

B cells as promising drug targets for autoimmune diseases

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Autoimmune diseases arise from a failure of immune tolerance, resulting in sustained responses against self-antigens. These disorders include systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), ANCA-associated vasculitis (AAV), systemic sclerosis (SSc), idiopathic inflammatory myopathies (IIM), multiple sclerosis (MS) and many others. Although they differ in tissue distribution and clinical presentation, they share chronic immune activation that progressively damages host tissues. Collectively, autoimmune diseases affect an estimated 5–10% of the general population and impose a considerable health-care burden. Many begin in early or middle adulthood, require long-term treatment, reduce quality of life and impose substantial costs through chronic pain, disability, organ damage, repeated monitoring and prolonged immunosuppression. Current therapies, including corticosteroids, conventional disease-modifying antirheumatic drugs, cytokine-targeting biologics and kinase inhibitors, have greatly improved disease control, yet many patients relapse, respond inadequately or develop cumulative toxicity. Thus, a major goal in autoimmune drug discovery is shifting from chronic suppression of inflammation toward immune resetting, whereby profound depletion of pathogenic immune cells is followed by reconstitution of a potentially less autoreactive immune repertoire, with the aim of achieving durable drug-free remission and, ultimately, disease prevention.

Among immune cells, B cells have emerged as particularly attractive therapeutic targets. Once viewed primarily as precursors of antibody-secreting plasma cells, B cells are now recognized to promote autoimmunity through several non-mutually exclusive mechanisms, including pathogenic autoantibody production, autoantigen presentation to T cells, inflammatory cytokine secretion and organization of pathogenic immune niches in blood and affected tissues. Autoantibodies are clinically useful biomarkers but can also mediate immune-complex formation, complement activation, tissue inflammation and organ damage. In many autoimmune conditions, autoreactive B cells escape central and peripheral tolerance checkpoints, persist in circulation or tissues and interact with T cells and innate immune cells to amplify disease. Rituximab and other anti-CD20 antibodies provided important proof that B cells are therapeutically targetable. However, CD20-targeted depletion does not eliminate all disease-relevant B-lineage populations, particularly CD20-negative plasmablasts, long-lived plasma cells and incompletely depleted tissue-resident B cells. Repeated dosing is often required, and durable drug-free immune reset is uncommon. These limitations have motivated B-cell-targeted therapies designed to achieve deeper, broader or more precisely timed depletion of pathogenic B-cell compartments.

Recent breakthroughs in cellular therapy have accelerated this field. CD19 is expressed across a broad range of B-lineage cells, including populations inefficiently targeted by CD20-targeted antibodies, making it an appealing target for deep B-cell depletion. Autologous CD19 chimeric antigen receptor T (CAR-T)-cell therapy has shown encouraging activity in treatment-refractory autoimmune diseases. In the phase 1/2 CASTLE basket trial, a single infusion of zorpocabtagene autoleucel (Zorpo-cel; MB-CART19.1) was tested in patients with severe SLE, SSc and IIM. Zorpo-cel is an autologous T-cell product engineered to express a CD19-specific CAR, enabling patient-derived T cells to recognize and eliminate CD19-expressing B cells after lymphodepleting conditioning. The trial reported a favorable early safety profile, with no cytokine release syndrome above grade 2 and no immune effector cell-associated neurotoxicity syndrome. Clinical responses were observed in most patients at 24 weeks, and all treated patients remained free of glucocorticoids and other immunosuppressive therapies during follow-up, extending to

several years in some patients.¹ These findings show that deep B-cell depletion can achieve more than transient disease control by inducing immune reconstitution compatible with drug-free remission. Importantly, B-cell repopulation alone should not be equated with immune resetting. In the CASTLE trial, reconstituted B cells were predominantly naive (>90%), with virtual loss of memory B-cell and plasmablast compartments, supporting qualitative remodeling of the B-cell compartment; however, the extent to which clonal diversity and central and peripheral B-cell tolerance checkpoints are restored remains to be fully defined. Long-term follow-up is needed to assess the durability of drug-free remission, and these therapies should be compared with conventional treatments in randomized controlled clinical trials.

