A Review of the Efforts and Hindrances of Modeling and Simulation of CAR T-cell Therapy

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Chimeric Antigen Receptor (CAR) T-cell therapy is an immunotherapy that has recently become highly instrumental in the fight against life-threatening diseases. A variety of modeling and computational simulation efforts have addressed different aspects of CAR T therapy, including T-cell activation, T- and malignant cell population dynamics, therapeutic cost-effectiveness strategies, and patient survival analyses. In this article, we present a systematic review of those efforts, including mathematical, statistical, and stochastic models employing a wide range of algorithms, from differential equations to machine learning. To the best of our knowledge, this is the first review of all such models studying CAR T therapy. In this review, we provide a detailed summary of the strengths, limitations, methodology, data used, and data lacking in current published models. This information may help in designing and building better models for enhanced prediction and assessment of the benefit-risk balance associated with novel CAR T therapies, as well as with the data collection essential for building such models.

Keywords: CAR T-cell therapy, Simulations, Mathematical model, Statistical model, Survival analysis, Cost-effectiveness.

1. INTRODUCTION

Despite recent therapeutic advances in treating cancer, issues such as variable treatment responses, high rate of relapse, and poor prognosis in relapsed/refractory (r/r) cancers continue to be major challenges. The Chimeric Antigen Receptor (CAR) T-cell therapy is a promising form of adoptive immune cell therapy. Patient T-cells are genetically modified to express CAR, consisting of a surface antigen-targeting antibody single chain variable fragment (scFv) fused to a signaling domain of the T cell receptor (TCR). These genetically-modified T-cells target and eliminate cancer cells expressing specific antigens. Since its first in vitro proof of concept demonstration on mouse MD45 cells in 1989 (1), CAR T-cell therapy has evolved significantly and has recently become available for medical use for a subset of cancer types and patients. In 2017, via Breakthrough Therapy Designation, the first autologous CAR T-cell therapies, tisagenlecleucel (tisa-cell) (KYMRIAH) (2) and axicabtagene ciloleucel (axi-cell) (YESCARTA) (3) for treating patients with hematological malignancies were approved, followed by the recent approval of brexucabtagene autoleucel (TECARTUS) in 2020 and all were enthusiastically received. The increasing interest in CAR T therapy is evident from the number of clinical trials; more than 700 registered CAR T therapy-based clinical trials were listed on ClinicalTrials.gov by the end of October 2020. CAR T-cells targeting different cancer types, including solid tumors of the liver, brain, breast (e.g. ClinicalTrials.gov identifier: NCT02541370), lung, pancreas (such as NCT02349724, NCT01869166), and many others (4), as well as infectious diseases (5), are in developmental and evaluation stages.
Modeling and its Importance for CAR T-Cell Therapy

Mathematical models have been widely used in biological and medical research. These models generate or validate hypotheses from experimental data, predict different possible outcomes through *in silico* simulations and are among the most prominent methods used to study several aspects of diseases, such as the interplay of complex immune responses and drugs/biologics (6, 7). Different modeling approaches can be considered to explore issues in drug development, including but not limited to disease progression (8-12), immune response to immunotherapy (13-17), and others (18-22). FDA’s recent Model-Informed Drug Development Pilot Program facilitates the development and application of exposure-based, biological, and statistical models derived from preclinical and clinical data sources. It also uses a variety of quantitative methods to help balance the risks and benefits of drug products in development (23).

Cancer biology involves complex dynamic interactions of cancer cells with their surrounding tissue microenvironment. Understanding the dynamics and interactions between the tumor cells, and the human immune system provides insight into how specific interventions such as immunotherapy aid in fighting cancer (24). Several mathematical models, statistical analyses, and computational tools have been proposed to analyze the cellular kinetics, cost-effectiveness, and patient survival statistics of CAR T-cell therapy specifically. These models have become instrumental in understanding the complex dynamics and interactions involved in CAR T-cell therapy.

