Restoring immune tolerance in neuromyelitis optica
Part I

ABSTRACT
Neuromyelitis optica (NMO) and spectrum disorder (NMO/SD) represent a vexing process and its clinical variants appear to have at their pathogenic core the loss of immune tolerance to the aquaporin-4 water channel protein. This process results in a characteristic pattern of astrocyte dysfunction, loss, and demyelination that predominantly affects the spinal cord and optic nerves. Although several empirical therapies are currently used in the treatment of NMO/SD, none has been proven effective in prospective, adequately powered, randomized trials. Furthermore, most of the current therapies subject patients to long-term immunologic suppression that can cause serious infections and development of cancers. The following is the first of a 2-part description of several key immune mechanisms in NMO/SD that might be amenable to therapeutic restoration of immune tolerance. It is intended to provide a roadmap for how potential immune tolerance restorative techniques might be applied to patients with NMO/SD. This initial installment provides a background rationale underlying attempts at immune tolerization. It provides specific examples of innovative approaches that have emerged recently as a consequence of technical advances. In several autoimmune diseases, these strategies have been reduced to practice. Therefore, in theory, the identification of aquaporin-4 as the dominant autoantigen makes NMO/SD an ideal candidate for the development of tolerizing therapies or cures for this increasingly recognized disease. Neurology.org/nn © 2016 American Academy of Neurology

GLOSSARY
APC = antigen-presenting cell; AQP4 = aquaporin 4; CAR = chimeric antigen receptor; DC = dendritic cell; EAE = experimental autoimmune encephalomyelitis; HLA = human leukocyte antigen; IgG = immunoglobulin G; IL = interleukin; MHC = major histocompatibility complex; NMO = neuromyelitis optica; PBMC = peripheral blood mononuclear cell; scFv = single chain variable fragment; SD = spectrum disorder; T1D = type 1 diabetes; TcR = T cell receptor; Treg = regulatory T cell.

RATIONALE FOR TOLERIZATION IN NMO Neuromyelitis optica (NMO) or NMO spectrum disorder (NMO/SD) represents a potentially devastating neuroinflammatory disease in which the spinal cord and optic nerve(s) preferentially undergo astrocyte damage and demyelination.1 Recent investigations into its pathogenesis have demonstrated NMO/SD to be distinct from multiple sclerosis (MS) (figure 1).2 Identification of pathogenic anti-aquaporin 4 (anti-AQP4) antibody (NMO–immunoglobulin G [IgG])3 in context of other clinical characteristics now secures a diagnosis in seropositive disease.

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Despite substantial advances in understanding NMO/SD, no existing regimen has been unambiguously proven to modify disease course, induce permanent remission, or restore lost neurologic function in adequately powered, prospective clinical trials. Continuing reliance on nonspecific agents, including corticosteroids, azathioprine, mycophenolate, and B cell depletion4,5 exposes patients to potentially serious adverse effects. Absence of animal models with complete fidelity to human NMO/SD has been a historical impediment to novel therapies. Improved diagnosis has facilitated greater focus on developing specific therapies. Antigen-specific approaches could restore immune tolerance to AQP4 and minimize epitope spreading. In NMO/SD, dysfunctions in checkpoints governing immune cell development contribute to autoreactive immunity (figure 2).

Considerable progress has been made in tolerizing strategies used to treat allergies,6 transplant and graft rejection,7 and drug hypersensitivity.8 In theory, antigen-targeted approaches spare normal immune functions. To date, similar strategies have yielded only limited success in other autoimmune diseases, such as type 1 diabetes (T1D),9 relapsing-remitting MS,10 and inflammatory bowel disease.11 Results thus far support the general concept that inhibition of antigen-specific T cell and/or B cell responses is achievable and may be durable. However, in some experimental models, tolerization strategies have worsened disease,12 perhaps because of uncertain disease etiology. Hence, in the specific context of NMO/SD, tolerization might have distinct advantages.

The Guthy-Jackson Charitable Foundation convened a meeting of experts in development of antigen-specific therapy. Key goals of this meeting were to ascertain the state-of-the-art in immune tolerization as it might be applied to NMO/SD and to catalyze innovative thinking. The following discussion considers specific opportunities and challenges to apply tolerization therapy to solve NMO/SD.

