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BIOPHARMA STRATEGY

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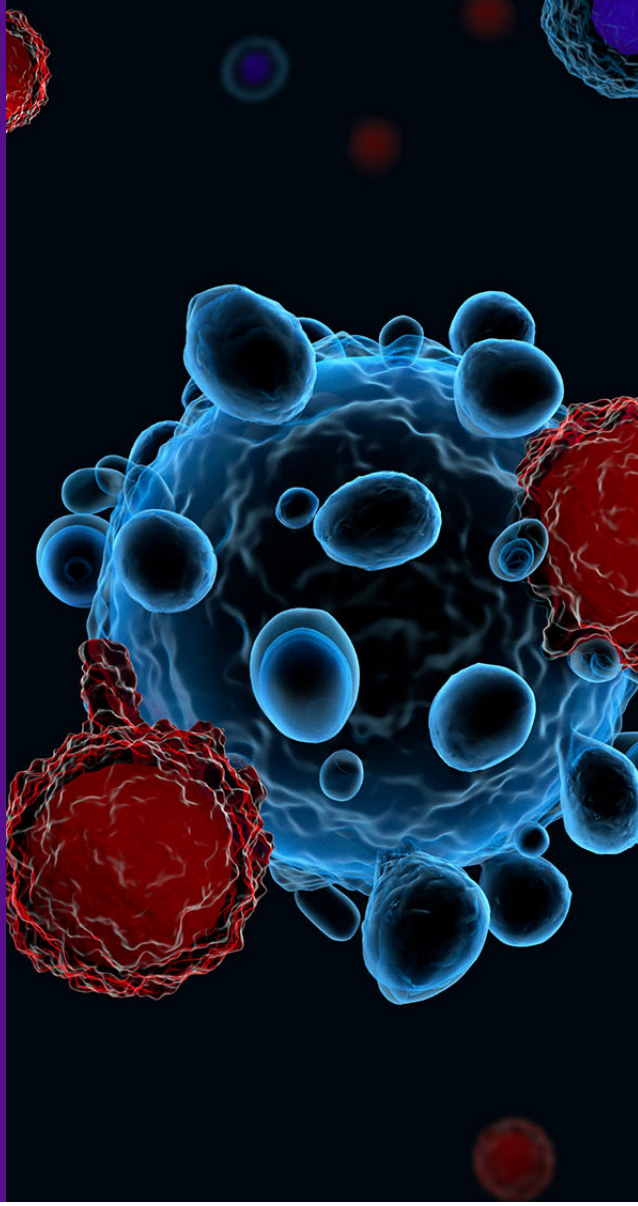


White Paper

In Vivo CAR Therapies

In vivo chimeric antigen receptor (CAR) therapies have rapidly risen to the forefront of biotech discussion over the past few years. New companies are emerging at breakneck speed, venture financing continues to surge, and the field has seen four multibillion-dollar acquisitions in the past year: EsoBiotec, Capstan, Orbital, and recently, Orna. The appeal is clear: the prospect of achieving CAR-T-like activity inside the body, without lymphodepletion, with lower toxicity, simpler manufacturing, and broad off-the-shelf scalability—essentially a "CAR-T 2.0" vision (**Table 1**).

In Vivo CAR Therapeutics Toolbox: Current Approaches

A key difference between ex vivo and in vivo CAR therapies is that in vivo approaches do not require lymphodepletion preconditioning. Because CAR reprogramming occurs directly within the patient, in vivo therapies can potentially avoid the immune depletion associated with traditional conditioning and help preserve overall immune system integrity. In ex vivo CAR-T, lymphodepleting chemotherapy creates space for CAR-T expansion and persistence, but at the cost of well-known risks, such as infection, leukopenia, and broader immune suppression. Inflammatory cytokine responses are also amplified. Eliminating this step is therefore one of the most attractive advantages of in vivo CAR platforms, particularly as companies expand into autoimmune diseases where rheumatologists have no experience with lymphodepletion.

To reprogram immune cells, in vivo CAR therapies rely on delivery vehicles that shuttle genetic instructions into target immune populations. Today, two platforms dominate this space: viral vectors and lipid nanoparticles (LNPs; **Figure 1**). Most clinical-stage

assets currently use viral vectors, particularly lentiviral systems, reflecting their established history in ex vivo CAR-T. Kelonia Therapeutics exemplifies this approach with an advanced lentiviral B-cell maturation antigen (BCMA) CAR-T that is currently being investigated in a Phase I trial for relapsed and refractory multiple myeloma.[1]

However, a clear shift is emerging in preclinical development: over 30 percent of new programs now use LNP-based delivery, potentially influenced in part by concerns around immunogenicity associated with systemic viral administration (**Figure 1**). That said, developers are also exploring additional vehicle classes. For instance, Sana Biotechnology uses engineered fusogens embedded within the fusosome membrane as its delivery vehicle. Fusogens are naturally occurring proteins that mediate cell-cell recognition and membrane fusion. Sana's platform uses an engineered henipavirus G protein, which normally binds ephrin-B2/B3 receptors, to facilitate cell recognition. G protein can also be selectively mutated to modulate this interaction. Upon receptor engagement, the G protein activates the associated F protein, which then drives membrane fusion and enables direct delivery of the therapeutic payload into the cytosol.[2] Nanocell Therapeutics, on the other hand, appears to use LNPs equipped with a targeting moiety that includes an antigen-binding region capable of recognizing human CD7, thereby facilitating selective engagement of T cells and/or natural killer (NK) cell.[3] To further address off-target delivery, some companies also turn to tighter control at the transcriptional level. For example, EsoBiotec, recently acquired by AstraZeneca for $1B,[4] is using a T-cell-specific promoter, enabling CAR expression only in T cells and minimizing off-target transduction.[5] Together, these efforts reflect the growing consensus that precise immune-cell targeting will be one of the critical pillars for the future success of in vivo CAR therapy.

