

The rise of in vivo CAR-T: Antibody-guided lipid nanoparticles enable a new direction in gene and cell therapy

A new generation of CAR-T engineering

Ten years after the clinical debut of chimeric antigen receptor T (CAR-T) therapy, researchers are now looking inward—literally. The concept of in vivo CAR-T, in which the patient's own T cells are reprogrammed inside the body, is reshaping how cell therapies might be manufactured and delivered.

In contrast to costly and time-consuming ex vivo manufacturing, in vivo CAR-T approaches use targeted gene delivery systems to introduce CAR-encoding material directly into circulating T cells. The goal is to simplify manufacturing and logistics, shorten turnaround time, and broaden accessibility—while maintaining the potent cytotoxic activity that defines CAR-T therapy.

The momentum behind in vivo CAR-T

This field has expanded rapidly. In 2025 alone, multiple high-profile collaborations and acquisitions have pushed the total deal value close to five billion US dollars. Simultaneously, academic literature is flourishing, showcasing impressive preclinical and early clinical data worldwide.

In September, *Nature Reviews Drug Discovery* published a landmark review by Prof. Carl June, the CAR-T pioneer, together with scientists from ten leading in vivo CAR companies, outlining current progress and key challenges in in vivo CAR-T engineering.

The consensus is clear: as delivery technologies improve, in vivo CAR-T may move from proof of concept to clinical reality within the decade.

Delivery is the decisive step

Achieving this vision depends on one crucial step: delivering the CAR gene precisely to T cells while avoiding uptake by undesired cells such as hematopoietic stem cells. Two technological platforms currently dominate clinical development:

1. **Engineered viral vectors** (primarily lentiviruses) that carry integrating payloads. Viral envelope proteins can be engineered to ensure selective gene transfer by displaying binders targeting T-cell-specific surface markers while eliminating interaction with natural cell surface receptors. This strategy supports stable, long-term CAR expression and is more suitable for indications requiring sustained immune activity.
2. **Lipid nanoparticles (LNPs)** that deliver transiently expressed RNA in a non-integrating form. By conjugating antibodies or antibody fragments to LNPs,

researchers can target specific immune cells. Ionizable lipids with high biodegradability and low reactogenicity make such systems possible to re-does, thus LNP platform offers flexibility for repeat dosing and superior safety control in sensitive indications.

Both routes are under active investigation, and each presents unique advantages in terms of persistence, control, and safety.

Antibody specificity defines targeting accuracy

In antibody-functionalized LNP systems, surface antibodies serve as molecular “addresses” that determine where the payload will go. High specificity and purity are therefore indispensable. Even subtle variations can shift biodistribution, leading to off-target gene transfer or unpredictable immune responses.

This is where Bio X Cell’s *in vivo*–grade antibodies play a vital role — enabling reliable, reproducible targeting performance in multiple pioneering studies.

Case Study 1: Long-lasting *in vivo* CAR-T combined with IL-6 silencing

A 2022 study from East China Normal University demonstrated that dual-function LNPs can both generate CAR-T cells and modulate cytokine release. The authors designed a plasmid encoding CD19 CAR together with IL-6 shRNA, packaged it into LNPs, and modified the surface with Bio X Cell’s anti-human CD3 antibody (clone OKT3, #BE0001-1) to achieve pan T cell targeting.

When administered leukemia-bearing NSG mice, these AntiCD3-LNPs accumulated in the lymph nodes and successfully transfected endogenous T cells. The engineered cells exhibited stable CAR expression for approximately three months, significantly prolonged survival to levels comparable with conventional CAR-T treatment, and effectively silenced IL-6 to mitigate cytokine release syndrome.

This dual-action approach highlights how *in vivo* platforms can be engineered for both efficacy and safety.

Case Study 2: Engineering extrahepatic antibody-LNPs for T cell targeting

In late 2023, Prof. Michael J. Mitchell’s team from the University of Pennsylvania developed a modular *antibody–LNP (Ab–LNP)* system for mRNA delivery to T cells beyond the liver. By conjugating antibody fragments against pan–T cell markers (CD3, CD5, CD7) to LNPs, the authors compared targeting efficiency, biodistribution, and functional performance.

Upon delivery of *CD19 CAR mRNA*, treated mice exhibited dose-dependent CAR expression, cytokine release, and up to 90% B cell depletion—demonstrating that *in vivo* CAR-T generation is feasible using nonviral vehicles.

The use of an anti-mouse CD3ε F(ab')₂ antibody fragment from Bio X Cell allowed efficient chemical conjugation to LNPs without enzymatic digestion, providing exceptional convenience and improving reproducibility.

Outlook

In vivo CAR-T studies illustrate a broader shift in therapeutic strategy: from *ex vivo* manipulation toward direct *in vivo* cellular engineering. The convergence of precise delivery nanotechnology, optimized genetic payloads, and biologically validated targeting ligands is bringing this concept closer to clinical translation.

Antibodies—long central to immunology—are now emerging as key tools in gene delivery. As more studies refine their targeting function and safety profile, antibody-guided LNPs may become a cornerstone of next-generation cell and gene therapies.

References

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