Journal of High School Science

Application of CD19-CAR T cell therapy in autoimmune diseases

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Submitted: August 22, 2025, Revised: version 1, October 20, 2025
Accepted: October 20, 2025

Abstract
Autoimmune diseases represent a broad group of chronic conditions characterized by loss of immune tolerance, autoreactive lymphocyte activation, and pathogenic autoantibody production. CD19-directed chimeric antigen receptor (CAR) T-cell therapy, originally developed for hematologic malignancies, has emerged as a promising strategy to directly eliminate autoreactive B cells and reprogram immune function. CD19-CAR T infusion can induce rapid remission, reduce autoantibody levels, and sustain drug-free disease control. Despite these encouraging results, current evidence is limited to small patient cohorts with short follow-up, leaving uncertainties regarding long-term safety, durability of remission, and the stability of immune reconstitution. Most studies implicitly assume that quantitative B-cell recovery equates to restored immune health, yet the *functional resilience* of the post-CAR-T immune system—its ability to protect against infection, respond to vaccines, and maintain durable tolerance—remains unexplored. To address this gap, we propose an integrated framework for evaluating the functional competence of immune reconstitution following CAR T-cell therapy and for designing next-generation targeting strategies. Functional recovery should be assessed not only by quantitative B-cell repopulation but also by vaccine responsiveness, infection surveillance, and immune repertoire diversity. Vaccine challenge studies and infection monitoring can reveal whether protective immunity is restored, while sequencing-based profiling of B- and T-cell repertoires can clarify whether regulatory balance and clonal diversity are re-established. In parallel, translational innovations such as dual-target CAR constructs (e.g., CD19 + BAFF-R) and chimeric autoantibody receptor (CAAR) T cells offer complementary solutions to broaden target coverage and improve selectivity. Moreover, Epstein–Barr virus (EBV)–mediated immortalization of patient-derived autoreactive B cells provides a feasible *ex vivo* platform for generating physiologically relevant antigenic stimuli during CAR engineering. This approach could yield T cells that are functionally "educated" to eliminate pathogenic clones while preserving protective immunity, thereby addressing the central challenge of rebuilding a resilient and tolerant immune system.

Keywords
Autoantibody, Autoimmunity, Autoimmune diseases, B cell, CAR T cell therapy, CD19, CLL, Immune reset, Lymphoma, Reprogramming immune function

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https://doi.org/10.64336/001c.146292

1. Introduction

Autoimmune diseases represent a diverse and heterogeneous group of chronic disorders in which the immune system mounts an aberrant response against self-antigens (1). These conditions—including systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, and inflammatory bowel disease—affect a substantial proportion of the global population, with prevalence estimates exceeding 10% (2). Incidence is disproportionately higher among women, the elderly, and socioeconomically vulnerable groups (2). Certain autoimmune diseases such as Graves' disease, Sjögren's syndrome, and coeliac disease have shown more than a twofold increase in incidence over the past two decades, underscoring their emergence as a major public health concern in the UK, based on 19 autoimmune diseases (2). A large-scale epidemiologic analysis conducted between 2000 and 2019, which included over 22 million individuals, identified approximately 1 million new autoimmune cases, highlighting the high frequency and growing burden of these disorders (2). Consistent with this, global analyses of age-standardized incidence rates from 1990 to 2019 revealed marked heterogeneity across regions and subtypes, yet demonstrated an overall rising trend that is projected to continue through 2040 (3).

The pathophysiology of autoimmune diseases is driven by a breakdown of immune tolerance, resulting in persistent autoreactive T- and B-cell responses, production of pathogenic autoantibodies, and chronic tissue inflammation that ultimately leads to organ damage. These mechanisms explain the broad spectrum of clinical manifestations and the relapsing, often refractory nature of autoimmune diseases (4).

Current therapeutic strategies primarily rely on broad immunosuppression, including glucocorticoids, conventional immuno - suppressants and targeted biologics. Corticosteroids are the prototypical immunosuppressive agent and remain a cornerstone of therapy but carry well-documented risks of gastrointestinal and metabolic toxicity (5). Long-term immunosuppression in general further increases susceptibility to opportunistic infections and malignancy. Despite decades of research and therapeutic development, a substantial proportion of patients still fail to achieve sustained clinical responses, reflecting the inherent limitations of current treatments and underscoring the need for novel, mechanism-based approaches (6).

The chronicity, high prevalence, and limited effectiveness of existing therapies translate into a considerable social and economic burden. Patients often experience lifelong disability, reduced quality of life, and diminished productivity, while healthcare systems face escalating costs related to ongoing treatment and complications. These challenges highlight the inadequacy of symptomatic control and the necessity of therapies that address the fundamental immunological drivers of disease (7).

Against this background, chimeric antigen receptor (CAR) T-cell therapy has emerged as a transformative therapeutic modality. Originally developed in oncology, CAR T cells are now being explored in autoimmunity as a strategy to "reset" the dysregulated immune system. By engineering patient-derived T cells to selectively target pathogenic immune subsets such as autoreactive or antibody-producing B cells, CAR T-cell

therapy offers the potential for long-term, drug-free remission rather than continuous immune suppression. Early clinical studies in treatment-refractory autoimmune diseases have demonstrated profound and durable responses, generating substantial enthusiasm and positioning CAR T-cell therapy as a promising frontier in the management of otherwise intractable autoimmune conditions (8).

