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New immunological approaches in treating and diagnosing CNS diseases

Kathy Guo¹ and Damir Janigro^{*,1,2,3}

¹Department of Cellular & Molecular Medicine, Cerebrovascular Research Cleveland Clinic Lerner College of Medicine, Cleveland, OH 44195, USA

²Department of Neurological Surgery, Cerebrovascular Research Cleveland Clinic Lerner College of Medicine, Cleveland, OH 44195, USA

³Department of Molecular Medicine, Cerebrovascular Research Cleveland Clinic Lerner College of Medicine, Cleveland, OH 44195, USA

Abstract

The immune system evolved to launch effective and specific responses against pathogens. A key feature of this defense mechanism is its ability to differentiate between self and nonself. However, in autoimmune diseases, the host's immune system fails to discriminate self versus foreign. The CNS is further protected by the blood–brain barrier. In spite of its ‘immune privilege,’ the brain is not protected from autoimmunity; perhaps paradoxically xenoantibodies can be used to treat neurological diseases. We describe patents covering treatment methods for CNS diseases with suspected or demonstrated autoimmune etiology. These include multiple sclerosis and, Alzheimer's and Parkinson's disease. The goal is to less invasively, yet efficiently, treat neurological diseases. Although autoimmune responses are often detrimental, recent studies have begun to harness, boost and induce immune responses as a mechanism of treatment. The patents discussed herein highlight new treatments for Alzheimer's and Parkinson's disease, multiple sclerosis, and seizure disorders.

Without the immune system, infectious agents ranging from bacterial to parasitic would result in infections leading to death. In addition to being able to detect and subsequently destroy and eliminate organisms or other toxic molecules that invade the body, the immune system is able to distinguish between both foreign and self molecules [1]. Because the immune system is able to make this differentiation, self tissue is not harmed when an immune response is induced. However, when the immune system fails to differentiate, the immune system begins to launch a defense against the host's own molecules, often resulting in chronic diseases. The result of such an occurrence will lead to **autoimmune diseases**, which are characterized by the launching of an immunologic reaction of an organism against its own tissues [2], an indication of a breakdown in the mechanisms that control and regulate the host's immune responses. Autoimmunity is simply the notion that either autoreactive T lymphocytes or antibodies that react with self-antigens are present in the body, though these factors do not necessarily directly correlate with the presence or onset of an autoimmune disease [2]. The presence of natural killer cells plays an important role in the innate-immune

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*Author for correspondence: Tel.: +1 216 312 3201 janigrd@ccf.org.

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system, acting as a defense mechanism against viral, parasitic and bacterial infections; however, they can also be triggered to launch responses against the self, thus leading to autoimmune diseases [3].

The **blood–brain barrier** (BBB) plays a critical role in protecting the brain against harmful substances, by separating the CNS and peripheral circulation [4]. The BBB consists of endothelial cells that are found in brain capillaries, lining the intraluminal side, as well as pericytes, astrocytes, extra cellular matrix and neurons (**Figure 1**). While the BBB gives a certain level of immune protection to the CNS, it is important to note that the term ‘immune privilege of the brain’ refers to other organs, rather than being absolute [5].

The immune privilege of the CNS is compartmentalized to the parenchyma, extending to the innate immune response [5,6]. When these mechanisms fail to function properly, thus failing to defend the host, autoimmune brain diseases result (**Figure 2**). Although autoimmunity is generally perceived as detrimental, resulting in diseases such as **Parkinson's disease** (PD) and **Alzheimer's disease** (AD), recent studies have suggested that autoimmune responses can also be used as a viable treatment option (**Figure 3**). Immunotherapy has been proven to be effective in treating tumors (**Figure 4**). Although much research has been conducted to find a treatment for these autoimmune brain diseases, new research has arisen that also examines the use of these autoimmune diseases as a tool for treating other problems, such as tumors (**Table 1**).

Treatment of autoimmune brain diseases

Ranked as the fourth leading cause of death in developed nations, AD is a neurodegenerative brain disease with a potential autoimmune component that results in memory loss, visual impairment and cognitive deficits [7,8]. In AD, the presence of both a BBB dysfunction and the presence of autoantibodies against the brain has suggested that it shares autoimmune disease features [9]. In patients affected by AD, there is a decrease in both oxygenation and cerebral blood flow located in the temporal lobe region, therefore leading to an overall decrease in oxygen metabolism [10]. In addition, the buildup of amyloid- β (A β) and neurofibrillary tangles is thought to lead to the development of AD [8]. These neurofibrillary tangles are made up of hyperphosphorylated **tau proteins**. A β is a peptide that contains approximately 38–43 amino acids, and stems off another protein that is larger, known as the amyloid precursor protein. As a result of enzymatic cleavage, the A β is deposited in the brain in the form of plaque, producing neurotoxic effects [11,12]. This buildup of plaque, along with the accumulation of A β , has been noted to contribute to cholinergic neuron death, providing an explanation for memory loss observed in individuals affected by AD. In the cerebral spinal fluid (CSF) of patients with AD, antibodies that specifically target cholinergic neurons have been found, pointing to the notion that an autoimmune response is in fact part of the pathogenesis of AD [13]. In addition to elevated amyloid in the CSF of AD patients, elevated levels of autoantibodies have been measured at different stages of the disease. Whether these are pathogenic remains unclear.

