FOLIA MEDICA CRACOVIENSIA
Vol. LXVI, 1, 2026: 43–57
PL ISSN 0015-5616 eISSN 2957-0557
DOI: 10.24425/fmc.2026.158984

CAR-Tography of modeling approaches and opportunities in cellular therapy of cancer

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Abstract: Chimeric Antigen Receptor CAR-T therapy represents a potent adoptive cell immunotherapy for cancer, yet its clinical application remains constrained by pronounced interindividual variability, severe adverse events, and restricted efficacy in solid tumors. Computational modeling has emerged as a critical framework for analyzing and characterizing CAR-T cell behavior to mitigate these clinical limitations. This systematic review synthesizes 20 computational models identified through targeted bibliographic search that were developed using human clinical datasets.

The reviewed studies employ a range of mathematical frameworks, including cellular kinetics and population pharmacometrics models, tumor-immune interaction models, quantitative systems pharmacology approaches, and multiscale mechanistic models. Across these frameworks, CAR-T cells are represented as dynamic populations undergoing expansion, contraction, persistence, and functional exhaustion. Many models further incorporate phenotypic stratification into functional subsets, most commonly effector and memory cells, to capture the multiphasic kinetics observed in clinical settings. Additional variables frequently include tumor burden, antigen expression, host immune cells, cytokines, and CAR-target complexes, reflecting different levels of biological detail and modeling objectives.

Based on this analysis, I propose a unified set of core variables that captures the key biological processes represented across existing models while providing a consistent structure for future modeling efforts. Together, these studies demonstrate that the choice and structure of variables used to describe CAR-T cell populations and their interactions are key determinants of model interpretability and translational relevance. Improved access to longitudinal clinical datasets and phenotype-resolved measurements will be essential for developing more predictive and clinically applicable computational models of CAR-T therapy.

Keywords: CAR-T therapies, cancer models, computational models, pharmacokinetics, immunotherapy.

Submitted: 16-Feb-2026; **Accepted in the final form:** 16-Mar-2026; **Published:** 31-Mar-2026.

Introduction

Cancer is characterized by the uncontrolled proliferation of transformed cells that undergo evolutionary processes driven by natural selection. Its development can be initiated by a wide range of factors, including genetic alterations, pathogenic agents, environmental exposures, and lifestyle-related influences. [1] Despite significant advances in cancer research, the disease remains a major global health challenge, and the development of effective and durable therapies continues to be a critical unmet need.

Chimeric Antigen Receptor (CAR)-T cell therapy is an adoptive cell immunotherapy that involves the genetic modification of patients or healthy donor T cells to express chimeric antigen receptors targeting cancer-associated antigens. These engineered cells are capable of specifically recognizing and eliminating malignant cells, offering a powerful therapeutic option. [2] CAR-T cell therapy has emerged as one of the most transformative approaches in cancer immunotherapy, with several products approved by the U.S. Food and Drug Administration (FDA) for the treatment of hematological malignancies. [3] Some approved therapies include Axicabtagene ciloleucel (Yescarta), Tisangileucel (Kymriah), Brexucabtagene autoleucel (Tecarus), Lisocabtagene maraleucel (Breyanzi), Idecabtagene vicleucel (Abecma) and Ciltacabtagene autoleucel (Carvykti). [4]

Despite these advances, CAR-T cell therapy is still associated with significant challenges. These include substantial interindividual variability in treatment response, difficulties in achieving durable or complete remissions, the occurrence of severe adverse events, and limited efficacy in patients with solid tumors and even those suffering from other hematological malignancies. [5] To address these challenges, computational modeling has emerged as valuable quantitative tool for analyzing and predicting CAR-T cell behavior, and therapy outcomes. [6]

Over the past few years, numerous computational models have been developed to investigate diverse aspects of CAR-T therapy, including the effects of lymphodepleting preconditioning, the role of inflammatory cytokines, exposure-response relationships, and the impact of intrinsic and extrinsic factors on treatment efficacy. Alongside the development of these models, several review articles have been published that comprehensively summarize modeling strategies and provide valuable insights into the current state of computational approaches in CAR-T research.

Chaudhury *et al.* proposed a taxonomy of cellular kinetic models describing the *in vivo* dynamics of CAR-T cells and their interactions with cancer cells. [7] Nukala *et al.* systematically reviewed models focusing on T-cell activation, malignant and host T cells population dynamics, and overall patient survival, with an emphasis on cost-effective therapeutic strategies. [8] Qi *et al.* reviewed models addressing the cellular phases and complex mechanisms of CAR-T therapy, with particular attention to immunological factors influencing treatment efficacy. [9] In 2024, Kirouac, Zmurchok and Morris utilized available CAR-T clinical data to demonstrate how mathematical models can quantitatively address key challenges in CAR-T therapy and support the development of effective clinical strategies. [10] More recently, in 2025, two additional reviews were published. Putignano *et al.* examined how computational approaches can enhance CAR-T therapy design and predict therapeutic outcomes, with a focus on antigen binding and CAR-T cell dynamics. [3] In parallel, Murias-Closas *et al.* emphasized the practical utility of existing models, highlighting that their effectiveness depends less on model complexity and more on the appropriate choice of mathematical framework and the availability of high-quality data. [11]

In this review, I provide a comprehensive and systematic overview of existing computational models of CAR-T cell therapies whose development has been informed by cancer clinical data.