2. Understanding the immune response

CAR T-cell therapy is best understood in the context of fundamental immune mechanisms. The immune system consists of diverse cellular subsets that cooperate to eliminate pathogens and abnormal cells. A key means of distinguishing immune cell types is through cluster of differentiation (CD) markers, which are proteins or glycoproteins expressed on the cell surface. These markers serve as identifiers of immune cell subsets and play essential roles in mediating cell–cell communication and functional specialization (9).

2.1. T cells

T lymphocytes are central mediators of cell-mediated immunity, providing both regulatory and cytotoxic functions. $CD4^+$ helper T cells recognize antigens presented by antigen-presenting cells on major histocompatibility complex (MHC) class II molecules. Upon activation, they differentiate into effector subsets that secrete cytokines, thereby enhancing and coordinating the activity of other immune cells (10). $CD8^+$ cytotoxic T cells recognize antigenic peptides presented on MHC class I molecules (11). Following activation, they exert direct cytotoxicity against infected or malignant cells (12). This process is mediated by perforin, which forms pores in the target cell membrane, and granzymes, which enter through these pores to initiate apoptosis (12). Cytotoxic T cells also produce interferon-γ (IFN-γ), further modulating immune responses (13). The ability of T cells to specifically recognize antigens and eliminate abnormal cells provides the conceptual foundation for CAR T-cell therapy.

2.2. Immune pathways

Two major pathways define adaptive immune responses. Cell-mediated immunity: Antigen-presenting cells such as macrophages process and present antigens to helper T cells, which in turn activate cytotoxic T cells. Activated cytotoxic T cells then eliminate infected or abnormal host cells (14). Humoral immunity: Helper T cells activate B lymphocytes, which subsequently differentiate into plasma cells. Plasma cells secrete antigen-specific antibodies that neutralize pathogens, opsonize them for phagocytosis, activate the complement cascade, and facilitate antibody-dependent cellular cytotoxicity. A subset of B cells differentiates into memory cells, ensuring rapid and robust responses upon re-exposure to the same antigen (15).

2.3. B cells

B lymphocytes contribute to immune defense through antigen presentation, antibody production, and immune memory.

2.3.1. *Maturation and differentiation*

B cells originate in the bone marrow, where they progress from pro-B cells to pre-B cells, then to immature B cells, and ultimately to mature B cells. Immature B cells begin to express the B-cell receptor (BCR), enabling recognition of specific antigens. Mature B cells circulate through peripheral lymphoid organs, where they encounter antigen and

undergo activation (15).

2.3.2. *Antigen presentation*

B cells internalize antigens recognized by the BCR, process them, and present antigenic peptides on MHC class II molecules to $CD4^+$ helper T cells, thereby bridging innate and adaptive immunity (15).

2.3.3. *Antibody production and effector mechanisms*

Upon activation with T-cell help, mature B cells differentiate into plasma cells, which secrete large amounts of antigen-specific antibodies. The binding of antibodies to antigens initiates several downstream effector mechanisms that collectively eliminate the pathogen. These are, Neutralization: Antibodies block pathogens or toxins from interacting with host cells, preventing infection or toxic damage. Complement activation: Antigen–antibody complexes activate the complement cascade, which amplifies inflammation, recruits immune effector cells, and can directly lyse target cells via the membrane attack complex. Opsonization and phagocytosis: The Fc portion of antibodies binds to Fc receptors on phagocytes, enhancing recognition and engulfment of antibody-coated antigens. Antibody-dependent cellular cytotoxicity (ADCC): Natural killer (NK) cells detect antibody-coated target cells through Fc receptors and induce apoptosis in those cells (16). Through these mechanisms, antibody production by plasma cells serves as a critical effector arm of humoral immunity.

2.3.4. *Immune memory*

A fraction of activated B cells differentiates into memory B cells, which persist long term and mediate rapid, potent secondary immune responses upon re-exposure to the same antigen (15).

3. CD19-CAR T cell therapy

3.1. Generation of CD19-CAR T cells

CD19-directed CAR T cells are produced by isolating autologous $CD3^+$ T lymphocytes from the patient, followed by genetic modification to introduce a CAR construct. This receptor is designed to recognize specific surface antigens, thereby redirecting T-cell activity toward defined cellular targets. Depending on the intended therapeutic application, CAR constructs can be tailored against different antigens; however, the most widely utilized target to date has been CD19, a surface marker expressed from the pro-B cell stage through immature and mature B cells, and up to pre-plasma cell differentiation. By exploiting this expression pattern, CD19-CAR T cells are capable of targeting a broad spectrum of B-cell populations across multiple stages of development (17).

3.2. Mechanism of action

Once infused, CD19-CAR T cells actively recognize and bind to CD19-expressing B cells. Upon engagement, they become activated, proliferate, and execute cytotoxic effector functions. A single CAR T cell is capable of engaging and eliminating multiple target cells sequentially, a phenomenon termed sequential killing. This results in widespread apoptosis of $CD19^+$ B cells, encompassing both pathogenic and normal subsets.

The therapeutic strategy of CD19-CAR T cells differs substantially from monoclonal antibody–based therapies such as rituximab, which specifically targets CD20. While

rituximab effectively eliminates mature B cells, it does not affect earlier developmental stages. By contrast, anti-CD19 CAR T cells eradicate a broader range of B cells, including pro- and pre-B cells, thereby providing a more comprehensive depletion of the B-cell compartment (18). This broader action is advantageous in diseases where autoreactive clones may arise from early B-cell progenitors, but it also carries the risk of profound B-cell aplasia and hypogammaglobulinemia (19).

