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Novel Targeted Therapies for Autoimmunity

E. William St.Clair, MD¹

¹Department of Medicine, Duke University Medical Center, Durham, NC.

Summary

The emergence of new targeted therapies is rapidly improving the treatment of autoimmune disease. These drugs have been variably designed to deplete specific T and B cell subsets, interrupt receptor-ligand interactions, and inhibit the activity of inflammatory mediators relevant to immune function. Abatacept, a costimulatory blocker, and rituximab, a B cell depleting antibody are among the approved therapies seeking new indications, while the newer therapies include Fc receptor-non-binding CD3-specific antibodies, IL-12/23 antibodies, an IL-6 receptor antagonist, a sphingosine-1-phosphate agonist, and small molecule inhibitors of intracellular protein kinases. Antigen-specific therapies are in their infancy, but the latest results administering glutamic acid dehydrogenase peptide to type 1 diabetics are promising. In the future, treatment strategies may increasingly explore the use of drug combinations acting at multiple sites of aberrant immunoregulation to achieve disease quiescence and immune tolerance.

Autoimmune diseases have attracted a rich pipeline of promising therapies targeting an array of cell surface molecules, soluble mediators, and intracellular proteins relevant to the function of immune cells. Monoclonal antibodies and soluble receptor fusion proteins continue to be the dominant tools of the trade because of their fine specificity and relatively few off target toxicities. However, small molecule inhibitors have enjoyed some recent successes in clinical trials and may soon revolutionize the therapeutic landscape because of their oral bioavailability and lower manufacturing costs.

This review will focus on emerging therapies for autoimmune disease currently undergoing evaluation in clinical trials. Varying in their mechanisms of action, these new drugs have been designed to regulate T and B cell function, alter lymphocyte migration, suppress the activity of inflammatory cytokines, inhibit intracellular kinases, and induce antigen-specific immune tolerance. The more successful of the newer therapeutics ameliorate a range of autoimmune conditions with remarkably varied clinical phenotypes, implying that some targets are hubs in a dysregulated immune system.

T cell agents

Drug candidates designed to alter T cell function can be generally divided into five categories: T cell receptor (TCR)-directed agents, co-stimulatory antagonists, antigen-specific strategies, cell depleting antibodies, and small molecule inhibitors of intracellular activation. The driving rationale behind the first three of these approaches is the two-signal hypothesis of CD4⁺ T cell

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Address correspondence and reprint requests to E. William St.Clair, M.D., Box 3874 DUMC, Durham, NC, 27710; stcla003@mc.duke.edu.

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activation: activation of a naïve CD4⁺ T cell requires both the stimulation of the T cell receptor (TCR) (signal 1) and co-stimulatory pathways (signal 2). Absence of the second signal results in T cell anergy. Two of the biologics approved for treating autoimmune disease, abatacept (CTLA4-Ig) and alefacept (LFA-3-IgG), selectively inhibit co-stimulatory pathways. Abatacept blocks the interaction between CD28 expressed on the surface of T cells and CD80/CD86 on the surface of antigen-presenting cells (APCs). Treatment with this agent has been shown in large clinical trials to reduce the signs and symptoms of rheumatoid arthritis as well as slow radiologic progression of joint damage (1,2). However, in a randomized, placebo-controlled phase II trial, abatacept failed to show treatment efficacy in patients with non-renal lupus on a background of oral corticosteroid therapy, making the point that co-stimulatory blockade is not a panacea for T cell-mediated autoimmunity in general. For several years, alefacept, the other approved costimulatory blocker, has been in clinical use as a treatment for psoriasis. It interferes with the activation of T cells by preventing the interaction between CD2 on T cells and LFA-3 on antigen-presenting cells (3). Given their potential to silence pathogenic T cells, abatacept and alefacept will continue to be of interest and likely find their way into combination regimens in the future.

