Remyelination-Promoting Human IgMs: Developing a Therapeutic Reagent for Demyelinating Disease

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Abstract Promoting remyelination following injury to the central nervous system (CNS) promises to be an effective neuroprotective strategy to limit the loss of surviving axons and prevent disability. Studies confirm that multiple sclerosis (MS) and spinal cord injury lesions contain myelinating cells and their progenitors. Recruiting these endogenous cells to remyelinate may be of therapeutic value. This review addresses the use of antibodies reactive to CNS antigens to promote remyelination. Antibody-induced remyelination in a virus-mediated model of chronic spinal cord injury was initially observed in response to treatment with CNS reactive antisera. Monoclonal mouse and human IgMs, which bind to the surface of oligodendrocytes and myelin, were later identified that were functionally equivalent to antisera. A recombinant form of a human remyelination-promoting IgM (rHIgM22) targets areas of CNS injury and promotes maximal remyelination within 5 weeks after a single low dose (25 μg/kg). The IgM isoform of this reparative antibody is required for in vivo function. We hypothesize that the IgM clusters membrane domains and

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associated signaling molecules on the surface of target cells. Current therapies for MS are designed to modulate inflammation. In contrast, remyelination promoting IgMs are the first potential therapeutic molecules designed to induce tissue repair by acting within the CNS at sites of damage on the cells responsible for myelin synthesis.

1   Multiple Sclerosis is a Disease of Myelin

Despite the recent re-examination of axon loss within the multiple sclerosis (MS) lesion, MS remains a disease primarily of myelin. Demyelination has long been the pathologic hallmark of the MS lesion. Loss of myelin is likely an early step [135] in a sequence of events leading to the loss of axons which can result in permanent neurologic deficits. Demyelination in MS is accompanied by varying degrees of inflammation, oligodendrocyte death, complement activation, antibody deposition, and gliosis [20, 79, 81, 152]. A hypothesis central to our therapeutic remyelinating strategies for MS is that demyelination is necessary but not sufficient for the development of disability. Demyelination likely predisposes axons to permanent injury via a second, immune-mediated assault [128, 129].

Models of human disease in animals confirm that demyelination is not sufficient for the development of neurologic deficits. In mice deficient in the major histocompatibility (MHC) Class I antigen-presenting arm of the immune system, virus-induced spinal cord disease results in chronic widespread demyelination without measurable neurologic deficits [125]. Axon function is largely preserved, likely due to the lack of a direct immune-mediated attack of the axon and an increase and redistribution of axonal ion channels. The implication of MHC Class I in neurologic deficit induction suggests that CD8+ T cells are a pathologic immune effector that directly assaults demyelinated axons. CD8+ T cells commonly mediate membrane lysis through the synthesis of perforin and Fas ligand, and perforin-deficient mice with persistent and chronic demyelination present with minimal neurologic deficits [101]. Similarly, humans with extensive CNS demyelination, identified by magnetic resonance imaging (MRI) and verified by pathologic examination of the tissue at biopsy or autopsy, can present with minimal or no neurologic deficits [93]. These data suggest that axons remain functional despite demyelination if subsequent damage is controlled. The primary function of mature myelinating oligodendrocytes may be to protect axons from external injury and to provide neurotrophic support. If true, then strategies that promote axon remyelination within a critical time period will ultimately be neuroprotective and limit permanent deficits.

2   Remyelination as a Normal Reparative Response

Spontaneous remyelination, visible pathologically as abnormally thin sheaths usually at the periphery of the lesion, occurs widely in patients with MS [42, 113, 149], and periods of remission may be associated with significant CNS remyelination.

Remyelination in acute MS lesions can be substantial [117]: up to 70% of MS lesions contain some degree of remyelination [80]. However, for the 50% of MS patients who suffer with progressive disease, remyelination is insufficient or may occur after the development of axonal deficits.

Remyelination in chronic MS lesions was thought to be limited, but a recent study [109] examining demyelinated lesions from 51 MS patients at autopsy reported that substantial remyelination, defined as the presence of shadow plaques, occurs in all clinical subtypes and at any time in disease progression. Therapeutic interventions to promote remyelination would ideally begin early in the disease course to limit disability, but therapy initiated late in disease may facilitate disability stabilization.

Why remyelination so often fails in MS is unclear; a number of reasons have been proposed, and the reason likely varies between individuals. Cells capable of remyelination, or factors that sustain their growth and differentiation, may be depleted from the lesion and adjacent CNS [44, 85]. In animal models of CNS damage, remyelination is accomplished by activating endogenous myelinating cells and recruiting progenitors from adjacent intact tissue [45, 102]. However, despite ineffective remyelination in MS, an abundant population of potential replacement cells, oligodendrocytes and their progenitors, are present even in chronic MS lesions [29, 30, 103, 170]. Why surviving cells fail to respond to the presence of tissue injury and demyelination is unknown, but their presence emphasizes that the lesion microenvironment is unsupportive of remyelination. Infiltrating immune cells or persistent virus infection may create a lesion environment containing a balance of inflammatory factors that inhibit remyelination. A progressive loss of axons also results in fewer substrates to remyelinate [129].

In contrast to what is observed in human disease, robust remyelination is the norm in most animal models of experimental demyelination. Demyelination can be induced by toxins such as cuprizone [21], ethidium bromide [172] or lysolecithin [51], autoimmune mechanisms (experimental autoimmune encephalomyelitis, EAE) [120], or by infection with corona virus, murine hepatitis virus (MHV) [53], or picornavirus (Theiler's murine encephalomyelitis virus or TMEV) [35, 134]. Complete spontaneous remyelination can occur in each of these models, suggesting that remyelination is a normal reparative response to injury. Lysolecithin-induced demyelination remyelinates rapidly and completely [18, 60], restoring axon conduction and recovery of motor function [61, 73, 144]. Repair is normally so quick in toxin-mediated models that it is far easier to identify agents that interfere with remyelination [16] than agents that accelerate it [18]. In most models, remyelination begins within 3 weeks of injury and is complete by 5 weeks.

