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Review Article

Advances in Chimeric Antigen Receptor T Cell Therapy: From First-Generation Constructs to Next-Generation Armoured and Allogeneic Platforms

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Abstract

Chimeric antigen receptor (CAR) T cell therapy has transformed the treatment landscape for haematological malignancies, with six products receiving FDA approval between 2017 and 2022. The University of Pennsylvania's Center for Cellular Immunotherapies, co-founded by Dr. Carl June and Dr. Bruce Levine, played a foundational role in translating CD19-targeting CAR-T therapy into clinical practice, while European centres including Institut Gustave Roussy have been integral to Phase III validation and post-marketing studies. This review comprehensively examines the structural evolution of CAR constructs from first to fourth generation, the immunological mechanisms underpinning tumour killing and therapy-associated toxicities, and the clinical performance of approved CAR-T products. We address key limitations including manufacturing complexity, cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), T cell exhaustion, and antigen loss, and review emerging strategies including armoured CAR-T cells, logic-gated CAR designs, CRISPR-engineered allogeneic CAR-T cells, and CAR-NK platforms. The expanding application of CAR-T technology to solid tumours and autoimmune diseases is also reviewed.

Keywords: *CAR-T Cells, Chimeric Antigen Receptor, Haematological Malignancies, Cytokine Release Syndrome, Icans, Allogeneic Car-T; Car-Nk, Solid Tumours, Cell Therapy*

Introduction

The concept of re-engineering T lymphocytes to express synthetic antigen receptors was first demonstrated experimentally in the early 1990s (Gross et al., 1989; Eshhar et al., 1993). Its clinical translation was led by Dr. Carl June's group at the University of Pennsylvania, whose 2011 New England Journal of Medicine reports of durable remissions in chronic lymphocytic leukaemia patients treated with CD19-targeting CAR-T cells electrified the oncology community (Porter et al., 2011). This work formed the scientific and intellectual foundation for tisagenlecleucel (Kymriah), co-developed by Penn and Novartis, the first CAR-T product to receive FDA approval (August 2017).

As of 2025, six CAR-T cell products have received regulatory approval, collectively having treated tens of thousands of patients worldwide. European centres, including Gustave Roussy (Villejuif, France), University College London, and Charité Berlin, have been central to post-marketing studies, real-world outcome analyses, and next-generation CAR construct development.

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The USA and France represent the leading national producers of both academic CAR-T innovation and clinical trial infrastructure.

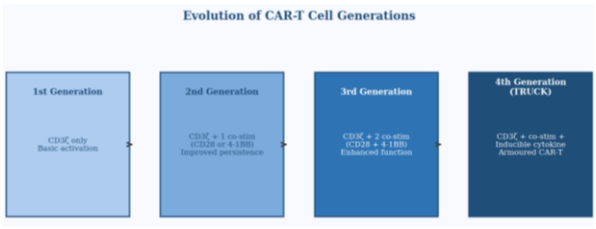

Figure 1: Structural and Functional Evolution Across Four Generations of CAR-T Cells. Developed from foundational work at Penn and subsequent European academic-industry collaborations. Co-stim = co-stimulatory domain; TRUCK = T cell redirected for universal cytokine-mediated killing.

2. CAR Construct Architecture and Generational Evolution

All CARs share a modular architecture: extracellular antigen-binding domain (typically scFv), hinge/spacer

region, transmembrane domain, and intracellular signalling domains (CD3ζ ± co-stimulatory domains). First-generation CARs incorporated CD3ζ alone with poor persistence. Second-generation CARs added CD28 (Yescarta/ axicabtagene) or 4-1BB (Kymriah/ tisagenlecleucel) co-stimulation, substantially improving clinical outcomes. Third-generation CARs incorporate two co-stimulatory domains. Fourth-generation TRUCKs additionally encode inducible cytokine transgenes, transforming CAR-T cells into local cytokine factories. Penn's foundational 4-1BB co-stimulatory domain choice in tisagenlecleucel versus CD28 in Memorial Sloan Kettering/NCI-derived axicabtagene illustrated how co-stimulatory domain selection profoundly affects T cell persistence and exhaustion kinetics (Milone & Bhatt, 2018).

Table 1: FDA-Approved CAR-T Cell Products — Targets, Indications, and Clinical Response Data (as of 2025)

Product (Brand)	Target	Indication	ORR (%)	CR (%)	Approval Year
Tisagenlecleucel (Kymriah)	CD19	B-ALL (paediatric/young adult)	81%	60%	2017
Axicabtagene ciloleucel (Yescarta)	CD19	Relapsed/refractory LBCL	83%	58%	2017
Brexucabtagene autoleucel (Tecartus)	CD19	Relapsed/refractory MCL	87%	62%	2020
Lisocabtagene maraleucel (Breyanzi)	CD19	Relapsed/refractory LBCL	73%	53%	2021
Idecabtagene vicleucel (Abecma)	BCMA	Relapsed/refractory MM	73%	33%	2021
Ciltacabtagene autoleucel (Carvykti)	BCMA	Relapsed/refractory MM	98%	78%	2022

ORR = overall response rate; CR = complete response; B-ALL = B cell ALL; LBCL = large B cell lymphoma; MCL = mantle cell lymphoma; MM = multiple myeloma; BCMA = B cell maturation antigen.