For autoimmune diseases, clinical testing of alemtuzumab (anti-CD52 monoclonal antibody), a potent T cell depleter, began in the early 1990s when it was shown to be ineffective for the treatment of rheumatoid arthritis (RA). Alemtuzumab has been explored recently as a possible treatment for relapsing-remitting multiple sclerosis (RRMS). In a phase II trial involving 334 patients with early RRMS, alemtuzumab significantly decreased the rate of clinical relapse, reduced the risk of sustained accumulation of disability, and lessened the T2-weighted lesion burden on magnetic resonance imaging (MRI) compared with interferon beta-1a treatment (4). These apparent clinical benefits came at a cost, as homeostatic peripheral T cell expansion following lymphocyte depletion triggered autoimmunity, as described previously with other T cell depleting therapies (5). In this study, immune thrombocytopenic purpura occurred in 6 (2.8%) of the alemtuzumab-treating patients, causing death in one case. Also, approximately 20% of patients receiving alemtuzumab were diagnosed with autoimmune complications of the thyroid gland.

Fc receptor (FcR)-non-binding CD3-specific antibodies are minimally depleting and alter TCR signals in a way that may induce immune tolerance. In type 1 diabetes mellitus (DM), FcR-non-binding CD3-specific antibodies are postulated to induce remission by two principle mechanisms: 1) induction of T cell apoptosis and anergy by modulating the T cell receptor-CD3 complex; and 2) induction of adaptive regulatory T cells that secrete transforming growth factor- β (6). The early results from clinical trials of anti-CD3 antibodies have been promising. Otelixizumab (ChAglyCD3), a CD3-specific antibody, was found to maintain residual β -cell function better than placebo in a randomized, placebo-controlled clinical trial of 80 new-onset type 1 diabetics (7). Treatment with tepilizumab [hOKT3 γ 1 (Ala-Ala)] also preserves pancreatic β -cell function in type 1 diabetics in association with the activation of peripheral blood CD8⁺CD25⁺ regulatory T cells (8). Phase III pivotal trials are in progress to confirm these findings, and the results should be available soon. Visilizumab, another FcR non-binding CD3-specific antibody, showed encouraging results in a phase I study of ulcerative colitis (UC) (9). However, its further development was halted due to lack of demonstrable treatment efficacy for UC in a subsequent trial.

Other therapies targeting T cells may have therapeutic utility in autoimmune disease. Daclizumab, for example, targets the α -subunit of the IL-2 receptor (CD25), curbing the expansion of activated T cells. In an open-label trial involving 15 subjects with RRMS, daclizumab treatment was associated with a reduction in MRI brain activity (10) but a reduction in the frequency and suppressive activity of circulating CD4⁺CD25⁺FoxP3⁺ T regulatory cells (11). However, the relevance of these seemingly paradoxical observations is uncertain in light

of the absence of information about the status of T regulatory cells in the central nervous system. In contrast, rapamycin (sirolimus), an oral inhibitor of the mammalian target of rapamycin (mTOR) pathway, has been recently found in type 1 diabetics to enhance the suppressive capacity of CD4⁺CD25⁺FoxP3⁺ T regulatory cells, and may therefore be useful for restoring defective suppressive T regulatory cell function (12).

Antigen-specific modulation of the immune response has been effective in mouse models of autoimmune disease via several routes of administration, including oral, nasal, and parenteral. A proposed mechanism for peptide induced tolerance is the presentation of self-antigen to the TCR in the absence of inflammatory cues that would up-regulate co-stimulatory molecules on antigen-presenting cells. In clinical trials, several different protocols have been used for inducing peptide-specific immune tolerance: soluble peptide injection, DNA vaccination, orally or nasally applied peptides, peptide-coupled-cells, and altered peptide ligands (13). Glatiramer acetate, which is administered by the subcutaneous route, is an example of an altered peptide ligand that has been approved for the treatment of RRMS.

