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Research Overview

Prospects for Therapeutic Vaccination With Glatiramer Acetate for Neurodegenerative Diseases Such as Alzheimer's Disease

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Strategy, Management and Health Policy				
Venture Capital Enabling Technology	Preclinical Research	Preclinical Development Toxicology, Formulation Drug Delivery, Pharmacokinetics	Clinical Development Phases I-III Regulatory, Quality, Manufacturing	Postmarketing Phase IV

ABSTRACT Neurodegenerative diseases, whatever their primary causes, are characterized by certain common features, one of which is their self-perpetuating nature. The ongoing progression of the disorder is due to the effects of destructive self-compounds, whose presence in the tissues is an outcome of the early phase of the disease and which gradually destroy remaining functional neurons. Studies in our laboratory have led to the recent formulation of a novel concept of protective autoimmunity as the body's mechanism of defense against these destructive self-compounds. This autoimmune response to central nervous system (CNS) insults is mediated by T-cells and presumably operates by activating and regulating local microglia and infiltrating macrophages (inflammatory response) to carry out their function of clearing destructive material from the tissue at risk. We suggest that a well-controlled autoimmunity counteracts and overcomes the destructive effects of the potentially harmful self-compounds, at the cost of some loss of tissue. An additional risk to the individual is the induction of an autoimmune disease, which is likely to occur if the autoimmune response is malfunctioning. An optimal balance of the various factors will lead to an outcome of maximal benefit at minimal cost to the tissue. A procedure for safely boosting the autoimmune response, by vaccination with a weak self-crossreactive antigen such as glatiramer acetate (also known as Cop-1) was found to protect rats from glutamate toxicity, a major mediator of the spread of damage and a well-known causative factor in neurodegenerative disorders. Cop-1, when administered according to a different regimen, is an FDA-approved drug for the treatment of multiple sclerosis. Different formulations of the same drug can therefore be used to treat two extreme manifestations of chronic degenerative diseases of the CNS. Drug Dev. Res. 56:143–149, 2002.

Key words: neurodegenerative diseases; Alzheimer's disease; therapeutic vaccination; protective autoimmunity

AUTOIMMUNITY LEADING TO A BENEFICIAL OUTCOME IN NEURODEGENERATIVE DISORDERS

Neurodegenerative syndromes are commonly associated with ongoing neuronal losses in the central nervous system (CNS). In all of these disorders, regardless of their location in the CNS, the progressive neuronal loss follows a similar pattern and is perpetuated by similar toxic mediators [Hovda et al., 1991]. It is interesting to note that destructive components common to neurodegenerative diseases have also been identified in autoimmune diseases viewed as myelin disorders, such as multiple sclerosis (MS) [Bjartmar and Trapp, 2001; Meyer et al., 2001; Olsson et al., 2000; Perry and Anthony, 1999]. Among these components are excitatory amino acids (such as glutamate), nitric oxide, and free radicals causing oxidative stress [Greenamyre et al., 1999; Hartwick, 2001; Rothstein,

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1995a,b]. Immune activity is widely thought to have negative effects in all patients with neurodegenerative disorders [Asghar and Pasch, 2000; Burt et al., 2000; Choy, 2000; McMurray, 2001; Wimer, 1998], not only in those with definite etiology of autoimmune disease.

Studies in our laboratory have shown that immune cells in general, and autoimmune T-cells in particular, play an essential role in protecting the injured CNS from the effects of self-destructive compounds (such as mediators of toxicity causing secondary degeneration) [Fisher et al., 2001; Hauben et al., 2000b; Moalem et al., 1999; Schwartz and Cohen, 2000; Schwartz and Kipnis, 2001]. In certain strains of rats with partial crush injury of the optic nerve [Yoles and Schwartz, 1998], we found that passive transfer of autoimmune T-cells reactive to myelin-related self-antigens confers a neuroprotective effect by reducing secondary degeneration of the damaged neural tissue [Fisher et al., 2001; Moalem et al., 1999], while at the same time inducing a transient autoimmune syndrome experimental autoimmune encephalomyelitis (EAE) [Ben-Nun and Cohen, 1982; Kim et al., 1998]. Further studies by our group showed that protective autoimmunity is a physiological response to the insult. The spontaneous ability to manifest a protective autoimmune response was found to vary among individuals, in apparent correlation with their ability to resist the induction (by myelin-associated antigens) of an autoimmune disease [Kipnis et al., 2001]. We further observed that a T-cell-dependent protective mechanism also operates when the CNS insult is of a biochemical rather than a mechanical nature [Schwartz and Kipnis, 2001]. Thus, direct exposure of the eye to glutamate (by intravitreal injection) causes dose-dependent death of the retinal ganglion cells, but the identical injection has different long-term effects on mice of differing genetic backgrounds. In mice deprived of mature T-cells, however, these strain-related differences were wiped out, so that the relatively resistant strains lost their advantage. Interestingly, boosting of the T-cell response by myelin-associated antigens, although beneficial when the insult was inflicted on the myelinated axons, had no effect when the insult was directed to the retinal ganglion cells [Schori et al., 2001a,b].