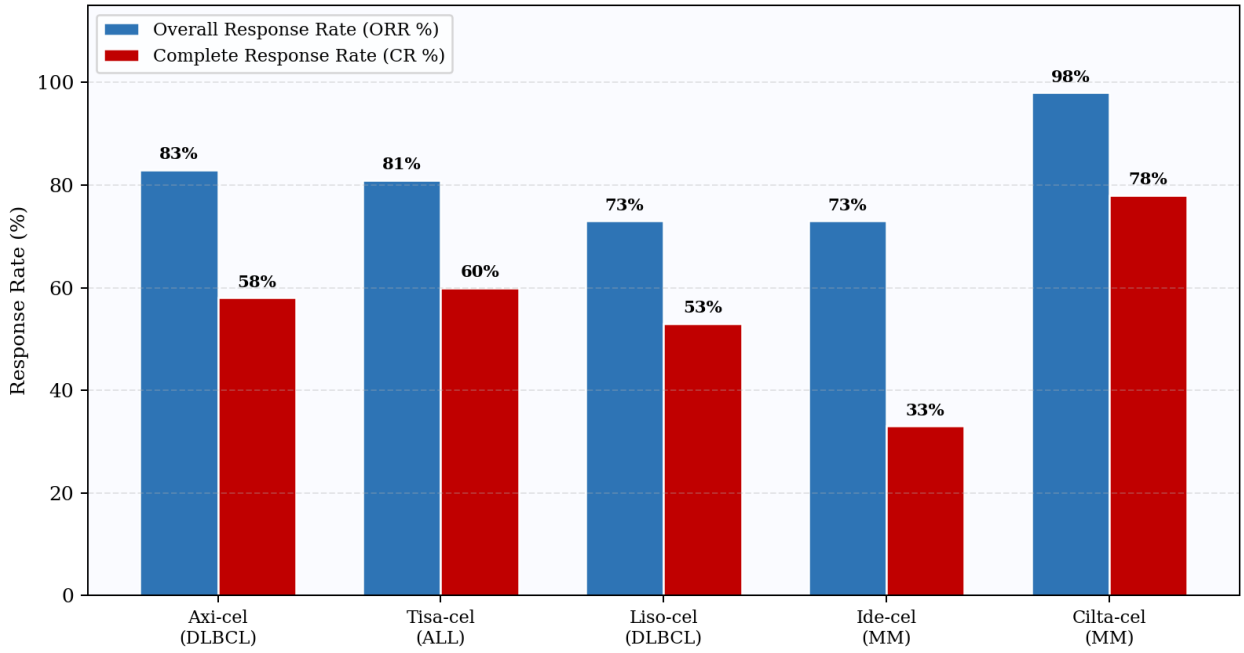

Figure 2: Clinical Response Rates of FDA-Approved CAR-T Products (2017–2025). ORR = overall response rate; CR = complete response rate. Based on pivotal trial data.

3. Toxicities: CRS and ICANS

CRS occurs in 50–90% of CAR-T patients, driven by massive cytokine secretion—primarily IL-6—from CAR-T cells and bystander macrophages. IL-6 pathway blockade with tocilizumab is the cornerstone of management (Lee et al., 2014). ICANS manifests as encephalopathy, aphasia, seizures, or cerebral oedema typically 4–7 days post-infusion; corticosteroids are the primary treatment. Gustave Roussy's real-world CARTO registry, enrolling CAR-T patients across French centres, has contributed important pharmacovigilance data on CRS and ICANS management outside the controlled trial setting.

4. Emerging Platforms

Allogeneic (off-the-shelf) CAR-T cells—derived from healthy donor T cells with CRISPR-Cas9-mediated TCR and HLA class I disruption—would enable standardised manufacturing and immediate availability, addressing current cost (>USD 400,000 per course) and access barriers (Depil et al., 2020). CAR-NK cells demonstrated 73% ORR in a Phase I/II trial with minimal CRS and no ICANS, suggesting improved safety (Liu et al., 2020). Both platforms are in advanced clinical development at Penn and multiple European centres.

5. Conclusions

CAR-T cell therapy has transitioned from experimental concept to standard-of-care for multiple relapsed/refractory haematological malignancies, with foundational work at Penn and clinical validation through international trials including major European centres. The continued evolution of CAR constructs, development of allogeneic platforms, and creative engineering solutions to solid tumour challenges ensure that CAR-T will remain among the most dynamic fields in cancer biotechnology.

References

Depil, S., Duchateau, P., Grupp, S. A., et al. (2020). 'Off-the-shelf' allogeneic CAR T cells: Development and challenges. Nature Reviews Drug Discovery, 19(3), 185–199.

Eshhar, Z., Waks, T., Gross, G., & Schindler, D. G. (1993). Specific activation and targeting of cytotoxic lymphocytes through chimeric single chains consisting of antibody-binding domains and gamma or zeta subunits. Proceedings of the National Academy of Sciences, 90(2), 720–724.

June, C. H., O'Connor, R. S., Kawalekar, O. U., et al. (2018). CAR T cell immunotherapy for human cancer. Science, 359(6382), 1361–1365.

Lee, D. W., Gardner, R., Porter, D. L., et al. (2014). Current concepts in the diagnosis and management of cytokine release syndrome. Blood, 124(2), 188–195.

Lim, W. A., & June, C. H. (2017). The principles of engineering immune cells to treat cancer. Cell, 168(4), 724–740.

Liu, E., Marin, D., Banerjee, P., et al. (2020). Use of CAR-transduced natural killer cells in CD19-positive lymphoid tumors. New England Journal of Medicine, 382(6), 545–553.

Porter, D. L., Levine, B. L., Kalos, M., et al. (2011). Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. New England Journal of Medicine, 365(8), 725–733.