Features	Ex vivo CAR	In vivo CAR
Engineering Approach	Autologous or allogeneic immune cells are harvested, genetically modified ex vivo, expanded, and reinfused into the patient	Genetic material encoding the CAR is delivered directly into endogenous immune cells in vivo using various vehicles
Immune Cell Type	Approved assets are targeting T cells, but other immune cells have been explored	Mostly T cells, but also other immune cells and pan CAR approaches
Vehicle Type	Primarily integrating viral vectors (e.g., lentivirus or retrovirus)	Mostly LNPs (de-targeted from hepatic tissue) or viral vectors (integrating or non-integrating) developed to target mainly T cells
Cargo Type	Predominantly DNA	Both DNA and RNA, with latter gaining increasing popularity
Conditioning Requirement	Lymphodepleting chemotherapy is required for CAR expansion/ persistence	Conditioning is not required; pre-existing immune cells are targeted in situ
Onset of Action	Delayed (2–4 weeks) due to manufacturing and expansion timelines	CAR expression can occur 1–3 days post-infusion
Pharmacokinetics & Persistence	Long-term CAR expression; persistence depends on vector type and immune cell phenotype	Transient or long-term; potentially tunable via re-dosing
Efficacy Profile	Strong efficacy in heme cancers; early responses in autoimmune disease	Early data from few patients; comparison to ex vivo remains unclear
Safety Profile	Risk of CRS, ICANS, prolonged B-cell aplasia, infections, hematological toxicities	Early data suggest reduced toxicities; long-term safety under investigation
Manufacturing & Scalability	Complex, individualized manufacturing; limited scalability	Off-the-shelf, cell-free production; higher scalability and broader access; lower cost
Clinical Maturity	Approved in heme malignancies; early-phase trials in autoimmune diseases (e.g., SLE, RA)	Early clinical development; first-in-human trials initiated in oncology and autoimmunity
Strategic Positioning	High-potency, curative potential in refractory disease; limited by logistics and toxicity	Promising for outpatient use, earlier-line intervention, broader patient populations

Table 1: Comparison Between Ex Vivo and In Vivo CAR Technologies. Abbreviations: **CRS**, cytokine release syndrome; **ICANS**, immune effector cell-associated neurotoxicity syndrome; **LNP**, lipid nanoparticle; **SLE**, systemic lupus erythematosus; **RA**, rheumatoid arthritis

Cargo formats are also diversifying. While each encode a CAR construct, they differ in stability, duration of expression, and cellular fate, for example using cell-specific control elements. While early in vivo programs relied on DNA-based cargos, the field is steadily shifting toward RNA (**Figure 1**). This shift is partly motivated by concerns about off-target genomic integration that could happen with lentiviral vectors and adeno-associated virus (AAV) systems.[6] As a result, many developers are adopting non-viral mRNA technologies, which enable transient CAR expression without integration, potentially offering a safer profile for in situ immune-cell engineering. However, the intrinsic instability of mRNA means that repeat dosing and tighter fine-tuning may be required, creating a practical challenge for maintaining sustained therapeutic activity. This has prompted exploration of alternative more stable RNA formats, such as circular RNA (circRNA). Here, one of the prime examples is Orbital, acquired by BMS, whose platform includes the lead circRNA-LNP CD19 program OTX-201.[7]