An obvious difference between human MS and models of acute demyelination is a persistent activation of the immune system. MHV-induced demyelination is accompanied by ataxia and paralysis, deficits that reverse following virus clearance and remyelination [86, 148]. TMEV infection of the SJL mouse strain results in a persistent immune response directed against chronic virus antigens in the CNS. The extent of demyelination plateaus by three 3 months after virus infection [89] with limited spontaneous remyelination throughout the rest of the animal's lifespan, making this a useful model to design and test remyelination-enhancing

therapies. TMEV-infected mice live with chronic demyelination for months to years. Spinal cord remyelination in the TMEV model plateaus at levels that are far from complete even after treatment with the most effective remyelination-promoting regents. The continued presence of Theiler's virus and progressive axonal injury and loss [155] likely account for the limits of histological repair and functional improvement. TMEV-infected mice develop progressive disability over the course of 3–9 months that can be measured with a number of objective performance tests [89, 125].

3   Strategies to Augment Remyelination

Current MS therapies have little effect on permanent and accumulating deficits. Most were designed to control the inflammation-based, MRI-visible aspects of the disease and were approved for clinical use based on a decrease in the relapse rate in short-term trials and a reduction of gadolinium-enhancing MRI lesions, a surrogate for reduced inflammation [68, 106]. Immunosuppressive therapies may not be efficacious in MS simply because inflammation is likely also required for CNS repair [19, 52]. Remyelination in active MS lesions [26] and in mouse models [17] proceeds in the presence of inflammation. The lesion environment consists of inflammatory elements that drive tissue repair as well as those that injure. Appropriate therapy depends on the clinical subtype of MS involved [80]. Patients with type II MS pathology (pronounced immunoglobulin, complement deposition, and a moderate loss of oligodendrocytes) will likely benefit from the removal of autoreactive antibodies. Type II MS patients respond to therapeutic plasma exchange more often than other subtypes with significant clinical improvement [69, 130, 167]. Improved treatments for MS must encourage rapid remyelination and selectively alter the inflammatory balance of the lesion.

3.1   Soluble Factors for Lesion Repair

Using soluble growth factors or cytokines to promote remyelination assumes that the injured CNS has cells capable of synthesizing myelin but that the environment does not support myelinogenesis. A number of factors important for oligodendrocyte survival, proliferation, and differentiation have been defined, including platelet-derived growth factor (PDGF-α) [105, 123], fibroblast growth factor 2 (FGF2) [10, 23, 119], neuregulin-1 [157], chemokine CXCL1 [126], insulin-like growth factor I (IGF-I) [90, 91] thyroid hormone [4, 43], neurotrophin-3 [13, 92], ciliary neurotrophic factor [14], and leukemia inhibitor factor [87]. In theory, administering the appropriate factor(s) to the demyelinated lesion could promote repair.

Soluble factor therapy to promote remyelination appears attractive but is presently unrealistic. While the existing industrial infrastructure can produce these

small molecules at a reasonable price, several unresolved issues surround this type of therapy. Myelinogenesis requires combinations of multiple factors available to cells in a specific temporal sequence [46, 171]. The pathology of the lesions involved and the type of surviving myelinating cells need to be determined before deciding which factor to provide. Administering the incorrect factor may interfere with remyelination [48, 100]. If demyelinated lesions lack oligodendrocyte progenitors, then factors that recruit new progenitors to the lesion may be beneficial. However, administering soluble factors that induce oligodendrocyte progenitor proliferation to a lesion already replete with progenitors may suppress remyelination. There are clear differences to be resolved between human oligodendrocyte lineage cells and their better characterized mouse and rat counterparts; human oligodendrocyte progenitors do not respond to mitogens known to drive proliferation in rodent cells [6, 116]. Most studies defining soluble remyelination factors have been carried out in models of acute focal demyelination with transient inflammation. It is unclear whether growth factors and cytokines alter remyelination in the presence of chronic inflammation, as is the case in MS. The generally recognized pleiotropic effects of most cytokines and growth factors exacerbate all the above concerns. Sustained soluble factor delivery to the CNS would need to be controlled and targeted.

3.2   Cell Transplantation for Lesion Repair

The transplantation of remyelination-competent cells is a clinically relevant approach to repair lesions lacking endogenous oligodendrocytes. Numerous experimental studies have demonstrated that oligodendrocytes or their progenitors survive, proliferate, migrate, and myelinate when transplanted directly into dysmyelinated mutant animals or experimentally demyelinated lesions [22, 37, 162]. Remyelination by transplanted glial cells can restore spinal cord conduction [156] and neurologic function [62]. However, transplantation into an inflammatory milieu with myelin loss has been less effective.

There is a risk that transplanted cells, upon arrival at the lesion site, will be rendered incapable of remyelination similar to the endogenous cells. Therapies to alter the lesion environment to promote the survival of the transplanted cells will be required as well. In a multifocal disease such as MS, it is impractical to stereotactically implant cells directly into every demyelinated lesion. The most viable approach is a peripheral vascular delivery of cells that can enter into the CNS and target areas of damage. Soluble inflammatory factors released from the area of injury likely guide exogenous as well as endogenous reparative cells [102].

The choice of cell type to use for transplantation therapy will need to withstand the political and ethical scrutiny of society and the patient. The most promising candidates are embryonic stem (ES) cells, multipotential neural stem cells, and glial restricted precursors. Each have each been isolated from diverse regions of the rodent and human CNS [107], can be expanded almost without limit, differentiated

in vitro [15] and when delivered intraspinally or intraventricularly can differentiate into myelinating cells in vivo [27, 47, 70, 78, 88, 115, 151, 173]. Appropriate Stem cells may be isolated from a patient's own bone marrow. Rodent bone marrow cells can differentiate into myelin-forming cells when transplanted into a focal demyelinated lesion [2, 3, 74, 137], and human bone marrow cells have a demonstrated neurogenic potential [94].