Many of the antigen-specific therapies in clinical trials for autoimmune disease have been summarized in an earlier review (13). Much of the current effort in this area has focused on type 1 DM and MS. Insulin and glutamic acid decarboxylase (GAD) are major self-antigens in type 1 DM, while myelin basic protein (MBP) is a dominant self-antigen in MS. Notably, the Diabetes Prevention Trial-Type 1 had previously shown that neither treatment with oral insulin nor insulin injections delayed the onset of type 1 diabetes in relatives at high risk for developing this disease (14,15). Recently, an injectable peptide displaying an epitope present in proinsulin but not insulin was evaluated in a phase I dose-ranging trial involving type 1 diabetics. Although the sample size was too small for any conclusions about clinical efficacy, the toxicity profile was acceptable and no evidence was found for induction of IgG anti-proinsulin antibodies or peptide-specific IFN- γ -secreting CD4⁺ T cells; however, 4 of 18 patients from the low dose group generated peptide-specific T cells secreting IL-10 (16). In another phase I/II randomized, dose-escalation trial involving patients with type 1 diabetes, weekly intramuscular administration of a DNA plasmid-encoding a full-length human proinsulin (BHT-3021, Bayhill Therapeutics) was shown to preserve β -cell function (as measured by C-peptide levels) and improve glycemic control for up to 12 months, while β -cell function in the placebo group declined as expected with no substantial change glycemic control (17). GAD-alum is the most advanced vaccine in clinical development for type 1 diabetes. Two subcutaneous injections of a GAD-alum vaccine have been shown in a randomized, placebo-controlled trial of 70 type 1 diabetics of recent onset to slow the rate of decline in fasting C-peptide levels (18). The GAD-alum group also showed changes in the immune function of peripheral blood cells, including increases in GAD-induced IL-5, IL-10, IL-13, and IL-17 as well as expression of FOXP3 and TGF- β .

Myelin basic protein (MBP) contains an immunodominant T cell epitope in the context of HLA-DR2, which is a genetic risk factor for MS susceptibility. This domain also contains the immunodominant B cell epitope, which is defined by residues 85–96 in MBP, and is included in MBP8298 (dirucotide), a peptide of therapeutic interest. In a recent phase II, placebo-controlled trial, intravenous dirucotide in doses designed to induce “high zone” tolerance was administered to 32 genetically-unrestricted patients with MS (19). No difference in clinical outcomes was apparent between the active and placebo treatment groups. However, a significant reduction in cerebrospinal fluid anti-MBP antibody levels was observed in all but 3 of the MBP8298-treated patients; these 3 patients produced anti-MBP antibodies that bound to an epitope outside the domain of the MBP8298 peptide. The results of MAESTRO-01 and -03, two pivotal phase III trials of MBP8298 treatment for secondary progressive MS, have not yet been published; however, preliminary results from MAESTRO-01 indicate that dirucotide treatment did not meet its primary endpoint of delaying disease progression.

BHT-3009, a tolerizing DNA vaccine encoding full-length human MBP, has also been studied in patients with secondary progressive MS. A recent phase I/II randomized, double-blind, placebo-controlled trial of BHT-3009 vaccination in 30 patients with RRMS or secondary progressive MS found that active treatment decreased the proliferation of circulating IFN- γ -producing, MBP-reactive CD4⁺ T cells and reduced the titers of CSF myelin-specific antibodies (20).

B cell-directed therapies

The success of rituximab, a chimeric anti-CD20 monoclonal antibody, for the treatment of RA has served as a proof-of-principle that targeting B cells can improve clinical outcomes of autoimmune disease. CD20 B cell depletion may ameliorate autoimmune disease by a variety of mechanisms (see Box). In the mouse, CD20 B cell depletion has been shown to predominately interfere with CD4⁺ T cell activation (21). CD20-specific antibodies deplete a subset of regulatory B cells that secrete IL-10, which has been shown to exacerbate the induction of experimental allergic encephalomyelitis, an animal model of MS (22). It is hypothesized that autoantibodies, such as rheumatoid factor, anti-desmoglein-1 and -3 (associated with pemphigus vulgaris), and anti-proteinase 3 (associated with Wegner's granulomatosis), whose serum levels fall after CD20 B cell depletion therapy, are the product of short-lived plasmablasts that depend on an influx of memory CD20⁺B cells. Conversely, autoantibodies whose serum levels are maintained following rituximab therapy may derive from long-lived plasma cells.