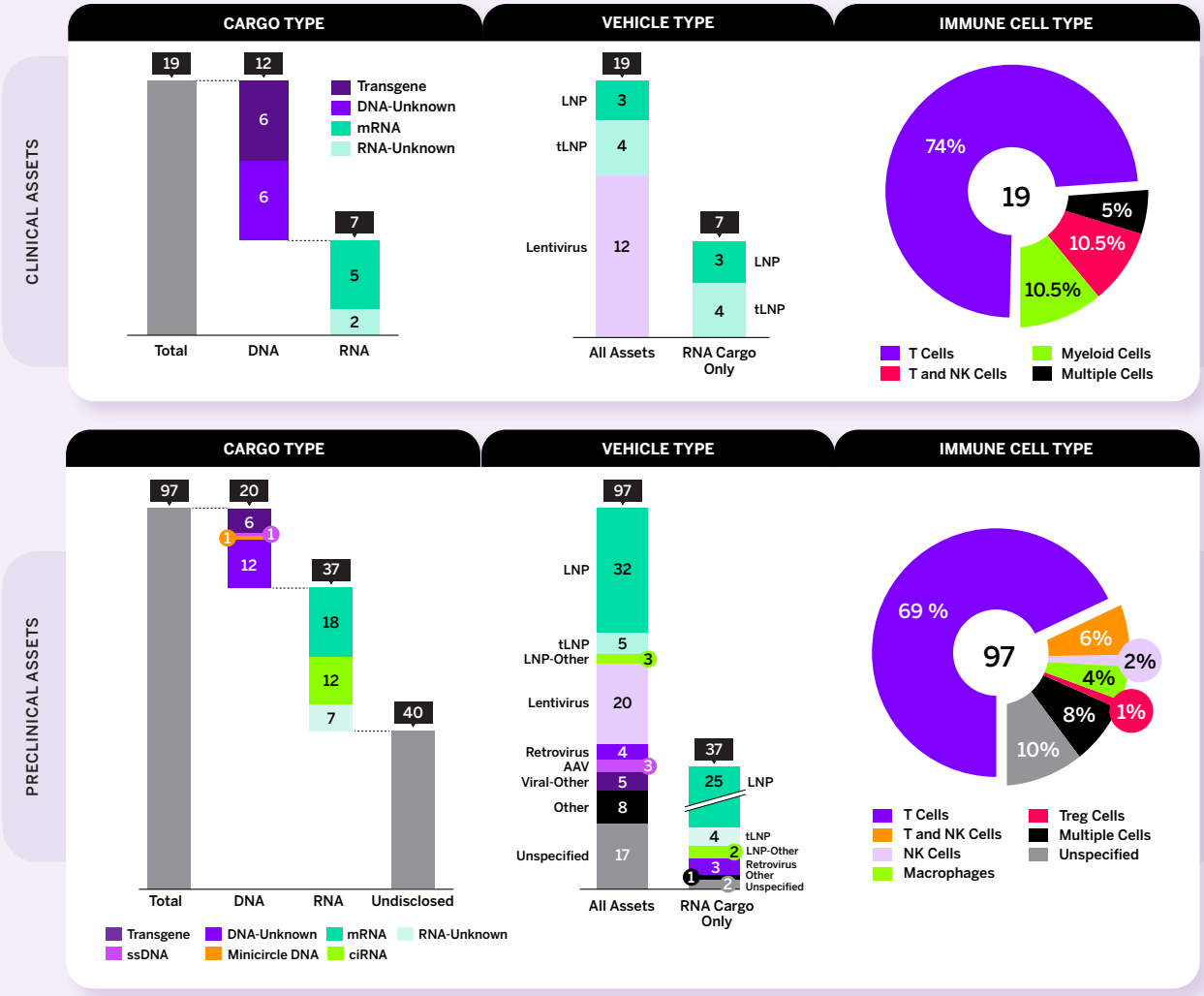


Figure 1: In Vivo CAR Assets Categorized by Immune Cell Type, Cargo, and Vehicle.
Both clinical and preclinical assets are classified into various groups. For vehicle types, those carrying RNA cargo are displayed separately in a bar plot. In the immune cell type section, "Multiple cells" category includes various combinations such as CAR-M/CAR-T; CAR-M/CAR-T/CAR-NK, PanCARs etc. Under vehicle type, "LNP-other" encompasses P-LNP and eLNP, "Viral-Other" includes VLPs and unspecified viral, and "Other" covers extracellular vesicles, fusosomes, polymeric nanoparticles, and unspecified non-viral vehicles.

CAR-M: CAR targeting macrophages, **CAR-NK**: CAR targeting natural killer cells, **ciRNA**: circular RNA, **LNP**: lipid nanoparticle, **tLNP**: targeted LNP, **P-LNP**: pullulan nanoparticle, **eLNP**: erythrocyte-derived membrane, **VLP**: virus-like particle, **ssDNA**: single-stranded DNA, **AAV**: adeno-associated virus

Beyond T Cells: Broadening the Immune Cell Horizon

Following the footsteps of ex vivo CAR therapies, in vivo CAR platforms are expanding beyond T cells to target a broader range of immune cells. Around 20 percent of programs now target NK cells, macrophages, myeloid cells, regulatory T cells (Tregs) or multiple immune subsets through pan-CAR strategies (**Figure 1**).

Clinically, Interius Bio's CD20 in vivo CAR (INT2104; now under Kite/Gilead) is designed to target both CAR-T and CAR-NK cells in vivo with their CD7-decorated lentivector. Its Phase I trial began in October 2024 for B-cell malignancies, though results are pending. Create Medicine (formerly Myeloid Therapeutics) initially focused on myeloid cell-targeting mRNA-LNP in vivo CAR therapies for solid tumors, but in 2025, the company rebranded to reflect an expanded strategy to multi-immune cell programming. Its two lead assets, targeting TROP2 and GPC3 (glycan 3), are currently in Phase I trials for solid tumors. Early data from 27 patients with TROP2-positive tumors showed low efficacy, with only one partial response observed in a patient with HR-positive breast cancer. Despite limited initial responses, both programs are now advancing into frontline combination trials alongside standard-of-care therapies.[8,9] In this setting, it will be interesting to see how in vivo CAR therapies compare with established antibody-drug conjugates (ADCs), particularly as ADCs expand into immunomodulatory payloads. Physician willingness to adopt novel modalities versus well-established ADCs may ultimately shape the potential role of in vivo CARs in the treatment landscape.

Another example of expanding beyond conventional immune-cell targets is the emergence of Treg-directed approaches. For instance, Tr1X Bio is a clinical-stage company focused on allogeneic type 1 regulatory T-cell (Tr1 Treg) and CAR-Tr1 Treg therapies designed to treat autoimmune and inflammatory diseases. Their CAR-Tr1 Treg therapy, TXR319, is currently in Phase I clinical development for progressive multiple sclerosis.[10] In parallel, Tr1X Bio is moving into the in vivo CAR arena, with an early in vivo CAR-Tr1 program listed in their pipeline, although detailed information has not yet been disclosed.