Of interest, studies administering neural stem cells intravenously into animals with CNS disease suggest that the transplanted cells induce repair by increasing the effectiveness of endogenous myelinating cells rather than by directly myelinating axons [115, 151]. Activated microglial cells concentrated at sites of CNS injury release soluble factors that direct neural stem cell migration and differentiation [1]. Similarly, dendritic cells transplanted into the injured spinal cord activate endogenous stem cells [95]. These studies suggest that a small number of transplanted cells, correctly targeted, may dramatically affect surviving oligodendrocyte progenitors and lesion repair by synthesizing cytokine and growth factors locally themselves or by stimulating other cells within the lesion to do so [59]. As with soluble factor-based repair strategies for MS, most cell transplantation-based strategies for remyelination have been tested only in dysmyelinating or acutely demyelinated lesions [40, 112, 169]. Limited data exist on the efficacy of cell transplantation to repair chronic immune-mediated demyelinating disease. For example, a clinical trial at Yale University stereotactically transplanting Schwann cells into MS patients was terminated prematurely after it was determined that none of the cells survived.

3.3   Immune-Mediated Lesion Repair

Clearly, manipulating cellular or humoral components of the immune system can promote endogenous CNS repair [34, 57, 99, 121, 132, 161] and increase repair by transplanted cells [141]. There are examples where interfering with immune cells and their effector molecules reduces myelin repair, suggesting that aspects of inflammation are important for remyelination [7, 75, 104]. Demyelination induced by lysolecithin in the spinal cord of B6 wild type mice remyelinates rapidly and completely, whereas remyelination in B6 Rag-1 mice, which lack mature T or B cells, is substantially impaired. Remyelination of spinal cord lesions is also greatly reduced in mice lacking CD4+ T cells, CD8+ T cells or macrophages [16, 75].

The transfer of activated immune cells can also potentiate repair of the injured CNS [54, 140]. When myelin basic protein-reactive T cells were injected peripherally into animals with spinal cord injury, T cells, B cells, and macrophages accumulated at the lesion site, and the local expression of macrophage- and astrocyte-associated neurotrophic factors increased [12]. T cells within demyelinated lesions may also drive remyelination by the local synthesis of oligodendrocyte modulatory factors [46, 71].

The phenomenon of preconditioning, an initial traumatic injury to the CNS (spinal cord) whereupon a subsequent injury at a distant site (optic nerve) facilitates an improvement in CNS repair [175], provides direct evidence of an innate organism-wide reparative system. The transfer of CNS antigen-activated splenocytes from CNS-lesioned animals substituted for a prior spinal cord lesion, leaving open the possibility that a protective immune response is either cellular or humoral (antibody) based. The immune response induced following CNS injury is likely a normal aspect of tissue repair. Damaged tissue and debris require removal, and an environment supportive of tissue repair needs to be established. However, the immune response repertoire varies across the human population [65], and therefore the response to injury varies as well.

Transient increases of the beneficial aspects of the immune response are likely safer than strategies designed to reduce detrimental aspects even if such therapy is required multiple times over the course of the disease. Therapies designed to restrict immune cells from the CNS for an extended period carry risks and may compromise immune control of latent virus infections [72, 96].

4 Antibodies Directed Against CNS Antigens Can be Pathogenic or Reparative

The existence of pathogenic autoantibodies has long been established in several peripheral neurologic syndromes including myasthenia gravis, Lambert Eaton syndrome, Guillain-Barré syndrome, acquired neuromyotonia [159] and, more recently, in the etiology of neuromyelitis optica or Devic's disease [76, 168]. In diseases mediated by pathogenic antibodies, reducing serum antibody levels by plasma exchange or immunosuppression should lead to clinical improvement. Resynthesis of pathogenic autoantibodies should lead to a return of clinical symptoms.

CNS-reactive antibodies also contribute to demyelination in MS. Active MS plaques contain a deposition of immunoglobulin and complement in 30%–50% of cases [82]. Plasma exchange, which reduces serum antibodies and complement, decreased the severity of fulminant MS exacerbations in all treated individuals demonstrating an antibody deposition pathologic phenotype (pattern II) [69]. This conclusively demonstrates the role of lesion antibody deposition in disease progression. The role of pathogenic demyelinating antibodies has been modeled in animals using anti-myelin oligodendrocyte glycoprotein (MOG). MOG antibodies administered to animals with established EAE increase disease severity and shift this predominately inflammatory model to a demyelinating disease [138].

Immunoglobulins are common within demyelinated lesions. Their presence may be due to an active immunoglobulin-based response to the CNS injury. Plasma cells, which secrete antibodies, are found within the demyelinated lesion itself [118], while oligoclonal bands have access to the entire CNS via the cerebrospinal fluid. Oligoclonal bands, one of the classic diagnostic criteria for MS, represent

individually distinct, dominant antibody clones of IgG and IgM isotype that remain stable throughout the disease [176]. The reason for or function of oligoclonal bands remains elusive, but one hypothesis is that the bands display the heterogeneity of an antibody-based reparative response across the population. Although there is much evidence that high affinity IgGs are pathogenic, there is increasing evidence that IgMs activate repair mechanisms in the face of tissue injury. The presence of IgMs within the MS lesion may explain why some patients enter remission [5] or progress with mild disease. IgMs have traditionally been considered to be confined to the vasculature. At a molecular weight of close to 1 million, there is no known membrane transporter that can pass a molecule of this size. Approximately 90% of the B lymphocytes in the circulation synthesize IgM class antibodies. The polyreactive IgM is the first line of defense in the event of a bacterial infection. The low affinity and high valency of the IgM allow it to aggregate bacteria for lysis and bind to carbohydrate residues. IgMs typically have lower affinity but high avidity due to a pentameric structure that presents ten potential binding sites.

The initial observation that autoreactive antibodies can enhance endogenous remyelination was demonstrated using the TMEV-induced model of demyelination [134]. In an attempt to exacerbate TMEV-initiated demyelinating disease, chronically infected SJL mice were immunized with spinal cord homogenate (SCH) in incomplete Freund's adjuvant. Immunization with SCH induces a polyclonal antibody response directed against multiple CNS antigens. Rather than worsening the course of disease in virus-infected mice, as would be expected when increasing the titer of anti-CNS antibodies, the spinal cords of SCH-immunized mice contained four to five times more remyelination by area than nonimmunized mice. Remyelination could be equally enhanced by the passive transfer of antiserum [132] or purified immunoglobulin [131] from uninfected animals immunized with SCH, demonstrating a direct beneficial role of antibodies in promoting myelin repair for the first time.