Given the fact that abnormal levels of protein aggregates in the brain are widely believed to be pathogenic in AD, it is not surprising that attempts to improve its clearance have been developed. Recently, research has been focusing on using immunotherapy in order to clear A β in treating AD. Sigurdsson and Asuni have developed a method of inhibiting the accumulation of tau neurofibrillary tangles in order to both prevent and treat AD [101]. This immunotherapy treatment was developed on the basis that anti-tau antibodies are able to clear the tau aggregates that are known to affect neuronal viability. The tau protein, responsible for maintaining axonal microtubule stability, is administered to individuals with AD. It clears aggregates from the brain, as well as slowing down the tangle-related

behavioral phenotype that is seen in individuals with AD [8]. In addition, perhaps paradoxically, a vaccine for this autoimmune disease has been developed that includes either an A β self-epitope or an A β 1–42. The goal is to treat AD by slowing down or even reversing the progression of the disease [102]. The inventors used a phosphorylated epitope to immunize P301L mice and they analyzed the tau pathology.

In the field of dementia diagnostic, Owen and Williams developed a strategy that provides a method for detecting and diagnosing the likelihood and the existence of AD. The method seeks to identify variants in *CLU/APOJ*, *PICALM*, *ABCA7*, *CR1* or *BINI* gene loci, as well as the *MS4A* gene cluster [103].

In the therapeutic arena for dementias the following inventions are notable. A patent obtained by Chen *et al.* provides a method for the diagnosis and detection of A β pathology/amyloidosis and neurological disorders associated with AD. This method specifically focuses on EPO and analogues, using claudin-5 and variants as a biomarker in the detection of AD, and in tracking the progression of AD. This method is based on the use of EPO, an agent in ameliorating early A β pathology/amyloidosis, as a component of the treatment of AD [104]. In addition, this method measures the level of Claudin-5, in comparison with a baseline value in an individual, as an indicator of the risk, and presence of AD.

The patent developed by Chumakov *et al.* teaches a new approach in treating AD and other disorders related to it through the use of therapies that modulate the cell stress response. This method uses an identified molecular pathway that contributes to the genesis of AD in order to use multiple drugs, either alone or in combination, to act as a treatment of AD [105]. This combination of at least two drugs will inhibit the cell's stress response, and modulate angiogenesis and the synapse function.

Blurton *et al.* patented a treatment that targets diseases that are linked with the deposition of A β peptides in the brain, and uses arylacetic acids and compounds that are related to both delay, and prevent, the onset of diseases such as AD and those related to dementia [106]. Blurton *et al.* accomplished this through the use of compounds of formula I, in targeting diseases that lead to the deposition of A β .

PD is a neurodegenerative brain disease with an auto-immune component that is characterized by the depletion of neurons in the substantia nigra in the brain, which produces dopamine, controlling the majority of movement in the body [14,15]. Similar to AD, PD is also classified as a protein deposition disorder; symptoms of PD include tremor and involuntary movements [16]. In PD, autoimmunity, including humoral immunity, has been found, and furthermore, through experimental autoimmune nigral damage, it has been found that this results in the degeneration of dopaminergic neurons, thus suggesting that PD is an autoimmune disease [17–20]. In PD, autoimmunity, including humoral immunity, has been found and furthermore, through experimental autoimmune nigral damage, it has been found that this results in the degeneration of dopaminergic neurons, thus suggesting that PD is an auto immune disease [17–20]. For the treatment of PD, Solomon presented a method through the use of an antibody on the bacteriophage that binds specifically with a pro-inflammatory cytokine in conjunction with a filamentous bacteriophage, resulting in a filamentous bacteriophage that lacks a mammalian cell internalization signal [107]. When the antibody-bearing phage is taken intranasally, it is transported to the brain. Once in the brain, cytokines are activated and the phage portions of these antibodies are able to pass through the BBB to inhibit α -synuclein buildup, thought to be responsible in the trafficking of both vesicles and the Golgi apparatus [21].

Another method of treating PD uses a ration of a viral vector that expresses the N-terminal signaling portion of Sonic Hedgehog (ShhN) [108]. The Shh and transcription factor target Gli-1 are used in combination with different gene therapy techniques to act as a treatment for PD. ShhN is a dopaminergic neuron differentiation factor, while Gli-1 is Shh's downstream transcription factor target (**Figure 5**).

In the field of therapeutics for PD, a patent by Delfani *et al.* focuses on influencing both neural progenitor and neural stem cells in producing progeny in order to replace those neurons that have been damaged or are missing. This method focuses on using a reagent that is known to regulate the proliferation, migration, differentiation, and survival of CNS cells through the modulation of platelet-derived growth factor or vascular endothelial growth factor [109]. This method exposes patients that are suffering from PD to these reagents in reducing the symptoms of PD.

