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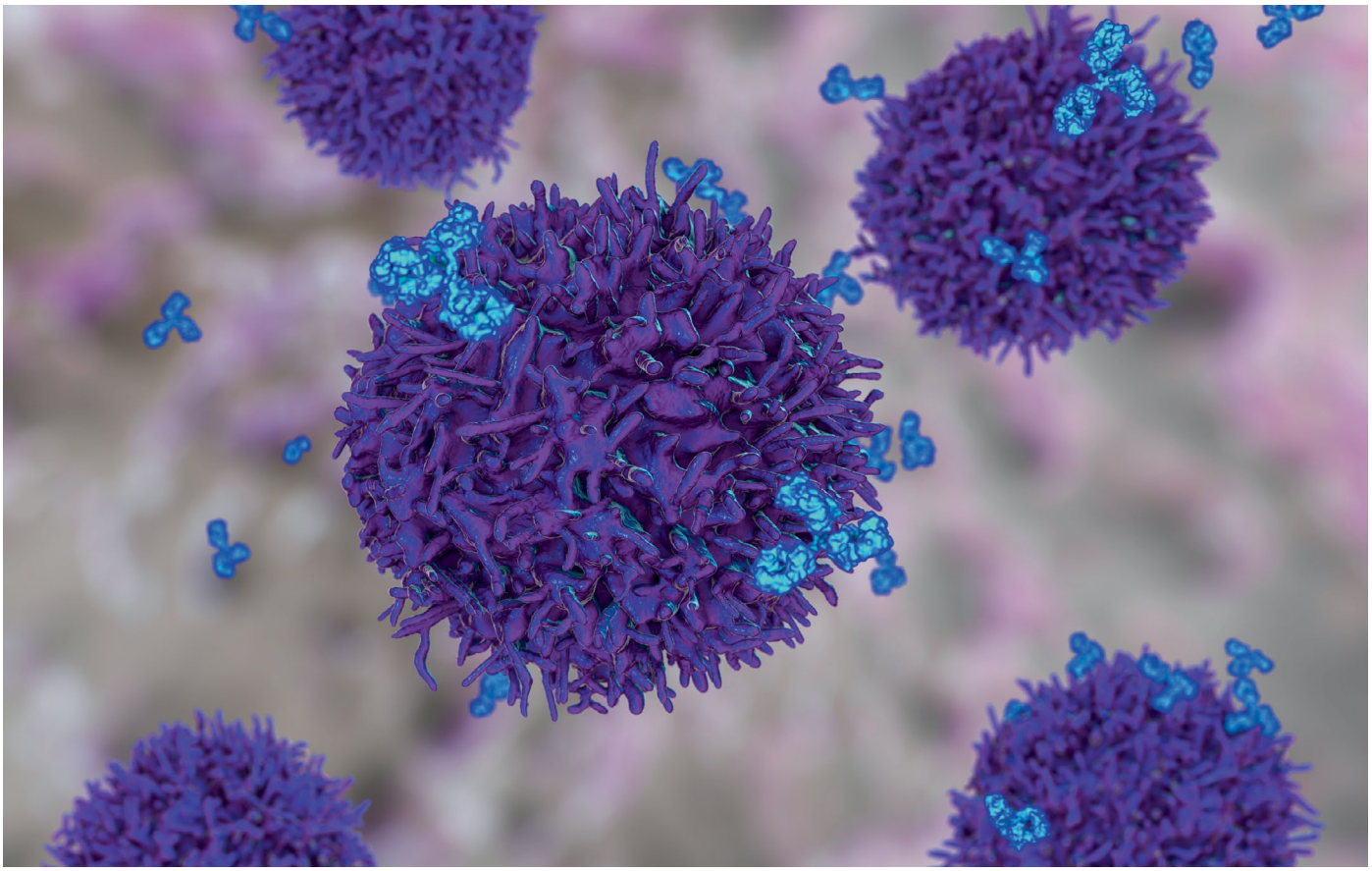

B CELL DEPLETION IN AUTOIMMUNE DISEASE: IN VIVO CAR-T OR T CELL ENGAGERS?

Deep B cell depletion is delivering transformative clinical results in autoimmune diseases. Dealmakers are wagering on the best tools for the job. **By Melanie Senior & Ricardo Grieshaber-Bouyer**

A growing body of clinical evidence suggests that deep B cell depletion can prolong remission from several autoimmune conditions, transforming treatment options in a field that has seen relatively few major advances in the last 20 years. Current cancer drugs like chimeric antigen receptor (CAR)-T cell therapies and T cell engagers (TCEs) are being redeployed to deplete autoimmune disease-causing B cell populations, enabling immune system 'reset' with new, non-pathogenic B cells. The market size – up to one in ten adults in developed countries such as the US and UK are affected by an autoimmune condition – has drugmakers scrambling to identify the safest, most effective and most practical B cell-depleting modalities.