A final point worth emphasizing is that, unfortunately, the path of expanding beyond T cells has not been without setbacks. Carisma Therapeutics, once a pioneer in macrophage-focused CAR therapies, collapsed in late 2025 after failing to secure funding or a buyer.[11] Despite early promise and an in vivo CAR collaboration with Moderna,[12] both Carisma Therapeutics' ex vivo and in vivo CAR-M programs were discontinued. The company's shutdown highlights the challenges of translating macrophage engineering into clinical success. This raises an important point: ex vivo platforms have taught us how challenging it can be to engineer non-T cells, and those lessons shape our expectations for in vivo approaches. Whether in vivo CAR strategies can ultimately move past these barriers remains an open question for the field. For any cell type without CAR proof of concept (PoC), the biological risk of an in vivo platform is inherently higher, especially for early-stage companies. And beyond biology, there is an investor dimension: developers need a clear differentiation hypothesis for why a non-T-cell CAR approach is justified.

Can In Vivo CAR Find a Niche in Heme Cancers?

Oncology remains the dominant indication across both clinical and preclinical in vivo CAR therapies (**Figure 2**). Most in vivo programs center on hematologic malignancies and target the "classics" —CD19, BCMA, and CD20. The strategy is unsurprising: companies are already taking on significant platform risk with in vivo delivery, so there is little incentive to compound that with target risk. Currently, the core question is whether in vivo platforms can reach, match, or even exceed the effectiveness of ex vivo CAR-T therapies in areas where those treatments are already well established.

Ex vivo CAR-Ts have set a benchmark in hematologic oncology. In relapsed/refractory B-cell malignancies, outcomes have improved dramatically: axi-cel (CD19 CAR-T) achieved an 83% overall response rate (ORR) in diffuse large B-cell lymphoma (DLBCL), with a median overall survival (mOS) of 25.8 months and ~51% 5-year disease-specific survival.[13] Similar results have been seen in B-cell acute lymphoblastic leukemia (B-ALL) with tisa-cel reporting an 81% ORR in children

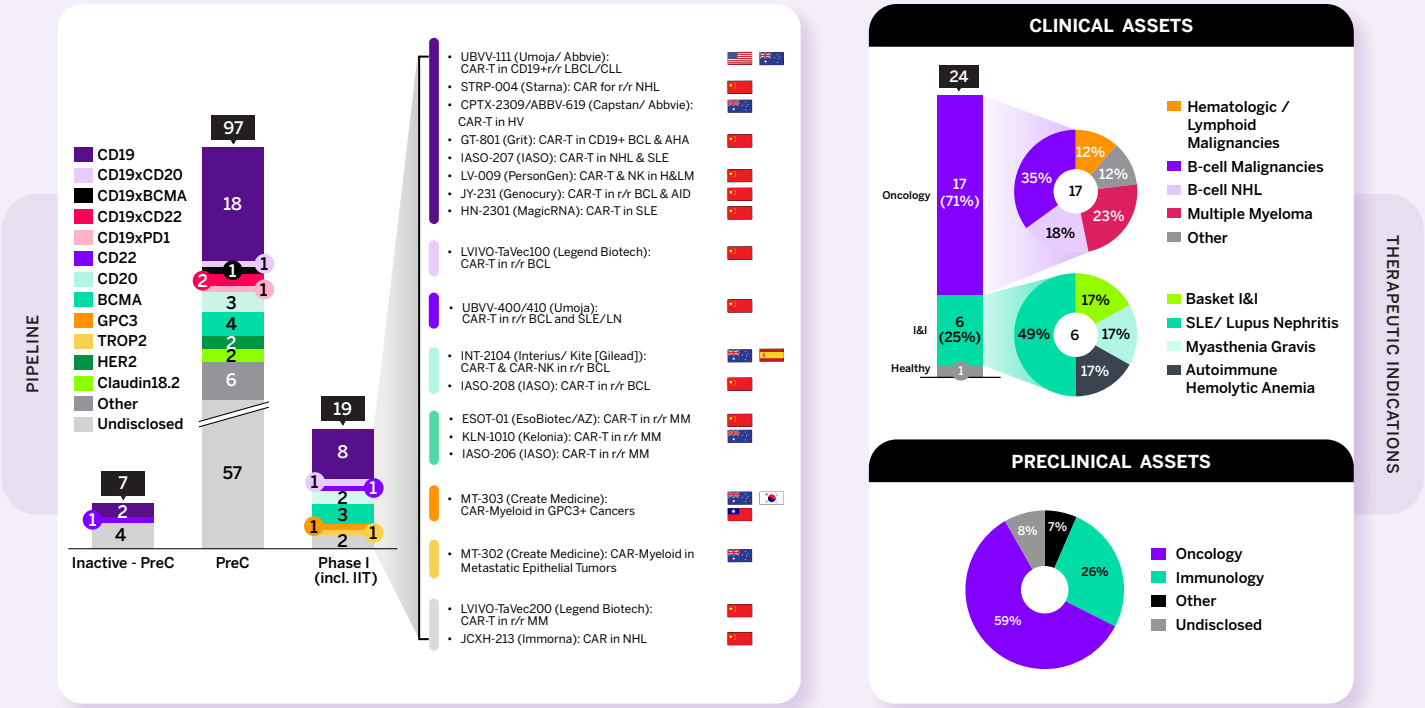


Figure 2: In Vivo CAR Pipeline by Target.
Data is sourced from GlobalData, filtered by Molecule Type (Gene Therapy) and using a Free Text Search ("in vivo CAR" OR "in situ CAR"), then further expanded through manual review of press releases, deals, and news articles. For each clinical asset the company name, immune cell type, and the clinical indication under investigation are specified. Flags indicate the countries where trials are ongoing, if data is available. On the right panel, clinical and PreCassets are organized by therapeutic areas and indications. The total count may not always align with the number of assets, as some are investigated in multiple indications. The "Other" category in the pipeline includes CXCR5, GPA33/GUCY2C, unspecified fibroblast targets, and TAA. On the right panel, "Other" for clinical assets include GPC3-expressing and epithelial tumors, and for PreCassets—neurology, longevity, musculoskeletal, and genetic disorders. Pipeline is updated as of February 2026.