The patent by Benatti *et al.* describes a method using the administration of a combination of safinamide or a MAO-B inhibitor, in conjunction with other treatments and agents such as levodopa/PDI or domapine agonists in treating PD. It has been found that combination, rather than a single treatment, of safin-amide and a MAO-B inhibitor is an effective form of treatment of PD, which allows for both the delay and improvement of symptoms [110].

Hong *et al.* obtained a patent for a treatment that uses postpartum-derived cells, such as that of the placenta or umbilical cord, in the use of treating neuro degenerative conditions of the substantia nigra or striatum [111]. The use of postpartum-derived cells in treating damaged neurological functions as a result of neurodegenerative conditions can help to repair, regenerate and improve neural tissue. Post-partum-derived cells were the target of this method, because they are substantially free of blood, as well as being able to both perform self-renewal and differentiating into cells with a neural phenotype.

It has been reported that the modulation of the vanilloid receptor VR1 (TRPV1 channel) activation can be used as a treatment for disorders such as epilepsy [112]. Status epilepticus is characterized by periods of either prolonged or repeated seizure; often the patient does not regain consciousness in the time period between the seizures [22]. TRPV1 channel is part of a family of calcium permeable nonselective cation channels (**Figure 5**) [23,24]. The TRPV1 channel activation results in long term synaptic depression, activated in the peripheral nervous system via resiniferatoxin (an activator of the vanilloid receptors), capsaicin (a component of red hot chili peppers that has been found to have an inhibitory effect on P-gP), thermal and chemical stimuli [25,26]. The method developed may be used for either the treatment or the prophylaxis of epilepsy. A TRPV1 antagonist is administered to individuals with epilepsy, or those who are at risk for developing epilepsy [112]. TRPV1 antagonists are believed to both prevent and reduce epileptic seizures. A TRPV1 can be administered one of several ways: orally, subcutaneously or intravenously.

In the treatment of neurodegenerative diseases including AD, PD and **multiple sclerosis** (MS), a novel noninvasive treatment has been developed [113]. This method involves the delivery of energy to specific nervous tissue by stimulating the vagus nerve. The vagus is a cranial nerve that has in the past been targeted to treat epilepsy, for example. However, the existing technology is invasive and requires surgery [27]. The inventors use a magnetic stimulator that is attached to coils that have toroidal (doughnut shaped) windings. These coils are then placed in contact with an electrically conducting medium. The nerve fibers of the patient, for example the vagal nerve in the neck, are then stimulated through the use of the coils to reduce neuro-inflammation [113]. A rationale for the use of transcutaneous fields as suggested by Simon *et al.* is the fact that the existing devices are invasive and surgical brain resections used to treat multiple-drug resistant epilepsy often damage healthy tissue

surrounding the diseased brain, thus creating ‘collateral damage’ and serious side effects [113]. Unlike brain resections, the effects of magnetic stimulation devices are claimed to be reversible, as well as nondestructive, which is in contrast to the previous methods used. This method uses external electrodes focused on specific nervous system targets to modulate and disrupt the hyperactive neuronal circuit transmission without obvious damage to healthy tissue.

MS is an autoimmune neurological disease that is brought on by immune cells such as B cells, T cells and macrophages that infiltrate the CNS [28–30]. In patients that have MS, demyelination in the CNS occurs, leading to axonal degeneration [1,31]. Although the exact pathogenesis of MS is still debated, evidence suggests that MS is an autoimmune disease. Strong indications suggesting that MS is an autoimmune disease include mononuclear cells infiltrating the brain parenchyma and the presence of CNS perivascular cuffs [32]. It has been found that an increase in $\gamma\delta$ T cells in the perivenular inflammatory cuffs are common in lesional MS brain, and perivascular changes are also observed in regions where chronic plaques and demyelinating lesions are present [33,34]. In MS, IL-17 has been found in both target tissue and sera of patients affected by MS and other autoimmune diseases, as IL-17 is involved in the induction of chemokines, matrix metalloproteases, and proinflammatory cytokines [35–37]. Altered cellular and molecular composition of the perivascular space is a correlate of MRI scan abnormalities. In human subjects, most of our knowledge on these changes comes from tissue biopsies or resected epileptic brain. While MS is obviously a different disease, the extensive changes that follow BBB disruption share common features and consist of cellular infiltrates and leakage of the serum component (including IgG) [5,38]. In patients that suffer from MS, an elevated level of immunoglobulin in the CSF has been noted, and the presence of oligoclonal bands, which are only noted in the diseased CSF, further suggest an autoimmune origin for MS [39].

In the field of MS diagnosis or therapy, the patents by Achiron and Gurevich are notable as they provide a means for determining the probability of a patient that is already diagnosed with probable MS, to actually develop definite diagnosis of MS. This is accomplished through determining the level of polynucleotide expression, in comparison to those that had probable MS that transitioned to definite MS to those that do not have MS [114].

Achiron *et al.* obtained a patent that details methods used for the treatment of symptoms of MS, through the use of vitamin D and other compounds related to it. Doses of a calciferol compound are administered to MS patients effectively. This alleviates symptoms such as reducing the frequency of relapse remitting MS, in addition to reducing the amount of fatigue seen in MS patients [115].

