

Myelin Repair Foundation Archived Research Summaries

Summaries – 2008

Bailey, S. L., B. Schreiner, and S. D. Miller. 2008. **CNS dendritic cells in inflammation and disease.** In: **Central Nervous System Diseases and Inflammation.** (T. E. Lane, M. Carson, C. Bergmann and T. Wyss-Coray, eds.). Springer, New York, NY. Pp 263-275.
<http://www.springerlink.com/content/l17910144487u803/>

Scientific Summary: CD11c⁺ DCs play a major role in both the *initiation* and *progression* of autoimmune inflammatory disease in the CNS. Since the CNS serves as the primary site where activation of pathogenic Th1/Th17 cells specific for endogenous myelin epitopes (*i.e.*, epitope spreading), which play a critical role in driving progressive autoimmune disease, the current data suggests that the inflamed CNS can function as a neo-lymphoid organ. In support of this our recent unpublished data indicates that expression of genes encoding multiple receptor:ligand pairs involved in lymphoid organogenesis (including LT α 1 β 2/LT β R, CXCL12/CXCR4, CSCL13/CXCR5, CCL21/CCR7, and CCL19/CCR7) are highly upregulated in the CNS. Further, mDCs are the main drivers of epitope spreading displaying the unique ability to acquire and present endogenous myelin peptides, to cluster specifically with naïve CD4⁺ T cells in the inflamed CNS and to polarize towards a Th17 phenotype when presenting endogenous myelin peptides. In conclusion, understanding the cues that determine DC signals to T cells will be crucial to understanding the fate of pathological (auto)immune inflammation in different tissues and diseases. Moreover, strategies targeting inhibition of the migration of myeloid DCs to the CNS may be an effective therapy for chronic immune-mediated CNS demyelinating diseases including MS.

Lay Summary: This review summarized the role of various subpopulations of dendritic cells in promoting and regulating immune responses in the CNS in mouse models of MS and discusses how manipulation of these cell populations could be exploited as a therapy for MS.

Carpentier, P. A., D. S. Duncan, and S. D. Miller. 2008. **Pattern recognition receptors in CNS disease.** In: **Central Nervous System Diseases and Inflammation.** (T. E. Lane, M. Carson, C. Bergmann and T. Wyss-Coray, eds.). Springer, New York, NY. Pp 131-152.

<http://www.springerlink.com/content/w686804555168173/>

Scientific Summary: CNS resident cells, particularly microglia and to a lesser extent astrocytes, express a variety of PRRs that allow them to respond to almost any pathogen invading the CNS. The ligation of PRRs activates a host of pro-inflammatory responses from these cells, including the production of type I interferons, nitric oxide, cytokines and chemokines. Additionally, microglia exposed to pathogens upregulate their ability to acquire, process and present antigen resulting in more efficient activation of activated T cells. In the CNS, PRRs are important for pro-inflammatory responses to pathogens. Interestingly, the inhibition of these pro-inflammatory responses can be beneficial or detrimental to host survival, depending on the particular pathogen and disease. Similarly, the chronic activation of PRRs may lead to neurodegeneration, but limited or controlled activation may be neuroprotective. These results suggest that the manipulation of PRR activation in the CNS may be a viable approach both in the treatment of CNS infections and neurodegenerative diseases, while dysregulation of this process may contribute to neuronal or oligodendrocyte cell death. This is a burgeoning field of research, and clearly more research is needed to determine the full range of PRR functions in the CNS.

Lay Summary: This review summarizes the role of specialized receptors called pattern recognition receptors on glial cells (microglia and astrocytes) in the CNS in mediating the protective response to infections in the brain and spinal cord. Collectively, when these receptors recognize pathogens they induce glial cells to produce a host of molecules which both directly and indirectly can lead to the killing and clearance of the infectious agents.

