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Mojtaba Farjam
Fasa University of Medical Sciences

Guang-Xian Zhang
Thomas Jefferson University

Bogoljub Ciric
Thomas Jefferson University

Abdolmohamad Rostami
Thomas Jefferson University

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Emerging Immunopharmacological Targets in Multiple Sclerosis

Mojtaba Farjam, MD, PhD[1], **Guang-Xian Zhang, MD, PhD**[2], **Bogoljub Ciric, PhD**[2], and **Abdolmohamad Rostami, MD, PhD**[2]

[1]Non-communicable Diseases Research Center, Department of Medical Pharmacology, School of Medicine, Fasa University of Medical Sciences, Fasa, Iran.

[2]Department of Neurology, Thomas Jefferson University, Philadelphia, PA 19107, USA.

Abstract

Inflammatory demyelination of the central nervous system (CNS) is the hallmark of multiple sclerosis (MS), a chronic debilitating disease that affects more than 2.5 million individuals worldwide. It has been widely accepted, although not proven, that the major pathogenic mechanism of MS involves myelin-reactive T cell activation in the periphery and migration into the CNS, which subsequently triggers an inflammatory cascade that leads to demyelination and axonal damage. Virtually all MS medications now in use target the immune system and prevent tissue damage by modulating neuroinflammatory processes. Although current therapies such as commonly prescribed disease-modifying medications decrease the relapse rate in relapsing-remitting MS (RRMS), the prevention of long-term accumulation of deficits remains a challenge. Medications used for progressive forms of MS also have limited efficacy. The need for therapies that are effective against disease progression continues to drive the search for novel pharmacological targets. In recent years, due to a better understanding of MS immunopathogenesis, new approaches have been introduced that more specifically target autoreactive immune cells and their products, thus increasing specificity and efficacy, while reducing potential side effects such as global immunosuppression. In this review we describe several immunopharmacological targets that are currently being explored for MS therapy.

Keywords

neuroimmunology; immunotherapy; multiple sclerosis

Corresponding Author: Dr. A. M. Rostami, Department of Neurology, Thomas Jefferson University, 901 Walnut Street, Philadelphia, PA 19107, USA. a.m.rostami@jefferson.edu.

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Declarations

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2. None of the co-authors have conflicts of interest.
3. This manuscript is not under review elsewhere.

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Introduction

Multiple sclerosis (MS) is a neurodegenerative disease of the central nervous system (CNS) that has devastating clinical outcomes in many patients. MS is a leading cause of neurological disability in young adults and in the middle-aged population (1); it imposes an incredibly high socio-economic burden on society (2), with medication making up a great share of these costs (3, 4). The majority of patients experience a relapsing-remitting (RR) clinical course, and gradual accumulation of neurological deficits can eventually cause permanent disabilities. A minority of patients suffer from a progressive clinical course characterized from the beginning by steady disease progression without remissions (primary progressive MS; PPMS), and there is no evidence that any treatment works in this type of MS or in secondary progressive MS (SPMS) (5). Even in RR-MS, which can be treated using several immunomodulatory medications, treatment outcomes have not been reported as unequivocally effective for all patients, i.e., the outcomes show wide inter-individual variations, likely due to the nonhomogenous nature of the disease course. The scientific strategy of choice for treating these types of disease is to better understand their pathophysiology.

It has been suggested that MS pathogenesis is initiated by activation of myelin antigen-specific T and B cells in the periphery (6, 7). While the origin of activation of these immune cells is not known, it has been proposed that certain autoantigens or organisms with peptide homology to these antigens might trigger this process (1, 8). These myelin-reactive cells, upon migrating into the CNS, encounter autoantigens, become reactivated, and an inflammatory cascade ensues that results in demyelination and axonal injury (9). In this scenario, T cells appear to play an important role, although B cells also contribute (10). Thus, targeting T cells, B cells and mediators involved in their activation provides major routes for therapeutic interventions in MS. Current treatment options basically target the immune system to modulate disease.

While a number of drugs for MS therapy are being developed, the longlasting neuroprotective efficacy of current drugs has not been confirmed (11). In almost all cases, immunopharmacology has been the basis for drug design and development. To date, there are several approved medications for MS, including interferon beta (IFN-β) 1a, IFN-β 1b, glatiramer acetate, mitoxantrone (12), natalizumab (13, 14), fingolimod, triflunomide, dimethyl fumarate (15) and a recently approved medication, alemtuzumab (16). These drugs, mainly through modulating or interfering with different aspects of immune responses, reduce the relapse rate or decrease the need for steroids during exacerbations. However, in many patients, the response to some drugs is suboptimal, and for other medications, safety is a concern. Moreover, there is debate on how and to what extent these medications can modify the long term course of the disease. Furthermore, the lack of curative modalities and low rate of compliance in taking medication are therapeutic issues in MS (17). The cost effectiveness of these drugs in MS is also under debate.

Current understanding of the immunopathogenesis of MS has identified novel immunological processes and molecules that could be pharmacologically modulated in order to provide more effective and less toxic drugs; new MS therapies are being investigated and

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clinical trials are underway, based on the fine immunological processes underlying MS. The effectiveness of every target in MS therapy is controversial, and T cells, B cells, their crosstalk mechanisms, and a handful of inflammatory mediators and processes are being studied.

In the following sections, a brief review is presented of therapies targeting immune system components, with the goal of providing novel immunopharmacological treatment options for MS.

1. Targeting T Cells in MS

T cells provide important targets for MS therapy. Different T cell types and their surface markers have been experimentally targeted based on the immunopathology of MS. In the periphery, as well as the CNS, autoreactive T cells differentiate into several subtypes of T cells including proinflammatory cytokine secreting T-helper (Th) 1 and recently discovered Th17 cells, both of which contribute to the development of autoimmune response (18). In contrast, Th2 and regulatory T cells (Tregs) are anti-inflammatory. T cell-directed therapies could be effective if stages of T cell activation at different phases of MS pathogenesis are properly targeted (Table 1).

1.1. Targeting CD4+ T Cells

It is believed that autoreactive CD4+ T cells play a central role in MS pathogenesis. Thus, CD4+ T cell targeting with anti CD4+ antibody (cM-T412) was tested as a therapeutic option, and clinical trials with this antibody were performed in RRMS patients (19, 20). In the trials, reduction of relapse rate was observed in patients treated with this antibody, and side effects were limited; however, its efficacy in reducing T2/FLAIR lesions in MRI was not shown. Based on this report, it was concluded that this strategy has no long-term clinical benefits (21). The reason for its ineffectiveness is not known, but it has been suggested that this strategy leads to depletion of all CD4+ T cells. While a proportion of CD4+ T cells are pathogenic in MS, some CD4+ T cells, such as Th2 and Tregs, have anti-inflammatory effects (18). Anti-CD4+ antibody depletes both pathogenic and protective CD4+ T cells, with the resulting net effect of therapeutic inefficacy. The failure of this clinical trial indicated the necessity of selectively targeting only pathogenic CD4+ T cells, and not the totality of these cells, as a proper approach for MS therapy.

1.2. Targeting CD52+ Immune Cells

CD52 is an orphan receptor on the surface of mature immune cells, such as lymphocytes and monocytes, whereas progenitor cells do not express CD52. Targeting CD52 with alemtuzumab, a humanized IgG1 kappa monoclonal antibody, selectively depletes mature cells while progenitor cells remain unaffected. Depletion of mature cells is rapid and induces durable lymphopenia after one course of treatment with alemtuzumab (22, 23). After depletion of mature lymphocytes, progenitor cells proliferate and a new population of T cells is formed, with regulatory T cells predominating in this newly constituted cell population. As a consequence, Alemtuzumab induces immunological reconstitution of T cell subsets, leading to modulation of the immune system by expansion of regulatory T cells (24).

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Alemtuzumab has been approved for treatment of chronic B lymphocytic leukemia (25) and is a candidate medication in T cell lymphomas and prevention of rejection in organ graft and bone marrow transplantation (26, 27). To study the potential of targeting CD52 in MS therapy, Alemtuzumab has been tested therapeutically in MS patients since 1991 (28, 29). This antibody proved to be effective in reducing demyelinated plaques, as shown on MRIs, and clinically decreased relapses in the relapsing-remitting form of MS, but did not show satisfactory modification of disability in this group. However, when tested in RRMS patients who had failed to respond to other treatments, the antibody was effective in decreasing the relapse rate. Furthermore, after five years of treatment, Alemtuzumab continued to show greater efficacy than interferon beta-1a (IFN-β-1a) in reducing relapse rate and in sustained improvement in patient disability (30). This disability-modifying effect encouraged continued investigations on Alemtuzumab for treatment of RRMS. In clinical trials Alemtuzumab was reported to be superior to IFNβ-1a and, despite safety concerns about the increased risk of emerging secondary autoimmune disorders such as thyroid autoimmunity, *idiopathic thrombocytopenic purpura* (ITP), Goodpasture's disease and glomerulonephritis, a phase III clinical trial of this antibody was completed in 2012 and the drug was submitted to the FDA for new drug application approval in RRMS. After a long challenge due to lack of evidence that the benefits outweighed side effects, the drug was finally approved by the FDA in November 2014 for RRMS patients who had not responded to two disease-modifying medications (16).

1.3. Targeting CD25 (Interleukin-2 Receptor α

CD25 (IL-2Rα) is the α chain of interleukin-2 receptor (IL-2R) expressed on T and B lymphocytes (31). IL-2, a pro-inflammatory cytokine, is secreted by activated T cells and stimulates proliferation, differentiation and activation of lymphocytes. Some findings indicate a contribution of IL-2R to the immunopathogenesis of MS. Certain polymorphisms of IL-2R genes have been found to be associated with increased susceptibility to MS (32). Furthermore, up-regulation of IL-2R on activated CD4+ T cells might be associated with disease activity in MS (33). Daclizumab is a humanized monoclonal antibody against CD25 (IL-2Rα). The drug likely acts as a pharmacological antagonist of IL-2R and decreases lymphocyte response to the trophic signals conferred by IL-2. This could inhibit IL-2-mediated proliferation of activated CD4+ T cells. Based on this mechanism of action, Daclizumab has been approved for treatment of some T cell-dependent disease states such as human T lymphotropic virus 1 (HTLV-1)-induced adult T cell leukemia (34) and allograft rejection prevention (35).

In contrast to its anti-$CD4^+$ activity, Daclizumab stimulates the expansion of a subpopulation of natural killer cells (NK cells) called CD16–CD56 bright NK cells through an IL-2 dependent mechanism (36). These cells have an immunomodulatory function, which might be beneficial in modifying autoimmunity (37). In MS, CD56bright NK cells cross the blood-brain barrier and kill autoimmune T cells in the CNS, likely through a direct cytotoxic effect on these T cells as suggested by results in vitro (36).