The largest deals and financings have focused on in vivo CAR programs[1] and T cell- or myeloid cell-engaging bispecific antibodies. AbbVie in June 2025 paid over $2 billion for Capstan Therapeutics and a CD19 CAR-T candidate in phase 1 for B cell-mediated

Table 1 | Key B cell depletion acquisitions and licensing deals, 2024–2025

Companies (deal type)	Date	Modality	Total cost or up front/milestones
Eli Lilly–Orna Therapeutics (acq.)	February 2026	In vivo CAR-T (mRNA–LNP, CD19)	Up to $2.4 billion
Sanofi–Dren Bio (collab.)	December 2025	MCE — broad B cell depletion discovery collab.	$100 million/$1.7 billion
Boehringer Ingelheim–CDR-Life (lic.)	November 2025	TCE (CD3 × CD19 × BCMA)	$48 million/$522 million
Johnson & Johnson–Kelonia Therapeutics (collab.)	November 2025	In vivo CAR-T	Undisclosed
BMS–Orbital Therapeutics (acq.)	October 2025	In vivo CAR-T (mRNA–LNP, CD19)	$1.5 billion
Gilead Sciences–Pregene Biopharma (collab.)	October 2025	In vivo CAR-T (lenti; targets undisclosed)	$120 million/$1.52 billion
Gilead Sciences–Interius BioTherapeutics (acq.)	August 2025	In vivo CAR-T and CAR-NK (lenti, CD20)	$350 million
Eli Lilly–LTZ Therapeutics (collab.)	Jul 2025	MCE research collab.	Undisclosed
AbbVie–Capstan Therapeutics (acq.)	June 2025	In vivo CAR-T (mRNA–LNP, CD19)	$2.1 billion
Otsuka Pharmaceutical–Harbour BioMed	June 2025	TCE (BCMA × CD3); ex-Greater China rights	$47 million (up front and near-term milestones)/$623 million
Cullinan Therapeutics–Genrix Bio (lic.)	June 2025	TCE (BCMA × CD3): velinotamig	$20 million/$692 million
Boehringer Ingelheim–Cue Biopharma	April 2025	TCE (CD19 × CMV-specific memory T cells)	$12 million/$345 million
AstraZeneca–EsoBiotec (acq.)	March 2025	In vivo CAR-T (lenti, BCMA)	$425 million/$575 million
Sanofi–Dren Bio (lic.)	March 2025	MCE (CD20)	$600 million/$1.3 billion
Prolium Bioscience–InnoCare Pharma and KeyMed Biosciences (lic.)	January 2025	TCE (CD20 × CD3); Prolium gets global (non-oncology) and ex-Asia (oncology) rights	Up to $520 million up front and in milestones
Roche–Poseida Therapeutics (acq.)	November 2024	Allog. CAR-T (CD19/CD20 & BCMA)	$1 billion/$500 million
Ouro Medicines–KeyMed Biosciences (lic.)	November 2024	TCE (BCMA × CD3)	$16 million/$610 million
Oblenio Bio–Nanjing Leads Biolabs (lic.)	November 2024	TCE (CD19 × BCMA × CD3); Oblenio launched with option on the drug	Up to $35 million/$579 million
GlaxoSmithKline–Chimagen Biosciences (lic.)	October 2024	TCE (CD19/CD20)	$300 million/$550 million
Candid Therapeutics–Vignette Bio and TRC 2004 (acq. & financing)	September 2024	BCMA × CD3 (from Vignette) and CD20 × CD3 (from TRC 2004), launching Candid	$370 million (capital raise)
Merck & Co.–Curon Biopharmaceutical (lic.)	August 2024	TCE (CD19)	$700 million/$600 million
Biogen–HI-Bio (acq.)	May 2024	Antibody (CD38): felzartamab	$1.15 billion/$650 million

Acq., acquisition; allog., allogeneic; CMV, cytomegalovirus; collab., collaboration; lenti, lentivirus; lic., licensing; LNP, lipid nanoparticle; BCMA, B cell maturation antigen; MCE, myeloid cell engager.

autoimmune diseases; Bristol Myers Squibb (BMS) followed suit months later with a $1.5 billion deal for Orbital Therapeutics and their CD19-targeted CAR. Sanofi signed a $600 million up-front licensing deal for Dren Bio's CD20-directed myeloid cell engager in March 2025 and expanded the collaboration at year-end .(Table 1).

Current B cell-targeted autoimmune disease drugs like the CD20 antibodies Rituxan (rituximab), Ocrevus (ocrelizumab) or Gazyva (obinutuzumab) work through continuous, long-term immunosuppression, and their symptom-curbing effects are temporary. Today's standard of care often includes daily steroids alongside chronic antibody therapy.