I focus specifically on how CAR-T cell behavior is represented across different modeling frameworks, with particular attention paid to the key variables and assumptions used to describe CAR-T cell dynamics, interactions with cancer, tumor and host cells, and measures of treatment effectiveness. By comparing a range of various modeling approaches, I aim to highlight both common strategies and important differences in how CAR-T therapies are conceptualized and simulated. Finally, I outline future directions for computational modeling, emphasizing the potential role of integrative, data-driven approaches supporting the optimization and personalization of CAR-T cell therapies.

Methods

A systematic literature review was conducted using the PubMed database to identify existing models of CAR-T therapies. An advanced search was employed using the keywords "CAR-T" AND "model" and "CAR-T" AND "computational model." Additionally, selected review articles addressing CAR-T modeling were reviewed to identify further relevant publications. [3, 7, 8, 9, 10, 11] The screening was conducted based on the full text of the identified articles. In total, 49 publications describing CAR-T therapy models were initially identified. These publications were subsequently evaluated for the use of human clinical data from cancer studies, while studies using data for other diseases, as well as those based exclusively on preclinical or other non-clinical data were excluded. As a result, 20 models met the inclusion criteria and were included in the final analysis.

Results

Sources and characteristics of clinical data

Clinical data form the foundation of computational models of CAR-T therapies, enabling quantitative descriptions of cell kinetics, treatment response, and interindividual variability to calibrate, validate, and assess the clinical relevance of these models. The reviewed studies relied on diverse clinical datasets covering multiple cancer indications and CAR-T cell constructs.

The majority of analyzed models were informed by hematological malignancies, including B-cell acute lymphoblastic leukemia (B-ALL), chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), large B-cell lymphoma (LBCL), non-Hodgkin lymphoma (NHL), mantle cell lymphoma (MCL), and multiple myeloma (MM) study data. [5, 6, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22] Several studies focused on chemotherapy-resistant or relapsed/refractory disease, reflecting clinical challenges associated with cancer treatments. [23, 24, 25, 26, 27]

Across hematological malignancies, CD19-targeting CAR-T cells were the most frequently modelled therapies. [13, 14, 15, 16, 17, 18, 19, 21, 24, 25, 26] These investigations focused predominantly on the Axicabtagene ciloleucel (Yescarta) [13, 14, 17, 18, 24] and Tisagenlecleucel (Kymriah) [14, 16, 18, 24, 26] while other utilized Lisocabtagene maraleucel (Breyanzi), [19] the IM19 product [25] and variant constructs including FMC63 or CAT19. [19] Furthermore, some evaluate various anti-CD19 constructs, featuring for example CD28 or 4-1BB co-stimulatory domains. [15, 21]

In multiple myeloma, computational models incorporated clinical data from trials evaluating anti-B-cell maturation antigen (BCMA) CAR-T cells, such as Ciltacabtagene autoleucel (Carvykti), Idecabtagene vicleucel (Abecma). [5, 14, 22, 27] Some studies also included multiple types of therapies, in cases when clinical data were from patients suffering from various malignancies. [5, 6, 12, 14, 20, 23]

Two studies utilized clinical data from allogeneic CAR-T therapies, with one incorporating information on lymphodepleting regimens with fludarabine or alemtuzumab to investigate their effects on CAR-T dynamics. [6, 28] Other models accounted for the management of treatment-related toxicities, including the use of corticosteroids or tocilizumab. [26]

Although less frequent, several models extended to solid tumors. These data were generally more heterogenous and limited in scope, and, in some cases, complemented by imaging-derived measurements, such as MRI data, or by patient-derived cellular data. [29] Models used data from patients suffering from non-small cell lung cancer, glioblastoma, melanoma, ovarian cancer, pancreatic cancer, advanced hepatocellular carcinoma, and metastatic castration-resistant prostate cancer. They addressed a broader range of CAR-T targets, including EGFR, EGFRvIII, IL13Rα2, mesothelin, GPC3, and PSMA. [5, 12, 18, 23, 29]