B cells had not received much attention as potential therapeutic targets in MS until recently, but several lines of evidence nevertheless implicate them in the pathogenesis of this disease (23). A single course of rituximab has been shown in a randomized, controlled trial of 104 patients with RRMS to significantly reduce the total number of gadolinium-enhancing brain lesions, an MRI-based index of disease activity (24). Open-label studies of patients receiving two courses of rituximab 6 months apart substantiate these results (25). Treatment with rituximab has also been found to be effective in a prospective trial of steroid-refractory patients with pemphigus vulgaris (26). In a phase II trial of 87 patients with type 1 diabetes, depletion of CD20⁺ B cells using rituximab led to a significantly higher C-peptide area under the curve at one year compared to placebo (27). These results imply that B cells play a role in the mechanisms of β -cell destruction. Despite initial encouraging data from small studies, rituximab has failed in two phase II/III trials to show a treatment benefit for non-renal lupus and lupus nephritis. The results of multicenter, randomized, controlled clinical trials of rituximab therapy for ANCA-associated vasculitis and inflammatory myositis are expected soon. Across all of the rituximab trials, it appears that repeated courses of rituximab therapy do not significantly increase the risk of infection. However, progressive multifocal leukoencephalopathy (PML) has occurred in patients receiving rituximab therapy, although the absolute risk of this complication is likely to be very low in the absence of concomitant immunosuppression (28).

Human anti-CD20 monoclonal antibodies, ocrelizumab and ofatumumab, are currently in development for the treatment of RA. Another CD20-related technology, small modular immunopharmaceuticals (SMIPs), utilizes single-chain polypeptides customized with specific effector functions. Among the first SMIPs in the pipeline, TRU-015 has been designed with potent antibody-dependent cellular cytotoxicity but limited complement-dependent cytotoxicity. Preliminary reports suggest TRU-015 effectively depletes CD20 B cells with an acceptable safety and tolerability profile (29).

Epratuzumab, which targets CD22 on the surface of B cells, has been studied mainly in SLE (30) and primary Sjögren's syndrome (31). More information about its clinical efficacy and

safety in SLE awaits the results of a large, multi-center phase II clinical trial. Abetimus sodium, a B cell-tolerogen, is composed of 4 identical strands of dsDNA, each containing 20 base pairs of unmodified native nucleotides covalently linked to a small molecule platform (32). It was designed to tolerize anti-dsDNA antibody-producing B cells in SLE. However, a phase III study of abetimus sodium for the treatment of SLE was recently stopped early for futility.

Other B-cell-directed agents have been developed that target the BAFF (B cell-activating factor belonging to the tumor necrosis factor family)/APRIL (a proliferation-inducing ligand) axis (33). Belimumab is a human monoclonal antibody to BAFF (also known as BLyS) currently in late stage clinical development for the treatment of SLE. In a phase I, dose-ranging study, a single dose of belimumab was well-tolerated and produced significant reductions in the percentages of circulating CD20⁺ B cells (34). The phase III development program for belimumab includes two, double-blind, placebo-controlled trials – BLISS-52 and BLISS-76 – in patients with serologically active lupus. It was recently announced that belimumab met its primary endpoint in BLISS-52. In a press release (35), treatment with belimumab plus standard of care was reported to produce a response rate of 57.6% and 51.7% for the 10 mg/kg and 1 mg/kg belimumab groups, respectively, compared with a rate of 43.6% for placebo plus standard of care. TACI (transmembrane activator and calcium modulator and cyclophilin ligand interactor) is a receptor that binds both BAFF and APRIL. Atacicept, which consists of TACI in covalent linkage with the Fc portion of IgG1, has been shown in phase I studies involving patients with RA and SLE to transiently reduce circulating B cells up to 60% and serum IgG levels by 15–20% (36,37). In an RA study, atacicept treatment was also associated with reductions in serum levels of rheumatoid factor and anti-citrullinated protein antibodies (37). Larger clinical trials of atacicept are in progress that will provide further information about its clinical efficacy and safety.

