William Blair

Equity Research
Healthcare | Biotechnology

October 22, 2025
Industry Report

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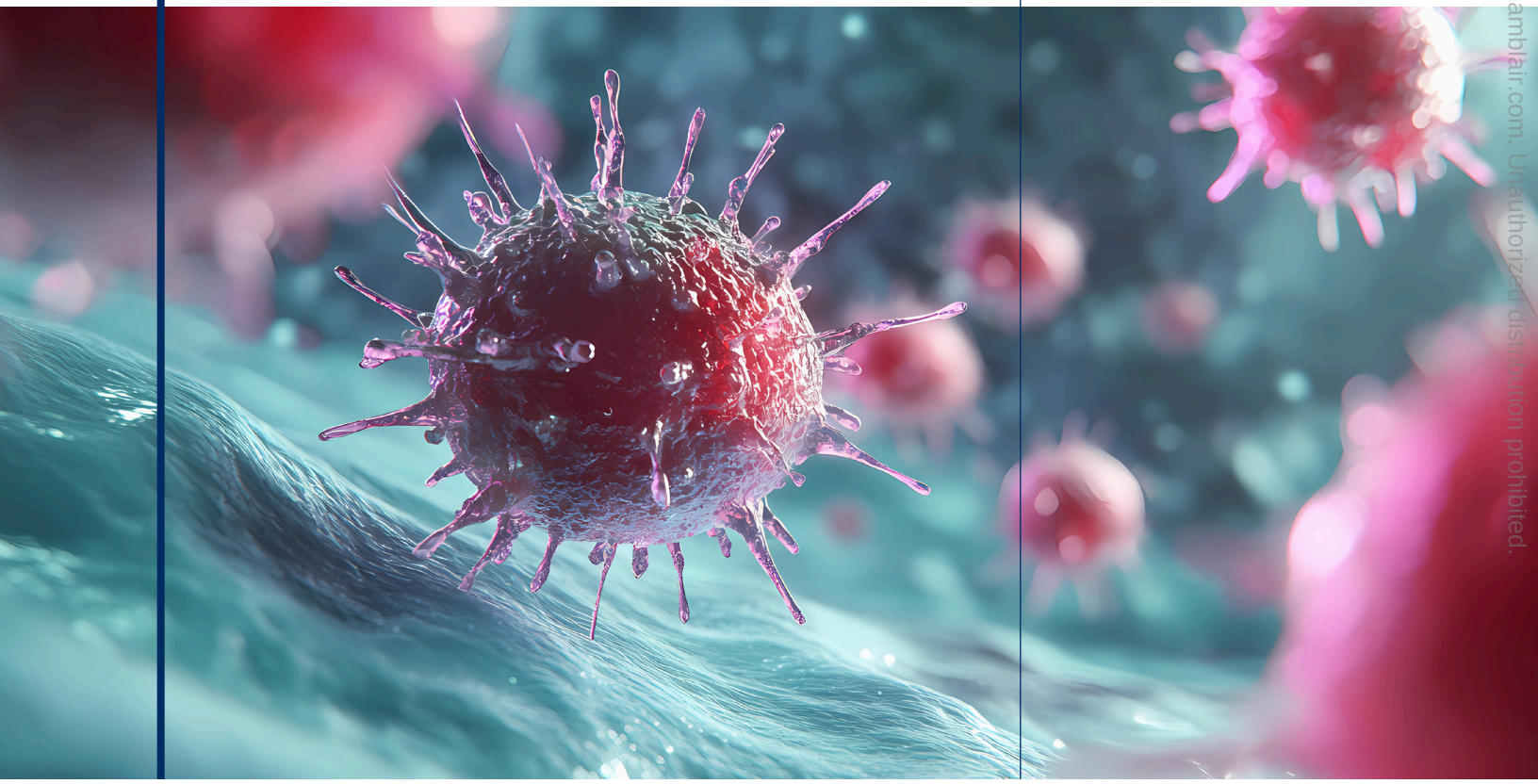
CELLect Horizons

Back to the Future: Revisiting the In Vivo CAR-T Landscape



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Executive Summary

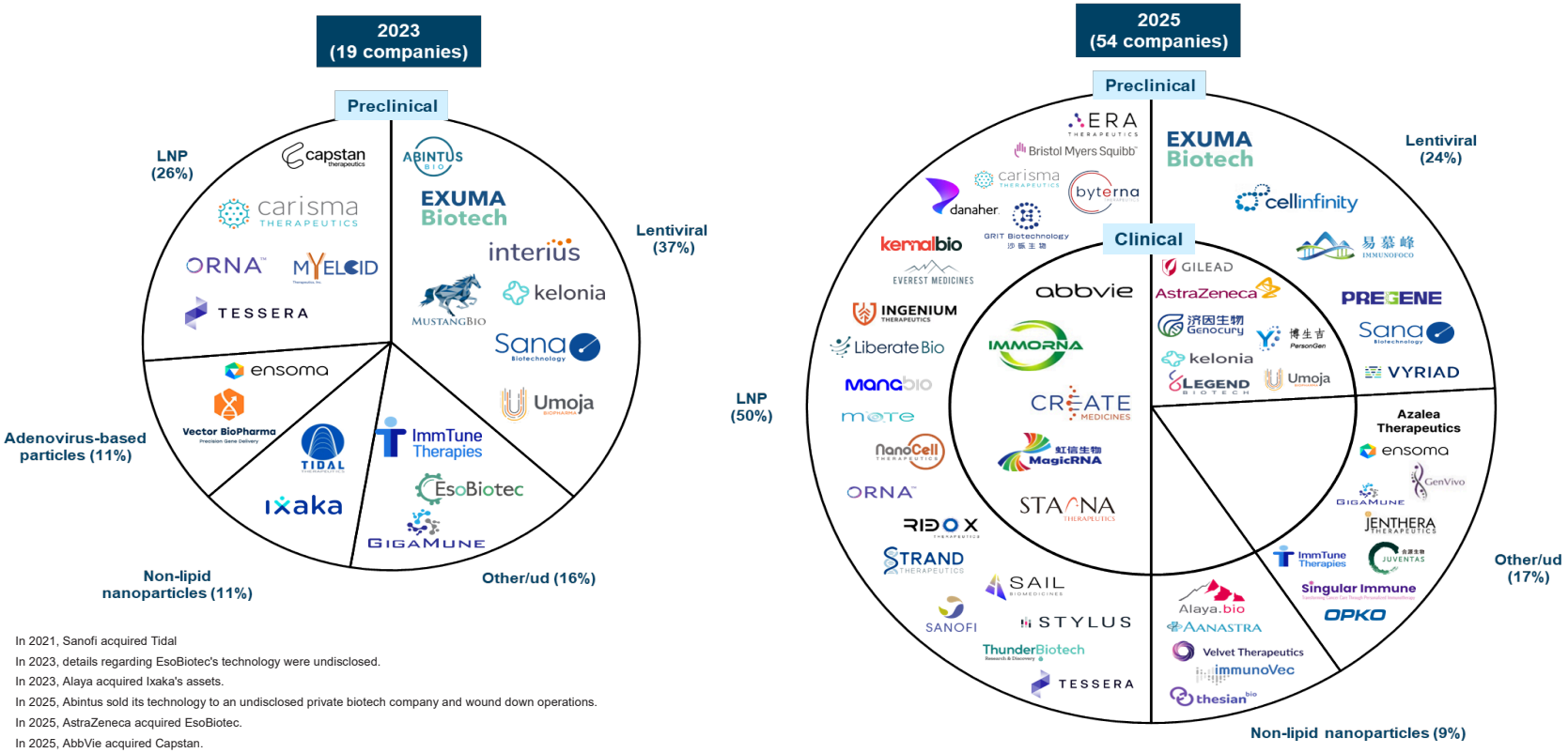
In our *CELLect Horizons* series, we examine cell and gene therapy platforms that we believe are on the cusp of generating data that could transform the therapeutic landscape. In a 2023 edition of this report, we detailed in situ engineering of CAR-T therapies, which were still an immature but promising concept at the time. Following the advancement of several candidates into the clinic and four high-profile acquisitions this year, in this edition of *CELLect Horizons,* we revisit the in vivo CAR-T landscape, summarize the progress companies in the space have made over the last two years, detail financing and business development in the space, and provide our perspectives on the field and the broader implications if the development of these modalities is successful.

Since our 2023 report, the number of companies developing in vivo CAR-T therapies has nearly tripled (exhibit 1, on the following page), with a quarter of companies now in early clinical development. We highlight that the majority of the growth in the field is attributable to new companies pursuing lipid nanoparticle (LNP)-based delivery, which has more than quadrupled in the past two years. We believe the increase in LNP-delivered in vivo CAR-T therapies has been driven by advancements in LNP and mRNA technology and increased enthusiasm for the potential of CAR-T for the treatment of autoimmune diseases.

Of the 12 companies that currently have an asset in clinical development, only one is initially pursuing clinical development in the U.S., while 7 are initially evaluating their assets in investigator-initiated trials (IITs) in China, and 4 have started their clinical trials in Australia. We believe this pattern is indicative of the reduced bureaucratic barriers, increased regulatory flexibility, and lower costs for first-in-human trials in some ex-U.S. geographies, which could potentially aid in accelerating clinical development.

Early clinical data from both lentiviral (LV) and LNP-based approaches have demonstrated that CAR-T cells generated in vivo are capable of expanding without the use of lymphodepletion and fully depleting peripheral B cells, which has translated into clinical responses in oncology and autoimmune patients. However, the clinical safety profile of in situ CAR-T approaches has been mixed, with some exhibiting benign safety profiles and others demonstrating high-grade CRS events similar to ex vivo CAR-Ts (exhibit 2, on page 5). Given each approach bears its own merits and drawbacks, we believe additional clinical data are needed to better determine which technology and/or cell targeting method will yield the optimal safety/efficacy profile. It also remains to be seen whether technologies that enable CAR transgene integration into the host genome (e.g., LV), and therefore durable CAR expression with a single treatment, or modalities that enable transient CAR expression but can be dosed repeatedly (e.g., LNP) will be more advantageous. In our view, it is likely that different approaches will ultimately be best suited for different applications (e.g., integrative CARs may be best suited to treat oncology whereas transient CAR expression may be sufficient for treating autoimmune diseases).

Exhibit 1
CELLect Horizons
Landscape of Companies Developing In Vivo CAR-T Therapies Based on Delivery Modality and Stage of Development



In 2021, Sanofi acquired Tidal
In 2023, details regarding EsoBiotec's technology were undisclosed.
In 2023, Alaya acquired Ixaka's assets.
In 2025, Abintus sold its technology to an undisclosed private biotech company and wound down operations.
In 2025, AstraZeneca acquired EsoBiotec.
In 2025, AbbVie acquired Capstan.
In 2025, Gilead acquired Interius.
In 2025, BMS acquired Orbital.
In 2025, Myeloid rebranded as Create Medicines.
Source: William Blair Equity Research

Exhibit 2
CELLect Horizons
Summary of Clinical Data Generated by In Vivo CAR Therapies

Company	AstraZeneca	CREATE MEDICINES	济因生物 Genocury	GILEAD	虹信生物 MagicRNA
Product	ESO-T01	MT-302	N/A	INT2104	HN2301
Target	BCMA	TROP2	CD19	CD20	CD19
Indication	MM	Epithelial Cancers	DLBCL	MCL	SLE
Patient size	4	5	1	1	5
Trial location	China	Australia	China	Australia	China
Evidence of CAR cell expansion	Yes	Yes	N/A	N/A	Yes
Evidence of target cell depletion	Yes	N/A	Yes	Yes	Yes
Clinical results	ORR: 100% CRR: 50%	N/A	ORR:100% CRR:100%	N/A	Average reduction in SLEDAI: ~8
Safety	Grade 3 CRS: 75% Grade 1 ICANS: 25% Grade 3 ALT/AST: 50%	No acute induction of complement proteins or IL-1β	No ICANS No CRS	No ICANS No CRS	Grade 1/2 CRS: 100%
Source	Jia Xu et al. *Lancet*. 2025	ASCO 2025	Company reports	Cellicon Valley 2025	Wang et al. *NEJM* 2025

In contrast to investor sentiment for public cell and gene therapy companies, which has largely declined over the last 24 months, private companies developing in vivo CAR therapies have raised over $427 million year-to-date, up 76% year-over-year. In addition, four companies developing in vivo CAR-Ts were acquired this year, with the deal values totaling $5 billion in aggregate. Although the lion's share of companies developing in situ CAR-T are still private (exhibit 3), we believe these acquisitions validate the disruptive potential of in vivo CAR-T and mark big pharma's entrance into the field.

Exhibit 3
CELLect Horizons
Landscape of Companies Developing In Vivo CAR-T Therapies Based on Market Cap

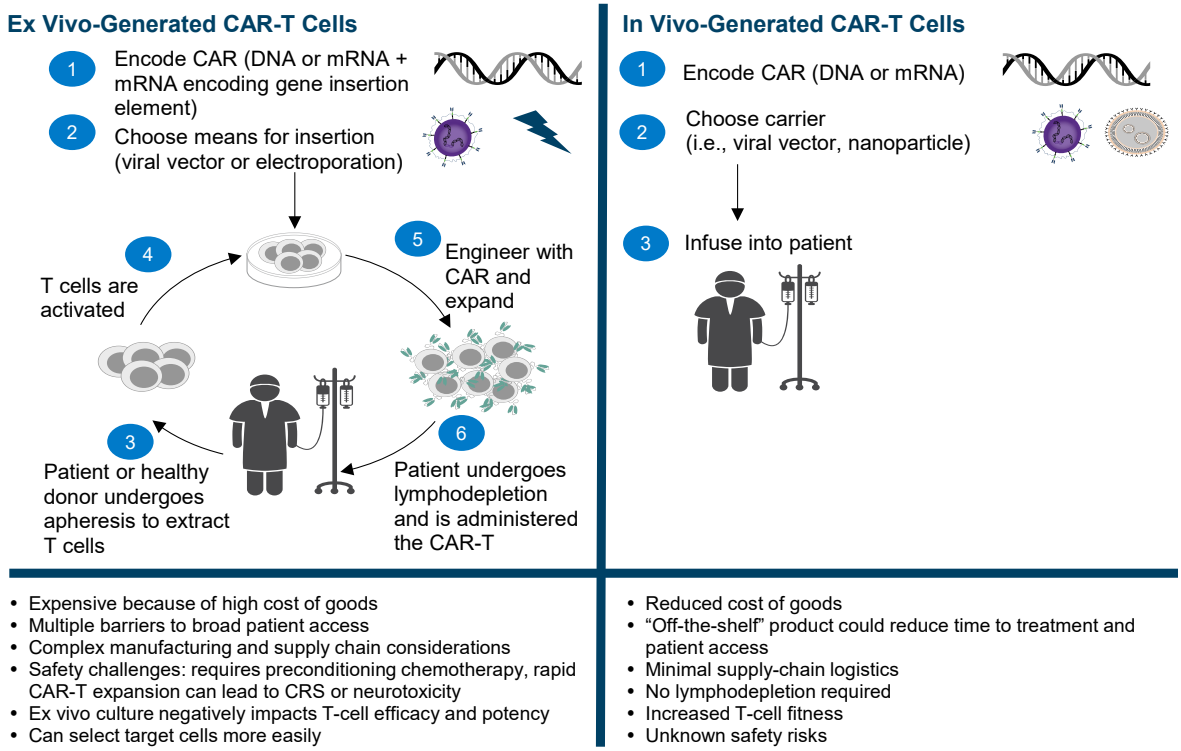
Source: William Blair Equity Research

We expect additional clinical data from several companies in late 2025 and early 2026 could provide increased insight into the risk/benefit profiles of various candidates and drive further business development activity. The successful development of in situ CAR-T has broad implications for oncology, immunology, and the genetic medicine fields. However, since the majority of in situ CAR-Ts in development target validated and approved antigen targets (e.g., CD19, BCMA, and CD20), their successful development could impact CAR-Ts that are commercially available or in late-stage development for oncology indications, including: Gilead's Yescarta and Tecartus, Bristol Myers's Breyanzi and Abecma, Novartis's Kymriah, Johnson & Johnson/Legend's Carvykti, Autolus's obe-cel, Allogene's cema-cel, and Arcellx's anito-cel. Similarly, the advancement of these approaches could negatively affect companies that are developing CAR-Ts for autoimmune diseases, including: Cabaletta's rese-cel, Kyverna's KYV-101, Novartis's YTB323, AstraZeneca's GC012F, Bristol Myers's CC-97540, Autolus's obe-cel, Allogene's ALLO-329, CRISPR's CTX112, and Nkarta's NKX019.

Overview of In Vivo CAR Engineering

Advances in gene therapy have ushered in a reimagining of CAR-T engineering in which ex vivo manufacturing is not necessary and instead T-cell programming could occur in vivo through the transient delivery of mRNA encoding the CAR or the permanent integration of the CAR transgene into the host genome. Such a technology could simplify cell engineering and reduce or remove some of the current barriers hindering broader access to ex vivo engineered CAR-T (exhibit 4).

Exhibit 4
CELLect Horizons
Ex Vivo vs. In Vivo CAR-T Path to Treatment



Source: William Blair Equity Research

However, various approaches to in vivo CAR delivery are being investigated, and each possesses unique advantages and disadvantages from safety, efficacy, and manufacturing perspectives (exhibit 5). While we broadly refer to this evolving field as in vivo CAR-T, we highlight that companies are taking different approaches with cell targeting based on their underlying technology and preferred cell targeting moieties, with some companies targeting a specific population of T-cells (i.e., CD8+), while others are targeting different (i.e., monocytes) or multiple immune cell subtypes (i.e., T cells and NK cells). While we review the companies developing in vivo CAR-Ts using these technologies later in the report, refer to our 2023 report for a more in-depth background on these various technologies.

Exhibit 5
CELLect Horizons
Benefits and Challenges of Various In Vivo Delivery Modalities

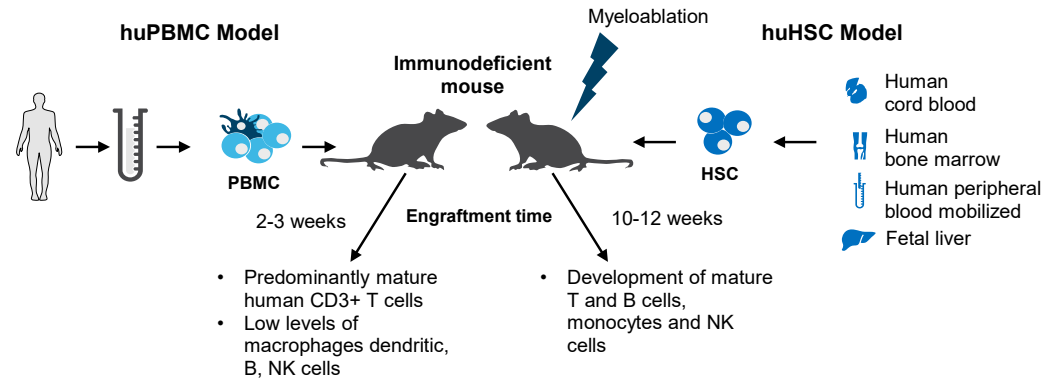
	Innate Tropism to T Cells	Transduction Efficiency	Ability to Integrate	Re-dosing Possible	Scalable Manufacturing	Limited Immunogenicity	Efficient Cell-Specific Targeting
Lentivirus	✓	✓	✓	X	✓	X	✓
LNP	X	✓	✓	✓	✓	✓	✓
Polymeric Nanoparticles	X	?	✓	✓	?	X	?

X No ✓ Yes ✓ Yes but with caveats ? Maybe

Source: Jennifer Adaire ASGCT 2020; adapted by William Blair Equity Research

Furthermore, initial proof-of-concept studies evaluating in vivo CAR delivery can be conducted in different preclinical models, making it increasingly challenging to evaluate the potency, safety, and efficacy of the various approaches. Most commonly, preclinical studies of in vivo CAR-delivery candidates are conducted in humanized mouse models, in which immunodeficient (e.g. NSG, NOD, or NOG) or immunocompetent mice are engrafted with either human peripheral blood mononuclear cells (PBMCs) or human CD34+ hematopoietic stem cells (HSCs). Human PBMC mouse models quickly and transiently produce high levels of functional and educated T-cell populations. However, due to the rapid T-cell expansion, the development of other hematopoietic lineages, such as macrophages, dendritic cells, NK cells, and B cells, are low or even absent in this model (Ludovic Bourŕe et al. *Crown Bioscience.* 2019). Humanized HSC mouse models are widely considered the more clinically relevant humanized model due to their ability to offer stable and long-term expression levels of B, T, and NK cells, which can better recapitulate the human immune system compared to NSG models. However, these models are complex and require mice to undergo myeloablation and recovery prior to HSC engraftment, which can delay study initiation 15-20 weeks post-engraftment (Ludovic Bourŕe et al. *Crown Bioscience.* 2018). Below is a schematic comparing the two humanized mouse models (exhibit 6).