New approaches aim to avoid these long treatment regimens and concurrent side effects. Alongside B cell-depleting CAR-T cell therapies and TCEs, developers are also harnessing other immune cell types, drug modalities and targets across a range of autoimmune conditions. No new B cell-depleting modality has yet been approved in the area, and even the most valuable deals are for assets still early in clinical or even in preclinical development. But the race is on to reach what could be a new treatment frontier. "The concept of drug-free remission — no signs of disease, and no therapy, over several years — is dramatic. It would not happen with [current] antibody therapy," says Georg Schett, vice president research at Friedrich Alexander University (FAU) in Erlangen, Germany.

Proof of concept: ex vivo CAR-T

Approved CAR-T therapies including Novartis's CD19-targeted Kymriah (tisagenlecleucel) or Johnson & Johnson's B cell maturation antigen (BCMA)-targeted Carvykti (ciltacabtagene) are engineered to recognize and destroy malignant B cells responsible for blood cancers like multiple myeloma or lymphoma. This approach can also knock out the self-directed B cells that underpin autoimmune diseases. Schett and his team have provided proof of concept for B cell depletion in autoimmune disease using autologous CAR-T cell therapies and set the benchmark for treatment efficacy and duration.

One of the first patients to receive CAR-T cell therapy in a non-cancer setting — a young adult with lupus — has been in drug-free remission since 2021. If that continues, by March 2026 she will have been in remission for five years, and "we would declare this patient cured," says Schett, whose team ran this case study and several larger studies (Table 2).

The more sustained responses seen with CAR-T cells relative to existing antibody therapies are likely to result from their ability to proliferate inside the body and from their active migration to reach B cells in a wider range of tissues than shorter-lived antibodies (which undergo passive diffusion). This matters because B cells show differential susceptibility

Table 2 | Selected clinical-stage cell therapy and T cell engager programs in autoimmune diseases

Sponsor	Cell therapy	Indications	Phase
Cartesian Therapeutics	BCMA CAR-T (RNA-encoded; autol.)	MG	3
Bristol Myers Squibb	CD-19 CAR-T (autol.): zolacabtagene autoleucel	SSc	3
		SLE, LN	2
Kyverna Therapeutics	CD-19 CAR-T (autol.)	Stiff person syndrome	2
Artiva Biotherapeutics	NK cell (allog.) + Rituxan	RA, SJD	2
Autolus	CD19 CAR-T (autol.): obecabtagene autoleucel	SLE, LN	2
Novartis	CD19 CAR-T (autol.): rapcabtagene autoleucel	IIM, SSc, SLE, LN, GPA, MPA	2
AstraZeneca	CD19/BCMA dual-targeting CAR-T (autol.)	SLE, SSc, IIM, RA, MS	1/2
Miltenyi Biotec	CD19 CAR-T (autol.)	SLE, SSc, IIM	1/2
Cabaletta Bio	CD19 CAR-T (autol.): resecabtagene autoleucel	SLE, SSc, IIM, multiple	1/2
Shenzhen MagicRNA Biotechnology	mRNA LNP encoding a CD19 CAR (in vivo)	SLE	1/2
		Graves' disease	1
Bristol Myers Squibb	CD19 CAR-T (autol.)	SLE, MG	1/2
	CD19 CAR-T (allog.)	SLE	1
Century Therapeutics	CD19 CAR NK (allog. iPSC derived)	SLE, SSc, IIM	1/2
Adicet Bio	CD20 CAR-T (allog.)	SLE, LN	1/2
Fate Therapeutics	iPSC-derived CD19 CAR-T (allog.)	SLE, SSc	1
Allogene Therapeutics	CD19/CD70 dual targeting CAR-T (allog.)	SLE, IIM, SSc	1
AbbVie (Capstan)	mRNA LNP with CD19 CAR-T (in vivo)	Healthy volunteers	1
Umoja Biopharma, Nanjing IASO Biotherapeutics	Lentiviral CD22 CAR-T (in vivo)	SLE, LN	1
Grit Biotherapeutics	mRNA LNP with CD19 CAR-T (in vivo)	Refractory AID	1
RiboX Therapeutics	Circular RNA-mediated CD19 CAR-T (in vivo)	Severe AID	1
Starna Therapeutics	mRNA LNP with CD19 CAR-T (in vivo)	Refractory AID	1
Sponsor (originator)	**T cell engager target (drug)**	**Indications**	**Phase**
Amgen	CD19 (blinatumomab)	RA, SLE	2
Roche	CD20 (mosunetuzumab)	SLE	2
	CD19	SLE	1
Candid Therapeutics (Genor Biopharma; Vignette Bio)	CD20	SLE	1/2
	BCMA (cizutamig)	SJD, IIM, RA, SSc, MG	
Xencor	CD20 (plamotamab)	RA	1b/2a
	CD19	IIM	1
Cullinan Therapeutics	CD19	RA, SLE, SJD	1
	BCMA (velinotamig)	SLE	1/2
Novartis	CD19	SLE, RA	1b
Ouro Medicines (KeyMed Biosciences)	BCMA (gamgertamig)	ITP, AIHA, SJD, IIM	1b
Qilu Pharmaceutical	BCMA/GPRC5D dual targeting	SLE	1b
AstraZeneca	CD19 (surovatamig)	SLE, RA	1
	CD20	SLE, IIM, RA	
Merck & Co. (Curon)	CD19	SLE, RA	1
GlaxoSmithKline (Chimagen)	CD19 and CD20	SLE	1
Regeneron	BCMA (vonsetamig)	LN	1
	BCMA (linvoseltamab) + dupilumab	Food allergy	
	CD20 (odronextamab)	LN	
Prolium (InnoCare, KeyMed Biosciences)	CD20	SLE	1
Janux Therapeutics	CD19	Not disclosed	1
Kali Therapeutics	BCMA and CD19	RA	1