Inhibitors of leukocyte migration

The potential intervention points for inhibitors of leukocyte migration include selectin-mediated rolling, chemoattractant signaling, integrin-mediated firm adhesion, migration across a chemotactic gradient, and tissue retention (38). Thus far, the most successful drug in this class has been natalizumab, a monoclonal antibody to α_4 integrin that was developed for the treatment of RRMS (39) and Crohn's disease (40). However, clinical trials and marketing of natalizumab were suspended in 2005 after PML was diagnosed in 3 trial participants (39). Natalizumab was reintroduced in 2006 with an updated product label warning about PML. Six cases of PML have been discovered following reintroduction of natalizumab (3 of these cases are described in reference 41); all of these additional cases have been associated with a duration of natalizumab therapy of 12 months or longer. Efalizumab, a monoclonal antibody to LFA-1 (CD11a-CD18), was approved in 2003 for the treatment of psoriasis. Since LFA-1 mediates leukocyte binding to endothelium and subsequent migration into tissue, treatment with efalizumab would be expected to block this pathway and reduce the accumulation of inflammatory cells at disease-affected sites. However, efalizumab was recently withdrawn from the market because of 3 reported cases of PML. Although increased risk of PML is not restricted to these two drugs, the experience to date raises the possibility that the anti-migratory actions of integrin inhibitors may decrease immune surveillance for the JC virus at sites of latent infection and underlie the emergence of PML.

Beyond the integrin inhibitors are the drugs that antagonize chemokines and chemokine receptors, and block lymphocyte egress. Innate and adaptive immune cells express a range of chemokine receptors on their cell surface that play fundamental roles in their migration into tissues, local activation, and efflux from tissues. Chemokine receptors transduce their signals through a G-coupled protein receptor amenable to blockade by oral compounds. Progress in this field has been slow; however, many drugs remain in the pipeline (38). Fingolimod

(FTY-720) holds promise as a new treatment for MS by promoting retention of lymphocytes in the lymph nodes and consequent migration into blood and sites of inflammation. When phosphorylated *in vivo*, fingolimod mimics sphingosine-1-phosphate (S1P) and acts as an agonist for the S1P family of receptors on lymphocytes. Oral therapy with fingolimod has been shown in a randomized, placebo-controlled phase II trial to be effective for the treatment of RRMS, with evidence of sustained benefits up to 2 years (42,43). Second generation S1P receptor agonists with potentially fewer side effects are currently in development.

Antagonists of cytokines and cytokine receptors

In this category of protein therapeutics, monoclonal antibodies targeting the IL-6 receptor (IL-6R) and IL-12/23 p40 rank as the most exciting of the new developments. Tocilizumab, a humanized IL-6R antibody, was approved in Japan in 2008 for the treatment of Castleman's disease, and is currently being reviewed by the U.S. Food and Drug Administration for the treatment of RA. Tocilizumab binds to both membrane-bound and soluble IL-6Rs (see Figure 1), interfering with IL-6 signaling (44). Several lines of evidence implicate overproduction of IL-6 in the pathogenesis of RA and juvenile idiopathic arthritis, as well as chronic inflammation in general (45). In clinical trials, tocilizumab infusions have been shown to significantly reduce the signs and symptoms of RA and delay radiographic progression of disease (46,47). Tocilizumab has also been shown to be effective for the treatment of systemic-onset juvenile idiopathic arthritis (48). The most common adverse effects from tocilizumab therapy have included infections, liver enzyme abnormalities, neutropenia, hyperlipidemia, and intestinal perforations.

The discovery of IL-23 and Th17 cells has revolutionized our views about the pathophysiology of chronic inflammatory disease (49). The sharing of subunits between IL-12 and IL-23 initially created some confusion about the roles of these cytokines in inflammation, but the subsequent elucidation of the structure of these cytokines and their receptors has shifted the paradigm for the differentiation of T effector cells to include not only the Th1 and Th2 cells, but also Th17 cells (Figure 2). IL-12 consists of a p35 and p40 subunit, while IL-23 contains the same p40 subunit but a unique p19 subunit. In randomized, placebo-controlled trials, ustekinumab, a human IL-12/23 (p40) monoclonal antibody, has been shown to significantly improve psoriasis, with approximately 60% of the patients having at least a 75% reduction from baseline in their psoriasis and severity index (50–52). These responses rival those observed with the tumor necrosis factor α antagonists. In phase II trials, ustekinumab has also been found to benefit patients with psoriatic arthritis (53) and Crohn's disease (54). Another IL-12/23 monoclonal antibody (ABT-874) is earlier in development and has also been shown to be effective for the treatment of psoriasis (55). Moreover, antibodies to IL-17A and the IL-17 receptor are undergoing clinical testing for the treatment of RA and psoriasis. The growing evidence for the pathogenic role of IL-17 in RA, psoriasis, Crohn's disease, and MS (49) suggest this cytokine and its receptor might be effectively exploited for therapeutic gain. IL-22 has been shown to be preferentially produced by IL-23-stimulated Th17 cells, and mediates the acanthosis (thickening of the skin) and dermal inflammation characteristic of psoriasis (56,57). Therefore IL-22 neutralization may be another way to inhibit the Th17-mediated pathway in this disease.