Two important pathophysiologic lessons can be learned from the success of CD19-specific CAR-T-cell therapies. First, clinical remission despite persistence of CD19-negative plasma cells suggests that these cells may not be essential for maintaining disease activity, at least in some patients with the autoimmune diseases studied to date, including SLE, SSc and IIM.^{1,2} However, this does not exclude a pathogenic contribution of plasma cells in specific diseases or patient subsets, as supported by clinical responses to plasma-cell-targeted therapies.³ Second, the profound B-cell depletion and clinical responses achieved with CD19 CAR-T-cell therapy raise the possibility that broader targeting of pathogenic B-cell populations, including those residing in affected tissues, may contribute to therapeutic efficacy. These findings highlight tissue-resident B cells as a potentially important therapeutic target in autoimmune disease.

Several related strategies are broadening the therapeutic landscape. Off-the-shelf allogeneic CD19 CAR-T cells could reduce manufacturing time, cost and logistical barriers associated with patient-specific products. In a recent study, genome-edited healthy donor-derived CD19 CAR-T cells induced deep B-cell depletion and clinical improvement in patients with refractory immune-mediated necrotizing myopathy and diffuse cutaneous SSc.² Although based on a small number of patients, these data suggest that scalable cellular therapy platforms could expand access to immune-resetting treatments for severe autoimmune disease.

B-cell-targeted bispecific T-cell engagers offer another promising approach. These agents redirect endogenous T cells to eliminate target B-lineage cells by simultaneously binding CD19 on B-lineage cells and CD3 on T cells, avoiding ex vivo cell manufacturing. CD19×CD3 T-cell engagers, such as blinatumomab, target CD19-expressing B cells, whereas BCMA×CD3 T-cell engagers, such as teclistamab, target BCMA-expressing cells, which is predominantly found in plasma cells and plasmablast-enriched compartments. This distinction is important because CD19-negative long-lived plasma cells persist after CD19-targeted therapies and, although not essential for maintaining disease activity in all patients, can contribute to pathogenic autoantibody production in specific diseases or patient subsets. In patients with treatment-refractory antisynthetase syndrome and SSc, blinatumomab and teclistamab reduced B-lineage cells in affected tissues, decreased autoantibody titers and were associated with clinical improvement.³ These findings suggest that the contribution of different B-lineage compartments, including plasma cells, varies by disease context and patient biology. However, these therapies also raise safety concerns, including cytokine release syndrome, infections, hypogammaglobulinemia and potential loss of protective humoral immunity. Together, these studies suggest that the B-cell compartment is not a single therapeutic target, but a developmental continuum that can be targeted at distinct stages according to disease