PreC: preclinical, **IIT**: Investigator-Initiated Trial, **CAR-M**: CAR targeting macrophages, **HV**: Healthy Volunteers, **BCL**: B-cell Lymphomas/Leukemias, **AID**: Autoimmune Disease, **SLE**: Systemic Lupus Erythematosus, **MG**: Myasthenia Gravis, **NHL**: Non-Hodgkin Lymphoma, **LBCL**: Large B-cell Lymphoma, **CLL**: Chronic Lymphocytic Leukemia, **AHA**: Autoimmune Hemolytic Anemia, **MM**: Multiple Myeloma, **LN**: Lupus Nephritis, **H&LM:** Hematologic and Lymphoid Malignancies, **r/r**: relapsed/refractory, **TAA:** tumor-associated antigens, **I&I:** Immunology and Inflammation. Pipeline status is updated as of February 2026.

and young adults.[14] In multiple myeloma BCMA CAR-T (cilta-cel) also achieved a high and durable response rate, with 98% ORR and a mOS of 60.7 months.[15,16] These data positioned CAR-T as a potentially curative option for selected patients.

However, these gains come with significant trade-offs. Acute toxicities remain a major concern: in ZUMA-1 (axi-cel), 93% of patients experienced cytokine release syndrome (CRS; 11% grade ≥3) and 64% had neurologic events (30% grade ≥3).[13] Manufacturing complexity and referral bottlenecks further limit access, with some estimates suggesting that only 1 in 5 of eligible patients receive CAR-T.[17] Interestingly, a recent analysis of 357 US patients with non-Hodgkin lymphoma intended for CAR-T found that 41% ultimately did not receive the infusion, most commonly due to ineligibility resulting from rapid disease progression (34%). Encouragingly, the time from consultation to infusion improved substantially over time, raising hope that ongoing process optimization may reduce future rates of disease-related ineligibility.[18] Overall, the number of patients treated with CAR-T therapies remains limited. Oribiotech, a cell and gene therapy manufacturing company, estimates that approximately 10,000 patients were treated in 2025 (similar to 2023 and 2024), bringing the cumulative total since the first CAR-T approval to around 45,000.[19]

The field has long recognized the need for simpler, off-the-shelf approaches. Bispecific T-cell engagers (BiTEs) such as blinatumomab (CD19xCD3) have been around for a while. Approved in 2014 for relapsed B-ALL, blinatumomab offers off-the-shelf convenience and a more favorable safety profile: any-grade CRS occurs in 14% of patients (5% grade ≥3), compared with ≥70% (grade ≥3 ~30%) for CAR-Ts. [20,21] Yet efficacy and durability are modest compared to CAR-T. A meta-analysis comparing blinatumomab vs. CAR-Ts in B-ALL reported pooled complete remission (CR) rates of 48% vs. 86%, and 2-year OS of ~25% vs. 55%, respectively.[22] A similar trend is seen for BCMA targeting therapies. In a retrospective analysis of 95 relapsed/refractory multiple myeloma patients who received either BCMA CAR-Ts (ide-cel or cilta-cel) or BCMA BiTEs (mostly teclistamab) in the US after prior BCMA-directed treatment, CAR-T outperformed BiTEs, showing an ORR of 79% vs. 51%, a median progression-free survival (mPFS) of 6 vs. 2 months, and mOS of 30 vs. 12 months, respectively.[23] These observations were confirmed by a meta-analysis looking into more than 2,000 patients.[24]

In Vivo CAR approaches aim to marry the accessibility of BiTEs with the transformative efficacy of ex vivo CAR-T. But could they deliver on both fronts? For now, this remains purely speculative. So far, most evidence comes from preclinical studies and a small number of initial clinical reports. Will these therapies match the depth and durability of ex vivo CAR-T responses? Or will they offer only moderate efficacy—better than BiTEs, but short of ex vivo CAR-T? The concept is compelling, but answers will depend on the next wave of human data. In 2026, key readouts to watch include, among others, Umoja's CD19, Interius Bio's CD20, and Kelonia's BCMA in vivo CARs.

In Vivo CAR in Autoimmunity

Autoimmune disease is rapidly emerging as the second major frontier for in vivo CAR development (**Figure 2**). Nearly one-third of preclinical pipelines now target this area, and several assets have already reached early clinical testing—for example, MagicRNA's HN-2301 in systemic lupus erythematosus (SLE) and myasthenia gravis (MG), and Genocury's JZ-231 autoimmune multi-indication basket trial (**Figure 2**). This comes as no surprise: in vivo CARs are clearly following the steps of ex vivo CAR-T and BiTE players, which are expanding into this space themselves. With no approved cellular or bispecific therapies yet, autoimmunity remains a wide-open opportunity. As programs across SLE, rheumatoid arthritis (RA), MG, and related disorders accelerate, an important question emerges: what insights have we gained to date?