AID, autoimmune disease; AIHA, autoimmune hemolytic anemia; allog., allogeneic; autol., autologous; GPA, granulomatosis with polyangiitis; IIM, idiopathic inflammatory myositis; ITP, immune thrombocytopenia; LN, lupus nephritis; MG, myasthenia gravis; MPA, microscopic polyangiitis; RA, rheumatoid arthritis; SJD, Sjogren's disease; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

BOX 1

B cell targets

Most of the almost 200 CAR-T and TCE assets in development across autoimmune diseases target CD19 or CD20, the most widely expressed antigens on B cells. CD19 is expressed during developmental stages from immature precursors — pro-B cells — to antibody-secreting plasmablasts and a portion of plasma cells. CD20's scope is slightly narrower — it does not feature on early pro-B cells or differentiated plasma cells but covers mature and memory B cells.

Yet clinical differences between the two targets remain incompletely understood — there are no head-to-head data comparing CD19 against CD20 using the same targeting modality. GlaxoSmithKline (after acquiring a molecule from Chimagen) and Candid Therapeutics are trying to cover the bases: Candid's trispecific CD19 × CD20 × CD3 is scheduled to enter the clinic in 2026. They are also working on a TCE targeting CD19 and BCMA, another popular target.

BCMA is expressed on (normal and malignant) B cells and on antibody-secreting plasma cells. Depleting plasma cells via BCMA or CD38 (the target of Johnson & Johnson's myeloma drug Darzalex (daratumumab)) may have differential benefit in some indications, relative to CD19- or CD20-mediated B cell depletion alone. Anti-BCMA drugs come with a particularly high risk of infection, however.

Other B cell targets under investigation include BAFF-R, TACI, CD21, CD22, CD79b, FCRL5 and GPRC5D.

to depletion depending on where they are located: those in blood are typically cleared most easily while B cells in the spleen, lymph nodes or bone marrow are more resistant[2]. Autologous CAR-T cells appear sufficiently potent and long-lasting to clear out even the most resistant B cells. And the CD19 antigen is expressed by B cells along almost the entire development pathway, from immature precursors (pro-B cells) to antibody-secreting plasmablasts and some plasma cells (Box 1). The broad, deep B cell depletion that results enables repopulation with naïve B cells — hence the term 'immune reset'.

This blanket approach is feasible because "we don't need B cells to survive," explains Schett (unlike, say, T cells or myeloid cells). And it's effective because the B cell wipeout affects other cells to achieve the new immune network homeostasis required for drug-free remission.

But cumbersome, lengthy administration and preconditioning requirements have constrained access to CAR-T cell therapy even in late-line oncology settings, where these therapies originated. The access challenges would be even harder to overcome in chronic autoimmune conditions, which tend to be managed in the community setting and which affect many more patients. Cytokine release syndrome (CRS), a common side effect of CAR-T cell therapy, is another major hurdle. "The transition from a therapy appreciated and welcomed by oncologists to one that's appreciated and welcomed by rheumatologists" is one challenge facing this emerging field, says Bruce Levine, professor in cancer gene therapy at the University of Pennsylvania and co-founder of Capstan.

The grail is therefore to achieve deep B cell depletion without the practical hurdles and with a better safety profile than existing autologous CAR-T cells. As big pharmas place their bets, battle lines are emerging between those chasing more convenient iterations of CAR-T cell therapy and those seeking protein-based equivalents such as bispecific antibodies.