Administered doses of CAR-T cells varies widely upon analyzed frameworks. Across modeling and clinical studies, total doses generally range from 10^7 to 10^9 cells per patient, with many analyses assuming representative flat doses around 10^8 cells or evaluating discrete levels between $1 \times 10^7$and 2.5×10^8 cells. [5, 6, 13, 14, 18] Several studies also examine specific clinical cohorts such as 6×10^6 to 2.4×10^8 cells or flat dose levels of 50, 150, 450, and 800 million cells. [14, 22, 28] Weight based doing is commonly used in hematological malignancies, typically within 3×10^5 to 3×10^6 cells/kg and broader ranges of $0.2 - 2 \times 10^6$ cells/kg, while other therapies are administered at approximately $0.5 - 2 \times 10^6$ cells/kg. [16, 17, 19, 25, 26, 27] Some models incorporate split infusion regimens of 10, 30, and 60 percent over three days, [6, 24] whereas others scale CAR-T cells dynamics to bone marrow levels. [15] Additional reported scenarios include patient specific doses such as 9.23×10^7 cells or 1.2×10^7 and 1.4×10^6 cells/kg in pediatric cases, [12, 20, 21] as well as body surface area-based regimens in solid tumors ranging from tens to hundreds of millions of cells/m^2 and total doses up to several billion cells. [23] Experimental analyses also evaluate effector to target ratios between 1:5 and 1:20 to study proliferation and exhaustion dynamics. [29]

Across all cancer types, clinical data were obtained directly from early-phase clinical trials, [16, 17, 22, 26, 27, 28] published clinical studies, [5, 6, 12, 15, 19, 20, 21, 22, 23, 24, 25] and patient-level datasets [5, 14, 15, 29] or supplemented with aggregated data from literature. [13, 18, 19] In one case, investigators constructed virtual patient populations based on existing clinical data to capture interindividual variability and the reliability of model predictions. [14] Additionally, some models combined clinical and preclinical data to compensate for limited data availability. [19, 22]

Parameters

The parametrization of the reviewed computational models generally relied on the combination of fixed values derived from existing literature and parameter estimates obtained from the characteristics of the analyzed datasets. [6, 17, 18, 19, 20, 22, 23, 24, 25] In addition to using fixed parameters, Antonini *et al.* applied Bayesian estimation methods including Monte Carlo Integration, Bayesian Inference, and Markov Chain Monte Carlo (MCMC) to estimate kinetic parameters and evaluate different algorithms to determine which provided the most accurate predictions. [12]

Another strategy involved estimating model parameters using both computational and experimental tools. Optimization methods included particle swarm optimization (PSO) based on minimizing the log mean squared error (MSE), the stochastic approximation expectation maximization algorithm for nonlinear mixed-effect modeling (NLME) with fixed and random parameters, and gradient-based optimization via Broyden–Fletcher–Goldfarb–Shanno (BFGS). [5, 13, 14, 15,

16, 20, 26, 27, 28] Moreover, real-time cell analyzer (RTCA) systems were used to obtain dynamic in vitro measurements that directly informed parameter estimation. [29]

Variables

The analyzed models represent diverse approaches to describing the dynamics of CAR-T cell therapy. The choice of modeling framework was primarily determined by the type of available data as well as by the study endpoints. While some models incorporated phenotypic differentiation of CAR-T cell subpopulations such as effector, memory, or exhausted cells, others treated CAR-T cells as a single aggregated variable and focused on their overall activity. A subset of models explicitly accounted for interactions with cancer cells, host immune cells, or both. Although the models varied considerably in complexity and scope, all could capture key mechanisms and clinically relevant outcomes of CAR-T cell therapy (Table 1).

Table 1. Overview of published mathematical models of CAR-T cell therapy across different cancer types, including the original model state variables and their unified categories.

Author, year	Cancer type(s)	Model state variables	Unified variables
Phenotype-structured CAR-T cell models			
Mueller-Schoell *et al.*, 2021 [17]	NHL (DLBCL, PMBCL, TFL)	Naïve CAR-T cells T_N [cells/μL], Terminally differentiated effector CAR-T cells T_{Eff} [cells/μL], Effector memory CAR-T cells T_{EM} [cells/μL], Central memory CAR-T cells T_{CM} [cells/μL], Metabolic tumor volume *CD*19+ [mL]	*I*, *E*, *M*, *T*
Liu *et al.*, 2021 [5]	B-ALL, CLL, DLBCL, MM, NSCLC, GBM	Effector CAR-T cell concentration *E* [copies/μg DNA], Memory-phenotypic CAR-T cell concentration *M* [copies/μg DNA]	*E*, *M*
Paixão *et al.*, 2022 [6]	B-ALL, CLL, DLBCL, MCL	Distributed CAR-T cells C_D [cells], Engrafted (Effector) CAR-T cells C_T [cells], Memory CAR-T cells C_M [cells], Exhausted CAR-T cells C_E [cells], Tumor cells *T* [cells]	*I*, *E*, *M*, *X*, *T*
Kirouac *et al.*, 2023 [14]	CLL, B-ALL, LBCL, MM	Effector CAR-T cells *TE* [cells or cells/ml], Memory CAR-T cells *TM* [cells or cells/ml], Exhausted CAR-T cells *TX* [cells or cells/ml], Tumor B cells *B* [cells or cells/ml], Tumor antigen levels B_A [amount]	*E*, *M*, *X*, *T*
Antonini *et al.*, 2024 [12]	Hematological malignancies	Distributed CAR-T cells C_D [cells], Effector CAR-T cells C_T [cells], Memory CAR-T cells C_M [cells], Exhausted CAR-T cells C_E [cells], Tumor cells *T* [cells]	*I*, *E*, *M*, *X*, *T*
Models incorporating immune interactions and toxicity			
Hardiansyah & Ng, 2019 [24]	CLL, B-ALL	Effector CAR-T cells *CARTE* [cells], Memory CAR-T cells *CARTM* [cells], B-cell tumor burden B_{PB} [cells], Pro-inflammatory cytokines *IL-6*, *IL-10*, *IFN-γ* [pg/ml]	*E*, *M*, *T*, *B*
Derippe *et al.*, 2022 [28]	B-ALL	Stem central memory CAR-T cells T_{SCM} [cells/L], Central memory CAR-T cells T_{CM} [cells/L], Effector memory CAR-T cells T_{EM} [cells/L], Host T cells or NK cells in the *Host*X1 [cells/L], Expanding host immune cells *Host*X2 [cells/L], Interleukin-7 concentrations *IL-7* [pg/mL], Lymphodepleting variables for Alemtuzumab *Alem* [μg/mL] and virtual chemotherapy *FC* [unitless]	*S*, *M*, *H*, *B*, *L*

