The complex etiology of multiple sclerosis

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1. Introduction

It is often tacitly assumed that multiple sclerosis (MS) is an autoimmune disease involving multifocal areas of brain lesions which contain axons demyelinated due to the initiation of an inflammatory response associated with the recruitment of lymphocytes autoreactive to myelin proteins [1]. The immunological data underlying this position include the isolation of myelin protein-reactive T cell clones from MS patients [1,2], the cytokine profile of these T cell clones which is consistent with a delayed type hypersensitivity (DTH) reaction believed to be a hallmark of autoimmune diseases [3], the demonstration of tissue destruction and axonal demyelination in rodents by myelin-reactive T cells from transgenic mice harboring the T cell receptor for an immunodominant epitope from myelin basic protein (MBP) deduced...
from T cell clones isolated from MS patients [4], the recapitulation of disease symptoms in laboratory animals following adoptive transfer of MBP-reactive lymph node cells [5], and the immunomodulatory effects of approved therapeutics showing clinical benefit in MS patients [3]. This autoimmune phenotype is felt to be reflective of most MS patients, classified as having relapsing/remitting disease (RRMS), and may even set the stage for the more rapidly progressive forms of MS (e.g., primary progressive, secondary progressive), where neurological deficit continues largely independent of any signs of the inflammatory based lesions [6].

This autoimmune profile and the associated biochemical pharmacology have been important drivers in drug discovery programs directed towards developing more effective therapies for MS. Included in these drug discovery approaches is the evaluation of prospective drugs in the primary animal model for MS, experimental autoimmune encephalomyelitis (EAE), which is constructed either by immunization with myelin antigens or via adoptive transfer of myelin protein-reactive T cells [1,3–7]. Importantly, currently marketed therapies for MS show efficacy in these EAE models [7]. Since the model is an important part of the decision tree in MS drug discovery programs, it is not surprising that most, if not all, current clinical trials for MS are with compounds targeting the purported altered immune/inflammatory response [8].

However, scrutiny of the clinical progress of treated patients shows disappointing results for the current therapies with regards to halting disease progression [6,9]. Moreover, observations from several groups have led to the appreciation that MS has a very complex etiology (e.g., [10]) which has led to a questioning of the tacit assumption that MS is indeed an autoimmune disease [6,11]. Questioning the autoimmune etiology of MS is not new [12] and has led some to postulate that MS may be a heterogeneous syndrome with at least the more progressive forms of the disease harboring a different, non-autoimmune etiology [13]. This commentary critiques the data which support and are at odds with the autoimmune etiology of MS and, in so doing, questions the logic of ‘staying the course’ in the pursuit of new and effective drugs for all forms of MS. More effective therapeutic regimens for MS patients will require creative approaches to limit fulminating inflammatory responses and also quell the neurodegenerative processes operant even in the early forms of the disease.

## 2. MS as an autoimmune disease

There are several lines of evidence to support the long-held belief that MS is indeed a disease with an autoimmune etiology.

### 2.1. Pathophysiology: an altered immune response

Numerous clinical observations support the position that MS is an autoimmune-driven disease. A key pathological finding in MS patient brains is the presence of diffuse, inflammatory plaques, primarily in the white matter and also now appreciated to extend into the gray matter [3,6,10]. The plaque contains an inflammatory cellular infiltrate, dominated by T cells and macrophages, and can contain areas of axonal demyelination, gliosis and loss of both axons and oligodendrocytes.

Acute lesions are likely the pathophysiological correlate of the clinical relapse in RRMS [14] although magnetic resonance imaging (MRI) techniques have demonstrated the appearance of far more lesions than suggested by monitoring clinical observations. This may reflect symptomatically silent areas of the brain which harbor some of these lesions, compensatory neuronal circuitry and/or insufficient demyelination to effect any clinical syndrome [6,14]. Thus, MRI offers a valuable mechanism for ostensibly assessing progression of disease which may not necessarily be correlated with clinical scores such as the expanded disability status scale (EDSS). Lesioned areas do have the capacity for remyelination which may not only counter inflammatory-initiated demyelination but also underlie remission following a relapse. However, over time, possibly years, this capacity wanes with resulting progression of the disease characterized with a more serious neurological deficit associated with neuronal dysfunction and axonal degeneration [3,6,14].