In vivo CAR

A shift to allogeneic ('off the shelf') CAR-T and in vivo CAR is already underway in cancer, and autoimmune applications have accelerated it[1]. In vivo CAR involves delivering genetic instructions to modify T cells inside the body, rather than engineering cells ex vivo. It avoids lymphodepleting chemotherapy, prolonged hospitalization and attendant costs, in theory combining "the transformative power of cell therapy with the accessibility and scalability of an off-the-shelf biologic," said Laura Shawver, then CEO of Capstan Therapeutics, announcing the AbbVie acquisition.

Capstan, Orbital and Orna Therapeutics use targeted lipid nanoparticles (LNPs) to deliver RNA encoding CD19 CARs. Using RNA rather than DNA reduces the risk of permanent genome integration, and LNPs appear less likely to be immunogenic than viral vectors, making it easier to re-dose, if necessary. They are also cheaper to make. "Development will be faster and costs will be lower for mRNA LNP than for viral vectors," predicts Levine, estimating that both in vivo CAR-T modalities will be up to 50 times less costly than ex vivo. Other pharma firms continue to place bets: Eli Lilly in February 2026 bought Orna and a clinic-ready in vivo cell therapy candidate deploying circular RNA to reprogram T cells.

In September 2025, Shenzhen, China-based MagicRNA Biotechnology published what it says is the first clinical data on an mRNA–LNP based in vivo CAR-T therapy[3]. Five patients with refractory systemic lupus erythematosus (SLE) were infused, without prior lymphodepletion, with one to three doses, 48 hours apart, of a CD19 CAR-encoding mRNA. Near-complete B cell depletion persisted for 7–10 days in all patients; some saw substantial decreases in disease activity index scores, representing near-remission. CRS cases were all relatively mild (grade 2 or below).

The data provides promising proof of principle. But it "doesn't show that in vivo mRNA can reset the B cell system," says Schett, who co-authored the study. The relatively short B cell depletion phase suggests incomplete B cell wipeout, he adds. That could be due to shorter CAR expression — a downside of current RNA approaches — or because the modified T cells are not hitting enough B cells.

Sending instructions for genetic alterations inside the body, rather than performing those changes ex vivo, makes the amount of depletion less predictable. That unpredictability makes it harder to determine the dose required to reprogram sufficient T cells. "Can you get enough drug into patients to achieve reset? And can you do so safely? Those are the questions" for in vivo CAR, says Schett.

Higher doses might ramp up B cell depletion, but could also lead to LNP-related toxicity, and/or more CRS. (Three of four patients in a recent human cancer study using lentivirus-based, BCMA-targeted in vivo therapy experienced grade 3 CRS[4]). In MagicRNA's LNP-based data, no CRS reports reached grade 3 in severity, and there was no neurotoxicity. But the safety bar in autoimmune disease will be much higher than in aggressive cancers like acute lymphocytic leukemia.

In vivo CAR "is not quite yet where it needs to be, in terms of CRS safety, for autoimmune," sums up Levine, "but I believe it will be with

more experience." The approach has been tested in just tens of patients with autoimmunity, versus hundreds treated with autologous CAR-T therapy. Capstan (now AbbVie) began a phase 1 study in mid-2025 of its in vivo CAR-T in about 40 patients; Orbital (now BMS) and Orna (now Eli Lilly) are in Investigational New Drug application-enabling studies.

Engaging endogenous T cells

The safety and convenience challenges of reprogramming T cells, whether inside or outside the body, have pushed many developers toward alternative B cell depletion methods. TCEs — bispecific antibodies or fusion proteins that draw together endogenous T cells and their B cell targets — also appear to do a good job.

The FAU Erlangen team, who have been using TCEs since late 2023, published updated data showing that six out of ten patients with refractory autoimmune diseases achieved drug-free remission with a follow-up of 15 months after receiving teclistamab, Johnson & Johnson's CD3 × BCMA-targeted TCE antibody, sold as Tecvayli for multiple myeloma[5]. All but one patient showed an initial clinical response. Undetectable levels of B cell antibody light chains in all patients led the researchers to suggest that fully differentiated, antibody-secreting plasma B cells were successfully depleted. Eight patients experienced CRS, but all cases were grade 1 or 2 and resolved with a single dose of the interleukin-6-targeted anti-inflammatory tocilizumab.

"T cell engagers could achieve the same [levels of B cell depletion] as CAR-T, while also being demonstrably safer, scalable and easier to administer," says Ken Song, chairman, president and CEO of Candid Therapeutics, launched in late 2024 with $370 million and two TCE antibodies in-licensed from China. One of them, CD3 × BCMA-targeted cizutamig, has now been given to over 40 patients with autoimmune disease. There have been only mild cases of CRS in only 10–15% of patients, says Song. That kind of safety profile — perhaps because TCEs harness existing T cells rather than triggering rapid T cell proliferation — "is critical when we think about adoption."