TMEV infection in SJL mice leads to chronic immune-mediated demyelination and progressive disability very similar to that observed in chronic progressive MS. The strength of this animal model in testing remyelination strategies lies in the limited level of spontaneous remyelination. In the SJL mouse strain, spontaneous remyelination of spinal cord lesions occurs in less than 10% of the total demyelinated lesion area. This character is in stark contrast to toxin-induced models, where complete remyelination is generally swift and complete. Using a model of damage where remyelination is not the norm allowed the identification of a serum-based, remyelination-promoting response. Even though remyelination-promoting IgMs accelerate remyelination speed in a lysolecithin toxin model [18], a laborious measurement of the density of remyelinated axons was required to demonstrate this phenomenon. Using the TMEV model, the demyelinating and remyelinating effects of a given therapy can be quickly assessed using a blinded binary spinal cord quadrant grading system to provide a sampling of repair throughout the spinal cord [163].

Monoclonal antibodies (mAbs) can reproduce the reparative effect of polyclonal antisera. Hybridomas generated from the B cells of SCH-immunized mice were screened in an antigen-independent manner for their ability to reverse chronic demyelination; two mouse mAbs (SCH79.08 and SCH94.03), out of hundreds of

screened clones, were efficacious in promoting remyelination [97]. Both mouse mAbs were IgMs (no IgGs were identified) and both bound to oligodendrocytes in culture. Subsequently, using binding to oligodendrocytes as the initial selection criteria, four additional mouse mAbs, all IgMs (A2B5, HNK-1, O1, and O4) [145] that promoted CNS remyelination in vivo, were identified [9, 161]. These IgMs are routinely used to identify and determine the maturation stage of oligodendrocytes. Given that binding to the surface of oligodendrocytes in culture could be used to select a group of mAbs for testing and that several of that group promoted remyelination, mAbs activity may involve direct stimulation of myelin-producing cells [8]. Because the antigens recognized by the mouse IgMs were all different and because the antigens appeared on the surface of oligodendrocytes at various times in maturation (from bipolar progenitor to postmitotic differentiated cells), it suggested that the in vivo effect was not antigen- or cell stage-specific.

5   Human Antibodies that Promote Remyelination

Using binding to oligodendrocytes as the initial screening criteria, human mAbs isolated from the sera of humans with lymphoproliferative disorders were tested for remyelination-promoting ability. The Mayo Clinic sera bank, a unique collection of over 125,000 samples collected over 40 years, was searched for samples with a monoclonal spike over 20 mg/ml from patients without evidence of antibody-based pathology. Antibodies isolated from serum provided serum-derived human monoclonal IgMs (sHIgM) and serum-derived human monoclonal IgGs (sHIgG). Of 102 mAbs preparations screened, six IgMs, but no IgGs, bound to the surface of oligodendrocytes in culture. All IgMs were tested in vivo for efficacy in promoting remyelination (Fig. 1A, B). sHIgM22 and sHIgM46 promoted significantly more remyelination than the other tested human IgMs [161]. Both IgMs bound to the surface of differentiated oligodendrocytes. sHIgM46 bound to multipolar cells clearly beyond the bipolar progenitor stage coincident with the expression of sulfatide. sHIgM22 bound to late-stage oligodendrocytes whose development coincided with the expression of MOG(Fig. 1E). This property mirrored the diversity of oligodendrocyte antigens and stages of differentiation recognized by reparative mouse IgMs.