Several groups have demonstrated a robust lymphocytic activation response to myelin associated proteins (e.g., MBP [2], proteolipid protein (PLP) [2,15], myelin oligodendrocyte glycoprotein (MOG) [2,16] and myelin-sequestered alpha B crystallin [17]) in cellular preparations isolated from blood and brain tissue from MS patients, lending credence to the presence of an altered autoimmune response. When isolated, the myelin protein-reactive T cell clones typically elaborate a T helper cell type-1 (Th-1) cytokine profile upon activation with the myelin protein antigens, an anticipated response should autoreactive T cells be involved in the pathophysiology [1,14]. Activated CD4+ T cells, isolated from MS patients, release more of the proinflammatory cytokine IL-17 compared to cells isolated from healthy donors [18], and transcripts of IL-17 were found to be elevated in brain lesions from MS patients compared to controls [19]. CNS lesions associated with an inflammatory infiltrate, and axonal demyelination, occur following the adoptive transfer of myelin protein-reactive T cells in EAE (e.g., [5]). Moreover, administration of an inadvertent encephalitogenic peptide of MBP to MS patients led to an exacerbation of disease [20].

An important diagnostic criterion for MS is the sign of increased intrathecal synthesis of immunoglobulins as detected by oligoclonal bands (OCBs) in samples of cerebrospinal fluid (CSF) [21]. The presence of these bands suggests an increased B cell response to brain resident antigen(s) [3,6]. The absence of these OCBs upon diagnosis has been reported to be associated with a less severe disease progression [21].

### 2.2. Immunomodulators effective as therapeutics

Although the exact mechanisms of action for the immunomodulatory drugs marketed for MS remain controversial, several (e.g., beta-interferon, glatiramir acetate and natalizumab) have been shown to be effective in limiting relapses as well as the development of new inflammatory lesions [1,3,14]. The logic for the use of beta-interferon (IFN-β; Avonex®, Rebif® or Betaseron®) in MS was, in part, spawned by findings that administration of gamma-interferon (IFN-γ) to patients...
exacerbated the course of disease [22]. IFN-β has the potential to activate immunomodulatory signaling pathways that can prevent the deleterious actions of Th-1 cytokines such as IFN-γ [23]. Glatiramer acetate (Copaxone) is believed to interfere with antigen presentation as it can effectively skew the activated T cell cytokine profile (e.g., during an antigen recall response) towards a composition of Th-2, anti-inflammatory cytokines [23]. The anti-VLA₄ biologic natalizumab (Tysabri) reduces the trafficking of mononuclear cells (e.g., CD4+, CD8+ T cells, B cells, plasma cells) into the CNS [24]. The efficacy of natalizumab on both reduction of lesion formation and relapses appears greater than that obtained with either IFN-β or glatiramer acetate [25]. Therefore, all of these marketed therapies can effectively downregulate aspects of altered immune responses which would be anticipated to underlie an autoimmune pathophysiology.

2.3. Pharmacogenomics consistent with an autoimmune etiology

The advances and availability of microarray technology have facilitated exploration of genetic factors involved in the etiology of MS. A genetic component of MS is posited due to the prevalence of cases within families and the high disease occurrence in some ethnic populations (particularly those of Caucasian origin) compared with others (African and Asian groups) irrespective of geographic location [26]. Familial association studies are well documented with the monozygotic twin of an MS patient showing a higher risk (25–30% concordance) for MS than observed for a dizygotic twin (2–5%) even among different populations [27].

Gene-expression profiling studies have indeed shown an association with immune/inflammatory-related genes in MS patients [19]. Linkage analysis data indicate susceptibility to MS is inherited and related to a locus which appears consistent with an autoimmune etiology. The most consistent data implicate the major histocompatibility complex (MHC) on chromosome 6p21 [14]. Association with the histocompatibility leukocyte antigen (HLA) DR2 haplotype (DRB1*1501–DQB1*0602) has been repeatedly demonstrated in multiple populations (e.g., [28]). The strongest association has been with HLA-DRB1 [28].