**POTENTIAL STRATEGIES FOR TOLERIZATION IN NMO**

**Inverse DNA vaccination.** Dolgin13 and Steinman14 have built on principles of classic desensitization originating with Jenner. While traditional vaccines induce immune responses to specific antigens, inverse vaccines promote immune tolerance. Diseases in which a known antigen underlies the pathophysiology would in theory represent the most promising candidates for tolerizing therapies. Thus, seropositive NMO/SD should be ideal for antigen-specific therapy, as autoimmune responses to AQP4 are believed to be fundamental to the disease.15-17 In clinical trials, pathogenic vs tolerogenic immune responses of T and B cells would necessarily be monitored. Other diseases with similarly implicated autoantigens include myasthenia gravis (acetylcholine receptor), Graves disease (thyrotropin receptor and thyroglobulin), and T1D (multiple insulin granule antigens).18

Inverse vaccination with DNA encoding proinsulin to reinforce tolerogenic immune checkpoints has been evaluated in patients in an early-phase clinical trial in T1D.18,19 The results suggest that immune...
tolerance to proinsulin can be induced \((p < 0.026)\). The study revealed an inverse relationship between antigen-restricted CD8\(^+\) T cells and serum proinsulin levels.\(^{18}\) A similar strategy has enabled proof-of-principle of altered responses to myelin basic protein in patients with MS.\(^{20,21}\) Although such approaches are attractive, relevant antigenic targets likely differ among patients and may change over time. For example, myelin oligodendrocyte glycoprotein may drive unique pathogenesis in NMO/SD and require specific tolerization strategies. Moreover, epitopes may differ in peptides as compared to parent proteins, and lipid or carbohydrate modification may influence presentation.

Inverse DNA vaccination targeting tolerization against AQP4 immunoreactivity has also been examined in experimental models of NMO/SD. A plasmid encoding AQP4 attenuated T and B cell responses specifically to this antigen, attesting to antigen specificity of this strategy (unpublished observations). In NMO/SD, clinical trials may be designed based on one or more diagnostic biomarker(s) of NMO-IgG seropositivity. In this approach, a diagnostic biomarker(s) is used as a surrogate of therapeutic efficacy and durability and serves as an outcome measure. This scenario approaches an idealized situation in which biomarkers are both the principal diagnostic gating targets and the major pathogenic factor(s).

**Antiautoreactive T cell vaccines.** Roles played by autoreactive T cells in mediating autoimmunity have been established in several animal models, and complemented observations made in human disease.\(^{22}\) In turn, therapeutic modulation of autoreactive T cell frequency and/or function in autoimmune diseases appears achievable.\(^{23}\) However, regulation of all immune responses results from the “checks and balances” imposed by both effector and regulatory T cell networks (figure 3). Thus, nonspecific depletion of effector T cells could diminish immune surveillance, leading to infections or cancer.\(^{24}\) Similarly, indiscriminate activation or depletion of regulatory T cells (Tregs) may also result in immune dysfunction. In particular, Tregs are capable of limiting the frequency and/or activity of individual autoreactive T cell clones through recognition of their unique T cell receptor (TcR) idiotypes.\(^{25}\) When T cells aberrantly recognize
self-antigens in an absence of adequate regulatory counterbalance, autoimmune disease might result.26
In NMO/SD, the pathogenic antibody response is dominated by class-switched IgG, indicating an underlying AQP4-reactive T cell activity.27,28 In addition, Th17 polarization of naive T cells leads to the secretion of proinflammatory cytokines in relation to target lesions, including interleukin (IL)-17A and granulocyte macrophage–colony stimulating factor.29 Such a proinflammatory cytokine profile may promote tissue destruction through recruitment of granulocytes or other cells capable of antibody-dependent cell cytotoxicity.

The observation that anti-idiotype Tregs can arise spontaneously and be associated with the resolution of autoimmunity led to the concept of T cell vaccination.30,31 This strategy invokes multiple immune functions that may mitigate autoimmune disease. For example, induction of idiotype-restricted CD4+ /CD25+ /FoxP3+ Tregs, IL-10–secreting CD4+ Tr1 cells, and CD8+ cytotoxic T cells can result, each capable of selectively targeting autoreactive T cells that express the idiotype represented by the immunizing T cells.32 T cell–based vaccines typically use attenuated autologous autoreactive effector T cells as immunogens32 in an amplification strategy designed to target and counteract autoreactive T cells. Theoretically, this process should selectively deplete and/or functionally attenuate pathogenic T cells carrying the corresponding idiotype. Restoring an adequate Treg influence theoretically should mitigate tissue dysfunction. Clinical trials have suggested a therapeutic benefit from T cell vaccination, with minimal side effects.33 In this regard, proof-of-principle has been demonstrated in several animal models.31 In addition, therapeutic trials applying this strategy to MS, rheumatoid arthritis, and systemic lupus erythematosus–associated nephritis have been undertaken. In some of these conditions, a T cell–based vaccine approach has demonstrated considerable promise.34–36