3.3. Clinical applications in hematologic malignancies

CAR T cell therapy was originally developed with oncological indications in mind, and CD19-directed approaches in particular have delivered remarkable clinical breakthroughs in B cell malignancies. Across clinical trials and real-world practice, this strategy has induced durable remissions in relapsed or refractory B cell cancers, achieving outcomes that were previously unattainable with conventional therapies.

3.3.1. *Chronic Lymphocytic Leukemia (CLL)*

CLL is the most common adult leukemia in the Western world, characterized by the accumulation of mature B lymphocytes in the blood, bone marrow, and lymphoid organs. It presents with a uniform cell phenotype but highly variable clinical outcomes, ranging from indolent disease to aggressive forms requiring early treatment (20). Chronic lymphocytic leukemia presents unique challenges for CAR T-cell therapy due to the intrinsic functional defects of T cells in this disease, which contribute to lower response rates compared with other B-cell malignancies. Nevertheless, despite these limitations, clinical studies have demonstrated that a subset of patients can achieve complete remission, providing proof-of-concept for the therapeutic potential of CAR T-cell therapy in CLL. These encouraging results have sustained ongoing research efforts to optimize CAR T strategies in this context (21).

Recently, lisocabtagene maraleucel (liso-cel) has received regulatory approval for both large B-cell lymphoma (LBCL) and CLL, reflecting advances in manufacturing and clinical application that have enabled consistent efficacy and safety profiles (22). In the primary efficacy cohort, liso-cel achieved a complete response or remission rate of 18% in patients with relapsed or refractory CLL following BTK inhibitor and venetoclax failure (23). Adverse events were manageable, with grade 3 cytokine release syndrome (CRS) occurring in 9% and grade 3 neurological events in 18% of patients, and no grade 5 events reported (23). These findings support the clinical activity of liso-cel with an acceptable safety profile in a heavily pretreated population (23).

3.3.2. *Lymphomas*

Lymphoma is a group of more than 90 malignant neoplasms of lymphocytes, broadly classified into Hodgkin and non-Hodgkin types, usually presenting with painless lymphadenopathy and, in advanced disease, systemic symptoms such as fever, weight loss, and night sweats (24). Relapsed or refractory B-cell lymphomas, including diffuse LBCL, have become a major clinical indication for CD19-CAR T therapy. Several CD19-directed products have been evaluated in this context, leading to durable responses in subsets of patients. Multiple CD19-CAR-T products have now received FDA approval for relapsed/refractory B-cell lymphomas.

Historically, the standard treatment for aggressive B-cell lymphomas consisted of chemotherapy-based immunotherapy regimens such as R-CHOP, followed in cases of relapse by high-dose chemotherapy with autologous stem cell transplantation (ASCT). Despite these intensive strategies, a significant proportion of patients—particularly those with relapsed or refractory disease—continued to experience poor long-term outcomes (25).

The introduction of CD19-targeted CAR T-cell therapy has markedly altered this therapeutic landscape. In patients with relapsed or refractory LBCL, CD19-CAR T therapy has demonstrated the ability to induce durable remissions in approximately 40% of cases, including those who previously failed multiple lines of treatment (26). Reflecting this advance, autologous CD19-CAR T products have received regulatory approval since 2017, establishing them as a novel therapeutic option for relapsed/refractory LBCL. Currently, three products—axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tisa-cel), and lisocabtagene maraleucel (liso-cel)—are approved by both the FDA and EMA (25).

Beyond systemic disease, recent studies have indicated that CD19-CAR T therapy may also be effective in primary and secondary central nervous system lymphoma, expanding its potential utility in previously excluded patient populations. Collectively, these findings underscore the transformative impact of CAR T-cell therapy in lymphoid malignancies and highlight its capacity to achieve long-term remission in patients with otherwise limited therapeutic options (27).

4. Autoimmune diseases and CD19-CAR T cell therapy

4.1. Pathogenic mechanisms of autoantibodies

Autoimmune diseases arise from the loss of immune tolerance, leading to aberrant recognition of self-antigens. Autoantibodies are central mediators of tissue inflammation and damage through six principal mechanisms (1). First, receptor agonist activity occurs when autoantibodies abnormally activate receptors (28); for example, in Graves' disease, thyroid-stimulating hormone receptor antibodies act as agonists, driving uncontrolled thyroid hormone production (29). Second, receptor antagonist activity is observed when autoantibodies inhibit normal receptor–ligand interactions, as in myasthenia gravis, where acetylcholine receptor antibodies prevent neuromuscular signaling. Third, ligand agonist activity arises when autoantibodies mimic soluble mediators such as cytokines or growth factors, thereby dysregulating downstream signaling pathways. Fourth, cytotoxicity is mediated through complement-dependent cytotoxicity (CDC) and ADCC, leading to direct destruction of target cells. Fifth, neutrophil activation occurs when antigen–antibody immune complexes engage Fc receptors and activate complement, promoting neutrophil recruitment, degranulation, and release of reactive oxygen species that amplify local inflammation.

Finally, acantholysis represents disruption of cell–cell adhesion, as exemplified in pemphigus vulgaris, where autoantibodies against desmogleins cause keratinocyte detachment and blister formation (30).

These diverse mechanisms illustrate how autoantibodies alter signaling, activate effector pathways, and compromise tissue integrity, thereby generating the heterogeneous clinical manifestations of autoimmune disease.

