Pharmacology of Living Therapeutics
(IO Translational White Paper Series)

White Paper #1

Beyond ADME: A New Pharmacokinetic Paradigm for Engineered T-Cell Therapies

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Author: Alexandra Sevko, PhD

Founder & Principal Consultant

IO Translational Ltd.

a.sevko@io-translational.co.uk

Executive summary

In 2017, the FDA approved the first engineered CAR-T cell product, Kymriah, for treatment of leukaemia and lymphoma (Freyer, 2018). This milestone established a novel class of living therapeutics, and since then the genetically engineered T-cell therapies have expanded beyond haematological malignancies into oncology, autoimmune diseases, and most recently, neurodegenerative disorders (Mitra, et al., 2023; Li, et al., 2024; Aliciaslan, et al., 2026).

Engineered T-cell therapeutics are living drugs which traffic, proliferate, differentiate into effector and memory populations, and are capable of long-term persistence. Living cellular therapeutics are intended to persist and provide sustained biological activity within the recipient long after administration (Mitra, et al., 2023; Kirouac, et al., 2024; Aliciaslan, et al., 2026; Anelli, et al., 2026). That is a fundamental difference from conventional drugs, which are designed to be eliminated after exerting their effect (Tonge, 2018) (Figure 1).

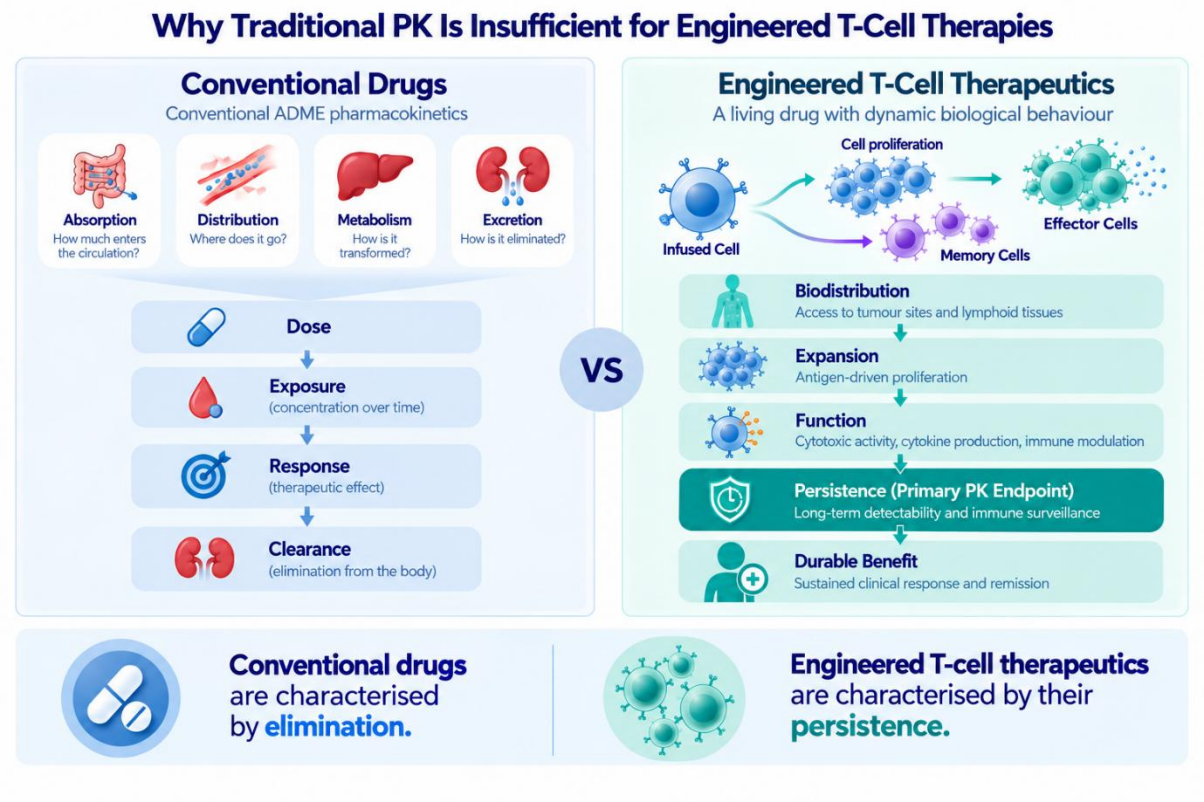


Figure 1. Traditional and engineered T-cell pharmacokinetics represent fundamentally different biological paradigms.