Carpentier, P. A., D. S. Duncan, and S. D. Miller. 2008. **Glial Toll-like receptor signaling in central nervous system infection and autoimmunity.** Brain Behav. Immun. 22:140-147. (*co-first authors).

http://www.ncbi.nlm.nih.gov/pubmed/17920811?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Scientific Summary: Innate immunity in the CNS depends primarily on the functions of glial cells, astrocytes and microglia, which are important for the early control of pathogen replication and direct the recruitment and activation of cells of the adaptive immune system required for pathogen clearance. Efficient immune responses are required for clearance of an invading pathogen, but dysregulation of a pro-inflammatory response in the CNS could lead to the development of autoimmunity. This review summarizes the activation of Toll-like receptors (TLRs) expressed on glial cells and the functional outcome of these interactions for CNS health and disease which depends on a delicate balance of the protective and toxic effects of molecules induced in the CNS following TLR ligation.

Lay Summary: This review article summarizes the role of glial cells (astrocytes and microglia) in controlling infections in the CNS. Since epidemiologic evidence strongly suggests that certain forms of MS are triggered as a secondary consequence of virus infection, understanding how glial cells respond to infections in the CNS using specialized receptors, termed Toll-like receptors, may provide important information on the pathogenesis of MS.

Carpentier, P. A., M. Teague Getts, and S. D. Miller. 2008. **Pro-inflammatory functions of astrocytes correlate with viral clearance and strain-dependent protection from TMEV-induced demyelinating disease.** *Virology*. 375:24-36

http://www.ncbi.nlm.nih.gov/pubmed/18289626?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Scientific Summary: Intracerebral infection of susceptible strains of mice, e.g. SJL/J, with Theiler's murine encephalomyelitis virus (TMEV) leads to a persistent CNS infection accompanied by development of a chronic-progressive inflammatory CNS autoimmune demyelinating disease which is clinically and pathologically similar to human multiple sclerosis. In contrast, resistant strains of mice, e.g. C57BL/6 (B6), effectively clear TMEV from the CNS and do not develop demyelinating disease. Although CD8⁺ T cells are crucial for viral clearance in B6 mice, SJL mice also mount potent CD8⁺ T cell responses against virus, thus the reason for the viral persistence in the CNS in these mice is unclear. Here, we examined innate anti-viral responses of CNS-resident astrocytes as a potential determinant of viral persistence and disease susceptibility. We demonstrate that B6 astrocytes produce significantly higher levels of cytokines, chemokines and adhesion molecules in response to TMEV infection, or stimulation with IFN- γ and TNF- α or poly I:C than SJL mice. In addition, TMEV more effectively induces MHC I molecules on B6 astrocytes than SJL, corresponding with an increased ability to activate TMEV-specific CD8⁺ T cells directly *ex vivo*. These results suggest that enhanced anti-viral responses of B6 astrocytes contribute to the ability of these mice to clear TMEV from the CNS and therefore to their resistance to the development of autoimmune demyelinating disease.

Lay Summary: This paper shows that astrocytes are important in mediating immunity in the CNS of mouse strains infected with Theiler's virus. Since this virus leads to an immune-mediated demyelinating disease in the CNS and serves as a viable model of MS, these studies suggest that astrocytes may play both protective as well as destructive roles in the pathogenesis of MS.

Lin W, Kunkler PE, Harding HP, Ron D, Kraig RP, Popko B. **Enhanced integrated stress response promotes myelinating oligodendrocyte survival in response to interferon-gamma.** Am J Pathol. 2008 Nov;173(5):1508-17.