Both positive human IgMs were isolated from patients with monoclonal gammopathy, a relatively common condition characterized by high concentrations of monoclonal serum antibody [33]. The remyelination-promoting human IgMs were not pathogenic to the patients that synthesize the molecules; neither presented with neurologic dysfunction despite carrying high levels of these IgMs for many years. The human IgMs identified in the initial screen all bind only to the surface of unfixed oligodendrocytes in a mixed glial culture; however, when incubated with unfixed slices of CNS tissue, five of the human IgMs bind to nonmyelin structures [19, 164]. This is also true of the well-characterized, remyelination-promoting mouse IgMs [165]. Only sHIgM22 retains a strong specific affinity for myelinated CNS tracts when used for immunocytochemistry on unfixed tissue slices (Fig. 1C, D).
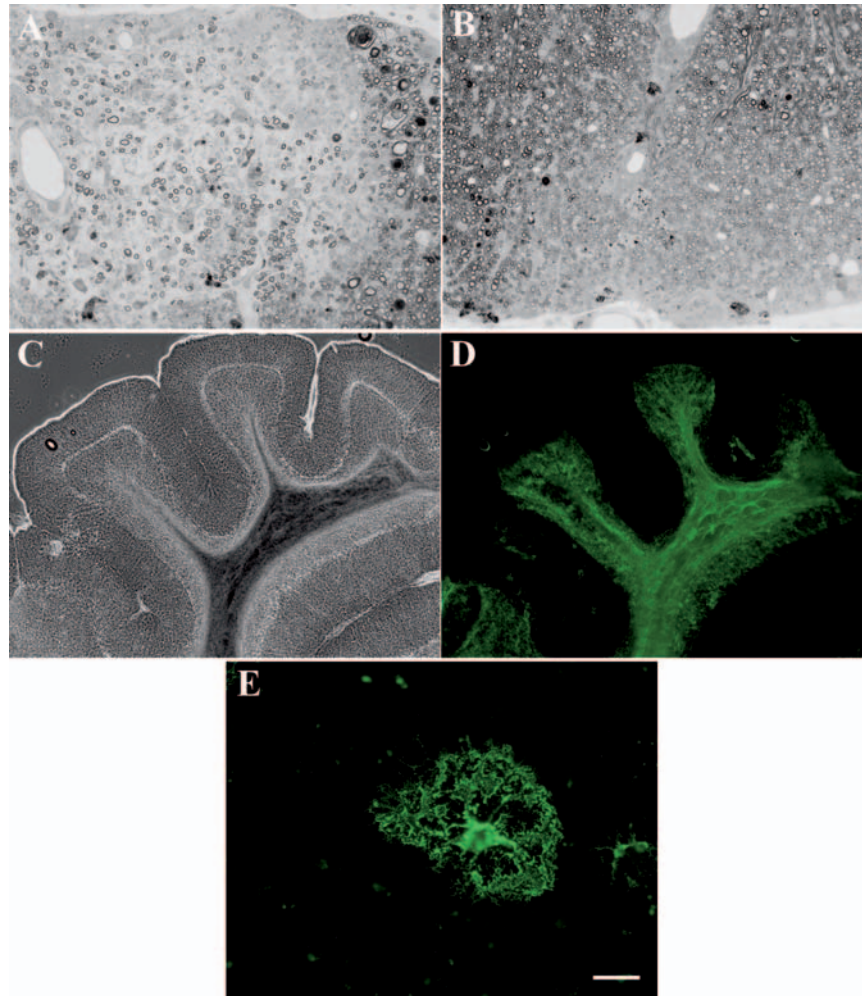
Fig. 1 HIgM22-mediated promotion of remyelination in the Theiler's murine encephalomy-elitis virus-induced model of demyelination. SJL mice with chronic virus infection present pathologically with widespread demyelination, little remyelination, and clear neurologic deficits. The spinal cords of mice administered a single dose of rHIgM22 reproducibly contain significant remyelination when analyzed histologically 5 weeks after treatment. **A** An example of a demyelinated lesion from the spinal cord of an animal treated with saline. **B** An example of remyelination within a demyelinated lesion from the spinal cord of an animal treated with rHIgM22. Spinal cord cross-sections were stained for the presence of myelin using p-para-phenylenediamine. Remyelinated axons are thinner than normal and therefore stain lighter. The remyelination promoting human IgM, rHIgM22, binds to myelinated CNS tracts and the surface of oligodendrocytes. **C** Phase contrast image of a slice of mouse cerebellum immun-ofluorescently labeled in **D**. **D** rHIgM22 binds specifically to myelin in unfixed slices of CNS tissue. **E** rHIgM22 binds to the surface of an oligodendrocyte isolated from the cortex of an adult rat

6 Role of Anti-CNS Antibodies in Endogenous Repair

One of the established MS treatments may act, in part, through an antibody-mediated repair mechanism. Glatiramer acetate (GA, Copolymer-1 or Copaxone) is an immunogenic mixture of synthetic peptides effective in reducing MS exacerbations, lesion load, and disability [63, 64]. All patients treated with GA develop antibodies to GA, and a correlation exists between anti-GA serum titers and the therapeutic efficacy of GA within an individual [25].

The passive transfer of affinity-purified polyclonal antibodies against GA into chronically demyelinated mice increased spinal cord remyelination twofold [154]. Anti-GA antibodies are similar in character to remyelination-promoting antibodies, binding to oligodendrocytes, astrocytes, and neurons in the spinal cord and to early stages of oligodendrocytes and microglia in culture. Antibodies to GA cross-react with MBP [77, 150], and treatment with MBP antisera promotes remyelination [133].

CNS-reactive antibodies may also enhance axon outgrowth following CNS trauma. Rodents immunized with SCH prior to spinal cord hemisection or optic nerve crush demonstrated enhanced axonal regrowth in both lesion models [41, 57] with functional improvement after spinal cord injury. This SCH immunization strategy was identical to that used to identify remyelination-promoting antisera and similarly resulted in increased sera titers of myelin-reactive antibodies. Animals with the best axon regrowth contained the highest titers of myelin-reactive serum antibodies, which, when assayed in vitro, allowed axon outgrowth on immobilized CNS myelin, a substrate normally inhibitory to neurite extension. Unfortunately, CNS-reactive antibodies from animals with enhanced axon regeneration were not isolated and passively transferred to nonimmunized animals, so it is unknown whether antibodies alone mediate the reparative response.

There are similarities between remyelination-promoting monoclonal IgMs and the IN-1 mouse monoclonal IgM that promotes axon regrowth and functional recovery following CNS injury [24, 28, 31, 49]. IN-1 binds to oligodendrocytes and myelin [136] and may block myelin antigens inhibition to axon outgrowth [139, 166]. The remyelination-enhancing ability of IN-1 in models of chronic demyelination remains untested. However, there is a growing appreciation that encouraging remyelination plays an important role in repairing spinal cord impact injury [108, 153].

7 A Recombinant Human IgM Promotes Remyelination in vivo at Doses Comparable to Growth Factors

Recombinant forms of the two human IgMs, designated rHIgM22 and rHIgM46, have been synthesized [98]. The mRNA encoding each IgM was isolated from the cellular fraction of that patient's blood, reverse-transcribed, and the cDNA used to synthesize recombinant IgMs containing a mouse J chain. The presence of the mouse J chain may be of great utility in following the molecule in non-mouse recipients.

Both IgMs retain the immunohistochemical characteristics and in vivo reparative properties of the serum-derived versions. rHIgM22 binds myelinated tracts in slices of CNS tissue with even higher specificity than sHIgM22, which likely contains additional serum IgMs. rHIgM22 binds only to myelin in CNS slices obtained from the mouse, rat, rabbit, primate, and human (unpublished observations). Choosing an IgM to pursue for clinical trial in humans was decided by the availability of a production cell line that consistently synthesized high levels of IgM that could be easily assayed by immunocytochemistry or ELISA assays and was stable in long-term storage. rHIgM22 met these criteria better than rHIgM46.

