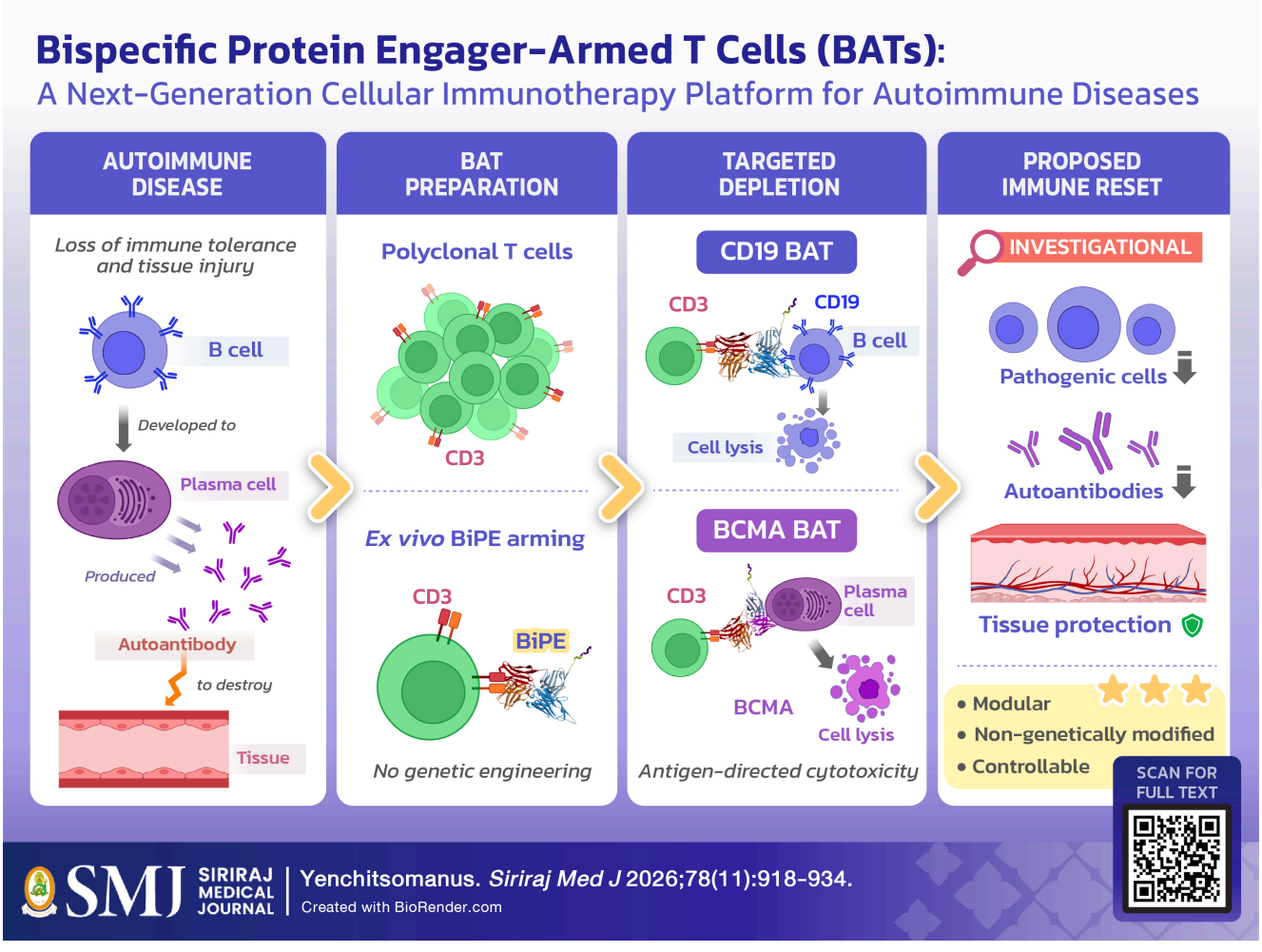
Bispecific Protein Engager-Armed T Cells (BATs): A Next-Generation Cellular Immunotherapy Platform for Autoimmune Diseases

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ABSTRACT

Autoimmune diseases arise from a loss of immune tolerance, leading to persistent immune-mediated tissue and organ damage. Although the diseases can be controlled by immunosuppressants and biologics, some patients are refractory, relapse after treatment discontinuation, or develop cumulative toxicities. Monoclonal antibodies targeting cytokines, B cells, B-cell activating factor, complement, and interferon pathways mitigate disease conditions but generally require repeated administration and rarely achieve durable treatment-free remission. CD19-directed chimeric antigen receptor (CAR) T cells have demonstrated sustained drug-free remission in some patients with severe refractory autoimmune diseases, providing early evidence that profound B-cell depletion followed by immune reconstitution may induce functional immune resetting. However, CAR-T therapy involves complex manufacturing, genetic modification, high costs, and risks including cytokine-release syndrome, neurotoxicity, cytopenias, infection, and prolonged hypogammaglobulinemia. Building on our group's preclinical development of cancer immunotherapies, the Siriraj-developed bispecific protein engager (BiPE)-armed T-cell (BAT) platform could potentially be adapted as a therapeutic strategy for selected autoimmune diseases. CD19-directed BATs could deplete autoreactive B cells, whereas B-cell maturation antigen (BCMA)-directed BATs could target pathogenic antibody-secreting plasma cells. BATs are generated by *ex vivo* arming of unexpanded polyclonal T cells with BiPEs that bind CD3 and a target-cell antigen, enabling antigen-directed cytotoxicity without genomic modification. This modular platform may provide adaptable, time-limited activity with reduced manufacturing complexity; however, its comparative efficacy, safety, durability, and cost-effectiveness remain to be established clinically. This review critically evaluates the therapeutic rationale, candidate targets and disease indications, current evidence, and key safety, manufacturing, and translational considerations for BAT therapy in autoimmune diseases.

Keywords: Autoimmune disease; bispecific protein engager-armed T cells; BATs; bispecific antibodies; CAR-T cells; B cells; plasma cells; immune resetting; cellular immunotherapy (Siriraj Med J 2026;78(11):918-934)

INTRODUCTION

Autoimmune diseases affect an estimated 5–10% of the global population and encompass more than 100 clinically distinct disorders.[1,2] They result from failure of immune tolerance, with autoreactive lymphocytes, autoantibodies, inflammatory mediators, and tissue-resident immune responses causing chronic organ injury.[3,4] Systemic lupus erythematosus (SLE), lupus nephritis (LN), rheumatoid arthritis (RA), neuromyelitis optica spectrum disorder (NMOSD), multiple sclerosis (MS), Sjögren syndrome, systemic sclerosis (SSc), myasthenia gravis (MG), inflammatory bowel disease (IBD), autoimmune cytopenias, and idiopathic inflammatory myopathies differ in clinical phenotype but share overlapping mechanisms of immune dysregulation.

Treatment has traditionally relied on glucocorticoids and broad immunosuppressive drugs, including cyclophosphamide, methotrexate, azathioprine, mycophenolate mofetil, and calcineurin inhibitors. These agents remain indispensable, but prolonged exposure may cause serious infection, malignancy, metabolic complications, infertility, and organ toxicity.[5] Biologic agents have improved selectivity by targeting cytokines, B-cell antigens, B-cell activating factor (BAFF), complement, and interferon signaling.[6,7] Nevertheless, primary non-response, loss of response, relapse after discontinuation, and persistent autoreactive plasma cells remain important limitations.

CD19-directed CAR-T therapy has changed the therapeutic concept of severe autoimmunity. In refractory SLE and other systemic autoimmune diseases, profound B-cell depletion has been associated with resolution of clinical disease and sustained drug-free remission, sometimes despite subsequent B-cell reconstitution.[8-10] These observations suggest that sufficiently deep removal of pathogenic immune-cell compartments can permit reconstitution of a less autoreactive immune repertoire. Yet current CAR-T approaches are resource intensive and may produce prolonged or difficult-to-reverse toxicity.[11]

A novel cellular immunotherapy platform—bispecific protein engager (BiPE)-armed T cells (BATs)—was recently developed by our research team at the Siriraj Center of Research Excellence for Cancer Immunotherapy (SiCORE-CIT) for cancer treatment.[12] Originally designed to target B-lineage antigens in leukemia and lymphoma or plasma-cell antigens in multiple myeloma, BATs may be adapted to selectively deplete pathogenic immune-cell populations in autoimmune diseases. In this platform, unexpanded polyclonal T cells are armed and activated *ex vivo* with BiPEs that bridge CD3 on T cells to a selected

surface antigen on target cells, generating a transient, antigen-directed cytotoxic cell product without permanent genetic modification. Our Siriraj-developed BAT platform is distinct from the bispecific antibody (BiAb)-armed activated T-cell (ATC) approach previously described by Lum and Sen, which uses Fc-containing bispecific antibodies.[13] Because target specificity is conferred by an externally applied engager rather than a genetically integrated receptor, BATs are modular, adaptable, and potentially more controllable. This review evaluates BATs as a candidate immune-resetting therapy for autoimmune diseases and defines the evidence required for translation from oncology to clinical applications in autoimmunity.