Song argues that TCEs are the only modality with the potential to offer safe, predictable B cell depletion and immune reset from a single treatment cycle, scalable manufacturing, and relatively convenient subcutaneous administration. The follow-up period for early clinical examples of TCE-mediated B cell depletion for immune reset is now approaching two years after a single treatment cycle. When setting up the company, "we looked at every [B cell-depleting] modality," Song recalls, including in vivo CAR, mRNA-based TCEs, natural killer cell engagers and myeloid cell engagers. "But we always came back to just the T cell engagers." (As *Nature Biotechnology* went to press, Candid announced a reverse merger with listed RallyBio alongside a $505 million financing.)

Cullinan Therapeutics sees similar promise in TCEs; the company raised $240 million in 2024 on the back of a pivot from oncology to autoimmune diseases. Rather than full-sized antibodies, Cullinan's lead autoimmune disease asset uses two single-chain variable fragments and a nanobody; the company says these smaller bispecific proteins will enable superior B cell targeting and binding. It expects phase 1b data in 2026 from its CD19 × CD3 × albumin-binding fusion protein in rheumatoid arthritis, SLE and Sjögren's syndrome (characterized by dry eyes, dry mouth and chronic fatigue). Like Candid and many other biotech companies, Cullinan is tapping assets and cost-effective development infrastructure from China. In June 2025, it paid $20 million up front for autoimmune development rights to Genrix Bio's BCMA × CD3 candidate velinotamig and hopes to generate early clinical and pharmacokinetic and pharmacodynamic data in China to inform study design and regulatory discussions in the United States and other Western markets.

Yet questions remain for this category, too — in particular, around durability and dosing. "More exploration of dose and dosing schedule is required to identify the most therapeutic regimen," said Jeffrey Jones, chief medical officer at Cullinan, at a Stifel event in November 2025. So far, evidence suggests an oncology-like dose of TCE is most effective. (In the first study of Blincyto (blinatumomab) in patients with refractory rheumatoid arthritis (RA), patients received much lower doses than used in oncology, likely precluding full B cell depletion in lymph nodes and full immune reset. Later, Tecvayli was used with a weight-based step-up dosing and one or several maintenance doses, which was more effective.) But "we don't expect a single dose will achieve durable reset," said Jones.

It remains to be seen how few doses — and how durable an effect — would be required to create the transformation across autoimmune therapy that TCE developers anticipate. For Candid's Song, one cycle of TCE treatment involving a few doses in less than a month, in exchange for two years' disease remission, is "quite compelling." Yet the idea of a 'one and done' therapy is what patients find particularly attractive, says Lynelle Hoch, president of BMS's cell therapy organization. She points to clinical data reported at the American College of Rheumatology Convergence meeting in Chicago in October 2025 from BMS's next-generation autologous CAR-T therapy zolacabtagene autoleucel in SLE, systemic sclerosis and immune-mediated myositis to argue that the tolerability gap between CAR-Ts and TCE is narrower than many assume. CRS cases associated with the therapy, which uses the same CAR as Breyanzi (lisocabtagene maraleucel) and has a faster manufacturing process, were low-grade and rapidly resolved[6].

How do TCEs stack up, so far, against CAR-T cell therapy? Early experience from the pioneering TCE studies at FAU's Clinical Trial Unit suggests that the therapeutic window may prove easier to predict with protein-based therapeutics than with in vivo CAR-T. "But we'll see," notes Schett.

Engaging myeloid cells: B cell depletion without CRS?

Others are engaging an entirely different category of immune cells for the B cell assault. Myeloid cells are a key component of the innate immune system. They are present in multiple tissues and adept at phagocytosis — engulfing and eliminating unwanted pathogens or cells, including, potentially, overactive disease-causing B cells.

In March 2025, Sanofi paid $600 million up front for Dren Bio's phase 1 bispecific myeloid engager that targets CD20 on B cells and dectin-1, a phagocytic receptor found on the surfaces of some myeloid cells. "CAR-T cells have demonstrated the proof of concept but have tolerability challenges. It begs for another solution," says Alyssa Johnsen, Sanofi's senior vice president, global therapeutic area head for immunology development.

Johnsen argues that harnessing myeloid cells' natural ability to attack and phagocytose wayward B cells may lead to more effective, safer B cell depletion than seen with TCEs or CAR-T approaches. "We know that myeloid cells recognize and remove foreign antigens and even compromised cells. Taking advantage of this existing physiological system … may generate at least as good, or even better, B cell depletion, with less CRS" than seen with systemic T cell-activating approaches, she says.

Dren's bispecific antibodies are designed to activate only myeloid cells that are close to target B cells (non-specific myeloid cell activation

BOX 2

Beyond B cell depletion

Other immune effector cells and mechanisms are under investigation to restore immune tolerance.

