Integrative Continuum: Accelerating Therapeutic Advances in Rare Autoimmune Diseases

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Annu. Rev. Pharmacol. Toxicol. 2012. 52:523–47

The *Annual Review of Pharmacology and Toxicology* is online at pharmtox.annualreviews.org

This article's doi:
10.1146/annurev-pharmtox-010611-134628

0362-1642/12/0210-0523$20.00

Keywords

orphan disease, neuromyelitis optica (NMO), therapy, repurposing

Abstract

Autoimmune diseases are chronic, life threatening, and of burgeoning public health concern. They rank among the 10 most common causes of death in women, and some have incidence rates surpassing those of heart disease and cancer. Emerging information regarding molecular and cellular mechanisms affords opportunities for the discovery of novel therapeutic strategies or the repurposing of FDA-approved pharmacologic agents. Yet, obstacles to drug development amplify as an inverse function of the incidence of rare autoimmune disease; challenges include heterogeneous clinical presentation, paucity of definitive biomarkers, and poorly validated measures of therapeutic response. An integrative continuum model to address these challenges is being applied to neuromyelitis optica (NMO)—a potentially devastating neurodegenerative process that has had limited therapeutic options. This model links target discovery with pharmacologic application to accelerate improved clinical efficacy. The application of such innovative strategies may help researchers overcome barriers to therapeutic advances in NMO and other rare autoimmune diseases.

INTRODUCTION

The immunology and diseases of autoimmunity are at the intersection of a new era—one in which broad concepts are shifting toward specific understanding at the molecular and cellular levels. In turn, these refinements are helping yield targeted molecular interventions. However, this increased scientific understanding of autoimmunity has not been effectively integrated into drug development. Many factors have contributed to this scenario, including ambiguity in clinical definitions, lack of specific biomarkers or methodological standards, diminishing numbers of physician-scientists, real and perceived scarcities of patient cohorts for meaningful clinical studies, and barriers to biotechnology and pharmaceutical development.

Despite these challenges, autoimmune disease has important, new opportunities for breakthroughs that result from a convergence of bioinformatics (e.g., provided by genomics, proteomics, metabolomics, and epigenetics) and innovative technology development (e.g., leading to new or repurposed therapeutic agents). Furthermore, the rising awareness of the impact of rare autoimmune diseases on individual and public health has altered priorities for funding in this area. Even so, we face obstacles to developing solutions to these diseases; surmounting such obstacles will require collaborative relationships among academia, industry, regulatory agencies, and patients.

In this article, we highlight emerging opportunities to accelerate advances from basic science to improved patient care through the use of an integrative continuum model. This model, implemented through The Guthy-Jackson Charitable Foundation (GJCF), focuses on neuromyelitis optica (NMO). The mission of GJCF is to catalyze advances in the prevention, treatment, and cure of NMO on the basis of the integration of interests shared by NMO patients, academia, industry, the National Institutes of Health (NIH), and the U.S. Food and Drug Administration (FDA). The goals of this article are to

- provide an overview of the impact of autoimmune diseases, increase awareness about them, and present opportunities to meet the challenges they pose;
- integrate emerging insights into molecular, cellular, tissue-based, and clinical facets of rare autoimmune disease into a framework for therapeutic advances;
- propose a blueprint—the integrative continuum model—to accelerate therapeutic advances in rare autoimmune diseases; and
- illustrate how this model is being applied to facilitate new pharmacologic approaches to better treat or ultimately cure NMO and other rare autoimmune diseases.

BARRIERS TO ADVANCES IN RARE AUTOIMMUNE DISEASES

Unrecognized Impact of Autoimmune Diseases

Autoimmune diseases have traditionally—but incorrectly—been considered rare diseases that are relatively insignificant to public health (1–3), and perhaps as a consequence, the prevention and treatment of autoimmune diseases have in general lagged those of other clinical disorders. Because few disease-specific markers have been identified, diagnosis of autoimmune diseases remains largely based on the exclusion of other diseases. Patients with autoimmune disease often experience limited medical benefit because of problems related to diagnosis and therapies with low specificity, poor efficacy, and toxic side effects.

Autoimmune diseases represent an underappreciated but burgeoning individual and public health concern: They affect 5%–8% of the U.S. population (>20 million individuals) (4) and are among the 10 leading causes of mortality in U.S. women <65 years of age, likely ranking even higher worldwide (5). The frequency of autoimmune disease is now equivalent to that of heart disease (6), with an incidence ~twofold greater than that of cancer (7–9). Autoimmune diseases

are estimated to affect >3% of the human population (1); some estimates project a 5%–10% prevalence of autoimmune diseases worldwide (2). Thus, autoimmune diseases annually affect hundreds of millions of lives.

The National Institute of Allergy and Infectious Diseases has estimated the annual U.S. health care cost of autoimmune diseases to be $100 billion (10), which is greater than the cost of cancer ($57 billion) and half the cost of cardiovascular disease (11). According to the 2008 medical care consumer price index, annual expenses of autoimmune disease per patient range from $1,100 for psoriasis to $21,710 for systemic lupus erythematosus (2), with a mean cost per patient of $12,400 among all autoimmune diseases. In addition to financial costs, patients with autoimmune diseases can suffer from pain, disability, and disfigurement along with negative effects on quality of life for themselves, families, caregivers, and society as a whole.

Autoimmune diseases present challenges for pharmacologic advances, including ambiguity in disease phenotypes, paucity of specific biomarkers, efficacy of new therapeutics in patients who have failed prior therapies (clinical equipoise), and accrual of cohort sizes sufficient for optimally powered clinical investigations. These challenges are considered in the ensuing discussion with the intention of identifying opportunities to surmount them.

Scientific and Clinical Barriers

Etiologies of rare autoimmune diseases include environmental and experiential factors superimposed on polygenic Mendelian factors and immunopathogenic pathways. These multiple potential etiologies constitute a barrier to the success of efforts to advance prevention, treatment, or cure.

Basic science. Two convergent themes present special challenges to developing therapies for autoimmune diseases: In vitro does not equal in vivo, and mice are not men. These themes, which apply to NMO and other autoimmune diseases described in this article (**Figure 1**), create challenges that include tissue specificity, recapitulation of immune pathways, adaptive immunity and immune hyperplasticity, suboptimal animal models, and the presence of cause versus the absence of an inhibitor. Each of these aspects is discussed below.

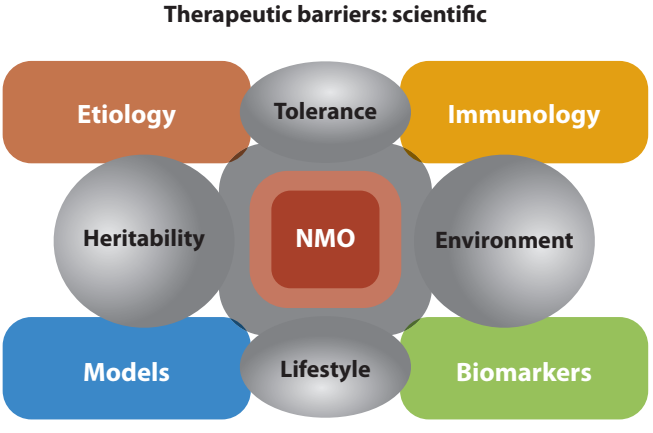

Figure 1

Primary scientific barriers to therapeutic advances in neuromyelitis optica (NMO) as a prototypic rare autoimmune disease. Interaction among these and other factors creates limitations to developing a knowledge base for such diseases and barriers to therapeutic advances to overcome them.

Tissue specificity. Understanding of autoimmune diseases requires a dissection of their underlying molecular and/or cellular events, particularly in the context of the affected tissue(s). This challenge is particularly important for neuroinflammatory diseases, in which the blood-brain barrier (also termed the neurovascular unit) can play a role, and in terms of affected tissues and the identification of disease biomarkers. For example, in neuroinflammatory diseases such as NMO, immune dysfunction resulting in astrocyte injury may originate within the periphery, the central nervous system, or both, but disease-specific biomarkers may not be identical in blood and cerebrospinal fluid. Recent approaches have sought to overcome these limitations and include the use of tissue slice models, which attempt to capture the molecular and cellular participants of disease within relevant target tissues (12).

Recapitulation of immune pathways. Pathogenesis in autoimmune disease likely relates to inappropriate antigen processing, presentation, and response. The number, type, and sequence of steps and molecular or cellular participants can create barriers to investigating such diseases outside a host. An autoimmune response may arise from an orchestrated series of events. First, antigen-presenting cells (e.g., dendritic cells, macrophages) detect an abnormal molecular determinant. Next, the determinant is processed by an endosomal or phagolysosomal pathway, such that the processed epitope(s) are presented in major histocompatibility complex I and/or II (MHC_I and/or MHC_{II}) contexts to naive T lymphocytes in secondary lymphoid tissues (e.g., lymph nodes, spleen). Subsequently, primary signaling can trigger T cell responses, whereas secondary signaling between T and B cells leads to B cell activation into plasma cells and antibody production. Ultimately, cytokine profiles related to upstream signaling shape downstream immune bias; for example, naive T cells presented with antigens in the context of acute-phase cytokines tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and transforming growth factor-β (TGF-β) often polarize to a Th17-polarized T cell (Th17) phenotype and express IL-17, IL-22, and IL-23. In turn, IL-22 prompts expression of the chemokine IL-8 from tissues, leading to margination and diapedesis of neutrophils and their accumulation in response to the IL-8 gradient. This example illustrates the numerous steps involved and thus the potential difficulty of developing in vivo therapies solely on the basis of information derived from in vitro or ex vivo systems.