Exhibit 6
CELLect Horizons
Schematic of Generation of Humanized Mouse Models



Source: Rajendra Kumari et al. *Current Protocols.* 2023

Learnings From the Last Two Years

Since the publication of our initial report on the space (In Vivo CAR-T: A Potentially Disruptive Force in Cell Therapy), several companies have advanced in vivo candidates into the clinic through company- or investigator-sponsored trials, providing clarity on several aspects that were previously points of concern for investors:

In vivo CAR-T cells will expand in vivo in humans without lymphodepletion.
Before introduction of ex vivo CAR-T cells into a patient, the patient undergoes lymphodepletion, also called preconditioning, to create a suitable environment for CAR-T cells to expand and persist, as well as to reduce the patient's tumor burden. Prior to the generation of clinical data, there was skepticism that CAR cells generated in vivo would not have the room or an adequate cytokine environment for optimal cell expansion. Although the clinical data is limited, early data from both viral (EsoBiotec) and nonviral approaches (MagicRNA) have demonstrated that CAR-T expansion with an in vivo CAR modality is possible without the use of lymphodepletion. Time to peak expansion with lentiviral-based approaches appears similar to ex vivo CAR-Ts (around 14 days). In contrast, expansion with LNP-based approaches is much more rapid, with peak expansion occurring around 6 hours after administration. However, given differences in how peak cell expansion is measured, it is unclear at this time if in vivo therapies can achieve the same magnitude of peak expansion as ex vivo cell therapies.

In vivo CAR therapies can fully deplete peripheral B cells in humans, which has translated into early efficacy.
Early PK data from both viral (e.g., Interius and EsoBiotec) and LNP (e.g., MagicRNA) modalities indicate treatment with in vivo CARs can lead to complete B-cell elimination in the peripheral blood of oncology and autoimmune patients, respectively. In addition, Genocury and EsoBiotec have reported diffuse large B-cell lymphoma (DLBCL) and multiple myeloma (MM) patients achieved complete responses, respectively, with responses maintained out to 3 months. Similarly, MagicRNA reported that SLE patients exhibited reduced SLEDAI-2K scores following treatment. Overall, this suggests in vivo CAR therapies are potent enough to generate clinical responses in oncology and autoimmune patients.

Acute clinical safety profiles are mixed, but no dose-limiting toxicities have been reported to date.
The acute clinical safety profile of lentiviral vector (LVV)-based in vivo therapies has been variable. Interius reported only two low-grade treatment-related events (grade 2 infusion-related reaction with 2e8 transduction units [TU] and grade 1 fatigue with 6.3e8 TU), and Genocury reported no CRS or ICANS (dose not reported); however, the adverse event profile with EsoBiotec's therapy was more severe. Grade 3 CRS was observed in three of four patients treated with 2.0e8 TU of EsoBiotec's therapy, which primarily occurred in the first 48 hours post-infusion. Patient two and four also experienced grade ≥3 elevated liver enzymes within the first two days. This acute toxicity profile is dissimilar from ex vivo CAR-Ts, for which the average time to CRS onset is 7 days and liver toxicity is not seen, suggesting the construct itself as opposed to CAR-T expansion may be causing the immediate inflammatory response. In addition, all patients treated with EsoBiotec's therapy exhibited grade 1 CRS between days 8 and 12, which coincided with peak CAR cell expansion. Regarding LNP modalities, while all five patients treated with MagicRNA's therapy experienced low-grade CRS, none experienced ICANS. In addition, levels of C-reactive protein increased after the first infusion but not subsequent infusions. However, while no clinically significant elevations in liver enzymes were reported, based on the supplemental figures, one patient did experience meaningful increases in liver enzymes following the third infusion. Furthermore, Create reported across all six evaluable patients treated with its therapy, and no acute induction of complement proteins

or IL-1β was observed. Overall, we believe the limited data suggest some LV and LNP modalities have a tolerable acute safety profile, but the toxicity profile may be dependent on the product and indication, similar to ex vivo CAR-T.

Remaining Questions and Future Outlooks

T cells, NK cells, macrophages, or all of the above?
With conventional CAR-T cell therapies, the manufacturing process starts by selecting for T cells from the apheresis material or the healthy donor material (in the case of allogeneic cell therapies). In contrast, in vivo CAR-cell therapies can be engineered to target other immune cell populations in addition to, or instead of, T cells (i.e., NK cells, macrophages, myeloid cells). Targeting multiple or alternative immune cell lineages could enhance antitumor responses, specifically in high tumor burden diseases such as solid tumors. This approach could also be beneficial in the treatment of autoimmune diseases that are not just B-cell driven. However, despite the unique characteristic of NK cells and macrophages to have increased resistance to the immunosuppressive tumor microenvironment, ex vivo CAR therapies using these cell types have shown limited clinical benefit in oncology. In addition, it is possible the reprogramming of several immune lineages into effector cells could lead to enhanced inflammatory signaling that is not tolerable. Hence, it is currently unclear which immune lineages are necessary for an enhanced therapeutic profile and if targeting multiple cell types would adversely impact the safety profile.

Transient or permanent CAR expression?
Depending on the delivery modality and payload used, CAR expression can be transient (e.g., mRNA encoding the CAR) or permanent (e.g., CAR transgene is integrated into the host genome using gene editing machinery or viral integration). While permanent integration does carry the risk of insertional oncogenesis, it allows for clonal CAR-T populations to durably persist, which will likely be advantageous in the context of oncology, wherein there is a high burden of diseased cells and all must be eliminated for a durable response. In contrast, transient expression may be more favorable in the context of autoimmune diseases, wherein there are fewer diseased cells, long-term cell depletion is likely not necessary or favorable for a durable response, or redosability is preferable. In exhibit 7, we summarize companies developing integrative versus non-integrative approaches for autoimmune diseases and oncology, and in exhibit 8, we compare some of the key aspects of RNA-based integrative CARs versus those developed using viral approaches.

Exhibit 7
CELLect Horizons
Select Companies Developing Integrative vs. Non-integrative Approaches

Companies Developing In Vivo CAR-T for Oncology Indications		
	Viral	**Non-viral**
Integrative CAR	AstraZeneca, ensoma, EXUMA Biotech, cellinfinity, 济因生物 Genocury, GILEAD, kelonia, GenVivo, Sana, LEGEND BIOTECH, 易慕峰 IMMUNOFOCO, 博生吉 PersonGen, Umoja, VYRIAD	danaher, NanoCell THERAPEUTICS, JENTHERA THERAPEUTICS, CREATE MEDICINES, TESSERA, STYLUS
Non-integrative CAR		AANASTRA, carisma THERAPEUTICS, CREATE MEDICINES, EVEREST MEDICINES, IMMORNA, INGENIUM THERAPEUTICS, kernalbio, Liberate Bio, STAINA THERAPEUTICS, Singular Immune, STRAND THERAPEUTICS, ThunderBiotech, Velvet Therapeutics
Companies Developing In Vivo CAR-T for Autoimmune Indications		
	Viral	**Non-viral**
Integrative CAR	EXUMA Biotech, GILEAD, Sana Biotechnology, 博生吉 PersonGen, Umoja BIOPHARMA, VYRIAD	STYLUS, NanoCell THERAPEUTICS, YolTech THERAPEUTICS
Non-integrative CAR		AANASTRA, abbvie, ERA THERAPEUTICS, Bristol Myers Squibb, EVEREST MEDICINES, kernalbio, Liberate Bio, SAIL BIOMEDICINES, CREATE MEDICINES, 虹信生物 MagicRNA, Singular Immune

Source: Company reports; William Blair Equity Research

Exhibit 8
CELLect Horizons
Comparison of Integrating Modalities for In Vivo CAR-T

	Lentivirus	**Non-viral**
Nucleic acid	DNA	RNA + DNA
Stability	High	Low
Half-life of delivery vehicle	8 hours	Hours to days
CAR expression	Months to years	Theoretically months to years
Commercial manufacturability	Creating scalable process is a challenge	Highly reproducible with validated manufacturing process
Key safety concerns	-Risk of insertional oncogenesis -Immunogenicity to lentiviral vector	-Immunogenicity to LNP and/or gene editing cargo -Risk of off-target editing
Repeat dosing	No	Potentially

Source: William Blair Equity Research

Is going ex-U.S. first a way to speed up clinical development?
Of the 12 companies with an in vivo CAR-T asset currently in clinical development, only Umoja is initially pursuing clinical development in the United States. Seven (AstraZeneca, Immorna, MagicRNA, Genocury, Starna, PersonGen, and Legend) are initially evaluating their assets in investigator-initiated trials (IITs) in China, and four (Interius, Capstan, Create and Kelonia) started clinical trials in Australia. Notably, while conducting IND-enabling studies, Umoja used pigtailed macaques as opposed to rhesus macaques; pigtailed macaques are permissive to the integrating vector-mediated transduction, while rhesus macaques harbor the innate host restriction factor tripartite motif-containing protein 5α (TRIM5α), which prevents retroviral infection by degrading the viral capsids. While U.S.-based or multinational trials will likely be required for eventual FDA approval, the location of first-in-human trials could provide certain advantages. Initiating first-in-human trials in the U.S. could allow sponsors to develop relationships with sites earlier and allow U.S. physicians to have hands-on experience with the asset, which could be beneficial as companies look to initiate pivotal studies. As for China, regulatory submission and scrutiny is not required for first-in-human trials, reducing the bureaucratic red tape and time to enter the clinic. This could in turn allow companies to evaluate assets and doses more rapidly, enabling them to optimize assets and protocols more quickly. The cost of conducting clinical trials in China is also significantly less compared to the U.S., which could be particularly appealing for companies with a finite cash runway. On the other hand, efficacy data from single-center studies in China have not consistently held up in multi-site, global trials, suggesting the translatability of the data could be limited. Other companies have sought to initiate clinical trials in Australia as opposed to the U.S. because of decreased use of CAR-Ts commercially, lower study costs, and faster clinical trial site onboarding, suggesting they could more rapidly enroll their trials with CAR-T-naïve patients and spend less money on clinical trial costs. Ultimately, the time to commercialization will also depend on the clinical data generated, and it remains unknown if in vivo CAR-Ts will eventually have to go head-to-head against ex vivo CAR-Ts (in the context of oncology) or other standard-of-care therapies (in the context of autoimmune disease).

Novel RNA payloads may have some benefits, but safety profile is still unknown.
Along with the steady increase in LNP-based in vivo CAR-T programs in development, there have also been an increase in the use of novel RNA payloads, particularly circular RNAs (circRNA) for CAR transgene expression. Unlike mRNA in a linear conformation, circRNA are covalently closed RNA molecules that form a loop, which is more stable than linear mRNAs because of the absence of 5' and 3' ends. These circRNAs contain a specific RNA sequence that allows ribosomes to bind to mRNA and initiate protein synthesis at an internal location, bypassing the typical cap-dependent protein translation process. Many of these circRNA-based technologies also build upon some of the limitations associated with conventional mRNA by incorporating programmable elements to increase protein expression further. Therefore, circRNA-based CARs could conceptually enable higher and more durable CAR expression on the cell membrane of functional immune cells than linear mRNAs, holding the potential to generate more effective effector cells. While a majority of companies utilizing circRNA for in vivo CAR-T are being applied for transient CAR expression, several companies are developing RNA-based therapies that express gene editing machinery to allow for integration of DNA CAR transgenes into the host genome. We also highlight some sponsors utilizing linear mRNA, like Create, have sought to optimize its stability and durability through targeted modifications.

In exhibit 9, we compare some of the key aspects of known RNA modalities being used for in vivo CAR-T and which companies are applying that technology currently. While we do not highlight it in the table, we note that translation initiation and elongation rates are less understood for unconventional RNA approaches, such as circRNAs, which we believe require additional validation because of the inserted translational elements. In addition, the immunogenicity of these novel RNAs remains debated and their manufacturability is not well described.

Exhibit 9
CELLect Horizons
Comparison of Novel RNA Modalities Being Evaluated for Transient In Vivo CAR-T

	mRNA	Unmodified circRNA	Synthetic circRNA	eRNA
Structure	Single-stranded, linear	Single-stranded, closed loop	Single-stranded, closed loop	Long non-coding RNA formulated into closed loop structure
Stability	Low	High	High	High
Translation Induction	5' cap-dependent mechanism	5' cap-independent mechanism in specific circRNAs	Variable based on circRNA design	Undisclosed
Protein Expression	Days	Weeks	≥ Unmodified circRNA	≥ Unmodified circRNA
Manufacturability	Highly reproducible with validated manufacturing process	Unknown	Unknown*	Unknown*
Immunogenicity	Yes	Yes (< mRNA)	Yes	Unknown
Select Companies	abvie, AANASTRA, ERA THERAPEUTICS, CREATE MEDICINES, GRIT Biotechnology, Manabio, MagicRNA		ORNA, STRAND THERAPEUTICS, RIBOX THERAPEUTICS, MOTE, Bristol Myers Squibb, byterna THERAPEUTICS	SAIL BIOMEDICINES

*Manufacturability will vary depending on RNA synthesis process, RNA fragment size, and circularization efficiency
Source: William Blair Equity Research

Manufacturability and scalability will be key for commercial success.
Similar to ex vivo CAR-Ts and gene therapies, we believe manufacturability and scalability will be critical for the commercial success of in vivo CAR-T assets. The manufacturing process will need to be consistent, as companies scale up production, which could be challenging for companies that utilize several components on the viral capsid or conjugated to the LNP for T-cell targeting and liver de-targeting. Scalability is also important because it will ultimately impact the cost of goods and profitability of these assets.

The depth of B-cell depletion, persistence of CAR-T cells, and durability of responses are still unknown.
The clinical data generated thus far have not extensively evaluated B-cell depletion, although some companies have demonstrated in monkeys that in vivo constructs lead to B-cell depletion in organs and regions aside from the peripheral blood. Therefore, it is still unclear if B cells in lymph nodes and the bone marrow are also being fully depleted in humans at this time with in vivo CAR-T. Similarly, no clinical data have been generated yet to support the class switching of B cells in

autoimmune patients following treatment with in vivo CAR-T. In addition, because of limited follow-up, it is not known how long CAR-T cells engineered in vivo persist. These data points will be critical in predicting the depth and durability of responses to in vivo CAR-T in both oncology and autoimmune patients and are necessary to better understand how the efficacy of the modality will compare to traditional ex vivo CAR-T.

Clinical data are needed to differentiate "winners."
Although we believe some in vivo CAR-T modalities may be better suited for specific indications, the preclinical evaluation of in vivo products is not standardized, leading to differences in animal models and data used to support the development of candidates. Overall, we believe this will make it challenging to compare the activity and safety profile of assets until they are in the clinic. Notably, the representation of CAR+ cells can differ between sponsors, which makes it difficult to compare maximum CAR-T expansion. Some companies have also used a reporter protein in preclinical studies as a surrogate for CAR expression. However, this may not be an accurate representation of CAR expression due to differences in the size and dynamics of translocation to the cell membrane.

In addition, some animal models may be less predictive of the clinical effect; the importance of using specific mouse and nonhuman primate (NHP) models for integrating in vivo platforms is discussed above. We highlight previous data shared by James Dahlman, an associate professor at Emory Medical School and Georgia Tech and cofounder of Guide Therapeutics (acquired by Beam Therapeutics), at the 2024 American Society of Gene and Cell therapy (ASGCT) conference demonstrating NHPs are a stronger predictor of LNP activity in humans (R^2=0.83), compared to mice (R^2=0.53), suggesting that LNP studies in mice could provide false positives and false negatives (ASGCT Recap: Next-Gen AAV Capsids, LNPs for Non-Hepatic Tissues, and Incremental Clinical Updates).

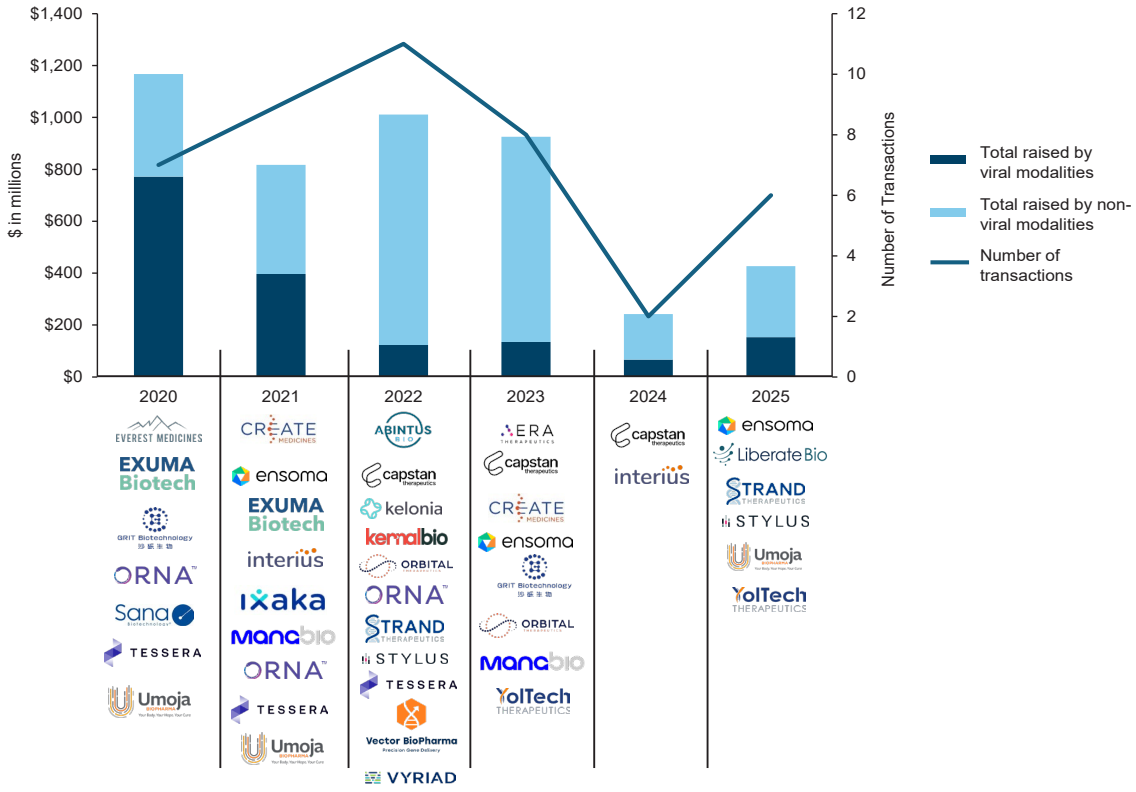
Agility of in vivo CAR-T approach could lead to large market opportunity even if efficacy is inferior to ex vivo CAR-T.
Despite the transformational efficacy with ex vivo CAR-T, in 2024 the seven FDA-approved CAR-T therapies generated $4.3 billion in global revenue, comprising only 12% of the multiple myeloma, non-Hodgkin lymphoma, and acute lymphocytic leukemia markets in aggregate. Although these markets and CAR-T's share of them are expected to grow steadily over the next 10 years, ex vivo CAR-Ts are inherently less accessible compared to other oncology products because they require lymphodepletion, personalized manufacturing, and prolonged monitoring, restricting the number of sites capable of administration. Since in vivo CAR-Ts are off-the-shelf and do not require lymphodepletion, they are inherently more accessible, and we believe they could be more readily used in the community setting, where ex vivo CAR-T is not widely used (dependent on their safety profile). Therefore, even if in vivo CAR-Ts are unable to demonstrate comparable efficacy to ex vivo CAR-Ts, we hold the view they could still capture a meaningful segment of the oncology market. Furthermore, if they demonstrate comparable or superior efficacy to ex vivo CAR-Ts, we think they could rapidly cannibalize the CAR-T market as well, which could impact current commercial CAR-Ts marketed by Gilead, Novartis, Bristol-Myers, Johnson & Johnson/Legend, and Autolus.