The patent obtained by Arnedillo *et al.* describes a method of diagnosing MS through determining the amounts of one or more miRNAs that are known to be correlated with MS [116]. This method was developed on the basis that certain miRNAs are not only expressed at different levels in MS patients, but as well as those in relapse status. This method is important in diagnosing MS, in addition to monitoring MS patients post-therapy. The levels of miRNA obtained from a sample from a patient can be compared with those of a control test subject using qRT-PCR.

Brod, in 2007, developed a method of treatment for MS, in addition, applicable to other autoimmune diseases as well, through administering a soluble immune response suppressor peptide. The administration of soluble immune response suppressor reduces both the frequency and severity of relapse, in addition to reducing the inflammation that is often associated with autoimmune diseases such as MS [117].

The patent obtained by Panzara and Rizzo provides a novel method in delaying and preventing the onset of MS. This may be used for patients that are either at risk of progressive MS, or relapsing MS [118]. MS patients are administered a VLA-4 blocking agent that results in the prevention or delay of MS.

The patent obtained by Khan and Benner is an MS treatment that focuses on targeting the inflammatory injuries that often accompany the progressive stages of MS, such as during relapses. The method seeks to achieve this by administering a gene-regulatory peptide, or a related functional analogue [119].

It has also been found that a CD20 antibody, when given in a specific dosing regimen, has been effective in treating MS [120]. CD20 is expressed on mature B-cells, beginning from the pro-B phase and increasing in concentration until maturity, and has been used as a target for the treatment of B cell leukemia (but see [40]). Patients suffering from relapsing-remitting MS, primary progressive MS, secondary progressive MS and progressive relapsing MS are given a dose of antibody that binds CD20, expressed on the surface of B-cells. Individuals are initially given 0.5–4 g, followed by a second exposure to the CD20 antibody from 16–20 weeks after the first exposure [120]. The CD20 antibody targets the CD20 antigen, which then binds to either normal or autoimmune B-cells.

Other research has shown that polypeptide therapeutics are useful in the treatment of autoimmune diseases such as MS [3]. The treatment comprises α -MSH monomers, which are α -melanocyte stimulating hormones produced from the precursor adrenocorticotrophic hormone and protein proopiomelanocortin [121]. In the past, it had been thought that the administration of α -MSH polypeptides was not active when given as an oral therapeutic. However, a recent study found that this treatment is in fact effective [3]. In studies conducted in mice, the treatment yielded results that include reduced symptoms and a dramatic decrease in the inflammation in the spinal cord. Because the treatments for autoimmune diseases are often chronic, a long term treatment would be ideal. Most current treatment methods require injectable therapeutics. Orally administered α -MSH treatment prevents tissue damage and has been found to be effective even over a prolonged period of administration [3].

Another approach to treat MS consists of targeting $\gamma\delta$ T cells [33]. These cells have been implicated in myelin injury, neurotoxicity and immunoregulation in MS. Thus, targeting this specific sub-population of cells may be prove to be of therapeutic importance in CNS disorders with an immune component.

Use of autoimmune response as a treatment

Although autoimmune responses are generally viewed as detrimental, Solomon has found a method that demonstrates that an induced autoimmune response can prevent brain inflammation brought on by diseases that are defined by amyloid aggregation [122]. This method is thought to be useful in treating AD, through either decreasing the amount of amyloid plaque or through decreasing the rate at which the plaque deposits. The inflammation pathway that is initiated via the binding of an Fc receptor to an immune complex is eliminated [122].

In AD, it is thought that short amyloid peptides that are deposited extracellularly are linked to the pathogenesis of the disease [123]. A β peptide is generated through amyloid precursor protein. This treatment works by inducing an immune response that inhibits the secretases of A β peptide from its precursor, and it should be possible to result in secretase-specific protease inhibitors that are able to penetrate the BBB [123]. This method blocks the β -secretase

from cleaving the precursor by inhibiting the *in vivo* formation of the A β peptide. This would in turn result in either inhibiting or preventing the development of AD [123].

Future perspective

New methods developed for the treatment of auto-immune diseases have become less invasive and more specific than those previously developed. Although there is a large amount of research and treatment methods dedicated to the prevention and treatment of autoimmune diseases such as MS and AD, R&D of using autoimmune responses as a means of treating neoplasm is becoming an exciting and expanding field.

The most exciting and effective future approach for many of these diseases is prevention, since reversal of symptoms, for example in advanced AD, seems unrealistic. Delaying AD onset may also prove valuable since it will improve quality of life, until perhaps other fatal diseases of old age appear. Ideally, one wishes to see the development of a 'smart phone' approach to immunomodulation whereby an immunologic pacemaker controls how and when the immune cascade is triggered. Another 'app' would consist of a program that constantly measures autoimmune titer and interacts with the controller unit in selecting what and when antibodies enter into the blood stream to fight foreign molecules while sparing the self-antigen. The same device will also be able to exaggerate the immune response for self-antigens present, for example, in tumor cells or brain regions where an immunological ablation takes care of dysfunctional neurons. Cost and miniaturization are obvious obstacles, but one needs to keep in mind that the first cardiac pacemaker was bigger than a large supermarket cart.