Immunopathological Basis for Targeted Immune-Cell Depletion

Loss of immune tolerance

Central tolerance removes highly autoreactive T and B lymphocytes during development in the thymus and bone marrow, whereas peripheral tolerance restrains cells that escape deletion through anergy, regulatory T cells (Tregs), inhibitory checkpoints, immune ignorance, and activation-induced cell death.[14,15] Genetic susceptibility—including variation in HLA, PTPN22, CTLA4, STAT4, IRF5, and TNFAIP3—interacts with environmental and hormonal factors, infections, ultraviolet radiation, smoking, and the microbiome to disrupt these safeguards.[16,17] The resulting loss of immune tolerance initiates and sustains autoimmune disease through interconnected B-cell, T-cell, myeloid-cell, cytokine, and tissue-resident pathways (Fig 1).

B cells and plasma cells

B cells promote autoimmunity by capturing self-antigens through the B-cell receptor, presenting them to CD4$^+$ T cells, producing proinflammatory cytokines, organizing ectopic lymphoid structures, facilitating epitope spreading, and differentiating into antibody-secreting cells.[18] The efficacy of anti-CD20 therapy in rheumatoid arthritis, multiple sclerosis, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, and pemphigus vulgaris underscores the pathogenic importance of B-cell compartment.[19] However, long-lived plasma cells pose a distinct therapeutic challenge because they often lack CD20, persist for years in bone marrow or inflamed-tissue niches, and continuously produce pathogenic autoantibodies.[20] These antibodies mediate tissue injury through immune-complex deposition, complement activation, Fc-receptor engagement, receptor blockade or stimulation, and direct cellular damage.[21] The persistence of CD20-negative plasmablasts and plasma cells may therefore contribute to incomplete responses and relapse after conventional B-cell depletion, providing a rationale for targeting antibody-secreting plasma cells through B-cell maturation antigen (BCMA), CD38, or CD138.[20,22-24]

T-cell and cytokine networks

Autoreactive CD4$^+$ T-cell subsets support inflammation and B-cell maturation. Th1 cells produce interferon-γ and activate macrophages; Th17 cells produce IL-17 family cytokines and recruit inflammatory cells; and T follicular helper cells promote germinal-center responses and affinity maturation.[25–27] Deficient or dysfunctional Tregs

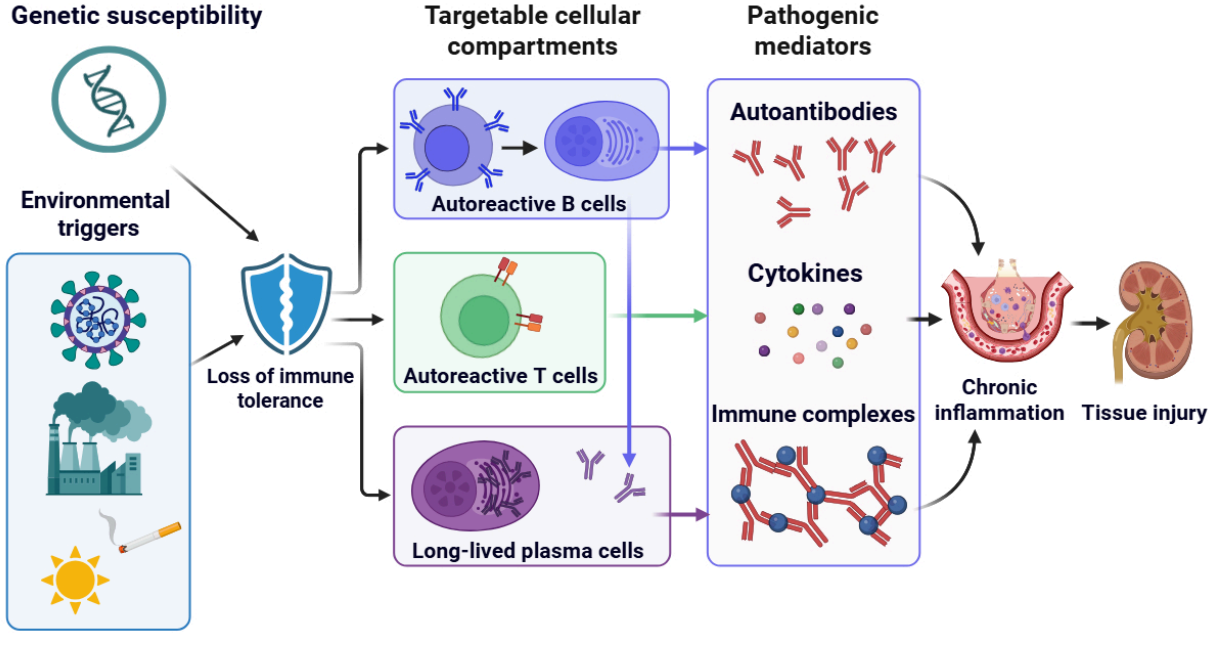


Fig 1. Immunopathogenesis and targetable cellular compartments in autoimmune disease. Genetic susceptibility and environmental triggers disrupt immune tolerance, enabling autoreactive B and T cells, plasma cells, autoantibodies, cytokines, and immune complexes to drive chronic inflammation and tissue injury.

further weaken peripheral tolerance.[28] Cytokines such as TNF-α, IL-1β, IL-6, IL-17, IL-23, type I interferons, interferon-γ, and B-cell activating factor (BAFF) amplify these cellular interactions.[29-32]

The networked nature of autoimmunity has two implications for cellular therapy. First, eliminating a single circulating population may not be sufficient when pathogenic cells also reside in tissues or when long-lived plasma cells maintain autoantibody production. Second, overly broad depletion can disrupt protective immunity. Rational BAT development must therefore match antigen expression, disease mechanism, compartment accessibility, and the desired depth and duration of depletion.

Therapeutic Lessons from Monoclonal Antibodies

Monoclonal antibodies established that selective immune intervention can control autoimmune disease with greater precision than broad immunosuppression (Table 1 and Fig 2). Anti-TNF agents—including infliximab, adalimumab, golimumab, and certolizumab pegol—are effective in RA, spondyloarthritis, psoriasis, Crohn disease, and ulcerative colitis.[33] Tocilizumab and sarilumab inhibit IL-6 receptor signaling in RA and selected inflammatory disorders.[34] B-cell-directed agents include rituximab for RA, ANCA-associated vasculitis, and pemphigus vulgaris; ocrelizumab and ofatumumab for MS; and other disease-specific agents that target CD19 or CD20.[19,35,36] Belimumab inhibits soluble BAFF in SLE and LN[37], whereas anifrolumab blocks IFNAR1 in moderate-to-severe SLE.[38] Complement inhibitors and additional cytokine-directed antibodies further illustrate the breadth of targetable immune pathways.

Despite these advances, most monoclonal antibodies suppress a pathway or deplete a subset only while adequate drug exposure is maintained. They may not reach tissue-resident pathogenic cells, remove long-lived plasma cells, or reset the autoreactive repertoire. Repeated dosing imposes cumulative cost and infection risk, while anti-drug antibodies, pathway redundancy, and disease heterogeneity can reduce efficacy.[39] For BAT development, the central lesson is that target validation alone does not guarantee durable remission; the required depth, anatomical distribution, and duration of depletion must also be defined.

Lessons from Bispecific Antibodies and First-Generation BATs

Bispecific antibodies (BsAbs) recognize two distinct antigens or epitopes and can redirect immune effector cells toward selected targets. In T-cell-redirecting formats, one arm binds CD3 and the other a target-cell antigen, promoting immune synapse formation, T-cell activation, and major histocompatibility complex (MHC)-independent cytotoxicity. Early hybrid and chemically conjugated BsAbs established the feasibility of redirecting polyclonal T cells toward tumor cells[40], whereas subsequent engineering generated full-length and fragment-based formats with improved stability, manufacturability, pharmacokinetics, and diverse Fc functions, valencies, and tissue distribution.[41] These

TABLE 1. Representative FDA-approved monoclonal antibodies used in autoimmune diseases.