The global market for autoimmune diseases is estimated to be over twice the size of the global oncology market, at an estimated $75 billion. Therefore, if successful, in vivo CAR-Ts could be more lucrative in autoimmune diseases compared to oncology. We believe that in situ CARs are particularly well suited for the treatment of nonmalignant B-cell disorders, wherein safety/tolerability will be paramount, because in vivo CAR-T approaches do not require preconditioning with chemotherapy, which is a major benefit given autoimmune diseases are most likely to impact women of childbearing age. If in vivo CAR-T successfully advance through clinical development, it could negatively affect companies that are developing CAR-Ts for autoimmune diseases, including: Cabaletta, Kyverna, Novartis, AstraZeneca, Bristol Myers, Autolus, Allogene, CRISPR, and Nkarta.

Financing Landscape and Partnerships

From 2020 to 2025, private companies developing in vivo CAR therapies raised a total of $4.6 billion (exhibit 10), with annual funding peaking in 2020 at $1.2 billion, which was largely driven by Sana's $700 million financing. Excluding the latter financing, the number of transactions, total amount raised, and average amount raised by in vivo CAR-T companies increased from 2020 to 2022. While total capital raised and the number of transactions decreased in 2023 and 204—consistent with the greater biotech landscape—funding and transactions have increased in 2025, with $427 million raised across six transactions year to date.

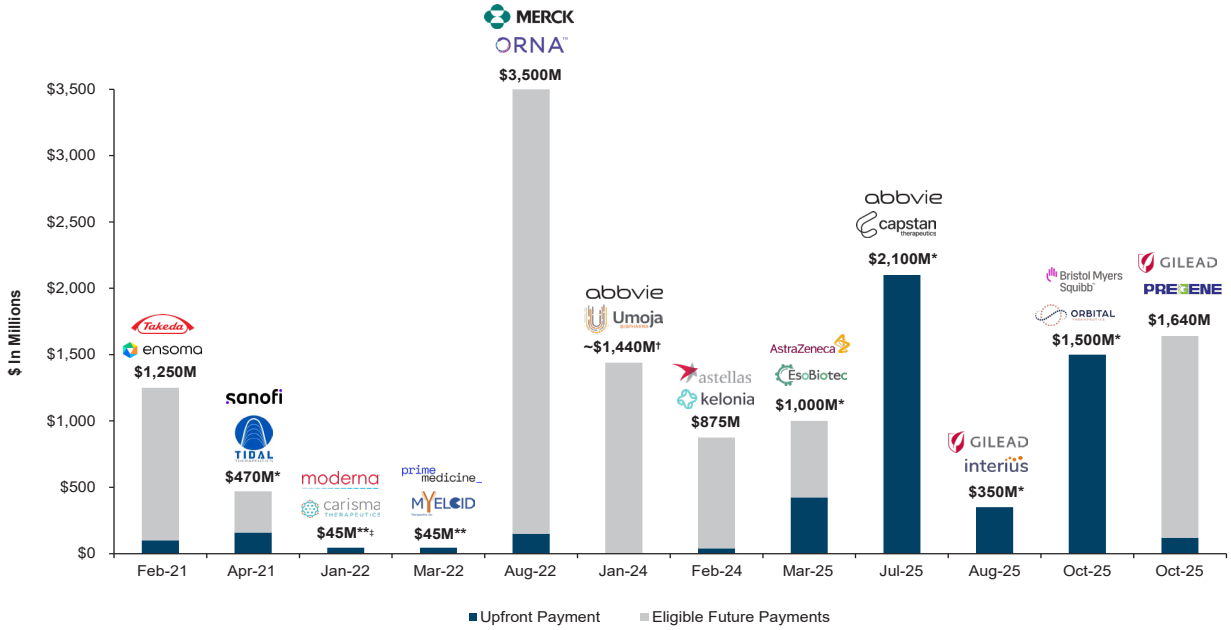
Exhibit 10
CELLect Horizons
Private Financing Raises of Companies Developing In Vivo CAR-T Cell Therapies From 2020 to 2025



Source: Company reports; William Blair equity research

Deal activity has also become more robust in 2025, with four acquisitions occurring so far in 2025, with cumulative upfront payments totaling $4.5 billion (exhibit 11). The most notable transaction was AbbVie's $2.1 billion acquisition of Capstan (see: Capstan Buyout Adds High-Risk, High-Reward Asset to Immunology Pipeline; Growing Interest in Immune Reset Across Modalities). We highlight that AbbVie is the only major pharma company to have engaged in business development with multiple in vivo CAR delivery platforms, which suggests it is taking a strong but diversified investment approach to the modality. In contrast, Johnson & Johnson and Autolus are the only companies with approved CAR-T therapies who have not yet partnered with or acquired an in vivo CAR-T company. We believe the former could be positioned to engage in future business development in the field. As clinical trials commence and early datasets continue to emerge, we anticipate deal activity within the in vivo CAR-T sector to continue.

Exhibit 11
CELLect Horizons
Disclosed Collaborations and Transactions in the In Vivo CAR-T Cell Space Since 2020



*Acquisitions
** Value of eligible future payments not disclosed
†AbbVie/Umoja upfront payment undisclosed
‡ Partnership terminated in 2025

Source: Company reports; William Blair Equity Research

Exhibit 12
CELLect Horizons
Collaborations and Transactions in the In Vivo CAR-T Cell Space of Undisclosed Amounts Since 2022

Companies	Year	Transaction Type	Transaction Details
ABINTUS BIO / Undisclosed private biotech	2025	Acquisition	Abintus Bio agreed to the sale of its technologies to a large private biotech (undisclosed). At the time of the acquisition, Abintus was a preclinical-stage company developing lentiviral-based in vivo CAR-T cell therapies.
VYRIAD / NOVARTIS	2024	Research Collaboration	The companies will develop in vivo CAR-T cell therapies for the treatment of oncology and/or immunology.
kelonia / ADIMAB	2022	Research Collaboration	Kelonia will leverage Adimab's expertise and tissue-specific antibodies that enable precise in vivo gene delivery to different tissues, as well as antibodies that can be leveraged within the therapeutic genetic cargo. The deal terms were not disclosed
kelonia / elevatebio	2022	Research Collaboration	Kelonia will use ElevateBio's lentiviral vector platform, process and analytical development expertise, and cGMP manufacturing capabilities to develop and advance novel manufacturing processes and manufacture Kelonia's products. The deal terms were not disclosed
ORNA™ / Simnova 先博生物	2022	Research Collaboration	The companies will develop multiple therapeutics in oncology. Under the terms of the agreement, Simnova will gain access in Greater China to certain programs built on Orna's isCAR technology, including Orna's lead anti-CD19 in situ CAR (isCAR) program, ORN-101. Orna received an undisclosed upfront payment from Simnova and is eligible for development, regulatory, and sales milestones along with royalties on any approved products derived from the collaboration

Source: Company reports

Lentivirus-Based Approaches

Cellinfinity Bio
Cellinfinity is a private biotech company developing autologous and in vivo CAR-T cells for the treatment of solid tumors. The company's pipeline lists one in vivo CAR-T asset in preclinical development, CIB-301, but its antigen target is not disclosed.

EsoBiotec (acquired by AstraZeneca)
In May 2025, AstraZeneca acquired EsoBiotec, then a private, clinical-stage biotechnology company developing lentiviral in vivo CAR-T cell therapies for the treatment of oncology and autoimmune diseases, including multiple myeloma and solid tumors. Under the terms of the agreement, AstraZeneca paid an initial payment of $425 million, with additional contingent consideration payments up to $575 million based on development and regulatory milestones.

For CAR delivery, EsoBiotec uses ENaBL-T, a T-cell-targeted LVV that induces CAR transgene expression under the control of a T-cell-specific promoter derived from endogenous human gene regulatory elements. The synthetic promoter is engineered to achieve functional expression of

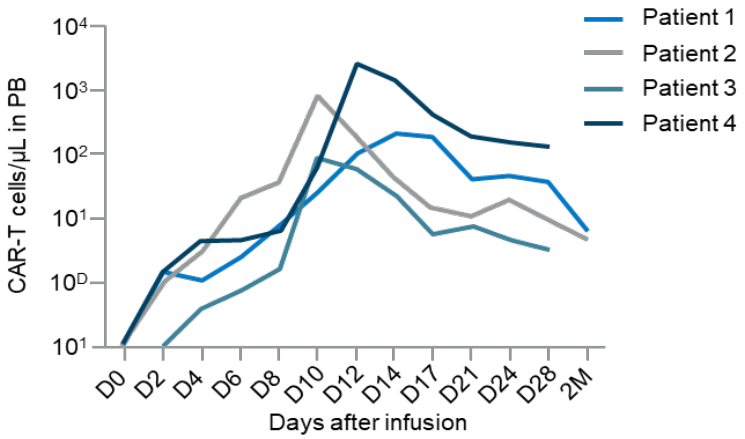
the CAR transgene exclusively in T cells. In addition, the envelope of ENaBL-T is MHCI-depleted and enriched with human CD47 to reduce complement-mediated inactivation and vector phagocytosis (Michela Milani et al. *Science Translational Medicine*. 2019). T-cell-specific transduction is achieved through a llama-derived, membrane-anchored nanobody (VHH) targeting the TCRαβ receptor, combined with a targeting-deficient VSV (vesicular stomatitis virus)-G protein for envelope stability and efficient membrane fusion.

The company's lead candidate was ESO-T01, which contained a clinically validated BCMA CAR construct for the treatment of multiple myeloma. In January 2025, EsoBiotec announced it had dosed the first patient in an investigator-initiated clinical trial in China of ESO-T01. The patient was treated with 0.25e9 TUs and achieved MRD negativity by day 28 with no significant adverse events reported.

In July 2025, the company published clinical data from the first four adult patients treated with ESO-T01 (Jia Xu et al. *Lancet*. 2025). All four patients received at least two lines of therapy. In addition, one patient received and progressed on prior treatment with BCMA/GPRC5D CAR-T cell therapy. All patients received a single intravenous infusion of ESO-T01 at 2.0e8 transduction units (TU). No lymphodepletion was administered prior to ESO-T01 infusion; however, all patients received preemptive promethazine hydrochloride.

Immediately following the infusion, all patients developed acute inflammatory reactions within the first 24 hours of treatment. The first patient treated (patient 1) exhibited several adverse events, including mild disturbance of consciousness, tremors in both upper limbs, and hypoxemia. However, symptomatic treatment with dexamethasone and gamma globulin resolved all symptoms within 48 hours. Following the events observed in patient 1, patients 2-4 received prophylactic treatment with dexamethasone prior to infusion. Grade 3 CRS was observed in three of four patients, which primarily occurred in the first 48 hours post-infusion. Patients 2 and 4 also experienced grade ≥3 elevated liver enzymes. Between days 8 and 12, grade 1 CRS occurred in all patients, which lasted for 1-4 days and coincided with a second peak in IL-6 and IL-10. CAR cell expansion peaked around day 12 and were detectable in the bone marrow, tumor tissues, and CSF (exhibit 13). Interestingly, patient 4, who had received prior CAR-T, had the highest Cmax posttreatment.

Exhibit 13
CELLect Horizons
CAR-T Expansion and Clinical Responses Following Treatment With EsoBiotech's ESO-T01



Patient	Response	Duration of follow-up	Predominant CAR-T population
1	sCR	3 months	CD8+,central memory
2	sCR	3 months	CD4+, naïve, central memory
3	PR	2 months	Effector, CD28-CD57+
4	PR	2 months	CD4+, naïve, central emory

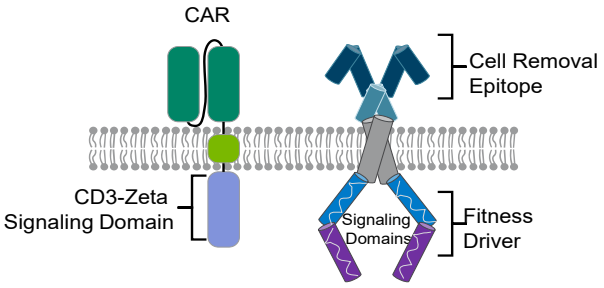
Source: Jia Xu et al. *Lancet*. 2025; adapted by William Blair Equity Research

In regard to efficacy, all patients achieved a response (100%), with patients 1 and 2 achieving a stringent complete response (sCR). Peak CAR-T cell levels were observed between days 10 and 17 and were detected in the bone marrow, tumor tissues, pleural effusions, and cerebral spinal fluid. The phenotypic profile for detected CAR+ T cells varied between patients. Patient 1 had a higher proportion of CAR+ T cells with a central memory phenotype, whereas patients 2 and 4 had a greater abundance of naive and central memory CAR+ T cells. Effector and CD28–CD57+ senescent T cells were enriched in CAR+ T cells of patient 3, which corresponded to unfavorable CAR T-cell expansion. Follow-up in the study was limited, with patients 1 and 2 having 3 months and patients 3 and 4 having 2 months.

Exuma Biotech

Exuma's GCAR platform delivers its CD3-targeted LVVs directly into a lymph node to generate CAR-T cells in vivo. The company's LVV encodes a CAR construct and a synthetic protein comprising an intracellular fitness driver domain and an extracellular epitope (exhibit 14). The fitness driver is engineered to optimize effector cell proliferation and persistence, while the extracellular domain acts as a safety switch to permit CAR-T cell removal via antibody infusion, if needed.

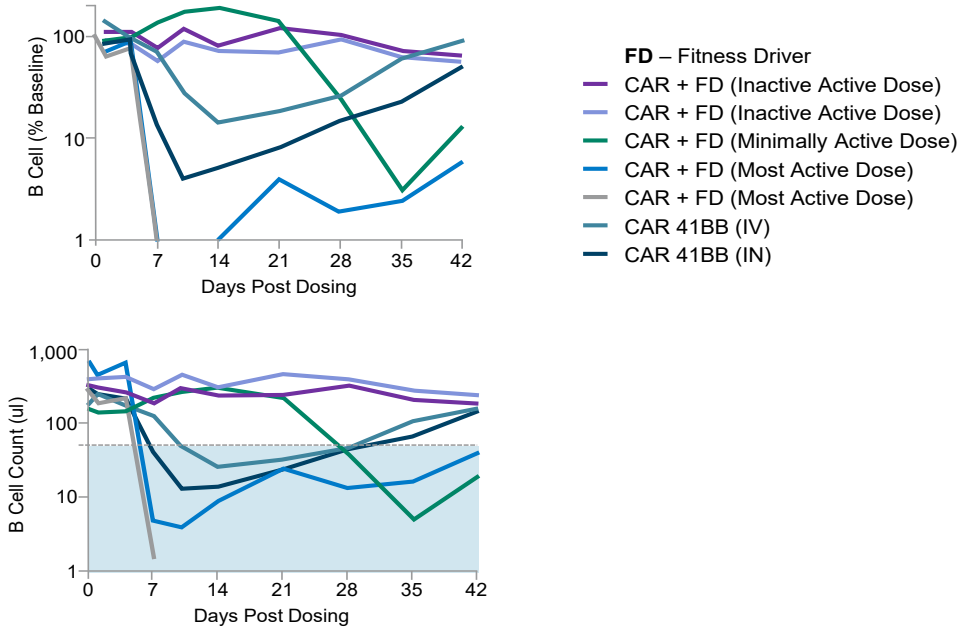
Exhibit 14
CELLect Horizons
Exuma's GCAR Platform



Source: Exuma Biotech

The company has previously shared preclinical data validating its GCAR platform in humanized mouse models (see our previous report for additional details: In Vivo CAR-T: A Potentially Disruptive Force in Cell Therapy). In NHP studies, B-cell depletion was observed at the highest GCAR doses (exhibit 15; note graphs are plotted on nonlinear scale). Notably, deeper B-cell depletion was seen with GCARs containing the fitness driver transgene. In July 2025, Exuma completed its pre-IND meeting with the FDA for its lead GCAR candidate and expects to submit an IND in the first half of 2026. Regarding manufacturing, Exuma has an internally developed GMP process at 25L scale.

Exhibit 15
CELLect Horizons
Exuma's GCAR Platform in NHPs



Source: Exuma Biotech; adapted by William Blair Equity Research

Separately, Exuma is developing a synthetic CAR ligand (SCL) for antigen independent CAR stimulation. The SCL comprises synthetic mRNA encapsulated in an LNP that is designed to be taken up and expressed by antigen-presenting cells so that it interacts and stimulates CAR-T cells that pass through lymphocytes during circulation, enhancing CAR-T persistence and limiting the need for CAR-T redosing. Exuma has stated the SCL could be ideal for cases with minimal residual disease.

Genocury Biotech

Genocury is a private Chinese biotech developing LVV-based in vivo CAR-Ts for the treatment of cancer. While the company's website does not provide details on its platform, in November 2024, the company published the first (to our knowledge) case report of a patient receiving in vivo CAR-T. A 64-year-old male with relapsed/refractory (r/r) DLBCL received a CD3-targeted LVV encoding a CD19 CAR-T, leading to peak CAR-T cell expansion on day 11. In contrast to other in vivo therapies in development, the patient received lymphodepletion with Cy/Flu prior to receiving the LVV. However, the patient achieved a partial response 35 days after infusion with only grade 1 CRS reported (Chen et al. *JITC.* 2024). In addition, in April 2025 the company reported another patient with r/r DLBCL achieved a complete response one month after being treated with Genocury's in vivo therapy, and this time the patient did not receive preconditioning therapy. It was reported the patient sustained their response through 90 days of follow-up and did not exhibit CRS or ICANS.

Immunofoco

Immunofoco is a private, China-based biotech company developing cell therapies for the treatment of solid tumors. The company's in vivo platform utilizes an LVV pseudotyped with a mutated MxV glycoprotein (MxV-G), which the company believes enhances the viral titer, enhances transduction efficiency, and enables more functional CAR-Ts. The mutated MxV-G prevents the transduction of non-T cells, and the company utilizes T-cell-targeting molecules to selectively transduce T cells. The company has not disclosed what indication or antigen its lead program will target.

Interius (acquired by Gilead)

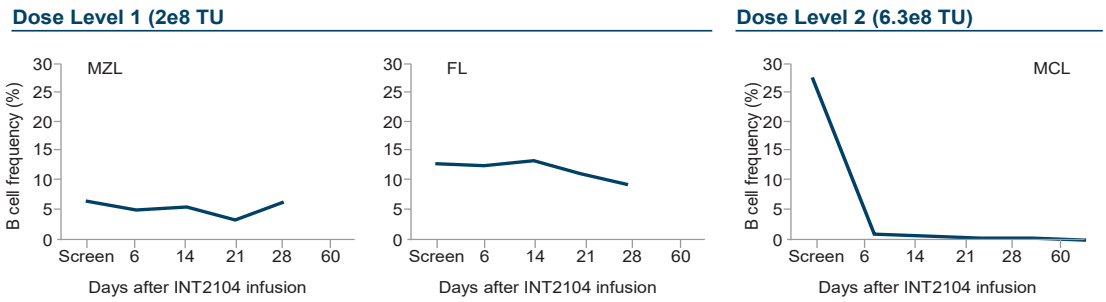
In August 2025, Gilead announced it was acquiring Interius BioTherapeutics, a private, clinical-stage biotechnology company developing a pseudotyped VSV-G LVV that can be engineered to target, transduce, and reprogram specific cells in the body using optimized targeting molecules and pH-dependent fusogens that only mediate cytoplasmic entry following endocytosis. Under the terms of the agreement, Gilead will pay a total of $350 million.

Interius's LV is infused via IV and aims to transduce T cells and NK cells by using a CD7 binder, creating a diverse effector population for tumor killing. However, different cell types could be targeted with future LVVs by switching the targeting moieties on the envelope, and the transgene cargo can be easily substituted based on the target of interest. Furthermore, CAR expression is controlled by a tissue-restricted promoter, enhancing vector safety, and tunable in vivo CAR cell expansion can be engineered into transduced cells using a "third signal" that is triggered by FDA-approved agonists.

Interius's lead candidate, INT2104, generates T and NK cells that express a fully human anti-CD20 CAR in vivo trial (for additional details on preclinical studies, see: In Vivo CAR-T: A Potentially Disruptive Force in Cell Therapy). At the 2025 Cellicon Valley Symposium (see: Takeaways From Cellicon Valley: In Vivo CARs, Cell Therapy for Autoimmune Diseases, and Gene Therapy Accessibility Updates), Interius shared clinical data for INT2104, which is currently being evaluated in a Phase I clinical trial in Australia and Europe for the treatment of patients with B-cell malignancies who have progressed after at least two lines of systemic therapy, including patients who have been treated with a CAR-T previously. Of the first 10 patients treated in the trial (DL1: 2e8 TU, n=8; DL2: 6.3e8 TU, n=2), only one patient at the low dose experienced a grade 2 infusion-related reaction, with all of safety events categorized as grade 1. Importantly, no CRS, ICANS, cytopenias requiring transfusion, vector shedding, or hypogammaglobulinemia requiring IVIg were reported and no patients required admittance to the ICU. Peripheral B-cell counts from two patients treated at dose level 1 and

one patient treated at dose level 2 were also shared. Although both patients treated at dose level 1 showed no change in their peripheral B-cell counts following treatment with INT2104, the patient treated at dose level 2 showed near-total B-cell ablation by day 6, which was maintained through day 60 (exhibit 16). Interius has begun treating patients at dose level 3 (2e9 TU) and dose level 4 (1e10 TU). In addition to INT2104, the company is also developing INT21016, which is designed to generated CD19 CAR-T and CAR-NK cells in vivo for the treatment of autoimmune diseases.