Prior studies of induced remyelination have used bolus doses of 500 μg of IgM per mouse (25 mg/kg) administered intraperitoneally (i.p.), a dose based on earlier studies of remyelination induced by polyclonal antisera [132]. A comparable dose of IgM for adult humans treated at 25 mg/kg would be 2 g, a large amount of monoclonal antibody. A recent study clarified several important characteristics of rHIgM22-induced repair of chronically demyelinated lesions including the minimal effective dose to promote remyelination in mice with clear neurologic deficits [163]. A remarkable characteristic of rHIgM22 is the small amount of mAb in a single dose required for maximal long-term repair in the spinal cord. rHIgM22 effectively promoted remyelination down to a dose of 500 ng per mouse, a dose 1,000-fold lower than that used in prior studies. A regression analysis fitting the mean percent remyelination and dosing to a standard dose response curve (Fig. 2) resulted in a median effective dose (EC50) of 460 ng ± 74 per mouse.

An estimate of the systemic in vivo concentration of rHIgM22 at the EC_{50} may be calculated by considering the treatment of a 20-g mouse with 460 ng of rHIgM22. Partition kinetics of the remyelination-promoting mouse IgM, SCH94.03 [58], determined that 0.1% of a 50-μg dose of ^{35}S-labeled SCH94.03 entered the CNS of demyelinated mice. 0.1% of a 460-ng dose of rHIgM22 distributed throughout the 1-ml volume of the mouse CNS is 0.46 ng/ml. Although the concentration of rHIgM22 appears quite low when diluted throughout the blood stream, the concentration of IgM within target tissue may be considerably higher. MRI has demonstrated rHIgM22 accumulation within demyelinated lesions in vivo [114]. Soluble growth factors similarly localize in vivo by binding to specific extracellular matrix molecules [50, 122]. rHIgM22 tagged with biotin was tracked in vivo by the binding of avidin to ultrasmall superparamagnetic iron oxide particles and visualized by MR imaging. rHIgM22 entered and accumulated within CNS lesions of chronically demyelinated mice. Control human IgMs also entered the CNS of demyelinated mice but did not accumulate, presumably due to the lack of target antigens. ^{35}S-labeled SCH94.03 also accumulated at demyelinated lesions in vivo as demonstrated by tissue section autoradiography [58]. These data suggest that the effective local concentration of rHIgM22 within the microenvironment of the demyelinated lesion is much higher than 0.5 ng/ml. The half-life of rHIgM22 in mouse sera was calculated to be 15 h, whereas the half-life of a normal mouse IgM in vivo is approximately 2 days [158]. Therefore, rHIgM22 must accumulate and signal in a short span of time.

rHIgM22-induced remyelination in the TMEV model occurs primarily between 3 and 5 weeks following treatment. This repair timeframe mimics precisely the
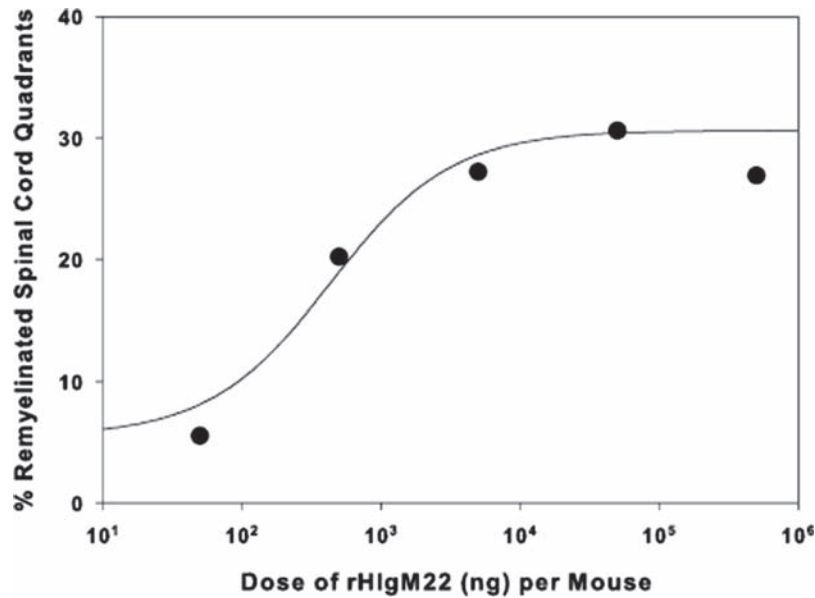
Fig. 2 Dose response curve for rHIgM22-induced in vivo spinal cord remyelination. A regression analysis calculated a standard dose response curve for rHIgM22-induced remyelination (four parametric logistic function, SigmaPlot). The mean percent of spinal cord quadrants with more than 75% of the demyelinated area remyelinated is plotted vs the dose of rHIgM22 administered once intraperitoneally [163]. Each dosing group contained 15–18 mice. The analysis predicts a median effective dose (EC50) of 460 ng ± 74 per mouse. This is equivalent to a 23-μg/kg dose. A comparable dose for a 70-kg adult human would be 1.6 mg of IgM

time course of spontaneous remyelination observed after lysolecithin-induced demyelination, where the bulk of remyelination is also accomplished between 3 and 5 weeks following injury [18, 171]. Treatment with rHIgM22 appears to shift this virus-induced model of chronic demyelination, which normally presents with little spontaneous remyelination, to one that remyelinates at the same rate as a classic model of toxic injury. Mice in the dosing studies were treated with rHIgM22 6 months after infection, and therefore, demyelinated lesions existed without repair for at least 3 months prior [89]. Then, following a single dose of rHIgM22, substantial repair was observed throughout the spinal cord within 3 weeks. A second dose of rHIgM22 administered 5 weeks after the first was no more effective than a single dose. However, we now know that neutralizing antibodies to rHIgM22 are synthesized in animals within a week of treatment, and the second dose was likely quickly inactivated (unpublished observations).

A quantitative MRI analysis of lesion volume has followed rHIgM22-mediated lesion repair in the TMEV model [114]. Individual chronically demyelinated mice were MR imaged prior to treatment and again 5 weeks later. Mice receiving 500 ug of rHIgM22 contained a significantly smaller mean lesion load, decreasing by

40.6% compared to a lesion load increased by 13.6% in control-treated mice. Lesion volume decreased in each of 13 mice treated with rHIgM22, whereas lesion volume increased in seven of eight mice treated with saline.