Adaptive immunity and immune hyperplasticity. Another challenge in studies of autoimmune diseases relates to the immense plasticity (i.e., adaptability in terms of types of antigens) and complexity of the immune system. Moreover, immune recognition and effector responses can evolve. For example, affinity maturation increases the specificity of antibodies generated in response to an antigen over time (13, 14), whereas, in contrast, epitope spreading can reduce the specificity of immune response by triggering autoreactivity to molecular bystanders of the original antigen (15, 16). Thus, an autoimmune disease that may originate as a result of one autoreactive antigen can progress as the result of another. For these reasons, investigations of autoimmune diseases may show snapshot effects (i.e., they do not reflect earlier or later time points); such effects pose a particular challenge in using genomic or proteomic approaches to investigate autoimmune diseases (17). Because autoimmune diseases are moving targets, their mechanisms of etiology, onset, and progression can be elusive and difficult to recapitulate in vitro or ex vivo. Even if reproduced in vivo, studies may require long time intervals, during which environmental and/or experiential variables can be difficult to control.

Suboptimal animal models. The aforementioned limitations to in vitro and/or ex vivo studies of autoimmune disease necessitate the use of the most relevant and discriminative animal model(s).

Unfortunately, several variables can limit the degree to which human autoimmune disease mechanisms and natural history can be re-created in animal models. For example, some animal models use nonspecific and/or undefined activating stimuli as immune agonists, e.g., complete Freund's adjuvant, pertussis toxin, and/or lipopolysaccharide. Such stimuli can bias host responses toward a proinflammatory response needed to induce disease, but their limited specificity may yield ambiguous immune causality. Likewise, the genetic backgrounds of experimental animals can profoundly influence outcomes. For example, the same antigen administered to Balb/C or C57/BL6 mice can produce noninflammatory responses (e.g., by Th2 and antibody effectors) or inflammatory responses (e.g., by Th1 or Th17 and cell-mediated effectors), respectively (18). Even if one controls for these factors, the relapsing-remitting aspects of autoimmune diseases can be difficult to replicate in animal models.

Presence of cause versus absence of an inhibitor. As self-reactivity is their common feature, autoimmune conditions may result from a lack of appropriate or effective control of immune response. Autoimmune diseases can arise from dysfunction in central or peripheral immune tolerance, such as failure to "edit" inappropriate B and/or T cells or recognition of self-antigens as foreign. Moreover, just as immune response that is biased (e.g., polarized) toward Th1 or Th17 paradigms promotes inflammation, other paradigms favor noninflammatory profiles (19). For example, T regulatory cells can decrease inflammation via expression of IL-10. Thus, deficiency or absence of negative regulation of immune response can facilitate autoimmune disease. Efforts to identify the loss of such inhibitory mechanisms can provide as many insights as those resulting from efforts to seek promoters of disease, although the former might prove more difficult. Efforts directed at promoters have been the major thrust of most traditional research.

Clinical therapy. Clinical investigations seeking to understand and solve autoimmune diseases have faced other challenges (**Figure 2**). Predominant themes regarding these challenges include pleiotropic disease phenotypes, biomarker ambiguity, perceived scarcity of patients, clinical equipoise, and lack of clinical and methodological standardization.

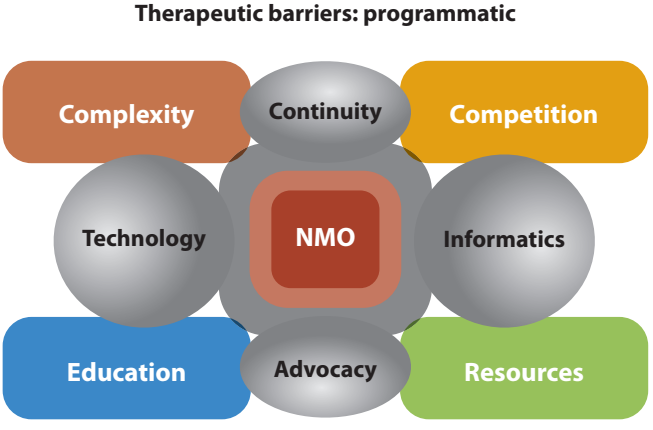

Figure 2

Programmatic barriers to therapeutic advances in neuromyelitis optica (NMO) as a prototypic rare autoimmune disease. Such obstacles can be complex and multifaceted and can arise from issues derived from missed opportunities for idea sharing and partnership. By unifying shared core values—and incentivizing mutual success through collaboration—investigators may overcome many such barriers. For example, requiring timely sharing of data and insights can speed advances.

Pleiotropic disease phenotypes. Among the most enigmatic characteristics of autoimmune diseases are their pleiotropic clinical signs and symptoms, including diverse manifestations, intermittent chronicity, and relapsing-remitting courses (20). In addition, standard treatments show considerable variability in response. For example, autoimmune diseases such as multiple sclerosis (MS) or NMO can be either glucocorticoid-sensitive or -resistant (21). Moreover, autoimmune diseases pose special challenges related to arresting or reversing active disease, in addition to preventing or minimizing the frequency and severity of relapses or progression.

Biomarker ambiguity. The lack of specific molecular, imaging, or clinical biomarkers has been a barrier to understanding pathogenesis and identifying efficacious therapies of autoimmune disease. Therapeutic efficacy has often been based on relatively qualitative endpoints, such as disability indices and subjective patient assessments (6). For example, the diagnosis of MS relies on relatively nonspecific brain imaging; oligoclonal bands recovered from the cerebrospinal fluid; clinical symptoms such as paresthesia, nystagmus, and incontinence; and the natural history of disease (e.g., relapsing, progressive, and other courses). By contrast, NMO is an exception as it has a biomarker that can distinguish it from related autoimmune diseases such as MS: anti-aquaporin-4 antibody, also termed anti-AQP4 or NMO-IgG (22, 23).

Perceived scarcity of patients. A historical barrier to expanded engagement of the pharmaceutical industry in developing therapies for autoimmune diseases has been the sense that there are too few patients who could benefit from treatment or could be recruited to provide adequate statistical power for clinically meaningful studies. Other barriers, such as ambiguous clinical phenotypes and limited biomarkers for rare autoimmune diseases, heighten the need to recruit subjects from many sites. Multisite trials require a consensus so that clinical assessment, sample acquisition and storage, and therapeutic evaluation are standardized. The coordination of a multisite consortium requires that institutional review board approval of studies with human subjects conform to a consensus among consortium participants. Time delays and costs resulting from such challenges can be prohibitive.

Such issues must be overcome, especially in light of an increasing awareness of the impact of rare autoimmune diseases. According to the European Organisation for Rare Diseases, rare diseases are defined as those having an incidence of <1 in 2,000 citizens (24), which is a challenge for identifying appropriate patients, recruiting and retaining them for longitudunal studies, and determining efficacy endpoints in these patients for clinical trials. However, across a larger population of 500 million citizens, one predicts $\sim$250,000 cases of rare diseases. In fact, 30 million individuals are estimated to suffer from more common autoimmune diseases in the 25 European Union countries, equivalent to 6%–8% of the total population (24).

Clinical equipoise. Clinical equipoise reflects the increased challenges involved in showing efficacy of new therapeutics in patients in whom prior therapies have failed. The concept of clinical equipoise integrates ethical and other considerations of particular applicability to rare autoimmune diseases (25), in which patients are often exposed to various treatment regimens. As the effectiveness of a given regimen wanes, it is an ethical imperative to use potentially more effective treatments, albeit ones that may produce more adverse effects; such changes in therapy may occur on multiple occasions. This therapeutic dilemma has numerous, unfortunate effects of special relevance to rare autoimmune diseases. First, as therapeutic efficacy declines with time, patients may ultimately have no effective therapy. Second, and of key importance to clinical trial design, patients who enter trials may be those whose disease is most refractory to therapy—thus, new potential therapies

are challenged to demonstrate efficacy in the most severely affected patients, or those in whom standard-of-care regimens have failed. Third, patients who are not benefited by more specifically targeted agents may be treated with less discriminant regimens that can produce more side effects. Finally, even if a newer therapeutic agent or strategy is approved for use, its potential for efficacy may be minimized, and its side effects magnified, in patients with late-stage or more complex disease.

Lack of clinical and methodological standardization. Ambiguity in clinical presentation is one difficulty in developing a systematic approach to advance the therapy of autoimmune disease. Another is the lack of standards in collection, processing, and storage of tissues and specimens. A third barrier to clinical translation is a lack of uniformity for inclusion, exclusion, efficacy, endpoint, and adaptive clinical study design. A lack of definitive biomarkers can be compounded by the absence of standard definitions of disease, such as relapse versus progression, further limiting the assembly of meaningful clinical data sets. Building a consensus regarding such criteria has proven effective in facilitating clinical and therapeutic advances in certain autoimmune diseases, such as Sjögren's syndrome (26).

Collectively, the aforementioned scientific, translational, and clinical barriers contribute to the so-called valley of death (a void in commercial interest and resources that often leads to a dead end in novel therapeutic development), which can prevent therapeutic advances (**Figure 3**). Thus, creative ways to traverse these barriers may afford the greatest chance to improve the treatment of rare autoimmune diseases such as NMO.