http://www.ncbi.nlm.nih.gov/pubmed/18818381?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Summary: Multiple sclerosis (MS) is a chronic autoimmune disease that affects the central nervous system (CNS). It is characterized by the loss of myelin, which is the multilayered membrane that surrounds and protects nerve fibers, as well as the loss of oligodendrocytes, which are the myelin producing cells of the CNS. Regeneration of oligodendrocytes and subsequent myelin repair are necessary to restore neurological function in MS patients. The immune cell-derived cytokine interferon- γ (IFN- γ), which becomes detectable in the CNS in the symptomatic phase of MS, is believed to inhibit oligodendrocyte regeneration and myelin repair. Our previous reports have shown that the deleterious effects of IFN- γ on myelin repair are associated with the activation of endoplasmic reticulum (ER) stress in oligodendrocytes. The ER represents an interconnected network of tubes and vesicles in which membrane and secreted proteins are synthesized and folded, and ER stress is a condition in which the protein processing capacity of the ER becomes overwhelmed. The ER resident kinase, pancreatic ER kinase (PERK), is activated by ER stress and coordinates an adaptive program known as the integrated stress response (ISR) by phosphorylating translation initiation factor 2 α (eIF2 α). The PERK-mediated ISR is essential for cell survival during ER stress. In this report we demonstrate that growth arrest and DNA damage 34 (GADD34), a stress-inducible regulatory subunit of a phosphatase complex that dephosphorylates eIF2 α , was selectively upregulated in oligodendrocytes in transgenic mice that ectopically expressed IFN- γ in the CNS. We also found that GADD34 deficient mice displayed increased levels of phosphorylated eIF2 α in oligodendrocytes when exposed to IFN- γ . Moreover, GADD34 deficiency significantly attenuated oligodendrocyte loss and myelin abnormalities in the CNS of IFN- γ transgenic mice. Salubrinal (sal), a small chemical compound, has been shown to specifically inhibit PP1-GADD34 phosphatase activity; resulting in sustained eIF2 α phosphorylation in ER stressed cells. Treatment with sal prolongs the stress response and protects cells from ER stress and viral infection. To test the beneficial potential of sal in oligodendrocyte loss and myelin abnormalities elicited by IFN- γ , we exploited an in vitro myelination model, the hippocampal slice culture. Treatment with sal elevated the levels of phosphorylated eIF2 α and ameliorated oligodendrocyte loss and myelin abnormalities in cultured hippocampal slices exposed to IFN- γ . Thus, we demonstrate that GADD34 inhibition, via genetic mutation or sal treatment, enhances the PERK-mediated ISR and reduces IFN- γ - induced oligodendrocyte loss and myelin abnormalities. Importantly, our data provide evidence that therapeutic strategies that enhance the ISR could promote oligodendrocyte survival and myelin repair in MS patients.

*Nair, A. and T. J. *Frederick, and S. D. Miller. 2008. **Astrocytes in multiple sclerosis; A product of their environment.** Cell. Mol. Life Sci. Published Online <http://dx.doi.org/10.1007/s00018-008-8059-5>. (*Co-first authors)

Scientific Summary: It has long been thought that astrocytes, like other glial cells, simply provide a support mechanism for neuronal function in the healthy and inflamed central nervous system (CNS). However, recent evidence suggests that astrocytes play an active and dual role in CNS inflammatory diseases such as multiple sclerosis (MS). Astrocytes not only have the ability to enhance immune responses and inhibit myelin repair, but they can also be protective and limit CNS inflammation while supporting oligodendrocyte and axonal regeneration. The particular impact of these cells on the pathogenesis and repair of an inflammatory demyelinating process is dependent upon a number of factors, including the stage of the disease, the type and microenvironment of the lesion, and the interactions with other cell types and factors that influence their activation. In this review, we summarize recent data supporting the idea that astrocytes play a complex role in the regulation of CNS autoimmunity.

Lay Summary: This review article summarizes the potential dual role of astrocytes in the CNS causing myelin destruction on one hand, while producing critical molecules which promote regeneration of myelin-producing oligodendrocytes as well as nerve axons.

Teague Getts, M., D. Getts, A. P. Kohm, and S. D. Miller. 2008. **The ER stress response as a therapeutic target in MS.** *Therapy. In press.* <http://www.futuremedicine.com/doi/abs/10.2217/14750708.5.5.631>

Scientific Summary: Multiple Sclerosis (MS) is an inflammatory demyelinating disorder of the central nervous system (CNS). Since current treatments are aimed at nonspecifically down-regulating inflammation and natural mechanisms of repair and remyelination within the CNS are inadequate for recovery of function, MS patients presently only have available treatments that delay symptom progression. The complex nature of this disease means that only multifaceted treatments hold the promise of a cure. Recent studies indicate that the ER stress response, a cellular pathway that allows a cell to survive and recover from a stressful event, could be elicited to help the myelin-generating and myelin-support cells of the CNS survive inflammatory insult.

Lay Summary: This review summarizes the published evidence that manipulating the activity of a complex of proteins involved in the endoplasmic reticulum (ER) stress response may possibly be employed to aid in myelin repair by helping the myelin-producing oligodendrocytes and myelin support cells such as astrocytes survive autoimmune damage in the CNS.