Although controversial, rHIgM22 may be considered a novel class of growth factor. The classical definition of a growth factor is a molecule that binds to a target cell, induces a biologic effect, and functions at extremely dilute concentrations. This definition implies interaction of the factor with a specific receptor linked to an amplification system. rHIgM22 fulfills this definition. rHIgM22 binds to the surface of oligodendrocytes and the myelin sheath, localizes to lesion sites in vivo, acts directly on oligodendrocytes in vitro, inducing $Ca2^+$ influx [111] and protection from apoptosis [55], and effectively promotes remyelination at concentrations in the nanogram to milliliter range.

8   The IgM Character of Remyelination Promoting Antibodies is Vital for Function

A large body of evidence supports our hypothesis that the in vitro and in vivo biologic effects of remyelination-promoting antibodies require the pentameric IgM structure. First, we have been unable to identify an IgG, either mouse or human, which promotes remyelination. A large number of mouse IgGs, the result of hybridoma fusions, were screened in vivo for efficacy in remyelination, and none induced significant repair. A total of 100 human sera samples containing IgG monoclonal peaks were screened for binding to the surface of mixed cortical glial cells and to unfixed slices of cerebellum and cortex, and none were identified. Second, recombinant IgG_4 versions of rHIgM22 and rHIgM46 did bind to myelin in tissue slices or to the surface of oligodendrocytes in culture and did not promote remyelination in chronic demyelinated mice even at 1,000 times the least effective dose of rHIgM22.

Our research group evaluated the ability of IgM fragments of SCH94.03 and sHIgM22 to induce remyelination [32]. The two IgMs displayed different requirements for in vivo function; subfragments of sHIgM22 (monomeric IgM and $F(ab')_2$) promoted remyelination, whereas sub-fragments of SCH94.03 did not. These studies were conducted prior to rHIgM22-dosing studies that demonstrated the small amounts of IgM required for in vivo function. Consequently, animals received far more than the minimum effective dose. Mice received the same mass of IgM or fragments of human IgM, a single 500-μg dose of sHIgM22 or IgM fragments or five weekly 100g doses of mouse IgM or IgM fragments. The molecular weight of an Fv fragment is 25,000 kD and an intact IgM, 900,000. Considering that the EC_{50} of rHIgM22 is 460 ng, a 1,000- to 36,000-fold dilution of intact IgM contaminating the test material could account for the observed in vivo remyelination. Therefore, it is erroneous to conclude that IgM fragments of sHIgM22 can induce remyelination.

Supporting the requirement of the IgM for biologic effect, intact pentameric sHIgM22 and SCH94.03 bound via immunocytochemistry to cultured oligodendro-

cytes and to cerebellar myelin tracts, whereas fragments of neither bound detectably. In addition, an isolated IgG1 spontaneous switch variant of antibody SCH94.03, in which the VDJ and VJ regions of the heavy and light chains of the IgM and IgG1 antibodies were identical, did not bind oligodendrocytes or cerebellar slices or promote remyelination.

Cross-linking IgGs into higher-order complexes may begin to approximate the pentameric structure of the IgM. When complexed with an anti-human γ chain secondary prior to immunocytochemistry, rHIgG$_4$22 was weakly detected decorating the surface of oligodendrocytes in culture (unpublished observations). A similar observation is reported using the anti-MOG IgG, 8-18C5. The IgG is innocuous when added to oligodendrocytes in culture but when subsequently cross-linked using a secondary antibody MOG partitions of into subdomains of oligodendrocyte membrane, and severe process retraction is induced [83]. An additional example of this phenomenon is observed using mAbs to gangliosides on neurons [160]. The addition of an anti-GT1b IgM to neurons in culture can directly block neurite extension. High-affinity IgGs against GT1b and anti-GD1 bound to the neurons and attenuated CNS myelin inhibition of neurite extension, presumably by interfering with gangliosides on the surface of the neuron from binding to myelin antigens. However, the IgGs could not block neurite extension themselves. Only when the anti- ganglioside IgGs were precomplexed into multivalent aggregates and then added to the culture could the IgGs directly block neurite extension. Anti-ganglioside antibodies are associated with a number of human neuropathies. Endogenous cross-linking of these antibodies may contribute to disease progression.

9 Mechanisms of Antibody-Mediated CNS Repair

The therapeutic efficacy of remyelination promoting IgMs has been demonstrated in both immune- and nonimmune-mediated demyelination models [19, 110], indicating that the underlying mechanism is not a modulation of a model-specific pathogenesis but likely a fundamental physiologic stimulation of a reparative mechanism. The exact mechanism of how a single small dose of rHIgM22 promotes widespread remyelination in vivo remains unclear, but two general hypotheses, not mutually exclusive, are favored (Fig. 3).