Conventional drug exposure is governed by ADME processes and elimination of the compound from the body (left panel). The kinetics of engineered T-cell therapies rely on biological behaviour and long-term persistence of therapeutic product (right panel). Source: Adapted from concepts discussed in Rotte, et al., 2022; Kirouac, et al., 2024; Li, et al., 2025; Anelli, et al., 2026.

Such unique characteristics of engineered T-cell therapeutics require a fundamental re-thinking of how therapeutic exposure and response are defined and measured (Kirouac, et al., 2024). The distinction between pharmacokinetics (PK) and pharmacodynamics (PD) becomes increasingly blurred for CAR- and TCR-T cells, as therapeutic efficacy depends not only on administered dose but also on the biological behaviour of the cells following infusion (Thudium Mueller, et al., 2017; Li, et al., 2025; Anelli, et al., 2026).

This white paper discusses a new PK concept for engineered T-cell therapies, which argues that persistence, rather than clearance, should be considered the defining PK endpoint of living cellular therapeutics.

A Multimodal PK Framework

Three major components shape the multimodal PK framework of engineered T-cell therapies, namely: the cellular product, the patient, and the tumour (in oncology indications) or pathological cell or tissue type (in non-oncology indications) (Figure 2). The interaction of these three factors influences biological behaviour and persistence of the infused cells and shape both therapeutic efficacy and duration of response (Kirouac, et al., 2024; Li, et al., 2025; Anelli, et al., 2026).

This framework therefore extends beyond PK in the conventional sense**.** The abundance of engineered T cells, their phenotype and function are biologically interdependent, blurring the traditional boundary between PK and PD for these living therapeutics. To describe the dynamic behaviour of engineered T cells following administration, the new term “cellular kinetics” was introduced to the field of cellular therapies by Grupp, Maude, and colleagues in 2017 (Thudium Mueller, et al., 2017).

Pharmacokinetic Journey of Engineered T-Cell Therapies

Engineered T cells are activated and expanded *ex vivo* during the manufacturing process and are distributed as cryopreserved living cells (Ayala Ceja , et al., 2024; Li, et al., 2025). The manufacturing of engineered T-cell therapies and the lymphodepletion procedures commonly performed before T-cell therapy infusion are reviewed elsewhere (Ayala Ceja , et al., 2024; Li, et al., 2025; and Lickefett, et al., 2023, respectively).

As discussed above, the pharmacokinetic behaviour of engineered T cells is not defined by progressive elimination, unlike conventional drug PK. Instead, a series of interconnected biological processes influence the cellular kinetics of the engineered T-cell product. These processes include biodistribution, expansion, function, contraction, and persistence (Figure 2).

Infusion. In preparation for adoptive T cell transfer therapy, patients are subjected to lymphodepletion. Lymphodepleting chemotherapy creates a favourable environment for engraftment by reducing competition for cellular and cytokine resources (Lickefett, et al., 2023; Ferry , et al., 2026).

On the day of the T-therapy administration, the cryopreserved cells are thawed and, in the majority of cases, administered by intravenous infusion (detailed in Rioufol & Wichmann, 2022). The cells then enter the circulation and begin distributing throughout the body. The intravenous administration remains the main route of engineered T-cell therapy; other regional routes are also applied (Cherkassky, et al., 2022). For the purpose of this white paper, we will focus on systemic intravenous administration.