The persistence of such autoreactivity reflects a breakdown in central and peripheral tolerance. Central tolerance occurs in the bone marrow for B cells and in the thymus for T cells, where autoreactive clones are normally eliminated through negative selection. In B-cell development, immature B cells recognizing self-antigen through the BCR undergo clonal deletion, anergy, or receptor editing (31). Similarly, developing thymocytes that bind self-peptide–MHC complexes with high affinity are deleted during negative selection, while those with weak interactions survive through positive selection. Peripheral tolerance provides an additional safeguard, eliminating or suppressing autoreactive lymphocytes that escape central tolerance. Regulatory subsets such as Tregs and Bregs play a pivotal role in this process. Failure of these mechanisms results in the persistence of autoreactive clones and the clinical expression of autoimmune disease (32).

4.2. Immune reset as a therapeutic strategy

The concept of immune reset has emerged as a therapeutic goal in autoimmunity. Rather than chronically suppressing immune activity, immune reset aims to eradicate pathogenic autoreactive clones and reconstitute a balanced, tolerant immune system, thereby enabling long-term drug-free remission. Earlier attempts to achieve immune reset employed high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (HSCT). While HSCT demonstrated the potential to induce durable remission, its clinical utility was limited by profound toxicity, treatment-related morbidity, and mortality (33).

4.3. CD19-CAR T and immune reset

CD19-CAR T cell therapy offers a novel and potentially safer approach to immune reset. By targeting CD19, which is expressed from the pro-B cell stage through mature B cells but absent on long-lived plasma cells, CD19-CAR T therapy results in broad and sustained depletion of the B-cell compartment, including autoreactive clones. This profound B-cell clearance effectively disrupts the autoantibody pool and allows immune reconstitution (33).

Clinical experience supports this mechanism. In a landmark case series, patients with treatment-refractory systemic lupus erythematosus achieved rapid and sustained remission following a single infusion of CD19-CAR T cells. Clinical responses were characterized by complete resolution of disease activity, disappearance of autoantibodies such as anti-dsDNA, and prolonged drug-free remission extending beyond one year in some cases. Similarly, early-phase studies in other autoimmune diseases, including idiopathic inflammatory myositis and systemic sclerosis, have reported encouraging outcomes, with substantial reductions in disease activity and no requirement for ongoing immunosuppressive therapy. These findings provide proof-of-concept that CD19-CAR T therapy can achieve a state of immune reset, with the potential to transform therapeutic paradigms in autoimmunity (34,35).

4.4. CD19-CAR T cell therapy in autoimmune diseases

4.4.1. *CD19-CAR T cell therapy in Systemic Lupus Erythematosus (SLE)*

SLE is a chronic autoimmune disease in which the immune system attacks the body's own tissues, leading to inflammation and multi-organ injury, most often involving the skin, joints, blood, and kidneys. Clinically, patients may present with fever, cytopenia, rash, arthritis, and proteinuria (a marker of lupus nephritis), while immunologic findings often include disease-specific autoantibodies and low complement levels (36). The disease is associated with markedly increased morbidity and mortality, with affected individuals exhibiting a two- to threefold higher risk of death compared to the general population. Conventional treatments - including glucocorticoids, immunosuppressants, and biologics - can control disease activity but rarely induce durable remission and expose patients to long-term risks such as infection and organ toxicity. These limitations underscore the need for more targeted and potentially curative approaches (37).

4.4.1.1. Preclinical insights

Experimental models have provided compelling rationale for the use of CAR T cells in lupus. In murine studies, anti-CD19 CAR T cells mediated more sustained B-cell depletion than conventional antibody-based therapies. CAR constructs incorporating 4-1BB costimulatory domains were particularly effective, even without prior cell purification, highlighting their robustness. Importantly, prophylactic infusion of CAR T cells before the onset of disease not only controlled established autoimmunity but also prevented progression altogether, indicating the capacity of CAR T to both treat and avert lupus pathogenesis (38-39).

4.4.1.2. Early human experience

The first clinical application of CD19-CAR T therapy in lupus was reported in five young patients (mean age 22 years) with severe, refractory SLE unresponsive to multiple immunosuppressants. Patients received autologous CD19-CAR T cells generated by lentiviral transduction of patient-derived T cells, expanded *ex vivo*, and infused following lymphodepletion with fludarabine and cyclophosphamide. The infused CAR T cells expanded efficiently *in vivo*, resulting in complete B-cell depletion, disappearance of anti-dsDNA antibodies, and rapid induction of clinical remission. Notably, remission was durable and achieved without ongoing immunosuppression. Adverse events were limited to mild CRS, which resolved with standard supportive care, and no severe toxicities were observed (40).

These promising findings were echoed in subsequent reports. In another case, a 15-year-old female with refractory lupus nephritis and an SLEDAI score of 23 achieved full remission following CD19-CAR T infusion. Post-treatment assessments revealed complete depletion of B cells, disappearance of arthritis, normalization of complement C3 and C4 levels, and loss of anti-dsDNA and ANA antibodies. Mild CRS occurred but resolved, and no immune effector cell–associated neurotoxicity syndrome (ICANS) or long-term marrow toxicity was observed. This case highlighted the potential of CAR T therapy to rescue patients with rapidly progressive disease from organ failure and dialysis dependence (41).

4.4.1.3. Expanded clinical studies

The feasibility of extending CAR T therapy to younger populations has also been tested. A phase I trial conducted at Seattle Children's Hospital enrolled 12 pediatric patients (<18 years) with refractory lupus, demonstrating safety and practicality of CAR T in this age group. Early outcomes suggested potential for durable remission in the absence of immunosuppression, marking a significant step toward broadening the clinical application of CAR T beyond adult patients (42).