Both ex vivo CAR-T and BiTE can induce strong remissions in severe autoimmune disease, but neither modality is reliably curative. Relapses occur as B cells re-emerge, and remission durability varies widely. However, comparing B-cell depletion across assets is challenging as most trials lack tissue biopsies. A rare comparative study of lymph-node biopsies across modalities found that only CAR-T achieved complete B-cell depletion in all tested patients, aligning with deeper and more sustained remissions. Blinatumomab, by contrast, produced partial depletion, likely influenced by its low initial dosing used in the study, leaving the true ceiling of BiTE efficacy uncertain.[25,26] This data could suggest that CAR-T's more aggressive activity, i.e., disrupting follicular lymph-node architecture, may underlie its deeper and more durable responses.

SLE remains the leading test case for both modalities, likely due to its strongly B-cell-driven pathology, high unmet clinical need, and the significant enthusiasm generated back in 2022–2023 following early reports of responses and drug-free remission in a few SLE patients treated with CD19 CAR-T.[27] More recently, other autologous CD19 CAR-T programs, such as MB-CART19.1, have shown remarkable early responses, with 90% of patients (9/10) achieving DORIS remission at six months.[28] Conversely, CD19×CD3 BiTE-like A-319 shows more modest early outcomes—only 2/10 patients were in DORIS remission at six months—but these rates rose over time to 40% (4/10) at nine months and 67% (2/3) at 12 months.[29] Since BiTEs can potentially be redosed, an open question is whether repeat dosing could further boost durability and help BiTEs close the gap on long-term disease control.

On safety, BiTEs appear more favorable than ex vivo CAR-T, with lower risks of immune effector cell-associated neurotoxicity syndrome (ICANS) and severe infections. A-319, for example, reported grade 1 CRS in 11/12 patients but no ICANS, no serious infections, and no grade ≥3 hematologic toxicity in SLE.[29] Next-generation BiTEs are pushing safety even further: Candid Therapeutics' cizutamig (BCMA×CD3) showed only 10% grade 1 CRS, no ICANS, and no infections mentioned across 20 autoimmune patients.[30] In contrast, some CAR-Ts like obe-cel (CD19xCD3) report 50% of any grade CRS, 33% grade ≥3 infection and grade 3 heme toxicities across six SLE patients.[31]

This sets the stage for in vivo CARs, but where exactly do they fit in this landscape? MagicRNA's HN-2301 (CD19, mRNA-LNP) provides an early look at what this modality could offer. In the first-in-human SLE trial, HN-2301 achieved complete depletion of circulating B cells in five patients and delivered meaningful clinical improvement within three months without severe toxicity.[32] If larger trials show durable remissions with a favorable safety profile, in vivo CARs could surpass ex vivo CAR-T in autoimmunity before the latter even reaches approval, as the need for lymphodepletion-based conditioning would become increasingly difficult to justify. Like BiTEs, in vivo CARs are also far easier to combine with other therapies than ex vivo CAR-T—a flexibility that could prove differentiating.

That said, major uncertainties remain. It is still unclear how in vivo CARs will compare with BiTEs, which are already trending safer and steadily improving through next-generation designs. It is far from guaranteed that in vivo CARs will ever match the depth and durability of responses seen with ex vivo CAR-T in early autoimmune reports. From a regulatory standpoint, it is uncertain whether agencies will tolerate the kind of safety trade-offs acceptable in oncology for the sake of deeper remission in chronic immunology indications. For now, the data across all modalities remain early, and the competitive landscape is evolving quickly—we may simply have to watch how this race unfolds.