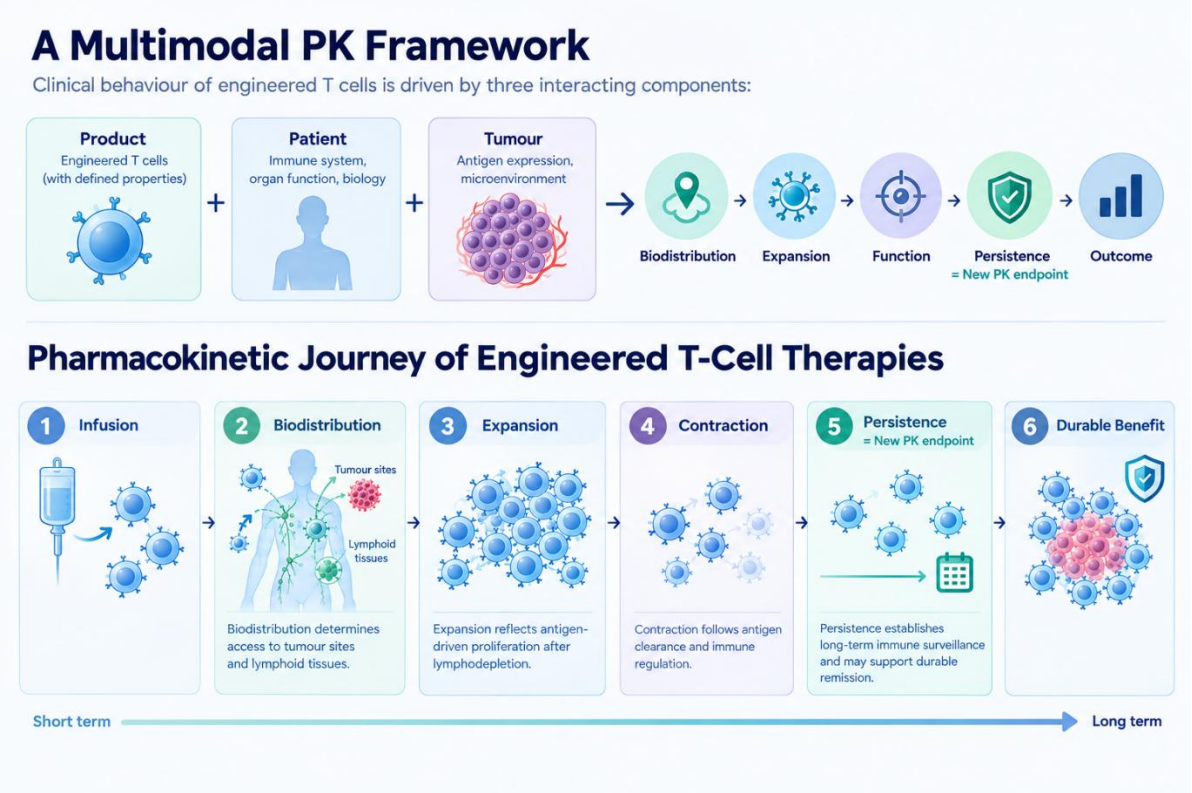


Figure 2. Pharmacokinetic journey of engineered T-cell therapies.

Interactions between the cellular product, the patient, and the tumour microenvironment determine therapeutic outcome and shape the multimodal PK framework (upper panel). Following infusion, engineered T cells undergo biodistribution, expansion, functional activity, contraction, and persistence (bottom panel).

Source: Adapted from concepts discussed in Thudium Mueller, et al., 2017; Rotte, et al., 2022; Kirouac, et al., 2024; Li, et al., 2025; Anelli, et al., 2026; and Wang, et al., 2026.

Biodistribution.

Following intravenous administration, engineered T cells traffic through the circulation and distribute across multiple tissues, including the tumour and secondary lymphoid organs (Kirouac, et al., 2024; Li, et al., 2025; Anelli, et al., 2026; Wang, et al., 2026). Organs with higher blood perfusion, such as the spleen, lung, kidneys, and liver, receive greater infiltration by engineered T cells as compared to poorly perfused organs, i.e. brain, bladder, ovary (Li, et al., 2025). Detectable engineered T-cells may become undetectable in the bloodstream within the first days after administration (Kirouac, et al., 2024; Li, et al., 2025).

Expansion. Upon antigen recognition, engineered T cells undergo rapid proliferation and differentiate into effector and memory populations (Li, et al., 2025; Anelli, et al., 2026). The peak of engineered T cell expansion measured in the peripheral blood occurs approximately 10-14 days after infusion (Rotte, et al., 2022; Li, et al., 2025; Anelli, et al., 2026).