Since all remyelination-promoting IgMs bind to oligodendrocytes and myelin [9, 161, 164], the recognition of those antigens in vivo is likely important for the mechanism of action. In the first alternative, remyelination-promoting IgMs directly target and signal oligodendrocytes and their progenitors within demyelinated lesions to facilitate their expansion and differentiation. Antisera reactive with CNS white matter antigens induce thymidine uptake when added to cultures of mixed CNS glia [132]. The direct binding of OL-specific antibodies initiate a variety of biochemical and morphological changes in these myelinating cells [11, 38, 84]. Electron microscopy of animals treated with anti-SCH immunoglobulin and pulsed with tritiated thymidine demonstrated proliferating cells with the
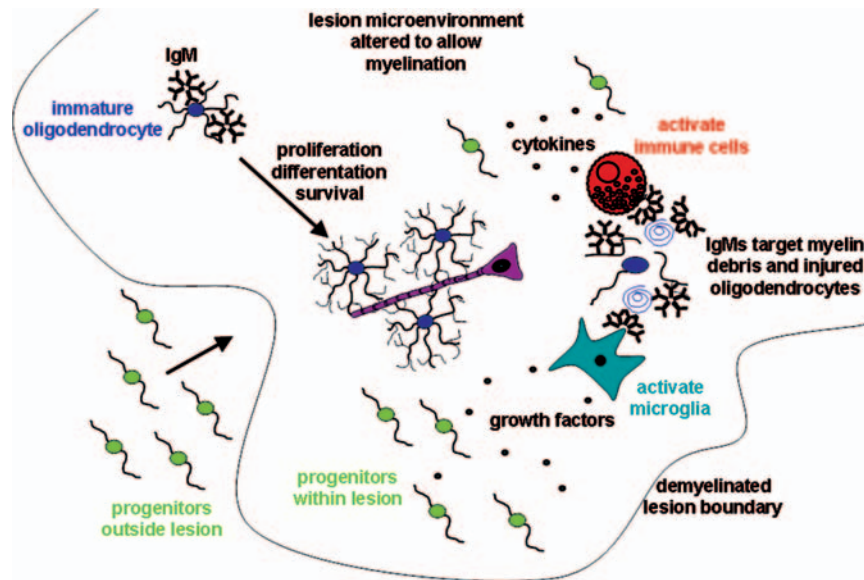
Fig. 3 Potential in vivo mechanisms of action of remyelination-promoting IgMs. We propose that in vivo, reparative IgMs target to and accumulate at demyelinated CNS lesions and act directly on cells responsible for the synthesis of myelin by binding to surface antigens on oligodendrocyte progenitors, enhancing their proliferation, differentiation or survival. Alternatively, remyelination-promoting IgMs, concentrated at the lesion by affinity to myelin debris and injured or dying oligodendrocytes, act on other cells within the lesion. Resident microglia or immune cells may be induced to release cytokines and growth factors that (1) recruit oligodendrocyte progenitors to the site of damage, (2) increase oligodendrocyte progenitor proliferation, or (3) alter the lesion micro-environment to support remyelination

morphological features of oligodendrocyte progenitors[127]. Antibodies that bind to the oligodendrocyte-specific antigens galactocerebroside, sulfatide and myelin/oligodendrocyte-specific protein elicit biochemical and morphological changes in glial cells [39], which are preceded by a calcium influx [38]. Transient calcium fluxes are also observed in a subpopulation of astrocytes and immature oligodendrocytes following the addition of remyelination-promoting IgMs to the culture media [111]. The ability of an IgM to promote remyelination strongly correlates with its ability to stimulate calcium influx. rHIgM22 also protects immature oligodendrocytes in vitro from stressor molecules. In mice treated with rHIgM22, a decreased expression of caspase family members and increased expression of proteins associated with myelination is observed [55]. Remyelination-promoting IgMs may elicit similar signals at oligodendrocyte progenitors in damaged tissue. We and others have proposed that mAbs initiate signals by binding to plasma membrane microdomains [55]. The pentameric structure of the IgM, which binds and clusters disparate portions of the plasma membrane, is critical for in vivo remyelination.

Antibodies that bind to neurons also directly induce signals and alter cell morphology. mAbs against ganglioside GM1 suppress neurite outgrowth in vitro and in vivo [146, 147], whereas anti-idiotypic antibodies to GM1 induce neurite extension [124]. mAbs to the ganglioside GD3 (R24) or to the cerebellar granule cell surface protein (TAG-1) induce activation of the Src family kinase Lyn and result in similar alteration in protein tyrosine phosphorylation. Reducing the concentration of membrane GD3 by removing surface carbohydrates eliminates mAb-mediated signaling through both GD3 and TAG-1 [66, 67] suggesting that membrane glycosphingolipids are required for GPI-linked protein-mediated signaling.

In the second alternative, remyelination-promoting IgMs enhance myelin repair by initiating a cascade of events in cells other than oligodendrocytes upon accumulation within the demyelinated lesion. Reparative IgMs accumulating at the lesion may shift the microenvironment toward one that favors remyelination. This may be accomplished by inducing astrocytes [111] or immune cells to synthesize cytokines and growth factors supportive of myelination [23, 29, 92, 174]. Recall, for example, that rHIgM22 induces Ca flux in astrocytes and oligodendrocytes. IgM molecules are common within the oligoclonal immunoglobulin bands in MS patients [142, 143]. Since so little of the correct IgM is required for repair in our models, plasma cells situated within the demyelinated lesion may provide a sufficient concentration of antibody to activate a reparative response.

The myelin-binding character of the IgM-variable region targets the antibody to the lesion, where other IgM domains signal adjacent cells. In support of this concept, pentameric Fcμ fragments of human IgM suppress oligodendrocyte proliferation and alter transcription in mixed glial cultures, possibly through the synthesis of IL-1β from activated microglia [56]. Whether myelin-binding IgM initiates a similar upregulation in microglia and astrocytes within the lesion remains to be determined.

10 Therapeutic Goal: Alter the Balance of Inflammation to Favor Regeneration

We hope that remyelination promoting IgMs will soon be a clinical treatment option. The first patients to be treated with rHIgM22 will likely occur in late 2007– the initial study focusing on safety of the IgM. To date, remyelination-promoting human IgMs have exhibited no toxicity *in vitro* or *in vivo*. This will be the first clinical trial to attempt to induce repair of the central nervous system by directly targeting the cells of the brain and spinal cord rather than modulating the immune system. Demyelination is an aspect of many other human diseases involving axon damage. Stroke, peri-natal anoxia, leukodystrophies and spinal cord injuries will all likely benefit from increased remyelination. Future studies will determine whether remyelination promoting IgMs are efficacious in models of other human neurologic diseases.

Reparative CNS-binding IgMs represent a new class of therapeutics for human diseases. IgM based reagents offer a specificity of binding, and potentially of action, not possible with other molecules. The property of rHIgM22 to target to sites of CNS damage after peripheral administration presents additional applications of this IgM in the treatment of disease. The antibody may be reengineered as a vector to deliver additional reparative molecules to demyelinated lesions. in patients lacking a sufficient number of myelinating cells remyelination promoting IgMs may be combined with glial cell transplantation to improve the reparative potential of the additional cells. Human monoclonal IgMs that recognize neuronal surface antigens [164] may be used to target molecules to areas of axon pathology in neurodegenerative diseases such as Alzheimer's [36] and spinal cord injury.

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