Studies like the admixture mapping scan identified a 95% credible interval on chromosome 1 containing 68 known genes [29]. While exciting and potentially valuable for suggesting new research avenues, these data are still nascent.

3. Preclinical models of MS

As mentioned above, EAE is a disease syndrome produced in animals which exhibits some of the symptomatology and pathology observed in MS patients. The phenomenon of EAE probably dates back to the neuroparalytic symptoms occasionally observed in patients vaccinated for rabies using infected animal brain tissue (reviewed in ref. [30]). Rivers and colleagues in 1933 demonstrated the induction of EAE in monkeys following inoculation with normal rabbit brain tissue [31]. The model is now commonly orchestrated in the laboratory with immunization of animals with myelin protein antigens or the adoptive transfer of myelin protein-reactive T cells with the ensuing disease syndrome capturing many of the symptoms of MS [1,4,5,7,14,32,33]. Lymphocytes isolated from the spleen of the affected animals display a robust proliferative and Th-1 cytokine response when incubated with the immunodominant peptide/protein (e.g., [32]). More recently, IL-17 has been implicated as an important encephalitogenic cytokine in EAE [33] and may be a key inflammatory cytokine in MS [3,18,19].

In the SJL strain of mice, immunization with myelin PLP antigen induces EAE with a relapsing/remitting syndrome (e.g., [7,32]) suggestive of the clinical setting for RRMS patients. Depending on the myelin protein and animal species/strain, a B-cell component can also be involved in the disease progression [34], also suggestive of the clinical situation. Transgenic mice have been instrumental in demonstrating development of EAE associated with MBP-reactive T cells isolated from MS patients. Mice ‘humanized’ for the T cell receptor, and its MHC Class II gene restriction element associated with a MBP T cell clone isolated from a MS patient, developed EAE following adoptive transfer of the respective T cells [4]. Moreover, mice engineered with an appropriate human HLA allele (e.g., HLADR2) and a T cell receptor specific for an immunodominant MBP peptide, spontaneously developed EAE [35]. Therefore, the EAE animal model provides investigators with an immune-driven pathophysiology the symptoms of which mimic aspects of the clinical disease.

Key to the validation of any animal model is the efficacy of the therapeutics which are approved for use in the clinical syndrome. Importantly, IFN-β, glatiramer acetate and natalizumab are quite effective in minimizing the disease index and dampening the ex vivo T cell proliferative and cytokine response in models of EAE [7,14]. Collectively these data lend additional credence for an autoimmune etiology for MS.

4. Inconsistencies with MS as an autoimmune disease

Several reports now exist in the literature which question the evidence that MS is an autoimmune disease. The observations in these reports suggest a much more complex pathophysiology and are listed below in the context of the evidence supporting the autoimmune etiology.

4.1. Myelin-reactive T cell clones can be isolated from MS patients

While clearly evident in blood samples from MS patients, myelin protein-reactive T cell clones harboring similar T cell receptor specificity and frequency can be isolated from most normal volunteers [2,3,12,14,17]. In a study involving monogygotic twins and MS, both affected (i.e., concordant for MS) and non-affected (i.e., discordant for MS) identical twins were found to exhibit overlapping peripheral blood CD8+ T cell receptor oligoclonality [36]. Demonstrating differences in myelin antigen reactivity in T cells, between MS patient and normal volunteer samples, may rely on methodological issues (e.g., isolation of high-avidity CD4+ T cells [2], but the presence of disease specific T cell clones for MS is not easily
demonstrable. In addition, non-MS CNS syndromes can show evidence of in vivo expansion of MBP-reactive T cells, as evidenced in blood and CSF fluid samples from patients with acute, ischemic cerebrovascular disease [37]. The difficulty in identifying a specific autoantigen for MS suggests a complex pathophysiology and also questions a solely autoimmune etiology for the disease.