THE INTEGRATIVE CONTINUUM MODEL FOR THERAPEUTIC ADVANCES: NEUROMYELITIS OPTICA AS AN EXAMPLE

The preceding discussion offers a context for considering key challenges in advancing the prevention, diagnosis, and treatment of rare autoimmune diseases. Below, a strategy to address these challenges is outlined: the integrative continuum model for accelerating therapeutic advances in NMO and potentially other similar diseases (27).

Blueprint: Integrative Approach to Solving Rare Autoimmune Diseases

The renowned biologist E.O. Wilson defined consilience as a unity of knowledge (28). This concept is especially applicable to autoimmune diseases, in which common threads may underlie diverse etiologies and clinical manifestations. Moreover, in an era of genomic, proteomic, clinical, and pharmaceutical databases, the need and opportunity to distill wisdom from complex data sets have never been greater. In this light, implementation of the integrative continuum model can coordinate diverse and complementary activities within a context that can accelerate advances (**Figure 4**).

Defining the problem. A first step in approaching new solutions to NMO was to explicitly define the problem, including limitations in knowledge, methods, and resources. The discovery of a specific autoantibody, anti-aquaporin-4 (also known as anti-AQP4 or NMO-IgG), which is present in ~70% of NMO patients, provided an advantageous starting point. However, a more complex immunologic relationship may exist because other autoimmune diseases, such as myasthenia gravis, often precede or are concurrent with NMO (29). Thus, anti-AQP4 may represent a surrogate signal for loss of tolerance, epitope spreading, or other multifactorial pathogenic mechanisms. Likewise, although it might seem simpler to consider NMO an antibody-mediated disease, T cell recognition

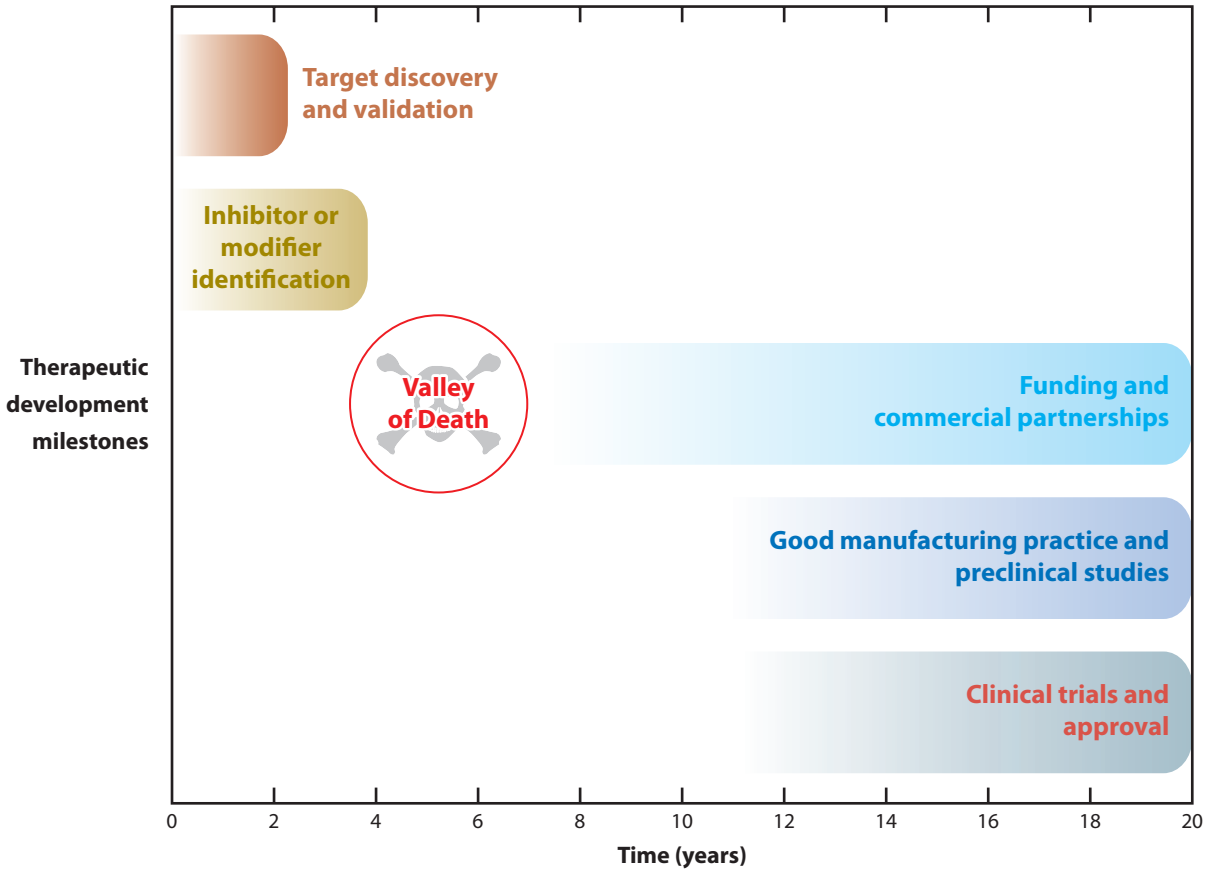

Figure 3

Conceptual timeline for milestones in therapeutic innovation. A major advantage of therapeutic repurposing is that a drug already developed and approved for one condition can be readily evaluated in another condition if there is sound scientific and clinical justification. This approach may help overcome the so-called valley of death during drug development and approval.

of an antigen (e.g., normal self-protein, autoantigen, or foreign antigen) is typically required for production of certain antibody subclasses by B cells. Furthermore, therapeutic regimens that are efficacious in some NMO patients and that target antibody-producing $CD20^+$ B cells (e.g., rituximab) do not consistently reduce anti-AQP4 IgG levels (30). Thus, NMO involves multiple types of lymphocytes (**Figure 5**), and one must consider the roles of T and B cells individually, as well as their potential interactions, in developing treatments for NMO in the context of a robust basic science, biorepository, and clinical research portfolio. Moreover, the absence of definitive genetic correlates to date implies that NMO is a polygenic disease. The lack of clear epidemiologic patterns, other than a greater prevalence in women, supported the view that NMO is potentially caused by a combination of endogenous (e.g., spontaneous, Mendelian, or complex genetic origins) and exogenous etiologies (e.g., environmental or microbial origins).

Insights can also be gained through the assessment of NMO in the context of knowledge about other autoimmune diseases such as longitudinal extensive transverse myelitis, transverse myelitis, MS, or similar disorders and that share clinical, genetic, immunologic, or perhaps even etiologic similarities with NMO. For example, NMO, MS, longitudinal extensive transverse myelitis, and

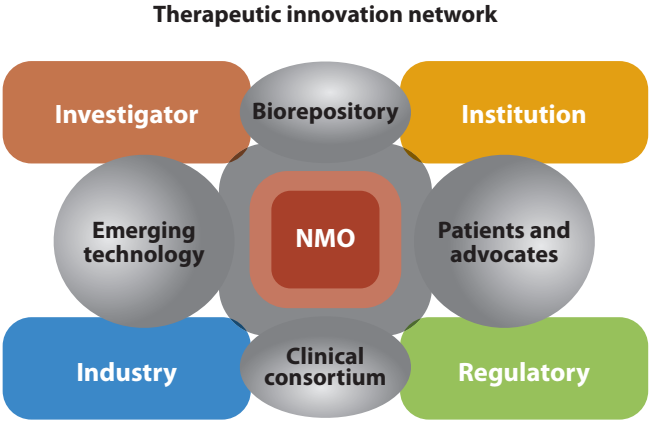

Figure 4

A therapeutic innovation network for neuromyelitis optica (NMO), based on the formation of alliances among stakeholders with complementary interests. Networks such as these are based on the integrative continuum model—thereby enabling the application of new knowledge as it emerges. This model has the potential to accelerate therapeutic advances for other diseases as well.

transverse myelitis target the cervical spinal cord and optic nerves, and Pham et al. (31) have recently shown that AQP4 may not be the only autoantigen targeted in NMO. Similarly, NMO can manifest as a monophasic disease (with one episode) or polyphasic disease (with multiple or variable episodes), a pattern that mirrors many neurological autoimmune disorders (32). Patients with NMO do not always have relapsing-remitting courses; rather, each subsequent episode may lead to a progressive increase in and/or irreversibility of tissue injury.

On the basis of the aforementioned information, it was necessary to address the likelihood that NMO is a disease that differs from MS and involves at least one known autoantibody, but that it may involve a multistep immunologic dysfunction without an established etiology. Addressing this challenge required expertise beyond that of any single discipline or laboratory.

Assembling a team of teams. In recent years, complexities of basic and clinical research have increased, and, in turn, there has been a shift from individual investigator laboratories to research teams that can investigate problems with complementary skills. This reality emphasizes the benefits of assembling of a "team of teams" to study NMO.

Transdisciplinary teams are composed of individuals from many disciplines with differing expertise; they can include patients and advocates, basic scientists, physicians, clinical study experts, public health educators, agency leaders [e.g., from the NIH, FDA, and/or Centers for Disease Control and Prevention (CDC)], industry leaders, media experts, administration and policy experts, and advisors. For example, a basic science team investigating NMO may include individuals with expertise not only in AQP4 molecular biology, antibody detection, deep sequencing genomics, T cell epitope analysis, and experimental animal models, but also in autoimmune disease, infectious disease, and neurology. Likewise, administrative, advisory, and policy teams integrate expertise from diverse perspectives including organizational management and biomedical informatics. Translational teams unite members and perspectives of other teams and also include teams that have expertise in clinical study design, pharmacology, and therapeutic development. A major strength of this strategy is that its shared vision assists not only in identifying barriers but also in enhancing solutions and approaches to overcome them.