Function. Expanded T cells must retain the capacity to mediate anti-tumour activity through direct cytotoxicity, cytokine secretion, and recruitment of additional immune responses (López-Cantillo , et al., 2022; Li, et al., 2025). Expansion alone is insufficient; functional competence is required for meaningful tumour control. Functional competence of engineered T-cell product depends not only on the characteristics of the original manufactured product. Several other contributing factors will impact cellular kinetics and function: the efficacy of engraftment, antigen presentation to activate the engineered T cell, trafficking of activated T cells to the tumour site, effective infiltration of the tumour and last, but not least, tumour microenvironment (Lickefett, et al., 2023; Li, et al., 2025; Wang, et al., 2026).

Contraction. Following peak expansion and tumour killing, the antigen burden declines and the effector T-cell population gradually subsides through normal immune regulatory mechanisms (Li, et al., 2025; Anelli, et al., 2026). The contraction phase can blend into the persistence, as an engineered T-cell product can be detectable in the peripheral blood for months or even years (Li, et al., 2025). This transition marks the shift from active tumour elimination toward long-term immune equilibrium.

Persistence. Durable therapeutic benefit depends on successful engraftment of infused T cells (López-Cantillo, et al., 2022; Li, et al., 2025; Wittling, et al., 2025; Ferry , et al., 2026). Interactions with the lymphoid microenvironment support further activation, proliferation, and differentiation into effector and memory T-cell populations (López-Cantillo, et al., 2022; Li, et al., 2025).

A proportion of engineered T cells survives as long-lived memory populations capable of continued immune surveillance (Li, et al., 2025; Anelli, et al., 2026). Memory populations of engineered T cells reside in secondary lymphoid organs and in tissues (McLellan & Ali Hosseini Rad, 2019; López-Cantillo, et al., 2022; Rotte, et al., 2022; Lickefett, et al., 2023; Li, et al., 2025), thus may not be detectable in the peripheral blood. Upon activation, memory T cells expand, form effector T cells, which subsequently home to the source of antigen, linking systemic expansion with local anti-tumour activity (McLellan & Ali Hosseini Rad, 2019; Li, et al., 2025).

Such dynamic redistribution highlights an important feature of T-cell PK: cells measured in peripheral blood may be actively trafficking to tissues where therapeutic activity occurs (Li, et al., 2025; Wang, et al., 2026). Persistent cells may support durable remission and represent the defining PK endpoint of engineered T-cell therapeutics (Kirouac, et al., 2024; López-Cantillo, et al., 2022; Li, et al., 2025; Anelli, et al., 2026).

This framework has important implications for how PK exposure should be interpreted. In conventional pharmacology, exposure is primarily determined by administered dose. For engineered T-cell therapies, however, exposure emerges from the biological behaviour of infused cells after administration (Kirouac, et al., 2024; López-Cantillo, et al., 2022; Li, et al., 2025; Anelli, et al., 2026).

Dose, exposure and therapeutic window: evidence from oncology clinical studies

In conventional pharmacology, administered dose of traditional chemotherapy therapy predicts exposure and, ultimately, therapeutic effect (Tonge, 2018).

For engineered T-cell therapies, this relationship is less straightforward, and administered dose does not define biological exposure (Rotte, et al., 2022; Kirouac, et al., 2024; Li, et al., 2025).

The current clinical evidence originates from both CAR-T and affinity-enhanced TCR-T therapy studies and is consistent across haemato-oncology and solid tumours (Rotte, et al., 2022; Kirouac, et al., 2024; Li, et al., 2025; Fan, et al., 2026; Wang, et al., 2026). In contrast, dose-response dynamics in engineered T-cell therapy for autoimmune disease follow a different pattern, reflecting lower target burden as compared to cancer, and even lower starting doses of transduced engineered T cells can achieve clinical effect even without massive expansion (reviewed in Kayser & Nagler, 2026). For the purpose of this white paper, we will focus on the dose-response profile for engineered T-cell therapy in oncology.