Larger clinical studies have corroborated these initial findings. In a multicenter trial of SLE patients treated with CD19-CAR T cells, robust B-cell depletion was consistently achieved, accompanied by a marked reduction in disease activity scores. Serologic improvements included decreased levels of dsDNA antibodies and normalization of complement factors C3 and C4. Importantly, restoration of vaccine responsiveness within three months of therapy suggested that immune reconstitution occurred in a functionally competent manner, supporting the concept of an immune reset (43).

4.4.1.4. Next-generation approaches

Beyond conventional CD19-directed therapy, bispecific CAR T constructs targeting both CD19 and BCMA have been investigated to enhance efficacy and durability. Dual-target (BCMA+CD19) cCAR-T has shown promising safety and efficacy signals in a small phase 1 cohort (~13 patients), with reports of clinical improvement and medication-free remission in individual cases. However, the sample size is small and follow-up is limited; larger, confirmatory studies are needed. Disease activity scores (SLEDAI-2K) dropped from a baseline mean of 10.6 to 2.7, and nine patients maintained remission without medication. Renal outcomes also improved significantly in patients with lupus nephritis, suggesting that combined B-cell and plasma cell targeting may offer superior long-term disease control. Reported adverse events were limited to mild CRS, with no severe or life-threatening complications (43).

4.4.1.5. Clinical implications

Taken together, accumulating evidence from preclinical models, case reports, and early-phase clinical studies demonstrates that CD19-CAR T therapy can induce profound and durable remission in SLE. The therapeutic mechanism is based on deep and sustained B-cell depletion, leading to elimination of autoantibody production, disruption of immune complex formation, and eventual reconstitution of a self-tolerant immune system. Unlike conventional therapies, CAR T therapy directly addresses the immunological drivers of disease, offering the possibility of long-term, drug-free remission. While further studies are needed to define durability, safety in larger cohorts, and long-term immune competence, CD19-CAR T therapy represents a paradigm shift in lupus management and a promising prototype for the treatment of other systemic autoimmune diseases.

4.4.2. *CD19-CAR T cell therapy in Multiple Sclerosis (MS)*

Multiple sclerosis (MS) is a chronic autoimmune disorder of the central nervous system (CNS) and the most common non-traumatic cause of disability in young adults. Its incidence is increasing worldwide, particularly among women, and although the precise etiology remains unclear, gene–environment interactions are strongly implicated. Current therapies largely focus on

immune modulation and symptom control but fail to provide a definitive cure (44).

4.4.2.1. Preclinical insights

B cells are now recognized as central players in MS pathogenesis, both as antigen-presenting cells and as producers of pathogenic antibodies within the CNS. Ectopic B-cell and plasma cell aggregates in the meninges and parenchyma contribute to local inflammation and demyelination, exacerbating disease progression. Given their pivotal role, targeted depletion of autoreactive B cells represents a rational therapeutic strategy. Importantly, CAR T cells have the ability to cross the blood–brain barrier, enabling direct targeting of CNS-resident B cells, plasmablasts, and plasma cells. Because CD19 is expressed across nearly all stages of B-cell development—including some short-lived plasma cells—CD19-CAR T therapy can achieve broad depletion of pathogenic B-cell populations implicated in MS (45).

Preclinical models demonstrated that CAR T cells can effectively deplete B cells in both peripheral and central compartments, resulting in measurable clinical improvement. However, these studies also highlighted potential risks: while meningeal B-cell clusters were reduced, paradoxical disease worsening was observed in some settings, likely due to concurrent depletion of regulatory B-cell subsets (46).

4.4.2.2. Early human experience

The first *in vivo* human application of CD19-CAR T therapy in MS was recently reported in two patients with progressive disease (47). Following infusion, both patients exhibited a reduction in cerebrospinal fluid antibody production that persisted for 64 days. Notably, no cases of ICANS were observed, underscoring early indications of safety.

Additional clinical insights are emerging from studies that included MS and other systemic autoimmune diseases. In a case series of six patients (median age 42 years), CAR T therapy led to improvements in systemic sclerosis features, with reductions in skin fibrosis and pulmonary inflammatory lesions (48). Although this study primarily focused on systemic sclerosis, the absence of MS disease progression during follow-up suggested a possible stabilizing effect of B-cell depletion in CNS autoimmunity as well.

4.4.2.3. Case study

Another illustrative case involved a 32-year-old female patient with dual diagnoses of scl-70–positive diffuse systemic sclerosis and ACPA-positive rheumatoid arthritis (49). Despite multiple immunosuppressive therapies, her systemic sclerosis continued to progress while RA remained partially controlled. Following CAR T infusion, she experienced grade II CRS that resolved within a week, along with transient neutropenia and elevated liver enzymes, all of which fully recovered. Complete $CD19^+$ B-cell depletion was achieved for 56 days, followed by reconstitution of transitional B cells at week 12 and emergence of naïve B cells by week 16, consistent with immune reset. Serologically, anti-scl-70 antibodies remained stable and ACPA seroconversion persisted for six months. This case demonstrates the potential of CAR T therapy not only in halting systemic sclerosis progression but also in resetting adaptive immunity across comorbid autoimmune conditions, with implications for MS where immune rebalancing is similarly needed.

4.4.2.4. Clinical implications

Collectively, these findings underscore the feasibility of CD19-CAR T therapy in MS, highlighting its ability to penetrate the CNS and eliminate autoreactive B cells in both peripheral and central compartments. The therapy holds promise for inducing long-term remission by fundamentally resetting the immune system. Nonetheless, important concerns remain, including the risk of CRS and ICANS, the high cost of treatment, and uncertainty about the durability of clinical benefit. Furthermore, the possibility of disease exacerbation due to depletion of regulatory B cells warrants careful evaluation.