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References

1. Janigro D. Are you in or out? Leukocyte, ion, and neurotransmitter permeability across the epileptic blood–brain barrier. *Epilepsia*. 2012; 53(Suppl. 1):26–34. [PubMed: 22612806]
2. Longo, DL.; Fauci, AS.; Kasper, DL.; Hauser, SL.; Jameson, JL.; Loscalzo, J. McGraw-Hill Medical; Berkshire, UK: 2011. Harrison's Principles of Internal Medicine, Eighteenth Edition..
3. Perricone R, Perricone C, De Carolis C, Shoenfeld Y. NK cells in autoimmunity: a two-edged weapon of the immune system. *Autoimmun. Rev.* 2008; 7(5):384–390. [PubMed: 18486926]
4. Lawther BK. Blood–brain barrier. *Cont. Educ. Anaesth. Crit. Care Pain.* 2011; 11(4):128–132.
5. Galea I, Bechmann I, Perry VH. What is immune privilege (not)? *Trends Immunol.* 2007; 28(1):12–18. [PubMed: 17129764]
6. Andersson PB, Perry VH, Gordon S. The acute inflammatory response to lipopolysaccharide in CNS parenchyma differs from that in other body tissues. *Neuroscience.* 1992; 48(1):169–186. [PubMed: 1584421]
7. Chorsky RL, Yaghai F, Hill WD, Stopa EG. Alzheimer's disease: a review concerning immune response and microischemia. *Med. Hypotheses.* 2001; 56(1):124–127. [PubMed: 11133269]
8. Dodel R, Neff F, Noelker C, et al. Intravenous immunoglobulins as a treatment for Alzheimer's disease: rationale and current evidence. *Drugs.* 2010; 70(5):513–528. [PubMed: 20329802]
9. D'Andrea MR. Add Alzheimer's disease to the list of autoimmune diseases. *Med. Hypotheses.* 2005; 64(3):458–463. [PubMed: 15617848]
10. Ishii K, Kitagaki H, Kono M, Mori E. Decreased medial temporal oxygen metabolism in Alzheimer's disease shown by PET. *J. Nucl. Med.* 1996; 37(7):1159–1165. [PubMed: 8965188]

11. Lue LF, Brachova L, Civin WH, Rogers J. Inflammation, a beta deposition, and neurofibrillary tangle formation as correlates of Alzheimer's disease neurodegeneration. *J. Neuropathol. Exp. Neurol.* 1996; 55(10):1083–1088. [PubMed: 8858005]
12. Cummings JL, Doody R, Clark C. Disease-modifying therapies for Alzheimer disease: challenges to early intervention. *Neurology.* 2007; 69(16):1622–1634. [PubMed: 17938373]
13. Chapman J, Bachar O, Korczyn AD, Wertman E, Michaelson DM. Antibodies to cholinergic neurons in Alzheimer's disease. *J. Neurochem.* 1988; 51(2):479–485. [PubMed: 3292704]
14. Monahan AJ, Warren M, Carvey PM. Neuroinflammation and peripheral immune infiltration in Parkinson's disease: an autoimmune hypothesis. *Cell Transplant.* 2008; 17(4):363–372. [PubMed: 18522239]
15. Villoslada P, Moreno B, Melero I, et al. Immunotherapy for neurological diseases. *Clin. Immunol.* 2008; 128(3):294–305. [PubMed: 18534912]
16. Li J, Zhu M, Manning-Bog AB, Di Monte DA, Fink AL. Dopamine and l-dopa disaggregate amyloid fibrils: implications for Parkinson's and Alzheimer's disease. *FASEB J.* 2004; 18(9):962–964. [PubMed: 15059976]
17. Abramsky O, Litvin Y. Automimmune response to dopamine-receptor as a possible mechanism in the pathogenesis of Parkinson's disease and schizophrenia. *Perspect. Biol. Med.* 1978; 22(1):104–114. [PubMed: 733451]
18. Le WD, Engelhardt J, Xie WJ, Schneider L, Smith RG, Appel SH. Experimental autoimmune nigral damage in guinea pigs. *J. Neuroimmunol.* 1995; 57(1–2):45–53. [PubMed: 7706439]
19. Orr CF, Rowe DB, Mizuno Y, Mori H, Halliday GM. A possible role for humoral immunity in the pathogenesis of Parkinson's disease. *Brain.* 2005; 128(Pt 11):2665–2674. [PubMed: 16219675]
20. Staines DR. Is Parkinson's disease an autoimmune disorder of endogenous vasoactive neuropeptides? *Med. Hypotheses.* 2007; 69(6):1208–1211. [PubMed: 17562359]
21. Cooper AA, Gitler AD, Cashikar A, et al. Alpha-synuclein blocks ER-Golgi traffic and Rab1 rescues neuron loss in Parkinson's models. *Science.* 2006; 313(5785):324–328. [PubMed: 16794039]
22. Kellinghaus C, Berning S, Immisch I, et al. Intravenous lacosamide for treatment of status epilepticus. *Acta Neurol. Scand.* 2011; 123(2):137–141. [PubMed: 20868429]
23. Caterina MJ, Leffler A, Malmberg AB, et al. Impaired nociception and pain sensation in mice lacking the capsaicin receptor. *Science.* 2000; 288(5464):306–313. [PubMed: 10764638]
24. Szallasi A, Blumberg PM. Vanilloid (Capsaicin) receptors and mechanisms. *Pharmacol. Rev.* 1999; 51(2):159–212. [PubMed: 10353985]
25. Kalia NP, Mahajan P, Mehra R, et al. Capsaicin, a novel inhibitor of the NorA efflux pump, reduces the intracellular invasion of *Staphylococcus aureus*. *J. Antimicrob. Chemother.* 2012; 67(10):2401–2408. [PubMed: 22807321]
26. Han Y, Tan TM, Lim LY. Effects of capsaicin on P-gp function and expression in Caco-2 cells. *Biochem. Pharmacol.* 2006; 71(12):1727–1734. [PubMed: 16674925]
27. Higgins D, Dix D, Gold ME. Vagal nerve stimulation: a case report. *AANA J.* 2010; 78(2):146–150. [PubMed: 20583461]
28. Merson TD, Binder MD, Kilpatrick TJ. Role of cytokines as mediators and regulators of microglial activity in inflammatory demyelination of the CNS. *Neuromolecular Med.* 2010; 12(2):99–132. [PubMed: 20411441]
29. Fernandez M, Montalban X, Comabella M. Orchestrating innate immune responses in multiple sclerosis: molecular players. *J. Neuroimmunol.* 2010; 225(1–2):5–12. [PubMed: 20537409]
30. Morelli A, Ravera S, Calzia D, Panfoli I. Impairment of heme synthesis in myelin as potential trigger of multiple sclerosis. *Med. Hypotheses.* 2012; 78(6):707–710. [PubMed: 22398388]
31. Alberts, B.; Bray, D.; Lewis, J.; Raff, M.; Roberts, K.; Watson, JD. *Molecular Biology of the Cell*, Third Edition. Garland Science; NY, USA: 1994.
32. Rose JW, Carlson NG. Pathogenesis of multiple sclerosis. *Continuum (Minneap. Minn.).* 2007; 13(5):35–62.
33. Chen Z, Freedman MS. gd T cells and multiple sclerosis: friends, foes, or both? *Autoimmun. Rev.* 2011; 10(6):364–367. [PubMed: 21195807]