Target	Drug	Major indications	References
TNF-α	Infliximab	RA, IBD	[33]
TNF-α	Adalimumab	RA, psoriasis, IBD	[33]
IL-6R	Tocilizumab	RA and selected inflammatory disorders	[34]
CD20	Rituximab	RA, ANCA-associated vasculitis, pemphigus vulgaris	[19]
CD20	Ocrelizumab	MS	[35]
CD20	Ofatumumab	MS	[36]
BAFF	Belimumab	SLE, LN	[37]
IFNAR1	Anifrolumab	SLE	[38]

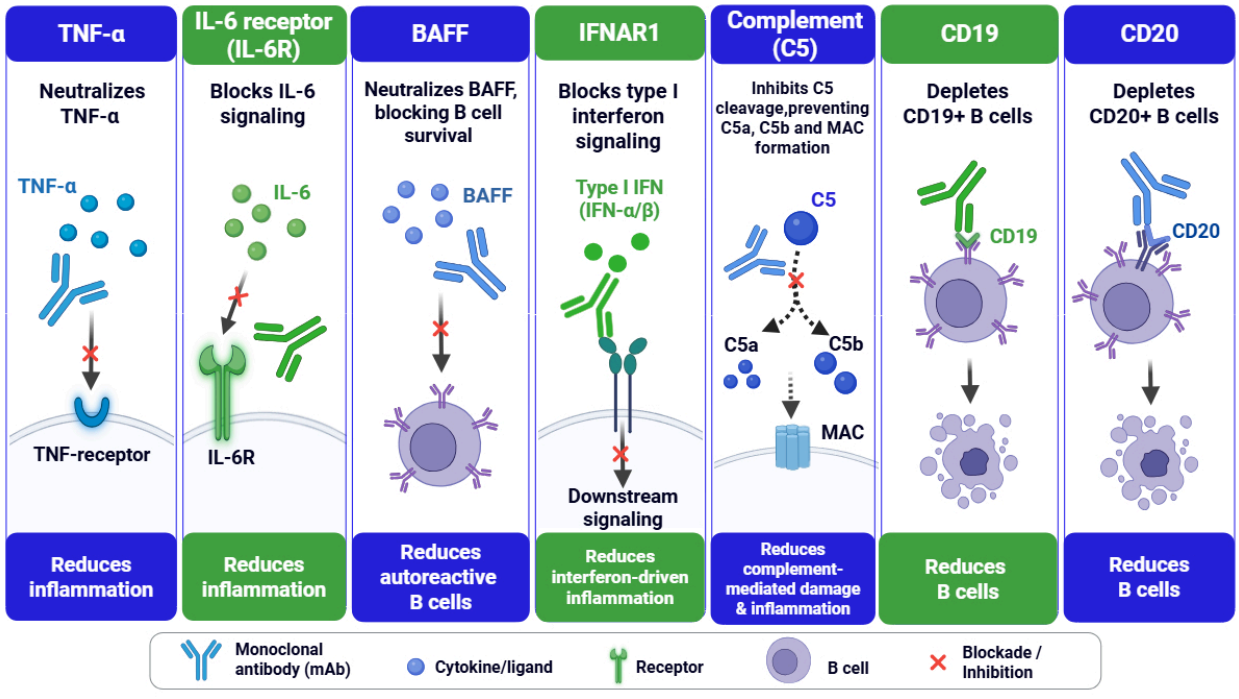


Fig 2. Major mechanisms of approved monoclonal antibodies in autoimmune disease. Representative targets include TNF-α, IL-6 receptor, BAFF, IFNAR1, complement, CD19, and CD20.

advances demonstrate that therapeutic efficacy and safety depend not only on target selection but also on molecular architecture and control of T-cell activation.

The first-generation bispecific antibody-armed T-cell (BsAb-T) approach extended this concept by separating T-cell preparation from target recognition. Activated T cells were expanded *ex vivo*, transiently armed with anti-CD3 × tumor-antigen bispecific antibodies, washed, and subsequently infused without permanent genetic modification.[12,13] The CD3-binding arm anchored the bispecific antibody to the T-cell surface, whereas the second arm mediated antigen-specific recognition and cytotoxicity. This *ex vivo* arming strategy provided a modular means of redirecting T-cell specificity without viral vectors or genomic integration. Clinical studies of HER2- and CD20-directed bispecific antibody-armed activated T cells demonstrated the feasibility of manufacturing and repeated administration, with no dose-limiting toxicities (DLTs) reported in the cited studies.[12,42,43] They also provided preliminary evidence of immune activation, partial clinical responses, and prolonged disease stabilization in subsets of patients with solid tumors or non-Hodgkin lymphoma.[42,43] Although these studies were conducted in oncology, they established clinical proof of concept for transiently armed, antigen-directed T-cell cytotoxicity.

These first-generation products provide an important conceptual foundation for autoimmune applications by demonstrating transient and adaptable target specificity without permanent genetic modification. Nevertheless, their translation was constrained by labor-intensive T-cell expansion, heterogeneous chemical conjugation, variable arming density, engager dissociation, uncertain tissue distribution and persistence, repeated-dosing requirements, and potential Fc-mediated effects and immunogenicity. The newer recombinant BiPE-armed BAT platform was developed to address several of these limitations through well-defined recombinant engagers and simplified T-cell preparation, although the proposed advantages require direct comparative validation. Successful application in autoimmune disease will depend on reproducible manufacturing, consistent arming potency, controlled depletion of pathogenic B-cell and plasma-cell populations, preservation or restoration of protective humoral immunity, and rigorous prospective evaluation of cytokine-mediated and infectious toxicities.

Lessons from CD3-Redirecting Bispecific Protein Engagers (BiPEs)

Mechanistic basis

CD3-redirecting bispecific T-cell engagers (BiTEs), also referred to here as bispecific protein engagers (BiPEs), simultaneously bind CD3 on T cells and a target-cell antigen, bringing the two cells into close proximity and promoting the formation of an artificial immune synapse. Throughout this review, the term BiPE is used

because BiTE is a registered trademark. This mechanism bypasses the requirement for antigen recognition by the native T-cell receptor and antigen presentation by major histocompatibility complex molecules. Synapse formation activates intracellular calcium signaling and induces T-cell degranulation, perforin and granzyme release, cytokine secretion, and ultimately target-cell apoptosis[12,44] (Fig 3).

This approach was clinically validated by blinatumomab, a CD19×CD3 bispecific T-cell engager used in B-cell acute lymphoblastic leukemia.[44,45] Subsequent approvals have included BCMA×CD3 agents (teclistamab and elranatamab), the GPRC5D×CD3 agent talquetamab, CD20×CD3 agents (epcoritamab, glofitamab, and mosunetuzumab), and the DLL3×CD3 agent tarlatamab[46–52] (Table 2). Although developed for cancer, these drugs validate antigens and cytotoxic mechanisms relevant to autoimmunity.

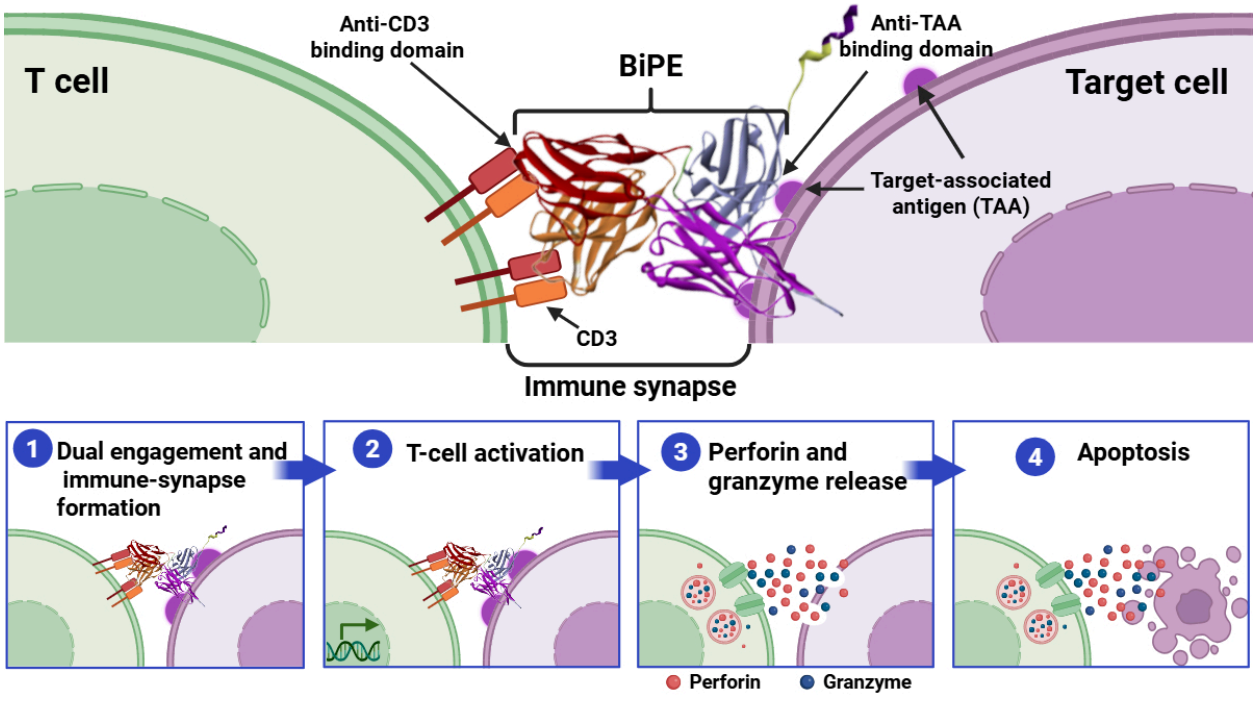


Fig 3. Mechanism of CD3-redirecting bispecific protein engager (BiPE). Simultaneous engagement of CD3 on T cells and a target-cell antigen promotes immune-synapse formation, T-cell activation, and perforin- and granzyme-mediated apoptosis.