Table 1. Cont.

Author, year	Cancer type(s)	Model state variables	Unified variables
Phenotype-structured CAR-T cell models			
Santurio *et al.*, 2025 [21]	B-ALL, CLL, MM	Injected CAR-T cells C_I [cells], Expander CAR-T cells C_E [cells], Persister CAR-T cells C_p [cells], Antigen-positive tumor cells T_P [cells], Antigen-negative tumor cells T_N [cells], Naïve macrophages M_i [cells], Activated macrophages M_a [cells], Interleukin-6 blood concentration *IL6* [pg/mL]	I, A, M, T, H, B
Models addressing antigen resistance and heterogeneity			
Liu *et al.*, 2022 [15]	B-ALL	Non-activated CAR-T cells n_{TN} [cells], Activated CAR-T cells n_{TA} [cells], CD19+ B-ALL cells n_P [cells], CD19- tumor cells n_N [cells]	*I, A, T*
Santurio *et al.*, 2024 [20]	B-ALL, ALL, CLL, MCL, DLBCL	Effector CAR-T cells C_T [cells], Memory CAR-T cells C_M [cells], Antigen-positive tumor cells T_P [cells/antigen], Antigen-negative tumor cells T_N [cells/antigen]	*E, M, T*
Predator-prey and tumor-immune interaction models			
Sahoo *et al.*, 2020 [29]	GBM	CAR-T cells *Y* [cells or cell index], Cancer cells *X* [cells or cell index]	*E, T*
Kimmel *et al.*, 2021 [13]	LBCL, *applicable to CLL, B-ALL, MCL	CAR-T cells *C* [cells/μL], CD19+ tumor cells *B* [cells], Normal T cells *N* [cells/μL]	E, T, H
Owens & Bozic, 2021 [18]	DLBCL, CLL, Metastatic Melanoma	CAR-T cells *C* [cells], Tumor cells *T* [cells], Endogenous effector cells *E* [cells], Chemotherapy concentration *M* [μM]	*E, T, H, L*
Multiscale mechanistic models			
Singh *et al.*, 2021 [22]	MM	Effector CAR-T cells $CAR - T_e$ [cells], Memory CAR-T cells $CAR - T_M$ [cells], CAR-target complexes C_{plx} [complexes/cell], Total tumor cells *Tumor* [cells], Serum M-protein *M – protein* [pg/mL], Soluble BCMA *sBCMA* [pg/mL]	*E, M, C, T, B*
Salem *et al.*, 2023 [19]	ALL, DLBCL	Effector CAR-T cells *E* [cells/L or cells/μL], Terminal effector CAR-T cells T_{Eff} [cells/L or cells/μL], Stem-cell memory CAR-T cells T_{SCM} [cells/L or cells/μL], Memory CAR-T cells *M* [cells/L or cells/μL], Central memory CAR-T cells T_{CM} [cells/L or cells/μL], Effector memory CAR-T cells T_{EM} [cells/L or cells/μL], CAR-target complexes C_{mplx} [complexes/cell], Tumor cells *Tumor* [cells/L or cells/μL]	*E, S, M, C, T*
Minnuci *et al.*, 2024 [25]	B-cell NHL	Infused CAR-T cells T_{inf} [nmol], Activated CAR-T cells T_{act} [nmol], Effector CAR-T T_{eff} [nmol], Memory CAR-T cells T_{mem} [nmol], Free CAR receptors *CAR* [nmol], Bound CAR-target complexes *CAR:CD19* [nmol], Antigen-expressing malignant cells *Tumor* [nmol], Endogenous lymphocytes *Endo* [nmol], Free CD19 antigen receptors m_{Ag} [nmol]	*I, A, E, M, C, T, H*

Table 1. Cont.