34. Wucherpfennig KW, Newcombe J, Li H, Keddy C, Cuzner ML, Hafler DA. Gamma delta T-cell receptor repertoire in acute multiple sclerosis lesions. *Proc. Natl Acad. Sci. USA.* 1992; 89(10): 4588–4592. [PubMed: 1374907]
35. Bettelli E, Oukka M, Kuchroo VK. T(H)-17 cells in the circle of immunity and autoimmunity. *Nat. Immunol.* 2007; 8(4):345–350. [PubMed: 17375096]
36. Matusevicius D, Kivisakk P, He B, et al. Interleukin-17 mRNA expression in blood and CSF mononuclear cells is augmented in multiple sclerosis. *Mult. Scler.* 1999; 5(2):101–104. [PubMed: 10335518]
37. Moseley TA, Haudenschild DR, Rose L, Reddi AH. Interleukin-17 family and IL-17 receptors. *Cytokine Growth Factor Rev.* 2003; 14(2):155–174. [PubMed: 12651226]
38. Biegler BW, Yan SX, Ortega SB, Tennakoon DK, Racke MK, Karandikar NJ. Clonal composition of neuroantigen-specific CD8+ and CD4+ T-cells in multiple sclerosis. *J. Neuroimmunol.* 2011; 234(1–2):131–140. [PubMed: 21397340]
39. Mattson DH, Roos RP, Arnason BG. Isoelectric focusing of IgG eluted from multiple sclerosis and subacute sclerosing panencephalitis brains. *Nature.* 1980; 287(5780):335–337. [PubMed: 7421992]
40. Beurskens FJ, Lindorfer MA, Farooqui M, et al. Exhaustion of cytotoxic effector systems may limit monoclonal antibody-based immunotherapy in cancer patients. *J. Immunol.* 2012; 188(7): 3532–3541. [PubMed: 22368276]
101. 2011. New York University: US8012936
102. 2011. Scarsdale: US0206742
103. 2012. University College Cardiff Consultants Limited: EP2449134
104. 2010. University of Zurich: EP2167115 A2
105. 2011. Pharnext: EP2282779
106. 2008. Merck Sharp & Dohme Limited: EP1773315
107. 2010. Ramot at Tel Aviv University Limited: WO0060073
108. 2011. Cedars-Sinai Medical Center: US0086804
109. 2012. Neuronova AB: EP1443955 B1
110. 2012. Newron Pharmaceuticals, SPA: WO0089353
111. 2006. Ethicon Incorporated: WO0071778
112. 2011. Brown University: US0166196
113. 2011. ElectroCore, LLC: US0152967
114. 2011. Tel HaShomer Medical Research infrastructure and Services Ltd: EP2121971 B1
115. 2007. Teva Pharmaceutical Industries Ltd: EP1796680
116. 2012. Administracion General De La Comunidad Autonoma De Euskadi: EP2451970
117. 2012. Research Development Foundation: EP1753447 A2
118. 2007. Biogen Idec MA Inc.: EP1833509
119. 2009. Biotempt BV: US7560433
120. 2010. Genentech, Inc.: US0233121
121. 2011. Research Development Foundation: US0059891
122. 2007. Ramot at Tel Aviv University Ltd: US0134247
123. 2011. Ramot at Tel Aviv University Ltd: US0070249

Key term

Autoimmune diseases: Characterized by the launching of an immunologic reaction of an organism against its own tissues; an indication of a breakdown in the mechanisms that control and regulate the host's immune responses.