The manufacture of autologous T cell vaccines is dependent first on identifying autoantigen-specific T cells within the peripheral blood of that patient. This goal is achieved by performing an epitope profiling assay, using overlapping peptides comprising the amino acid sequence of the target antigen. The assay readout is based on the detection of proinflammatory cytokines induced by immunodominant peptides within the target antigen. This strategy thereby identifies peptides and the associated T cell responses most relevant to the autoimmune disease in an affected individual. Next, bulk T cell lines are expanded in vitro from an autologous peripheral blood sample against the selected peptides to provide sufficient numbers of autoreactive T cells to meet dosing requirements. These particular T cells are aliquoted and cryopreserved. On demand, a dose-equivalent is thawed, formulated, and attenuated by irradiation before subcutaneous administration. Methods currently in use allow a single-cycle
Dendritic cell vaccines. Dendritic cells (DCs) present antigens to immune cells, including those with regulatory and autoreactive function, through major histocompatibility complex (MHC) class I and II restriction. Normally, DCs present self-antigens but do not drive autoreactive immune responses. Thus, autoreactive T cells are inactivated or energized because of low MHC expression, inadequate costimulation (e.g., inducing anergy), or tolerogenic costimulation (e.g., PD-L1 [programed death ligand 1], IL-10, etc.). In addition, DCs have important roles in maintaining tolerance by promoting regulatory cells, such as CD4+ and CD8+ Tregs, and IL-10–producing regulatory B cells.37 Immature human DCs are readily generated in the laboratory from blood monocytes and can be engineered to maintain tolerogenic phenotypes. Indeed, DC-based therapies have now entered clinical trials focusing on NMO/SD (ClinicalTrials.gov identifier: NCT02283671).

As a strategy for inducing immune tolerance in T1D, DC administration has proven relatively safe.36–42 Here, granulocyte macrophage–colony stimulating factor/IL-4 was used to generate immature CD11c+ DCs from monocytes in vitro. Transition to a proinflammatory DC phenotype is concerning when DCs are administered to human patients. To mitigate this concern, immature DCs can be treated in vitro with immunosuppressive agents such as corticosteroids, vitamin D3, and/or IL-1043 before their use as tolerizing vaccines. The resulting DCs exhibit durable tolerogenic phenotypes that prolong organ allograft survival in mice. Notably, this conditioning enhances the tolerogenic properties of DCs and induces high-level IL-10 production, which inhibits activated Th1 and Th17 cells, induce Tregs, and suppress autoreactive B cell functions. A related strategy involves loading of immature DCs with antisense oligonucleotides targeting key costimulatory molecules such as CD40, CD80, or CD86. Alternatively, viral vectors encoding immune-regulatory factors may potentiate tolerogenic DCs. Of note, the maintenance of DC immaturity also allows these cells to migrate into lymph nodes following antigen exposure, enhancing their tolerogenic potential.

Loading immature DCs with either native or synthetic peptides or whole antigens may also promote antigen-specific tolerance through induction of regulatory lymphocytes. This strategy addresses multiple autoantigens and/or epitopes within a target antigen(s). Thus, the goal is conditional presentation of self-antigenic epitopes by DCs to yield Treg induction. Using the entire antigen affords presentation of a broader repertoire of peptides selected by relevant MHC alleles, and potentially avoids artificial epitope(s) selection. In this respect, preloading microparticles containing antigen might facilitate DC uptake and favor tolerogenic phenotypes. Of note, early studies in which rodents were vaccinated with autoantigen-loaded DCs demonstrated antigen-specific, durable, and effective tolerance. These principles have been applied in human trials of T1D.42 Advantages may also emerge from strategies in which DCs are allowed to antigen-load in situ.