TABLE 2. Selected FDA-approved CD3-redirecting bispecific protein engagers (BiPEs).

Drug	Target	Principal oncology indication	References
Blinatumomab	CD19×CD3	B-cell acute lymphoblastic leukemia	[44,45]
Teclistamab	BCMA×CD3	Multiple myeloma	[46]
Elranatamab	BCMA×CD3	Multiple myeloma	[47]
Talquetamab	GPRC5D×CD3	Multiple myeloma	[48]
Epcoritamab	CD20×CD3	B-cell lymphoma	[49]
Glofitamab	CD20×CD3	B-cell lymphoma	[50]
Mosunetuzumab	CD20×CD3	Follicular lymphoma	[51]
Tarlatamab	DLL3×CD3	Small-cell lung cancer	[52]

Relevance to autoimmune disease

CD19 and CD20 provide access to broad B-cell compartments, whereas BCMA is enriched on plasmablasts and plasma cells. The clinical activity of CD19-, CD20-, and BCMA-directed T-cell engagers demonstrates that endogenous polyclonal T cells can eliminate these populations efficiently. This supports analogous BAT designs for antibody-mediated autoimmune diseases (Table 3). Early clinical reports describe clinical benefits of blinatumomab and teclistamab in patients with treatment-refractory autoimmune connective tissue diseases[56] and of a BCMA-targeted T-cell engager in patients with autoimmune hemolytic anemia.[57] OM336, a BCMA×CD3 T-cell engager, is under phase 1b evaluation in autoimmune cytopenias (NCT07083960), although clinical efficacy has yet to be established.[58] These developments support the clinical potential of soluble BiPEs in autoimmunity and provide context for evaluating BATs, whose proposed advantages require clinical validation.

Conversely, oncology experience also highlights predictable risks: CRS, neurotoxicity, cytopenias, hypogammaglobulinemia, opportunistic infection, and target-dependent injury to normal tissues. Soluble engagers distribute pharmacologically active molecules throughout the circulation and may require repeated or continuous administration, particularly for short-half-life formats. In contrast, *ex vivo* arming of T cells may reduce the total engager dose and localize activity to an infused cellular carrier. By limiting prolonged systemic exposure, this surface-loading strategy could provide a more controlled safety profile. Nevertheless, cytokine release, redistribution to non-target tissues, and on-target depletion of normal immune cells require rigorous experimental evaluation.

CAR T-Cell Therapy as Proof of Concept for Immune Resetting

CAR T cells express synthetic receptors comprising an antigen-binding domain, a hinge region, a transmembrane domain, and intracellular costimulatory and CD3ζ signaling modules[53,54] These receptors enable major histocompatibility complex–independent antigen recognition, and the engineered T cells can expand and persist after infusion. In autoimmune diseases, CAR T cells may promote immune resetting by depleting autoreactive B cells and/or plasma cells, followed by reconstitution of a less autoreactive B-cell and plasma-cell compartments (Fig 4).

CD19-directed CAR T-cell therapy has produced rapid and profound B-cell depletion in severe, treatment-refractory SLE, accompanied by reduced disease activity, disappearance or marked reduction of autoantibodies, normalization of complement, withdrawal of glucocorticoids and immunosuppressants, and sustained remission.[8,9] Responses have also been reported in LN, SSc, idiopathic

TABLE 3. Candidate BAT targets for autoimmune diseases.

Target	Principal cell population	Candidate applications	References
CD19	Broad B-cell lineage; some plasmablasts	SLE, LN, Sjögren syndrome, SSc, IIM, autoimmune cytopenias	[8–10,18,55]
CD20	Mature B cells	RA, MS, vasculitis, pemphigus vulgaris	[19,35,36]
CD22	B cells	B-cell-driven autoimmunity	[22]
BAFF-R	B cells	B-cell-driven autoimmunity	[30]
BCMA	Plasmablasts and plasma cells	LN, MG, pemphigus vulgaris, autoimmune cytopenias	[20,22,23,55]
GPRC5D	Plasma cells (expression best validated in malignant plasma cells)	Exploratory plasma-cell targeting; autoimmune target expression requires validation	[48]
CD38	Plasma cells and other activated immune cells	Autoantibody-mediated diseases	[20,22]
CD138	Plasma cells and selected non-hematopoietic tissues	Plasma-cell-driven autoimmunity	[20,22,24]

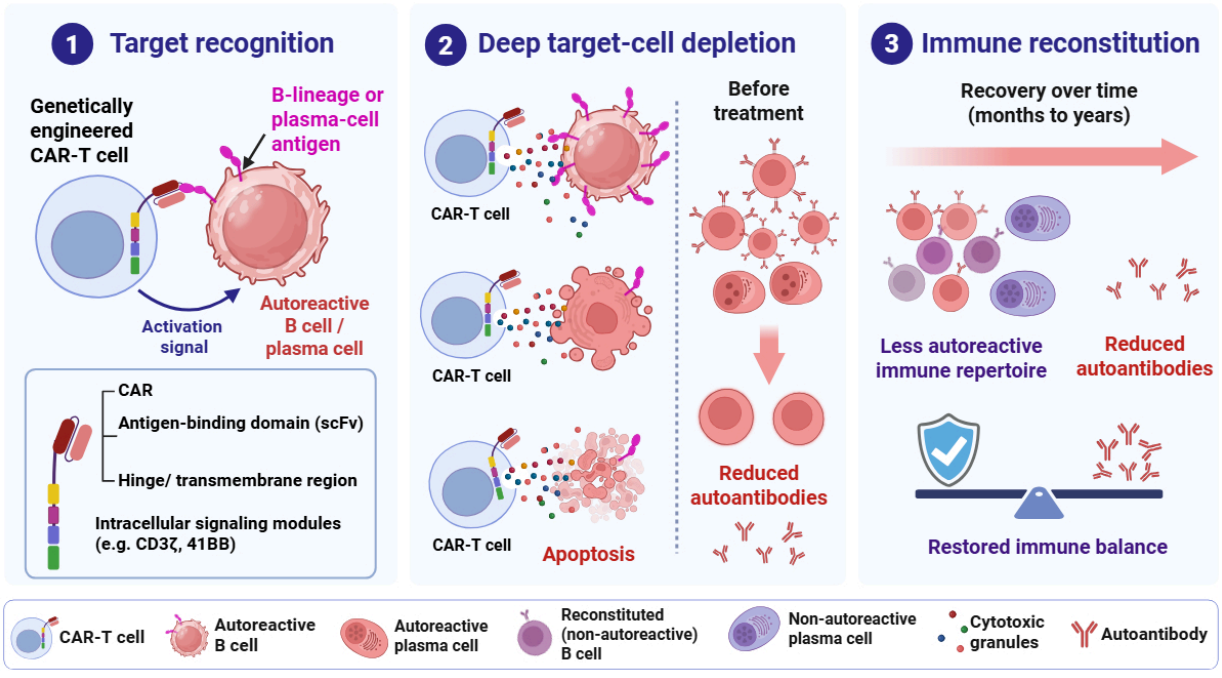


Fig 4. CAR-T-mediated immune resetting. Genetically engineered T cells recognize a B-lineage or plasma-cell antigen, produce deep target-cell depletion, and may permit reconstitution of a less autoreactive immune repertoire.

inflammatory myopathies, MG, Sjögren syndrome, and autoimmune cytopenias.[9,10,55] Persistence of remission after B-cell reconstitution in some patients suggests qualitative renewal of the B-cell compartment rather than temporary pharmacological suppression.

CD19 targeting may not eliminate mature, long-lived plasma cells. BCMA-directed CAR T cells and combined CD19/BCMA strategies are therefore being explored to extend depletion across B-cell differentiation. Dual targeting could reduce incomplete depletion or relapse but may also increase hypogammaglobulinemia and infection risk. The appropriate target breadth is likely to vary according to disease mechanism, the cellular source of pathogenic autoantibodies, previous treatment, and the urgency of organ rescue.