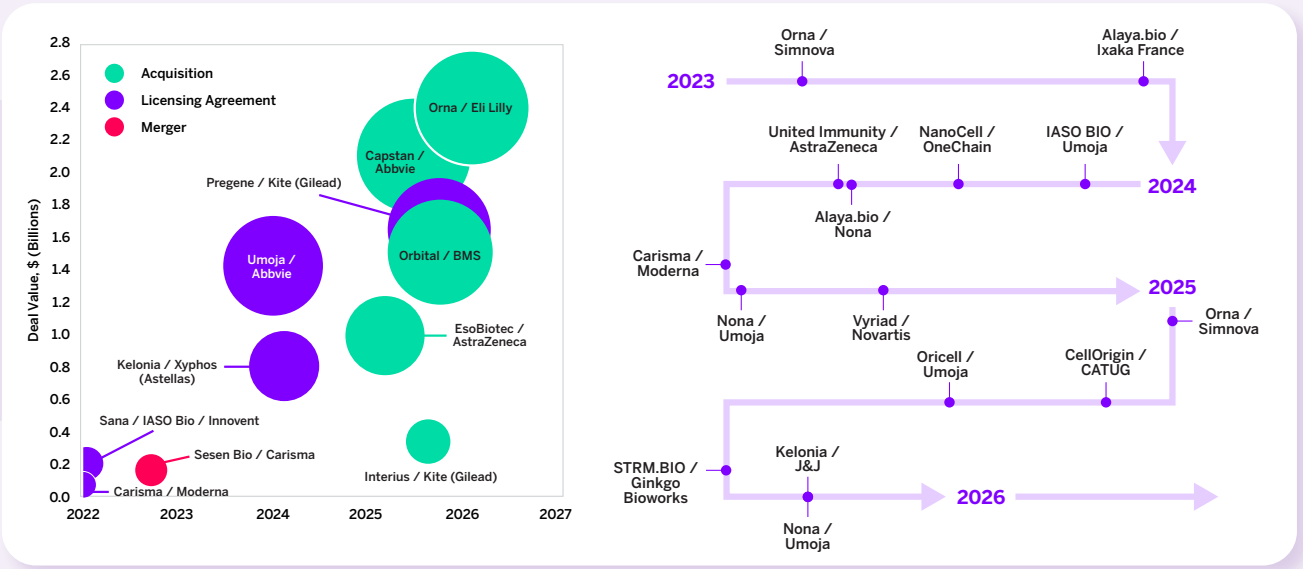
Facing the FDA's New Regulatory Reality

The FDA spent 2025 reshaping the regulatory map for cell and gene therapies. In September, the agency released three draft guidance documents that signaled a more flexible, innovation-oriented position.[33] They encouraged adaptive trial designs, external controls, and master protocols (especially for small or rare populations), and reaffirmed access to RMAT (Regenerative Medicine Advanced Therapies) designation and accelerated approval pathways, contingent on rigorous long-term follow-up. [34,35] In essence, the FDA opened the door for newer modalities, including in vivo CAR platforms, to generate evidence more efficiently.

By December, the tone sharpened. In a JAMA Viewpoint from senior FDA officials, the agency stated clearly that future oncology CAR-T approvals will require randomized trials showing superiority over existing therapies.[36] Single-arm studies, once the norm for ex vivo CAR-T approvals, will no longer suffice where active comparators exist. The FDA also pushed for clinically meaningful endpoints (EFS, PFS, OS) rather than response-based surrogates, unless strongly justified. At the same time, the removal of REMS (Risk Evaluation and Mitigation Strategies) requirements for approved ex vivo CAR-Ts signaled confidence in clinicians' ability to manage toxicity, shifting regulatory focus toward comparative performance and durability.

For in vivo CAR developers, this shift creates a split regulatory path. In crowded oncology indications, like Diffuse Large B-Cell Lymphoma (DLBCL), myeloma, and others with established ex vivo CAR-T or effective alternatives, in vivo CARs must demonstrate meaningful differentiation from current standards of care. Many candidates target the same antigens (CD19, BCMA), raising the critical questions: if efficacy gains are modest, can safety or ease-of-use truly carry the case with regulators? And if not, will this push in vivo CARs toward a regulatory bottleneck in busy oncology indications? In contrast, in settings without approved CAR-Ts (e.g., autoimmune diseases, earlier-line use, rare or poorly treated cancers), regulatory flexibility remains. Here, single-arm trials, external controls, and platform-based approaches may still be acceptable when the unmet need is high and early data are compelling.

DEALS IN THE SPACE



KEY VENTURE FINANCING ROUNDS

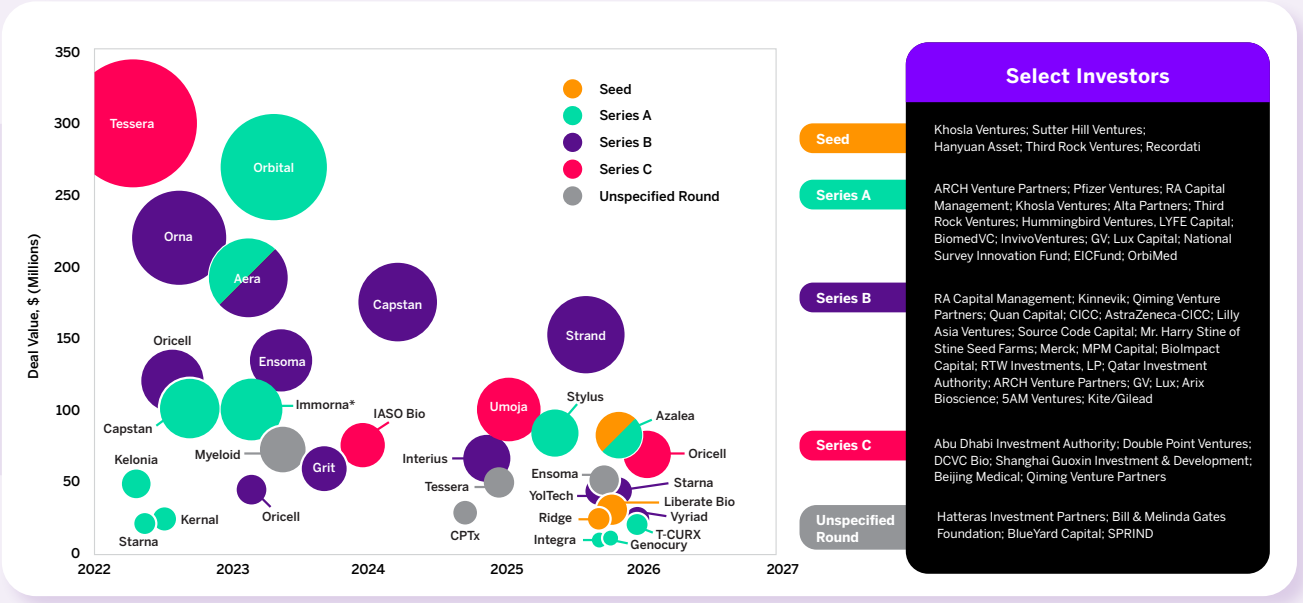


Figure 3: Major Deals in the In Vivo CAR Space.
The deal value (since 2022) indicates the maximum amount a company may receive under the agreement. Partnerships since 2023 without disclosed figures are displayed in the top right. For VC financing, the value reflects the funds raised during a particular investment round at a given point in time. VC deals under $10 million are not included. VC deal ranges ($M): Seed (8–31), Series A (7–270), Series B (25–221), Series C (70–300). Selected investors from funding rounds are listed at the bottom right. Data is compiled from GlobalData, Google News, company websites, and PitchBook.
VC: venture capital; *Immorna's VC round is categorized under Series A+ and A++;
Deal status is updated as of February 2026.