As discussed above, engineered T cells are living therapeutics. Unlike conventional drugs, the infused T cell numbers will increase due to expansion in response to antigen recognition (Rotte, et al., 2022; Li, et al., 2025; Anelli, et al., 2026). The magnitude of expansion depends on multiple factors, including: heterogenous T cell population in the original product (López-Cantillo, et al., 2022; Kirouac, et al., 2024; Li, et al., 2025), selected lymphodepletion regimen (Lickefett, et al., 2023; Ferry , et al., 2026), and tumour antigen abundance (Kirouac, et al., 2024; Li, et al., 2025; Wang, et al., 2026). Consequently, two patients receiving the same dose may have different magnitudes of T cell expansion, different persistence of engineered T cells, and different clinical benefit. Furthermore, the inconsistency in dosing approaches reported in different studies complicates the interpretation of dose-response relationships (Rotte, et al., 2022; Kirouac, et al., 2024; Li, et al., 2025). Some studies administer a fixed number of cells, whereas others use body weight-based or body surface area-based dosing. In their systematic review, Anand Rotte and colleagues normalised doses from different CAR T-therapy oncology programmes to enable cross-study comparisons (Rotte, et al., 2022). As a result, direct comparison of administered dose across studies should be approached cautiously (Figure 3).

Despite differences in dosing strategies, several observations emerge from the clinical literature. Clinical data across multiple CAR-T and TCR-T therapy programmes have demonstrated that:

- higher administered dose does not always correlate with efficacy (Rotte, et al., 2022; Kirouac, et al., 2024);
- increasing dose above the threshold of efficacy does not improve clinical response (Rotte, et al., 2022; Kirouac, et al., 2024);

- higher doses are associated with increased toxicity (Rotte, et al., 2022; Anelli, et al., 2026);
- expansion of administered T cells *in vivo* is more predictive of response than infused cell dose (Thudium Mueller, et al., 2017; Rotte, et al., 2022; Anelli, et al., 2026).