4.2. **OCBs are found in CSF from MS patients**

OCBs in the CSF are an important diagnostic indicator for MS; however, the presence of these bands is a common finding with neuroinflammatory, chronic infectious disease states of the CNS [21,38]. In infectious diseases such as tuberculous and meningitis, the oligoclonal immunoglobulin is specific for the pathogen [39]; however, in MS, attempts to identify the specific target antigen have been largely unsuccessful. Quantification of OCBs for prognosis has been problematic [21] and some investigators have found that OCB-positive and OCB-negative MS patients are similar in their clinical presentation and disease progression [40].

4.3. **The demyelinating lesions in MS brain are initiated by an inflammatory cellular infiltrate**

The trademark inflammatory lesion of MS is believed to be a sine qua non for precipitating a relapse condition, ostensibly due to axonal demyelination as a consequence of the aberrant proinflammatory response resulting from the cellular infiltrate [3,6,10]. As noted above, current therapies have been shown to significantly decrease relapse rates as well as the number of inflammatory lesions as imaged via MRI methodologies. However, newly formed lesions in RRMS patients have been observed to be largely devoid of inflammatory cellular infiltrate but instead can present as extensive oligodendrocyte apoptosis as the early initiating event [10,11]. Such damage may be causative for a subsequent inflammatory response as well as demyelination [41]. The extent of lymphocyte infiltration in lesions also appears to be region dependent as analysis of intracortical demyelinating lesions showed no significant lymphocytic infiltrate [42]. Moreover, indices of neuronal dysfunction can be observed in normal–appearing white matter of MS patients with little or no discernible demyelinating lesion load [43]. Thus, it appears that demyelination, neuro-dysfunction and possibly neurodegeneration can occur in MS brain independent of the trademark inflammatory lesion.

4.4. **Therapeutics targeting the abnormal immune/inflammatory response show efficacy in MS**

The currently approved therapies have clearly shown significant efficacy decreasing the relapse rate as well as in the formation of new lesions in double-blind placebo controlled trials [1,3,14,23–25]. The immunomodulatory therapies have also shown efficacy in altering the ex vivo inflammatory cytokine profile in cellular preparations [1,3,15]. However, the decrease in relapse rate and the associated decrease in the formation of new inflammatory lesions have not clearly translated into a substantial benefit for these patients with regards to progressing into the more serious forms of the disease [1,6,9,12,13], suggesting that inflammation may be a downstream and/or secondary response to other factors or processes involved in the initiation and progression of MS. Supporting this hypothesis is the observation that disease progression in MS has been found to be independent of either the frequency or number of relapses in RRMS patients [9,12,13]. Therefore, the trademark inflammatory lesion may be more associated with exacerbations of an existing disease rather than its progression. The current therapeutics may effectively target the fulminating immune response component of MS, but do not clearly prevent the progression of neurological deficit in MS patients.

Questions also arise regarding the benefit of interfering with certain aspects of the putative abnormal immune/inflammatory response in MS. A therapeutic strategy which has proven successful for autoimmune syndromes, the anti-TNF-α biologics, is curiously ineffective in MS and has actually been reported to cause increases in disease activity in MS patients [44]. This result suggests a deviation in therapeutic efficacy, regarding neutralization of TNF-α, with MS from autoimmune diseases such as rheumatoid arthritis, psoriasis and inflammatory bowel disease. It is important to note that TNF-α has been reported to exert both neurotoxic and neuroprotective roles, possibly region-specific, in the brain [45] which would seemingly complicate interpretation of clinical data in MS with anti-TNF-α therapies.

It has been reported that certain immunoglobulins, possibly IgM antibodies, which may be naturally occurring autoantibodies, may be of value in promoting remyelination of central axons by stimulating oligodendrocyte activity [46]. Beneficial ‘bystander’ effects of T cells may occur; T cell clones isolated from MS patients secrete leukemia inhibitory factor which is protective for oligodendrocytes [47] and acute CNS inflammatory responses may be an important stimulus for myelin repair [48]. Finally, as noted above the biochemical pharmacology of some existing therapeutics may be quite complex. Treatment of MS patients with IFN-β can be associated with an upregulated expression, rather than a diminution, of Th-1-relevant genes as reported when transcripts were analyzed from peripheral blood mononuclear cells (PBMCs) [49]. These observations add to the complexity of both deciphering the pathophysiology and understanding the role of inflammatory responses in MS.