In clinical trials, Daclizumab has been effective in decreasing relapses in RRMS (38), an effect that was more pronounced in patients with highly active RRMS. This greater efficacy

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in highly active disease appears to be important as there are few effective treatments for this subtype of RRMS (39). Moreover, combining Daclizumab with IFN-β in a therapeutic regimen has been clinically and radiologically beneficial in patients with limited response to interferon (40–44). Although based on some reports, the safety of Daclizumab is a matter of concern (45), other reports indicate the safety of the drug after two years of administration to RRMS patients (46).

1.4. Targeting T cell Activation

1.4.1. Altered Peptide Ligands (APL)—The first step in activation of T cells is recognition of the “MHC-peptide complex” by the T cell receptor (TCR) (47). To prevent T cell activation, TCR can be blocked by altering peptides that bind to TCR but cannot activate T cells. These “altered peptide ligands (APLs" have a minor structural modification compared to immunogenic peptide ligands and compete with them in binding to TCR. By antagonizing the “MHC-peptide complex,” T cell activity will be inhibited (48, 49). It has been proposed that APL can provide a selective and specific tool for modulation of T cell response to a “known antigen” (49).

Several autoantigens are thought to contribute to MS pathogenesis, such as myelin basic protein (MBP) and myelin oligodendrocyte glycoprotein (MOG). Some of these antigens have been used as templates for APLs (50). A number of experimental studies with APLs carried out in the animal model of MS, experimental autoimmune encephalomyelitis (EAE), have shown suppression of CNS inflammation and improvement of neurological deficits (51–54).

In clinical trials, however, the safety and efficacy of different APLs have not been proven (49, 55). For example, five out of six clinical trials testing an APL of MBP failed to show any benefit in MS (56). In addition, unacceptable immunological side effects have been reported (57). In a phase II study (58), an APL exacerbated disease in a few patients, and systemic hypersensitivity reactions in some patients have been reported (57). In a phase III multicenter randomized 2-year, double-blind, placebo-controlled study using an APL of MBP, its efficacy in secondary progressive MS (SPMS) patients was not proven (55). An APL of MOG35-55, recombinant TCR ligand 1000 (RTL1000), has proved effective in reversing neurological deficits in EAE (59, 60) and had a favorable toxicity profile and promising outcomes in MS clinical trials (61, 62).

Although seemingly attractive, the APL approach has considerable shortcomings. For example, there is no evidence that the same autoantigen/peptide drives pathology in all MS patients. In other words"one APL for all MS patients” is not likely to be a feasible approach. It would be ideal to have a “personalized” APL approach based on the auto-antigen response of individual MS patients.

1.4.2. Targeting T cell Co-stimulatory Pathways—T cells are activated when their receptors (TCRs) recognize antigens presented by antigen-presenting cells (APCs). Binding TCR to the MHC-peptide complex is essential but not sufficient for activation of T cells after exposure to antigens. T cell activation also depends on additional costimulatory signals (63). Given that lack of co-stimulatory signals prevents T cell activation, blockade of co-

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stimulatory pathways has been suggested for modulation of T cell-mediated autoimmunity (64). The role of co-stimulatory pathways in MS pathogenesis has been investigated, and blocking these pathways has been proposed as a potential pharmacological intervention (65).

CD40:CD40L (66) and CD28:B7 (67) pathways are likely to be the critical co-stimulatory axes in MS pathogenesis (65). Furthermore, CD40: CD40L interactions have been suggested to be related to B cell activation, resulting in initiating and propagating rapid and vigorous immune memory responses (68).

Targeting CD40/CD40L co-stimulatory pathway was reported to be effective in amelioration of autoimmunity in an animal model of MS (69). However, thromboembolic events occurred that caused termination of clinical trials in other diseases such as lupus (70). These safety concerns have prevented further testing of any therapy based on inhibition of this pathway.

Inhibition of the CD28:B7 co-stimulatory pathway is now thought to be a more promising approach in modulating autoimmunity (71). Expression of CD28 on T cells and of B7-1 and B7-2 on APCs is believed to be important in T cell activation (69, 72). Inhibition of the CD28-B7 co-stimulatory pathway would likely block activation of T cells. CTLA4Ig (abatacept) is a fusion protein that inhibits CD28, with subsequent interruption of the CD28-B7 co-stimulatory pathway (72, 73). CTLA4Ig appears to be safe and effective in the treatment of some autoimmune diseases (74–77). Further, based on solid data on the efficacy of CTLA4Ig in animal experiments (78), clinical trials using this medication were started in RRMS patients. CTL4Ig has been reported to be safe in phase 1 clinical trials (79), and a phase II trial to clarify the efficacy of CTLA4Ig in RRMS is ongoing (NCT01116427) (70).

2. Targeting B Cells in MS

T cells are thought to be the main immune cells playing a role in the immunopathogenesis of MS. However, oligoclonal IgG bands detected in cerebrospinal fluid (CSF) from MS patients, and B cells found in demyelinating plaques, suggest a role for B cells (7). The role of B cells in MS was substantiated after observing amelioration of disease following B cell depletion (80). B cells could contribute to MS pathogenesis in several possible ways, including antibody production (81), antigen presentation, secretion of regulatory cytokines (82, 83), and as a reservoir for the Epstein-Barr virus (EBV) (84, 85). Although there is controversy about the role of EBV in MS, epidemiologic studies suggest that EBV might play a role. In pathological studies, it has been reported that activated EBV was found in the meninges in SPMS (24) but this observation has not been confirmed by others (86). B cells can also be considered a source for non-immunoglobulin molecules, perhaps cytokines, which diffuse from the meninges into the cortical gray matter (87).

B cells have been targeted in MS with the hope of providing a treatment strategy (Table 1). Rituximab is a humanized monoclonal antibody (mAb) that binds to the CD20 antigen on B cells (except for plasma cells) and is thought to trigger B cell cytotoxicity (88). The drug has a rapid and long-term effect on lowering the number of B cells. Rituximab has been approved for treatment of non-Hodgkin’s B cell lymphoma and rheumatoid arthritis (RA) by the FDA.

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In MS, rituximab has been effective in decreasing relapse rates and MRI parameters of disease activity (89). Trials are continuing to show the safety and efficacy of rituximab in RRMS patients (90). According to reports on phase II studies, relapse rate and MRI lesions were decreased in RRMS patients receiving ritoximab (91). Moreover, in a multicenter trial for PPMS patients, rituximab reduced disease progression in patients younger than 51 years old, and particularly those with inflammatory lesions shown by MRI scan (92). Considering the acceptable toxicity profile and relatively good efficacy of Rituximab, continuation of the trials on RR and progressive MS is warranted. Other antibodies against CD20 on B cells (Ocrelizumab and Ofatumumab) are being also studied in the treatment of MS (93, 94).

Although B cell depletion in MS therapy is somewhat promising, there are doubts regarding the results (95). Some B cell-targeted therapies failed to show efficacy. Blocking receptors for B cell stimulatory factor (BAFF) was not successful (96). This study indicates that B cells play complex roles in MS and that B cell-based therapies need more investigation (97).

3. Targeting Cytokines in MS

The cytokine network shapes a crosstalk system for immune cells involved in the immunopathogenesis of MS. The classification of cytokines as “pro-inflammatory” and “antiinflammatory” can provide a rationale for cytokine-based MS therapy (98) (Table 2). However, there are no reports supporting the targeting of cytokines to treat MS. Interleukin-12 (IL-12) and tumor necrosis factor (TNF) are two examples of unsuccessful efforts. Both cytokines have been reported to be upregulated in MS (99–101). A high serum level of both cytokines has been associated with exacerbation and development of active MRI lesions in progressive and RRMS patients (102–104), findings that led to attempts to target these cytokines in MS (99). Clinically, however, anti-IL-12/23 antibodies have not been reported to be effective in MS (105). Incidence of adverse events was not significantly different across treatment groups, although a numerically greater percentage of serious adverse events was reported for anti-IL-12 antibody-treated groups (105). TNF is a proinflammatory cytokine which has been studied in EAE and MS. TNF has two biologically active forms, soluble and transmembrane (106). Clinical trials using either the non-selective TNF antagonist (lenercept) or anti-TNF antibody (infliximab) reported worsening of clinical symptoms and MRI parameters of disease activity in MS patients (107, 108). However, more recently it has been shown that selective inhibition of soluble TNF significantly suppressed ongoing EAE (109), and it might therefore be effective in MS therapy.

Importantly, recent studies in animal models of MS have shown that granulocyte-macrophage colony-stimulating factor (GM-CSF) is necessary for development of CNS inflammation, and that T cells are its relevant source, indicating that GM-CSF may play a critical pathogenic role in MS (110–111). Indeed, Phase I clinical trials testing the effect of GM-CSF blockade on MS are ongoing and reported to be generally safe (112).

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4. Vaccination in MS

Vaccination against T cells, TCR vaccines and DNA vaccines are three investigational approaches to treat MS (Table 3).

T cell vaccination (TCV) is an immunization against pathogenic T cells. It is expected that TCV could modulate the pathogenesis of MS. To develop vaccines, myelin-reactive T cells from the blood or cerebrospinal fluid (CSF) of MS patients are collected, expanded and re-infused to the patients. In response to TCV, regulatory T cells that recognize activation markers on the vaccine cells are expanded (113) and can suppress myelin-reactive T cells (114, 115). It has also been proposed that TCV can stimulate anti-inflammatory cytokine secretion by Th2 cells; this secretion of anti-inflammatory cytokines is independent of the antigen specificity of activated T cells and might be an immunomodulatory consequence of TCV (116).

TCV has been reported to provide resistance to EAE induction and reduction of relapse rate in EAE-induced animals (113, 117, 118). In clinical trials, a modest reduction in relapse rate was reported in vaccinated individuals with RRMS (119–121). In RRMS patients who did not respond to fist-line medications, TCV was claimed to be effective (122). In a study of 4 SPMS patients, TCV has been reported effective in depleting myelin-reactive T cells, with no obvious clinical improvement (i.e., two patients were stable, one with reduced EDSS, and another one with advanced EDSS) (123). More recently, the first controlled, double-blind trial with TCV in relapsing progressive MS has been performed by Karussis et al. TCV significantly improved the walking capacity of patients, with the relapsing rate reduced by 89.6% vs. 42.9% in placebo treatment, while no significant changes were observed in MRI parameters. Importantly, the feasibility and safety of this treatment have also been demonstrated (124).

TCR Vaccines (TCRV): TCRs are essential for antigen recognition and subsequent activation of T cells. Certain variable regions (V-region) of TCRs are over-expressed on pathogenic T cells in MS patients, and V-regions have been used in the development of TCRV (125–126). TCRV has been reported to be safe and effective in decreasing the relapse rate in MS patients. Clinical improvement after TCRV has been attributed to enhanced function of regulatory T cells that recognize TCR determinants (127–129).

DNA Vaccines are induced by injection of pieces of DNA, constructed by genetic engineering. DNA vaccines contain "antigen coding genes" (130). It has been hypothesized that these DNA pieces are integrated into the genome and cause cells to produce antigens of a specific type. Hypothetically, production of autoantigens induces tolerance. Based on these assumptions, different types of DNA vaccines encoding myelin antigens have been tested in EAE. Some reports support protective effects of DNA vaccines in EAE, but this is controversial (131–143). Studies on human vaccines are limited. A DNA vaccine encoding the full-length MBP molecule (BHT-3009) was reported to be safe during a phase I/ II clinical trial (144). In a phase II trial, BHT-3009 was claimed to reduce lesions in MRI (145). However, neither improvement in clinical outcomes, nor neuroprotective effects have been documented (146, 147).