Despite these challenges, CD19-CAR T therapy represents a highly innovative therapeutic avenue in MS, with the potential to achieve what current disease-modifying therapies cannot: durable remission and direct targeting of pathogenic B-cell populations within the CNS.

4.4.3. *CD19-CAR T cell therapy in Rheumatoid Arthritis (RA)*

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disorder characterized by persistent synovial inflammation, progressive joint destruction, and production of disease-associated autoantibodies. Among these, anti-citrullinated protein antibodies (ACPAs) are particularly relevant, being strongly associated with disease activity and structural damage (50). Current therapeutic regimens—such as glucocorticoids, conventional disease-modifying antirheumatic drugs (DMARDs), and biologics like rituximab—have significantly improved outcomes. However, they are not curative, frequently require lifelong administration, and are associated with systemic risks including infection and malignancy due to broad immunosuppression (51).

4.4.3.1. Preclinical insights

B cells play a central role in RA pathogenesis by accumulating within the synovial compartment, where they drive autoantibody production and perpetuate inflammatory cascades. Rituximab, an anti-CD20 monoclonal antibody, depletes mature B cells and has been widely used in RA treatment. However, its non-selective immunosuppression can compromise host defense and carries risks of infection and cancer. In contrast, CAR T therapy offers the possibility of more precise targeting of pathogenic B-cell subsets while enabling long-term immune reprogramming.

Innovative *in vitro* approaches have demonstrated this principle. By selecting known RA-associated autoantigens such as citrullinated peptides and tagging them with fluorescein isothiocyanate (FITC), researchers engineered T cells expressing an anti-FITC CAR. These CAR T cells selectively recognized and eliminated autoreactive B cells carrying FITC-tagged citrullinated antigens. This proof-of-concept confirmed that CAR T cells could be engineered to specifically eradicate autoreactive B-cell clones while sparing the broader immune repertoire (51).

4.4.3.2. Early human experience

Clinical observations have further substantiated the therapeutic potential of CAR T in RA. In one case, a patient with dual ACPA-positive RA and acetylcholine receptor (AChR) antibody–positive myasthenia gravis achieved clinical remission of RA following CD19-CAR T infusion. The treatment led to a marked decline in ACPA titers, consistent

with clinical improvement, whereas myasthenia gravis outcomes improved independently of antibody levels. This suggests that while CAR T effectively eliminates autoreactive B cells and reduces autoantibody load in RA, the relationship between antibody titers and clinical disease activity may vary depending on the autoimmune condition (52).

Importantly, approximately 2.7% of RA patients exhibit polyrefractory disease, defined by resistance to multiple DMARDs. These patients represent a critical unmet need in rheumatology. In such cases, CD19-CAR T therapy has shown promise by inducing profound and durable depletion of both $CD19^+$ B cells and autoreactive plasma cells. This dual targeting not only suppresses ongoing autoantibody production but also offers the potential for long-term, drug-free remission through immune reset (53).

4.4.3.3. Clinical implications

Together, *in vitro* and early clinical findings highlight the unique potential of CD19-CAR T therapy in RA. Unlike rituximab, which primarily eliminates mature B cells, CAR T cells can achieve deeper and more sustained clearance of autoreactive B-cell and plasma cell populations. This allows for a more fundamental reset of the immune system, potentially transforming disease management for patients who have exhausted conventional therapies. Although large-scale clinical trials are still needed, CD19-CAR T therapy stands as a promising frontier for the treatment of refractory RA, with the capacity to achieve durable remission and significantly improve patient outcomes.

4.5 Functional competence and translational design proposal

A central unresolved question in the application of CD19-CAR T cell therapy for autoimmune diseases is whether immune reconstitution after treatment is *functionally competent*. Current reports often equate B cell repopulation or immunoglobulin recovery with restored immunity, yet these quantitative measures do not determine whether the immune system regains its ability to protect against infection, respond to vaccines, and maintain long-term self-tolerance (54, 55). To address this gap, we propose an integrated framework for assessing immune competence following CAR T cell therapy and suggest future research directions related to optimizing targeting strategies.

4.5.1. *Functional competence framework*

Comprehensive evaluation should include vaccine challenge assays, infection surveillance, and immune repertoire profiling. Vaccine response studies, such as those assessing antibody titers after influenza or SARS-CoV-2 vaccination, can provide an accessible correlate of immune protection. Evidence from CAR-T recipients shows that vaccination before or after therapy is feasible and elicits measurable, though often attenuated, antibody responses—indicating that such assays can serve as practical tools to assess functional immune recovery (54). Distinct infection profiles emerge across recovery phases after CAR T-cell therapy—bacterial infections dominate the early neutropenic period, whereas viral infections increase once partial immune reconstitution occurs. Monitoring strategies should therefore align with these temporal risks to evaluate functional restoration of host defense (56). Immune repertoire analysis, using sequencing-based profiling of B- and T-cell diversity, can

further reveal whether reconstitution favors naïve or memory subsets and whether regulatory balance is re-established. High-throughput sequencing of BCR and T-cell receptor (TCR) genes, combined with phenotypic classification by CD markers such as CD19, CD27, CD45RA, and CD45RO, enables precise discrimination between naïve and memory populations and helps track the restoration of clonal diversity after CAR T-cell therapy (57).