Author, year	Cancer type(s)	Model state variables	Unified variables
Phenotype-structured CAR-T cell models			
Parmar *et al.*, 2025 [23]	B-cell lymphoma, MPM, OVCA, PDAC, HCC, mCRPC	Effector CAR-T cells C_e [cells/L], Memory CAR-T cells C_m [cells/L], CAR-target complexes C_{TE} [number of complexes], Antigen-expressing tumor cells V^{TAA} [L], Antigen-negative tumor cells V^{NO-TAA} [L], Host T lymphocytes R [cells/L], Virtual lymphodepleting therapy A [virtual units]	E, M, C, T, H, L
Population and pharmacometric models of CAR-T kinetics			
Mueller *et al.*, 2018 [16]	B-ALL	Observed transgene levels of CAR-T cells in copies/μg of genomic DNA	
Stein *et al.*, 2019 [26]	B-ALL	Observed transgene levels of CAR-T cells in copies/μg of genomic DNA, as a sum of effector CAR-T cells E and memory CAR-T cells M	
Wu *et al.*, 2022 [27]	MM	Observed transgene levels of CAR-T cells in copies/μg of genomic DNA, as a sum of fast-eliminated CAR-T and sustained CAR-T subpopulations	

Legend: I — Infused/Initial CAR-T cells (Distributed, Naïve, Injected, Non-activated, Infused), A — Activated/Proliferating/Expander CAR-T cells, E — Effector/Engrafted CAR-T cells (active tumor-killing population) [in case of only CAR-T cells, assumed Effector], S — Stem-cell memory CAR-T cells, M — Memory CAR-T cells (Central, Effector, Persister), X — Exhausted CAR-T cells (Non-functional), C — Complexes CAR-Target, T — Tumor/Cancer cells and tumor-related variables (unified all malignant cells/solid tumors, antigen positive/negative cells), H — Host cells (T cells, NK cells, Macrophages), B — Biomarkers (Cytokines, Soluble proteins), L — Lymphodepletion/chemotherapy

Phenotype-structured CAR-T cell models

A major group of models represents CAR-T cells as multiple phenotypic compartments to capture multiphasic expansion–contraction profiles, functional maturation, and long-term persistence. Paixão *et al.* developed an ordinary differential equation (ODE)-based model aimed at establishing a biological foundation for multiphasic kinetics of CAR-T. CAR-T cells were represented as phenotypic subpopulations, including distributed (C_D), effector (C_T), memory (C_M) and exhausted (C_E). By incorporating tumor cells (T) variable, the authors described the CAR-T cell life cycle during therapy, in which distributed cells undergo activation, engraftment and differentiate into active effector cells. Tumor persistence stimulates CAR-T cell expansion but also promotes differentiation into a memory pool that supports long-term persistence or transition into an exhausted state due to chronic stimulation. [6]

Building upon this framework, Antonini *et al.* introduced Bayesian parameter estimation to optimize patient-specific model calibration. They evaluated several MCMC algorithms, including Metropolis-Hastings, DEMetropolis, and DEMetropolisZ, to address sparse clinical data and interindividual variability. While retaining the same mathematical description of CAR-T cell dynamics, their work emphasized the probabilistic nature of biological interactions, thereby providing an option for personalized treatment planning. [12]

Liu *et al.* focused on retrospective characterization of multiphasic CAR-T cell kinetics to identify factors influencing proliferation and persistence. Their immune-dynamic model included effector (*E*) and memory (*M*) CAR-T cell compartments. Effector cells were assumed to undergo exponential expansion upon antigen recognition. Following tumor clearance, a fraction of effector cells differentiated into long-lived memory cells, while the remaining population underwent activation-induced cell death. [5]

Phenotypic differentiation was also incorporated by Kirouac *et al.* in an antigen-driven toggle switch ODE model integrated with machine learning techniques. This study focused on deconvoluting clinical variability and predicting patient outcomes based on pre-infusion CAR-T product transcriptomes. CAR-T cells were classified as memory (*TM*), effector (*TE*) differentiated into non-cytotoxic effector (*TE*1) and cytotoxic effector cells (*TE*2), and exhausted cells (*TX*). The model additionally included variables describing B-cell tumor burden (*B*) and tumor antigen levels (B_A), which drive the transition of memory cells into expanding non-cytotoxic and subsequently cytotoxic effector populations. Persistent tumor burden leads to chronic antigen stimulation and CAR-T cells exhaustion, whereas effective tumor lysis by effector cells reduces antigen levels and enables regeneration of the memory compartment. [14]

A distinct approach was proposed by Mueller-Schoel *et al.* who developed a quantitative systems pharmacology (QSP) framework for early survival prediction. CAR-T cells were represented as naïve (T_N), central memory (T_{CM}), effector memory (T_{EM}), and terminal effector (T_{Eff}) cells, alongside metabolic tumor volume variable (*CD*19+). The model demonstrated maturation of CAR-T cells from naïve to central and effector states, with proliferation and differentiation driven by metabolic tumor volume. All phenotypes except terminal effector cells contributed to tumor reduction through nonlinear cytotoxic killing mechanisms. [17]