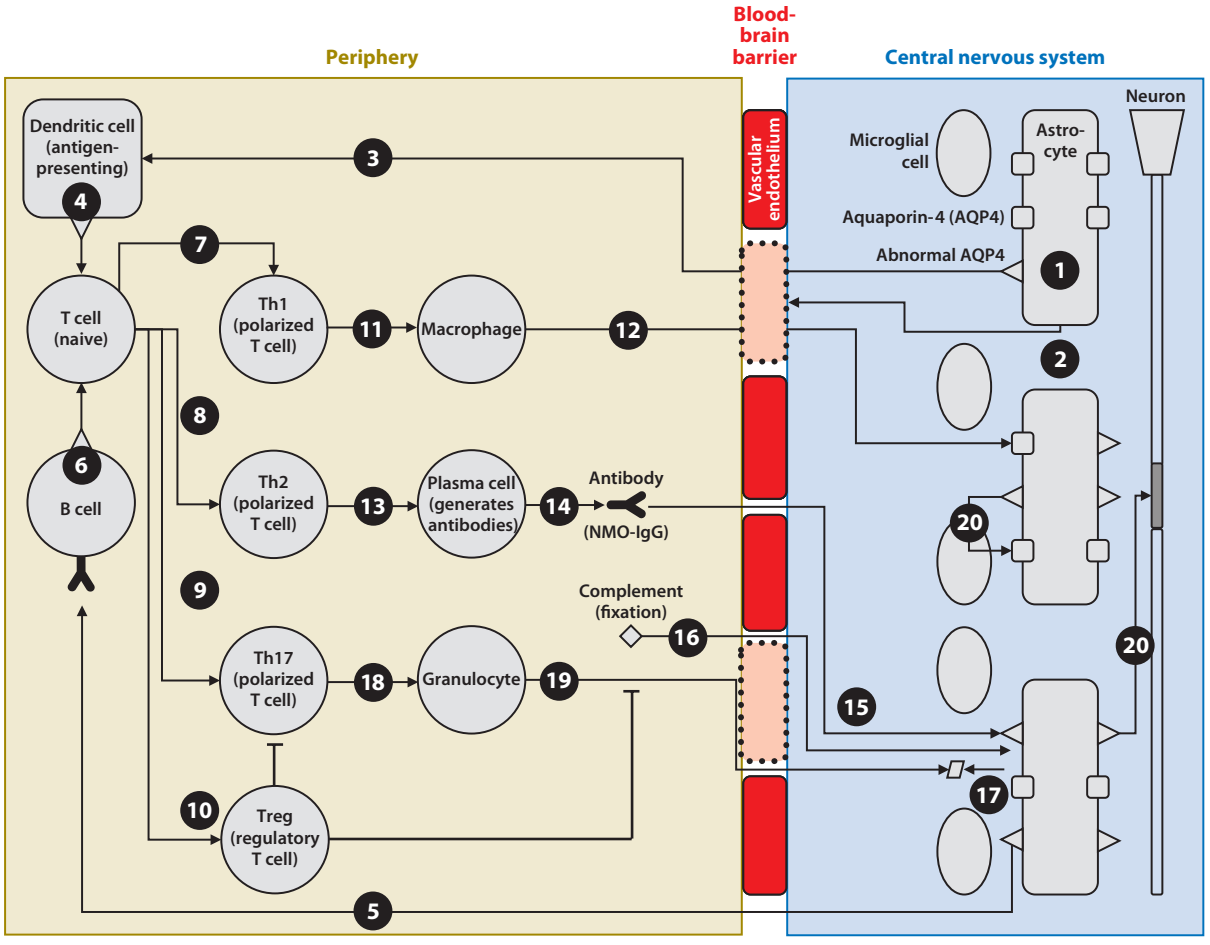

Figure 5

Hypothesized molecular and cellular determinants in neuromyelitis optica (NMO). Each number represents an immunologic component or event hypothesized to contribute to NMO: **1**, change in aquaporin-4 (AQP4) structure; **2**, altered astrocyte signaling [e.g., tumor necrosis factor (TNF), interleukin-6 (IL-6)]; **3**, detection and processing of abnormal AQP4 by dendritic cells [antigen-presenting cells (APCs)]; **4**, presentation of abnormal AQP4 epitopes to naive T cells; **5**, clonal selection of naive B cells by recognition of abnormal AQP4 epitopes; **6**, B cells may serve as APCs to present abnormal AQP4 to naive T cells; **7**, Th1 polarization of T cells (e.g., IL-12 context leading to interferon-γ production); **8**, Th2 polarization of T cells (e.g., IL-4 and IL-13 context); **9**, Th17 polarization of T cells (e.g., IL-6, TNF, and transforming growth factor-β context for induction of IL-17-producing T cells and generation of IL-22 and IL-23); **10**, failure of regulatory T cells (Tregs) to modulate autoreactive T and B cells; **11**, activation of Th1 effector cells such as macrophages; **12**, inflammation due to Th1 effector cells; **13**, activation of Th2 effector cells, such as plasma cells; **14**, autoantibody production (e.g., NMO-IgG); **15**, autoantibody targeting of abnormal AQP4 on astrocytes; **16**, complement fixation on bound autoantibody; **17**, cleavage of complement proteins creates inflammatory stimuli (e.g., C5a); **18**, activation of Th17 effector cells, such as granulocytes; **19**, infiltration of granulocytes into the central nervous system, which drives inflammation; **20**, possible antigen spreading, which promotes reactivity against other central nervous system components (e.g., myelin) and causes inflammatory demyelination and interference in neuroconductivity. (See also the **Supplemental Visualizing NMO tool**; follow the **Supplemental Materials link** from the Annual Reviews home page at **http://www.annualreviews.org**.)

Supplemental Material

Designing an adaptive research portfolio. A key to solving complex autoimmune diseases may be the implementation of an adaptive framework that incorporates emerging advances in basic, translational, and clinical research. However, it can be challenging to redefine priorities that change over time while maintaining research momentum. The approach used for NMO has involved a real-time sharing of ideas, reagents, protocols, and outcomes in a manner that is not typical of standard academic models. This approach leverages advances in related diseases and fields as well (e.g., rheumatology, allergy). In these ways, the integrative continuum model is designed to develop a robust, adaptive research portfolio to identify potential therapeutic targets and development pathways that overcome traditional barriers. Furthermore, the integrative continuum model builds on emerging strengths, learns from successes and setbacks, seeks disease promoters and inhibitors, advances from within and beyond NMO, fosters ideas and data sharing, and coordinates efforts in real time. Each of these characteristics is discussed below.

- Builds on emerging strengths: An overarching strategy was to create a research portfolio that leveraged existing skills and knowledge in novel ways. To this end, the research portfolio was designed to be a blend of relatively low-risk/systematic studies with high-risk/breakthrough approaches.
- Learns from successes and setbacks: Integral to research progress was the design of studies that would afford understanding of why an experiment or clinical therapy may have failed, not simply that it did so.
- Seeks disease promoters and inhibitors: Searching for the absence of a disease inhibitor differs greatly from searching for the presence of a disease promoter, which is more traditionally sought. An optimal research portfolio must incorporate studies of both such facets of autoimmune disease.
- Advances from within and beyond NMO: Connecting experts within and beyond the NMO field was deemed important to generate fresh viewpoints that catalyze new thinking. Such an approach not only might facilitate the discovery of breakthroughs in NMO but also might advance understanding of autoimmune diseases that share common (or potentially universal) mechanisms. This aspect also fosters an interactive research and patient community that prioritizes NMO but integrates important information for other autoimmune diseases.
- Fosters idea and data sharing: Breakthroughs in medical science may be just as likely to be heralded by "we didn't expect to see that" as they are by "Eureka!" If shared in a mutually beneficial context, research findings can help prioritize new ideas, resources, and approaches. Having experts monitor progress can also help anticipate breakthroughs and avoid duplication of effort.
- Coordinates effort in real time: Acceleration of progress requires the swift translation of key discoveries into clinical studies. In the integrative continuum model, advisors offer investigators constructive feedback to facilitate the rapid linkage of therapeutic candidates to molecular and cellular targets.