Zhang, H., J. R. Podojil, X. Luo, and S. D. Miller. **Intrinsic and induced regulation of the age-associated onset of spontaneous experimental autoimmune encephalomyelitis.** *J. Immunol.* 2008 Oct 1;181(7):4638-47.

http://www.ncbi.nlm.nih.gov/pubmed/18802066?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Scientific Summary: Multiple sclerosis (MS) is characterized by perivascular CNS infiltration of myelin-specific CD4⁺ T cells and activated mononuclear cells. T cell receptor (TCR) transgenic mice on the SJL background specific for proteolipid protein (PLP)₁₃₉₋₁₅₁ (5B6 Tg mice) develop a high incidence of spontaneous experimental autoimmune encephalomyelitis (sEAE). We examined the intrinsic mechanisms regulating onset and severity of sEAE. CD4⁺ T cells isolated from the cervical lymph nodes (cLN), but not spleens, of disease 5B6 Tg mice are hyper-activated when compared to age-matched healthy mice and produce both IFN- γ and IL-17 indicating that the cLN is the initial peripheral activation site. The age-associated development of sEAE correlates with a decline in both the functional capacity of natural regulatory T cells (nTregs) and in PLP₁₃₉₋₁₅₁-induced IL-10 production and a concomitant increase in IL-17 production. Anti-CD25-induced inactivation of nTregs increased the incidence and severity of sEAE. Conversely, induction of peripheral tolerance via the i.v. injection of PLP₁₃₉₋₁₅₁-pulsed, ECDI-fixed APCs (PLP₁₃₉₋₁₅₁-SP) inhibited the development of clinical disease concomitant with increased production of IL-10 and conversion of Foxp3⁺ Tregs from CD4⁺CD25⁻ progenitors. These data indicate that heterogeneous populations of Tregs regulate onset of sEAE and that induction of peripheral tolerance can be exploited to prevent/treat spontaneous autoimmune disease.

Lay Summary: This investigation examined the factors controlling the induction of CNS demyelination in a 'spontaneous' model of disease. Transgenic mice were engineered in which all of the T cells were specific for a portion of the myelin proteolipid protein (PLP), the major protein constituent of myelin. Approximately 80% of these mice develop clinical signs of paralytic disease by 80-100 days of age. The results showed that the myelin-specific T cells in these mice are first activated in a lymphoid organ called the cervical lymph nodes indicating that myelin proteins can leak from the central nervous system and accumulate in this site. Secondly, the results showed that the age-associated development of disease in these animals correlated with a decline in the regulatory activity of a T cell subset called 'regulatory' T cells which have recently been shown to be defective in patients with MS. Lastly, the data shows that spontaneous disease in these animals can be inhibited by the induction of immunologic tolerance to the portion of PLP recognized by the T cells. The significance of these findings is that they indicate that immune tolerance can be employed to prevent/treat spontaneous CNS autoimmune disease.

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Bailey, S. L., B. Schreiner, E. J. McMahon, and S. D. Miller. **CNS myeloid dendritic cells presenting endogenous myelin peptides preferentially polarize CD4⁺ Th17 cells in relapsing EAE.** (2007), *Nat. Immunol.* 8:172-180.

http://www.ncbi.nlm.nih.gov/pubmed/17206145?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Scientific Summary: Peripherally-derived CD11b⁺ myeloid (mDC), plasmacytoid (pDC), CD8 α ⁺ (CD8 DC) DCs, and macrophages accumulate in the CNS during relapsing EAE (R-EAE). During acute PLP178-191-induced R-EAE, transgenic T cells (139TCR) specific for the PLP139-151 relapse epitope cluster with mDCs in the CNS, are activated and T_H-17 differentiated. CNS mDCs present endogenously acquired peptide driving proliferation and IL-17 production from naive 139TCR cells *in vitro* and *in vivo*. mDCs uniquely biased T_H-17 and not T_H1 differentiation correlating with their enhanced expression of TGF- β 1, IL-6 and IL-23. pDCs and CD8 DCs were superior to macrophages, but significantly less efficient than mDCs at presenting endogenous peptide to induce T_H-17 cells. These findings strongly implicate a critical role for CNS mDCs in driving relapses in R-EAE.

