS, although this has yet to occur. High-throughput screens have identified multiple antimuscarinic drugs with good remyelination potential but use of at least benztropine may be problematic due to dose limiting side effects. Also identified by screens, clemastine, with similar antimuscarinic but also antihistamine effects, may be useful in remyelination in MS. Other drugs identified through other means such as rHIgM22 are in the beginning stages of clinical trials. Drug repurposing, through screens or more serendipitously, has found that many drugs could enhance remyelination, including benztropine, clemastine, quetiapine, fusadil, olesoxime, and ibudilast, among others. Many other these identified drugs are undergoing clinical trials, some with endpoints that examine remyelination. Difficulties exist in design of clinical trials to identify remyelination in a cost-efficient, sensitive, and reproducible manner. In addition, funding for clinical trials of repurposed drugs may be difficult to acquire, which may lead clinicians and insurers to an uncertain position of whether to use certain treatments. However, with recent dramatic advances in remyelination research, we are optimistic that many new remyelination treatments for MS will arise and be in use in the next decade or so.

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P- Reviewer: Cao QLL, Sotelo J **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Jiao XK

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