CAR T-cell therapy nonetheless has important limitations. Autologous production requires leukapheresis, genetic engineering, specialized good manufacturing practice (GMP) facilities, extensive release testing, and a vein-to-vein interval that may be problematic in rapidly progressive disease. Commercial oncology products are costly, and persistent engineered cells can make toxicity difficult to reverse. CRS, immune effector cell-associated neurotoxicity syndrome (ICANS), prolonged cytopenias, infection, and loss of humoral immunity remain clinically important.[11] These constraints motivate approaches that preserve directed T-cell cytotoxicity while reducing manufacturing complexity and biological persistence.

BAT Platform: Design, Mechanism, and Therapeutic Position

Product concept and mechanism

BATs are generated by incubating isolated T cells *ex vivo* with a BiPE that binds CD3 and a selected target-cell antigen.[13,23,24,59] After removal of unbound BiPE, the armed T cells are infused into the recipient (Fig 5). Surface-bound BiPE redirects BATs toward antigen-expressing cells, promotes immunological synapse formation, and triggers perforin- and granzyme-mediated apoptosis (Fig 6). Target engagement may also induce release of interferon-γ, TNF-α, and IL-2, which can augment cytotoxic activity but may contribute to inflammatory toxicity.

Because target specificity is conferred by the antigen-binding component of the BiPE rather than by permanent genetic modification of the T cell, a common T-cell starting product could, in principle, be armed with different BiPEs or defined combinations of engagers. Functional activity is expected to diminish as surface-bound BiPEs dissociate and infused T cells contract, potentially providing more controllable exposure than persistently active CAR-T cells. Nevertheless, the kinetics, tissue distribution, and duration of functional arming must be empirically characterized for each BAT product.

Our previous studies established BATs as a modular, non-genetically modified platform for redirecting T cells against multiple myeloma (MM). BATs armed

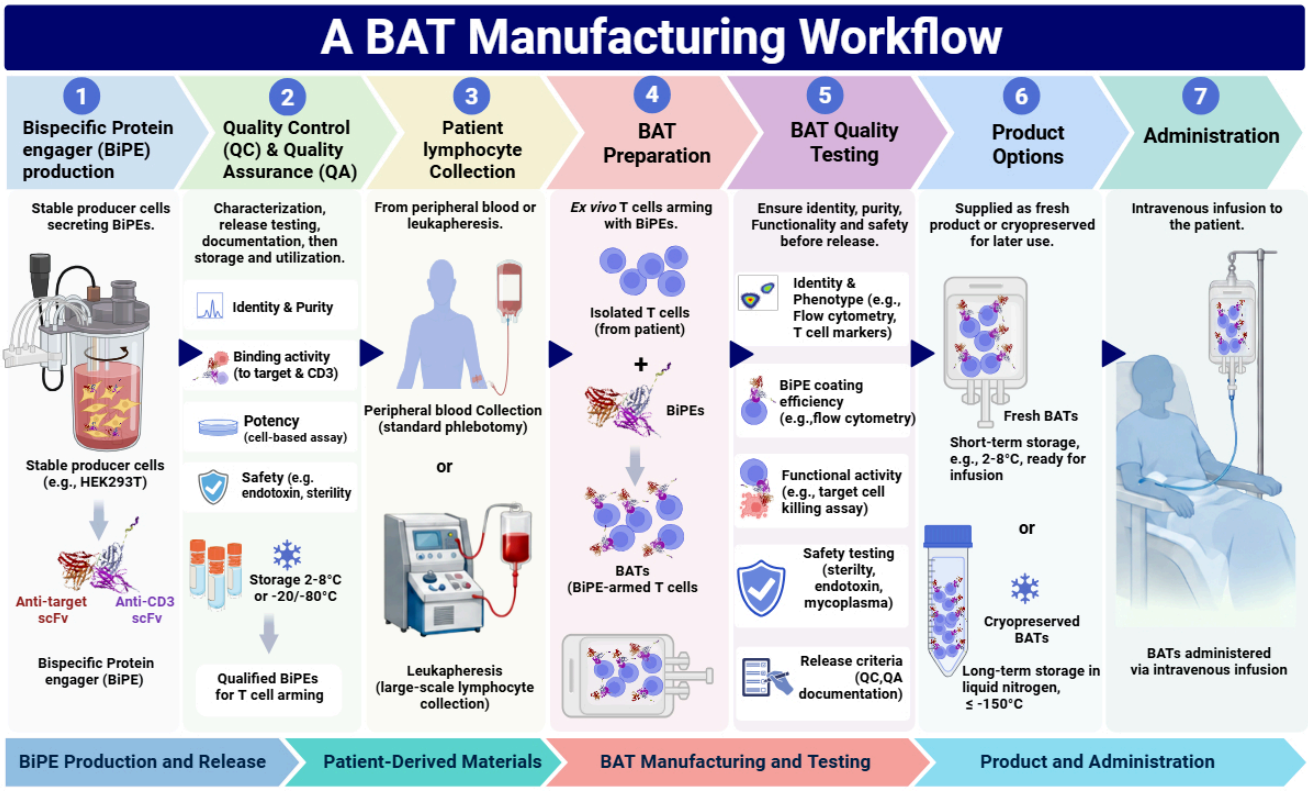


Fig 5. BAT manufacturing workflow. T cells are collected, armed and activated *ex vivo* with a target-specific BiPE, washed, quality tested, and administered fresh or after cryopreservation.

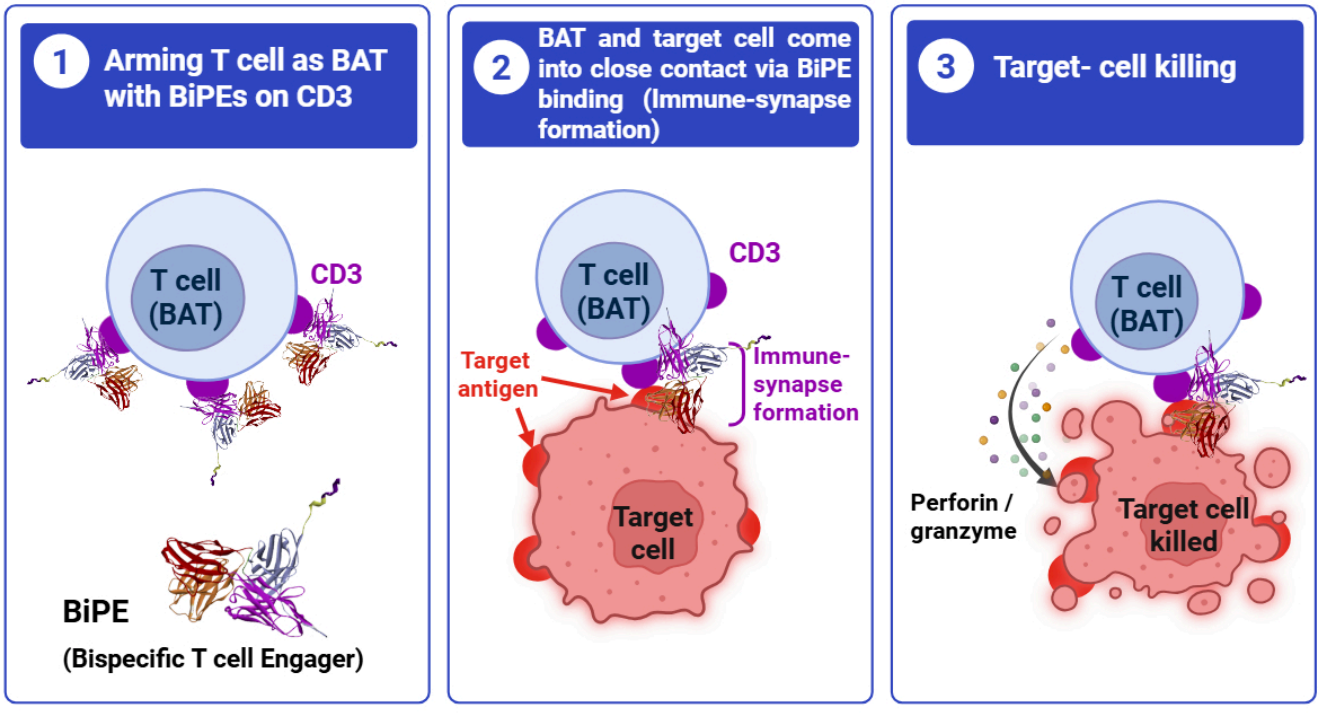


Fig 6. Mechanism of BAT-mediated cytotoxicity. Surface-bound BiPEs connect CD3 on the armed T cell to a disease-associated antigen, enabling immune-synapse formation and target-cell killing without permanent genetic modification.

with anti-BCMA × anti-CD3 or anti-CD138 × anti-CD3 BiPEs induced antigen-specific T-cell activation, proliferation, cytokine production, and cytotoxicity against BCMA- or CD138-expressing MM cells, outperforming unarmed T cells in the tested models, including at low effector-to-target ratios.[23,24] Although IL-6 levels were not significantly elevated in these preclinical studies, this finding does not demonstrate a reduced clinical risk of CRS, which must be closely monitored and rigorously evaluated in clinical trials. Dual BATs targeting BCMA and B7-H3 broadened recognition across antigenically heterogeneous MM models and may reduce vulnerability to single-antigen loss; however, their principal benefit was expanded antigen coverage rather than synergistically enhanced cytotoxic potency, with activity influenced by antigen density, BiPE-binding properties, and the balance of CD3 engagement.[59] These findings support the investigation of BATs in autoimmune diseases, particularly those involving heterogeneous autoreactive B-cell and plasma-cell populations that persist despite conventional immunosuppression or CD20-directed therapy. BCMA- and CD138-directed BATs may enable depletion of pathogenic antibody-secreting plasma cells, while CD19-, CD20-, CD22-, and BAFF-R-directed BATs are also under development to target distinct B-cell compartments. Dual-targeting strategies may further broaden coverage of autoreactive populations. Clinical translation will require careful optimization of target selection, BiPE dose, arming efficiency, and treatment duration, accompanied by rigorous evaluation of cytokine-mediated toxicities, protective plasma-cell depletion, hypogammaglobulinemia, infection risk, and subsequent immune reconstitution.