Exhibit 16
CELLect Horizons
Complete B-cell Depletion Seen in Patient Treated at DL2 of INT2104



Source: Interius presentation at Cellicon Valley 2025; adapted by William Blair Equity Research

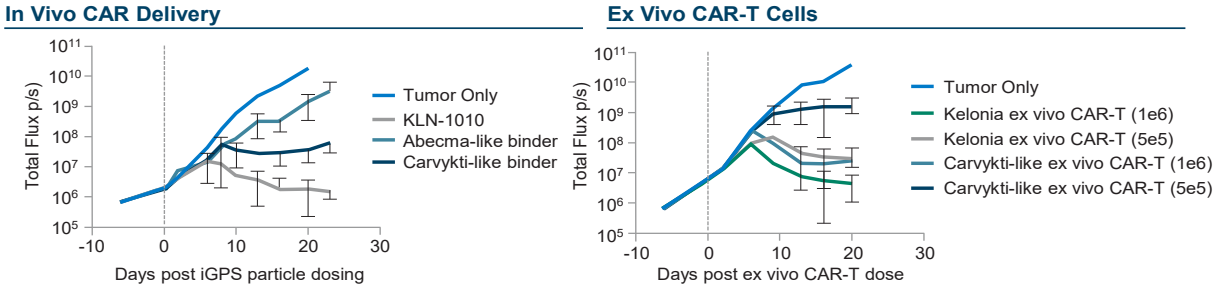
Interius has reported INT2104 is produced by WuXi Advanced Therapeutics using a LV manufacturing process developed by Interius. While the Phase I process was based on adherent cells, the company plans to use a suspension process for its Phase II study, which could increase productivity tenfold and reduce COGS to less than $5,000 per dose.

Kelonia Therapeutics

Kelonia is a clinical-stage biotech company developing an in vivo gene placement system (iGPS) technology that is based on the work of Michael Birnbaum, Ph.D., an associate professor of biological engineering at MIT, and Michael Fischbach, Ph.D., an associate professor of bioengineering and microbiology and immunology at Stanford University. The iGPS technology is an LVV that has been engineered with CD3-targeting molecules and an independent, de-targeted fusogen that is pH-dependent.

Kelonia's lead candidate, KLN-1010, utilizes the company's proprietary BCMA-targeted CAR packaged in the iGPS system for the treatment of multiple myeloma. In preclinical mouse models, an ex vivo CAR-T expressing KLN-1010's CAR binder performed similarly to an ex-vivo CAR expressing a CAR similar to the one in Carvykti. In addition, in vivo CAR delivery using Kelonia's proprietary CAR achieved superior tumor control compared to particles expressing the CAR constructs found in Abecma and Carvykti (exhibit 17).

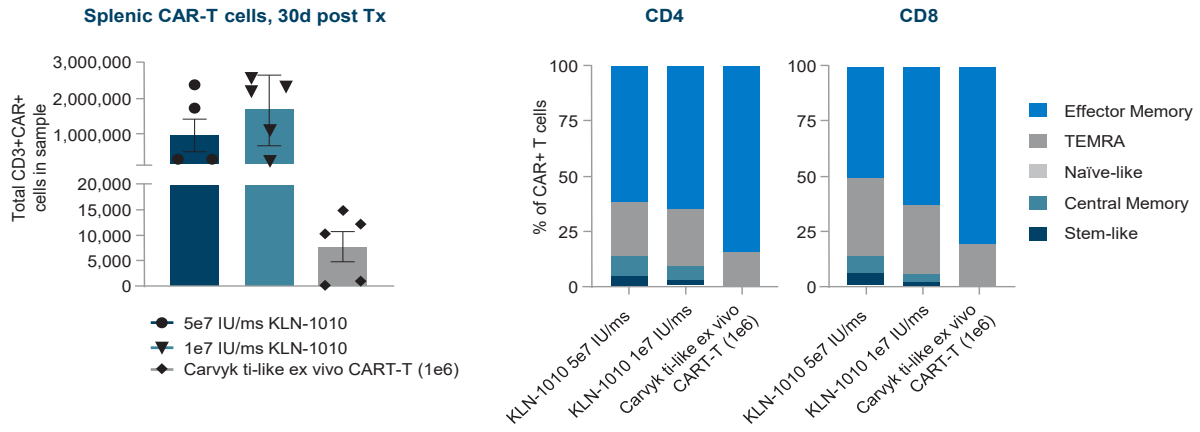
Exhibit 17
CELLect Horizons
Activity of Kelonia's CAR Compared to Commercial BCMA CAR-Ts



Source: Kelonia; adapted by William Blair Equity Research

The company also claims CAR-T cells generated via KLN-1010 (1e7 IU) had greater expansion, higher proliferative capacity, and improved persistence compared to ex vivo Carvykti-like CAR-T cells (1e6 cells). In addition, KLN-1010 generated more CAR-T cells with a central memory and stem-like phenotype, which could contribute to KLN-1010's persistence (exhibit 18). Using immunostaining the company has demonstrated the majority of CAR+ cells off T cells, with rare CD3- CAR+ mononuclear cells observed. CAR+ T cells have been reported circulating throughout mouse tissues, including the bone marrow and ovaries, but there was no evidence of germ cell transduction.

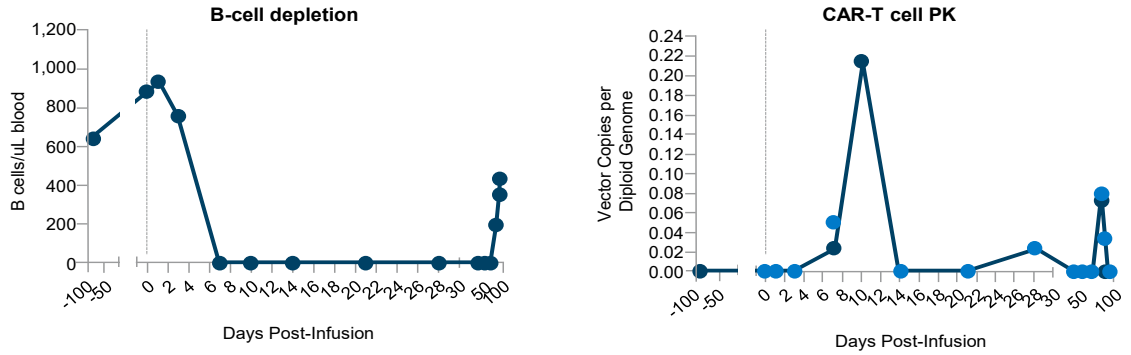
Exhibit 18
CELLect Horizons
Expansion and Phenotype of KLN-1010 Transduced T Cells



Source: Kelonia; adapted by William Blair Equity Research

To validate B-cell depletion in NHPs, Kelonia engineered iGPS particles encoding a CD20 CAR. Complete B-cell depletion was observed in all NHPs treated with 1e8 IU/kg and was accompanied by CRS and neurotoxicity. B-cell reconstitution occurred two months posttreatment, which also correlated with reemergence of CAR-T cells (exhibit 19), a hallmark of memory T-cell response. Notably, iGPS particles were undetectable in the serum three days posttreatment.

Exhibit 19
CELLect Horizons
Kelonia's iGPS Particles in an NHP



Source: Kelonia company reports; adapted by William Blair Equity Research

On August 19, 2025, the company reported the first patient had been treated with KLN-1010 in the Phase I inMMyCAR study at Royal Prince Alfred Hospital in Sydney, Australia. While acute safety data on the patient was not shared, we anticipate the company presenting clinical data from the trial in the future.

Kelonia has established strategic collaborations with several companies, with the most recent being with Xyphos Biosciences, a wholly owned subsidiary of Astellas, in 2024. Under the terms of the agreement, the companies will use Kelonia's iGPS platform in combination with Xyphos's ACCEL technology platform that uses its convertibleCAR to develop up to two in vivo CAR-T cell programs. Kelonia also has active collaborations with Adimab and ElevateBio for development of proprietary tissue-specific antibodies and lentiviral production, respectively.

Last, the company has shared it is using a scalable suspension manufacturing process and predicts its COGS will be less than $10,000 per patient.

Legend Biotech
In May 2025, Legend announced plans to expand into in vivo CAR-T utilizing a lentiviral-based approach with novel T-cell recognition and safety signals. During the company's 2025 second-quarter earnings call, the company briefly highlighted its approach referred to as TaVec (T-cell activation vector), which will use engineered LV particles to target T cells for activation and transduction. Legend has engineered mutations in the glycoprotein to prevent binding to LDLR thereby limiting transduction of non-T cells. In addition, management previously stated that the in vivo CARs will include T-cell "armoring" modifications to resist immune suppression mechanisms (see: First-Quarter Earnings: Revenue Beat Driven by Continued Penetration in Earlier Lines; Company Exploring In Vivo CAR-T). In June 2025, Legend reported that it dosed the first few non-Hodgkin lymphoma (NHL) patients in an investigator-initiated trial of its first in vivo candidate targeting CD19xCD20. The company plans to manufacture its TaVec assets out of its Philadelphia R&D facility, which is on track to be completed in the second half of 2025.

PersonGen Biotherapeutics
PersonGen is a China-based biotech company specializing in developing CAR-T therapies. The company's GUIDED platform uses a LVV that has been modified to de-target certain tissue and re-target T cells for in vivo engineering of CAR-T and CAR-NK cells. The LVV has also undergone optimizations to reduce immune rejection and improve transfection efficiency. The company's pipeline contains three in vivo CAR-T assets targeting CD19 for the treatment of B-cell malignancies and

autoimmune diseases, CD19 and PD1 for the treatment for autoimmune diseases, and an undisclosed antigen target for treating solid tumors. The CD19 asset is currently being evaluated in an investigator-initiated trial in China, while the other two assets are still on preclinical development.

Pregene Biopharma

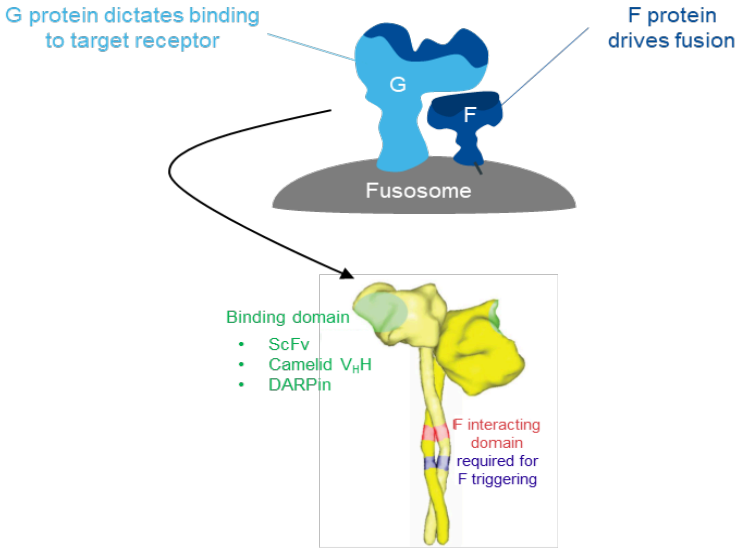
Pregene is a China-based biotech company focused on developing CAR-T and CAR-NK therapies. The company's proprietary in vivo platform uses engineered lentiviral vectors to reprogram a patient's own immune cells into therapeutic CAR-T or CAR-NK cells, with vector modifications designed to improve tissue targeting, reduce immunogenicity, and increase transduction efficiency. Pregene also helped EsoBiotech design its CAR-T and advance it into clinical trials. Pregene has not disclosed any of its internal in vivo CAR-T assets.

In October 2025, Gilead's Kite Pharma entered into a collaboration with Pregene focused on the development of in vivo CAR-T therapies. Under the terms of the agreements, Gilead paid Pregene $120 million upfront with the potential for $1.52 billion in future milestone payments. No timelines or target indications under the collaboration have been disclosed.

Sana Biotechnology

Sana is developing in vivo–delivered CAR therapies using an IV-delivered modified VSV-G LVV that expresses a paramyxovirus-derived fusosome system on the viral envelope instead of VSV-G. The fusosome system is a two-part system in which one part (G protein) dictates the cell specificity and the other initiates cell membrane fusion, enabling the viral payload to enter the cell (F protein; exhibit 20). The receptor-binding domain of the G protein has been mutated, so it is incapable of recognizing its endogenous target receptor, and has been engineered to contain a protein sequence conferring the ability to recognize the desired antigen or use scaffolds (i.e., scFv, V_HH DARPin) appended to the G protein to bind the desired protein/cell. Once the G protein recognizes the target, the G protein activates the F protein through an interaction domain, allowing fusion and cellular entry to occur. The company's lead in vivo CAR candidate is SC299, which selectively delivers an anti-CD19 CAR to CD8+ T cells (for additional details on preclinical studies see: In Vivo CAR-T: A Potentially Disruptive Force in Cell Therapy). Sana expects to file an IND for SG299 as early as 2026 for the treatment of B-cell cancers and autoimmune diseases.

Exhibit 20
CELLECT Horizons
Sana's Paramyxovirus-Derived Fusogen



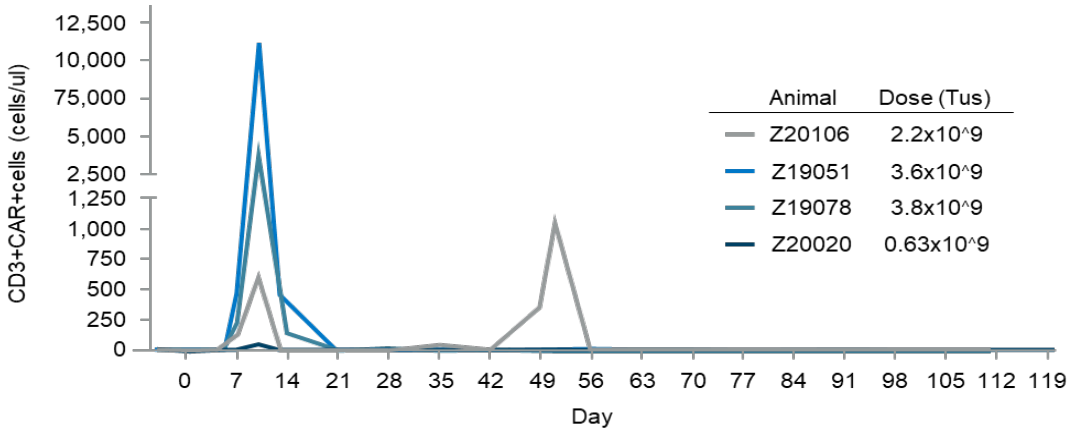
Source: Sana company reports

Umoja Biopharma

Umoja Biopharma is private biotech company developing in vivo engineered CAR therapies using three of its platform technologies: VivoVec, rapamycin-activated cytokine receptor (RACR), and TumorTag. VivoVec is Umoja's gene delivery platform, which is based on a third-generation LVV pseudotyped with the cocal fusion glycoprotein and engineered to express an anti-CD3 scFV and co-stimulatory molecules (e.g., CD80 and CD58) to promote CD3+T-cell transduction and activation. Compared with VSV-G, cocal is resistant to serum inactivation in humans, improving in vivo persistence and enabling direct administration. Umoja has also incorporated a multidomain fusion (MDF) protein into its VivoVec platform to enable greater antitumor efficacy at lower doses. The RACR system comprises a chimeric heterodimer consisting of an FKBP extracellular unit attached to an IL-2Rγ signaling domain and an FRB extracellular unit attached to an IL-2Rβ signaling domain. In the presence of rapamycin, the RACR system confers resistance to mTOR via FRB scavenging of rapamycin-FKBP12 complexes and promotes CAR-T cell proliferation and survival via heterodimer engagement leading to increased IL-2 intracellular signaling (Michels et al. *J Immunother Cancer* 2023). TumorTag is Umoja's universal CAR tumor targeting platform, which uses a small molecule that binds to cancer and its stromal cells, "tagging" them as targets for CAR-T cells.

In 2024, Umoja published proof-of-concept data in an NHP model (M nemestrina [i.e., southern pig-tailed macaques]) using MDF VivoVec particles expressing an anti-CD20 CAR (Nicolai et al. *Blood*. 2024). As part of a dose de-escalation study, all four animals tested received different doses of MDF VivoVec particles (0.63e9, 2.2e9, 3.6e9, or 3.8e9 TUs). Following intranodal (IN) treatment with MDF VivoVec particles, three of the four animals achieved rapid CAR-T generation at seven days (exhibit 21), which coincided with loss of circulating B cells. Notably, the animal without CAR-T expression received the lowest dose of VivoVec particles (0.63e9 TUs). CAR-T cell expression was undetectable in all animals by day 21; however, one animal experienced re-expansion of CAR-T cells at day 42, which returned to 0% at day 56. This event correlated with a reappearance of a small population of B cells on study day 42. In the three animals with CAR-T expression, prolonged B-cell depletion was detected in all animals through 56, 63, and 76 days of treatment.

Exhibit 21
CELLECT Horizons
CAR-T Cell Expansion in NHPs Treated With Umoja's VivoVec Particles



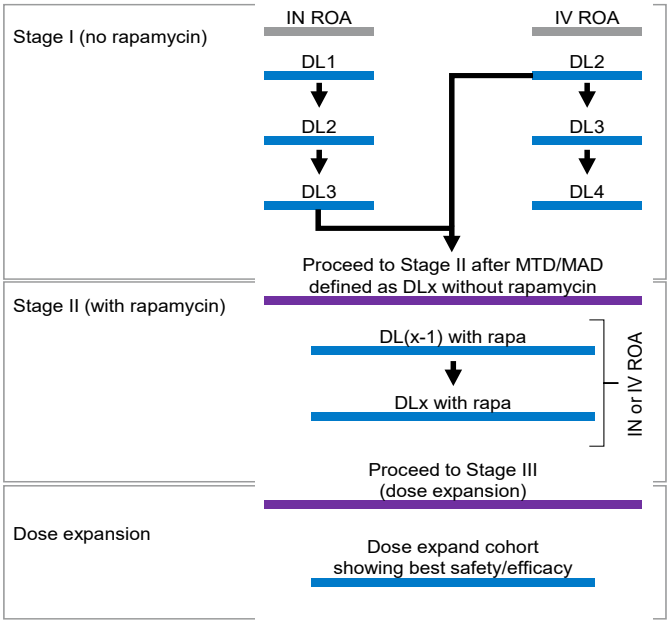
Source: Nicolai et al. *Blood.* 2024; adapted by William Blair Equity Research

In regard to safety, elevated C-reactive protein (CRP) levels were detected in the blood shortly before CAR-T cells were detectable. CRP levels normalized at day 14 as CAR-T cells were lost from detection, suggesting that these events are CAR-T-cell–mediated rather than particle-driven. In addition to CRS symptoms, mild tremors and brief seizure activity in the first two animals treated

was observed. These events also coincided with peak CAR T-cell expansion and were resolved with tocilizumab and anakinra. In addition, CAR DNA was mainly present in the lymph nodes, with very low expression also seen in the spinal cord.

UB-VV111 is Umoja's lead clinical program for hematological malignancies that expresses a CD19 CAR through its RACR system. In July 2024, the FDA cleared Umoja's IND for UB-VV11 and the company is currently enrolling patients in the Phase I INVICTA-1 trial (for additional details on preclinical studies see: In Vivo CAR-T: A Potentially Disruptive Force in Cell Therapy). The company plans to use IN administration to establish safety with UB-V111, with the hopes of transitioning to IV infusions after clearing dose level 2 (exhibit 22). Once the maximum tolerated dose and multiple ascending doses have been established the company plans to evaluate UB-VV11 (IV and IN) with rapamycin. The company anticipates having early clinical data from the program in late 2025 or early 2026.