4.5.2. *Targeting strategies*

4.5.2.1. Expansion of target coverage: Dual-target CAR

Dual-target CAR constructs such as CD19 + BAFF-R designs have been developed to prevent antigen-loss relapse and enhance long-term immune reconstitution. BAFF-R (B-cell activating factor receptor) is a TNF-receptor–family protein expressed throughout B-cell maturation, including on certain CD19-negative malignant or autoreactive B cells. Because BAFF-R signaling promotes B-cell survival and proliferation, combining CD19 and BAFF-R recognition broadens target coverage and mitigates relapse caused by antigen escape or incomplete depletion of pathogenic clones (58).

4.5.2.2. Improvement of selectivity: CAAR T cells and EBV-LCLs

Although CD19-CAR T therapy eliminates most B cells through antigen-directed cytolytic activity against $CD19^+$ cells across nearly all stages of B-cell maturation, this broad depletion approach may transiently impair protective humoral immunity (55). To refine selectivity, *antigen-specific chimeric autoantibody receptor (CAAR) T cells* have been designed to eliminate only autoreactive B cells. In pemphigus vulgaris, pathogenic autoantibodies bind to desmoglein 3 (Dsg3), a desmosomal adhesion protein on keratinocytes, disrupting cell–cell junctions and causing blister formation. CAAR-T cells exploit this disease mechanism by incorporating Dsg3 as the extracellular recognition domain of the CAR construct. This configuration enables them to selectively recognize and kill B cells whose B-cell receptors bind Dsg3—precisely the clones responsible for producing pathogenic autoantibodies (59).

Furthermore, this concept could be extended by directly utilizing a patient's own autoreactive B cells to generate personalized CAR-T constructs. These autoreactive B cells could be immortalized *ex vivo* using Epstein–Barr virus (EBV), a human herpesvirus that naturally persists within B cells for life. Most individuals acquire EBV infection during childhood, where it remains latent without causing clinical symptoms, establishing stable, long-term survival of the host B-cell pool. By immortalizing the patient's autoreactive B-cell clones with EBV, researchers could create EBV–lymphoblastoid cell lines (EBV-LCLs) which are durable cell lines that express the same autoantigenic receptors responsible for disease pathogenesis. Exposing the patient's T cells to these EBV-immortalized B cells during *ex vivo* CAR generation could produce T-cell products that are functionally "educated" by disease-relevant autoreactive B cells. Such T cells might selectively eliminate pathogenic autoreactive clones while sparing protective immune subsets, thereby minimizing the immunosuppressive side effects observed with conventional CD19-CAR T cell therapy and fundamentally addressing concerns regarding

the functional competence of the reconstituted immune system. However, it should also be acknowledged that EBV itself has been implicated as a potentiator of autoimmune diseases. Recent evidence indicates that EBV nuclear antigens such as EBNA2 and EBNA3C interact with host autoimmune risk loci, promoting proinflammatory gene expression and tolerance breakdown in diseases including systemic lupus erythematosus and Sjögren's syndrome (60). This duality—where EBV can serve both as a biological tool for B-cell immortalization and as a potential amplifier of autoimmune activation—underscores the need for stringent control of viral latency and comprehensive biosafety assessment before any translational application.