Potential advantages and limitations

BAT manufacturing does not require viral-vector modification of therapeutic T cells, thereby avoiding vector-mediated genomic integration and its associated risk of insertional mutagenesis. The modular design may facilitate target adaptation, dose fractionation, and repeat administration while simplifying manufacturing and potentially reducing cost. Surface-bound delivery may also require less total BiPE than soluble-engager therapy[13,23,24,59], potentially limiting systemic exposure and reducing, although not eliminating, the risks of CRS and ICANS.

For illustration, a 70-kg patient receiving 10 million BATs/kg would receive 700 million BATs. At an arming ratio of 10 ng BiPE per million T cells[23,24,59], preparation would require 7 μg BiPE. Assuming 80% binding efficiency, removal of unbound protein, and retention of bound BiPE until infusion, the product would carry approximately 5.6 μg BiPE. This mass is approximately 25.5-fold lower than the cumulative 143 μg blinatumomab administered during a reported 12-day continuous intravenous infusion cycle for autoimmune disease, and 750–18,750-fold lower than individual teclistamab doses of 0.06–1.5 mg/kg in a 70-kg patient.[56] These illustrative comparisons concern administered protein mass, not effective dose: differences in molecular format, target, route, exposure duration, and cell-associated delivery preclude conclusions about pharmacological equivalence, comparable efficacy, or improved safety. Direct comparative studies are required to determine whether BATs reduce the engager dose needed for therapeutic activity.

These potential advantages remain largely unproven in autoimmune disease. Limited BAT persistence may improve controllability but could require repeat dosing or limit the depth and duration of immune-cell depletion. Engager shedding or transfer, variable arming density, heterogeneous T-cell fitness, and rapid product clearance may further affect potency and product consistency. Despite transient targeting, activated T cells can still cause cytokine-mediated toxicity, depletion of protective immune cells, and infection-related complications. BATs therefore require evaluation as a distinct therapeutic platform with specific pharmacological, manufacturing, and safety considerations; greater safety than CAR-T-cell therapy cannot be assumed.

A key translational gap is the fitness of autologous T cells from patients with severe refractory autoimmune diseases, which may differ substantially from the healthy-donor or cancer-patient T cells evaluated in preclinical BAT studies. Chronic immune activation and prior immunosuppressive therapies may alter T-cell abundance, phenotype, exhaustion, and function, potentially compromising BAT cytotoxicity and persistence; their effects on BiPE arming efficiency and surface retention remain unknown. Potential mitigation strategies include collecting autologous T cells after a clinically appropriate drug washout and documented recovery of T-cell numbers and function, where disease control permits treatment interruption. Alternatively, healthy HLA-matched related or unrelated donor T cells could be considered for BAT preparation, although HLA matching alone does not prevent graft-versus-host disease or host rejection. These approaches require validation through assessment of BAT arming, potency, persistence, and safety.

Therapeutic positioning

Table 4 compares key characteristics of four therapeutic platforms: monoclonal antibodies, soluble CD3 engagers,

TABLE 4. Comparison of therapeutic platforms.

Feature	Monoclonal antibodies	Soluble CD3 engagers	CAR-T cells	BATs
Genetic modification	No	No	Yes	No
Primary mechanism	Blockade, depletion, or immune modulation	Endogenous T-cell redirection	Engineered T-cell recognition	Armed T-cell redirection
Manufacturing complexity	Low	Low	Very high	Moderate (projected)
Typical persistence	Days to weeks	Hours to weeks, format dependent	Months to years	Transient; duration not yet established
Target flexibility	Moderate	High	Requires new construct and cell product	High through modular arming
Repeat dosing Treatment cost	Usually required High	Usually required High	Often single infusion Very high	May be required Potentially lower; not yet established
Principal concerns	Chronic immunosuppression, infection	CRS, infection, repeated exposure	CRS, ICANS, prolonged cytopenias and immune deficiency	CRS, variable arming, uncertain durability
Evidence in autoimmune disease	Extensive	Limited	Emerging clinical evidence	Preclinical concept; clinical evidence needed

CAR T cells, and BATs. Monoclonal antibodies benefit from established manufacturing processes and generally predictable pharmacology, but they often require repeated or long-term administration. Soluble CD3-engaging molecules can elicit potent T-cell-mediated cytotoxicity; however, they expose endogenous circulating T cells systemically to pharmacologically active engagers. CAR T cells can produce profound and durable target-cell depletion but require genetic modification and may remain functionally active for months or years. BATs may represent an intermediate approach that combines adoptively transferred cytotoxic cells with modular target specificity and potentially controllable persistence (Fig 7). Accordingly, BATs warrant evaluation in patients who require deeper immune-cell depletion than conventional biologics typically achieve but for whom prolonged activity of genetically engineered cellular therapy may be unnecessary or impractical.

BATs could potentially initiate immune resetting if they achieve sufficiently deep and sustained depletion of autoreactive B cells and/or plasma cells, permitting reconstitution with non-pathogenic populations. This would require adequate tissue penetration and targeting of disease-driving cellular compartments to limit survival or re-expansion of pathogenic clones. Given their transient activity, BATs may require repeated administration; the necessary duration of depletion and role of lymphodepletion conditioning remain unresolved. Immune resetting therefore cannot be inferred from temporary depletion alone and requires longitudinal evidence of repertoire renewal and sustained treatment-free remission after immune reconstitution.

Target Selection and Potential Disease Applications

B-cell targets

The major candidate surface antigens for B-cell-directed BAT therapy are summarized in Fig. 8. CD19 is broadly expressed from early B-cell development through most mature B-cell stages[18] and is retained on a subset of plasmablasts. Accordingly, CD19-directed BATs could deplete naïve, memory, and activated autoreactive B cells, thereby disrupting autoantigen presentation, limiting pathogenic B–T-cell interactions, and reducing the generation of new antibody-secreting cells. CD20 is a well-established therapeutic target expressed on most mature B cells and has been clinically validated in RA,

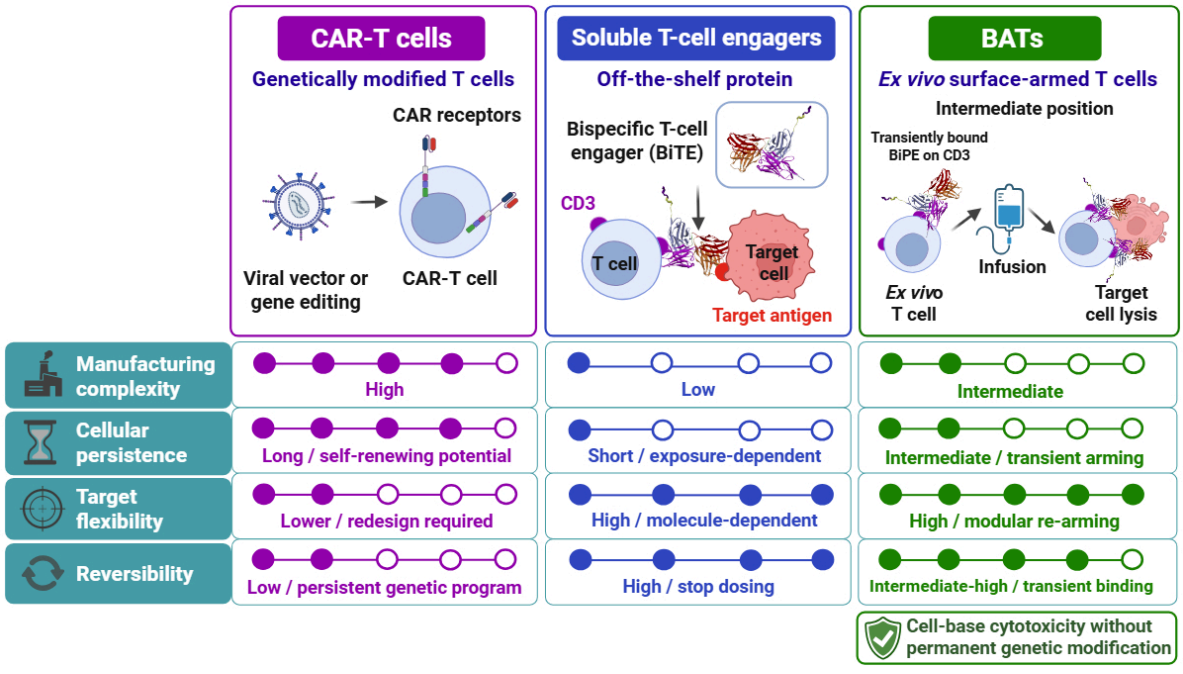


Fig 7. Therapeutic positioning of BATs. BATs occupy an intermediate position between soluble T-cell engagers and CAR-T cells with respect to manufacturing complexity, persistence, target flexibility, and reversibility.