These and other results led us to propose that protective autoimmunity is the body's mechanism of protection and repair in the case of insults by self-compounds and that autoimmune disease is an outcome of failure to control this mechanism [Schwartz and Kipnis, 2001]. We further suggest that autoimmunity and neurodegenerative disorders are two extreme manifestations of the same process, namely, an autoimmune response, and that the competition between self-destructive compounds and autoimmunity determines the final outcome and expression of the process.

We recently observed that retinal ganglion cells subjected to glutamate insult can benefit from autoimmune T-cells that are specifically reactive to antigens residing in the eye. It thus appears that for T-cells to be beneficial, they should be activated within the site of their activity. This means that they should recognize their antigen-presenting cells at that site [Schwartz and Mizrahi, 2002].

Based on our results, it seems that the presence of activated microglia or invading macrophages at the sites of CNS tissue damage in acute or chronic disorders cannot be used as an argument either for or against the contribution of such cells to the well-being of the damaged tissue. It is possible that the reason for the initial recruitment and activation of these immune cells is to facilitate the clearance of cell debris and threatening self-compounds from the site, either by aiding phagocytosis or by activating the resident microglia so as to increase their buffering capacity in a receptor-specific manner [Schwartz and Kipnis, 2002].

Taken together, the results described above suggest that the immune system can protect against the consequences of CNS insults. It is also clear that the protective immune response should be well-regulated. To translate the protective response into a therapeutic vaccine, it is necessary to find a way to boost the T-cell response to self-antigens residing at the site of damage while avoiding the development of an autoimmune disease, which would endanger the tissue. In seeking a potent antigen that would meet the criteria of activating self-reactive T-cells without risking healthy tissue, we decided to test Cop-1 [Kipnis et al., 2000; Schori et al., 2001a], a compound that (when administered according to a different regimen) has proved useful as a treatment for patients with the relapsing–remitting form of MS [Sela, 1999a,b]. Experimental results from our group support the possible use of Cop-1 as a therapeutic vaccine for other neurodegenerative disorders, not necessarily in the category of autoimmune diseases.

Cop-1 IN AUTOIMMUNE DISEASE

Copolymer 1 or Cop-1 (Copaxone®), also known as glatiramer acetate, is a synthetic amino acid polymer (4.7–11 kDa) composed of four amino acids (L-alanine, L-lysine, L-glutamic acid, and L-tyrosine) in a defined molar ratio [Teitelbaum et al., 1971, 1997b]. It was originally synthesized to mimic the activity of myelin basic protein (MBP) in inducing EAE in laboratory animals [Teitelbaum et al., 1997a], but was found to be nonencephalitogenic and even to suppress MBP-

induced EAE [Weiner, 1999]. Cop-1 blocks chronic-relapsing EAE induced in an (SJL/J × Balb/c) F_1 mouse model by application of mouse spinal cord homogenate or encephalitogenic peptides of proteolipid protein (PLP) [Teitelbaum et al., 1996]. The polymer is thought to bind to the relevant major histocompatibility complex (MHC) proteins and activate T-suppressor cells triggered by determinants common to Cop-1 and MBP [Teitelbaum et al., 1997a].