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Overall, T cell vaccination and T cell receptor vaccination studies have been limited and not particularly impressive. Further studies are required to advocate vaccination in MS therapy.

5. Induction of Tolerance in MS

Immunologic tolerance is a condition in which the immune system cannot respond to a specific antigen as a consequence of previous exposure. This process can prevent or decrease the immune response to self-antigens. Central tolerance occurs in the thymus, and peripheral tolerance develops in the blood; both processes include deletion and functional unresponsiveness of auto-reactive lymphocytes (148). Expansion of regulatory T cells is also seen during development of tolerance. By eliminating these harmful cells through tolerance, autoimmunity could be prevented (148). Some T cells, however, may escape elimination and remain in the repertoire (149). If these T cells are reactivated by triggering factors, they could likely contribute to the pathogenesis of autoimmune diseases including MS (150). Indeed, myelin-reactive T cell lines have been established from healthy subjects, indicating failure for central tolerance for myelin antigen reactive T cells (151). Induction and amplification of peripheral tolerance to eliminate or modify self-reactive T cells is believed to be a potential treatment strategy for autoimmune states (18). To induce tolerance, tolerogenic antigens can be administered by different routes (intravenous, intranasal or oral) (152).

Induction of tolerance has been examined in numerous EAE/MS studies. In EAE animals, intravenous tolerance induction resulted in clonal deletion (153) of myelin-specific T cells and expansion of regulatory T cells (154–156). In addition, reduced disease severity in chronic EAE was seen. However, no further prevention of disease progress has been documented (157, 158). Furthermore, therapeutic treatment of EAE animals with antigens appears to be less effective than prophylactic antigen infusion before EAE induction (154, 159).

One route of antigen-specific tolerance induction is via oral mucosa. The oral administration route has specific characteristics in tolerance induction. The mucosa of the gut is equipped with a vast immune system that can process orally ingested antigens (160). Sustained interface of an antigen with the gut immune system might provide a “mucosal tolerance” against the antigen. Oral administration of tolerogenic antigens has been found to modulate the course of EAE in animals (161, 162). Clonal deletion of “antigen-specific autoreactive T cells” and induction of regulatory T cells (163, 164) have been suggested as mechanisms of action.

Earlier clinical trials in MS patients reported that oral tolerance was effective in disease modulation (165). Unfortunately during a larger trial, those favorable results (163) were not confirmed. This discrepancy may be due to the diverse doses of antigens tested (166). In a randomized, placebo-controlled phase 1/2 trial, it was found that induction of antigen-specific tolerance in MS with DNA encoding MBP (BHT-3009) effectively reduced antigen-specific immune responses both in the peripheral immune system and the CNS, with good safety and tolerability (167). Studies for the long-term clinical efficacy of antigen-specific tolerance induction in MS patients are required.

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Nasal mucosa is another route for delivery of antigens to develop tolerance (168, 169). Intranasal administration of antigens to EAE-induced animals has been reported to modulate disease course (170); however, studies in human MS are still lacking.

Another approach to induce tolerance is attachment of antigens to splenocytes or blood cells and infusing those cells. This “cell-bound tolerogenic peptide method” can be used for tolerization against several antigens, thereby extending tolerogenicity to a more general array of antigens involved in the pathogenesis of MS. By using this method in animals, inhibition of induction and modulation of relapses in EAE has been achieved (171–173).

6. Stem cell-based therapies in MS

Bone marrow-derived mesenchymal stem cells transplantation has had both neuro-regenerative and immunomodulatory effects in MS. These cells as well as hematopoitic stem cells are easily obtained from adults; their therapeutic application is believed to be safe and to have the potential of playing a pivotal role in MS therapy (174–176). As regards immunomodulation and neuroprotection exerted by stem cells, this method could have potential as a therapeutic approach for MS.

Conclusion

While great progress in MS therapy has been made in the last two decades, current therapies are still largely ineffective, with potential side effects such as serious toxicities or global immunosuppression. Due to a better understanding of MS immunopathogenesis in recent years, new candidates have been introduced as therapeutic targets, including specific molecules on the surface of pathogenic CD4+ T and B cells, as well as the soluble products of these cells, e.g., proinflammatory cytokines. Further, promising findings have been obtained in the induction of myelin autoantigen-specific tolerance without disturbing the global immune system; these novel approaches will increase specificity and efficacy and reduce potential side effects such as global immunosuppression in future MS therapy. Nevertheless, their validation as practical MS therapies is dependent on the final favorable results. Further, although these immunomodulatory therapies are beneficial in preventing future CNS tissue damage, neuroregenerative approaches to reconstitute already damaged CNS tissues, e.g., demyelination, axonal loss and neuronal loss, will be of great importance in maximizing recovery of neurological functions.

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REFERENCES

1. Goodin DS. The epidemiology of multiple sclerosis: insights to disease pathogenesis. Handbook of clinical neurology. 2014; 122:231–266. PubMed PMID: 24507521. [PubMed: 24507521]
2. Adelman G, Rane SG, Villa KF. The cost burden of multiple sclerosis in the United States: a systematic review of the literature. Journal of medical economics. 2013; 16(5):639–647. PubMed PMID: 23425293. [PubMed: 23425293]

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3. Jennum P, Wanscher B, Frederiksen J, Kjellberg J. The socioeconomic consequences of multiple sclerosis: a controlled national study. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology. 2012 Jan; 22(1):36–43. PubMed PMID: 21669514. [PubMed: 21669514]
4. Jankovic SM, Kostic M, Radosavljevic M, Tesic D, Stefanovic-Stoimenov N, Stevanovic I, et al. Cost-effectiveness of four immunomodulatory therapies for relapsing-remitting multiple sclerosis: a Markov model based on data a Balkan country in socioeconomic transition. Vojnosanitetski pregled Military-medical and pharmaceutical review. 2009 Jul; 66(7):556–562. PubMed PMID: 19678581. [PubMed: 19678581]
5. Feinstein A, Freeman J, Lo AC. Treatment of progressive multiple sclerosis: what works, what does not, what is needed. Lancet Neurol. 2015 Feb; 14(2):194–207. PubMed PMID: 25772898. [PubMed: 25772898]
6. Goverman J. Autoimmune T cell responses in the central nervous system. Nature reviews Immunology. 2009 Jun; 9(6):393–407. PubMed PMID: 19444307. Pubmed Central PMCID: 2813731.
7. Disanto G, Morahan JM, Barnett MH, Giovannoni G, Ramagopalan SV. The evidence for a role of B cells in multiple sclerosis. Neurology. 2012 Mar 13; 78(11):823–832. PubMed PMID: 22411958. Pubmed Central PMCID: 3304944. [PubMed: 22411958]
8. Mirshafiey A, Kianiaslani M. Autoantigens and autoantibodies in multiple sclerosis. Iranian journal of allergy, asthma, and immunology. 2013 Dec; 12(4):292–303. PubMed PMID: 23996705.
9. Fletcher JM, Lalor SJ, Sweeney CM, Tubridy N, Mills KH. T cells in multiple sclerosis and experimental autoimmune encephalomyelitis. Clin Exp Immunol. 2010 Oct; 162(1):1–11. PubMed PMID: 20682002. eng. [PubMed: 20682002]
10. Constantinescu CS, Kamoun M, Dotti M, Farber RE, Galetta SL, Rostami A. A longitudinal study of the T cell activation marker CD26 in chronic progressive multiple sclerosis. Journal of the neurological sciences. 1995 Jun; 130(2):178–182. PubMed PMID: 8586983. [PubMed: 8586983]
11. Van der Walt A, Butzkueven H, Kolbe S, Marriott M, Alexandrou E, Gresle M, et al. Neuroprotection in multiple sclerosis: a therapeutic challenge for the next decade. Pharmacology & therapeutics. 2010 Apr; 126(1):82–93. PubMed PMID: 20122960. [PubMed: 20122960]
12. Le Page E, Leray E, Edan G, French Mitoxantrone Safety G. Long-term safety profile of mitoxantrone in a French cohort of 802 multiple sclerosis patients: a 5-year prospective study. Multiple sclerosis. 2011 Jul; 17(7):867–875. PubMed PMID: 21325016. [PubMed: 21325016]
13. Balcer LJ, Galetta SL, Polman CH, Eggenberger E, Calabresi PA, Zhang A, et al. Lowcontrast acuity measures visual improvement in phase 3 trial of natalizumab in relapsing MS. Journal of the neurological sciences. 2012 Jul 15; 318(1-2):119–124. PubMed PMID: 22521274. [PubMed: 22521274]
14. Kerbrat A, Le Page E, Leray E, Anani T, Coustans M, Desormeaux C, et al. Natalizumab and drug holiday in clinical practice: an observational study in very active relapsing remitting multiple sclerosis patients. Journal of the neurological sciences. 2011 Sep 15; 308(1–2):98–102. PubMed PMID: 21665227. [PubMed: 21665227]
15. Marta M, Giovannoni G. Disease modifying drugs in multiple sclerosis: mechanisms of action and new drugs in the horizon. CNS & neurological disorders drug targets. 2012 Aug 1; 11(5):610–623. PubMed PMID: 22583439. Epub 2012/05/16. eng. [PubMed: 22583439]
16. Havrdova E, Horakova D, Kovarova I. Alemtuzumab in the treatment of multiple sclerosis: key clinical trial results and considerations for use. Ther Adv Neurol Disord. 2015 Jan; 8(1):31–45. PubMed PMID: 25584072. Pubmed Central PMCID: 4286943. [PubMed: 25584072]
17. Pozzilli C, Schweikert B, Ecari U, Oentrich W, BetaPlus Study g. Supportive strategies to improve adherence to IFN beta-1b in multiple sclerosis--results of the betaPlus observational cohort study. Journal of the neurological sciences. 2011 Aug 15; 307(1-2):120–126. PubMed PMID: 21636099. [PubMed: 21636099]
18. O'Brien K, Gran B, Rostami A. T-cell based immunotherapy in experimental autoimmune encephalomyelitis and multiple sclerosis. Immunotherapy. 2010 Jan; 2(1):99–115. PubMed PMID: 20231863. eng. [PubMed: 20231863]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

19. Lindsey JW, Hodgkinson S, Mehta R, Mitchell D, Enzmann D, Steinman L. Repeated treatment with chimeric anti-CD4 antibody in multiple sclerosis. Annals of neurology. 1994 Aug; 36(2):183–189. PubMed PMID: 8053654. eng. [PubMed: 8053654]

20. Lindsey JW, Hodgkinson S, Mehta R, Siegel RC, Mitchell DJ, Lim M, et al. Phase 1 clinical trial of chimeric monoclonal anti-CD4 antibody in multiple sclerosis. Neurology. 1994 Mar; 44(3 Pt 1): 413–419. PubMed PMID: 8145907. eng. [PubMed: 8145907]

21. van Oosten BW, Lai M, Hodgkinson S, Barkhof F, Miller DH, Moseley IF, et al. Treatment of multiple sclerosis with the monoclonal anti-CD4 antibody cM-T412: results of a randomized, double-blind, placebo-controlled, MR-monitored phase II trial. Neurology. 1997 Aug; 49(2):351–357. PubMed PMID: 9270561. eng. [PubMed: 9270561]

22. Cox AL, Thompson SA, Jones JL, Robertson VH, Hale G, Waldmann H, et al. Lymphocyte homeostasis following therapeutic lymphocyte depletion in multiple sclerosis. European journal of immunology. 2005 Nov; 35(11):3332–3342. PubMed PMID: 16231285. eng. [PubMed: 16231285]

23. Hill-Cawthorne GA, Button T, Tuohy O, Jones JL, May K, Somerfield J, et al. Long term lymphocyte reconstitution after alemtuzumab treatment of multiple sclerosis. Journal of neurology, neurosurgery, and psychiatry. 2012 Mar; 83(3):298–304. PubMed PMID: 22056965. Epub 2011/11/08. eng.