Kinase inhibitors

The p38 mitogen-activated protein kinases (MAPKs), Janus kinases (JAKs), spleen tyrosine kinase (Syk), and protein tyrosine kinases such as ABL play critical roles in the activation of lymphocytes, macrophages, neutrophils, and mast cells. p38 MAPK had been at the center of attention for more than a decade because it lies downstream of a signaling hub through which diverse extracellular stimuli regulate the generation of TNF- α and IL-1 β . Thus far, many

attempts to develop a small molecule inhibitor of p38MAPK have failed due to drug-related toxicities or limited clinical efficacy. For example, pamapimod, a p38 α MAPK inhibitor, was recently shown in a randomized, controlled trial to be less effective for the treatment of RA than methotrexate (58).

In contrast, the oral JAK3 inhibitor, CP-690,550, has demonstrated clinical efficacy in a randomized, placebo-controlled phase II trial involving 264 patients with active RA (59). JAK3 exclusively associates with the IL-2 receptor γ -chain (γ_c), which is a component of the receptors for IL-4, IL-7, IL-9, IL-15, and IL-21. Adverse events have included an increased risk of infection and neutropenia. Further studies will be needed to confirm these findings and expand the safety database. An oral Syk kinase inhibitor (R788, fostamatinib disodium) has reached a similar stage of development. It had been shown in a 12-week randomized, placebo-controlled trial of 189 patients with active RA despite methotrexate therapy to produce significant improvement in clinical disease activity (60). The predominant side effects of fostamatinib in this study were dose-related instances of diarrhea and neutropenia. Syk, a cytoplasmic tyrosine kinase, mediates immunoreceptor signaling in mast cells, macrophages, neutrophils, and B cells, and has been shown in RA to be a key regulator of TNF α and matrix metalloproteinase production by synovial fibroblasts. However, in a phase IIb clinical trial in RA, the group treated with fostamatinib did not show significantly higher response rates than the placebo group at 3 months (61). In contrast to the earlier study, the study population in this phase IIb trial consisted of biologic failures (e.g. refractory to treatment with at least one TNF inhibitor), which historically responds less favorably to therapeutic intervention than a group of inadequate responders to methotrexate.

It may have been surprising to learn that imatinib mesylate, a BCR-ABL tyrosine kinase inhibitor, could inhibit collagen-induced arthritis (62) and autoimmune diabetes in NOD mice (63). These discoveries have sparked an upsurge of interest in compounds that target the BCR-ABL kinase, as well as other tyrosine kinases (64). Imatinib mesylate also specifically and potently inhibits c-Fms, c-Kit, and the platelet derived growth factor receptor. Clinical trials are underway evaluating imatinib mesylate for the treatment of systemic sclerosis, while others testing this drug in RA and type 1 diabetes are in the planning stage.

Future strategies and approaches

A robust pipeline of new agents is gradually changing the face of treatment for autoimmune disease. The challenge is not the identification of new targets, but predicting their therapeutic success. Not a day goes by without the publication of a new target with a newly discovered function. The choice of therapeutic targets to move forward into the clinic has been based to date on results from animal studies and correlative human research. It is unfortunate but true that experiments of new interventions in animal models have poorly predicted success in humans despite similarity of clinical phenotypes. Thus, progress has often been slow and incremental until the results of a clinical trial validate a target as crucial to human disease pathogenesis (e.g. TNF for RA, psoriasis, Crohn's disease, and ankylosing spondylitis). Presently, the lack of a systematic approach to evaluate the translational potential of nascent therapeutic targets represents a significant barrier to drug development. Several factors may contribute in the future to "translational success", including the selection of the appropriate biomarkers to predict and assess drug efficacy and toxicity and the identification of disease subsets to be considered in evaluating treatment response (65). However, a breakthrough in the efficiency of target validation may ultimately require a deeper knowledge of the pathogenic mechanisms of disease.