The precise mechanisms by which Cop-1 prevents the development of EAE and ameliorates MS are not yet fully understood. Nevertheless, some important immunological properties of this copolymer have been discovered. Cop-1 shows partial cross-reactivity with MBP, mediated both by T-cells and by antibodies. Cop-1 can serve as an antagonist of the T-cell antigen receptor for the MBP immunodominant epitope [Aharoni et al., 1998]. It can also bind to various MHC class II molecules [Fridkis-Hareli et al., 1997] and prevent them from binding to T-cells with several antigen-recognition properties. In a recently published commentary, Hafler [2002] Hafler referred to Cop-1 as a "universal APL" (altered peptide ligand) or a "universal antigen" and formulated a novel view of the effect of Cop-1 in patients with MS. In rodents, Cop-1 suppresses the encephalitogenic effect of myelin-associated autoreactive T-cells. Passive transfer of Cop-1-specific T-cells was found to prevent the development of EAE induced in rats or mice by MBP [Aharoni et al., 1993], PLP [Teitelbaum et al., 1996], or whole spinal cord homogenate [Aharoni et al., 1997]. In humans, daily treatment with Cop-1 leads to a tendency to the development of a response of the Th2/Th3 type over time [Duda et al., 2000].

Cop-1-activated T-cells were found to be neuroprotective in several models of CNS injury as well, where myelin-associated antigens are not active, such as the insult caused by direct exposure of retinal ganglion cells to glutamate toxicity [Schori et al., 2001a]. Thus, on the basis of our results as well as suggestions in the literature, we view Cop-1 as an antigen that has the capacity for low-affinity activation of a wide range of self-reactive T-cells and thereby overcomes the specificity barrier of tissue self-antigens. Being similar to both self-antigens and weak, Cop-1 can serve the two goals of activating self-reactive T-cells without risk of autoimmune disease and failing to activate dominant self-epitopes. It therefore seems that, if administered according to a suitable regimen in each case, enabling different modes of action, treatment with Cop-1 can be beneficial against both autoimmune diseases (e.g. MS) and neurodegenerative diseases (e.g. Alzheimer's disease, AD). In the former case, the Cop-1 molecules are used to suppress a wide range of self-reactive T-cells, whereas in the latter case they activate the immune response in a well-regulated way. The regimen will differ in these two cases.

Csp-1 AS A WEAK UNIVERSAL SELF-ANTIGEN—A SAFE THERAPEUTIC VACCINE FOR NEURODEGENERATIVE DISORDERS

Our initial assumption was that Cop-1, by cross-reacting with MBP or other components of myelin, might enable Cop-1-specific T-cells to recognize the damaged tissue, accumulate there, and undergo activation resulting in neuroprotection [Kipnis et al., 2000]. More recent studies showed, however, that T-cells reactive to Cop-1 do not proliferate when exposed to myelin proteins [Qin et al., 2000]. After partial crush injury of the rat optic nerve, myelin epitopes are exposed at the site of injury. Following injury, peripheral lymphocytes—regardless of their antigenic specificity—enter the CNS [Owens et al., 2001; Schmidt et al., 1997]. T-cells reactive to myelin proteins are activated at the site of injury or in the cervical lymph nodes, where the drainage of CNS antigens probably takes place [Aloisi et al., 2000a,b]. Recent studies in our laboratory showed that activation of autoimmune T-cells after injury is a prerequisite for neuroprotection and that such activation can be boosted by immunization with self-antigens (in this case, myelin proteins) [Fisher et al., 2001; Hauben et al., 2000a,b]. These findings led us to suggest that upon passive transfer of Cop-1-specific T-cells or active immunization with Cop-1, T-cells arriving at the site of injury will serve a dual role: first, they will trigger proinflammatory activity, and later they will terminate their own activation [Kipnis et al., 2000]. Examination of this possibility indeed showed that Cop-1-reactive T-cells accumulate in the normal (undamaged) optic nerve, where only myelin-specific T-cells can accumulate, but that their numbers are smaller than those of the accumulated myelin-specific T-cells. These findings pointed to cross-reactivity of Cop-1-activated T-cells with myelin proteins in vivo. Activated Cop-1-reactive T-cells produce neurotrophic factors, but their pattern of neurotrophin expression differs from that of MBP-reactive activated T-cells [Kipnis et al., 2000]. Accordingly, the mechanism we suggested was that Cop-1-reactive T-cells, after arriving at the site of the injury, are weakly reactivated by self-antigens residing at the lesion site. Such reactivated T-cells were shown to produce cytokines associated with both Th1 (INF-γ and Th2 (IL-4), indicating that Cop-1-reactive T-cells have the potential for self-regulation. We suggest that the reactivated proinflammatory Cop-1 cells in turn activate the resident microglia, as suggested above, facilitating their ability to clear the lesion site of toxic