Exhibit 22
CELLect Horizons
Design of Umoja's Phase I INVICTA-1 trial of UB-V111



Source: Umoja company reports

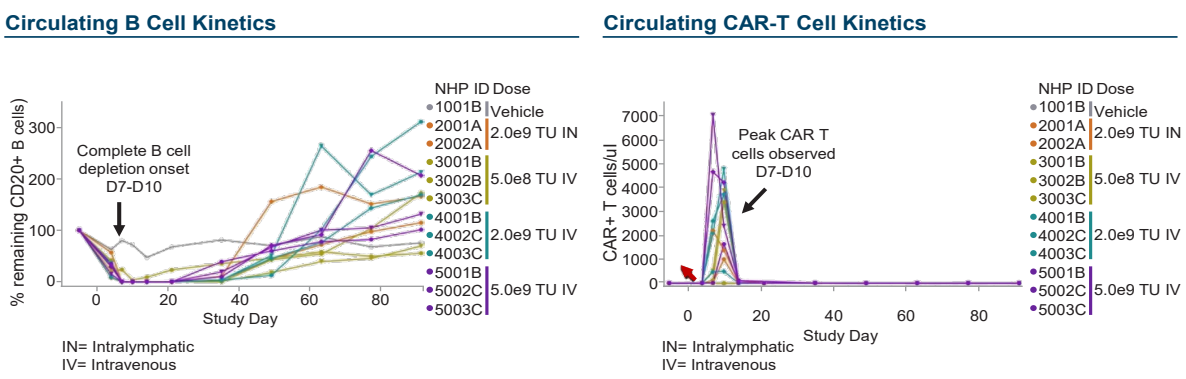
In January 2024, Umoja and AbbVie announced a collaboration agreement to develop multiple in situ-generated CAR-T cell therapy candidates in oncology. Under the terms of the agreement, AbbVie has an exclusive option to license Umoja's CD19 directed in situ-generated CAR-T cell therapy candidates, which includes UB-VV111. Under a second agreement, the companies will develop up to four additional in situ-generated CAR-T cell therapy candidates for discovery targets selected by AbbVie. Umoja may be eligible to receive up to $1.44 billion in aggregate for option exercise fees and development and regulatory milestones, with the potential for Umoja to earn additional sales-based milestones and tiered royalties on worldwide net sales.

Umoja is developing its lead internal program (retains all rights except in greater China) UB-VV400, a CD22 CAR for the treatment of oncology and autoimmune disease. At the 2024 Society for Immunotherapy of Cancer conference, the company shared preclinical data in humanized mouse models wherein UB-VV400 infusion achieved robust expansion of CAR+ T cells in vivo, which correlated

with complete tumor clearance and improved survival. Notably, cotreatment with rapamycin further augmented UB-VV400 antitumor activity in mice. Umoja and its partner, IASO Biotherapeutics, are conducting a Phase I investigator-sponsored trial for UB-VV400 in CD22+ patients with large B-cell lymphoma (LBCL) and follicular lymphoma grade 3B (FL3B). Notably, all five doses with UB-VV400 will be evaluated using IV administration. The company plans to file an IND in the U.S. and clinical trial authorization (CTA) in Australia for a Phase I dose-confirmation trial in 2026, with the potential to initiate single-arm registrational studies in 2027 or 2028.

At the 2024 American Society of Hematology (ASH) conference, Umoja also shared preclinical data from its third in vivo therapy, UB-VV310, which expresses an anti-CD20 CAR. At multiple doses, a single infusion of UB-VV310 via IN or IV in NHPs achieved rapid and complete CAR-T cell generation (exhibit 23), followed by B-cell aplasia with B-cell reemergence around day 40. Interestingly, unlike in its other NHP study, CAR-T cells did not re-expand with the repopulation of B cells. Transient increases in temperature were observed at peak CAR-T cell expansion, but no significant impact on body weight or changes in liver enzymes were observed. Lastly, biopsy analysis from treated animals showed that UB-VV310 was highly restrictive to immune cells, with <1% of other cell types positive for CAR expression.

Exhibit 23
CELLect Horizons
Pharmacokinetics of Umoja's UB-VV310 in NHPs



Source: Umoja ASH 2024; adapted by William Blair Equity Research

Vyriad

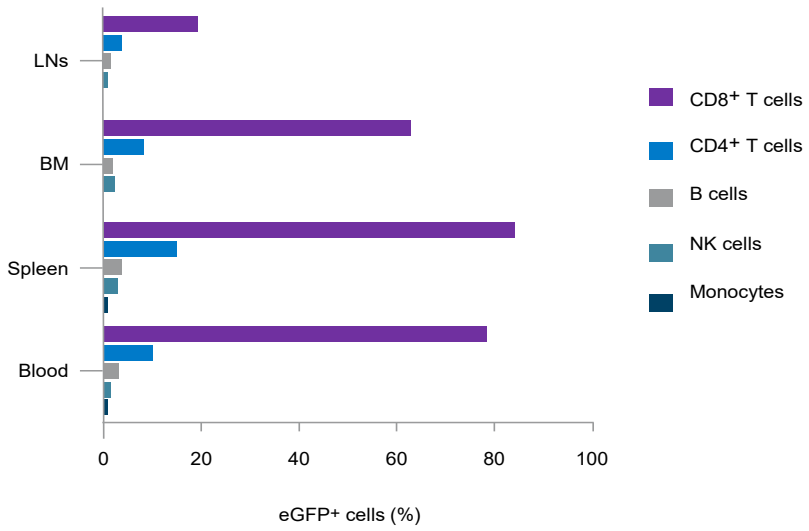
Vyriad is a private biotech company developing next-generation targeted genetic therapies. Vyriad's in vivo lentiviral CAR-T platform utilizes LVV with mutated VSV-G that displays a targeting molecule on the G-protein, thereby preventing VSV-G's natural tropism and instead retargeting to specific immune cells (CD3+). The company is developing at least two programs for the treatment of oncology and immunology, and its first candidate is being developed in collaboration with Novartis. Vyriad is also developing a wholly owned asset for the treatment of multiple myeloma and anticipates entering the clinic in the first half of 2026.

Lipid Nanoparticle (LNP)-Based Approaches: Transient CAR Expression

Aera Therapeutics

Aera Therapeutics is a private, preclinical-stage genetic medicines company developing tissue-targeted, nonviral delivery technologies for oncology and genetic diseases. The company's in vivo CAR-T platform utilizes its targeted LNP (tLNP)technology, which comprises proprietary ionizable lipids and novel liver de-targeting lipids linked (ester-type) to different targeting moieties for cell type specificity. Specifically, Aera believes its targeting ligands are smaller and more readily manufacturable compared to other LNP programs in development. Encapsulated in the tLNP are mRNA cargo optimized for potent and extended transgene expression. In a humanized HSC CD34+ mouse model, tLNPs containing mRNA encoding eGFP primarily transduced CD8+ T cells in the lymph nodes, bone marrow, spleen, and blood 24 hours posttreatment (exhibit 24). We note that the humanized HSC mouse model can produce multiple immune lineages, including NK cells, B cells, and monocytes, suggesting that Aera's tLNPs are highly specific to CD8+ T cells.

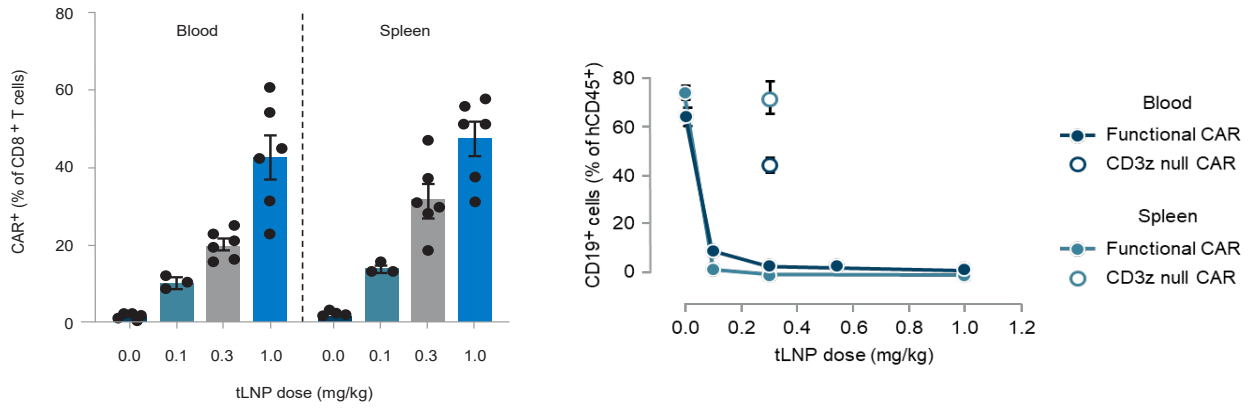
Exhibit 24
CELLect Horizons
Cells Transduced by Aera's tLNP Platform Are Primarily CD8+ Cells



Source: Aera company reports; adapted by William Blair Equity Research

At the 2025 ASGCT conference, the company presented additional data in mice demonstrating CAR expression in over 40% of CD8+ T cells in the blood and spleen, following two injections at 1 mg/kg (exhibit 25). Treatment with Aera's therapy also led to dose-dependent CD19+ T-cell depletion.

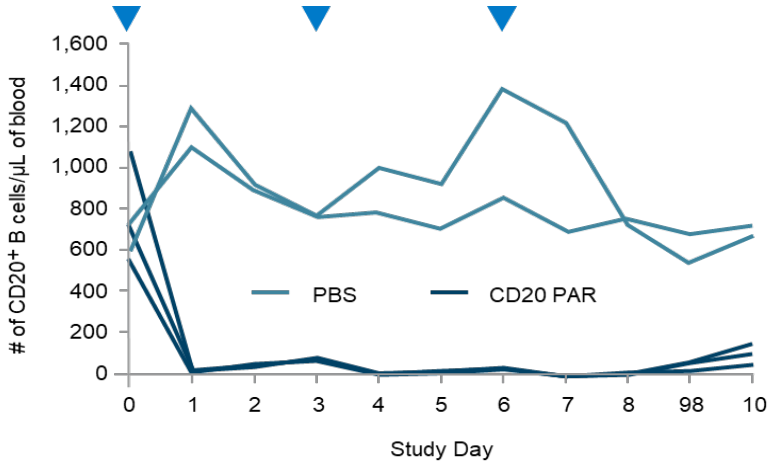
Exhibit 25
CELLect Horizons
Treatment With Aera's tLNP Platform Led to CAR-T Cell Generation and B-Cell Depletion in Mice



Source: Aera ASGCT 2025; adapted by William Blair Equity Research

The company also demonstrated the activity of its tLNPs in NHP studies using a surrogate anti-CD20 CAR (NHPs do not express CD19). Rapid CD20+ B-cell depletion was seen following the first dose of Aera's tLNP (0.25 mg/kg) and was maintained through day 10 with two additional doses (exhibit 26). Pharmacokinetics data from the NHPs indicates high levels (about 10,000 ng/mL) of CAR mRNA following each dose, with mRNA levels approaching 1 ng/mL by day 3.

Exhibit 26
CELLect Horizons
Treatment With Aera's tLNP Platform Led to B-Cell Depletion in NHPs



Source: Aera company reports; adapted by William Blair Equity Research

Aera's lead program, AERA-109, is an mRNA-based in vivo CD19 CAR-T cell therapy comprising tL-NPs targeting T cells for the treatment of autoimmune diseases. Aera plans to initiate IND-enabling studies by year-end 2025 and file an IND for AERA-109 in 2026.

Capstan Therapeutics (acquired by AbbVie)
In June 2025, AbbVie announced that it agreed to acquire Capstan Therapeutics, a private, clinical-stage biotechnology company developing RNA-based therapies for in vivo delivery and treatment of autoimmune disorders, solid tumors, fibrosis, and monogenic blood disorders. Under the terms of the agreement, AbbVie paid up to $2.1 billion in cash at closing. While the most recent status of Capstan's assets is undisclosed, we briefly highlight Capstan's technology and data shared by the company prior to the acquisition.

Capstan's in vivo CellSeeker platform is fully nonviral and comprises a proprietary LNP that is ionizable and biodegradable, a targeting antibody, and RNA encoding the CAR construct, allowing for transient and tunable CAR expression. The company's lead candidate was CPTX2309, which was being developed for the treatment of autoimmune disorders through targeted delivery of CD19 CAR to CD8+ T cells. In preclinical data shared at the 2024 American College of Rheumatology (ACR) conference (see: ACR 2024 Recap: Cell Therapy and T-Cell Engager Clinical Data Reaffirm B-Cell Depletion Approach, but Fuel Modality Debate), Capstan demonstrated that a single dose of CPTX2309 generated CAR-T cells in vivo and led to rapid B-cell clearance in mice. In addition, a series of five doses given to mice biweekly appeared to be well tolerated. In NHP studies, treatment with the company's CD20 asset, CPTX2309-S, achieved up to 80% CAR+ T cells in circulation following three doses. B-cell depletion, seen in both peripheral blood and tissue samples, was also noted at all dose levels tested, followed by B-cell reconstitution beginning around 27 days posttreatment. Notably, the recovering B cells demonstrated a predominantly naïve profile, highlighting CPTX2309's potential to generate immune reset. The team also demonstrated CPTX2309's ability to generate CD19 CAR-T cells in vitro with T cells derived from autoimmune disease patients' samples and in return kill each patient's corresponding primary B cells.

In June 2025 Capstan announced that it dosed the first patients in the Phase I trial of CPTX2309. The Phase I study initiated in Australia will evaluate safety, tolerability, pharmacokinetics, and pharmacodynamic activity (i.e., peripheral B-cell depletion and recovery) of CPTX2309 treatment in healthy volunteers at several dose levels.

Byterna Therapeutics
Byterna, a private China-based biotech, is developing in vivo CAR-T cell therapies using its high-efficiency and scarless platform (HSP) to make circular mRNA (cmRNA), which is delivered via T-cell targeted LNPs for the treatment of hematologic cancers and autoimmune diseases. According to the company's website, its HSP process is highly efficient and does not require the introduction of extra nucleotides. In a 2024 paper, the company's cmRNA took longer to achieve peak CAR protein expression levels compared to a linear mRNA, but the resulting protein was more densely expressed and detectable for twice as long. While the subsequent experiments support the increased durability in CAR expression with cmRNA, it is evaluated by electroporating the mRNA into cells ex vivo before injecting them into mice (Hu et al. *bioRxiv.* 2024). Therefore, it is unclear if the enhanced expression is maintained when delivered via LNP. Byterna's website does not provide any additional details on which indications the company is targeting.

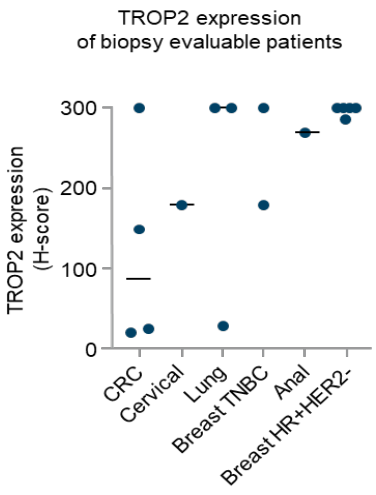
Carisma Therapeutics
In January 2022, Carisma Therapeutics and Moderna entered a strategic collaboration to develop in vivo-engineered CAR-M therapies for the treatment of cancer and autoimmune disease. As of February 2025, Moderna had nominated 12 oncology research targets under the collaboration. However, in March 2025 Moderna agreed to terminate the oncology field exclusivity, which would allow Carisma to pursue in vivo CAR-M programs outside the 12 nominated oncology targets.

Everest Medicines
Everest, a China-based biotech, is developing in vivo CAR-T cell therapies using mRNA-based payloads expressed in targeted LNPs for the treatment of cancer and autoimmune diseases. The company's in vivo programs are in preclinical development, but its website does not provide additional details on Everest's technology platform or the specific indications it is targeting.

Create Medicines (previously Myeloid Therapeutics)
Create Medicines is a clinical-stage company developing therapies that reprogram cells in vivo using mRNA and/or retrotransposon-mediated gene insertion. Create's in vivo engineering platform uses LNPs that can selectively target myeloid cells or target a combination of myeloid cells, NK cells, and T cells. In addition, Create has developed a novel CAR construct that is engineered by fusing a tumor recognition scFv with a cell-specific adaptor (e.g. CD89 for myeloid cells, TCR for T cells). Thereby, stable expression of the CAR requires the endogenously expressed adapter protein, enabling cell-selective expression of the CAR and permitting multiple CARs to be encoded in one product. For additional details on Create's early preclinical validation studies see: In Vivo CAR-T: A Potentially Disruptive Force in Cell Therapy.

Create's most advanced in vivo program, MT-302, delivers a TROP2-targeting CAR in vivo to myeloid cells for the treatment of advanced epithelial cancers. TROP2 is a validated antigen in oncology as evidenced by clinical findings with several TROP2-targeting antibody-drug conjugates (ADC), which has led to the approval of two products (Trodelvy and Datroway). With a CAR-T approach, Create anticipates MT-302 would elicit a stronger comprehensive immune response leading to lower tumor recurrence. In September 2023, the company announced that it had dosed the first patient in the Phase I, Australian multicenter study in adults (NCT05969041). At the 2025 ASCO conference, Create shared preliminary correlative biomarker analysis from the patients treated in the ongoing Phase I study. As of March 23, 2025, 25 patients had been dosed intravenously with MT-302 at one of six dose levels. Importantly, TROP2 protein expression was detected in biopsies collected from all patients, with expression levels ranging considerably between tumor types (exhibit 27).

Exhibit 27
CELLect Horizons
Design of Phase I Trial of MT-302 and TROP2 Expression



Source: Create company reports; adapted by William Blair Equity Research

In a single patient treated at dose level 4 (cohort 5), the half-life of MT-302 was between 33 hours and 36.6 hours. At the intertumoral level, 10% of the tumor myeloid cells in the patient were CAR+, suggesting proper expression on target cells and their colocalization to the tumor. Broader immune activation was also observed which correlated with production of antitumor effector cytokines and checkpoint upregulation. Last, repeat dosing was tolerated. The company has now treated 30 patients in the trial across 12 heterogeneous solid tumor sub-types and will share updated data at the Society for immunotherapy in Cancer conference (SITC) 2025. Based on the Phase I results, Create now plans to evaluate MT-302 in combination with checkpoint inhibitors and chemotherapy in the frontline setting for Gastroesophageal Junction cancers.

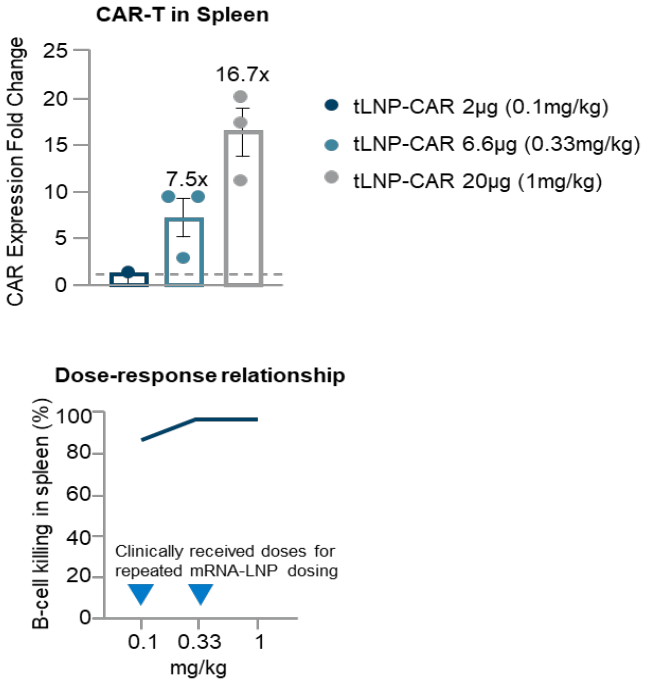
Create is also developing MT-303, a GPC3-tagreting in vivo CAR for the treatment of hepatocellular carcinoma (HCC). In July 2024, the company announced that it dosed the first patient in the Phase I trial evaluating MT-303 in adults with advanced or metastatic HCC. In January 2025, the company shared an analysis from a single patient case study following treatment with MT-303. The patient was 62 years old at the time of treatment, with previous treatments including: resection, multiple ablations, 1L atezolizumab, and bevacizumab. At day 50 post-infusion with MT-303, the patient experienced a 57% lesion area reduction. The company noted that initial clinical activity was observed in the cohort 1 patients, with MT-303 being well tolerated at repeat dosing. In addition, no dose-limiting toxicities have been observed. The company has treated approximately 10 patients with Mt-303 and anticipates initiating a front-line study of MT-303 in combination with atezolizumab and bevacizumab for frontline HCC in the future.