Small phase I clinical trials exploring DC vaccines in autoimmune disease have largely focused on T1D or rheumatoid arthritis. Evidence to date suggests that tolerizing DC therapies are safe. However, larger trials will be required to more thoroughly assess safety and efficacy. Despite the great interest in further assessing DC vaccines in the prevention, modulation, and curing of autoimmune diseases, key questions remain. These include optimization of DC dosing, vaccination frequency (e.g., boosting), route of administration, and identification or validation of biomarkers for assessing therapeutic efficacy.

NMO/SD appears to represent an ideal disease for DC therapy because a dominant and T cell–restricted autoantigen (AQP4) has been identified. If successful, this approach should be used as early in the disease course as is possible. The rationale for this strategy is to prevent or ameliorate the expansion of inflammatory AQP4–restricted or other antigen-restricted T lymphocytes, thereby minimizing broader tissue injury. In addition, such early intervention could in concept minimize the potential for antigen spreading or reversal of antigenic ignorance.

Antigen-coupled presentation. Antigen-specific tolerization in animal models of disease has been pursued by a number of laboratory groups. Among these models are those for experimental autoimmune encephalomyelitis (EAE), Theiler virus–induced encephalitis, tolerance to organ transplantation, and therapy for severe allergy.43–50 Use of peptide-coupled or chemically fixed antigen-presenting cells (APCs) by Miller et al.6 has been one strategy. Here, unmodified splenocytes are pulsed in vitro with a disease-relevant autoantigen(s), together with a coupling agent. The host is immunized using these cells, with the goal of inducing tolerance to a target autoantigen(s). This approach was effective in reducing disease activity in a model of relapsing-remitting EAE in SJL.
mice. The strategy may also be attractive as prophylaxis for allotransplantation and the attenuation of alloreactive immune responses. Key advantages of this approach may include: (1) extensive experience in EAE and other autoimmune disease models; (2) realistic potential for targeting multiple autoantigens; (3) acceptable safety profiles in preclinical studies; (4) an apparent absence of epitope spreading; and (5) positive preliminary evidence for efficacy. These attributes provide a strong rationale for applying this approach to individuals with antigenically characterized autoimmune diseases such as NMO/SD.

This strategy has been translated to human trials using unaltered autologous peripheral blood mononuclear cells (PBMCs) as APCs following their isolation by therapeutic leukapheresis. In MS, isolated cells are first pulsed in vitro with a mixture of immunodominant myelin peptides that are identified as targets of the high-avidity myelin-specific T cell response. A phase I trial was conducted in which patients received graded dosages of peptide-coupled and fixed autologous PBMCs. Results suggested this approach was well tolerated, and induced neither immune reactivity to myelin peptides nor triggered disease relapses. Rather, the data demonstrated that the abundance of myelin-reactive T cells was substantially reduced. Several putative mechanisms of action have been attributed to this strategy. First, APC presentation of cross-linked peptide(s) can lead to anergy and/or functional silencing of T cells resulting from inadequate second-signaling. Here, the dominant mechanisms are most likely related to T cell recognition of peptide-coupled antigen complexes. In this scenario, T cells and/or APCs undergo apoptosis and are phagocytosed by a special subset of immature DCs or macrophages in the splenic marginal zone. These immature DCs/macrophages can present an autoantigen peptide(s) in a tolerogenic manner (e.g., IL-10) to pathogenic, autoreactive T cells. Each of these pathways might help dampen autoimmunity. Induction of Tregs is also likely critical in suppressing autoreactivity. Tolerization with peptide-coupled, fixed PBMCs undergoing apoptosis in vivo does not lead to the induction of anti-DNA autoantibodies. The relevant mechanism(s) involved in this immune tolerizing strategy and how it might be applied to human diseases require further study.

Despite promising results in animals, human studies have been limited to demonstrating that the abundance of myelin-specific T cells is substantially reduced; however, this phase I study was not designed to elucidate specific mechanisms of action. The above tolerization approach with AQP4-coupled fixed APCs could, in theory, be readily adapted to NMO/SD. Moreover, epitope spreading can occur in this disease and may be attenuated by this strategy (reviewed in reference 57). Thus, tolerization with the entire AQP4 holoprotein or derivative immunodominant peptides may dampen autoreactivity against AQP4 and secondary autoantigen targets, providing clinical benefit. Naturally, technical challenges are likely to arise in these therapeutic strategies and their approach to the clinic. Moreover, specific biomarkers for determining efficacy will be needed to unambiguously inform the therapeutic benefit. Nonetheless, this approach holds promise for restoring immune tolerance in NMO/SD and other autoimmune conditions.