compounds in a receptor-specific manner, as well as to display enhanced phagocytic activity for nonspecific clearance. The activated T-cells also produce neurotrophic factors and activate microglia to produce neurotrophic factors [Barouch and Schwartz, 2002].

We suggest that the autoimmune response be viewed as the individual's protective physiological response to any CNS insult, whether it be caused by exogenous invading microorganisms, by mechanical trauma, or by destructive self-compounds evoked by stress originating within the body itself. Autoimmune disease is then one extreme situation where the autoimmune response overshoots and gets out of control. The other extreme is a degenerative disorder, where the autoimmune response is not strong enough for effective protection and degeneration therefore continues. Thus, inflammation might be seen in both of these pathological conditions, but it will require distinct therapeutic handling in each case.

DIFFERENTIAL MODES OF Cop-1 ADMINISTRATION IN PATIENTS WITH MS AND WITH NEURODEGENERATIVE DISORDERS

If Cop-1 acts as a universal antigen, questions arise in connection with the optimal therapeutic regimens of Cop-1 for different conditions. Should patients with autoimmune diseases be treated in the same way as patients with acute or chronic neurodegenerative disorders? In the case of autoimmune disease, where the regulation of autoimmunity is malfunctioning, there is a need to shut off the autoimmune clones. In the case of acute CNS injury or chronic neurodegenerative disorders, on the other hand, there is a need for neuroprotection, initially requiring the participation of active autoimmune clones and subsequently needing tight control to shut off the autoimmune response at the right time.

Reports indicate that MS patients treated with Cop-1 initially show a Th1-type response, which later switches towards Th2 [Farina et al., 2001; Neuhaus et al., 2001], considered to be a favorable phenotype in such patients. From this stage onward, each application of Cop-1 boosts the Th2-type response and weakens the Th1-type response, until there is no response to Cop-1 at all [Duda et al., 2000; Neuhaus et al., 2000]. This eventual lack of response might reflect anergy of effector T-cells (primarily specific to myelin or to other self-proteins) caused by overstimulation with Cop-1. Alternatively, or in addition, it might reflect overactivation of regulatory T-cell clones and their consequent inhibition of effector clones (regardless of their antigenic specificity). Whatever the underlying mechanism, this type of progression of the autoimmune response was found to be beneficial in patients with autoimmune diseases.

In acute neurodegenerative disorders, the aim of therapy is to boost the local immune response at the lesion site in a well-regulated way. Accordingly, the early and transient Th1 (effector) response is a welcome phenomenon, essential for stopping the process of damage caused by self-destructive compounds. It can be achieved by Cop-1 vaccination, which allows an induced Th1 (effector) immune response to be accompanied by a regulatory response. In patients with chronic neurodegenerative disorders, the timing and amount of each booster application should incorporate the Th1 phase. During this phase (which is probably very short) the affinity of the Th1 cells for self-epitopes is relatively low, so the development of an autoimmune disease during the Th1 phase window is avoided, whereas the desired activation of phagocytes for clearing of myelin debris is probably achieved.

Glutamate is a major mediator of toxicity in neurodegenerative disorders, including AD [Ferrarese et al., 2001; Liang et al., 2002; Takahashi et al., 2002; Vajda, 2002]. Thus, regardless of the primary risk factors (many of which are not yet known), in patients with degenerative diseases the loss of neurons continues even after the risk is diminished. Considerable research attention has therefore been directed to neutralizing the mediators of continuing degeneration, among which one of the most prominent is glutamate. The finding by our group that vaccination with Cop-1 protects neurons from the consequences of direct glutamate insults suggested that this might be a promising therapy for both acute and chronic insults in which glutamate is known to play a key role. It is important to bear in mind that MS is now recognized not only as a disorder related to myelin, but also as a neurodegenerative disorder [Heales et al., 1999; Matute et al., 2001; Torreilles et al., 1999]. Giving Cop-1 to patients with MS according to the same regimen as for patients with neurodegenerative disorders might therefore be worth considering.