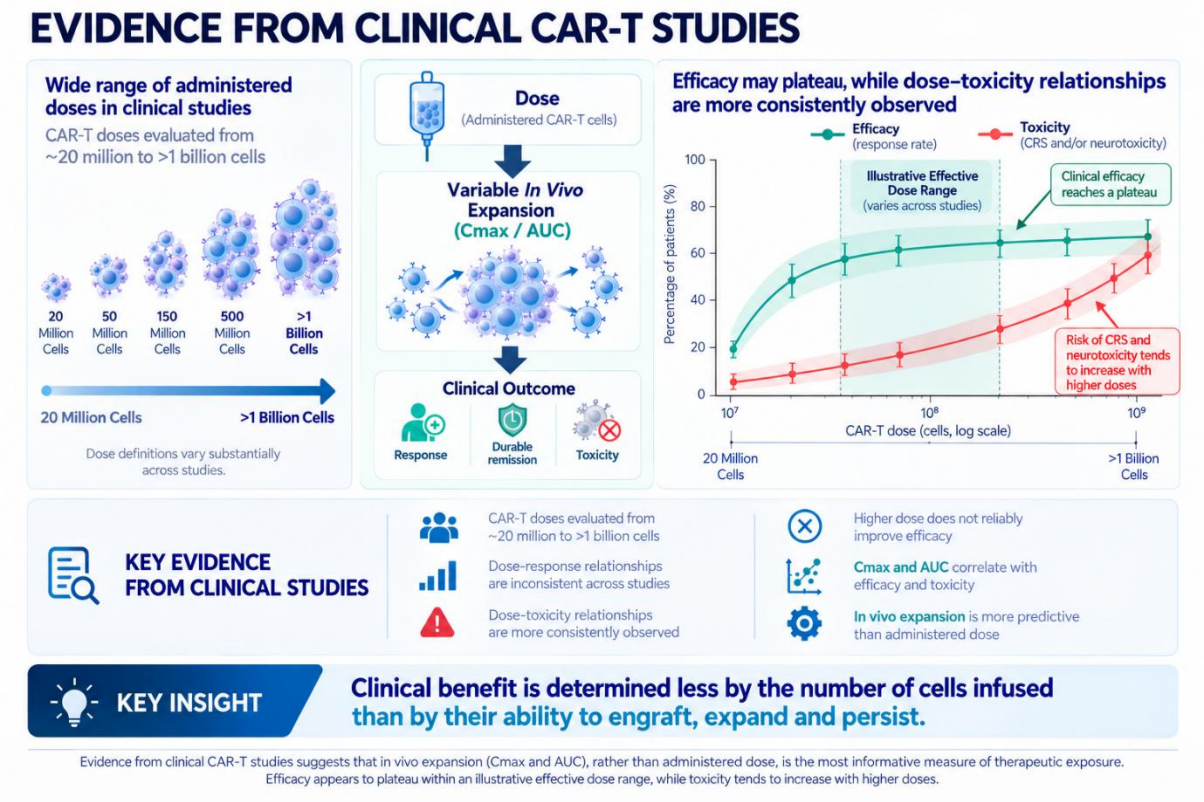


Figure 3. Evidence from Clinical CAR-T Studies demonstrates that in vivo expansion is a stronger determinant of outcome than infused cell dose.

The range of engineered T cell doses reported in the literature (left panel). Expansion of engineered T cells in vivo shows a stronger association with efficacy than infused cell dose (middle panel). Increasing dose above the effective range may increase toxicity without proportionally improving clinical benefit (right panel).

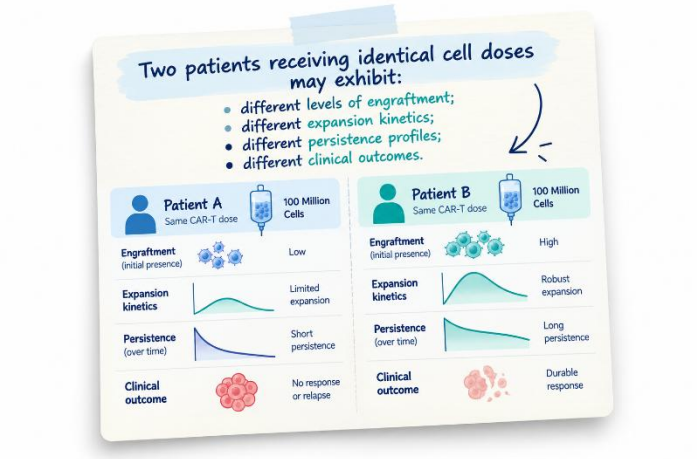
Source: Adapted from concepts reviewed in Thudium Mueller, et al., 2017; Rotte, et al., 2022; Kirouac, et al., 2024; Anelli,et al., 2026).

As summarised in systematic reviews of clinical data from multiple CAR-T and TCR-T programmes by Rotte and colleagues and Anelli and colleagues, there is a therapeutic window in engineered T cell therapies. Increasing the infused cell number above the effective dose range does not improved efficacy, and poses increasing risk of toxicity, including cytokine release syndrome (CRS) and neurotoxicity (Rotte, et al., 2022; Anelli,et al., 2026).

Across both haematological malignancies and solid tumours, engineered T-cell doses have ranged from approximately 20 million to more than 1 billion cells (Rotte,

et al., 2022; Anelli,et al., 2026; Fan, et al., 2026). Despite this wide variability, evidence for a clear dose-response relationship remains limited.

These observations support the concept of a **dose plateau**, introduced by Rotte and colleagues, which postulates that the engraftment and expansion have stronger predictive value than administered dose (Rotte, et al., 2022). Increasing T-cell numbers above the optimal therapeutic dose does not improve the patient response rates but increases the risk and severity of toxicities (Rotte, et al., 2022).