Innovative strategies for advancing the treatment of autoimmune disease may come from the successful application of multi-component therapies. For example, combining agents such as

an anti-CD3 monoclonal antibody with a proinsulin vaccine may restore immune tolerance in type 1 diabetes more effectively than either approach alone by inactivating autoreactive T cells at the same time as stimulating potent suppressor mechanisms, such as T regulatory cells. These two agents may function synergistically due to their complementary modes of action. Adjunctive anti-inflammatory therapy could further reduce the activation of effector T cells by decreasing co-stimulatory signals, tipping the balance further towards a quiescent state. Other synergistic combinations may target the same pathway or related pathways, and yield particularly efficacious therapies.

Simultaneous targeting of inflammatory and repair pathways, such as using anti-CD3 in combination with a glucagon-like peptide that stimulates β -cell proliferation, may return inflamed and damaged tissue to a normally functioning state more fully than single faceted approaches. Also novel targets, such as the immunoproteasome, may emerge that uniquely offer superior clinical possibilities because they lie at the intersection of multiple immune pathways. Recently, it was shown that a selective inhibitor of LMP7, an immunoproteasome subunit, reversed signs of disease in collagen-induced arthritis (66). Inhibition of LMP7 not only blocked class I major histocompatibility complex antigen presentation, but also inhibited production of IL-23 by monocytes and interferon- γ and IL-2 by T cells. Finally, novel agents such as bifunctional antibodies may provide opportunities to target multiple cytokines or signaling pathways at once, creating unique synergies. Gaining a foothold on autoimmune disease from a single intervention modulating a specific molecule or biological process is proving to be a daunting challenge in the face of a complex dysregulated immune system. Restoring balance to these robust yet dysfunctional systems which in autoimmunity consist of multiple dysregulated cell types on varied genetic backgrounds will likely require higher complexity strategies (67,68).

The potential mechanisms of B cell-directed therapies for autoimmune disease

Rituximab, a B cell depleting antibody, rapidly eliminates CD20+ B cells, with initial return in 4–6 months. By depleting CD20+B cells, rituximab may inhibit the production of auto-antibodies, which form immune complexes that stimulate an inflammatory response. Since B cells effectively display antigen and provide co-stimulation, CD20+ B cell depletion may also reduce T cell activation. B cells release cytokines that both stimulate and inhibit inflammation. The formation of organized lymphoid structures also depends on B cells and their products. Therapies targeting the BAFF/APRIL axis may alter B cell survival and promote self-tolerance.

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A **B**

Figure 1. Tocilizumab produces global blockade of IL-6 receptor signaling (41,42)

IL-6 acts via receptor complexes containing at least one subunit of gp130. A) Binding to the membrane-bound IL-6R. IL-6 first binds to the IL-6R on target cells, which in turn, associates with gp130, leading to dimerization of gp130 and subsequent intracellular signaling. The membrane bound IL-6R has restricted expression on hepatocytes, neutrophils, monocytes, macrophages, and a subset of T cells. B) Trans-signaling through the soluble IL-6 receptor (sIL-6R). sIL-6R derives from proteolysis of the transmembrane IL-6R or alternatively spliced transcripts. Many cells expressing only the gp130 complex are responsive to sIL-6R in the presence of IL-6. They include early hematopoietic progenitor cells, T cells, neural cells, smooth muscle cells, mesothelial cells, and endothelial cells (adapted from reference 69).

Figure 2. Blockade of IL-12 and IL-23 pathways

The differential production of IL-12 and IL-23 by dendritic cells determines the polarization of TH1 and TH17 cell differentiation. Increasing evidence from animal models and results of clinical trials indicate a key role for IL-23 and TH17 cells in autoimmune-driven inflammation. The IL-12p40 antibodies under clinical development block both the IL-12 and IL-23 driven pathways. Awaited with interest is the more focused therapeutic targeting of the IL-23/TH17 axis.