Create is developing additional in vivo CAR assets, including MT-304, which delivers a HER2 CAR to NK and myeloid cells for the treatment of breast cancer, however the company is initially evaluating it in a basket study of pretreated HER2+ solid tumors. The company has initiating a Phase I/II trial of MT-304 which will evaluate it as a monotherapy and in combination with anti-PD1, with the first patient expected to be treated in the fourth quarter of 2025. The company is also developing CRT-401, which will be its first product co-formulated with a pan-LNP containing a HER2 CAR designed to be expressed in myeloid and NK cells, and a T-cell targeted LNP designed to deliver a TROP2 CAR. Last, the company is developing CRT-402, which delivers a CD19 CAR to T-cells for autoimmune diseases and hematological malignancies. Notably, CRT-402 can be formulated to deliver an episomal mRNA, allowing for transient expression, or Create's fully human retrotransposon, which allows for CAR gene integration

Grit Biotechnology

Grit Biotechnology is a private China-based company developing tumor-infiltrating lymphocytes (TIL) for the treatment of cancer. Grit's disclosed pipeline is focused on TIL cell therapies, but at the 2025 ASGCT conference the company shared preclinical data highlighting its capabilities in the in vivo CAR-T cell space. For transduction of T cells, Grit's approach uses antibody conjugated LNPs generated using its cell-targeted lipid-based amplification of mRNA payload (CLAMP) technology, which supports compatible and scalable GMP production. Targeted LNPs (tLNPs) target a receptor on CD4 and CD8 T cells (target receptor undisclosed) and encapsulate the mRNA cargo. In humanized PBMC mouse models, infusion of tLNPs encoding CD19 CAR mRNA led to 15% CAR+ expression in the spleen, which led to complete B-cell depletion 24 hours posttreatment (exhibit 28). The company also shared similar studies in HSC mouse models, wherein complete B-cell depletion was observed 7 days posttreatment.

Exhibit 28
CELLect Horizons
Treatment With Grit's tLNP Led to CAR expression in Splenic T Cells and Killing of Splenic B Cells in Mice



Source: Grit ASGCT 2025; adapted by William Blair Equity Research

For translation in cancer models, Grit analyzed tLNPs in immunodeficient B-ALL (B-cell acute lymphoblastic leukemia) mouse models, wherein a single dose led to rapid and durable tumor elimination. Notably, percentage of CD4+ and CD8+ T cells ranged between 10% and 60% at all doses evaluated. Grit plans to initiate toxicology studies in the near term. Grit has not disclosed if it plans to further advance its in vivo platform or what indications it plans to pursue with it.

Immorna
Immorna is a private, China-based biotech company developing mRNA-based therapeutics. In March 2025, Immorna announced the first patient had been dosed with its lead in vivo CAR-T, JCXH-213, a proprietary targeted lipid complex nano particle that delivers an mRNA encoding a CAR to T cells, NK cells, and macrophages. The company has not disclosed what antigen JCXH-213 targets, but it is for the treatment of cancer.

Ingenium Therapeutics
Ingenium is a private biotech company that was established in November 2011 as a spin-off of the Korea Research Institute of Biosciences and Biotechnology. The company is focused on engineering NK-cell therapeutics, including one in vivo CAR-NK product for the treatment of solid tumors. The asset uses a LNP delivery system to deliver mRNA and transiently produce CAR-NK cells. It is still in preclinical development and no additional information is publicly available on it.

Kernal Bio
Kernal Bio is developing mRNA-based therapies for the treatment of autoimmune diseases and oncology. The company's lead candidate, KR-402, is an in vivo CAR-T therapy program developed using Kernal Bio's mRNA 2.0 platform. This platform uses a selective mRNA that only translates in

specific cells and is delivered by an LNP that is decorated with antibodies for targeted delivery to T cells. KR-402's antigen target has not been disclosed, but the company has indicated it is being developed initially for multiple sclerosis and B-cell malignancies.

In October 2025, it was announced that the U.S.'s Advanced Research Projects Agency for Health (ARPA-H) awarded Kernal Bio up to $48 million to advance its in vivo CAR-T program.

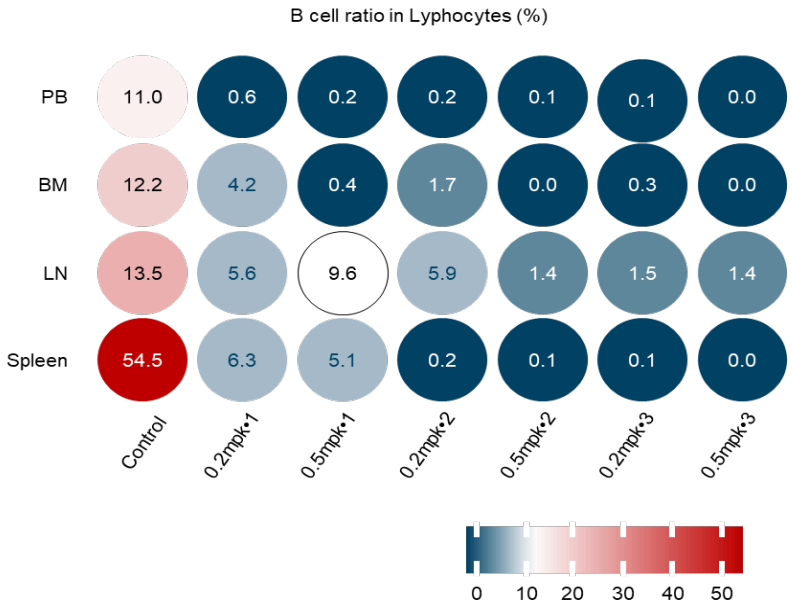
Liberate Bio

Liberate Bio is a private company developing LNP-delivered extrahepatic therapeutics, including in vivo delivery of CARs to macrophages and monocytes for the treatment of cancer. In October 2025, the company shared preclinical data demonstrating its in vivo CAR-M therapy depleted over 99% of circulating B cells in NHPs after two doses. Transient increases in cytokines, including IL-6 and TNF-α, were observed after each dose and resolved within 48 hours. Less than 1% LNP delivery occurred in T cells and no signs of T-cell proliferation were observed. Liberate Bio plans to advance its first in vivo CAR-M into the clinic in the second half of 2026 through an investigator-initiated trial. The company's initial clinical focus will include autoimmune indications, such as systemic lupus erythematosus and multiple sclerosis, as well as oncology programs, including MM.

MagicRNA Biotech

MagicRNA Biotech is a China-based biotech company developing in vivo CAR-T therapies. The company's technology uses an engineered cell-targeted lipid nanoparticle (EnC-LNP) platform for in vivo delivery to a host of tissues including immune system, central nervous system, and tumor cells. The EnC-LNP technology comprises a proprietary antibody fragment for tissue targeting and proprietary ionizable lipids. The company's lead program, H2N301, is an engineered CD8 T-cell–targeted LNP encapsulating a CD19 CAR mRNA for the treatment of B-cell–mediated autoimmune diseases, such as lupus and myasthenia gravis. In September 2025, the company's letter to the editor of the *New England Journal of Medicine* was published, which detailed the evaluation of HN2301 in NHPs and five SLE patients (Wang et al. *NEJM* 2025). NHPs were administered a version of HN2301 targeting CD20 at 0.2 mg/kg or 0.5 mg/kg once, twice, or three times (injections were spaced by 2 days). Seven days from the first administration, CAR expression was reported in CD8 T cells and monocytes, with no expression in CD4 T cells and very low expression in NK cells. Dose-dependent and administration-dependent decreases in B cells were observed, including in the peripheral blood, spleen, lymph nodes, and bone marrow (exhibit 29). An additional study evaluating 1 to 3 doses of 0.2 mg/kg of the construct in NHPs showed B cells that reestablished in the peripheral blood 30 days after treatment were primarily naïve.

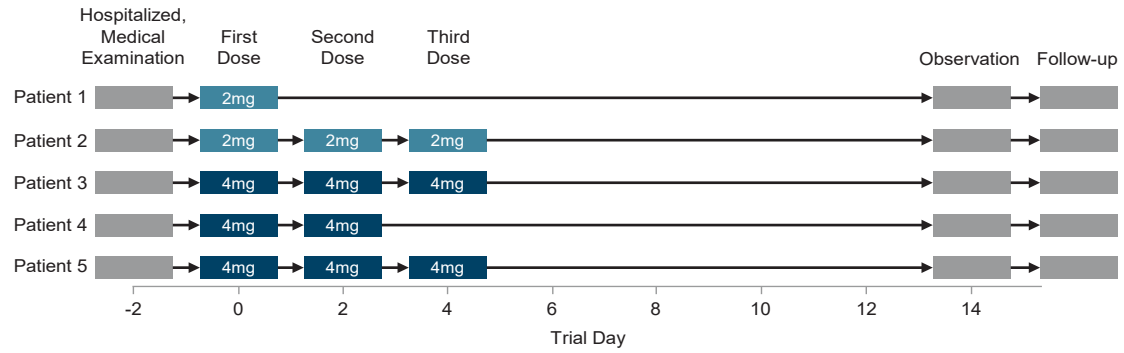
Exhibit 29
CELLect Horizons
B-Cell Depletion in NHPs Following MagicRNA's Therapy



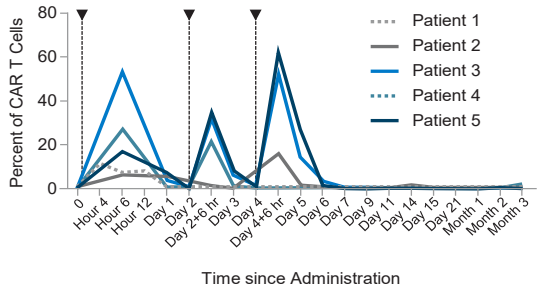
Source: Wang et al. *NEJM* 2025

The five SLE patients were all females, had an average SLEADAI-2K score of 13.4 (range: 8-22), and were refractory to several therapies. The patients were given one to three doses of 2 mg or 4 mg of HN2301 (exhibit 30; top). Peak CAR expansion was seen within 6 hours of the first dose, with subsequent CAR expansion peaks seen in patients who received additional doses of 4 mg.

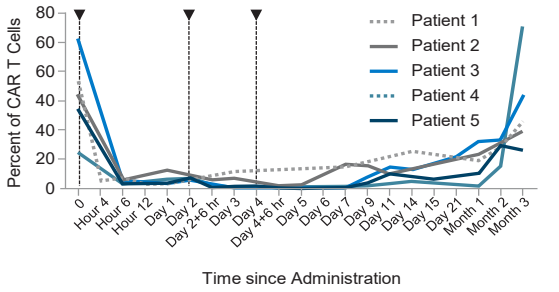
Exhibit 30
CELLect Horizons
CAR-T Expansion and B-Cell Depletion in SLE Patients Following MagicRNA's HN2301



Percent of CAR-T Cells Relative to CD8+ T Cells in Peripheral Blood after Administration of HN2301



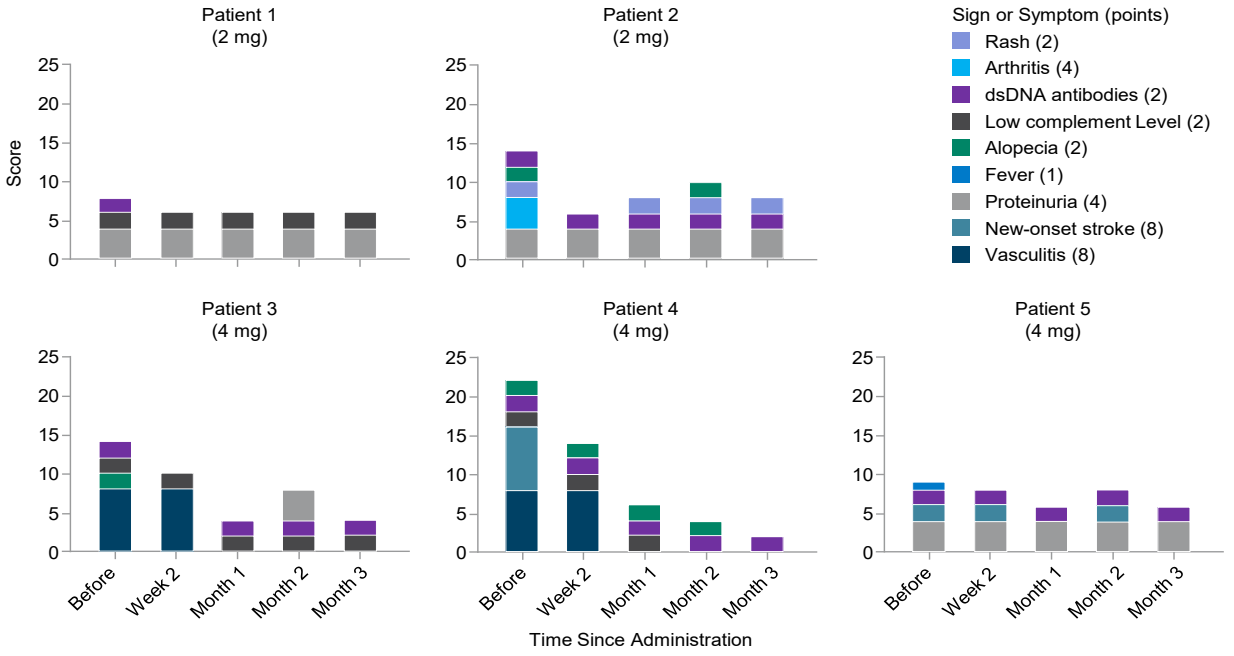
Percent of CD19+ B Cells Relative to Total Lymphocytes in Peripheral Blood after Administration of HN2301



Source: Wang et al. *NEJM* 2025; adapted by William Blair Equity Research

All patients exhibited a rapid decline in peripheral B cells, which was sustained for about 2 months. Disease activity decreased in all patients at varying degrees (exhibit 31). Patients 1 and 2 resumed MMF therapy 1 to 2 months posttreatment, and patient 3 resumed cyclosporine A three months posttreatment. All five patients experienced low-grade CRS, three of which were treated with tocilizumab, but there were no instances of ICANS and retreatment was not associated with an increase in liver enzyme levels.

Exhibit 31
CELLect Horizons
Reduction in SLEDAI Scores After MagicRNA's HN2301



Source: Wang et al. *NEJM* 2025; adapted by William Blair Equity Research

Mana.bio

Mana.bio is an AI-based drug delivery company focused on developing DNA and RNA gene therapies using LNPs. Mana's proprietary suite of machine learning (ML) models designs and optimizes passively targeted LNPs that do not require targeting ligands. At the 2025 ASGCT conference, the company shared preclinical in vivo data in humanized mice, demonstrating enhanced green fluorescent protein (eGFP), a marker protein, transfection of CD4/CD8 at 24 hours when treated with a single infusion of eGFP mRNA LNPs at 0.65 mg/kg. Across the four LNP candidates evaluated, eGFP positivity rates ranged between 18% and 30% in CD3+ cells and between 10% and 30% in CD4+/CD8+ cells. Notably, similar transduction rates were observed in NHPs treated at low (0.5 mg/kg), medium (0.9 mg/kg), and high (1.2 mg/kg) doses for 24 hours. A small percentage of eGFP positive cells were observed in the liver in treated animals, but most of the expression was from macrophages and not endothelial cells or hepatocytes. Liver enzyme (AST) and cytokine elevations (interferon gamma-induced protein 10) were observed at 6 hours, but these levels slowly declined at 12- and 24-hour timepoints. The company has not officially disclosed plans to investigate its LNP platform for in vivo CAR-T.

MOTE Therapeutics

MOTE Therapeutics is a private biotech company developing in vivo CAR-T using novel RNA circularization technology. No other details regarding MOTE's programs or technology have been disclosed.

Orbital Therapeutics (being acquired by Bristol Myers Squibb)

Orbital is a private preclinical-stage company developing RNA-based therapies focused on reprogramming the immune system in vivo. Orbital's platform includes both circular and linear RNA cargo for targeted delivery to immune cells. Its lead program, OTX-201, is an optimized circular RNA encoding a CD19 CAR delivered via LNPs for the treatment of autoimmune disease. At the 2025 mRNA-Based Therapeutics Summit, Orbital shared preclinical data in NHPs demonstrating complete B-cell depletion with OTX-201. The company plans to advance OTX-201 into the clinical in first half 2026.

In October 2025, Bristol Myers announced that it had agreed to acquire Orbital for $1.5 billion.

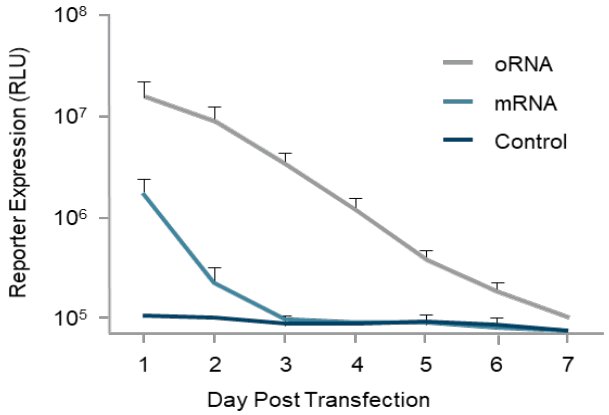
Orna Therapeutics

Orna Therapeutics is a preclinical-stage biotech company developing engineered circular RNA (oRNA) and proprietary LNPs, based on the research of Dan Anderson, Ph.D., professor in the department of chemical engineering, the Institute for Medical Engineering and Science, the Koch Institute for Integrative Cancer Research, and the Harvard-MIT Division of Health Science and Technology at MIT. The oRNA molecules are engineered as linear RNAs that undergo highly efficient autocatalytic circularization, simplifying production, increasing protein expression, and resisting in quick degradation compared with linear RNA. The oRNA molecules are packaged into LNPs, which when delivered in vivo are trafficked to target cells via serum proteins that attach to the LNP surface.

For oRNA optimization, Orna uses its proprietary high-throughput screening FoRCE platform (Formulated oRNA Cell-based Evaluation) to evaluate several thousands of oRNA variants in LNPs in different cell types to identify which oRNA sequences have the ideal performance in vivo. In addition, Orna's oRNA constructs consist of multiple expression elements found in viruses to increase transgene potency and durability. For LNP generation, Orna has two delivery platforms: panCAR, which targets multiple immune cell lineages, and SiTu Editing in the Marrow (STEM), which targets stem cells in the bone marrow.

Although Orna will apply its technology to treating genetic and infectious diseases, its initial focus is on in vivo CAR delivery. The company first disclosed preclinical data from its lead in situ CAR (isCAR), ORN-101, at the 2023 ASGCT conference. ORN-101 utilizes immunotropic LNPs to deliver an oRNA encoding an anti-CD19 CAR to multiple immune cells (for additional details on ORN-101 preclinical data, see: In Vivo CAR-T: A Potentially Disruptive Force in Cell Therapy). More recently, Orna shared preclinical data highlighting the potential of its platform in autoimmune diseases. At the ASGCT 2025 conference, Orna shared data demonstrating the use of CD19 panCAR LNPs to activate human T cells in vitro for CD19 CAR expression. Importantly, Orna demonstrated improved transgene protein expression with its oRNA in primary T cells than control mRNA, suggesting that translation initiation and elongation kinetics are not inhibited, but improved, with the Orna's IRES-driven cap-independent translation (exhibit 32).

Exhibit 32
CELLect Horizons
Orna's oRNA Leads to Higher Reported Expression in Human Primary T Cells Than mRNA

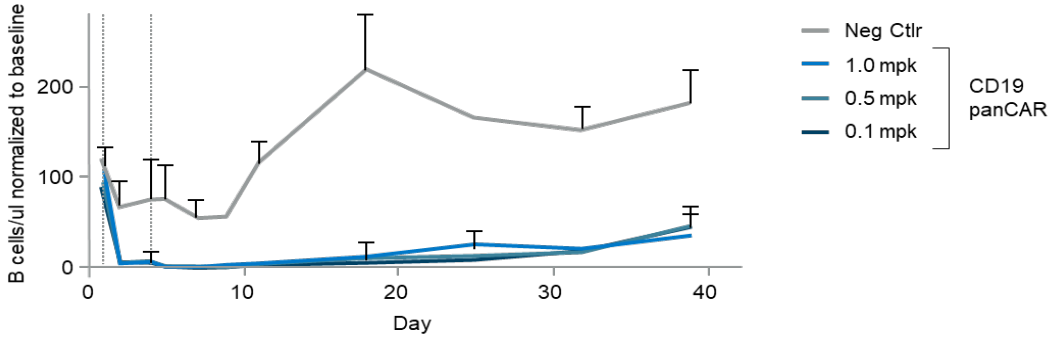


Source: Orna company reports; adapted by William Blair Equity Research

Orna also demonstrated the in vivo efficacy of its CD19 panCAR LNPs in humanized lupus mouse models, wherein CD19 panCAR treatment led to complete elimination of peripheral B cells. While peripheral B cells in the control mice also slowly decreased during the study, authors noted that pristane, the molecule used to induce autoimmune responses in mice, causes general lymphopenia over time. Similar to lupus mice treated with rituximab, infusion with CD19 panCAR treatment led to significant reductions in B cells in the spleen, bone marrow, and lymph node. Importantly, B-cell reductions in only the CD19 panCAR mice correlated with reductions in autoantibody titers at week 12.