Creating catalytic resources. Efforts to facilitate basic and clinical research programs have included:

- an annual NMO research roundtable to connect researchers, patients, care givers, and advocates;
- provision of key molecular reagents (e.g., recombinant human and rodent AQP4, monoclonal anti-AQP4 antibodies) to investigators to perform research studies;
- novel experimental models (e.g., transgenic mice, ex vivo organ slice models, and similar tools to investigate pathogenesis) and assay systems (e.g., high-throughput screening capabilities)

to accelerate identification of compounds or biological agents that interfere with pathogenic mechanisms of NMO;

- genomic, proteomic, and bioinformatic data to drive collaborative mining of antigenic or immunologic determinants and candidate biomarkers in NMO;
- an NMO biorepository that has matched clinical and biological samples from NMO patients of diverse demography, epidemiology, disease course, treatment history, and clinical outcome;
- standardized protocols, operating procedures, and best practices for recruiting NMO and control patients, as well as collecting, processing, storing, archiving, and physically or electronically transporting biospecimens or clinical data in an HIPAA-approvable way;
- an NMO-specific clinical consortium to coordinate patient recruitment, facilitate the evaluation of novel therapies or those that can be repurposed in NMO, and integrate these resources with the NMO biorepository;
- the provision of traveling nurse phlebotomist resources to NMO patients for participation in the NMO biorepository at no cost to the patients;
- development of therapeutic candidate programs to prioritize FDA-approved drugs that might be used to treat NMO, on the basis of new information regarding biomarkers and clinical evidence (e.g., see **Table 1** and **Figures 5** and **6**); and
- an online community (Spectrum; see Reference 33) that supports NMO patients and advocates, provides research and education materials, stimulates interaction with other autoimmune disease interest groups, offers an open forum for sharing ideas and experiences, and cites updates and other resources for all stakeholders.

Engaging Key Stakeholders and Resources

Essential to accelerating therapeutic advances in NMO or other rare autoimmune diseases is the involvement of all key stakeholders, including patients, their families and advocacy groups, and health care professionals within and beyond the specific disease and clinical specialties involved in patient care. Progress in therapy also requires partnership with commercial stakeholders, as well as agencies such as the NIH and FDA. It is also important to educate educators (e.g., medical schools and training programs) along with organizations engaged in efforts to better treat or cure autoimmune diseases (34). Online resources, Web-based tools, and Internet applications can also be harnessed to help distribute information among stakeholders.

Building consensus and coordination among stakeholders (including all those noted above) is an essential step for advancing discovery and clinical care in autoimmune diseases in general and NMO in particular. The NIH, CDC, and FDA have sought to improve awareness, enhance research, and facilitate industry participation by addressing the unique challenges of rare autoimmune diseases. The next section focuses on the roles played by the NIH and industry that are believed to be essential in meeting the challenges of rare autoimmune diseases.

National Institutes of Health. In the past decade, the NIH has invested an increasingly greater amount of resources (grant funding, training programs, and coordinating efforts) in autoimmune diseases in general and rare autoimmune diseases in particular by growing two complementary aspects of its autoimmune diseases program (35). First, it has targeted studies of mechanisms, biomarker discovery, and therapeutic development (see below), and it has stabilized research infrastructure and efforts to encourage training of new clinician scientists in autoimmune diseases. Second, the NIH has supported multidisciplinary clinical research networks to attract clinical investigators, simplify clinical trial design to reduce costs and enable more efficient studies, facilitate stratification of patients in terms of disease stage and phenotype, and promote

earlier and more accurate diagnoses (35). To meet these objectives, the NIH has sought to connect stakeholders through translational or clinical research networks such as the Immune Tolerance Network (ITN) (**http://www.immunetolerance.org;** see also Reference 36). The ITN exemplifies a clinical research consortium designed to accelerate advances in immune tolerance therapy.

The NIH has also created the Autoimmunity Centers of Excellence, which currently focus on six diseases: systemic lupus erythematosus, MS, pemphigus, rheumatoid arthritis, scleroderma, and Sjögren's syndrome. Furthermore, it has established the Autoimmune Disease Prevention Centers, which seek to develop and evaluate novel strategies for autoimmune disease prevention and biomarker discovery. The NIH also supports ClinicalTrials.gov, a searchable, publicly accessible database of active and completed clinical trials that are federally or privately supported. In addition, the National Institute of Environmental Health Sciences prioritizes efforts to define (*a*) the role of genetic determinants in promoting or modulating autoimmune diseases; (*b*) potential roles of environmental and infectious agent exposure or timing in the development of autoimmune disease; and (*c*) interactions of hormones or gender differences with potential environmental, infectious, or genetic factors in the development of autoimmune diseases.

Although the NIH supports mechanisms to facilitate clinical advances, even in clinical trials for common diseases, approximately 50% of study sites in the U.S. fail to enroll a sufficient number of patients (37). Rare autoimmune diseases face an even greater challenge in patient recruitment and retention. The NIH-supported General Clinical Research Center program is being converted to Clinical and Translational Science Institutes (CTSIs) as one approach to help address this issue (38). Likewise, the Clinical and Translational Science Awards (CSTA) Pharmaceutical Assets Portal (**http://CTSApharmaportal.org**) enables researchers to obtain candidate or approved drugs for testing in new ways. The NIH also supports programs such as CSTA-IP (**http://www.rochesterctsa.org/ip/**) that facilitate responsible stewardship of intellectual property, and the ResearchMatch tool (**http://www.ResearchMatch.org**) links >50 CTSI-supported institutions into a research database with clinical data from studies conducted outside the U.S. The collective goals of these resources are to provide assistance in trial design, streamline regulatory processes, and enable improved statistical and adaptive clinical trial approaches in an effort to facilitate clinical advances.

To assist in managing these emerging assets as related to autoimmune disease, the NIH Autoimmune Diseases Coordinating Committee (NADCC) was established in 1998. The NADCC includes 14 NIH institutes, along with FDA, CDC, and Veterans Administration program leaders. The NADCC provides a biennial report to Congress, holds forums for patient and advocate participation, and seeks to facilitate improved prevention, diagnosis, and treatment of autoimmune diseases.

Industrial investment in rare autoimmune diseases. A formidable obstacle to the application of clinical solutions to rare autoimmune diseases is that only ~1 in 1,000 compounds discovered reaches clinical trials and that only 1 in 10 of those receives FDA approval. Numerous factors contribute to this low success rate (**Figure 3**).

Three major challenges must be overcome in convincing industrial stakeholders to undertake efforts in therapeutic development for rare autoimmune diseases: (*a*) Optimal therapeutic targets must be chosen when neither etiology nor unique pathogenic mechanisms are known; (*b*) the reason previous agents and strategies failed in treating a specific autoimmune disease must be understood; and (*c*) the financial investment in developing therapeutics for rare autoimmune diseases must be justified in light of substantial risks and perceived limitations in the patient population. Ironically, these challenges shine an optimistic light on the opportunity to apply innovative therapeutics to

Table 1 Nonexhaustive list of molecules being considered for potential repurposing or novel therapeutic agents or strategies in NMO and related autoimmune inflammatory diseases

Pathogenic step(s)	Mechanistic target(s)	Therapeutic candidate(s)	Developmental phase(s)
Autoreactive T cells	Tc receptor		
	TcR/MHC	Antigen-coupled targeting	Discovery
	Costimulation		
	CTLA-4 (CD152)	Ipilimumab[a]	U.S. FDA review
	CD28/B7.1 (CD80)/B7.2 (CD86)	Abatacept	U.S. FDA approved[b]
		AMP-110	Preclinical
		Belatacept	Phase II trials
	Signal transduction		
	JAK2/STAT5	Lestaurtinib	Phase II trials
	RORγt/NF-κB/STAT3	OPB-31121	Phase I trials
		RTA-402	Phase I/II trials
	Clonal expansion		
	IL-7/IL-7R (CD127)	α-IL-7/IL-7R MAb	Preclinical
	Cytokine expression		
	IFN-γ	Fontolizumab	Phase II trials
	IL-12/IL-23 (p40 subunit)	Ustekinumab	Phase I/II/III trials
	IL-17A/IL-17F	AIN457	Phase I/II trials
	IL-22	Fezakinumab	Phase I/II trials
	IL-23 (p19 subunit)	AMG827	Phase I trials
		LY2525623	Phase II
Autoreactive B cells	Bc receptor		
	BcR/autogen	Antigen-coupled targeting	Discovery
	Costimulation		
	CD40/CD40L	Lucatumumab	Phase I trials
		Teneliximab	Preclinical
	Bc/Tc interaction		
	CD28/CD80/CD86/BcR	Galiximab	Phase I/II trials
	Signal transduction		
	BAFF/BLyS	Belimumab	U.S. FDA approved[b]
	Clonal expansion		
	CD19 (proplasma)	Blinatumomab	Phase I/II trials
	CD20 (prememory)	Ofatumumab	Phase I/II/III trials
		Rituximab	U.S. FDA approved[b]
	Memory		
	$CD78^+/CD138^+/CD45^-$	α-CD78/CD138 MAb	Preclinical
	Cytokine expression		
	IL-4	Mepolizumab	Phase II trials
		Pascolizumab	Phase II/III trials
	IL-5	Reslizumab	Phase I/II trials
	IL-13	Anrukinzumab	Phase I/II trials
		Lebrikizumab	Phase I/II trials
α-AQP4 (NMO-IgG)	Competitive inhibition		
	AQP4	Aquaporumab	Preclinical
	Neutralization		
	AQP4 IgG idiotype(s)	α-idiotypic networks	Discovery

(*Continued*)

Table 1 (*Continued*)

Pathogenic step(s)	Mechanistic target(s)	Therapeutic candidate(s)	Developmental phase(s)
Complement	Amplification		
	C5	Eculizumab	U.S. FDA approved[b]
		EV576	Preclinical
Chemokines	Anaphylactins		
	C5a (CD88)	α-C5a MAb	Preclinical
	Chemotaxins		
	CXCL8 (IL-8)	Reparixin	Phase II trials
	CCL11 (eotaxin)	Rolipram	U.S. FDA approved[b]
Granulocytes	Chemotaxis		
	C5aR	CCX168	Phase II trials
	Enzymatic function		
	Elastase	Sivelestat	Approved in Japan[b]
Inflammation	Immune polarization		
	IL-6	Elsilimomab	Preclinical
		Siltuximab	Phase II/III trials
	IL-6R	Tocilizumab	Phase II trials
	TGF-β	SB-431542	Preclinical
	TNF	Adalimumab	U.S. FDA approved[b]
		Certolizumab	U.S. FDA approved[b]
		Etanercept	U.S. FDA approved[b]
		Golimumab	U.S. FDA approved[b]
		Infliximab	U.S. FDA approved[b]
	Immune modulation		
	IL-10	Prevascar	Phase II trials
		Tenovil	Phase II trials

[a]To support unbiased presentation, molecules are listed alphabetically in each of the respective subclasses with no intended preference for any agent or commercial entity.