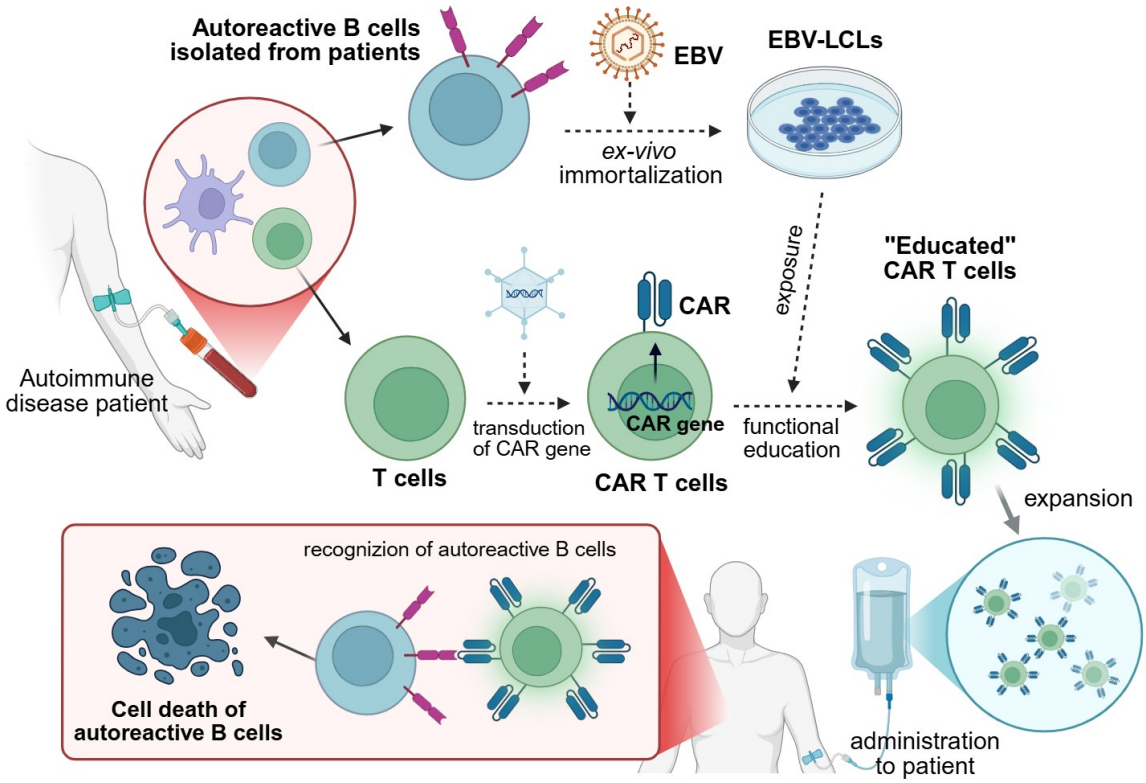

Figure 1. Schematic overview of patient-specific CAR T cell generation using EBV-immortalized autoreactive B cells. Autoreactive B cells isolated from patients with autoimmune disease are immortalized ex vivo through Epstein–Barr virus (EBV) infection to generate Epstein–Barr virus–transformed lymphoblastoid cell lines (EBV-LCLs). These EBV-LCLs retain expression of disease-relevant autoantigenic B-cell receptors, serving as physiologically relevant stimulatory cells for autologous T cells during CAR engineering. Exposure to these EBV-immortalized autoreactive B cells enables functional "education" of CAR T cells, promoting selective cytotoxicity toward pathogenic clones while sparing protective immune subsets. This strategy aims to minimize off-target immunosuppression and facilitate balanced immune reconstitution.

5. Conclusion

CD19-CAR T cell therapy has already transformed the treatment of blood cancers, producing outcomes that once seemed unattainable with standard therapies. Its central mechanism—the deep and sustained removal of $CD19^+$ B cells, including autoreactive subsets—offers a strong

scientific basis for extending this approach to autoimmune diseases. These conditions, though clinically diverse, share a unifying pathology involving abnormal B-cell activation, autoantibody production, and the breakdown of immune tolerance. By directly targeting these drivers, CD19-CAR T therapy offers the possibility not only of controlling disease but also of fundamentally reprogramming the immune system.

Early clinical reports in systemic lupus erythematosus, multiple sclerosis, and rheumatoid arthritis lend support to this idea. In patients who had exhausted all other treatment options, CD19-CAR T infusion has led to profound and sometimes long-lasting remissions, disappearance of autoantibodies, and sustained B-cell depletion. These findings suggest that the principle of CAR T—precise elimination of pathogenic B-cell populations—applies equally well to autoimmunity as it does to cancer, and they highlight the remarkable translational potential of this strategy.

At the same time, important limitations remain. The existing evidence is restricted to small patient cohorts with relatively short follow-up, which leaves critical uncertainties about long-term safety, the durability of remission, and the stability of immune reconstitution. Potential side effects, including cytokine release syndrome, neurotoxicity, and prolonged hypogammaglobulinemia, must be carefully assessed in larger trials. Practical barriers are also significant: the high cost and complex manufacturing processes limit accessibility, and the heterogeneity of autoimmune diseases raises questions about whether results from one condition can be generalized to others. Addressing these challenges will require adequately powered, multi-center clinical trials, integration of predictive biomarkers for patient selection, and innovations to make CAR-T manufacturing more scalable and affordable.

Yet beyond these recognized challenges lies a deeper and less explored question: does CAR T therapy achieve true immune resilience? Most studies so far have focused on quantitative outcomes—such as B-cell depletion, autoantibody reduction, and eventual B-cell recovery. While these are valuable markers, they do not tell us whether the reconstituted immune system is *functionally competent*. This distinction is critical. If B cells repopulate but remain autoreactive, remission may be temporary. If B cells return but the immune system fails to mount protective responses to pathogens or vaccines, patients may face dangerous immune deficiency. Conversely, if immune reconstitution establishes both protective immunity and durable tolerance, then CAR T therapy could represent not just a temporary reprieve but a genuine reset of immune health.

This resilience gap—the uncertainty surrounding the quality, durability, and balance of immune recovery—is central to evaluating the future of CAR-T therapy in autoimmune diseases. It reframes the question from “Can CAR T induce remission?” to “Can CAR T rebuild a resilient immune system that is both protective and tolerant?” Answering this question requires long-term, systematic studies that track not only disease activity but also vaccine responsiveness, infection rates, immune repertoire diversity, and recurrence of autoreactivity. Such work would provide a more complete understanding of whether remission induced by CD19-CAR T therapy

reflects a fundamental reprogramming of the immune system or merely a temporary suppression of autoreactivity.

To bridge this gap, this study provides an overview of emerging technologies proposed in recent literature and suggests new perspectives and future research directions. Target coverage can be expanded through dual-target CARs (such as CD19 + BAFF-R combinations). In addition, CAAR T cells and *ex vivo* patient-specific education systems provide complementary approaches to refine selectivity and reduce off-target depletion. Among these, Epstein–Barr virus (EBV)–mediated immortalization of autoreactive B cells represents a feasible and ethically acceptable model to mimic pathogenic B-cell behavior *ex vivo.* By immortalizing patient-derived autoreactive B cells as EBV–lymphoblastoid cell lines (EBV-LCLs), researchers can expose autologous T cells to physiologically relevant antigens before CAR engineering. This approach could generate CAR-T cells that are not only cytolytic toward disease-driving clones but also "educated" to promote balanced immune reconstitution.

Future mechanistic studies must map how CAR T reshapes immune networks, including B-cell memory, plasma cell persistence, and T-cell regulation. Functional assays should be incorporated to evaluate resilience, including vaccine challenges and infection surveillance. Future investigations building on this conceptual framework may establish CAR T cell therapy not only as a curative intervention for refractory autoimmunity but also as a model for immune re-education, transforming CD19-CAR T therapy from an experimental rescue approach into a broadly applicable strategy to restore immune balance and achieve durable remission in autoimmune diseases.

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