Our group was the first to point out that glaucoma can be viewed as a disease in which the continuing progression of degeneration, even after treatment with antihypertensive drugs, is the result of a process reminiscent of the secondary degeneration that occurs after acute injury to the optic nerve [Schwartz et al., 1996]. In view of these findings, as well as related observations reported in the literature, we considered testing Cop-1 as a vaccine for the treatment of glaucoma. Using a rat model of high intraocular pressure, we showed that a single vaccination with Cop-1 at the time of initiation of a pressure increase

resulted in protection (of up to 6-fold) of retinal ganglion cells from death assessed 3 weeks later [Schori et al., 2001a].

In seeking the antigen specific for particular sites of injury, it became clear that boosting of the autoimmune response by vaccination with the physiological native self-peptide is bound to carry a risk of autoimmune disease induction in individuals whose genetic background does not enable proper control of the autoimmune response. This might explain why the use of the native β-amyloid-derived peptide [Lemere et al., 2001; Monsonego et al., 2001; Morgan et al., 2000; Schenk et al., 2001], although effective, might have caused adverse effects in some patients with AD. One way to overcome this problem might be to make use of altered self-peptides for neurodegenerative conditions [Hauben et al., 2001]. As we have previously proposed, Cop-1 being a universal weak antigen might be an optimal solution for this purpose.

SUMMARY

On the basis of a series of experiments carried out in our laboratory, we have suggested that the T-cell-mediated protective response evoked by a CNS insult is harnessed by the body to assist local innate immune mechanisms to cope with the insult-induced secretion of destructive self-compounds [Schwartz and Kipnis, 2001]. This T-cell-mediated response needs to be rigorously regulated in order to provide protection without risk of inducing an autoimmune disease. Vaccination with Cop-1 appears to provide a safe way to both regulate and boost the response.

Degeneration is a chaotic process, involving the activity of numerous physiological compounds. Some of these compounds (for example, glutamate), although normally essential for CNS function, become toxic when (as a result of the insult) their normal concentrations are exceeded. Pharmacological intervention aimed at reducing the toxicity of a particular compound is likely to be accompanied by an undesirable disruption of that compound's normal functioning and might also interfere with the functioning of other compounds. Protective autoimmunity appears to be the body's own mechanism of coping with conditions of stress, such as those caused by CNS insults of various types. Taken together, the findings of our group and those of others further support our contention that the immune response evoked by CNS trauma is always at least potentially beneficial, but it needs to be properly regulated for the beneficial effect to be expressed. If properly regulated and suitably boosted, protective autoimmunity, such as that supplied by vaccination with Cop-1, is therefore likely to provide the most physiological and global therapeutic effect of any known treatment modality for neurodegenerative disorders such as AD.

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REFERENCES

Aharoni R, Teitelbaum D, Arnon R. 1993. T suppressor hybridomas and interleukin-2-dependent lines induced by copolymer 1 or by spinal cord homogenate down-regulate experimental allergic encephalomyelitis. Eur J Immunol 23:17–25.

Aharoni R, Schlegel PG, Teitelbaum D, Roikhel-Karpov O, Chen Y, Arnon R, Sela M, Chao NJ. 1997. Studies on the mechanism and specificity of the effect of the synthetic random copolymer GLAT on graft-versus-host disease. Immunol Lett 58:79–87.

Aharoni R, Teitelbaum D, Sela M, Arnon R. 1998. Bystander suppression of experimental autoimmune encephalomyelitis by T cell lines and clones of the Th2 type induced by copolymer 1. J Neuroimmunol 91:135–146.

Aloisi F, Ria F, Adorini L. 2000a. Regulation of T-cell responses by CNS antigen-presenting cells: different roles for microglia and astrocytes. Immunol Today 21:141–147.

Aloisi F, Serafini B, Adorini L. 2000b. Glia-T cell dialogue [In Process Citation]. J Neuroimmunol 107:111–117.