In NHP studies, Orna showed that CD19 panCAR infusions at three doses led to rapid B-cell depletion in two days, which was sustained out to day 8. Similar to the kinetics observed with treatment with autologous CAR-T cells, at three weeks peripheral B cells levels slowly rebounded (exhibit 33).

Exhibit 33
CELLect Horizons
NHPs Treated With Orna's CD19 panCAR Had a Rapid Reduction in B Cells



Source: Orna company reports; adapted by William Blair Equity Research

The company also plans to share additional preclinical data on its lead in vivo CAR at the ACR 2025 meeting. The company plans to submit an IND and initiate a Phase I/II trial of its CD19 in vivo CAR in B-cell–mediated autoimmune diseases by 2026.

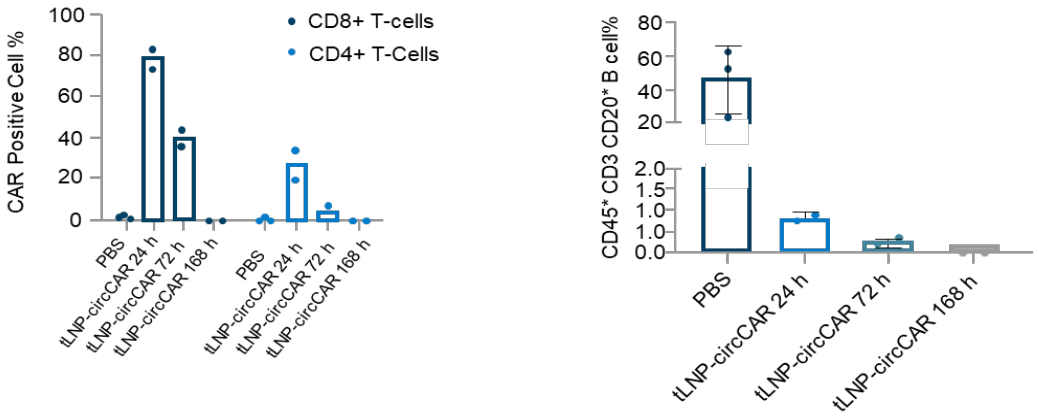
In August 2022, Orna entered a collaboration with Merck to discover, develop, and commercialize multiple programs, including vaccines and therapeutics in infectious diseases and oncology. Under the terms of the agreement, Merck made an upfront payment to Orna of $150 million, and Orna will be eligible to receive up to $3.5 billion in development, regulatory, and sales milestones associated with the progress of the programs and royalties for any approved products derived from the collaboration. Merck also invested $100 million of equity in Orna's series B financing round.

In January 2023, Orna entered a collaboration agreement with Shanghai Xianbo Biotech Co., Ltd. (Simnova), in which Simnova will lead the clinical development, regulatory submissions, and commercialization in China of certain oncology-directed programs developed by Orna, including a CD19 in vivo CAR candidate. In addition, Orna will gain access to investigator-initiated clinical trials in China to accelerate the validation of select programs in patients. Orna received an upfront payment from Simnova and is eligible for development, regulatory, and sales milestones along with royalties on any approved products derived from the collaboration. In 2023, the companies expanded their collaboration to include BCMA as a target for its in vivo panCAR for the treatment of multiple myeloma. The companies anticipate filing an IND and initiating Phase I/II trials for the two candidates in B cell malignancies by 2026.

RiboX Therapeutics

RiboX Therapeutics is a private Chinese biotech developing next-generation RNA therapies for genetic diseases and oncology. The foundation of RiboX's RNA technology is its circular RNAs (circRNAs), which are covalently closed, single-stranded RNAs that are broadly expressed in metazoans and other eukaryotic cells. Importantly, these circular RNAs have inherent stability with resistance to known exonucleases. In addition, similar to most circular RNAs, RiboX's circRNAs also have low immunogenicity. For delivery, RiboX uses its proprietary delivery platform, which utilizes an ionizable LNP conjugated to a specific antibody targeting T cells. At the 2025 ASGCT conference the company shared initial preclinical data from its platform for the development of in vivo CAR-T cell therapies. In humanized PBMC mouse models, a single injection of targeted LNP-circCARs (tLNP-circCAR) expressing CD19 CAR led to rapid transduction of T cells, with up to 40% CD4+ and 80% CD8+ T cells positive for the CD19 CAR. As expected with an RNA therapy, CAR positivity decreased by roughly half at 72 hours, with CAR-T levels undetectable at 168 hours. Notably, tLNP-circCAR correlated with robust and rapid depletion of circulating B cells, with no detectable B cells at 168 hours (exhibit 34). RiboX also demonstrated activity in mouse models for B-ALL, which showed rapid tumor regression in tumor bearing mice treated with two injections of tLNP-circCAR.

Exhibit 34
CELLect Horizons
Mice Treated With RiboX's tLNP-circCAR Showed Rapid CAR Expression and B-Cell Elimination



Source: RiboX ASGCT 2025; adapted by William Blair Equity Research

The company will present additional preclinical data on the in vivo generation of CD19 CAR-T cells using its tLNP-circCAR system at the upcoming ACR 2025 conference. Based on the abstract, we expect the presentation will include data from humanized NOG-PBMC mice bearing CD19+ NALM-6-Luc lymphoma xenografts and NHPs. The company has not disclosed what indications it plans to pursue with its in vivo CAR-T platform.

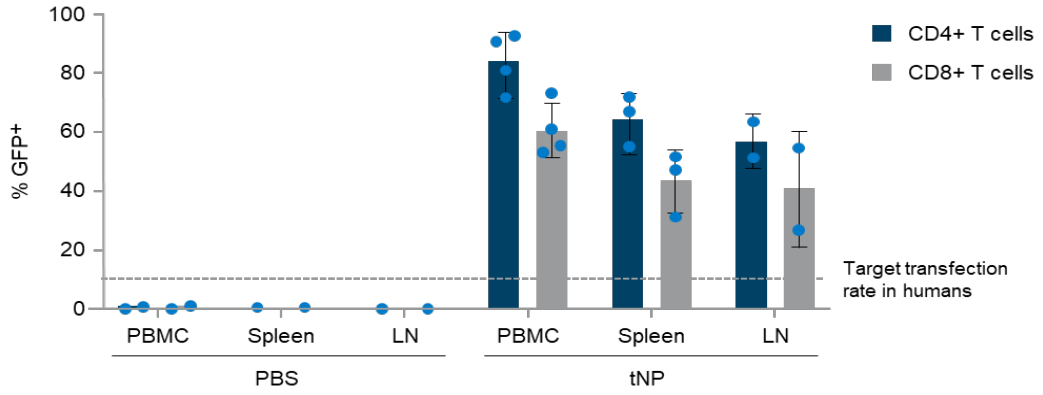
Sail Biomedicines

Sail Biomedicines is a private preclinical-stage company developing reprogrammable medicines using RNA therapies. Before launching as Sail, the company was known as Laronde before merging with Senda Biosciences in 2023. Sail's RNA platform technology is based on a novel RNA known as endless RNA (eRNA). The technology was invented by a team led by Dr. Avak Kahvejian at Flagship Pioneering, which sought to transform the therapeutic capabilities of long non-coding RNA (lncRNA). Long non-coding RNAs are found naturally in the circular form in mammalian cells, thus reducing the risk of exonuclease degradation. However, unlike traditional mRNA molecules, these lncRNAs do not interact with ribosomes. To circumvent this limitation, Sail Biomedicines has

generated a proprietary, closed-loop RNA construct engineered to be translatable. Sail's eRNAs also contain multiple programmable elements to enhance translation. For delivery, Sail uses targeted nanoparticles, which comprise a validated LNP core conjugated to targeting ligands. The company has also stated the LNP contains proprietary ionizable lipids to aide in endosomal escape.

At the 2025 ASGCT conference, the company shared preclinical data highlighting key functional aspects of its platform. In NHPs, a single IV infusion with T-cell-targeted nanoparticles led robust expression in CD4+ and CD8+ T cells in the periphery, spleen, and lymph nodes (exhibit 35). Importantly, no signs of GFP expression were observed in the hepatocytes.

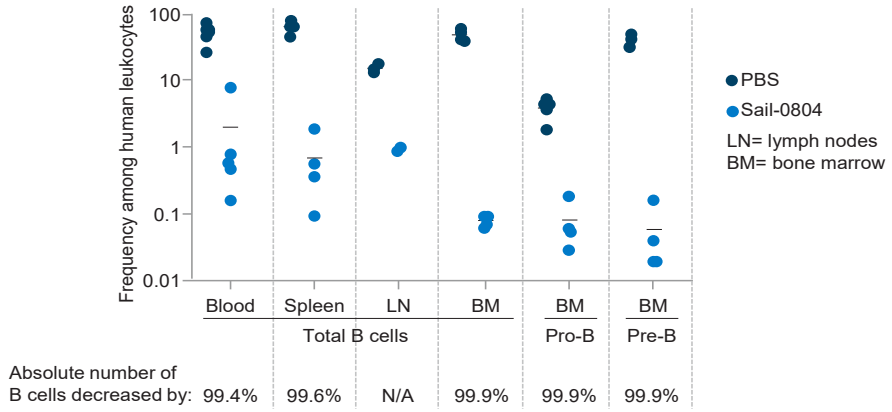
Exhibit 35
CELLect Horizons
NHPs Treated With Sail's Target NPs Showed CAR-T Expression in Key Regions



Source: Sail; adapted by William Blair Equity Research

Sail's lead CAR-T cell candidate, SAIL-0804, contains an eRNA-encoded CD19 CAR for the treatment of autoimmune diseases. In a humanized HSC mouse model, IV injections with SAIL-0804 achieved near-complete B-cell depletion across multiple B-cell compartments including bone marrow, spleen, and blood three days after dosing (exhibit 36).

Exhibit 36
CELLect Horizons
B-Cell Depletion Seen Across Compartments 3 Days After Treatment With SAIL-0804



Source: Sail ASGCT 2025; adapted by William Blair Equity Research

Sanofi
In April 2021, Sanofi acquired Tidal, then a private, preclinical-stage biotechnology company developing mRNA-based approaches for in vivo immune cell reprogramming, for an upfront payment of $160 million with up to an additional $310 million if certain milestones were achieved. Tidal's technology was based on proprietary nanoparticles that enabled selective mRNA delivery to immune cells, including the ability to deliver mRNA encoding CARs to T cells. At the time of the acquisition, Sanofi made public comments about bringing CAR-T cell therapies to a broader patient population, however the company has not provided updated information on its research utilizing Tidal's platform.

Starna Therapeutics
Starna is a private, China-based biotech company leveraging its selective targeted RNA delivery (STAR) LNP platform to deliver linear or circular RNA to specific tissues or cells. In June 2025, a Phase I trial evaluating the company's in vivo CD19 CAR-T asset, STR-004, was initiated in China for the treatment of r/r NHL. Although it is unclear what immune cells STR-004 is intended to transduce, patients in the trial will receive weekly treatment doses for 4 consecutive weeks, suggesting CAR-T cells are being transiently produced.

Strand Therapeutics
Strand Therapeutics is a private biotech company developing RNA-based therapies for the treatment of cancer. While the company's lead programs utilize mRNA for cytokine expression in tumors, its early-stage pipeline consist of circRNA programs for in vivo CAR delivery. For sufficient expression of the CAR, novel IRES sequences are introduced into the circRNAs, which improves transgene expression by 5-10x in T cells compared to standard IRES. Another unique aspect of Strand's circRNAs is the inclusion of micro RNAs (miRNAs) that allow for suppressed expression of the circRNA in certain tissues. Strand generated genetic "circuits" that can detect a desired molecular signature in a cell that could activate miRNA-mediated suppression of the RNA payload. While Strand has not disclosed its lead tumor targets, the company plans to evaluate two programs for the treatment of hematological malignancies.

Thunder Biotech
Thunder Biotech is a private company developing genetically engineered macrophages (MOTO-CAR) for the treatment of cancer. The company's in vivo platform utilizes LNP-encapsulated mRNA encoding a CAR. In addition, the LNP is designed to specifically target M2 macrophages.

Lipid Nanoparticle (LNP)-Based Approaches: Durable CAR Expression Through Transgene Integration

Cytiva (a Danaher company)
Cytiva is developing a LNP-based system for in vivo gene CRISPR gene editing that is designed to engineer CAR-T cells in situ for the treatment of solid tumors. The company has not disclosed any additional details pertaining to its platform or in vivo CAR-T pipeline. In October 2025, Cytiva was awarded an undisclosed amount by the U.S.'s ARPA-H to advance its in vivo CAR-T programs.

Nanocell Therapeutics
Nanocell is a private preclinical-stage company developing nonviral DNA-based approaches for in vivo CAR-T cell therapy for the treatment of cancer and autoimmune disease. Nanocell's targeted LNPs, referred to as NCtx, target CD7, which primarily expressed on T and NK cells. The company also utilizes DNA and RNA-transposases for transgene integration and long-term expression. To ensure NCtx is able co-deliver DNA and mRNA, the company utilizes minicircular DNA, which has

a small and more compact structure. In a recent publication in the *Journal for ImmunTherapy of Cancer*, Nanocell shared proof of concept of its NCtx in several humanized tumor mouse models. In huPBMC mouse models of leukemia, a single infusion of NCtx containing either a CD19 CAR or CD19/CD22 CAR led to robust CAR expression on T cells, which coincided with complete tumor control in all treated mice. In huHSC mice treated with NCtx containing a CD19/CD22 CAR, 7 of 12 mice exhibited complete tumor elimination. Importantly however, mice that did not respond had insufficient T-cell numbers pretreatment, highlighting there is likely a minimal T-cell population threshold for effective in vivo CAR-T generation. The company's lead candidate delivers a dual CD19/CD22 CAR for B-cell malignancies.

Stylus Medicine

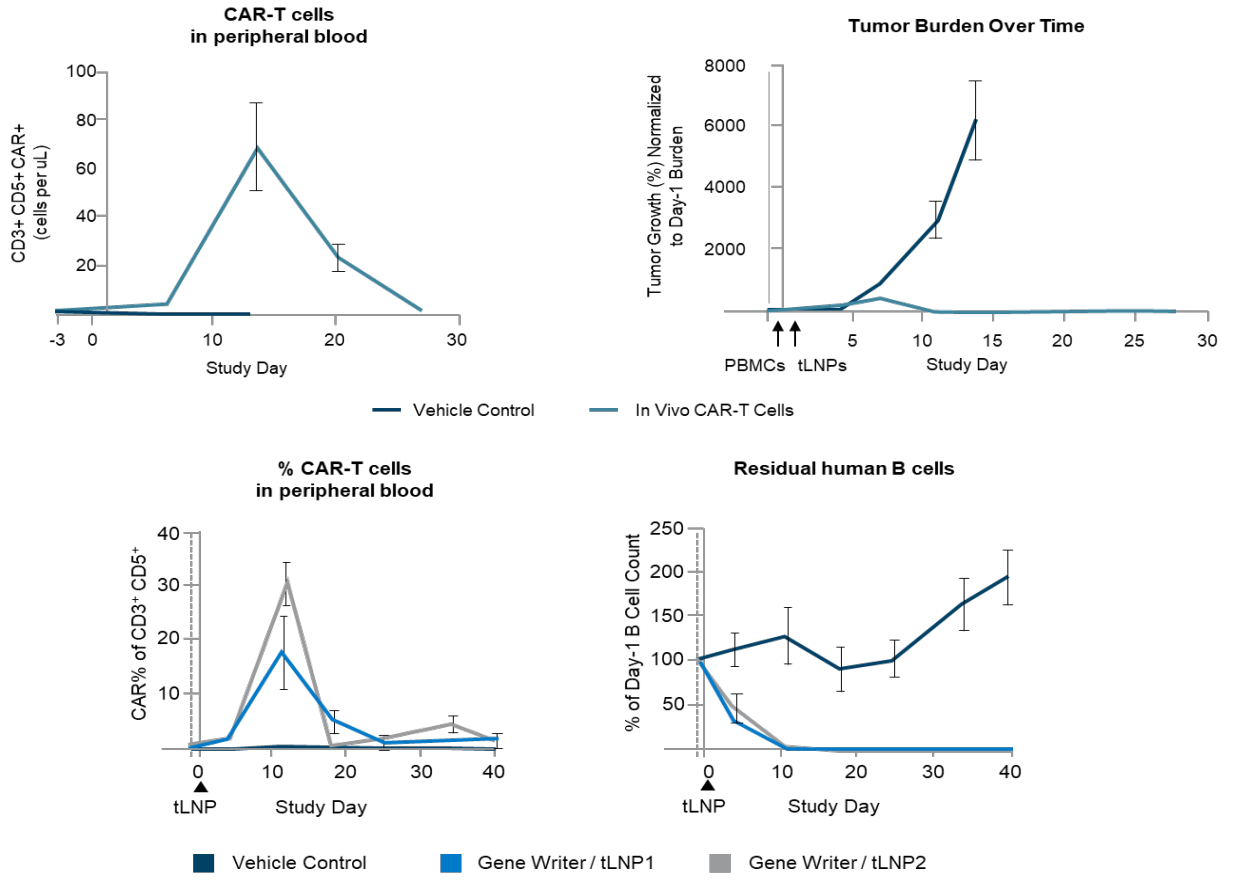
Stylus Medicine is developing in vivo genetic therapies, including in vivo CAR-T via its recombinase platform, which utilizes large serine recombinases (LSRs) for site-specific gene insertion. Notably, the LSR technology can integrate a given payload without causing double-strand DNA breaks in the host genome. In addition to using an all nonviral LNP system, Stylus's technology is efficient for dividing and non-dividing cells and can insert payloads greater than 13.5 kilobases. Stylus's LSRs target genomic safe harbor regions, which are specific regions where foreign DNA can be inserted without disrupting the normal function of the host cell. At the 2025 ASGCT conference, Stylus shared conceptual details of its LSRs technology for its in vivo CAR-T approach in which LNPs contain mRNAs expressing the LSR and DNA payloads encoding the therapeutic payload. In xenograft mouse models for B-ALL, Stylus demonstrated that a single IV infusion of targeted LNPs containing LSR + CD19 CAR DNA led to complete ablation of mouse tumors. Management has noted that the efficiency of its LSR technology does not change with larger payloads. While the company's website states its approach could be applicable to oncology and autoimmune diseases, no additional details regarding Stylus's in vivo CAR-T have been disclosed.

Tessera Therapeutics

Tessera is a preclinical biotech company developing next-generation genetic medicines by leveraging multiple platforms that can correct single nucleotides, delete or insert short DNA sequences, and write entire genes into the genome. The company uses proprietary LNPs to deliver mRNA encoding its gene writing machinery. Specific to its efforts in targeting T cells for in vivo editing, the company plans to deliver mRNA encoding retrotransposons, which would integrate a CAR into the host DNA. At the 2025 ASGCT conference, Tessera demonstrated the capabilities of its in vivo gene writing platform in T cells. In humanized PBMC tumor mouse models, a single infusion of targeted LNPs containing RNA gene writers for a CD19 CAR transgene led to robust expression of CAR-T cells, which correlated with complete tumor ablation (exhibit 37; top). The company also shared similar preclinical data with a candidate delivering a CD20 CAR (exhibit 37; bottom). While the company has not disclosed its specific targets, its website indicates it will pursue oncology indications.

In October 2025, Tessera was awarded $41.3 million by the U.S.'s ARPA-H to advance its in vivo CAR-T programs.

Exhibit 37
CELLect Horizons
B-Cell Depletion in Various Mouse Models Following Treatment With Tessera's RNA Gene Writer



Source: Tessera ASGCT 2025; adapted by William Blair Equity Research

YolTech Therapeutics

YolTech is a private biotech company based in China that is developing in vivo gene editing therapies. Its approach combines gene editing technologies with a proprietary LNP delivery system. Although the company's most advanced pipeline assets target metabolic and genetic diseases, its pipeline does contain an in vivo CAR-T asset, YOLT-401, which targets an undisclosed antigen for the treatment of autoimmune diseases. YOLT-401 is still in preclinical development and no additional information has been shared on the asset.