Lay Summary: The progression of disease in the relapsing-remitting experimental autoimmune encephalomyelitis model of MS in the SJL mouse is characterized by a phenomenon called 'epitope spreading'. Simply put, epitope spreading means that as myelin destruction progresses, immune responses to myelin proteins which are not initially recognized by the autoimmune response become activated in response to tissue destruction in the CNS and mediate disease relapses. Counter to immunologic dogma, our previous studies had shown that T cells specific for these newly released 'spread' epitopes were activated primarily in the CNS itself. The current paper tested which cells in the CNS were responsible for engulfing the released epitopes and subsequent activation of the T cells. Surprisingly, it was shown that a population of antigen presenting cells called myeloid dendritic cells (mDCs) which migrated into the CNS from the peripheral blood was primarily responsible for activating the new T cells and for inducing them to make a soluble factor (IL-17) which has recently been shown to be primarily responsible for carrying out destruction of myelin in the CNS.

Dugas, Jason C.; Ibrahim, Adiljan; Barres, Ben A.. **A Crucial Role for p57^{Kip2} in the Intracellular Timer that Controls Oligodendrocyte Differentiation.** *Journal of Neuroscience* (2007), 27(23): 6185-6196.

http://www.ncbi.nlm.nih.gov/pubmed/17553990?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Summary: During brain development and remyelination, new oligodendrocytes are generated from precursor cells termed oligodendrocyte precursor cells (OPCs). The number of oligodendrocytes available for myelination depends upon the number of times each OPC divides. It was previously shown that OPCs have an intrinsic timing mechanism that counts and limits how many times they can divide. An OPC can divide

a maximum of approximately eight times before its daughter cells simultaneously cease proliferating and differentiate into oligodendrocytes. It was postulated that over time the level of an intracellular molecule might synchronously change in each daughter cell, ultimately reaching a level that prohibited additional proliferation, but the identity of this timing molecule has not been known. In this paper, the authors report the discovery of this timing molecule in OPCs. They identify it as the cyclin-dependent kinase inhibitor p57(Kip2) (Cdkn1c). Cyclin kinases are enzymes that drive OPC division. Cell division stops when inhibitors of cyclin kinases build up to sufficient level to inhibit their activity. The authors show that when levels of p57(Kip2) are experimentally increased that OPCs stop dividing and differentiate into oligodendrocytes prematurely. In contrast, they found that when levels of P57(Kip2) are experimentally lowered that OPCs continue dividing far longer than normal and fail to differentiate into oligodendrocytes. Thus by controlling p57(Kip2) levels, the numbers of OPCs and thus oligodendrocytes can be controlled. These findings suggest an approach for enhancing the rate of new oligodendrocyte generation and remyelination in Multiple Sclerosis.

Miller, S. D., E. J. McMahaon, B. Schreiner, and S. L. Bailey. 2007. **Antigen presentation in the CNS by myeloid dendritic cells drives progression of relapsing experimental autoimmune encephalomyelitis.** Ann. N.Y. Acad. Sci. 1103:179-191. http://www.ncbi.nlm.nih.gov/pubmed/17376826?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Scientific Summary: Chronic progression of relapsing experimental autoimmune encephalomyelitis (R-EAE), a mouse model of multiple sclerosis, is dependent on the activation of T cells to endogenous myelin epitopes, *i.e.* epitope spreading. This review focuses on the cellular and molecular mechanisms underlying the process of epitope spreading. Surprisingly, activation of naïve T cells to endogenous myelin epitopes in SJL mice undergoing R-EAE occurs directly in the CNS, a site generally perceived to be immunologically privileged. Determination of the antigen presentation capacity of APC populations purified from the CNS of mice with established R-EAE shows that peripherally-derived CD11b⁺CD11c⁺CD45^{hi} myeloid dendritic cells (mDCs) most efficiently present endogenous myelin antigens to activate *both* pre-activated effector myelin-specific T cells and naïve T cells. The mDCs which drive epitope spreading preferentially polarize pathogenic Th17 responses correlating with their enhanced expression of TGF-β1, IL-6 and IL-23. Both B220⁺CD11c⁺ plasmacytoid (pDCs) and CD8α⁺CD11c⁺ (CD8 DCs) were superior to CD11b⁺CD11c⁻CD45^{hi} macrophages, but less efficient than mDCs at presenting endogenous peptide to induce Th17 cells. In contrast, CNS-resident CD11b⁺CD11c⁻CD45^{low} microglia purified from the inflamed CNS were found to be largely incapable of activating either naïve or effector T cells.