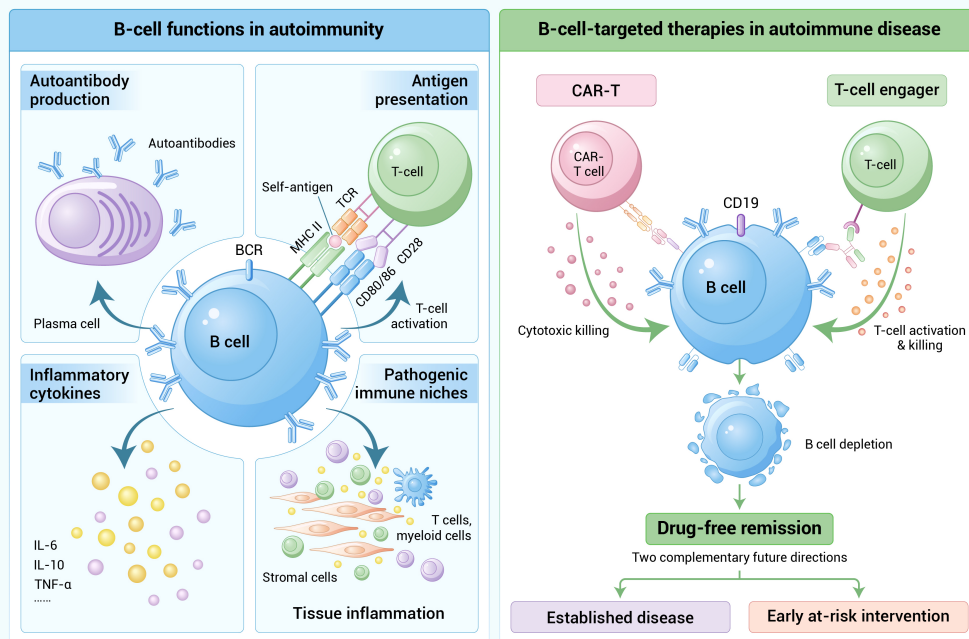


Figure 1. Pathogenic B-cell functions and B-cell-targeted therapeutic strategies in autoimmune disease In autoimmune diseases, pathogenic B cells promote disease through autoantibody production, antigen presentation, inflammatory cytokine secretion, and the formation of pathogenic immune niches. B-cell-targeted therapies, including CAR-T cells and T-cell engagers, can achieve deep B-cell depletion and drug-free remission. Future strategies may pursue two complementary directions: deep immune resetting in established autoimmune disease and selective targeting of pathogenic B-cell states in at-risk individuals.

immune disease, deep depletion strategies such as CD19 CAR-T cells, T-cell engagers and BCMA-targeted plasma-cell therapies may provide a path toward durable remission. In preclinical or early disease, the goal should be safer, selective interception of pathogenic B-cell states before irreversible tissue damage occurs. This will require biomarkers that identify individuals most likely to progress, targets that distinguish pathogenic B cells from protective humoral immunity and dosing

mechanism, dominant pathogenic cell state and desired depth of immune depletion. Importantly, emerging evidence suggests that B-cell targeting may extend beyond established autoimmune disease to earlier disease interception, before irreversible tissue damage occurs.

This possibility raises an important conceptual question for drug discovery. Although intensive B-cell-targeted therapies are currently being developed primarily for severe refractory autoimmune diseases, could B-cell-targeted intervention be moved earlier in the disease trajectory to intercept autoimmunity before clinical disease develops? Rheumatoid arthritis provides a useful model for exploring this possibility. Anti-citrullinated protein antibodies can be detected years before clinically apparent inflammatory arthritis, defining an at-risk phase in which preventive intervention might be possible. Recent longitudinal multi-omics analysis of at-risk individuals demonstrated systemic inflammation and activation signatures in naive T and B cells before clinical RA. Progression to clinical disease was associated with coordinated T- and B-cell dysregulation rather than simply higher circulating autoantibody titers.⁴ These findings support the concept that autoimmune pathogenesis begins before formal clinical diagnosis and that preclinical immune states may provide biomarkers and therapeutic targets for selective disease interception.

Our recent findings further highlight this opportunity by identifying a pathogenic B-cell state before clinical RA onset. Longitudinal single-cell multi-omics of B cells from autoantibody-positive individuals who subsequently developed RA identified an expansion of activated naive B cells before clinical arthritis. These cells exhibited a pro-inflammatory and senescence-like transcriptional program, expressed polyreactive and autoreactive IgM B-cell receptors, infiltrated RA synovium and functioned as potent antigen-presenting cells capable of activating anti-citrullinated antigen CD4⁺ and CD8⁺ T cells. Mechanistically, chronic exposure to citrullinated antigens and CpG synergistically promoted naive B-cell activation and senescence.⁵ These findings suggest that pathogenic B-cell activation is not merely a consequence of established autoimmune inflammation, but may contribute to the transition from at-risk autoimmunity to clinically apparent disease.

The next phase of B-cell-targeted drug discovery should therefore move in two complementary directions (Figure 1). For severe established autoim-

strategies that avoid unnecessary long-term immunodeficiency. If these challenges can be addressed, the B-cell compartment may become not only a therapeutic target for autoimmune disease treatment but also a platform for prevention.

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AUTHOR CONTRIBUTIONS

X.W. and L.S.v.D. conceived, drafted, and revised the manuscript. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.