Building on this, the FDA has now begun to specify how such flexibility should apply in autoimmune indications, providing a clearer framework for non-oncology CAR therapy development. In February 2026, the agency released the article listing their early expectations.[37] The FDA specifies that early trials should focus on refractory disease, generally after failure of second-line therapies, though severe phenotypes may justify case-by-case flexibility. Given the uncertainties around long-term safety and the potential for lifelong impact, developers must also carefully assess fertility risks and ensure robust long-term follow-up. The FDA noted that primary and key secondary endpoints selected in Phase I will shape late-phase development, with

a strong emphasis on the importance of reducing chronic immunosuppression and ultimately achieving durable, drug-free remission. In sum, the FDA is signaling a higher bar in oncology and a clearer, opportunity-rich path in autoimmunity—setting the stage for in vivo CAR companies to navigate both.

Deals and Investment Landscape: A Market on the Move

Despite the many unknowns surrounding the true potential of in vivo CAR therapies, they have seen a surge in investment and deal activity. Another Jennifer Doudna–founded startup, Azalea Therapeutics, launched with $82M in combined Seed and Series A financing led by Third Rock Ventures, aiming to deliver transient CRISPR-Cas9 cargo using its proprietary Enveloped Delivery Vehicle (EDV) platform to reprogram T cells.[38] EDVs are virally derived particles that can package and transport genome-editing ribonucleoproteins (RNPs) into cells. Interestingly, Azalea's approach requires more than one delivery vessel: an EDV to deliver the CRISPR scissors, which creates an opening to insert the new CAR gene, and an AAV vector to deliver that gene.[39] Other early-stage activity includes Liberate Bio, which raised $31M in Seed funding to advance its CAR-macrophage and monocyte platform[40], and Germany's T-CURX, which secured a $20M Series A for its non-viral clinical CAR-T programs in AML and solid tumors.[41]

On the acquisition front, the space has seen continued consolidation by major players (**Figure 3**). Building on our previous discussion of induced-proximity therapeutics, it is striking how in vivo CAR deals are already approaching the values of far more established modalities. Although targeted protein degradation deals are typically larger on average, some in vivo CAR transactions are now landing in a similar range, even though the modality remains at a much earlier scientific stage. AbbVie's $1.44B deal for Umoja's in vivo CAR asset in 2024 is comparable to $1.6B it committed for Neomorph's molecular glue degrader in early 2025.[42,43]Similarly, the Kite/Gilead deal with Pregene, with $120M upfront and a total value of $1.64B, underscores the same pattern.[44] BMS's $1.5B acquisition of Orbital Therapeutics further reinforces big pharma's positioning in this space.[45] Lastly, Eli Lilly has entered the field by acquiring Orna Therapeutics in a deal valued at up to $2.4B—the largest transaction in the space to date.[46] Taken together, six major companies—AbbVie, Lilly, BMS, AstraZeneca, Kite/Gilead, and J&J—have secured acquisitions, partnerships or licensing agreements in the in vivo CAR space over the past 18 months. This deal landscape indicates that pharma and investors are willing to place substantial early bets on in vivo CAR platforms, even in the absence of meaningful clinical validation.

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Abbreviations

AAV: Adeno-Associated Virus

ADC: Antibody-Drug Conjugate

B-ALL: B-Cell Acute Lymphoblastic Leukemia

BiTE: Bispecific T-Cell Engager

CAR-M: CAR Therapy Targeting Macrophages

CircRNA: Circular RNA

CRS: Cytokine Release Syndrome

DLBCL: Diffuse Large B-Cell Lymphoma

DORIS: Definition Of Remission In SLE Score

EDV: Enveloped Delivery Vehicle

EFS: Event-Free Survival

FDA: Food and Drug Administration

HR: Hormone Receptor

ICANS: Immune Effector Cell-Associated Neurotoxicity Syndrome

LNP: Lipid Nanoparticles

MG: Myasthenia Gravis

(m)OS: (Median) Overall Survival

(m)PFS: (Median) Progression-Free Survival

NK Cells: Natural Killer Cells

ORR: Objective Response Rate

RA: Rheumatoid Arthritis

REMS: Risk Evaluation And Mitigation Strategies

SLE: Systemic Lupus Erythematosus

Tregs: Regulatory T Cells.

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Closing Remarks

Few modalities have generated as much buzz recently as in vivo CARs. The technology is compelling, offering clear theoretical advantages over ex vivo predecessors, with the potential to unlock mass-market opportunities in autoimmune disease. But can they truly deliver on these promises? The future of in vivo CARs will depend not only on emerging clinical data but also on a fast-shifting regulatory climate. The FDA's recent tightening of oncology standards has raised the bar: in vivo CARs must now compete on value, not novelty. This creates uncertainty for developers. What level of superiority will regulators expect? In autoimmune settings, where ex vivo CAR-Ts and BiTEs are advancing quickly, what evidence will in vivo platforms need for approvals? Will depth of remission matter more than long-term tolerability or could a cleaner safety profile justify non-inferiority? The path forward is navigable, but only for programs ready to generate rigorous data, differentiate clearly, and engage regulators early. The next wave of results will determine whether in vivo CARs emerge as true competitors to ex vivo CAR-T or carve out a distinct role in the broader cell and gene therapy landscape.

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