Lay Summary: Following on the previous paper (Bailey, et al. 2007. Nat. Immunology 8:172-180) this paper compared the ability of myeloid dendritic cells (mDCs) to other inflammatory cells infiltrating the CNS during relapsing experimental autoimmune encephalomyelitis to activate T cells. mDCs were shown to be far more efficient than plasmacytoid DCs, lymphoid DCs, and macrophages in activating T cells involved in epitope spreading. Interestingly, microglia cells which are normally found in the CNS were incapable of activating T cell responses. This data indicates that therapies targeting mDCs are likely to be effective in preventing progression of EAE and perhaps MS. We are currently determining the extent of mDC infiltration into the CNS of MS patients.

Miller, Stephen D.; Turley, Danielle M.; Podojil, Josephe R.. **Antigen-specific tolerance strategies for the prevention and treatment of autoimmune disease.** *Nature Reviews: Immunology* (2007), Vol. 7, 665-677.

[http://www.ncbi.nlm.nih.gov/pubmed/17690713?ordinalpos=&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.SmartSearch&log\\$=citationsensor](http://www.ncbi.nlm.nih.gov/pubmed/17690713?ordinalpos=&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.SmartSearch&log$=citationsensor)

Scientific Summary: Since the ability of the host to differentiate between self and infectious non-self antigens is critical for host survival, development of safe and effective antigen-specific therapies to treat patients with autoimmune diseases is critical. This new generation of antigen-specific therapies must therefore allow for the specific tolerization of self-reactive immune cells without altering host immunity to infectious insults. Experimental models and clinical trials for the treatment of autoimmune disease have identified putative mechanisms by which antigen-specific therapies induce tolerance. While strides have been made in the development of efficient antigen-specific therapies, transitioning these therapies from bench to bedside has remained difficult.

Lay Summary: This review article compares and contrasts various antigen-specific 'immune tolerance'-based therapies for their mechanisms and efficacy in treating animal models of MS as well as those currently in use or shortly to be tested in clinical trials for therapy of MS in patients. There is an emphasis on discussion on tolerance induced using antigen-coupled peripheral blood lymphocytes that is in the final stages of planning for a clinical trial to be carried out by our lab in collaboration with Dr. Roland Martin, Univ. of Hamburg, which is being supported by the German government and Myelin Repair Foundation.

Turley, D. M. and S. D. Miller. 2007. **Peripheral tolerance induction using ECDI-fixed APCs uses both direct and indirect mechanisms of antigen presentation for prevention of EAE.** *J. Immunol.* 178:2212-2220.

http://www.ncbi.nlm.nih.gov/pubmed/17277126?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Summary: MRF scientists are currently in the final stages of implementing a clinical trial in collaboration with Dr. Roland Martin, Univ. of Hamburg, testing immune tolerance to a cocktail of myelin antigen peptides for treatment of new onset relapsing-remitting MS. This therapy involves isolation of patient peripheral blood leukocytes (PBLs) followed by chemically coupling the PBLs with a mixture of six myelin peptides (known to trigger autoimmune T cell responses in patients) and subsequent intravenous re-administration of the peptide-fixed PBLs. This tolerance method has been used by the lab for years to study therapy in the experimental autoimmune encephalitis (EAE) model of MS in mice. This paper shows that the tolerance works because the chemical, called ethylene carbodiimide, used to attach the myelin peptides to the PBLs induces a certain form of cell death (called apoptosis) and that antigen-presenting cells in the spleen of the recipient mouse engulf these apoptotic cells and induce inactivation of myelin-specific autoreactive T cells via an indirect mechanism (cross-tolerance). Further determination of the cellular and molecular mechanisms by which tolerance is induced is a major focus of ongoing experiments.