[b]Approval for indication other than neuromyelitis optica.

Abbreviations: AQP4, aquaporin-4; BAFF, B cell activating factor; Bc, B cell; BcR, B cell receptor; BLyS, B lymphocyte stimulator; CTLA, cytotoxic T lymphocyte-associated antigen; IFN, interferon; IL, interleukin; JAK, Janus kinase; MAb, monoclonal antibody; MHC, major histocompatibility complex; NF-κB, nuclear factor κB; ROR, retinoid-related orphan receptor; STAT, signal transducer and activator of transcription; Tc, T cell; TcR, T cell receptor; TGF, transforming growth factor; TNF, tumor necrosis factor.

rare autoimmune diseases. For example, the autoimmune disease therapy "market" has grown ~10% annually since 2008 and is predicted to increase further (from $38 billion to $67 billion by 2014) (39). In part, this sharp increase has resulted from increasing recognition of the impact of autoimmune disease on public health (3, 4, 11, 35). Also, unrealized opportunity is being recognized: For example, until belimumab (Benlysta®) received FDA approval in 2011, no new drug had been licensed for treating systemic lupus erythematosus for nearly 50 years.

One emerging factor that has prompted commercial interest in autoimmune disease therapy is the opportunity for repurposing—using a drug developed and approved for one disease to treat another disorder. The growing realization that certain autoimmune diseases may have overlapping or common pathways or targets gives the pharmaceutical industry a rationale for repurposing. Repurposing a drug offers many advantages and incentives. First, a company that invested time and money into developing a safe and effective agent that received FDA approval for one indication may assess that agent for its efficacy in another disease without onerous preclinical development

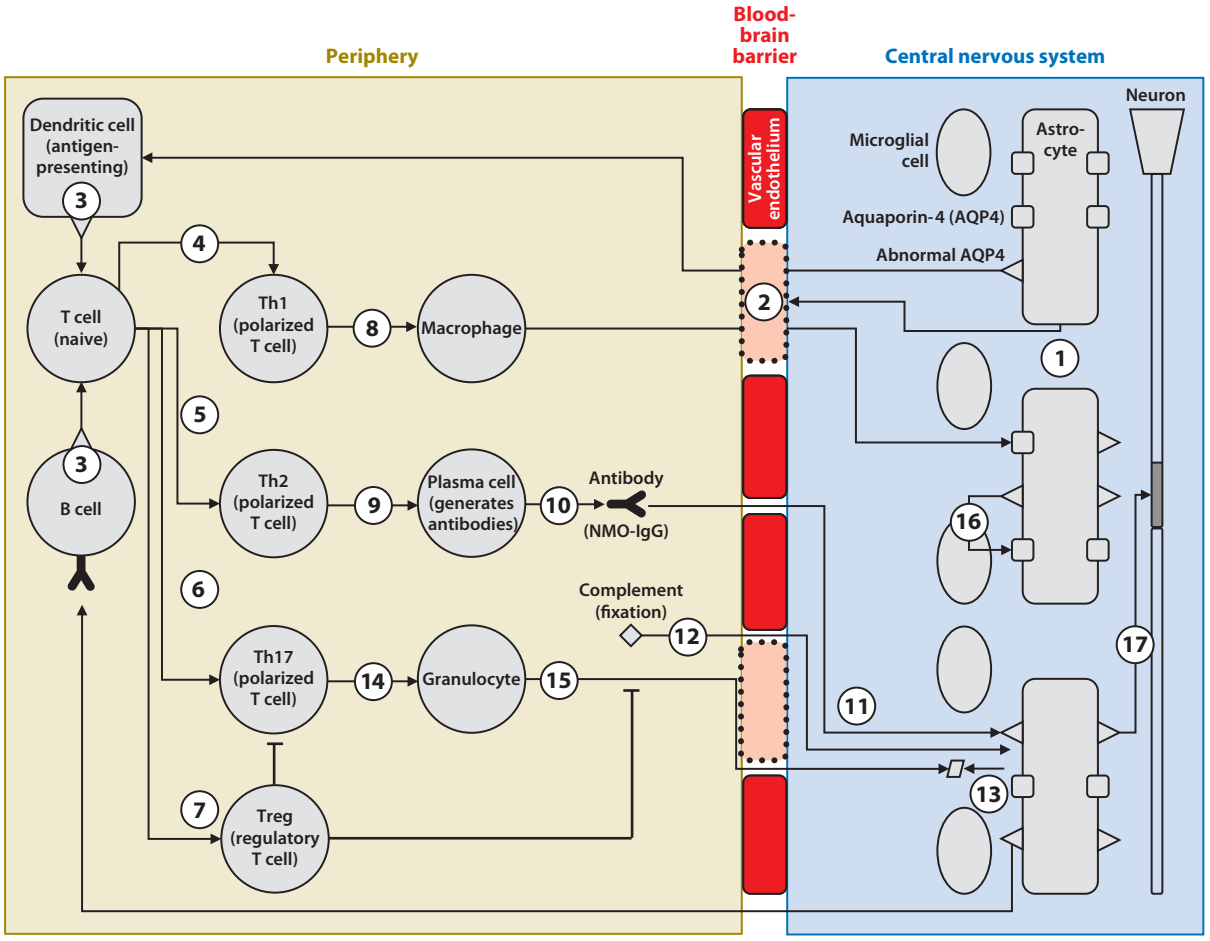

Figure 6

Hypothesized therapeutic targets and candidates in neuromyelitis optica (NMO). Each number represents a potential target for therapeutic intervention on the basis of emerging evidence: **1**, suppression of astrocyte proinflammatory signals (e.g., α-IL-6, α-TNF); **2**, restoration of the blood-brain barrier (also termed the neurovascular unit; e.g., α-VEGF-A); **3**, interference of dendritic cell, T cell, and B cell interactions and inflammatory second-signals (e.g., α-CD40/CD40L or α-CD80/CD86/CD28); **4**, interference with Th1 polarization (e.g., α-T_{bet}, α-STAT4, or α-IL-12); **5**, inhibition of Th2 or B cell activation events (e.g., α-BAFF/BLyS); **6**, inhibition of Th17 polarization (e.g., α-RORγτ or α-IL-23); **7**, activation of autoimmune-modulating systems (e.g., CTLA4 or adoptive transfer of Tregs); **8**, hypothetical blockade of Th1 cytokines (e.g., interferon-γ); **9**, inhibition of key Th2 cytokines (e.g., α-IL-4, α-IL-5, or α-IL-13); **10**, inhibition of B cell subsets such as proplasma (e.g., $CD19^+CD20^-$), naive (e.g., $CD19^+CD20^+$), and plasma (e.g., $CD19^+CD20^-CD138^+$) B cells; **11**, innovative approaches to develop protective antibody responses (e.g., beneficial monoclonal antibody or induction of α-idiotypic networks via development of tolerance); **12**, complement inhibition (e.g., α-C1q, α-C5); **13**, inhibition of specific inflammatory consequences of complement fixation (e.g., α-C5a) or related chemotactic signals (e.g., chemokines), or induction of complement-modulating mechanisms (e.g., CD59, decay-accelerating factor, or C1-INH); **14**, blockade of Th17 pathway cytokines (e.g., α-IL-17, α-IL-22, α-IL-23); **15**, inhibition of inflammatory mechanisms of granulocytes (e.g., chemotaxis, elastase); **16**, restoration of immune tolerance; **17**, repair of central nervous system injury through tissue regeneration. Abbreviations: AQP4, aquaporin-4; BAFF, B cell activating factor; BLyS, B lymphocyte stimulator; CTLA, cytotoxic T lymphocyte-associated antigen; IL, interleukin; INH, inhibitor; ROR, retinoic acid–related orphan receptor; STAT, signal transduction activator of transcription; TNF, tumor necrosis factor; Treg, regulatory T cell; VEGF, vascular endothelial growth factor. (See also the **Supplemental Visualizing NMO tool**; follow the **Supplemental Materials link** from the Annual Reviews home page at **http://www.annualreviews.org**.)

Supplemental Material

or the de novo need to demonstrate safety. Second, repurposing can benefit from clinical study designs used for the initial approval. Third, patients benefit from participating in an accelerated evaluation of treatments that show therapeutic promise for the new indication.

Although this evolving landscape of drug development provides optimism for the therapy of autoimmune disease, there are potential barriers. For example, immune and inflammatory responses are homeostatic, with mechanisms that are usually more beneficial than detrimental. Therapies for autoimmune disease that induce immune suppression may also diminish host defenses against infectious and neoplastic diseases. In addition, biological agents are generally expensive drugs (with a mean annual cost per patient ranging from ~$10,000 to >$100,000); it is uncertain if third-party payers will agree to cover these costs. Progress in development and FDA approval of drugs for autoimmune diseases will likely require more specific markers of disease pathogenesis, outcomes, and endpoints of drug efficacy, along with new clinical and laboratory standards for the selection and monitoring of therapy.