Key term

Blood–brain barrier: The intact blood–brain barrier plays an important role in protecting the CNS from exogenous molecules. The blood–brain barrier is a selectively permeable barrier, thus molecules such as sodium, potassium, glucose and certain amino acids can only pass through via transport proteins that are present.

Key terms

Parkinson's disease: Neurodegenerative, possibly autoimmune disease, which is characterized by the depletion of neurons in the substantia nigra of the brain. Neurons in this region produce dopamine and control the majority of body movements.

Alzheimer's disease: Disease with an autoimmune component that results in memory loss, visual impairment and cognitive deficits. In patients affected by Alzheimer's disease, there is a decrease in both oxygenation and cerebral blood flow located in the temporal lobe region, leading to an overall decrease in oxygen metabolism. In addition, the buildup of amyloid- β and neurofibrillary tangles is thought to lead to the development of Alzheimer's disease.

Tau proteins: Play an important role in maintaining axonal microtubule stability.

α -synuclein: Synuclein protein primarily found in neurons and glia making up as much as 1% of all proteins in the cytosol. Normally, α -synuclein is present in an unstructured soluble form, but it can aggregate to form insoluble tangles as in Lewy bodies in Parkinson's disease.

Multiple sclerosis: Autoimmune neurological disease that is brought on by immune cells including antibody-secreting B cells, autoreactive T cells and macrophages that infiltrate the CNS. In patients that have multiple sclerosis, demyelination and axonal degeneration in the CNS occur.

Executive summary

- Immunity is essential for life but is also implicated in several neurological disorders.
- Autoimmune diseases are consequences of misguided activity of T and B cells.
- Circulating auto-antibodies involved in these neurological disorders can be targeted and functionally inactivated by other antibodies.
- In a similar way, antibodies for misfolded or wrongly assembled proteins can clear the brain tissue from neurotoxic complexes.
- The fine line between autoantigen targeting, neurological diseases and therapy is further blurred by stimulators of immune response against brain tumors.
- All these targets can be reached by traditional (drugs) or futuristic (e.g., magnets) means.

Figure 1. The intact blood–brain barrier plays an important role in protecting the CNS from circulating molecules, ions and cells

The BBB is a selectively permeable barrier, thus molecules such as sodium, potassium, glucose and certain amino acids can only pass through via transport proteins. Endothelial cells line the intraluminal surface of blood capillaries forming tight junctions. Multidrug resistance proteins and glucose transporters can also be found within the BBB. The selectivity of the BBB may play a detrimental role when it comes to drug delivery though, by not allowing certain CNS drugs to pass through the BBB.

BBB: Blood–brain barrier.

Figure 2. In autoimmune diseases, a leakage of the blood–brain barrier may occur, allowing normally sequestered CNS proteins to leak from the brain into the bloodstream Brain-specific antigens are taken up by the dendritic cells, potentially leading to an autoimmune response due to antigen unmasking.

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Figure 3. In many autoimmune diseases, a leakage of the blood–brain barrier may cause normally sequestered antigens to escape from the brain into the bloodstream (A) If specific antigens are taken up by the dendritic cells, this may potentially lead to an autoimmune response due to antigen unmasking. (B) If these potential auto-antigens are taken up by dendritic cells, this may potentially lead to an autoimmune response (C) due to antigen unmasking (D). Antigen leakage, however, may not be the mechanism because slow release of antigens into the bloodstream would be predicted to induce tolerance rather than autoimmunity. Alternatively, molecular mimicry may occur. Molecular mimicry exploits sequence similarities between foreign and self-derived peptides, which can be sufficient to cause cross-activation of autoreactive T or B cells. In the case of multiple sclerosis, molecular mimicry is plausible but not fully documented; this is different from acute inflammatory demyelinating polyneuropathy/Guillain-Barré. In the latter autoimmune disease, a misguided immune response to foreign antigens targets host nerve tissues.

Figure 4. Immunotherapy in treating Alzheimer's disease and cancers

Immunotherapy has been found to be an effective means in treating Alzheimer's disease (autoimmune disease), in addition to its effectiveness in combating cancers. However, Parkinson's disease and multiple sclerosis are autoimmune diseases that are not treated using immunotherapy.

Figure 5. Sonic Hedgehog is a protein that is important in the development of the CNS
Shh is responsible for the proliferation and regeneration of neural precursor cells. The G-protein-coupled receptors (including both patched and smoothened) activate Shh signaling to occur. Gli-1, Gli-2 and Gli-3 are a family of transcriptional activators, and are thought to be located downstream of the smoothened pathway. TRPV1 is responsible for regulating and detecting body temperature.
Shh: Sonic Hedgehog.