Asghar SS, Pasch MC. 2000. Therapeutic inhibition of the complement system. Y2K update. Front Biosci 5:E63–81.

Barouch R, Schwartz M. 2002. Autoreactive T cells induce neurotrophin production by immune and neural cells in injured rat optic nerve: implications for protective autoimmunity. FASEB J (in press).

Ben-Nun A, Cohen IR. 1982. Experimental autoimmune encephalomyelitis (EAE) mediated by T cell lines: process of selection of lines and characterization of the cells. J Immunol 129:303–308.

Bjartmar C, Trapp BD. 2001. Axonal and neuronal degeneration in multiple sclerosis: mechanisms and functional consequences. Curr Opin Neurol 14:271–278.

Burt RK, Marmont A, Schroeder J, Rosa R, Traynor AE. 2000. Intense immune suppression for systemic lupus—the role of hematopoietic stem cells. J Clin Immunol 20:31–37.

Choy EH. 2000. Oral toleragens in rheumatoid arthritis. Curr Opin Investig Drugs 1:58–62.

Duda PW, Schmied MC, Cook SL, Krieger JI, Hafler DA. 2000. Glatiramer acetate (Copaxone) induces degenerate, Th2-polarized immune responses in patients with multiple sclerosis. J Clin Invest 105:967–976.

Farina C, Then Bergh F, Albrecht H, Meinl E, Yassouridis A, Neuhaus O, Hohlfeld R. 2001. Treatment of multiple sclerosis with Copaxone (COP): Elispot assay detects COP-induced interleukin-4 and interferon-gamma response in blood cells. Brain 124:705–719.

Ferrarese C, Aliprandi A, Tremolizzo L, Stanzani L, De Micheli A, Dolara A, Frattola L. 2001. Increased glutamate in CSF and plasma of patients with HIV dementia. Neurology 57:671–675.

Fisher J, Levkovitch-Verbin H, Schori H, Yoles E, Butovsky O, Kaye JF, Ben-Nun A, Schwartz M. 2001. Vaccination for neuroprotection in the mouse optic nerve: implications for optic neuropathies. J Neurosci 21:136–142.

Fridkis-Hareli M, Teitelbaum D, Pecht I, Arnon R, Sela M. 1997. Binding of copolymer 1 and myelin basic protein leads to clustering of class II MHC molecules on antigen-presenting cells. Int Immunol 9:925–934.

Greenamyre JT, MacKenzie G, Peng TI, Stephans SE. 1999. Mitochondrial dysfunction in Parkinson's disease. Biochem Soc Symp 66:85–97.

Hafler DA. 2002. Degeneracy, as opposed to specificity, in immunotherapy. J Clin Invest 109:581–584.

Hartwick AT. 2001. Beyond intraocular pressure: neuroprotective strategies for future glaucoma therapy. Optom Vis Sci 78:85–94.

Hauben E, Butovsky O, Nevo U, Yoles E, Moalem G, Agranov G, Mor F, Leibowitz-Amit R, Pevsner E, Akselrod S, Neeman M, Cohen IR, Schwartz M. 2000a. Passive or active immunization with myelin basic protein promotes recovery from spinal cord contusion. J Neurosci 20:6421–6430.

Hauben E, Nevo U, Yoles E, Moalem G, Agranov E, Mor F, Akselrod S, Neeman M, Cohen IR, Schwartz M. 2000b. Autoimmune T cells as potential neuroprotective therapy for spinal cord injury. Lancet 355:286–287.

Hauben E, Agranov E, Gothilf A, Nevo U, Cohen A, Smirnov I, Steinman L, Schwartz M. 2001. Posttraumatic therapeutic vaccination with modified myelin self-antigen prevents complete paralysis while avoiding autoimmune disease. J Clin Invest 108:591–599.

Heales SJ, Bolanos JP, Stewart VC, Brookes PS, Land JM, Clark JB. 1999. Nitric oxide, mitochondria and neurological disease. Biochim Biophys Acta 1410:215–228.

Hovda DA, Yoshino A, Kawamata T, Katayama Y, Becker DP. 1991. Diffuse prolonged depression of cerebral oxidative metabolism following concussive brain injury in the rat: a cytochrome oxidase histochemistry study. Brain Res 567:1–10.