Given that the administered dose alone provides limited predictive value for anti-tumour efficacy, conventional PK metrics were reinterpreted to reflect cellular kinetics that correlate with clinical response (Thudium Mueller, et al., 2017; Kirouac, et al., 2024), and are now recommended by the FDA for clinical pharmacology considerations (U.S. Food and Drug Administration; Center for Biologics Evaluation and Research., 2024):

- **Cmax** measured either by flow cytometry or as copies of engineered T-cell transgene copies per µg of genomic DNA, reflects peak cellular expansion, as opposed to conventional administered exposure (Thudium Mueller, et al., 2017; Kirouac, et al., 2024; U.S. Food and Drug Administration; Center for Biologics Evaluation and Research., 2024), and **Clast,** the last observed measurable concentration (U.S. Food and Drug Administration; Center for Biologics Evaluation and Research., 2024).
- **Tmax** captures the time at which maximal cellular expansion occurred (Thudium Mueller, et al., 2017; Kirouac, et al., 2024; U.S. Food and Drug Administration; Center for Biologics Evaluation and Research., 2024), and Tlast together with the timing of Clast (U.S. Food and Drug Administration; Center for Biologics Evaluation and Research., 2024)
- **AUC** represents cumulative cellular abundance over time (Mueller et al, 2017; Kirouac et al., 2024). The FDA recommends the use of partial AUC (U.S. Food and Drug Administration; Center for Biologics Evaluation and Research., 2024) (FDA 2024).
- **Therapeutic window (**Rotte et al., 2022**), or therapeutic index (**Kirouac et al., 2024**)** is defined by the balance between sufficient cellular expansion and persistence, resulting in optimal efficacy and manageable toxicity. Kirouac and colleagues proposed to quantify therapeutic index for T-cell therapies by examining estimated EC50 values **(**Kirouac et al., 2024**).**

For conventional drugs, a higher dose generally leads to higher exposure.

For engineered T-cell therapies, the biologically relevant exposure is not the administered dose itself but rather the *in vivo* behaviour of the cells following infusion (Thudium Mueller, et al., 2017; Rotte et al., 2022; Kirouac et al., 2024).

Persistence as the new PK endpoint.

Taken together, the expansion and persistence of genetically engineered T-cell therapeutics define the key cellular PK endpoints, as opposed to drug clearance in conventional PK (Thudium Mueller, et al., 2017; Rotte et al., 2022; Mitra, et al., 2023; Kirouac et al., 2024).

Moreover, the manufacturing protocols and genetic construct designs are optimised to enhance T cell function, improve persistence and reduce exhaustion (López-Cantillo, et al., 2022; Mitra, et al., 2023; Li, et al., 2025; Aliciaslan, et al., 2026; Wang, et al., 2026). Persistence of engineered T-cell therapeutics *in vivo* is associated with clinical response (Thudium Mueller, et al., 2017; Rotte et al., 2022; Mitra, et al., 2023; Li, et al., 2025; Aliciaslan, et al., 2026; Wang, et al., 2026), but also with potential late effects, including clonal expansion of engineered T cells (Anelli, et al., 2026).

Long-term follow-up as long-term PK

Long-term follow-up studies are commonly regarded as safety requirements (Queen, et al., 2026; Anelli, et al., 2026). However, longitudinal monitoring may also provide PK-relevant information on cellular persistence, biological fate, and, where assessed, functional state years after infusion (Anelli, et al., 2026; Kirouac et al., 2024).

Long-term follow-up can therefore serve a dual purpose: safety surveillance and extended characterisation of T-cell pharmacokinetics.

Future directions

The emerging field of quantitative pharmacology for living drugs is integrating mechanistic biology with computational modelling to improve prediction of clinical outcomes (Kirouac et al., 2024; Queen, et al., 2026). Technologies likely to shape future PK assessment include liquid biopsy, advanced cellular biomarkers, tissue PK, molecular imaging, ImmunoPET, and systems pharmacology modelling (reviewed in López-Cantillo, et al., 2022; Anelli, et al., 2026). These approaches will be explored in subsequent white papers in this series.

Conclusions

1. Engineered T-cell therapies cannot be adequately described using classical ADME pharmacology.

2. Clinical outcome is determined more by engraftment, expansion, and persistence than by infused dose.

3. Persistence should be considered the defining longitudinal PK endpoint of engineered T-cell therapeutics.

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AI Assistance Disclosure

Microsoft Copilot and ChatGPT (OpenAI) were used to support language refinement, technical editing, structural review, and the development of visual concepts and figures. AI-generated outputs were critically reviewed, edited, and validated by the author. All scientific interpretations, conclusions, and final content decisions remain the sole responsibility of the author.

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