24. Zhang X, Tao Y, Chopra M, Ahn M, Marcus KL, Choudhary N, et al. Differential reconstitution of T cell subsets following immunodepleting treatment with alemtuzumab (anti-CD52 monoclonal antibody) in patients with relapsing-remitting multiple sclerosis. Journal of immunology. 2013 Dec 15; 191(12):5867–5874. PubMed PMID: 24198283.

25. Pettitt AR, Jackson R, Carruthers S, Dodd J, Dodd S, Oates M, et al. Alemtuzumab in Combination With Methylprednisolone Is a Highly Effective Induction Regimen for Patients With Chronic Lymphocytic Leukemia and Deletion of TP53: Final Results of the National Cancer Research Institute CLL206 Trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012 May 10; 30(14):1647–1655. PubMed PMID: 22493413. eng. [PubMed: 22493413]

26. van den Hoogen MW, Hoitsma AJ, Hilbrands LB. Anti-T-cell antibodies for the treatment of acute rejection after renal transplantation. Expert opinion on biological therapy. 2012 May 15. PubMed PMID: 22583145. Eng.

27. Hale G, Cobbold S, Waldmann H. T cell depletion with CAMPATH-1 in allogeneic bone marrow transplantation. Transplantation. 1988 Apr; 45(4):753–759. PubMed PMID: 3282358. Epub 1988/04/01. eng. [PubMed: 3282358]

28. Moreau T, Thorpe J, Miller D, Moseley I, Hale G, Waldmann H, et al. Preliminary evidence from magnetic resonance imaging for reduction in disease activity after lymphocyte depletion in multiple sclerosis. Lancet. 1994 Jul 30; 344(8918):298–301. PubMed PMID: 7914262. eng. [PubMed: 7914262]

29. Marrie R, Horwitz R, Cutter G, Tyry T, Campagnolo D, Vollmer T. Comorbidity, socioeconomic status and multiple sclerosis. Multiple sclerosis. 2008 Sep; 14(8):1091–1098. PubMed PMID: 18728060. [PubMed: 18728060]

30. Coles AJ, Fox E, Vladic A, Gazda SK, Brinar V, Selmaj KW, et al. Alemtuzumab more effective than interferon beta-1a at 5-year follow-up of CAMMS223 clinical trial. Neurology. 2012 Apr 3; 78(14):1069–1078. PubMed PMID: 22442431. eng. [PubMed: 22442431]

31. Espinoza-Delgado I, Ortaldo JR, Winkler-Pickett R, Sugamura K, Varesio L, Longo DL. Expression and role of p75 interleukin 2 receptor on human monocytes. J Exp Med. 1990 May 1; 171(5):1821–1826. PubMed PMID: 2110244. eng. [PubMed: 2110244]

32. Wang LM, Zhang DM, Xu YM, Sun SL. Interleukin 2 receptor alpha gene polymorphism and risk of multiple sclerosis: a meta-analysis. The Journal of international medical research. 2011; 39(5): 1625–1635. PubMed PMID: 22117963. Epub 2011/11/29. eng. [PubMed: 22117963]

33. Phillips SM, Bhopale MK, Hilliard B, Zekavat SA, Ali MA, Rostami A. Suppression of murine experimental autoimmune encephalomyelitis by interleukin-2 receptor targeted fusion toxin, DAB(389)IL-2. Cellular immunology. 2010; 261(2):144–152. PubMed PMID: 20042183. eng. [PubMed: 20042183]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

34. Waldmann TA, Longo DL, Leonard WJ, Depper JM, Thompson CB, Kronke M, et al. Interleukin 2 receptor (Tac antigen) expression in HTLV-I-associated adult T-cell leukemia. Cancer Res. 1985 Sep; 45(9 Suppl):4559s–4562s. PubMed PMID: 2990687. eng. [PubMed: 2990687]
35. Sandrini S. Use of IL-2 receptor antagonists to reduce delayed graft function following renal transplantation: a review. Clinical transplantation. 2005 Dec; 19(6):705–710. PubMed PMID: 16313313. eng. [PubMed: 16313313]
36. Poli A, Michel T, Theresine M, Andres E, Hentges F, Zimmer J. CD56bright natural killer (NK) cells: an important NK cell subset. Immunology. 2009 Apr; 126(4):458–465. PubMed PMID: 19278419. Pubmed Central PMCID: 2673358. Epub 2009/03/13. eng. [PubMed: 19278419]
37. Bielekova B, Catalfamo M, Reichert-Scrivner S, Packer A, Cerna M, Waldmann TA, et al. Regulatory CD56(bright) natural killer cells mediate immunomodulatory effects of IL-2Ralpha-targeted therapy (daclizumab) in multiple sclerosis. Proceedings of the National Academy of Sciences of the United States of America. 2006 Apr 11; 103(15):5941–5946. PubMed PMID: 16585503. eng. [PubMed: 16585503]
38. Milo R. The efficacy and safety of daclizumab and its potential role in the treatment of multiple sclerosis. Ther Adv Neurol Disord. 2014 Jan; 7(1):7–21. PubMed PMID: 24409199. Pubmed Central PMCID: 3886384. Epub 2014/01/11. Eng. [PubMed: 24409199]
39. Giovannoni G, Radue EW, Havrdova E, Riester K, Greenberg S, Mehta L, et al. Effect of daclizumab high-yield process in patients with highly active relapsing-remitting multiple sclerosis. J Neurol. 2014 Feb; 261(2):316–323. PubMed PMID: 24375015. Pubmed Central PMCID: 3915085. Epub 2014/01/01. eng. [PubMed: 24375015]
40. Bielekova B, Howard T, Packer AN, Richert N, Blevins G, Ohayon J, et al. Effect of anti-CD25 antibody daclizumab in the inhibition of inflammation and stabilization of disease progression in multiple sclerosis. Arch Neurol. 2009 Apr; 66(4):483–489. PubMed PMID: 19364933. eng. [PubMed: 19364933]
41. Bielekova B, Richert N, Howard T, Blevins G, Markovic-Plese S, McCartin J, et al. Humanized anti-CD25 (daclizumab) inhibits disease activity in multiple sclerosis patients failing to respond to interferon beta. Proceedings of the National Academy of Sciences of the United States of America. 2004 Jun 8; 101(23):8705–8708. PubMed PMID: 15161974. eng. [PubMed: 15161974]
42. Rose JW, Watt HE, White AT, Carlson NG. Treatment of multiple sclerosis with an anti-interleukin-2 receptor monoclonal antibody. Annals of neurology. 2004 Dec; 56(6):864–867. PubMed PMID: 15499632. eng. [PubMed: 15499632]
43. Wynn D, Kaufman M, Montalban X, Vollmer T, Simon J, Elkins J, et al. Daclizumab in active relapsing multiple sclerosis (CHOICE study): a phase 2, randomised, double-blind, placebo-controlled, add-on trial with interferon beta. Lancet Neurol. 2010 Apr; 9(4):381–390. PubMed PMID: 20163990. eng. [PubMed: 20163990]
44. Rose JW, Burns JB, Bjorklund J, Klein J, Watt HE, Carlson NG. Daclizumab phase II trial in relapsing and remitting multiple sclerosis: MRI and clinical results. Neurology. 2007 Aug 21; 69(8):785–789. PubMed PMID: 17709711. eng. [PubMed: 17709711]
45. Oh J, Saidha S, Cortese I, Ohayon J, Bielekova B, Calabresi PA, et al. Daclizumab-induced adverse events in multiple organ systems in multiple sclerosis. Neurology. 2014 Mar 18; 82(11):984–988. PubMed PMID: 24532277. Epub 2014/02/18. eng. [PubMed: 24532277]
46. Giovannoni G, Gold R, Selmaj K, Havrdova E, Montalban X, Radue EW, et al. Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECTION): a multicentre, randomised, double-blind extension trial. Lancet Neurol. 2014 Mar 18. PubMed PMID: 24656609. Epub 2014/03/25. Eng.
47. Racioppi L, Ronchese F, Matis LA, Germain RN. Peptide-major histocompatibility complex class II complexes with mixed agonist/antagonist properties provide evidence for ligand-related differences in T cell receptor-dependent intracellular signaling. J Exp Med. 1993 Apr 1; 177(4): 1047–1060. PubMed PMID: 8384651. Pubmed Central PMCID: 2190984. Epub 1993/04/01. eng. [PubMed: 8384651]
48. Bachmann MF, Speiser DE, Zakarian A, Ohashi PS. Inhibition of TCR triggering by a spectrum of altered peptide ligands suggests the mechanism for TCR antagonism. European journal of immunology. 1998 Oct; 28(10):3110–3119. PubMed PMID: 9808179. eng. [PubMed: 9808179]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