4.5. **Pharmacogenomic profile**

Although the MHC locus appears important in MS susceptibility, the estimated proportion of the total genetic susceptibility attributed to this locus ranges between 20 and 50% [50]. Therefore, much of the genetic effect in MS remains to be explained. The strong association with HLA-DR2 is certainly of interest; however, the non-autoimmune disease narcolepsy has also been reported to have a very tight linkage with the HLA-DR2 haplotype (DQB1*0602) [reviewed in ref. [51]].

Not all gene expression data are consistent with an autoimmune etiology for MS. For example, van Baarsen et al. [52] concluded that the transcriptional profile they observed in PBMCs from a sub-population of RRMS patients resembled a virus response signature. Mameli et al. [53] used...
qRT-PCR and immunohistochemistry techniques to determine the expression of MS-associated retrovirus/human endogenous retrovirus W (MSRV/HERV-W) and human herpesvirus 6 (HHV-6) in autopsied brain and PBMCs from MS patients. Viral genomic expression of MSRV/HERV-W, but not of HHV-6, was increased in samples from MS tissue compared to tissue from non-MS patients. These data are consistent with a possible viral pathogen involvement in the disease course with some MS patients.

5. MS as an infectious disease

Prima facie evidence has also been advanced to support an infectious etiology for MS and was, in part, instrumental in conducting clinical trials with IFN-γ [22,54]. Considering MS as an infectious disease is also relevant since a pathogen could be involved in the generation of autoreactive T cells via molecular mimicry [55–57]. Infectious agents are ideally suited as suspects for the initiation of MS since their fingerprint have been observed in tissues from MS patients and infectious agents are capable of inducing an inflammatory response; however, to date a causative association of any particular pathogen with MS has been elusive. Both bacterial (e.g., [55]) and viral (e.g., [54,56]) infections have been proposed with primary candidates being Chlamydia pneumoniae [55], HHV-6 [54], Epstein–Barr virus (EBV) [54,58] and MSRV/HERV-W [53]. A pathogen may also exert a direct role in the pathophysiology of MS by the cytopathological effect caused by its replication in neurons or oligodendrocytes which could also prompt, in some cases, a fulminating immune/inflammatory response [55,56]. The listed candidate pathogens (a) infect both oligodendrocytes and/or neurons, (b) induce latent infections which can reactivate, and reactivation episodes have been linked with relapses in RRMS patients, (c) populate both MS patient blood and brain tissue as determined by analysis of pathogen genomic DNA and mRNA and (d) have been implicated as relevant target antigens for the OCBs in MS [53–58]. Some signs of patient benefit have been noted in clinical trials with antibiotics [55] and antivirals [58]; however, determination of efficacy in appropriate patient populations will probably necessitate new trials with more careful attention to such issues as entry criteria (e.g., PCR positive for the particular pathogen) or anti-viral activity of the proposed therapeutic in relevant host cells (e.g., [55,58]).

6. New therapeutic approaches

The complex etiology of MS will necessitate the development of new mechanistic approaches for improving upon the existing therapeutic armamentarium. These approaches will no doubt include addressing different pathways and targets underlying the aberrant immune response but also must focus on preventing the pathophysiological signaling leading to neurodegeneration. The following section is not inclusive of all the approaches being developed for MS, but represent examples of novel targets which hold promise for halting progression of disease.

6.1. New approaches to immunomodulation

6.1.1. Laquinimod as a novel immunosuppressant

The quinolinecarboxamide derivative laquinimod effectively ameliorates disease progression in EAE [59] and has shown promise in early clinical trials in RRMS [60]. The mechanism of action for laquinimod is not clear, but the drug does exhibit a seemingly obligatory action for an archetypical immunomodulator, that of skewing the T cell cytokine production towards a Th-2 type profile. However, evaluation in an EAE model showed that laquinimod exerted a synergistic effect when combined with IFN-β [59]. Combination regimen may provide value to non-responders to IFN-β in RRMS.