**T cell receptor engineering.** The αβ TcR is the critical antigen recognition determinant on CD4+ and CD8+ T cells, conferring both antigen specificity and sensitivity. TcR diversity results from rearrangement of multiple genes (Figure 2). A key difference from antibodies is the requirement that αβ TcRs bind to peptide ligands displayed through the APC MHC. This MHC restriction focuses T cell activity against cells that bear the respective antigen. This mechanism facilitates targeting to antigen-enriched anatomical sites such as lymph nodes and infected tissues while effector T cells promote immune responses against foreign or endogenous autoantigens. CD4+ Tregs suppress these responses (part II).

Improved understanding of TcR-driven immune recognition should yield strategies to harness these cells in treating autoimmune diseases. For example, autoreactive TcR functions may be redirected to modulate their disease-propagating phenotypes. By comparison, ongoing efforts to generate therapeutic autologous T cells targeting cancer involve engineering TcRs specific to cancer peptide/class I MHC antigens. These cells mature into effector T cells ex vivo that are then administered to the patient. Initial attempts involved CD8+ T cell clones exhibiting relatively low affinities (KD range 10–100 μM). However, subsequent engineering has yielded higher affinity TcRs with KD ranges from 0.1 to 1 μM. Moreover, TcRs targeting class I antigens do not require the CD8 coreceptor and are thus capable of recruiting effector CD4+ T cells against cancer cells expressing their cognate target antigen. Conceivably, this approach might also prove useful in targeting autoreactive cells. To date, TcR engineering has been accomplished using several methodologies, including yeast and phage display.

Engineered TcRs can be delivered using a variety of strategies. These include administration as soluble agents, via gene transfer, or as adoptive T cell therapies. Soluble TcRs will likely require affinities comparable to those of antibodies (KD in nM or pM range), and formatting as immunoglobin fusions, bispecific agents with anti-CD3, or as fusions with immunoregulatory molecules such as cytokines. A high-
affinity TcR against a class II MHC fused to IL-10 has been developed as a means for downregulating autoimmune responses. Optimizing the tissue targeting of these constructs remains challenging.

Adoptive T cell transfer of enriched Tregs has also been used as a method of antigen-specific tolerization. Yet, optimal delivery of antigen-specific, stable Tregs remains to be determined. Moreover, TcR affinity and specificity of Tregs is less well characterized than those of effector T cells. Several studies have demonstrated that introducing class I–restricted TcR into Tregs can redirect their specific activities, and that TcRs with $K_D$s of approximately 1 μM may be of sufficient avidity to drive Treg activity. TcRs directed against class I targets required lower affinities than those in effector CD4+ T cells that promote Treg activity.

Opportunities to generate mouse models and therapeutic T cells targeting AQP4 would appear to be numerous. For example, in a mouse model, an immunogenic response can be elicited with effector T cells (CD4+ and/or CD8+) expressing an AQP4-specific antibody (scFv) fused to a chimeric antigen receptor (CAR). Redirection of Tregs to suppress effector cells could provide greater therapeutic potential and utilize CARs directed against AQP4. Alternatively, conventional TcRs targeting AQP4 peptide/MHC class I complexes such as human leukocyte antigen (HLA)-A2 (which are expressed by 40% of the population) might prove effective. Possible advantages of CARs include their potential use of scFv from existing monoclonal antibodies. Furthermore, the same scFv used in effector T cells to initiate pathogenic responses could instead be engineered to a Treg phenotype. Here, scFv affinity could be optimized using single-site complementarity determining regions mutations. Treg signaling and activity would depend on the CAR signaling domain specificity and affinity, as well as density of AQP4 displayed on target cells. Animal models that more precisely recapitulate human disease would represent significant advances toward these goals.

The TcR approach offers potential advantage over scFv/CAR, including direct targeting of Treg activity to class I–bearing tissues and regional lymph nodes, where AQP4 might be cross-presented by MHC. Ostensibly, this strategy might arrest or reverse cross-presentation of AQP4 antigens by class II MHC, which may occur early in the development of NMO/SD. If so, this approach may also mitigate epitope spreading. The generation of TcRs against AQP4 peptides that bind to HLA-A2 would be relatively straightforward, given the extensive knowledge of its binding motifs and the likelihood that AQP4 contains cognate epitopes. The TcR affinity in this scenario may prove inadequate, but such limitations might be overcome through the generation of CAR mutants.