Accessing Specialized Resources

The NIH and FDA have specialized resources to speed preventive, diagnostic, and therapeutic advances in rare autoimmune diseases by accelerating the steps in the pipeline of drug development, from the development of new chemical entities to the repurposing of approved drugs. Such resources include the following:

- NIH Office of Rare Diseases Research (NORDR): This organization (**http://rarediseases.info.nih.gov/**) aims to coordinate and support research on rare diseases, identify and respond to rare disease research opportunities, and provide information on rare diseases per the Rare Diseases Act of 2002 (Public Law 107-280).
- NIH Center for Translational Therapeutics (NCTT): In 2010, the NIH Chemical Genomics Center (NCGC) and NIH Center for Therapeutics for Rare and Neglected Diseases (CTRND) were united to form NCTT (**http://nctt.nih.gov/**), administered through the National Human Genome Research Institute. This program prioritizes the optimization of chemical structures of potential drug candidates to enhance efficacy and/or minimize toxicity, assessment of drug candidates in appropriate (FDA-required) safety and efficacy models, and evaluation of FDA-approved drugs in cells and animals in terms of therapeutic potential for rare or neglected diseases. This consortium of technology resources and expertise, created as part of the NIH Common Fund (formerly the NIH Roadmap for Medical Research), seeks to integrate industrial-scale technologies (e.g., high-throughput screening) and compound libraries to evaluate agents that may have therapeutic utility.
- Orphan Drug Act: Orphan diseases are rare diseases for which no effective therapy exists. The FDA defines a rare disease as one with a prevalence of <200,000 individuals. Per FDA guidelines, an orphan drug is a small molecule or biologic drug that is used to prevent, diagnose, or treat a rare disease in the U.S. or a drug that will not be profitable within seven years of FDA approval. The Orphan Drug Act (Public Law 97-414) seeks to advance the development of products for improved diagnosis, prevention, or treatment of rare diseases. Since its inception, the Orphan Drug Act has facilitated approval of >350 orphan drugs versus ~10 prior to its formation in 1983 (40). The heightened interest in orphan drug development offers industry sponsors possible financial incentives, including longer marketing exclusivity than other drugs receive; a tax credit for costs of clinical research; and a waiver of certain fees. The Prescription Drug User Fee Act of 1992 was also implemented to aid generation of funds for new drug development and approval.

- Rare Disease Repurposing Database: This database, established by the FDA Office of Orphan Products Development, facilitates evaluation of orphan drugs and/or repurposing of approved drugs in treating rare diseases.
- ITN: As noted above, the ITN was established by the NIH to link academia, agencies (e.g., NIH, FDA), and industry to accelerate development of immune tolerance therapies in autoimmune and other immunological diseases. The ITN facilitates coordinated investigation of mechanisms leading to loss and restoration of tolerance, integrating hypothesis-driven research with clinical trial design and implementation. The ITN also seeks to define new biomarkers and therapeutic strategies for immune tolerance in human disease (36).

Accelerating Identification of Pharmacologic Targets in Neuromyelitis Optica

Efforts described herein have facilitated new insights into loss of immune tolerance, effector cells, molecules, and pathways and have made strides in defining candidate biomarkers and clinical course in NMO (**Figure 5**). Through an integrative process, these advances have revealed potential targets for innovative therapeutic applications in NMO and other autoimmune diseases (**Figure 6**).

Prioritizing Candidate Agents for Repurposing in Neuromyelitis Optica Therapy

Improved strategies for effective treatment of NMO will rely on agents that target molecular and cellular determinants of the disease. Conceptual examples of novel candidates or candidates that may potentially be considered for repurposing in this regard are illustrated in **Table 1**.

The relationship between AQP4 and anti-AQP4, as well as the upstream triggers and downstream consequences of this interaction, illustrates potential opportunities for such strategies. In this sense, anti-AQP4 is a tool for reverse immunology—a chance to retrace the downstream molecular and cellular footprints of a disease as a way to discover its upstream causes. For example, anti-AQP4 is predominantly IgG subclass 1 (IgG_1), an Ig subclass that is usually dependent on T cell antigen recognition and activation of B cells for antibody production (41). Thus, autoreactive T cells are likely to be early contributors to NMO. Polymorphisms in the IL-7 receptor α chain (e.g., single-nucleotide polymorphism rs6897932) confer risk for MS, a disease closely related to NMO (42). Therapeutic agents that may modulate activation of this receptor on autoreactive T cells or dendritic cell antigen presentation to these cells may represent opportunities for therapy in NMO or other autoimmune diseases.

B cells that make NMO-IgG are subordinate to autoreactive T cells that have lost tolerance to AQP4 or related antigens (41, 43). The molecular signaling events that allow T and B cell interactions are emerging as potential targets in NMO (44, 45). Several such strategies are hypothesized: (*a*) blocking B cell antigen presentation and induction of autoreactive T cells [e.g., mechanistic target CD40/CD40L and corresponding therapeutic candidates lucatumumab and teneliximab, which are in preclinical development or clinical trials; mechanistic targets CD28/CD80 or CD86 and corresponding therapeutic candidate galiximab, which is in clinical trials (46)]; (*b*) preventing B cell activation or conversion of B cells to plasma cells [e.g., mechanistic target BAFF/BLyS and therapeutic candidates belimumab and related therapies (47)]; and (*c*) reducing overall B cell impact on disease and/or antibody production at the proplasma cell stage [target CD19 and therapeutic candidate blinatumomab, a bispecific T cell engager in clinical testing (48)], prememory cell stage [target CD20 and therapeutic candidates ofatumumab, rituximab, and radiolabeled tositumomab

(49–51)], or mature plasma or B memory cell stage [e.g., $CD22^+$, $CD78^+$, $CD138^+$, $CD45^-$ (52)]. The reported efficacy of rituximab in treating NMO is an example of repurposing an agent developed for other diseases (49): Originally developed to treat B cell lymphoma, rituximab has become an important therapeutic option for treating NMO on the basis of evidence that B cell–generated NMO-IgG is a pathogenic molecular participant in NMO.

Other strategies might be used as alternatives to inhibit autoreactive B cells, pathogenic antibodies, and related effectors of inflammation. For example, IL-4 and IL-13 are cytokines involved in Th2 polarization of naive T cells (42). Monoclonal antibodies targeting IL-4 [e.g., pascolizumab (53)] and IL-13 [e.g., anrukinzumab, lebrikizumab (54)] are in preclinical and clinical development. Similarly, because IL-5 can promote a Th2 paradigm (55), its inhibition is also a potential strategy for NMO or similar autoimmune diseases. The IL-5-targeting monoclonal antibody mepolizumab received Orphan Drug designation by the FDA for the treatment of hypereosinophilic syndrome, and a clinical trial of reslizumab (another such antibody) was recently completed for the treatment of this syndrome (56).

The binding of NMO-IgG to AQP4-expressing astrocytes is generally viewed as a critical molecular-cellular interaction that underlies NMO (32, 57). The realization that anti-AQP4 autoantibodies are largely categorized as IgG_1 provided opportunities for novel clinical uses of repurposed agents in NMO. In human beings, IgG_1 is particularly efficient in activating the classical complement pathway, leading to injury of the targeted tissues—in this case, astrocytes—and generation of inflammatory derivatives (e.g., C5a). Thus, intervention to block complement fixation was a logical therapeutic strategy in NMO. A trial is under way to treat NMO patients with a progressive or high relapse rate of disease using the anti-C5 drug eculizumab (58), originally developed to treat paroxysmal nocturnal hemoglobinuria [a disease in which complement fixation is injurious (59)].

Other research on NMO has included studies to assess T cell polarization (and the Th17 pathway), as it may be unique to NMO or have implications for multiple autoimmune diseases (44). Conceptually, the paradigm relates to antigen (e.g., AQP4) presentation by dendritic cells in the context of what may be a specific cytokine triad: TNF, IL-6, and TGF-β (60). The Th1 pathway (e.g., interferon-γ) as well as the Th2 pathway (e.g., IL-4) may modulate the role of Th17-polarized T cells. Various inhibitors of TNF are FDA-approved (e.g., adalimumab, certolizumab, etanercept, golimumab, infliximab), as are inhibitors of the IL-6 pathway [e.g., tocilizumab, which acts at the IL-6 receptor to inhibit its actions (61)]. Such agents could be evaluated in NMO. Other inhibitors of IL-6 (e.g., elsilimomab, siltuximab) are currently undergoing clinical development (62). There are potential untoward consequences of inhibiting cytokines such as TNF and IL-6, which are inextricably linked to critical host defenses (63–65). Latent infections that are kept in check by pathways involving TNF and IL-6 and could relapse include latent viral pathogens (e.g., cytomegalovirus, herpes), tuberculosis, and persistent fungal infections. Moreover, IL-6 may have beneficial effects on astrocyte homeostasis.