Other Technologies/Nondisclosed for Delivery of In Situ CARs

Aanastra

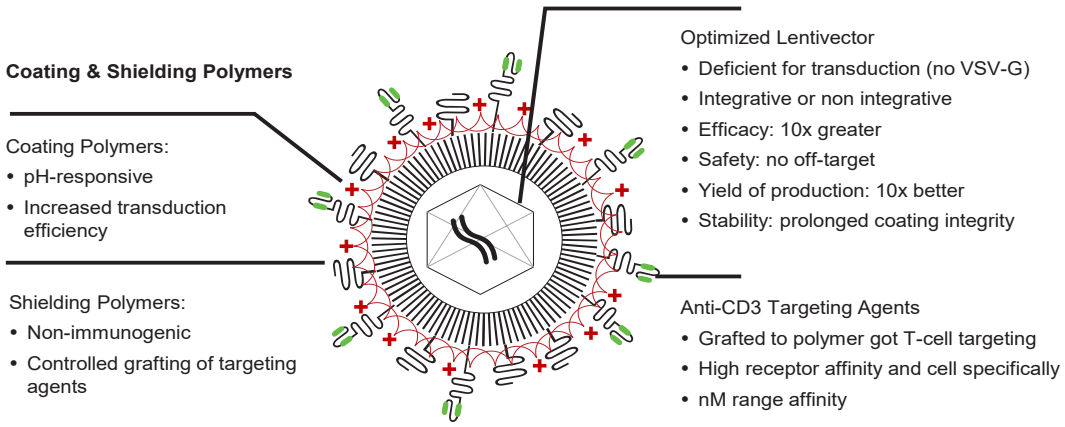
Aanastra is a private preclinical biotech company developing in vivo-targeted RNA therapeutics for the treatment of cancer and genetic diseases. The company's technology is based on proprietary RNA and proprietary peptides complexed together for targeted in vivo delivery. Aanastra's lead in vivo CAR-T candidate, AAN-14x, is designed to deliver a CD19 CAR for the treatment of autoimmune disease and hematological malignancies. At the 2025 AACR conference, the company shared preclinical data, which utilizes a novel peptide to deliver mRNA to target tissue. Aanastra's

peptides form stable nanoparticle complexes to deliver mRNA to T cells expressing CD3/CD5 receptors. Humanized mice treated with nanoparticles containing CD19 CAR mRNA at 1 mg/kg at days 0 and 5 achieved robust expression of CAR-positive CD3 T cells, with CAR-T positivity maintained at over 10% for at least 13 days. Notably, within 12 hours of infusion of CD3/CD5 nanoparticles, 10%-20% of T cells were CD19 CAR-T cells and over 90% of B cells in mice were eliminated. No liver or kidney toxicity and metabolic anomalies were detected in blood samples following treatment with nanoparticles. The company has not officially disclosed plans to investigate its RNA platform for in vivo CAR-T.

Alaya.bio

In October 2023, Alaya.bio, a private in vivo gene delivery biotech company acquired Ixaka, then a private, preclinical-stage biotech company developing in vivo CAR-T cell therapies. The financial terms under the agreement were not disclosed. At the 2025 ASGCT conference, Alaya.bio shared early studies highlighting its in vivo gene delivery technology, which uses a transduction-deficient lentivector encapsulated in a polymeric nanoparticle (exhibit 38). The nanoparticles are pH-responsive for increased transduction efficiency and non-immunogenic. The shielding polymers also contain anti-CD3 targeting agents that allow for nanomolar affinity to T cells. The encapsulated LVV is optimized for long-term stability, safety, and manufacturability. Interestingly, the company claims the use of the LVVs allows for transient and permanent gene expression.

Exhibit 38
CELLect Horizons
Schematic of Alaya's In Vivo Gene Delivery Technology



Source: Alaya.bio ASGCT 2025; adapted by William Blair Equity Research

At the conference, Alaya also shared transduction efficiency with its novel polymeric nanoparticles (nontargeting) in tumor bearing immunocompetent mice, wherein infusion of CD19 CAR NPs generated CAR-T cells that subsequently led to complete elimination of tumor cells and was associated with extended survival compared to control treated mice. Elevated liver enzyme levels were observed on days 7 and 31 post-systemic administration of non-targeting nanoparticles. There were no changes in pro-inflammatory cytokines observed compared to control mice. Separately, in immunodeficient mice engrafted with human PMBCs, infusion with non-targeting nanoparticles lead to long-term CD19 CAR expression out to 80 days after treatment. Future and ongoing studies for the company include conjugation of CD3 polymeric NPs, and validation of the platform in syngeneic and humanized mouse models. The company also plans to evaluate the versatility of its platform with different cargos such as RNA, pDNA, and non-integrative vectors.

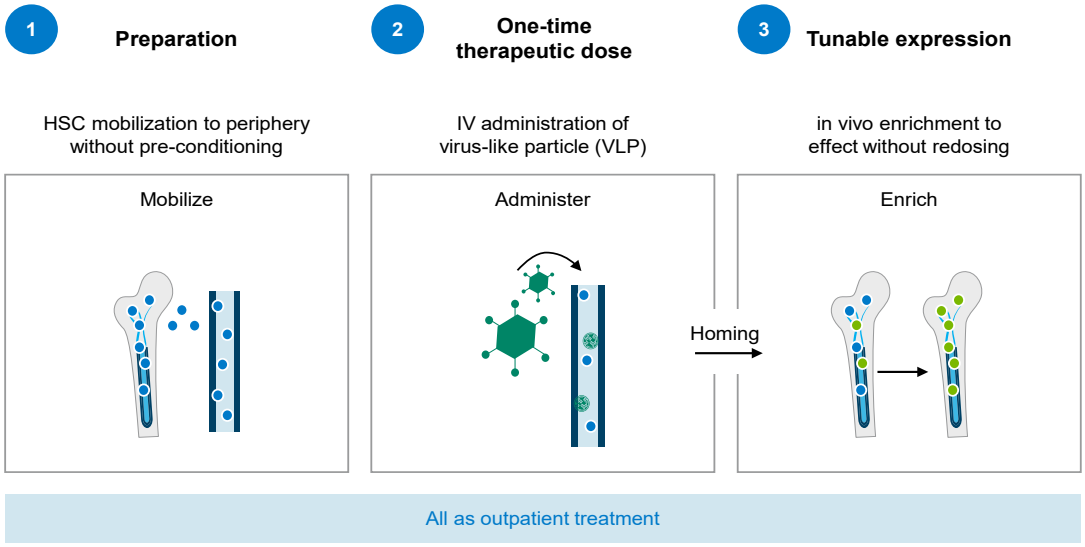
Azalea Therapeutics

Azalea Therapeutics is a private company that spun out of the lab of Jennifer Doudna. While limited information is available on the company, in 2024 it published a paper detailing the delivery of Cas9-packed in enveloped delivery vehicles (Cas9-EDVs) to T cells in vitro and in vivo in mice, leading to the in vivo generation of CAR-T cells (Hamilton et al. Nature Biotechnology. 2024).

Ensoma

Ensoma is a genomic medicines company developing in vivo treatments for genetic diseases and oncology indications. The company's Engenious platform uses an engineered helper-dependent adenovirus 5/35 (HDAd5/35+) that targets CD46 on HSCs to deliver gene modification technologies, including CRISPR, base editing, and prime editing, directly to HSCs or the various cell types that arise from these cells (i.e., T, B, and myeloid cells). To avoid potential immunogenicity, all viral genes are removed from Ensoma's virus-like particles (VLPs) thus expanding payload capacity to up to 35 kB, which could allow the expression of multiple genes. Ensoma envisions treatment to include HSC mobilization (without preconditioning), followed by a single IV administration of a VLP targeting peripheral HSC. Following VLP transfection, HSCs will home back to the bone marrow to generate multilineage CAR+ immune cells (exhibit 39).

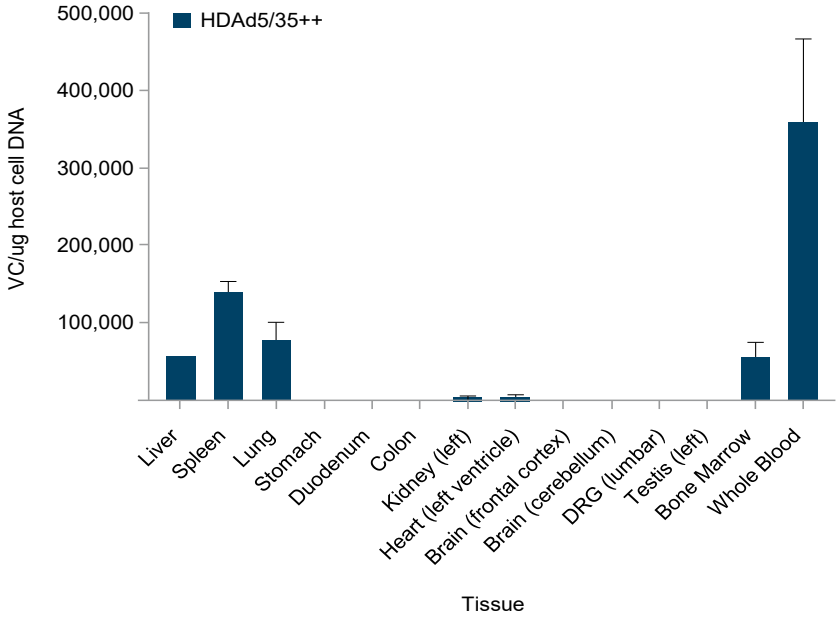
Exhibit 39
CELLect Horizons
Administration Process for Ensoma's VLPs



Source: Ensoma company reports; adapted by William Blair Equity Research

Ensoma's VLP platform has also demonstrated strong liver de-targeting in NHPs, with a majority of transduced cells found in the whole blood, where HSCs will be found post-mobilization (exhibit 40).

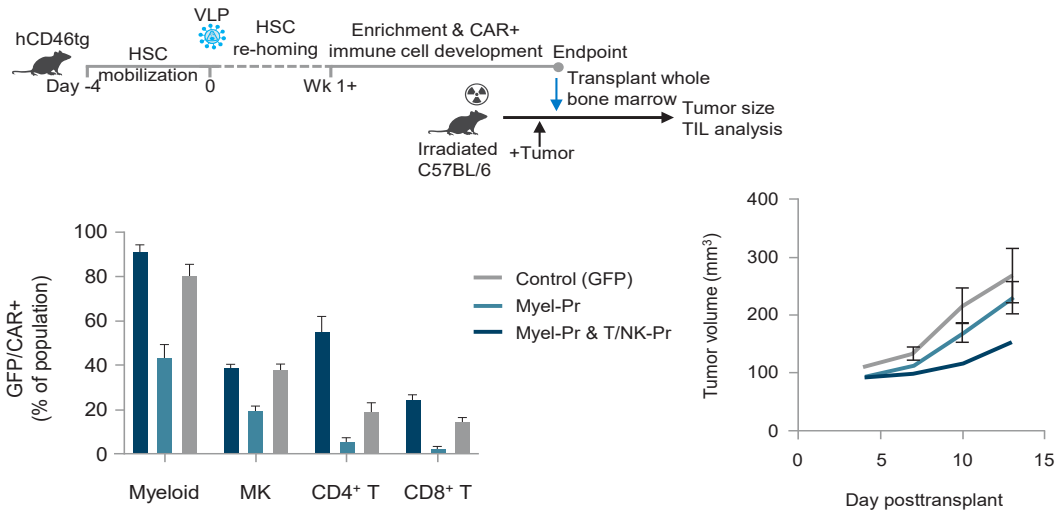
Exhibit 40
CELLect Horizons
Distribution of Ensoma's VLP-Transduced Cells in NHPs



Source: Ensoma company reports; adapted by William Blair Equity Research

At the 2025 ASGCT conference, Ensoma presented preclinical data supporting the use of its in vivo HSC editing platform for the generation of CAR-T cells. For CAR delivery, Ensoma's VLPs target PMBCs, giving rise to CAR+ myeloid, T, and NK cells. In addition, VLP can integrate into mobilized HSCs, giving rise to durable CAR+ HSCs with self-renewal potential. To evaluate antitumor effects with VLPs, Ensoma first transfected humanized HSC mice with anti-HER2 CAR VLPs constructs containing promoters for myeloid cells or myeloid, T, and NK cells. Weeks after the CAR+ immune cells are enriched, whole bone marrow from the transfected humanized mice are transplanted into a HER2+ tumor bearing and irradiated mouse. CAR expression in immune cells was detectable at day 25 posttransplant, but antitumor activity was only observed in mice given cells that contained the myeloid, NK, and T cell promoter (exhibit 41).

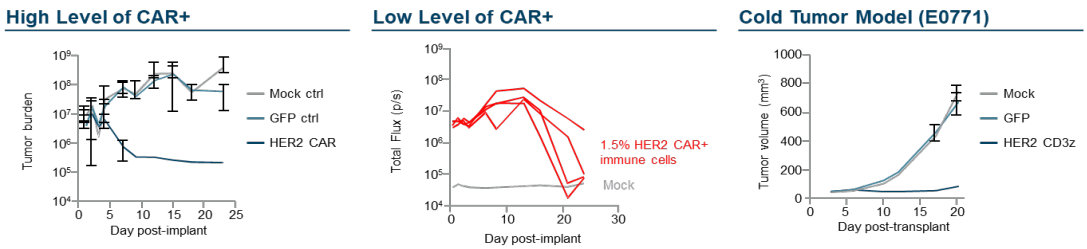
Exhibit 41
CELLect Horizons
CAR Expression and Tumor Control in Mice Administered Ensoma's VLPs With Different Promoters



Source: Ensoma ASGCT 2025; adapted by William Blair Equity Research

Ensoma has also conducted experiments in human HER2 immunocompetent mouse models, wherein VLP-transduced HSCs achieved greater antitumor activity (exhibit 42; left). Notably, tumor regression was observed in mice transplanted with low levels of CAR positivity (exhibit 42; middle). In another immunocompetent mouse model well-characterized for its "cold" immunological tumor microenvironment, transplanted CAR+ cells also achieved persistent tumor inhibition, suggesting that CAR activity on innate and immune cells can overcome highly immunosuppressive TMEs (exhibit 42; right). Ensoma plans to nominate its first VLP candidate in the fourth quarter of 2025, which will be for patients with solid tumors.

Exhibit 42
CELLect Horizons
CAR Expression and Tumor Control in Mice Administered Ensoma's VLPs



Source: Ensoma company reports; adapted by William Blair Equity Research

GenVivo

GenVivo is a private, biotech company developing vector-based immunotherapies. The company's in vivo CAR-T platform utilizes a gamma-retrovirus encoding a CAR armored with IL12 and herpes simplex virus enhanced thymidine kinase (HSV-eTK) to generate CAR-T and CAR-NK cells. The HSV-eTK acts as a safety switch in case severe adverse events emerge. The company's vector transduces actively dividing T-cells and is engineered with cell-specific transduction targeting

and regulatory elements, such as transcription factors and microRNAs, to enhance selectivity. The company's lead in vivo candidate, GEN-310, delivers a CD19 CAR for the treatment of B-cell malignancies. In vitro, PBMC transduction of the CD19 encoding vector led to elimination of NALM-6 lymphoma cells when at a 0.07:1 effector to target cell ratio. The company is continuing to conduct preclinical work on GEN-310.

GigaMune
GigaMune is developing in vivo cell therapies for the treatment of multiple myeloma, acute myeloblastic leukemia, and inherited blood disorders. While GigaMune's website does not provide additional details on the company's technology or recent progress, in 2025, the company has submitted patent filings to the U.S. patent office for nucleic acid-guided nucleases and engineered enveloped vectors, suggesting ongoing research in genome editing (Johnson et al. 2025). No further details have been disclosed.

ImmTune Therapies
ImmTune is developing highly selective, efficient delivery vectors for in-patient generation of cell and gene therapies. ImmTune's website does not provide any additional details on the company's technology platform or which indications it is targeting.

Immunovec
Immunovec is developing in vivo engineered cell therapies for autoimmune diseases, solid tumors, and genetic disorders. The company's proprietary platform combines synthetic, cell type-specific promoters to enable precise and durable expression of therapeutic payloads within targeted cells. The company is leveraging a biodegradable polymer nanoparticle to deliver DNA-based payloads. The company's lead program is designed to deliver a CD19 CAR to NK cells. For the treatment of autoimmune diseases. In October 2025, the company was awarded $40.7 million from the Advanced Research Projects Agency for Health (ARPA-H) Engineering of Immune Cells Inside the Body (EMBODY) program to accelerate the development of its lead program. The company has not shared additional information about its platform or pipeline at this time.

Jenthera Therapeutics
Junthera is a private, Canada-based company developing in vivo gene editing therapies. Uniquely, the company uses ribonucleoprotein as opposed to viruses or nanoparticles to deliver gene editing machinery to the cell. The company has a preclinical in vivo CAR-T program in development for the treatment of B-cell lymphoma.

Juventas
Juventas is a China-based biotech company focused on developing cell therapies. The company's pipeline states it has three in vivo CAR-T assets in development, but there are no additional details available regarding its antigen target or underlying technology.

Opko Health
Opko's subsidiary, ModeX, is developing next-generation biologics for cancer and infectious diseases. The company's pipeline lists an in vivo CAR-T in preclinical development for the treatment of lymphoma and autoimmunity. No additional details on the program or the underlying platform have been shared.

Singular Immune
Singular has developed an innovative recombinant protein-based platform for in vivo cell engineering, called iCAR. The iCAR consists of an effector cell targeting domain, disease cell targeting domains, and signal inducer domains. Following administration of the iCAR, the protein targets and binds to a receptor on the surface of the immune cell using the cell targeting domain. After it is bound, the iCAR is internalized into the cell wherein an enzyme in the immune cell cleaves

a peptide within the iCAR, separating the cell-targeting domain from the rest of the protein. The antigen targeting and signal inducer domains then migrate and translocate on the cell membrane. The company has several in vivo CAR-T and CAR-NK therapies in development for the treatment of solid tumors hematological malignancies, and autoimmune diseases, although their antigen targets are not disclosed.

Thesian Bio

Thesian is developing novel gene therapies using a locked virus-like particle (VLP) that requires a specific co-receptor expressed on CD4 and CD8 T-cells. This mechanism unlocks the fusogen and delivers the CAR payload, minimizing off-target effects. No additional information is available on Thesian's specific in vivo CAR-T development candidates.

Velvet Therapeutics

Velvet is a preclinical-stage biotech developing in vivo CAR delivery using amino acid nanoparticles for delivery of minicircle DNA. The company's website notes that it is evaluating three undisclosed solid tumor antigen targets in preclinical studies.

The prices (10/20) of the common stock of other public companies mentioned in this report follow:

AbbVie, Inc. (Outperform)	$232.06
Allogene Therapeutics, Inc. (Outperform)	$1.29
Arcellx, Inc. (Outperform)	$86.77
AstraZeneca PLC	$83.87
Astellas Pharma Inc.	$10.78
Autolus Therapeutics Plc (Outperform)	$1.70
Bristol Myers Squibb Company (Market Perform)	$43.59
Cabaletta Bio, Inc. (Outperform)	$2.82
Carisma Therapeutics, Inc.	$0.04
CRISPR Therapeutics AG (Outperform)	$73.97
Danaher Corporation (Outperform)	$208.39
Gilead Sciences, Inc.	$123.11
Legend Biotech Corp. (Market Perform)	$32.91
Johnson & Johnson	$193.72
Kyverna Therapeutics, Inc. (Outperform)	$7.50
Merck & Co, Inc.	$86.32
Moderna, Inc. (Market Perform)	$27.24
Novartis AG	$131.79
Nkarta, Inc. (Market Perform)	$2.44
Prime Medicine, Inc.	$6.18
Sana Biotechnology, Inc.	$5.56
Sanofi SA	$49.73
Takeda Pharmaceutical Co.	$14.08

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DOW JONES: 46924.70
S&P 500: 6735.35
NASDAQ: 22953.70

Additional information is available upon request.

Current Rating Distribution (as of October 22, 2025):

Coverage Universe	Percent	Inv. Banking Relationships *	Percent
Outperform (Buy)	73	Outperform (Buy)	10
Market Perform (Hold)	27	Market Perform (Hold)	3
Underperform (Sell)	1	Underperform (Sell)	0

*Percentage of companies in each rating category that are investment banking clients, defined as companies for which William Blair has received compensation for investment banking services within the past 12 months.

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