Kim G, Kohyama K, Tanuma N, Arimito H, Matsumoto Y. 1998. Persistent expression of experimental autoimmune encephalomyelitis (EAE)-specific Vbeta8.2 TCR spectratype in the central nervous system of rats with chronic relapsing EAE. J Immunol 161:6993–6998.

Kipnis J, Yoles E, Porat Z, Cohen A, Mor F, Sela M, Cohen IR, Schwartz M. 2000. T cell immunity to copolymer 1 confers neuroprotection on the damaged optic nerve: possible therapy for optic neuropathies. Proc Natl Acad Sci USA 97:7446–7451.

Kipnis J, Yoles E, Schori H, Hauben E, Shaked I, Schwartz M. 2001. Neuronal survival after CNS insult is determined by a genetically encoded autoimmune response. J Neurosci 21: 4564–4571.

Lemere CA, Maron R, Selkoe DJ, Weiner HL. 2001. Nasal vaccination with beta-amyloid peptide for the treatment of Alzheimer's disease. DNA Cell Biol 20:705–711.

Liang Z, Valla J, Sefidvash-Hockley S, Rogers J, Li R. 2002. Effects of estrogen treatment on glutamate uptake in cultured human astrocytes derived from cortex of Alzheimer's disease patients. J Neurochem 80:807–814.

Matute C, Alberdi E, Domercq M, Perez-Cerda F, Perez-Samartin A, Sanchez-Gomez MV. 2001. The link between excitotoxic oligodendroglial death and demyelinating diseases. Trends Neurosci 24:224–230.

McMurray RW. 2001. Bromocriptine in rheumatic and autoimmune diseases. Semin Arthritis Rheum 31:21–32.

Meyer R, Weissert R, Diem R, Storch MK, de Graaf KL, Kramer B, Bahr M. 2001. Acute neuronal apoptosis in a rat model of multiple sclerosis. J Neurosci 21:6214–6220.

Mizrahi T, Hauben E, Schwartz M. 2002. The tissue-specific self-pathogen is the protective self-antigen: the case of uveitis. J Immunology (in press).

Moalem G, Leibowitz-Amit R, Yoles E, Mor F, Cohen IR, Schwartz M. 1999. Autoimmune T cells protect neurons from secondary degeneration after central nervous system axotomy. Nat Med 5:49–55.

Monsonego A, Maron R, Zota V, Selkoe DJ, Weiner HL. 2001. Immune hyporesponsiveness to amyloid beta-peptide in amyloid precursor protein transgenic mice: implications for the pathogenesis and treatment of Alzheimer's disease. Proc Natl Acad Sci USA 98:10273–10278.

Morgan D, Diamond DM, Gottschall PE, Ugen KE, Dickey C, Hardy J, Duff K, Jantzen P, DiCarlo G, Wilcock D, Connor K, Hatcher J, Hope C, Gordon M, Arendash GW. 2000. A beta peptide vaccination prevents memory loss in an animal model of Alzheimer's disease. Nature 408:982–985.

Neuhaus O, Farina C, Yassouridis A, Wiendl H, Then Bergh F, Dose T, Wekerle H, Hohlfeld R. 2000. Multiple sclerosis: comparison of copolymer-1-reactive T cell lines from treated and untreated subjects reveals cytokine shift from T helper 1 to T helper 2 cells [In Process Citation]. Proc Natl Acad Sci USA 97:7452–7457.

Neuhaus O, Farina C, Wekerle H, Hohlfeld R. 2001. Mechanisms of action of glatiramer acetate in multiple sclerosis. Neurology 56:702–708.

Olsson T, Dahlman I, Wallstrom E, Weissert R, Piehl F. 2000. Genetics of rat neuroinflammation. J Neuroimmunol 107:191–200.

Owens T, Wekerle H, Antel J. 2001. Genetic models for CNS inflammation. Nat Med 7:161–166.

Perry VH, Anthony DC. 1999. Axon damage and repair in multiple sclerosis. Philos Trans R Soc Lond B Biol Sci 354:1641–1647.

Qin Y, Zhang DQ, Prat A, Pouly S, Antel J. 2000. Characterization of T cell lines derived from glatiramer-acetate-treated multiple sclerosis patients. J Neuroimmunol 108:201–206.