49. Bielekova B, Martin R. Antigen-specific immunomodulation via altered peptide ligands. J Mol Med (Berl). 2001 Oct; 79(10):552–565. PubMed PMID: 11692152. eng. [PubMed: 11692152]
50. Wucherpfennig KW, Catz I, Hausmann S, Strominger JL, Steinman L, Warren KG. Recognition of the immunodominant myelin basic protein peptide by autoantibodies and HLA-DR2-restricted T cell clones from multiple sclerosis patients. Identity of key contact residues in the B-cell and T-cell epitopes. The Journal of clinical investigation. 1997 Sep 1; 100(5):1114–1122. PubMed PMID: 9276728. eng. [PubMed: 9276728]
51. Brocke S, Gijbels K, Allegretta M, Ferber I, Piercy C, Blankenstein T, et al. Treatment of experimental encephalomyelitis with a peptide analogue of myelin basic protein. Nature. 1996 Jan 25; 379(6563):343–346. PubMed PMID: 8552189. eng. [PubMed: 8552189]
52. Crowe PD, Qin Y, Conlon PJ, Antel JP. NBI-5788, an altered MBP83-99 peptide, induces a T-helper 2-like immune response in multiple sclerosis patients. Ann Neurol. 2000 Nov; 48(5):758–765. PubMed PMID: 11079539. Epub 2000/11/18. eng. [PubMed: 11079539]
53. Darlington CL. NBI-5788 Neurocrine. Curr Opin Investig Drugs. 2005 Jul; 6(7):747–751. PubMed PMID: 16044672. eng.
54. Darlington C. MBP-8298, a synthetic peptide analog of myelin basic protein for the treatment of multiple sclerosis. Curr Opin Mol Ther. 2007 Aug; 9(4):398–402. PubMed PMID: 17694453. eng. [PubMed: 17694453]
55. Freedman MS, Bar-Or A, Oger J, Traboulsee A, Patry D, Young C, et al. A phase III study evaluating the efficacy and safety of MBP8298 in secondary progressive MS. Neurology. 2011 Oct 18; 77(16):1551–1560. PubMed PMID: 21975206. eng. [PubMed: 21975206]
56. Multiple Sclerosis: National clinical guideline for diagnosis and management in primary and secondary care. London: National Institute for Health and Clinical Excellence: Guidance; 2004.
57. Kappos L, Comi G, Panitch H, Oger J, Antel J, Conlon P, et al. Induction of a nonencephalitogenic type 2 T helper-cell autoimmune response in multiple sclerosis after administration of an altered peptide ligand in a placebo-controlled, randomized phase II trial. The Altered Peptide Ligand in Relapsing MS Study Group. Nature medicine. 2000 Oct; 6(10):1176–1182. PubMed PMID: 11017151. eng.
58. Bielekova B, Goodwin B, Richert N, Cortese I, Kondo T, Afshar G, et al. Encephalitogenic potential of the myelin basic protein peptide (amino acids 83-99) in multiple sclerosis: results of a phase II clinical trial with an altered peptide ligand. Nature medicine. 2000 Oct; 6(10):1167–1175. PubMed PMID: 11017150. Epub 2000/10/04. eng.
59. Burrows GG, Meza-Romero R, Huan J, Sinha S, Mooney JL, Vandenbark AA, et al. Gilt required for RTL550-CYS-MOG to treat experimental autoimmune encephalomyelitis. Metabolic brain disease. 2012 Jun; 27(2):143–149. PubMed PMID: 22392628. Pubmed Central PMCID: 3348371. Epub 2012/03/07. eng. [PubMed: 22392628]
60. Sinha S, Miller L, Subramanian S, McCarty OJ, Proctor T, Meza-Romero R, et al. Binding of recombinant T cell receptor ligands (RTL) to antigen presenting cells prevents upregulation of CD11b and inhibits T cell activation and transfer of experimental autoimmune encephalomyelitis. J Neuroimmunol. 2010 Aug 25; 225(1-2):52–61. PubMed PMID: 20546940. Pubmed Central PMCID: 2924959. Epub 2010/06/16. eng. [PubMed: 20546940]
61. Yadav V, Bourdette DN, Bowen JD, Lynch SG, Mattson D, Preiningerova J, et al. Recombinant T-Cell Receptor Ligand (RTL) for Treatment of Multiple Sclerosis: A Double-Blind, Placebo-Controlled, Phase 1, Dose-Escalation Study. Autoimmune Dis. 2012; 2012:954739. PubMed PMID: 22548151. eng. [PubMed: 22548151]
62. Offner H, Sinha S, Burrows GG, Ferro AJ, Vandenbark AA. RTL therapy for multiple sclerosis: a Phase I clinical study. J Neuroimmunol. 2011 Feb; 231(1-2):7–14. PubMed PMID: 20965577. Pubmed Central PMCID: 3026883. Epub 2010/10/23. eng. [PubMed: 20965577]
63. Podojil JR, Miller SD. Molecular Mechanisms of T cell Receptor and Costimulatory Molecule Ligation/Blockade in Autoimmune Disease Therapy. Immunol Rev. 2009 May; 229(1):337–355. [PubMed: 19426232]
64. Viglietta V, Khoury SJ. Modulating co-stimulation. Neurotherapeutics. 2007 Oct; 4(4):666–675. PubMed PMID: 17920548. eng. [PubMed: 17920548]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

65. Allen SD, Rawale SV, Whitacre CC, Kaumaya PT. Therapeutic peptidomimetic strategies for autoimmune diseases: costimulation blockade. J Pept Res. 2005 Jun; 65(6):591–604. PubMed PMID: 15885118. eng. [PubMed: 15885118]

66. Girvin AM, Dal Canto MC, Miller SD. CD40/CD40L interaction is essential for the induction of EAE in the absence of CD28-mediated co-stimulation. J Autoimmun. 2002 Mar; 18(2):83–94. PubMed PMID: 11908941. eng. [PubMed: 11908941]

67. Hartmann FJ, Khademi M, Aram J, Ammann S, Kockum I, Constantinescu C, et al. Multiple sclerosis-associated IL2RA polymorphism controls GM-CSF production in human TH cells. Nature communications. 2014; 5:5056. PubMed PMID: 25278028.

68. Bar-Or A, Oliveira EM, Anderson DE, Krieger JI, Duddy M, O'Connor KC, et al. Immunological memory: contribution of memory B cells expressing costimulatory molecules in the resting state. Journal of immunology. 2001 Nov 15; 167(10):5669–5677. PubMed PMID: 11698439. Epub 2001/11/08. eng.

69. Girvin AM, Dal Canto MC, Rhee L, Salomon B, Sharpe A, Bluestone JA, et al. A critical role for B7/CD28 costimulation in experimental autoimmune encephalomyelitis: a comparative study using costimulatory molecule-deficient mice and monoclonal antibody blockade. Journal of immunology (Baltimore, Md : 1950). 2000 Jan 1; 164(1):136–143. PubMed PMID: 10605004. eng.

70. Chitnis, T.; Khoury, SJ. multiple sclerosis therapeutics. forth ed. New York: Cambridge University Press; 2011.

71. Mikulkova Z, Praksova P, Stourac P, Bednarik J, Michalek J. Imbalance in T-cell and cytokine profiles in patients with relapsing-remitting multiple sclerosis. Journal of the neurological sciences. 2011 Jan 15; 300(1-2):135–141. PubMed PMID: 20884014. [PubMed: 20884014]

72. Bour-Jordan H, Esensten JH, Martinez-Llordella M, Penaranda C, Stumpf M, Bluestone JA. Intrinsic and extrinsic control of peripheral T-cell tolerance by costimulatory molecules of the CD28/ B7 family. Immunological reviews. 2011 May; 241(1):180–205. PubMed PMID: 21488898. Pubmed Central PMCID: 3077803. Epub 2011/04/15. eng. [PubMed: 21488898]

73. Bluestone JA, St Clair EW, Turka LA. CTLA4Ig: bridging the basic immunology with clinical application. Immunity. 2006 Mar; 24(3):233–238. PubMed PMID: 16546089. Epub 2006/03/21. eng. [PubMed: 16546089]

74. Abrams JR, Lebwohl MG, Guzzo CA, Jegasothy BV, Goldfarb MT, Goffe BS, et al. CTLA4Ig-mediated blockade of T-cell costimulation in patients with psoriasis vulgaris. The Journal of clinical investigation. 1999 May; 103(9):1243–1252. PubMed PMID: 10225967. Pubmed Central PMCID: 408469. Epub 1999/05/04. eng. [PubMed: 10225967]

75. Abrams JR, Kelley SL, Hayes E, Kikuchi T, Brown MJ, Kang S, et al. Blockade of T lymphocyte costimulation with cytotoxic T lymphocyte-associated antigen 4-immunoglobulin (CTLA4Ig) reverses the cellular pathology of psoriatic plaques, including the activation of keratinocytes, dendritic cells, and endothelial cells. J Exp Med. 2000 Sep 4; 192(5):681–694. PubMed PMID: 10974034. eng. [PubMed: 10974034]

76. Mease P, Genovese MC, Gladstein G, Kivitz AJ, Ritchlin C, Tak PP, et al. Abatacept in the treatment of patients with psoriatic arthritis: results of a six-month, multicenter, randomized, double-blind, placebo-controlled, phase II trial. Arthritis Rheum. 2011 Apr; 63(4):939–948. PubMed PMID: 21128258. Epub 2010/12/04. eng. [PubMed: 21128258]

77. Emery P, Durez P, Dougados M, Legerton CW, Becker JC, Vratsanos G, et al. Impact of T-cell costimulation modulation in patients with undifferentiated inflammatory arthritis or very early rheumatoid arthritis: a clinical and imaging study of abatacept (the ADJUST trial). Annals of the rheumatic diseases. 2010 Mar; 69(3):510–516. PubMed PMID: 19933744. Pubmed Central PMCID: 2927615. Epub 2009/11/26. eng. [PubMed: 19933744]

78. Schaub M, Issazadeh S, Stadlbauer TH, Peach R, Sayegh MH, Khoury SJ. Costimulatory signal blockade in murine relapsing experimental autoimmune encephalomyelitis. Journal of neuroimmunology. 1999 May 3; 96(2):158–166. PubMed PMID: 10337914. eng. [PubMed: 10337914]

79. Viglietta V, Bourcier K, Buckle GJ, Healy B, Weiner HL, Hafler DA, et al. CTLA4Ig treatment in patients with multiple sclerosis: an open-label, phase 1 clinical trial. Neurology. 2008 Sep 16; 71(12):917–924. PubMed PMID: 18794494. eng. [PubMed: 18794494]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