MS, ANCA-associated vasculitis, pemphigus vulgaris, and other B-cell-mediated autoimmune diseases.[19] However, its absence from most plasmablasts and plasma cells limits its ability to directly eliminate established antibody-secreting populations. CD22, another B-lineage-restricted surface antigen, has an expression profile distinct from those of CD19 and CD20[22] and may therefore provide an alternative or complementary target for single or combinatorial BAT strategies. BAFF-R is expressed predominantly on transitional and mature B cells and therefore represents a potential target for depletion of autoreactive B-cell populations. In contrast, BAFF-R is downregulated during differentiation into antibody-secreting cells, whereas TACI (transmembrane activator and calcium modulator and cyclophilin ligand interactor) and BCMA become more prominent. Thus, BAFF-R-directed BATs would be expected to preferentially deplete autoreactive B cells while largely sparing plasmablasts and plasma cells.[30] Collectively, these differences in lineage and differentiation-stage expression provide a biological rationale for selecting individual B-cell targets, or combining them with plasma-cell-directed targets, according to the cellular drivers of specific autoimmune diseases.

Plasma-cell targets

Candidate immunotherapeutic targets expressed on plasmablasts and plasma cells include BCMA, CD38, CD138, and GPRC5D (Fig 8). BCMA is preferentially expressed on antibody-secreting cells, particularly plasmablasts and plasma cells, making it an attractive target for diseases driven by pathogenic autoantibodies, including SLE/LN, MG, pemphigus vulgaris, and autoimmune cytopenias.[20,22,23] CD38 and CD138 may enable broader depletion of antibody-secreting cells; however, their expression in additional hematopoietic and nonhematopoietic tissues increases the potential for on-target, off-disease toxicity.[20,22,24] GPRC5D is clinically validated as a target in plasma-cell malignancies, but its expression and functional relevance in normal and autoreactive antibody-secreting cells remain incompletely characterized. Its application in autoimmune disease should therefore be considered exploratory.[48] Moreover, clinical experience with GPRC5D-directed therapies in multiple myeloma has identified characteristic taste, cutaneous, hair, and nail toxicities, consistent with GPRC5D expression in keratinized tissues.[48] Because plasma-cell depletion may impair protective humoral immunity, the required depth and duration of depletion must be balanced against therapeutic benefit and the risks of hypogammaglobulinemia and infection.

Multi-compartment targeting

Sequential or combined BAT products directed against autoreactive B cells and antibody-secreting plasma cells—such as CD19 × CD3 or CD20 × CD3 BATs paired with BCMA × CD3 BATs—may achieve more comprehensive immune-cell depletion than single-target

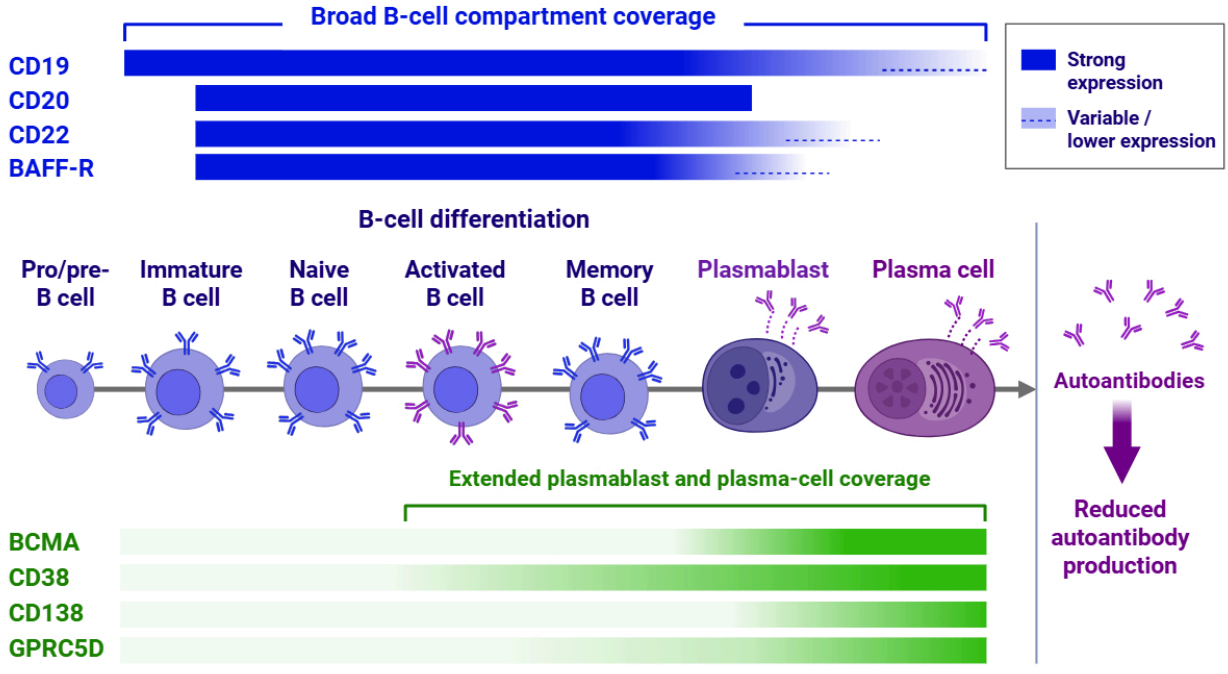


Fig 8. Candidate BAT targets across B-cell differentiation. CD19, CD20, CD22, and BAFF-R target broad B-cell compartments, whereas BCMA, CD38, CD138, and GPRC5D extend coverage toward plasmablasts and plasma cells.

therapy.[22,59] GPRC5D could provide an alternative or complementary plasma-cell target only if expression on the relevant pathogenic cells is demonstrated.[48] Broader and deeper depletion may increase the risks of hypogammaglobulinemia, infection, and target-specific off-tissue toxicity; therefore, simultaneous and sequential strategies should be compared directly using biomarker-guided patient selection and staged dose escalation.

Candidate Diseases

Systemic lupus erythematosus and lupus nephritis. SLE is sustained by autoreactive B cells, plasmablasts, plasma cells, autoantibodies, immune complexes, and inflammatory tissue injury. CD19- or CD20-directed BATs could broadly deplete B-cell populations, whereas BCMA-, GPRC5D-, CD38-, or CD138-directed BATs could target persistent antibody-secreting cells.[8,18,20,37,38,55] Severe refractory lupus nephritis (LN) may represent a compelling initial indication because of its substantial morbidity, incomplete responses to current therapies, and measurable clinical, serological, and renal outcomes.

Rheumatoid arthritis. B cells contribute to rheumatoid arthritis through autoantibody production, antigen presentation, and cytokine secretion. CD19- or CD20-directed BATs may achieve deeper B-cell depletion than monoclonal antibodies; however, their incremental benefit must justify the additional risks in a disease with several effective approved therapies.[19,32]

Neuromyelitis optica spectrum disorder. AQP4-IgG-positive NMOSD is mediated by pathogenic autoantibodies produced by plasmablasts and plasma cells.[20-22,60] CD19-directed BATs could target the broader autoreactive B-cell lineage, whereas BCMA-directed BATs could potentially deplete persistent antibody-secreting cells, thereby reducing AQP4-IgG production and relapse risk. GPRC5D-directed therapy would require prior demonstration of target expression on the pathogenic antibody-secreting compartment.

Multiple sclerosis. The efficacy of ocrelizumab and ofatumumab validates B cells as therapeutic targets in multiple sclerosis.[35,36] BATs must demonstrate added value over these highly effective therapies and establish whether peripheral B-cell depletion can adequately control compartmentalized central nervous system inflammation.