Models incorporating immune interactions and toxicity

Several mechanistic frameworks explicitly incorporated host immune compartments and inflammatory mediators to explain variability in CAR-T expansion and the emergence of clinically relevant toxicities. Derippe *et al.* applied a mechanistic modeling approach to quantify the interplay between lymphodepletion, homeostatic cytokines, and the host immune system in the context of allogeneic CAR-T cells kinetics. CAR-T cells were represented as stem central memory (T_{SCM}), central memory (T_{CM}), and effector memory (T_{EM}) subpopulations in blood and tissue compartments. Additional variables included host T or NK cells (*HostX*1), expanding host immune cells (*HostX*2), interleukin-7 (*IL* – 7) concentration, lymphodepleting agent alemtuzumab (*Alem*), and virtual chemotherapy (*FC*). The model demonstrated that host immune cells recognize and eliminate allogeneic CAR-T cells. However, lymphodepletion reduces host cell abundance, thereby increasing the availability of homeostatic cytokines such as IL-7, which in turn enhances CAR-T cell expansion and persistence. [28]

Cytokine dynamics were also incorporated in the model developed by Santurio *et al.*, who used a multilayer mechanistic approach to characterize the temporal development of macrophage-mediated cytokine release syndrome (CRS), a common toxicity associated with CAR-T therapy. CAR-T cells were divided into injected (C_I), expanding (C_E), and persisting (C_P) subpopulations. The inclusion of antigen-positive and antigen-negative tumour cells (T_P, T_N), naïve and activated macrophages (M_i, M_a), and IL-6 concentrations allowed the authors to demonstrate that tumour cell killing releases damage-associated molecular patterns (DAMPs), which activate naïve macrophages.

Furthermore, interactions between CAR-T cells and macrophages establish a positive feedback loop that drives excessive IL-6 secretion by activated macrophages, potentially leading to CRS. [21]

Hardiansyah and Ng developed a QSP model to quantify the relationships between CAR-T cell dose, disease burden, and systemic inflammatory responses. CAR-T cells were represented as effector (*CART E*) and memory (*CART M*) populations in blood and tissue compartments. By incorporating malignant B cells (B_{PB}) and cytokines such as *IL-6, IL-10*, and *IFN-γ*, the model demonstrated that effector CAR-T cells expand upon interaction with malignant B cells, triggering localized secretion of pro-inflammatory cytokines. Importantly, the results indicated that cytokine peak levels correlate more strongly with baseline tumour burden than with the administered CAR-T cell dose. [24]

Models addressing antigen resistance and heterogeneity

A smaller but conceptually important set of models extended tumor dynamics to include antigen-negative or low-antigen phenotypes, enabling the study of immune escape under therapeutic pressure.

Several studies focused on antigen resistance and heterogeneity. Liu *et al.* developed a nonlinear mixed-effects ODE model to predict late responses to CAR-T therapy. CAR-T cells were described as activated (n_{TA}) and non-activated (n_{TN}), while tumor cells were divided into antigen-positive (n_P) and antigen-negative (n_N) populations. Activated CAR-T cells proliferated while eliminating antigen-positive tumor cells. Therapeutic pressure shifted the tumor population toward antigen-negative cells, which evade direct CAR recognition but may be partially eliminated via bystander killing mediated by lysis of neighboring antigen-positive cells. [15]

In complementary study, Santurio *et al.* investigated how a continuous distribution of antigen density on the tumor surface influences resistance development and treatment outcomes. CAR-T cells were described as effector (C_T) and memory (C_M) cells. Tumor cells were distributed along a continuous antigen expression variable (x), with state variables representing densities of antigen-positive and antigen-negative tumor cells at antigen level x (T_P, T_N), as well as the total tumor population (T). CAR-T-mediated therapeutic pressure induced a reversible phenotypic drift, whereby tumor cells temporarily downregulated antigen expression to evade immune attack and returned to homeostatic levels as CAR-T cell pressure declined. [20]

Predator-prey and tumor-immune interaction models

To reduce model dimensionality while retaining interpretability, several studies adopted predator-prey or tumor-immune interaction structures that focus on mutual stimulation, cytotoxicity, and exhaustion.

A subset of studies employed predator–prey frameworks to describe CAR-T cell behavior. Kimmel *et al.* developed a tumor extinction model incorporating CAR-T cells as a cumulative variable (C), normal T cells (N) and antigen-presenting tumor cells (B). CAR-T cells and endogenous T cells competed for a limited homeostatic carrying capacity, with CAR-T cells acting as predators. Therapeutic success depended on CAR-T cells driving tumor cells to stochastic extinction before being outcompeted by the recovering host immune system. [13]