80. Martin F, Chan AC. B cell immunobiology in disease: evolving concepts from the clinic. Annual review of immunology. 2006; 24:467–496. PubMed PMID: 16551256. Epub 2006/03/23. eng.
81. Lyons JA, Ramsbottom MJ, Cross AH. Critical role of antigen-specific antibody in experimental autoimmune encephalomyelitis induced by recombinant myelin oligodendrocyte glycoprotein. European journal of immunology. 2002 Jul; 32(7):1905–1913. PubMed PMID: 12115610. Epub 2002/07/13. eng. [PubMed: 12115610]
82. Lund FE, Garvy BA, Randall TD, Harris DP. Regulatory roles for cytokine-producing B cells in infection and autoimmune disease. Current directions in autoimmunity. 2005; 8:25–54. PubMed PMID: 15564716. Epub 2004/11/27. eng. [PubMed: 15564716]
83. Duddy ME, Alter A, Bar-Or A. Distinct profiles of human B cell effector cytokines: a role in immune regulation? Journal of immunology. 2004 Mar 15; 172(6):3422–3427. PubMed PMID: 15004141. Epub 2004/03/09. eng.
84. Pender MP. Infection of autoreactive B lymphocytes with EBV, causing chronic autoimmune diseases. Trends Immunol. 2003 Nov; 24(11):584–588. PubMed PMID: 14596882. Epub 2003/11/05. eng. [PubMed: 14596882]
85. Farjam M, Ebrahimpour A, Fakhraei B. CD21 positive B cell: a novel target for treatment of multiple sclerosis. Medical hypotheses. 2013 May; 80(5):556–557. PubMed PMID: 23384704. [PubMed: 23384704]
86. Willis SN, Stadelmann C, Rodig SJ, Caron T, Gattenloehner S, Mallozzi SS, et al. Epstein-Barr virus infection is not a characteristic feature of multiple sclerosis brain. Brain : a journal of neurology. 2009 Dec; 132(Pt 12):3318–3328. PubMed PMID: 19638446. eng. [PubMed: 19638446]
87. Lisak RP, Benjamins JA, Nedelkoska L, Barger JL, Ragheb S, Fan B, et al. Secretory products of multiple sclerosis B cells are cytotoxic to oligodendroglia in vitro. Journal of neuroimmunology. 2012 May 15; 246(1-2):85–95. PubMed PMID: 22458983. [PubMed: 22458983]
88. Cragg MS, Walshe CA, Ivanov AO, Glennie MJ. The biology of CD20 and its potential as a target for mAb therapy. Current directions in autoimmunity. 2005; 8:140–174. PubMed PMID: 15564720. eng. [PubMed: 15564720]
89. Stuve O, Cepok S, Elias B, Saleh A, Hartung HP, Hemmer B, et al. Clinical stabilization and effective B-lymphocyte depletion in the cerebrospinal fluid and peripheral blood of a patient with fulminant relapsing-remitting multiple sclerosis. Arch Neurol. 2005 Oct; 62(10):1620–1623. PubMed PMID: 16216948. Epub 2005/10/12. eng. [PubMed: 16216948]
90. Bar-Or A, Calabresi PA, Arnold D, Markowitz C, Shafer S, Kasper LH, et al. Rituximab in relapsing-remitting multiple sclerosis: a 72-week, open-label, phase I trial. Annals of neurology. 2008 Mar; 63(3):395–400. PubMed PMID: 18383069. Epub 2008/04/03. eng. [PubMed: 18383069]
91. Hauser SL, Waubant E, Arnold DL, Vollmer T, Antel J, Fox RJ, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. N Engl J Med. 2008 Feb 14; 358(7):676–688. PubMed PMID: 18272891. Epub 2008/02/15. eng. [PubMed: 18272891]
92. Hawker K, O'Connor P, Freedman MS, Calabresi PA, Antel J, Simon J, et al. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. Annals of neurology. 2009 Oct; 66(4):460–471. PubMed PMID: 19847908. Epub 2009/10/23. eng. [PubMed: 19847908]
93. Chaudhuri A. Ocrelizumab in multiple sclerosis: risks and benefits. Lancet. 2012 Mar 31; 379(9822):1196–117. author reply 7. PubMed PMID: 22464382. Epub 2012/04/03. eng. [PubMed: 22464382]
94. Nightingale G. Ofatumumab: a novel anti-CD20 monoclonal antibody for treatment of refractory chronic lymphocytic leukemia. Ann Pharmacother. 2011 Oct; 45(10):1248–1255. PubMed PMID: 21896924. eng. [PubMed: 21896924]
95. He D, Guo R, Zhang F, Zhang C, Dong S, Zhou H. Rituximab for relapsing-remitting multiple sclerosis. Cochrane Database Syst Rev. 2013; 12:CD009130. PubMed PMID: 24310855.
96. Kappos L, Hartung HP, Freedman MS, Boyko A, Radu EW, Mikol DD, et al. Atacicept in multiple sclerosis (ATAMS): a randomised, placebo-controlled, double-blind, phase 2 trial. Lancet Neurol. 2014 Apr; 13(4):353–363. PubMed PMID: 24613349. [PubMed: 24613349]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

97. Hoffmann FS, Kuhn PH, Laurent SA, Hauck SM, Berer K, Wendlinger SA, et al. The immunoregulator soluble TACI is released by ADAM10 and reflects B cell activation in autoimmunity. Journal of immunology. 2015 Jan 15; 194(2):542–552. PubMed PMID: 25505277. Pubmed Central PMCID: 4282951.

98. Hedegaard CJ, Krakauer M, Bendtzen K, Lund H, Sellebjerg F, Nielsen CH. T helper cell type 1 (Th1), Th2 and Th17 responses to myelin basic protein and disease activity in multiple sclerosis. Immunology. 2008 Oct; 125(2):161–169. PubMed PMID: 18397264. eng. [PubMed: 18397264]

99. Selmaj K, Raine CS, Cannella B, Brosnan CF. Identification of lymphotoxin and tumor necrosis factor in multiple sclerosis lesions. The Journal of clinical investigation. 1991 Mar; 87(3):949–954. PubMed PMID: 1999503. Pubmed Central PMCID: 329886. Epub 1991/03/01. eng. [PubMed: 1999503]

100. Hofman FM, Hinton DR, Johnson K, Merrill JE. Tumor necrosis factor identified in multiple sclerosis brain. J Exp Med. 1989 Aug 1; 170(2):607–612. PubMed PMID: 2754393. Pubmed Central PMCID: 2189402. Epub 1989/08/01. eng. [PubMed: 2754393]

101. van Oosten BW, Barkhof F, Scholten PE, von Blomberg BM, Ader HJ, Polman CH. Increased production of tumor necrosis factor alpha, and not of interferon gamma, preceding disease activity in patients with multiple sclerosis. Arch Neurol. 1998 Jun; 55(6):793–798. PubMed PMID: 9626770. eng. [PubMed: 9626770]

102. van Boxel-Dezaire AH, Hoff SC, van Oosten BW, Verweij CL, Drager AM, Ader HJ, et al. Decreased interleukin-10 and increased interleukin-12p40 mRNA are associated with disease activity and characterize different disease stages in multiple sclerosis. Annals of neurology. 1999 Jun; 45(6):695–703. PubMed PMID: 10360761. eng. [PubMed: 10360761]

103. Nicoletti F, Patti F, Cocuzza C, Zaccone P, Nicoletti A, Di Marco R, et al. Elevated serum levels of interleukin-12 in chronic progressive multiple sclerosis. Journal of neuroimmunology. 1996 Oct; 70(1):87–90. PubMed PMID: 8862139. Epub 1996/10/01. eng. [PubMed: 8862139]

104. Spuler S, Yousry T, Scheller A, Voltz R, Holler E, Hartmann M, et al. Multiple sclerosis: prospective analysis of TNF-alpha and 55 kDa TNF receptor in CSF and serum in correlation with clinical and MRI activity. Journal of neuroimmunology. 1996 May; 66(1-2):57–64. PubMed PMID: 8964914. Epub 1996/05/01. eng. [PubMed: 8964914]

105. Vollmer TL, Wynn DR, Alam MS, Valdes J. A phase 2, 24-week, randomized, placebo-controlled, double-blind study examining the efficacy and safety of an anti-interleukin-12 and-23 monoclonal antibody in patients with relapsing-remitting or secondary progressive multiple sclerosis. Multiple sclerosis. 2011 Feb; 17(2):181–191. PubMed PMID: 21135022. Epub 2010/12/08. eng. [PubMed: 21135022]

106. Taoufik E, Tseveleki V, Chu SY, Tselios T, Karin M, Lassmann H, et al. Transmembrane tumour necrosis factor is neuroprotective and regulates experimental autoimmune encephalomyelitis via neuronal nuclear factor-kappaB. Brain : a journal of neurology. 2011 Sep; 134(Pt 9):2722–2735. PubMed PMID: 21908876. [PubMed: 21908876]

107. TNF neutralization in MS: results of a randomized, placebo-controlled multicenter study. The Lenercept Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group. Neurology. 1999 Aug 11; 53(3):457–465. PubMed PMID: 10449104. Epub 1999/08/17. eng. [PubMed: 10449104]

108. van Oosten BW, Barkhof F, Truyen L, Boringa JB, Bertelsmann FW, von Blomberg BM, et al. Increased MRI activity and immune activation in two multiple sclerosis patients treated with the monoclonal anti-tumor necrosis factor antibody cA2. Neurology. 1996 Dec; 47(6):1531–1534. PubMed PMID: 8960740. Epub 1996/12/01. eng. [PubMed: 8960740]

109. Brambilla R, Ashbaugh JJ, Magliozzi R, Dellarole A, Karmally S, Szymkowski DE, et al. Inhibition of soluble tumour necrosis factor is therapeutic in experimental autoimmune encephalomyelitis and promotes axon preservation and remyelination. Brain : a journal of neurology. 2011 Sep; 134(Pt 9):2736–2754. PubMed PMID: 21908877. Pubmed Central PMCID: 3170538. [PubMed: 21908877]

110. Rostami A, Ciric B. Role of Th17 cells in the pathogenesis of CNS inflammatory demyelination. Journal of the neurological sciences. 2013 Oct 15; 333(1-2):76–87. PubMed PMID: 23578791. Pubmed Central PMCID: 3726569. [PubMed: 23578791]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

111. Rasouli J, Ciric B, Imitola J, Gonnella P, Hwang D, Mahajan K, et al. Expression of GM-CSF in T Cells Is Increased in Multiple Sclerosis and Suppressed by IFN-beta Therapy. Journal of immunology. 2015 Jun 1; 194(11):5085–5093. PubMed PMID: 25917097. Pubmed Central PMCID: 4433790.

112. Constantinescu C, Asher A, Fryze W, Kozubsk W, Aram J, Tanasescu R, et al. Randomized phase 1b trial of MOR103, a human antibody to GM-CSF, in multiple sclerosis. Neurology: Neuroimmunology and neuroinflammation. 2015 May 21.2(4) Epub May 21, 2015.