Sjögren syndrome and systemic sclerosis. B-cell hyperactivity and autoantibody production provide a rationale for CD19- or CD20-directed BATs, supported by emerging responses to CD19-directed CAR-T therapy.[9,19,22,61] Nevertheless, organ-specific outcomes, irreversible tissue damage, and the optimal timing of intervention require careful evaluation.

Myasthenia gravis and other autoantibody-mediated diseases. In myasthenia gravis, pemphigus vulgaris, autoimmune hemolytic anemia, and immune thrombocytopenia, the direct pathogenic roles of autoantibodies support evaluation of both B-cell- and

plasma-cell-directed approaches.[19-22,55] BCMA-directed BATs may be particularly relevant when autoantibody production persists despite CD20-directed depletion; GPRC5D-directed BATs should be considered only after disease-specific target expression has been established.

BATs targeting activated T cells or myeloid populations—including OX40, ICOS, CD25, CD64, or CD86—are also conceptually feasible but remain less developed. Because these antigens are shared with protective immune-cell subsets, such approaches may have narrower therapeutic windows than B-cell- or plasma-cell-directed strategies.

Safety and Clinical Development

Acute immune-effector toxicities

CRS is the principal anticipated acute toxicity, based on experience with CD3-redirecting engagers and CAR-T cells.[53,54] Rapid T-cell activation may cause fever, hypotension, hypoxia, and organ dysfunction. First-in-human trials should use conservative dose escalation, step-up or fractionated dosing, close early monitoring, and predefined management algorithms. Because ICANS risk with BATs in autoimmune disease is unknown, prospective neurological assessment is required.

On-target immune deficiency

Targeting CD19, CD20, or BCMA may cause prolonged immune-cell depletion, hypogammaglobulinemia, impaired vaccine responses, and infection. Baseline assessment should include immune-cell subsets, immunoglobulins, infection history, vaccination status, and relevant latent infections. Follow-up should monitor immune reconstitution, immunoglobulin recovery, infections, and the need for antimicrobial prophylaxis or immunoglobulin replacement.

Target specificity and patient selection

Candidate targets should be evaluated across normal tissues and immune subsets, including cells that upregulate the antigen during inflammation. Pharmacodynamic biomarkers should measure the depth and duration of target-cell depletion in blood and, where feasible, affected tissues. Early trials should prioritize severe, active, treatment-refractory disease with measurable activity and potentially reversible organ dysfunction.

Durability and retreatment

Transient BAT activity may improve controllability but limit durable immune resetting. Trials should assess BAT persistence, target-cell depletion, immune-repertoire reconstitution, autoantibody kinetics, organ response, and treatment-free remission. Retreatment may be feasible but requires evaluation of BiPE immunogenicity, target expression, immune reconstitution, and T-cell fitness.

Repeated BAT administration may elicit anti-drug antibodies (ADAs) against the anti-CD3 or anti-target scFvs of BiPEs, potentially impairing binding, accelerating BiPE clearance, and reducing BAT potency. Although the low BiPE load and removal of unbound protein may limit exposure compared with repeated soluble BiPE infusions, a lower ADA risk remains unproven because cell-bound BiPE remains accessible to circulating antibodies. Retreatment studies should monitor binding and neutralizing ADAs, BiPE surface retention, and BAT cytotoxicity. Humanized or fully human scFvs may reduce, but cannot eliminate, immunogenicity.

Lymphodepletion conditioning

Whether BAT therapy requires lymphodepletion conditioning remains unresolved. Initial clinical studies could evaluate BATs without conditioning. If insufficient persistence or efficacy supports its use, a reduced-intensity regimen could be investigated, although the agents, doses, and timing would require prospective evaluation. Conditioning would add risks of cytopenias, infection, and organ toxicity, potentially diminishing the safety advantages of transient BAT therapy; its benefit must therefore be weighed against these additional risks.

Manufacturing and Translational Development

Manufacturing workflow

A BiPE typically comprises an anti-CD3 single-chain variable fragment (scFv) linked to an scFv directed against a B-cell, plasmablast, or plasma-cell antigen. For example, an expression cassette may be introduced into HEK293T cells to generate a stable BiPE-secreting producer cell line. The secreted BiPE is then purified from culture supernatant, characterized, and used to arm T cells (Fig 5). The producer-cell engineering method is distinct from genetic modification of the final therapeutic T-cell product.

Autologous BAT manufacturing comprises blood collection, T-cell isolation, BiPE arming, removal of unbound protein, formulation, release testing, and fresh infusion or cryopreservation[13,23,24,59] (Fig 5). Unlike CAR-T manufacturing, BAT production avoids genetic modification of the therapeutic cells but still requires aseptic processing, reproducible arming, and validated potency testing.

Product characterization and release testing

Release criteria should include T-cell identity and composition, viable cell count, viability, arming

efficiency or surface BiPE density, functional potency, sterility, mycoplasma, endotoxin (Fig 5), and relevant process- or product-related impurities. Potency assays should demonstrate BiPE-dependent target recognition and cytotoxicity, with cytokine release assessed as a complementary functional and safety-related attribute. Stability studies should define retention of identity, viability, arming, and potency during the intended hold period and after cryopreservation, when applicable.

Autologous and allogeneic development

Autologous BATs minimize alloreactivity but retain individualized logistics and product variability. Allogeneic BATs could improve availability and scalability but introduce risks of graft-versus-host disease, rejection, and limited persistence. Mitigation may require donor selection, defined T-cell subsets, alloreactive-cell depletion, or gene editing, although genetic modification would increase manufacturing complexity.

Translational evidence required

Preclinical studies should define antigen-density thresholds, target selectivity, serial killing, cytokine profiles, BiPE stability, biodistribution, tissue access, and activity against patient-derived cells. BATs should be compared with unarmed T cells and, where feasible, the corresponding monoclonal antibody, soluble engager, and CAR-T cells. Models should also evaluate depletion of normal immune cells, infection risk, and recovery of humoral immunity.

Future Perspectives

The immediate priority is to establish whether BATs improve the therapeutic index of immune-cell depletion rather than maximize engineering complexity. Early development should target diseases with a well-defined pathogenic cell population, substantial unmet need, measurable responses, and biological rationale for transient depletion. Severe refractory SLE/LN and selected autoantibody-mediated diseases meet many of these criteria.

Biomarker-guided strategies could align BAT targets with dominant pathogenic compartments. Flow cytometry, autoantibody profiling, B-cell receptor sequencing, single-cell transcriptomics, and tissue analysis may distinguish CD19/CD20-driven disease from persistent plasma-cell-mediated autoimmunity and determine whether remission reflects transient depletion or durable immune-repertoire renewal.

Dual-target or trispecific platforms may broaden depletion or provide co-stimulation but increase pharmacological uncertainty. Additional specificities should therefore address demonstrated antigen escape, incomplete compartment depletion, or a defined mechanistic need. Cryopreservation, standardized arming, and centralized manufacturing could improve consistency and accessibility. Ultimately, comparative clinical studies must determine whether BATs provide meaningful advantages over optimized biologics, soluble engagers, or CAR-T cells.

CONCLUSIONS

Monoclonal antibodies, CD3-redirecting BiPEs, and CAR T cells demonstrate both the therapeutic potential and the risks of targeted immune-cell depletion. CAR T-cell studies provide proof of concept that profound B-cell depletion can induce durable, treatment-free remission in severe autoimmune diseases; however, genetic engineering, complex manufacturing, high cost, and potentially prolonged immune deficiency may limit broader use.

BATs combine *ex vivo*-prepared T cells with externally applied, target-specific BiPEs, offering a modular, non-genetically modified approach to immune-cell depletion. Proposed advantages include adaptable targeting, controllable functional persistence, simpler manufacturing, low cost, and independent or combined targeting of B cells and plasma cells. These potential advantages require validation in comparative preclinical studies and carefully designed clinical trials.

Successful translation will depend on defining target expression, tissue access, product potency, depletion kinetics, acute and delayed toxicity, immune reconstitution, and treatment-free remission. If these requirements are met, BATs could bridge the gap between repeatedly administered biologics and persistent CAR T cells, providing a scalable immune-resetting strategy for selected patients with refractory autoimmune diseases.

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Conflicts of Interest

The author declares no conflicts of interest related to this review.

Author Contributions

PY is the sole author and was responsible for conceptualization, planning and structuring the review, collecting data and gathering information, drafting the original manuscript, and reviewing and editing the final manuscript. The author has read and approved the final version of the manuscript.

Use of Artificial Intelligence

The author declares that artificial intelligence (AI) tools were used to assist with literature searching, manuscript-draft preparation, and English-language editing, and to improve writing clarity. The author retains full responsibility for the originality, conceptualization, structure, scientific content, and integrity of the article.

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