6.1.2. Sphingosine-1-phosphate (SIP-1) receptor agonists

Activation of SIP-1 receptors on lymphocytes leads to an internalization of these receptors which effectively removes a cell surface signaling event important for the egress of lymphocytes out of peripheral nodal tissue [61]. The orally active immunosuppressant FTY720 (fingolimod), upon phosphorylation in vivo, acts as an agonist on SIP-1 receptors and, thus, decreases circulating lymphocyte counts. In a Phase 2 clinical trial in RRMS patients, fingolimod reduced the number of new gadolinium-enhanced lesions as well as annualized relapse rate versus the placebo arm, although the disability scores (EDSS) were similar for the fingolimod and placebo groups at the end of the study [62]. Some of the known adverse events with fingolimod (e.g., bradycardia) may be avoided by analogs more selective for particular SIP-1 receptors [63], although the occurrence of opportunistic infections may reflect a liability of inhibiting the immunosurveillance function of circulating lymphocytes. It is currently not clear if levels of lymphocytes in CSF are decreased in patients treated with fingolimod.

6.1.3. Fumaric acid esters

Compositions of fumaric acid esters have been marketed in Europe for psoriasis (e.g., Fumaderm®) and have recently shown promise in early clinical trials for RRMS [64]. The immunomodulatory mechanism of action for these compositions is not clear but may involve a combined effect of skewing T cell cytokine responsiveness towards a Th-2 type, anti-inflammatory, profile and inhibition of lymphocyte trafficking by downregulating the expression of cell adhesion glycoproteins [64,65]. Interestingly, the immunosuppressant activity of fumaric acid esters may be triggered by inducing the expression of the anti-inflammatory stress protein heme-oxygenase 1 [65]. Therefore, the fumaric acid ester mixtures may have multiple beneficial effects including immunomodulation as well as a protective action against brain oxidative injury.

6.1.4. Pyrimidine synthesis inhibitors

Teriflunomide, the active metabolite of leflunomide, blocks immune cell proliferation through suppression of pyrimidine nucleotide biosynthesis by inhibiting the enzyme dihydroorotate dehydrogenase [66]. The associated immunomodulation may also be a consequence of teriflunomide interfering with the formation of the immunological synapse between antigen presenting cells and T cells [66]. Moreover, leflunomide has been shown to possess separate immunomodulatory and anti-viral activities in a preclinical model of solid organ...
transplantation [67]. This bifunctionality may be of value in MS patients with a concomitant viral component operative in disease progression. Teriflunomide was shown to ameliorate disease progression in EAE and was effective in reducing active lesions per MRI scan in a double-blind trial in relapsing MS patients [68].

6.1.5. Cannabinoid receptor agonists
Cannabis-based medicine has been shown to be associated with improvements in various symptoms such as pain, spasticity, bladder-related problems and muscle spasm in some MS patients [69]. The active constituents of cannabis, the cannabinoids, primarily exert their effects following binding to their G-protein coupled receptors, CB₁ and CB₂ [70]. In an adoptive transfer model of EAE (MBP-reactive T cells), intraperitoneal administration of the non-selective cannabinoid receptor agonist WIN-2 decreased clinical disease score and caused an increased apoptosis of the myelin-reactive T cells [71]. This effect on the encephalitogenic T cells was shown to be mediated, at least in part, by the CB₂ receptor subtype which is found primarily in the periphery on immune cells. A similar involvement of CB₂ receptors for the protective effects of WIN-2 was also demonstrated in a MOG-immunization model of EAE [72]. Therefore, a peripherally acting CB₂ agonist may show promise in alleviating symptoms associated with an altered immune function in MS patients without CNS-associated side effects.