113. Lider O, Beraud E, Reshef T, Friedman A, Cohen IR. Vaccination against experimental autoimmune encephalomyelitis using a subencephalitogenic dose of autoimmune effector T cells (2). Induction of a protective anti-idiotypic response. J Autoimmun. 1989 Feb; 2(1):87–99. PubMed PMID: 2568841. eng. [PubMed: 2568841]

114. Lohse AW, Spahn TW, Wolfel T, Herkel J, Cohen IR, Meyer zum Buschenfelde KH. Induction of the anti-ergotypic response. International immunology. 1993 May; 5(5):533–539. PubMed PMID: 8318456. eng. [PubMed: 8318456]

115. Quintana FJ, Cohen IR. Anti-ergotypic immunoregulation. Scand J Immunol. 2006 Sep; 64(3): 205–210. PubMed PMID: 16918688. eng. [PubMed: 16918688]

116. Zang YC, Hong J, Tejada-Simon MV, Li S, Rivera VM, Killian JM, et al. Th2 immune regulation induced by T cell vaccination in patients with multiple sclerosis. European journal of immunology. 2000 Mar; 30(3):908–913. PubMed PMID: 10741408. eng. [PubMed: 10741408]

117. Lider O, Reshef T, Beraud E, Ben-Nun A, Cohen IR. Anti-idiotypic network induced by T cell vaccination against experimental autoimmune encephalomyelitis. Science. 1988 Jan 8; 239(4836):181–183. PubMed PMID: 2447648. eng. [PubMed: 2447648]

118. Ben-Nun A, Wekerle H, Cohen IR. Vaccination against autoimmune encephalomyelitis with T-lymphocyte line cells reactive against myelin basic protein. Nature. 1981 Jul 2; 292(5818):60–61. PubMed PMID: 6974307. eng. [PubMed: 6974307]

119. Medaer R, Stinissen P, Truyen L, Raus J, Zhang J. Depletion of myelin-basic-protein autoreactive T cells by T-cell vaccination: pilot trial in multiple sclerosis. Lancet. 1995 Sep 23; 346(8978): 807–808. PubMed PMID: 7545769. Epub 1995/09/23. eng. [PubMed: 7545769]

120. Zhang J. T-cell vaccination for autoimmune diseases: immunologic lessons and clinical experience in multiple sclerosis. Expert review of vaccines. 2002 Oct; 1(3):285–292. PubMed PMID: 12901569. Epub 2003/08/07. eng. [PubMed: 12901569]

121. Zhang JZ, Rivera VM, Tejada-Simon MV, Yang D, Hong J, Li S, et al. T cell vaccination in multiple sclerosis: results of a preliminary study. J Neurol. 2002 Feb; 249(2):212–218. PubMed PMID: 11985389. Epub 2002/05/03. eng. [PubMed: 11985389]

122. Achiron A, Lavie G, Kishner I, Stern Y, Sarova-Pinhas I, Ben-Aharon T, et al. T cell vaccination in multiple sclerosis relapsing-remitting nonresponders patients. Clinical immunology. 2004 Nov; 113(2):155–160. PubMed PMID: 15451472. Epub 2004/09/29. eng. [PubMed: 15451472]

123. Correale J, Lund B, McMillan M, Ko DY, McCarthy K, Weiner LP. T cell vaccination in secondary progressive multiple sclerosis. J Neuroimmunol. 2000 Jul 24; 107(2):130–139. PubMed PMID: 10854647. eng. [PubMed: 10854647]

124. Karussis D, Shor H, Yachnin J, Lanxner N, Amiel M, Baruch K, et al. T cell vaccination benefits relapsing progressive multiple sclerosis patients: a randomized, double-blind clinical trial. PloS one. 2012; 7(12):e50478. PubMed PMID: 23272061. Pubmed Central PMCID: 3522721. [PubMed: 23272061]

125. Offner H, Vandenbark AA. T cell receptor V genes in multiple sclerosis: increased use of TCRAV8 and TCRBV5 in MBP-specific clones. Int Rev Immunol. 1999; 18(1-2):9–36. PubMed PMID: 10614737. eng. [PubMed: 10614737]

126. Oksenberg JR, Panzara MA, Begovich AB, Mitchell D, Erlich HA, Murray RS, et al. Selection for T-cell receptor V beta-D beta-J beta gene rearrangements with specificity for a myelin basic protein peptide in brain lesions of multiple sclerosis. Nature. 1993 Mar 4; 362(6415):68–70. PubMed PMID: 7680433. eng. [PubMed: 7680433]

127. Vandenbark AA, Chou YK, Whitham R, Mass M, Buenafe A, Liefeld D, et al. Treatment of multiple sclerosis with T-cell receptor peptides: results of a double-blind pilot trial. Nature medicine. 1996 Oct; 2(10):1109–1115. PubMed PMID: 8837609. eng.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

128. Vandenbark AA. TCR peptide vaccination in multiple sclerosis: boosting a deficient natural regulatory network that may involve TCR-specific CD4+CD25+ Treg cells. Curr Drug Targets Inflamm Allergy. 2005 Apr; 4(2):217–229. PubMed PMID: 15853744. eng. [PubMed: 15853744]

129. Bourdette DN, Whitham RH, Chou YK, Morrison WJ, Atherton J, Kenny C, et al. Immunity to TCR peptides in multiple sclerosis. I. Successful immunization of patients with synthetic V beta 5.2 and V beta 6.1 CDR2 peptides. Journal of immunology (Baltimore, Md : 1950). 1994 Mar 1; 152(5):2510–2519. PubMed PMID: 7510746. eng.

130. Liu MA. DNA vaccines: a review. J Intern Med. 2003 Apr; 253(4):402–410. PubMed PMID: 12653868. eng. [PubMed: 12653868]

131. Weissert R, Lobell A, de Graaf KL, Eltayeb SY, Andersson R, Olsson T, et al. Protective DNA vaccination against organ-specific autoimmunity is highly specific and discriminates between single amino acid substitutions in the peptide autoantigen. Proceedings of the National Academy of Sciences of the United States of America. 2000 Feb 15; 97(4):1689–1694. PubMed PMID: 10677519. eng. [PubMed: 10677519]

132. Bourquin C, Iglesias A, Berger T, Wekerle H, Linington C. Myelin oligodendrocyte glycoprotein-DNA vaccination induces antibody-mediated autoaggression in experimental autoimmune encephalomyelitis. European journal of immunology. 2000 Dec; 30(12):3663–3671. PubMed PMID: 11169409. eng. [PubMed: 11169409]

133. Tsunoda I, Kuang LQ, Tolley ND, Whitton JL, Fujinami RS. Enhancement of experimental allergic encephalomyelitis (EAE) by DNA immunization with myelin proteolipid protein (PLP) plasmid DNA. J Neuropathol Exp Neurol. 1998 Aug; 57(8):758–767. PubMed PMID: 9720491. eng. [PubMed: 9720491]

134. Lobell A, Weissert R, Eltayeb S, de Graaf KL, Wefer J, Storch MK, et al. Suppressive DNA vaccination in myelin oligodendrocyte glycoprotein peptide-induced experimental autoimmune encephalomyelitis involves a T1-biased immune response. Journal of immunology (Baltimore, Md : 1950). 2003 Feb 15; 170(4):1806–1813. PubMed PMID: 12574345. eng.

135. Wefer J, Harris RA, Lobell A. Protective DNA vaccination against experimental autoimmune encephalomyelitis is associated with induction of IFNbeta. Journal of neuroimmunology. 2004 Apr; 149(1-2):66–76. PubMed PMID: 15020066. eng. [PubMed: 15020066]

136. Selmaj K, Kowal C, Walczak A, Nowicka J, Raine CS. Naked DNA vaccination differentially modulates autoimmune responses in experimental autoimmune encephalomyelitis. Journal of neuroimmunology. 2000 Nov 1; 111(1-2):34–44. PubMed PMID: 11063819. eng. [PubMed: 11063819]

137. Walczak A, Szymanska B, Selmaj K. Differential prevention of experimental autoimmune encephalomyelitis with antigen-specific DNA vaccination. Clin Neurol Neurosurg. 2004 Jun; 106(3):241–245. PubMed PMID: 15177776. eng. [PubMed: 15177776]

138. Lobell A, Weissert R, Storch MK, Svanholm C, de Graaf KL, Lassmann H, et al. Vaccination with DNA encoding an immunodominant myelin basic protein peptide targeted to Fc of immunoglobulin G suppresses experimental autoimmune encephalomyelitis. J Exp Med. 1998 May 4; 187(9):1543–1548. PubMed PMID: 9565646. eng. [PubMed: 9565646]

139. Ho PP, Fontoura P, Platten M, Sobel RA, DeVoss JJ, Lee LY, et al. A suppressive oligodeoxynucleotide enhances the efficacy of myelin cocktail/IL-4-tolerizing DNA vaccination and treats autoimmune disease. Journal of immunology (Baltimore, Md : 1950). 2005 Nov 1; 175(9):6226–6234. PubMed PMID: 16237121. eng.

140. Garren H, Ruiz PJ, Watkins TA, Fontoura P, Nguyen LT, Estline ER, et al. Combination of gene delivery and DNA vaccination to protect from and reverse Th1 autoimmune disease via deviation to the Th2 pathway. Immunity. 2001 Jul; 15(1):15–22. PubMed PMID: 11485734. eng. [PubMed: 11485734]

141. Robinson WH, Fontoura P, Lee BJ, de Vegvar HE, Tom J, Pedotti R, et al. Protein microarrays guide tolerizing DNA vaccine treatment of autoimmune encephalomyelitis. Nat Biotechnol. 2003 Sep; 21(9):1033–1039. PubMed PMID: 12910246. eng. [PubMed: 12910246]

142. Bar-Or A, Vollmer T, Antel J, Arnold DL, Bodner CA, Campagnolo D, et al. Induction of antigen-specific tolerance in multiple sclerosis after immunization with DNA encoding myelin

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

basic protein in a randomized, placebo-controlled phase 1/2 trial. Arch Neurol. 2007 Oct; 64(10): 1407–1415. PubMed PMID: 17698695. eng. [PubMed: 17698695]

143. Fissolo N, Montalban X, Comabella M. DNA-based vaccines for multiple sclerosis: current status and future directions. Clinical immunology (Orlando, Fla). 2012 Jan; 142(1):76–83. PubMed PMID: 21163708. eng.
144. Correale J, Fiol M. BHT-3009, a myelin basic protein-encoding plasmid for the treatment of multiple sclerosis. Curr Opin Mol Ther. 2009 Aug; 11(4):463–470. PubMed PMID: 19649992. eng. [PubMed: 19649992]
145. Garren H. A DNA vaccine for multiple sclerosis. Expert opinion on biological therapy. 2008 Oct; 8(10):1539–1550. PubMed PMID: 18774921. eng. [PubMed: 18774921]
146. Garren H, Robinson WH, Krasulova E, Havrdova E, Nadj C, Selmaj K, et al. Phase 2 trial of a DNA vaccine encoding myelin basic protein for multiple sclerosis. Ann Neurol. 2008 May; 63(5):611–620. PubMed PMID: 18481290. eng. [PubMed: 18481290]
147. Garren H. DNA vaccines for autoimmune diseases. Expert review of vaccines. 2009 Sep; 8(9): 1195–1203. PubMed PMID: 19722893. Epub 2009/09/03. eng. [PubMed: 19722893]
148. Xing Y, Hogquist KA. T-cell tolerance: central and peripheral. Cold Spring Harbor perspectives in biology. 2012; 4(6) PubMed PMID: 22661634. eng.
149. Turley DM, Miller SD. Prospects for antigen-specific tolerance based therapies for the treatment of multiple sclerosis. Results Probl Cell Differ. 2010; 51:217–235. PubMed PMID: 19130025. eng. [PubMed: 19130025]
150. Goverman JM. Immune tolerance in multiple sclerosis. Immunological reviews. 2011 May; 241(1):228–240. PubMed PMID: 21488900. eng. [PubMed: 21488900]
151. Burns JB, Rosenzweig A, Zweiman B, Lisak RP. Isolation of myelin basic protein reactive T-cell lines from normal human blood. Cell Immunol. 1983; 81:435–440. [PubMed: 6196128]
152. Kearney ER, Pape KA, Loh DY, Jenkins MK. Visualization of peptide-specific T cell immunity and peripheral tolerance induction in vivo. Immunity. 1994 Jul; 1(4):327–339. PubMed PMID: 7889419. eng. [PubMed: 7889419]
153. Liblau RS, Tisch R, Shokat K, Yang X, Dumont N, Goodnow CC, et al. Intravenous injection of soluble antigen induces thymic and peripheral T-cells apoptosis. Proceedings of the National Academy of Sciences of the United States of America. 1996 Apr 2; 93(7):3031–3036. PubMed PMID: 8610163. eng. [PubMed: 8610163]
154. Hilliard BA, Kamoun M, Ventura E, Rostami A. Mechanisms of suppression of experimental autoimmune encephalomyelitis by intravenous administration of myelin basic protein: role of regulatory spleen cells. Experimental and molecular pathology. 2000 Feb; 68(1):29–37. PubMed PMID: 10640452. eng. [PubMed: 10640452]
155. Zhang GX, Yu S, Li Y, Ventura ES, Gran B, Rostami A. A paradoxical role of APCs in the induction of intravenous tolerance in experimental autoimmune encephalomyelitis. Journal of neuroimmunology. 2005 Apr; 161(1-2):101–112. PubMed PMID: 15748949. eng. [PubMed: 15748949]
156. Li H, Zhang GX, Chen Y, Xu H, Fitzgerald DC, Zhao Z, et al. CD11c+CD11b+ dendritic cells play an important role in intravenous tolerance and the suppression of experimental autoimmune encephalomyelitis. J Immunol. 2008 Aug 15; 181(4):2483–2493. PubMed PMID: 18684939. eng. [PubMed: 18684939]
157. Baker D, O'Neill JK, Gschmeissner SE, Wilcox CE, Butter C, Turk JL. Induction of chronic relapsing experimental allergic encephalomyelitis in Biozzi mice. Journal of neuroimmunology. 1990 Aug; 28(3):261–270. PubMed PMID: 2373763. eng. [PubMed: 2373763]
158. Pryce G, O'Neill JK, Croxford JL, Amor S, Hankey DJ, East E, et al. Autoimmune tolerance eliminates relapses but fails to halt progression in a model of multiple sclerosis. Journal of neuroimmunology. 2005 Aug; 165(1-2):41–52. PubMed PMID: 15939483. eng. [PubMed: 15939483]
159. Hilliard B, Ventura ES, Rostami A. Effect of timing of intravenous administration of myelin basic protein on the induction of tolerance in experimental allergic encephalomyelitis. Multiple sclerosis (Houndmills, Basingstoke, England). 1999 Feb; 5(1):2–9. PubMed PMID: 10096096. eng.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