In the modified Lotka–Volterra CARRGO model, Sahoo *et al.* focused on deconvoluting the proliferation and exhaustion rates of CAR-T cells to better understand treatment efficacy in solid

tumors. The model described interactions between CAR-T cells (Y) and cancer cells (X) as the only state variables. Cancer cells acted as a stimulus for CAR-T cell expansion while simultaneously serving as a driver of functional exhaustion. Using this framework, the authors demonstrated that lower CAR-T cell doses were associated with higher per-cell tumor killing efficiency but led to more rapid exhaustion of the CAR-T cell population. [29]

Owens and Bozic adapted the tumor–immune interaction model originally proposed by Kuznetsov *et al.*, [30] to assess the impact of preconditioning on CAR-T therapeutic success. In this ODE system, CAR-T cells (C) expanded and eliminated tumor cells (T), while chemotherapy (M) reduced tumor burden and endogenous effector cells (E), thereby decreasing competition for resources. [18]

Multiscale mechanistic models

Multiscale models link CAR-T pharmacology and trafficking with tumor burden and biomarkers, allowing CAR-target binding and tissue distribution to be reflected in systemic kinetics and efficacy. There have also been models developed within frameworks ranging from molecular receptor binding to whole-body physiology.

Parmar *et al.* developed a physiologically based pharmacokinetic–pharmacodynamic (PBPK–PD) model to characterize CAR-T cell trafficking and anti-tumor activity in solid tumors, explicitly accounting for host immune competition as well as the effects of lymphodepletion. The model described vascular (CV) and extravascular (CEV) CAR-T concentrations across organs, CAR–target complexes (C_{TE}), host T cells (R), antigen-positive (V^{TAA}) and antigen-negative tumor cells (V^{NO-TAA}). In this framework, CAR-T cells extravasate from the blood into tissue interstitial spaces and recirculate via lymphatic flow. Molecular engagement with antigen-expressing tumor cells leads to the formation of CAR–target complexes, driving CAR-T expansion and tumor cell depletion, while recovering host T cells compete for immunological space. [23]

In the work of Singh *et al.*, the objective was similar, aiming to establish a quantitative relationship between CAR affinity, antigen abundance, and tumor depletion in order to characterize CAR-T cell activity. In this mechanistic PK–PD model, effector ($CAR - T_e$) and memory ($CAR - T_M$) cells were assessed in blood and bone marrow, together with CAR–target complexes (C_{plx}), total tumor cells (*Tumor*), and soluble biomarkers like serum M-protein and soluble BCMA. CAR-T cells rapidly distributed to the bone marrow, which represents the site of action, where interaction with BCMA led to complex formation. These interactions drove effector proliferation and differentiation into a persistent memory pool while inducing tumor cell lysis, which was monitored through reductions in biomarker levels. [22]

Salem *et al.* developed a multiscale mechanistic cellular kinetic–pharmacodynamic (CK–PD) model to describe *in vitro* and *in vivo* CAR-T cell dynamics in patients with cancer. The model included CAR-T cells stratified into CD4+ and CD8+ subsets and further differentiated into stem cell memory (T_{SCM}), central memory (T_{CM}), effector memory (T_{EM}), effector (E) and terminal effector (T_{Eff}) immunophenotypes, distributed between peripheral blood (PB) and bone marrow (BM) compartments. Additional state variables included CD19+ tumor cells (*Tumor*), as well as CAR–tumor target complexes (C_{mplx}) formed upon antigen engagement. CAR-T cells interacted with tumor cells through the formation of CAR–target complexes, which simultaneously drove tumor cell killing and CAR-T cell expansion. Expansion was restricted to early immunophenotypes, while CAR-T cells progressively transitioned toward terminal effector states over time. Tumor

depletion reduced antigen availability, thereby modulating CAR-T expansion, contraction, and long-term persistence through feedback between tumor burden and immunophenotypic composition. [19] CAR-T cells were described in a similar manner by Minucci *et al.* in a semi-mechanistic CK–PD model that directly linked molecular-scale receptor binding to systemic T cell kinetics and tumor growth. In this approach, the receptor binding fraction dictated the rates of naïve cell activation and effector-mediated tumor killing. Activated cells underwent multiple divisions to form the cytotoxic effector CAR-T cell pool, which subsequently transitioned into the CAR-T cell memory state. [25]

Population and pharmacometric models of CAR-T kinetics

Finally, population and pharmacometric models prioritize statistical characterization of CAR-T exposure profiles and covariate effects, supporting exposure-response and exposure–safety analyses. Other models focus primarily on pharmacometric and population-based cellular approaches to describe these processes. Wu *et al.* developed a two-compartment population PK model to support exposure–safety and efficacy analyses. Their model assessed CAR transgene copies in a rapidly eliminated CAR-T compartment and a sustained CAR-T compartment. A series of transit compartments and an empirical lag time were used to represent the delay between infusion and measurable transgene levels in the blood. Following expansion, the model described a biphasic decline, in which a fraction of cells was rapidly eliminated while the remaining cells transitioned into a sustained state. [27]