6.1.6. Rho kinase inhibitors
The small GTP-binding proteins of the Rho subfamily exert multiple effects on signaling pathways via downstream effectors [73]. Rho kinases (ROCKs) represent the first such effectors characterized and are expressed both centrally and peripherally where they are implicated in fundamental cellular processes including migration, proliferation and survival. Activation of ROCKs appears important for mediating the negative effects on neurite regrowth and neurite growth cone following injury by myelin-associated inhibitors such as NOGO-A, myelin-associated glycoprotein and oligodendrocyte myelin glycoprotein [73]. The selective ROCK inhibitor fasudil has been reported to reduce the incidence and severity of symptoms in a PLP-immunization model of EAE in mice [74]. Animals treated with fasudil had less inflammatory cellular infiltration, demyelination and axonal damage in spinal cord sections compared with vehicle treated animals. In addition, the PLP recall proliferation response in splenocytes and lymph node cells from fasudil-treated mice was less robust and caused an increased apoptosis of the myelin-reactive T cells [74]. This effect on the encephalitogenic T cells was shown to be mediated, at least in part, by the CB₂ receptor subtype which is found primarily in the periphery on immune cells. A similar involvement of CB₂ receptors for the protective effects of WIN-2 was also demonstrated in a MOG-immunization model of EAE [72]. Therefore, a peripherally acting CB₂ agonist may show promise in alleviating symptoms associated with an altered immune function in MS patients without CNS-associated side effects.

6.2. Cell based therapies

6.2.1. Hematopoietic stem cell transplantation
Hematopoietic (blood or bone-marrow derived) stem cell transplantation (HSCT) following intense immunosuppression (e.g., with chemotherapy) has been evaluated as a potential treatment for MS in Phase 1/2 clinical trials [78]. This approach is based on the rationale of eradicating an aberrant immune response due to autoreactive cells and re-establishing a competent immune system with hematopoietic precursor cells. Moreover, the approach was supported by preclinical data showing HSCT experiments in animal models of EAE resulting in a diminution in disease score [79]. A recent assessment on autopsy material from more progressive MS patients concluded that disease progression (e.g., demyelination, neurodegeneration) continued in these patients despite an absence of inflammatory infiltration into white matter lesions and a decrease in MRI activity [78]. The possibility remains that HSCT may benefit MS patients at an earlier stage of disease; however, the treatment was initially touted as being appropriate for only severe forms of the disease.

6.2.2. Oligodendrocyte-lineage cells derived from human embryonic stem cells
Differentiation of human embryonic stem cells (hESCs) into oligodendrocytes and their progenitors holds promise for providing a valuable source of these cells for studying effects of compounds on lineage commitment in vitro and in vivo, as well as for possible therapeutic treatment in demyelinating diseases [80]. Transplantation of such differentiated hESCs into the spinal cord of mice harboring deficient myelin, due to a deletion mutation in MBP (shiverer mouse model), resulted in the formation of functional, multi-layered, compact myelin [80]. Initial evaluation in clinical syndromes associated with focal areas of demyelination and damage, such as spinal cord injury, may be the prudent path, but this approach may be an important option for future treatment regimen in MS.

7. Denouement
MS is a disease state with an extremely complex pathophysiology which poses challenges for conducting drug-discovery programs for new effective therapies. Staying the course by
focusing on MS as an autoimmune disease relies on the rationale that advances over existing standard of care will come with orally active facsimiles or with compounds which exert either a broader or more novel anti-inflammatory profile. The former would be an important advance considering existing therapeutics regarding convenience, and the latter might hopefully capture a greater response rate in RRMS and/or to prevent disease progression. This strategy would, however, seemingly eliminate primary progressive MS as an indication since there is little or no autoimmune/inflammatory signature in these patients (e.g., [13,14]). Moreover, the strategy may inadequately address the progression of RMS into secondary progressive disease. A case could be made for anti-microbials/anti-virals but isolation of a specific agent has not been successful and thus this approach would likely involve extensive research into the latent and lytic forms of candidate pathogens with regards to the relevant cells associated with demyelination and neurodegeneration. Effective therapeutic intervention in MS may require regenerative medicine approaches, such as the in vivo or ex vivo expansion and mobilization of progenitor cells in order to minimize the axonal damage in early stage disease as well as to provide relief in the progressive forms of MS. Such an approach may need to act in conjunction with immunomodulatory therapies but has the opportunity to treat MS as a single disease syndrome rather than a heterogeneous collection of different etiologies, although the complex pathogenesis of MS may require a more individualized assessment in selecting the optimal treatment for a particular patient [10]. It is our bias that development of transformational therapeutics for MS will necessitate a change in course requiring an amalgam of approaches expanding beyond the more parochial view of autoimmunity.

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