160. Mowat AM. Anatomical basis of tolerance and immunity to intestinal antigens. Nature reviews Immunology. 2003 Apr; 3(4):331–341. PubMed PMID: 12669023. Epub 2003/04/02. eng.

161. Bitar DM, Whitacre CC. Suppression of experimental autoimmune encephalomyelitis by the oral administration of myelin basic protein. Cell Immunol. 1988 Apr 1; 112(2):364–370. PubMed PMID: 2451570. eng. [PubMed: 2451570]

162. Higgins PJ, Weiner HL. Suppression of experimental autoimmune encephalomyelitis by oral administration of myelin basic protein and its fragments. Journal of immunology (Baltimore, Md : 1950). 1988 Jan 15; 140(2):440–445. PubMed PMID: 2447178. eng.

163. Faria AM, Weiner HL. Oral tolerance: therapeutic implications for autoimmune diseases. Clin Dev Immunol. 2006 Jun-Dec;13(2-4):143–157. PubMed PMID: 17162357. eng. [PubMed: 17162357]

164. Weiner HL, da Cunha AP, Quintana F, Wu H. Oral tolerance. Immunological reviews. 2011 May; 241(1):241–259. PubMed PMID: 21488901. eng. [PubMed: 21488901]

165. Weiner HL, Mackin GA, Matsui M, Orav EJ, Khoury SJ, Dawson DM, et al. Double-blind pilot trial of oral tolerization with myelin antigens in multiple sclerosis. Science. 1993 Feb 26; 259(5099):1321–1324. PubMed PMID: 7680493. eng. [PubMed: 7680493]

166. Faria AM, Weiner HL. Oral tolerance: mechanisms and therapeutic applications. Adv Immunol. 1999; 73:153–264. PubMed PMID: 10399007. eng. [PubMed: 10399007]

167. Bar-Or A, Vollmer T, Antel J, Arnold DL, Bodner CA, Campagnolo D, et al. Induction of antigen-specific tolerance in multiple sclerosis after immunization with DNA encoding myelin basic protein in a randomized, placebo-controlled phase 1/2 trial. Arch Neurol. 2007 Oct; 64(10): 1407–1415. PubMed PMID: 17698695. [PubMed: 17698695]

168. Bai XF, Link H. Nasal tolerance induction as a potential means of immunotherapy for autoimmune diseases: implications for clinical medicine. Clin Exp Allergy. 2000 Dec; 30(12): 1688–1696. PubMed PMID: 11122206. eng. [PubMed: 11122206]

169. Mestecky J, Husby S, Moldoveanu Z, Waldo FB, van den Wall Bake AW, Elson CO. Induction of tolerance in humans: effectiveness of oral and nasal immunization routes. Annals of the New York Academy of Sciences. 1996 Feb 13.778:194–201. PubMed PMID: 8610973. eng. [PubMed: 8610973]

170. Bai XF, Shi FD, Xiao BG, Li HL, van der Meide PH, Link H. Nasal administration of myelin basic protein prevents relapsing experimental autoimmune encephalomyelitis in DA rats by activating regulatory cells expressing IL-4 and TGF-beta mRNA. J Neuroimmunol. 1997 Dec; 80(1-2):65–75. PubMed PMID: 9413260. eng. [PubMed: 9413260]

171. Miller SD, McRae BL, Vanderlugt CL, Nikcevich KM, Pope JG, Pope L, et al. Evolution of the T-cell repertoire during the course of experimental immune-mediated demyelinating diseases. Immunological reviews. 1995 Apr.144:225–244. PubMed PMID: 7590815. eng. [PubMed: 7590815]

172. Smith CE, Eagar TN, Strominger JL, Miller SD. Differential induction of IgE-mediated anaphylaxis after soluble vs. cell-bound tolerogenic peptide therapy of autoimmune encephalomyelitis. Proceedings of the National Academy of Sciences of the United States of America. 2005 Jul 5; 102(27):9595–9600. PubMed PMID: 15983366. Pubmed Central PMCID: 1172278. Epub 2005/06/29. eng. [PubMed: 15983366]

173. Turley DM, Miller SD. Peripheral tolerance induction using ethylenecarbodiimide-fixed APCs uses both direct and indirect mechanisms of antigen presentation for prevention of experimental autoimmune encephalomyelitis. Journal of immunology (Baltimore, Md : 1950). 2007 Feb 15; 178(4):2212–2220. PubMed PMID: 17277126. eng.

174. Karussis D, Kassis I, Kurkalli BG, Slavin S. Immunomodulation and neuroprotection with mesenchymal bone marrow stem cells (MSCs): a proposed treatment for multiple sclerosis and other neuroimmunological/neurodegenerative diseases. Journal of the neurological sciences. 2008 Feb 15; 265(1-2):131–135. PubMed PMID: 17610906. [PubMed: 17610906]

175. Gosselin D, Rivest S. Immune mechanisms underlying the beneficial effects of autologous hematopoietic stem cell transplantation in multiple sclerosis. Neurotherapeutics. 2011 Oct; 8(4): 643–649. PubMed PMID: 21904792. Pubmed Central PMCID: 3250285. [PubMed: 21904792]

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176. Burman J, Iacobaeus E, Svenningsson A, Lycke J, Gunnarsson M, Nilsson P, et al. Autologous haematopoietic stem cell transplantation for aggressive multiple sclerosis: the Swedish experience. Journal of neurology, neurosurgery, and psychiatry. 2014 Oct; 85(10):1116–1121. PubMed PMID: 24554104.

177. Biasi G, Facchinetti A, Monastra G, Mezzalira S, Sivieri S, Tavolato B, et al. Protection from experimental autoimmune encephalomyelitis (EAE): non-depleting anti-CD4 mAb treatment induces peripheral T-cell tolerance to MBP in PL/J mice. Journal of neuroimmunology. 1997 Mar; 73(1-2):117–123. PubMed PMID: 9058767. [PubMed: 9058767]

178. Turner MJ, Pang PT, Chretien N, Havari E, LaMorte MJ, Oliver J, et al. Reduction of inflammation and preservation of neurological function by anti-CD52 therapy in murine experimental autoimmune encephalomyelitis. Journal of neuroimmunology. 2015 Aug 15.285:4–12. PubMed PMID: 26198912. [PubMed: 26198912]

179. Phillips SM, Bhopale MK, Constantinescu CS, Ciric B, Hilliard B, Ventura E, et al. Effect of DAB(389)IL-2 immunotoxin on the course of experimental autoimmune encephalomyelitis in Lewis rats. Journal of the neurological sciences. 2007 Dec 15; 263(1-2):59–69. PubMed PMID: 17603081. [PubMed: 17603081]

180. Weber MS, Prod'homme T, Patarroyo JC, Molnarfi N, Karnezis T, Lehmann-Horn K, et al. B-cell activation influences T-cell polarization and outcome of anti-CD20 B-cell depletion in central nervous system autoimmunity. Annals of neurology. 2010 Sep; 68(3):369–383. PubMed PMID: 20641064. Pubmed Central PMCID: 3375897. [PubMed: 20641064]

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Table 1

Targeting T and B cells in MS

TARGETING T AND B CELLS IN MULTIPLE SCLEROSIS			
Targeting Markers on T Cells			
Pharmacological Target	**Experimental Results if Available**	**Clinical Outcomes**	**References**
CD4+ T Cells	Effective in EAE	No long-term benefits	(21,177)
CD52+ Cells	Effective in EAE	FDA-approved drug (Alemtuzumab)	(16, 178)
CD25 (IL-2R)	Effective in EAE	Drug under study (daclizumab)	(39, 179)
Targeting T Cell Activation in MS			
Altered Peptide Ligands			
MBP	Effective in EAE	No evidence of clinical benefit to date	(51, 54)
MOG	Effective in EAE	No evidence of clinical benefit to date	(59, 61)
Targeting T cell Co-stimulatory Pathways			
CD40/CD40L	Effective in EAE	Studies discouraged due to suspected risks of adverse effects	(69–70)
CD28:B7	Effective in EAE	Reported safe in phase I trials	(78–79)
Targeting Markers on B Cells			
CD20	Effective in EAE	Clinical trials ongoing On Rituximab	(91, 180)

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Table 2

Targeting cytokines in MS

Pharmacological Target	Clinical Outcomes	References
IL-12/IL-23 (p40)	Not effective in MS	(105)
TNF	Not effective in MS Neither TNF antagonist nor Anti-TNF antibody	(107–108)
GM-CSF	Phase I clinical trial ongoing	112

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Table 3

Vaccination in MS

Pharmacological Target	Clinical Outcomes	References
TC Vaccine	Promising in some clinical aspects, but not MRI measures	(124)
TCR Vaccine	Some effectiveness reported	(128)
DNA Vaccine	Few human trials, some promising results	(145)