Regulatory T cells (T-regs). Sonoma Biotherapeutics, Quell Therapeutics and GentiBio are engineering T-regs to restore immune system balance. Sonoma's autologous T-reg cell therapy targets inflammation-associated citrullinated proteins and has shown early efficacy in a trial treating six patients with RA. Also in early clinical testing is chemotherapy-free conditioning via a CD2-targeted fusion protein that depletes T cells, potentially enhancing T-reg cell therapy effectiveness. Sonoma received a $45 million milestone payment from partner Regeneron in 2024; Quell received a second milestone in 2025 from partner AstraZeneca for an irritable bowel disease-focused T-reg candidate and is also developing a CD19 CAR T-reg therapy for multiple autoimmune indications. GentiBio has an irritable bowel disease-focused partnership with BMS, but BMS and other investors were not sufficiently convinced by T-reg-focused Abata Therapeutics' multiple sclerosis program; the Third Rock Ventures-founded biotech closed in 2025.

Dendritic cells. Dendritic cells are specialized for presenting antigens to T cells. They are the target of Evoq Therapeutics' NanoDisc technology, which has attracted partners including Gilead, Amgen and, in October 2025, Sanofi. The technology delivers lipid-packaged antigens that prompt dendritic cells into restoring immune tolerance by upregulating anti-inflammatory regulatory T cells and cytokines[9]. Evoq's most advanced program is a development candidate for celiac disease.

Natural killer (NK) cells. NK cells collude with antibodies to destroy unwanted cells or pathogens. They also have an immunomodulatory role and are more amenable to off-the-shelf use than T cells, as they lack receptors that trigger host-cell attack.

Artiva Biotherapeutics has begun a phase 2a study of its allogeneic NK-based cell therapy, in combination with Rituxan, in refractory RA, Sjogren's disease, idiopathic inflammatory myositis and systemic sclerosis and is pursuing the same approach with Roche's Gazyva (obinutuzumab) in SLE. Gazyva, used in hematology since 2013, was approved for lupus nephritis in October 2025. Nkarta has a similar program in phase 1 in lupus nephritis and scleroderma.

Targeted antibody or protein degraders. Developers are also exploring antibody-degrading approaches to autoimmune diseases. Approved myasthenia gravis drugs including Argenx's Vyvgart (efgartigimod), UCB's Rystiggo (rozanolixizumab) and Johnson & Johnson's Imaavy (nipocalimab) block the neonatal Fc receptor to reduce the half-life of disease-causing immunoglobulin G (IgG). Other companies including Biohaven Pharmaceuticals are developing direct degraders of IgG antibodies; Avilar Therapeutics lists an oral IgG degrader in early discovery.

GlycoEra and Lycia Therapeutics use bifunctional molecules to directly shuttle disease-causing antibodies into cells' lysosomal degradation machinery. GlycoEra's lead targets IgG4 antibodies implicated in pemphigus and myasthenia gravis; Lycia's programs tackle immunoglobulin E antibodies and thyroid stimulating hormone receptor autoantibodies implicated, respectively, in allergic diseases and Graves' disease[10].

Meanwhile, groups including Monte Rosa Therapeutics, Nurix Therapeutics, Kymera Therapeutics and C4 Therapeutics (with partners) are targeting and degrading intracellular signal transducing proteins implicated in autoimmunity, such as BTK, IRAK4 or RIPK2, with some programs in early clinical trials[11].

Some researchers are conjugating cytotoxic payloads such as monomethyl auristatin E onto antibodies targeted at CD6 on errant T cells[12], or taking pyrrolobenzodiazepine to CD45-positive hematopoietic stem cells as a pre-transplantation conditioning agent. No clinical data are yet available from such antibody–drug conjugates in autoimmune diseases.

could be disastrous, as they are potent sources of pro-inflammatory cytokines). Dectin-1 is expressed on multiple cell types, including macrophages and neutrophils. These cells are good at phagocytosis and represent the first line of defense against pathogens.

Whether these theoretical advantages translate into complete B cell depletion, as seen with T cell-redirecting therapies, remains unproven. Detractors point to the limited success of CAR-macrophages at the now-bankrupt Carisma Therapeutics; also noteworthy is Myeloid Therapeutics' October 2025 rebranding as Create Medicines to reflect a broader focus on multiple immune cell lineages.

Yet the myeloid hypothesis is sufficiently compelling to have brought Sanofi back to Dren's table in December 2025. The French group committed another $100 million (and up to $1.7 billion) to a broader B cell depletion collaboration, deploying the privately owned biotech's myeloid cell engager and phagocytosis platform across multiple autoimmune diseases.