Table 1

Novel treatments for autoimmune diseases and use of immunotherapy for cancers.

Name	Patent number	Assignee	Inventor(s)	Ref.
<i>Treating autoimmune diseases using immunotherapy</i>				
Immunotherapeutic compositions for the treatment of Alzheimer's disease	US0206742 A1	Scarsdale	Peter Blackburn and Stephen Grimes	[102]
Tau fragments for immunotherapy	US8012936 B2	New York University	Einar Sigurdsson and Ayodeji Asuni	[101]
<i>Treating autoimmune diseases</i>				
Diagnosis and treatment of Alzheimer's disease	US0206742	University College Cardiff Consultants Ltd	John Michael Owen and Julie Williams	[103]
Treatment for Alzheimer's disease	EP2167115 A2	University of Zurich	Feng Chen, Jan Grimm and Roger Nitsch	[104]
New therapeutic approaches for treating Alzheimer disease and related disorders through a modulation of cell stress response	EP2282779 A1	Pharnext	Ilya Chumakov, Daniel Cohen, Oxana Guerassimenko and Serguei Nabirochkin	[105]
Arylacetic acids and related compounds for treatment of Alzheimer's disease	EP1773315 B1	Merck Sharp and Dohme Ltd	Peter Blurton, Frank Burkamp, Ian Churcher, Timothy Harrison and Joseph Neduvellil	[106]
Method for treating Parkinson's disease	WO0060073	Ramot at Tel Aviv University Ltd.	Beka Solomon and Haim M Dimant	[107]
Treatment of Parkinson's disease	US0086804 A1	Cedars-Sinai Medical Center	Pedro Lowenstein and Maria Castro	[108]
PDGF-BB for the treatment of Parkinson's disease	EP1443955 B1	NeuroNova AB	Kioumars Delfani, Marie Ann Janson H Georg Kuhn, Karlheinz Plate, Anne Schanzer, Frank-Peter Wachs and Ming Zhao	[109]
Methods for treatment of Parkinson's disease	WO2004089353	Newron Pharmaceuticals S.P.A.	Luca Benatti, Carlo Benatti, Ruggero Fariello and Patricia Salvati	[110]
Treatment of Parkinson's disease and related disorders using postpartum derived cells	EP1835924 A2	Ethicon, Incorporated	Klaudyne LS Hong, C Brian Kramer, J DarinMessina, Sanjay Mistry and J Michael Romanko	[111]
Treatment and prophylaxis of epilepsy and febrile seizures	US0166196 A1	Providence	Julia A Kauer, Barry W Connors, Jennifer A Kim and Helen E Gibson	[112]
Non-invasive treatment of neurodegenerative diseases	US0152967 A1	ElectroCore, LLC., Morris Plains	Bruce Simon, Joseph P Errico and John T Raffle	[113]
Methods and kits for diagnosis of multiple sclerosis in probable multiple sclerosis subjects	EP2121971 B1	Tel Hashomer Medical Research Infrastructure and Services Ltd	Anat Achiron and Michael Gurevich	[114]

Name	Patent number	Assignee	Inventor(s)	Ref.
Methods of treating symptoms of multiple sclerosis using vitamin D and related compounds	EP1796680 A2	Teva Pharmaceutical Industries Ltd	Anat Achiron, Liat Hayardeny, Dina Kofler, David Ladkani, Zeev Mazor, Irit Pinchasi and Aharon Schwartz	[115]
Methods for the diagnosis of multiple sclerosis based on its miRNA expression profiling	EP2451970 A1	Administracion General De La Comunidad Autonoma De Euskadi	Ruben Armananzas Arnedillo, Borja Calvo Molinos, Inaki Inza Cano, Adolfo Lopez de Munain Arregi, Jose Antonio Lozano Alonso, Javier Olascoaga Urtaza and David Otaegui Bichot	[116]
Immune response suppressor and treatment of multiple sclerosis	US0059891 A1	Bellaire	Staley A Brod	[117]
<i>Treating autoimmune diseases</i>				
Delaying or preventing onset of multiple sclerosis	EP1833509 A2	Biogen Idec MA, Inc.	Michael Panzara and Marco Rizzo	[118]
Delaying or preventing onset of multiple sclerosis	US7560433 B2	Biotempt BV	Nisar Ahmed Khan and Robbert Benner	[119]
Method for treating multiple sclerosis	US0233121 A1	Genentech, Inc.	Paul A Frohna	[120]
α -MSH therapies for treatment of autoimmune disease	US0059891	Research Development Foundation	Staley A Brod	[121]
<i>Immunotherapy</i>				
Prevention of brain inflammation as a result of induced autoimmune response	US0134247 A9	Ramot AT Tel Aviv University Ltd	Beka Solomon	[122]
Immunizing composition and method for inducing an immune response against the β -secretase cleavage site of amyloid precursor protein	US0070249 A1	Ramot At Tel-Aviv University Ltd	Beka Solomon	[123]