Rothstein JD. 1995a. Excitotoxic mechanisms in the pathogenesis of amyotrophic lateral sclerosis. Adv Neurol 68:7–20.

Rothstein JD. 1995b. Excitotoxicity and neurodegeneration in amyotrophic lateral sclerosis. Clin Neurosci 3:348–359.

Schenk D, Seubert P, Ciccarelli RB. 2001. Immunotherapy with beta-amyloid for Alzheimer's disease: a new frontier. DNA Cell Biol 20:679–681.

Schmidt S, Linington C, Zipp F, Sotgiu S, de Waal Malefyt R, Wekerle H, Hohlfeld R. 1997. Multiple sclerosis: comparison of the human T-cell response to S100 beta and myelin basic protein reveals parallels to rat experimental autoimmune panencephalitis. Brain 120:1437–1445.

Schori H, Kipnis J, Yoles E, WoldeMussie E, Ruiz G, Wheeler LA, Schwartz M. 2001a. Vaccination for protection of retinal ganglion cells against death from glutamate cytotoxicity and ocular hypertension: Implications for glaucoma. Proc Natl Acad Sci USA 98:3398–3403.

Schori H, Yoles E, Schwartz M. 2001b. T-cell-based immunity counteracts the potential toxicity of glutamate in the central nervous system. J Neuroimmunol 119:199–204.

Schwartz M, Cohen IR. 2000. Autoimmunity can benefit self-maintenance [In Process Citation]. Immunol Today 21:265–268.

Schwartz M, Kipnis J. 2001. Protective autoimmunity: regulation and prospects for vaccination after brain and spinal cord injuries. Trends Mol Med 7:252–258.

Schwartz M, Kipnis J. 2002. Multiple sclerosis as a by-product of the failure to sustain protective autoimmunity: a paradigm shift. Neuroscientist (in press).

Schwartz M, Belkin M, Yoles E, Solomon A. 1996. Potential treatment modalities for glaucomatous neuropathy: neuroprotection and neuroregeneration. J Glaucoma 5:427–432.

Sela M. 1999a. The concept of specific immune treatment against autoimmune diseases. Int Rev Immunol 18:201–216.

Sela M. 1999b. Specific vaccines against autoimmune diseases [In Process Citation]. CR Acad Sci III 322:933–938.

Takahashi M, Stanton E, Moreno JI, Jackowski G. 2002. Immunoassay for serum glutamine synthetase in serum: development, reference values, and preliminary study in dementias. Clin Chem 48:375–378.

Teitelbaum D, Meshorer A, Hirshfeld T, Arnon R, Sela M. 1971. Suppression of experimental allergic encephalomyelitis by a synthetic polypeptide. Eur J Immunol 1:242–248.

Teitelbaum D, Fridkis-Hareli M, Arnon R, Sela M. 1996. Copolymer 1 inhibits chronic relapsing experimental allergic encephalomyelitis induced by proteolipid protein (PLP) peptides in mice and interferes with PLP-specific T cell responses. J Neuroimmunol 64:209–217.

Teitelbaum D, Arnon R, Sela M. 1997a. Cop 1 as a candidate drug for multiple sclerosis. J Neural Transm Suppl 49:85–91.

Teitelbaum D, Arnon R, Sela M. 1997b. Copolymer 1: from basic research to clinical application. Cell Mol Life Sci 53:24–28.

Torreilles F, Salman-Tabcheh S, Guerin M, Torreilles J. 1999. Neurodegenerative disorders: the role of peroxynitrite. Brain Res Brain Res Rev 30:153–163.

Vajda FJ. 2002. Neuroprotection and neurodegenerative disease. J Clin Neurosci 9:4–8.

Weiner HL. 1999. Oral tolerance with copolymer 1 for the treatment of multiple sclerosis [Comment]. Proc Natl Acad Sci USA 96:3333–3335.

Wimer BM. 1998. Immunosuppressive applications of PHA and other plant mitogens. Cancer Biother Radiopharm 13:99–107.

Yoles E, Schwartz M. 1998. Degeneration of spared axons following partial white matter lesion: implications for optic nerve neuropathies. Exp Neurol 153:1–7.