AQP4 antigen–specific approaches must address issues well beyond TcR and CAR affinity. These include untoward conversion of Tregs to pathogenic phenotypes such as those exhibiting either Th1 or Th17 paradigms, accurate tissue targeting, and promotion of memory and stability. It is possible that the same tolerance checkpoints currently being considered for rapid deletion of undesirable T cells transferred in cancer could be applied to NMO/SD.

SUMMARY AND PROSPECTUS: PART I Immune tolerization attempts to restore central or peripheral tolerance, thereby suppressing autoimmune diseases. There is reason for optimism that this approach might offer substantial clinical benefit to individuals with NMO/SD. DNA vaccination, T cell vaccination, tolerogenic DCs, and peptide-coupling strategies have advanced to clinic trials. Other promising approaches (e.g., CAR-based or Treg-based therapeutics) are in earlier developmental stages in autoimmune diseases. Yet, defining target cell lineages to yield durable efficacy, and determining stage of disease development optimal for intervention remain crucial ongoing challenges. Past failures using similar strategies have provided critical insights that, despite the complexities of existing and emerging technologies for promoting tolerance, should illuminate the pathway forward. If so, such advances in treatment could benefit individuals with NMO/SD and other autoimmune diseases, including arresting disease progression, prolonging intervals to remission, enabling tissue repair, and ultimately avoiding chronic immunosuppressive therapy.

AUTHOR CONTRIBUTIONS
Larry Steinman: drafting/revising the manuscript. Amit Bar-Or: drafting/revising the manuscript. Jacinta M. Behne: revising the manuscript. Daniel Benitez-Rubio: drafting/revising the manuscript. Peter S. Chin: drafting/revising the manuscript. Michael Clare-Salzler: drafting/revising the manuscript. Donald Healey: drafting/revising the manuscript. James I. Kim: drafting/revising the manuscript. David M. Kranz: drafting/revising the manuscript. Andreas Lutterotti: drafting/revising the manuscript. Pablo Villosoada: drafting/revising the manuscript. Cheng-Hong Wei: drafting/revising the manuscript. Howard L. Weiner: drafting/revising the manuscript. Scott S. Zamvil: drafting/revising the manuscript. Michael R. Yeaman: drafting/revising the manuscript. Andreas Lutterotti: drafting/revising the manuscript.

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L. Steinman served on the scientific advisory board for Novartis, Receptos, Atreca, tolerion, Teva, received travel funding and/or speaker honoraria from Biogen, Bayhill, Bayer, Celgene, Receptos, is on the editorial board for "Multiple Sclerosis Journal, Proceedings of the National Academy of Science," holds a patent for antigen-specific tolerance, has a patent pending for cytokines and type 1 interferons, is on the speakers bureau for Bioatlas. A. Bar-Or is on the scientific advisory board for Dionox, Receptos-Celgene, Roche/Genentech, Novartis, GSK, Guthy-Jackson Greater Good Foundation, Immune Tolerance Network, received travel funding and/or speaker honoraria from Receptos-Celgene, Roche/Genentech, Novartis, Sanofi-Genezyme, GSK, served on the editorial board for "Neurology®, Clinical and Experimental Neuroimmunology," consulted for Diogenex, Receptos-Celgene, Roche/Genentech, Novartis, Sanofi-Genezyme, GSK, received research support from Novartis, Sanofi-Genezyme. J.M. 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Yekman is on the scientific advisory board for Guthy-Jackson Charitable Foundation, served as an associate editor for PLoS Pathogens, holds patents for Vaccines targeting drug-resistant pathogens, immunotherapies targeting drug-resistant pathogens, novel anti-inflammatory biological therapies, novel anti-inflammatory small molecules, novel biological regulating programmed cell death, consulted for Guthy-Jackson Charitable Foundation, received research support from Novadigm Therapeutics, Inc., Metacin Inc., US Department of Defense, NIH, holds stock or stock options for Novadigm Therapeutics, Inc., Meta- cin, Inc., receives license fee and royalty payments from Novadigm Therapeutics. T.J. Smith received research support from NIH, University of South Denmark, Bell Charitable Foundation, RPB Foundation, is a member of the Guthy-Jackson Charitable Foundation scientific advisory board, and holds patents covering the blockade of insulin-like growth factor receptor-1 in autoimmune diseases. 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