The first clinical data from Dren's compound may be available by the end of 2026. A phase 1 safety study is enrolling close to 40 patients with various autoimmune conditions including SLE, cutaneous lupus erythematosus, Sjögren's syndrome, polymyositis and diffuse cutaneous systemic sclerosis.

Beyond B cells

The emerging applications of B cell depletion have done more than offer the prospect of a cure for some conditions. They are also accelerating scientists' understanding of the immune system itself and of the precise mix of cell types, mechanisms and targets driving particular autoimmune diseases.

Clinical success has, so far, been linked to achieving deep depletion. But autoimmune conditions vary. Many of the most prevalent, including SLE and myasthenia gravis, are strongly B cell driven and should respond well to B cell depletion. But in others, like psoriasis, T cells and dendritic cells are more important than B cells. Conditions like

myositis and systemic sclerosis are proving harder to unravel.

Indiscriminate B and plasma cell depletion, though not life-threatening, can lead to a loss of vaccine-induced humoral immunity (conferred by long-lived plasma cells), which could be unsuitable or dangerous for some patients.

"B cells aren't the only part of the immune system driving disease," says Sanofi's Johnsen. "Yet B cell depletion provides a roadmap to start thinking about whether we could use this approach – removing a subset of cells – on other components of the system to drive disease remission" (Box 2).

Efforts are underway to achieve greater specificity. Some programs target B cells that recognize particular autoantigens. Desmoglein 3 (DSG3), for example, is a cell adhesion protein implicated in a skin-blistering autoimmune condition called pemphigus vulgaris, and the target of an autologous CAR-T program in phase 1/2 at Cabaletta Bio.

The challenge for these programs is determining whether the target antigen is indeed the main disease-causing factor: Cabaletta appears to have deprioritized early trials of a similar program targeting B cells responsible for autoantibodies against muscle-specific kinase (MuSK), implicated in myasthenia gravis, for example.

Many sizes to fit all

As scientists home in on the most effective, safest depleting modalities and start to reveal the cellular fingerprints of individual autoimmune conditions, "we're likely to see a variety of approaches," says Sanofi's Johnsen, including more selective ones.

Some of the most refractory conditions may respond best to CAR-T cell therapy. Larger numbers may most effectively be helped using antibody- or protein-based approaches. Others still may benefit from immune 'dimming' rather than full-scale depletion and reset. Emerging data using TCEs appear to support the idea of dialing down, rather than turning off, B cell activity[5]. Granted, existing therapies like Rituxan can be considered immune dimmers. But a lower, 'dimming' dose of TCEs (or potentially myeloid cell engagers), aimed at optimizing safety over maximum efficacy, may offer a patient with mild to moderate disease good tolerability and convenience while still providing superior efficacy relative to the current standard of care, and eliminating the need for revaccination. Given widely different risk profiles across autoimmune disease, "it may make sense to give up a little on efficacy to maintain tolerability and safety," says Johnsen.

The heterogeneity of autoimmune diseases, combined with still-emerging B cell depletion data, explains why larger firms like Sanofi or BMS are hedging bets. "We are working with multiple modalities to figure out the best way to achieve immune reset," says Robert Plenge, BMS's executive vice president and chief research officer. BMS's BCMA × CD3 TCE alnuctamab is in phase 1 for refractory SLE (development in multiple myeloma was terminated after phase 1 for strategic reasons)[7], and the pharma has other undisclosed discovery-stage assets focused on B cell reset or tissue repair in autoimmunity. BMS spun out its other immunology assets in 2025.

The first B cell-depleting autoimmune therapies could reach the market soon. Cartesian Therapeutics has not announced regulatory timing for its autologous CAR-T program in phase 3 in myasthenia gravis, but Kyverna Therapeutics expects to submit autologous mivocabtagene autoleucel in the first half of 2026, backed by positive data from a 26-patient phase 2 trial in stiff person syndrome. The FDA has signaled its enthusiasm for CAR-T therapies' potential benefits in autoimmune disease but also concerns over long-term safety[8]. Candid's Song anticipates that a first TCE may follow before the end of the decade, adding that "TCEs will become the primary modality, if you want B cell depletion."

Not all patients with autoimmune disorders will. But even if no clear winner emerges from the CAR-T versus TCE battle, clinical outcomes from B cell depletion have set a new efficacy benchmark across autoimmunity and drawn attention to related activity, including tolerogenic vaccines (designed to induce antigen-specific immune tolerance) and thymus regeneration, the focus of a handful of preclinical startups including Thymmune Therapeutics, Zag Bio and Basel-based TECregen.

Ultimately, these efforts will benefit more patients and drive more deals. "Excitement is justified," says the University of Pennsylvania's Levine. "As long as we stay short of irrational exuberance."

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Competing interests

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