Stein *et al.* developed a nonlinear mixed-effects (NLME) cellular kinetic model to characterize CAR-T cell kinetics and evaluate the impact of anti-inflammatory comedications (tocilizumab and corticosteroids) on expansion rates. The model captured exponential growth of CAR transgene copies driven by antigen binding, followed by biexponential contraction. [26] Similarly, Mueller *et al.* applied noncompartmental cellular kinetic analysis and population modeling to evaluate the impact of CAR-T therapy on clinical outcomes. [16]

Discussion

The utility of computational models represents a significant step toward understanding the complexity of CAR-T cell therapy. The majority of existing models rely on ordinary differential equations (ODEs) to describe interactions between therapeutic and cancer cell populations, spanning a wide range of frameworks, from empirical compartmental models to advanced quantitative systems pharmacology (QSP) and physiologically based pharmacokinetic (PBPK) approaches. Notably, the field has undergone a clear methodological shift from purely descriptive models aimed at fitting observed concentration-time profiles toward mechanistic frameworks that incorporate prior biological knowledge and explicitly account for interindividual variability.

The primary strength of mechanistic models lies in their ability to provide biologically interpretable insights into cellular populations and their interactions within the context of human physiology. These models enable exploration of causal relationships underlying treatment response, persistence, toxicity, and resistance. However, their major limitation remains parameter identifiability, as such models typically require high-quality, information-rich datasets to reliably reproduce clinically relevant outcomes. In contrast, empirical models are structurally simpler and more flexible, allowing them to accommodate heterogeneous datasets collected across different

studies, time points, and patient populations. Nevertheless, their limited biological resolution restricts their ability to support mechanistic interpretation of therapeutic failure, resistance, or disease relapse.

Across modeling frameworks, CAR-T cells are commonly described through phenotypic differentiation into functional subsets, most frequently effector, memory, and exhausted populations. Some models further refine this representation by distinguishing between expanding and persister cells or by explicitly incorporating antigen specificity. Such phenotypic stratification enables accurate representation of the multiphasic CAR-T cell kinetics observed clinically across different malignancies. Moreover, this approach facilitates identification of intrinsic cellular determinants that may influence patient outcomes.

A key challenge in accurately modeling these processes is the limited availability of longitudinal clinical data that directly quantify CAR-T cell phenotypic subsets. Commonly used bioanalytical methods, such as qPCR and flow cytometry, often provide measurements of total CAR-T cell abundance rather than detailed phenotypic resolution. Consequently, many models rely on fixed parameters or literature-based assumptions to resolve identifiability constraints, which may introduce uncertainty regarding model structure and the biological accuracy of the framework.

Conclusions

This review provides a focused synthesis of how CAR-T cell behavior is represented in computational models developed using human clinical data. Across a wide range of mathematical frameworks, from empirical cellular kinetic models to multiscale QSP and PBPK-PD approaches, CAR-T cells are consistently conceptualized as dynamic, interacting populations whose expansion, contraction, persistence, and functional exhaustion critically determine therapeutic outcomes. By systematically comparing these representations, this work highlights both common modeling strategies and key conceptual differences in how CAR-T cell dynamics are formalized.

A central conclusion of this review is that phenotypic stratification of CAR-T cells has emerged as a unifying principle for capturing clinically observed multiphasic kinetics. More detailed frameworks further extend this representation to include functional roles such as antigen-driven state transitions, and compartment-specific behaviors. These modeling choices enable the translation of clinical observations into quantitative descriptors of CAR-T cell functionality and support interpretation of treatment outcomes.

Importantly, this study demonstrates that the choice of CAR-T cell representation, rather than the overall mathematical complexity of the model, largely determines its interpretability and applicability. Models that align the level of CAR-T cell description with available clinical data and study objectives offer the greatest translational value. In contrast, increasing biological detail without adequate data support may limit parameter identifiability and reduce predictive robustness.

Looking forward, the continued refinement of CAR-T cell representations will depend on improved access to longitudinal, phenotype-resolved clinical data and standardized reporting of cellular measurements. Integration of emerging data modalities, combined with modeling strategies, is expected to further enhance the ability of computational models to support optimization and personalization of CAR-T cell therapies. Ultimately, unified frameworks for robust and biologically grounded representations of CAR-T cells will be essential for translating computational modeling into applicable tools for the clinical development and application of cellular immunotherapies.

Conflict of interest

None declared.

Abbreviations

ALL — acute lymphoblastic leukemia
B-ALL — B-cell acute lymphoblastic leukemia
CLL — chronic lymphocytic leukemia
DLBCL — diffuse large B-cell lymphoma
GBM — glioblastoma
HCC — hepatocellular carcinoma
LBCL — large B-cell lymphoma
MCL — mantle cell lymphoma
mCRPC — metastatic castration-resistant prostate cancer
MM — multiple myeloma
MPM — malignant pleural mesothelioma
NHL — non-Hodgkin lymphoma
NSCLC — non-small-cell lung cancer
OVCA — ovarian adenocarcinoma
PDAC — pancreatic ductal adenocarcinoma
PMBCL — primary mediastinal B-cell lymphoma
TFL — transformed follicular lymphoma

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