Achieving greater specificity in targeting the IL-17 pathway in autoimmune diseases will likely require inhibition of its more unique constituents. T cells that produce IL-17A or IL-17F stimulate production of IL-22, IL-23, and other proinflammatory cytokines (66, 67). In turn, these signals along with cognate chemokines (e.g., CXCL8) or complement fixation derivatives (e.g., C5a or CD88) can promote activation, chemotaxis, and targeted infiltration of granulocytes (e.g., neutrophils, eosinophils) to sites of antibody-mediated astrocyte injury—events consistent with the histopathology observed in human NMO tissue (68). Although still in clinical testing, inhibitors of the Th17 pathway are among the near-term opportunities for highly specific biological therapies for NMO. For example, one possibility is the blockade of crucial early events in Th17-polarized T cell activation, which is mediated by retinoic acid–related orphan receptor γτ (RORγτ) (60, 67).

Engagement of RORγτ activates signal transduction activator of transcription-3 (STAT3), driving Th17 polarization. Inhibitors of IL-22 [e.g., fezakinumab (ILV-094)] are in Phase I/II trials (see **http://clinicaltrials.gov/ct2/results?term=fezakinumab**). Furthermore, if Th17 pathways are important for NMO, it may be feasible to modulate autoreactive Th17 pathogenesis by intervening in IL-23-mediated signaling. IL-23p19 is of particular interest in this respect: It is unique to IL-23, and its inhibition spares key functions of IL-12, which shares the IL-23p40 subunit (69, 70). Potential opportunities also exist downstream of such targets for the modulation or prevention of NMO through interference in Th17 chemokine pathways or interference with inflammatory actions of granulocytes [e.g., elastase inhibition; sivelestat (71)]. For an interactive consideration of candidate targets and potential therapeutic agents, see the **Supplemental Visualizing NMO tool**.

Supplemental Material

Strategies that enhance antigen-specific modulation of autoimmune inflammation are additional approaches that are under consideration as therapies for NMO and other autoimmune diseases. Exogenous administration or endogenous upregulation of IL-10 and adoptive transfer of disease-modulating T regulatory cells are such approaches (72, 73). Other potential targets include cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) or related immune-modulating pathways of autoreactive T cell activation. It may also be feasible to develop agents that compete with pathogenic NMO-IgG antibodies (e.g., aquaporumab; 74), thus creating therapies that spare disease symptoms or progression. Repurposing of agents such as statins that can increase expression of CD59 on putative NMO target tissues and thereby protect against inadvertent complement fixation is another mechanism-directed approach of possible consideration for treatment of NMO.

Other potential targets in controlling NMO and/or other autoimmune diseases include macrophages; $CD8^+$ T cells; natural killer cells and pathways (e.g., IL-15); rogue γδ T cells; B1b cells; blood-brain barrier (neurovascular unit) integrity; and regeneration of astrocytes, neurons, and myelin. Multitargeted strategies may be necessary for long-term control of NMO or other autoimmune diseases.

Restoration of immune tolerance to AQP4 and perhaps other antigens involved in NMO may ultimately be essential to cure the disease. It may be possible to induce T cell tolerance, anti-idiotypic antibodies, or networks (75–77). However, until there are means to restore immune tolerance or intervene in upstream pathogenesis, inhibiting downstream effects is key to curtailing neurological damage and symptoms in NMO patients. This strategy affords time to identify and validate molecular and cellular therapeutic targets in NMO and, in so doing, perhaps advance knowledge and clinical management of other autoimmune diseases as well.

Measuring Progress

The ability to measure progress toward key milestones is important to any process that is designed to adapt and improve. Such findings can help assess progress and guide future steps. With respect to NMO, these indicators have included the following.

- Participating investigators: There are now >100 investigators in the GJCF network; their locations, primary disciplines, and areas of expertise are diverse.
- Peer-reviewed publications and citations: The number and frequency of citations of peer-reviewed publications provide measures of focused research and progress (a search for the term neuromyelitis optica on Thomson Reuters's Web of Knowledge in September 2011 yielded 1,366 results; see also **Supplemental Figure 1**).
- Clinical advances: The GJCF biorepository for NMO increased from 21 to 170 patient participants between 2008 and 2011, and a new clinical trial of NMO patients was initiated

(58). Several clinical studies are ongoing or in the planning stages for the evaluation of innovative therapies in NMO patients.

The most important—indeed, the only—measure by which success will ultimately be defined is the achievement of safe and effective treatments to arrest and perhaps reverse NMO and other autoimmune diseases. The advances noted above provide optimism that the integrative continuum model can accelerate progress toward these goals.

SYNTHESIS AND PROSPECTUS

Autoimmune diseases are generally persistent and incapacitating, and they can be life-threatening conditions that represent a growing public health threat. Collectively, they are as common as heart disease or cancer and are leading causes of death in women. Emerging insights into pathogenesis afford new opportunities for discovery and application of preventive or therapeutic strategies, including strategies using targeted biological agents. Drug development has been slow owing to barriers imposed by scientific, clinical, commercial, and regulatory uncertainties. These obstacles include the need for molecular, clinical, and therapeutic biomarkers; new etiologic insights; and ways to hasten efficacious therapeutic advances. Moreover, it is likely that therapeutic combinations may be required for optimal treatment of some or all autoimmune diseases.

The integrative continuum model seeks to accelerate advances by coordinating stakeholders and resources through cultivation and optimization of a network of real-time, idea-sharing partnerships. To date, its application has promoted progress in discovery, translation, and clinical momentum to meet the challenge of the rare autoimmune disease NMO. Ideally, such paradigms may accelerate similar advances in other autoimmune diseases.

The twenty-first century heralds an unprecedented convergence of opportunities with respect to therapy of autoimmune diseases. These include (*a*) advances in immunology that reveal molecular and cellular networks and thereby provide increasingly specific potential therapeutic targets; (*b*) the capacity of informatics to distill wisdom from large databases that hold genomic, proteomic, metabolomic, and clinical meaning; (*c*) innovations in technology that can help turn laboratory discoveries into safe and effective agents that target specific determinants of disease; (*d*) expertise in industry and regulatory agencies to effectively steward development and clinical approval of new medications; and (*e*) increased awareness of the prominent impact that autoimmune diseases have on patients, health care systems, and society. The recognition of these themes affords new opportunities to advance from an age of suboptimal diagnosis and nonspecific treatment to one in which specific and targeted approaches are used to prevent, diagnose, treat, and perhaps ultimately cure autoimmune diseases.

DISCLOSURE STATEMENT

The authors are administrators or advisors for the GJCF. K.V.H. and J.M.B. are cofounders of All Greater Good Foundation, which is a GJCF partner engaged in public health education. K.V.H. is president of Premier Health Care, Inc., a private clinical practice. J.M.B. serves in education management capacities for NASA's Jet Propulsion Laboratory and McREL (the Mid-continent Research for Education and Learning). T.J.S. serves as chief scientific advisor and medical advisor to the Graves' Disease Foundation. M.R.Y. is a founder and shareholder of NovaDigm Therapeutics, Inc., and ImmunoTx Inc., which target antibiotic-resistant infections. He is founder of Metacin, Inc., a multimedia and consulting service for research and education. The authors have no conflicts of interest with respect to this review, and they were not paid by any of the aforementioned entities to write it.

ACKNOWLEDGMENTS

We appreciate the helpful comments of Dr. Larry Steinman (Stanford University) and Dr. Daniel Rotrosen (NIH/National Institute of Allergy and Infectious Diseases). We also thank Julia Heying, Megan Kenneally, Derek Blackway, and Daniel Behne of the All Greater Good Foundation (San Diego) for their continuing efforts. Although it is impossible to recognize every researcher, institution, and publication in the scope of this article, we express appreciation for all who labor to help understand and cure NMO and other autoimmune diseases. Finally, the field of NMO and rare autoimmune diseases owes a debt of gratitude to Ms. Victoria Jackson and Mr. Bill Guthy, GJCF founders.

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RELATED RESOURCES

Accelerated Cure Project. **http://www.acceleratedcure.org**

American Autoimmune Related Diseases Association, Inc. **http://www.aarda.org**

Brent L, Cohen IR, Doherty PC, Feldmann M, Matzinger P, et al. 2006. Crystal ball gazing—the future of immunological research viewed from the cutting edge. *Clin. Exp. Immunol.* 147:1–10

Guthy-Jackson Charitable Foundation. *Pioneering a new scientific research model*. **http://www.guthyjacksonfoundation.org/videos/pioneering-a-new-scientific-research-model/**

National Organization for Rare Disorders. **http://www.rarediseases.org**

Transverse Myelitis Foundation. **http://www.myelitis.org**

NOTE ADDED IN PROOF

Emerging studies suggest that additional pathways may be potential targets for drug repurposing in NMO. Such agents include (*a*) inhibitors of lymphocyte trafficking into the central nervous system (e.g., fingolimod, a sphingosine-1-phosphate receptor inhibitor that is FDA-approved; and natalizumab, an α-4-integrin inhibitor that is FDA-approved); (*b*) inhibitors of specific B cell subsets (e.g., ocrelizumab, a humanized monoclonal antibody that targets $CD20^+$ B cells, in Phase II/III clinical trials; and epratuzumab, a monoclonal antibody that targets $CD22^+$ B cells, in Phase I/II clinical trials); and (*c*) inhibitors of autoreactive lymphocytes (e.g., alemtuzumab, a monoclonal antibody targeting $CD52^+$ lymphocytes, in Phase II/III clinical trials).

Annual Review of Pharmacology and Toxicology

Volume 52, 2012

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Errata

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