There have been reviews highlighting, for instance, the use of mathematical models in cancer (25) and demonstrating the utility of ordinary differential equation-based mechanistic models to study T-cell activation (26). Notably, Markaryan et al. (25) provided a very detailed description of proposed models covering single cells, multicellular interactions, and multiscale/spatio-temporal frameworks to better understand the complex tumor microenvironment. However, no reviews focus strictly on modeling efforts for CAR T-cell development. This review of the computational models studying various aspects of CAR T-cell therapy could help modelers and immunologists better understand currently available models, associated issues and potential solutions; for example, what kinds of data can be collected during clinical trials that are useful in developing a model assessing the benefit-risk of CAR T-cell therapy or are helpful in efficient management of the adverse effects.

Literature Search Methodology

Using a customized search query developed by an expert FDA librarian, we conducted a literature search of five scientific publication databases (PubMed, Embase, Web of Science, Google Scholar and BioRxiv) limiting the search to English language and identified 360 articles. The authors UN, MRM, and ONY after removing duplicates and carefully reviewing all article titles and abstracts, selected 28 articles for this indepth review. These 28 articles were selected as they were studying different aspects of CAR T-cell therapy (such as therapeutic efficacy, safety, and cellular kinetics) using various types of modeling and simulation approaches (found using keywords such as probabilistic, mathematical, statistical, and predictive). The authors UN, MRM, ONY, and XW independently prepared article summaries which were later discussed, compared and condensed. Models that focused on molecular dynamics (MD) simulations of CAR molecules were considered beyond the scope of this review and excluded. Details of our custom search query and systematic literature search can be found in the supplementary text along with expansions of all acronyms used in this article.
2. CAR T-CELL MODELING AND SIMULATION EFFORTS

In this section, we review modeling and simulation approaches assessing different dimensions of CAR T-cell therapy. Each article is unique in terms of its model/algorithms type, the data (at population, individual patient, or cellular levels), and modeling tools. In Table 1, we list the articles that we reviewed in detail, and in Figure 1 we show various modeling and simulation efforts studying different aspects of CAR T-cell therapy.

![Figure 1: Modeling and simulation efforts in the CAR T-cell therapy field. A. Areas of mathematical model development for the improvement of CAR T-cell therapy. B. Mathematical modeling approaches to address different aspects of CAR T therapy. Deterministic models developed using ordinary differential equations (ODEs) were used to describe the change of cell populations over time; and partial differential equations (PDEs) described the change of cell populations over time and space. Some ODE-based models include QSP, Pharmacokinetic and Pharmacodynamic models. Stochastic models are implemented through a set of ODEs with the addition of variables/parameters that change randomly. These models, in general, can also be executed with machine learning approaches. Statistical models were developed using regression and decision tree analysis, ANOVA, Partial Least Squares, Bayesian theory. Models to study patient-survival and therapy cost-effectiveness were statistical models.](image-url)

2.1. Modeling approaches for CAR T-cell product characterization

The optimization and standardization of CAR T-cell production is important in achieving favorable safety and efficacy profiles and ensuring cost-effectiveness of treatment. Strategies to improve CAR T-cell-
mediated antitumor immune response include modifying different parts of the CAR molecule, optimizing 
*ex vivo* T-cell manufacturing conditions, manipulating anti-apoptotic and cytokine genes involved in T-cell 
survival, and reversing T-cell exhaustion (27).

Computer models and simulations help to quantify and characterize the highly complex interplay between 
CAR T-cell product properties and patient outcomes.

**2.1.1. CAR Molecules and Models of CAR T-Cell Activation Signaling Cascade:**
CAR T-cells can be directly activated via CAR in an HLA-independent manner, unlike TCR-redirected T-cells. 
A CAR molecule consists of an intracellular signaling domain and an extracellular antigen-recognizing 
domain (ARD). As described in Figure 1A, the extracellular domain carries a single chain variable fragment 
(scFv) antibody that is designed to bind to the target antigen. The CAR intracellular domain consists of a 
signaling domain, CD3ζ, which is derived from human TCR. This is the structure of the first generation of 
CARs. The next generations of CARs are equipped with a co-stimulatory domain, either CD28 or 4-1BB 
(second generation) or both CD28 and 4-1BB (third generation), in addition to the CD3ζ signaling domain, 
providing them with better proliferative capacity, tumoricidal activity, and increased cytokine secretion 
(28). The fourth-generation CARs are additionally equipped with inducible expression cassettes for a 
transgenic protein (e.g., a cytokine). Studying the underlying mechanisms of activation of CAR T-cells 
compared to natural response of TCR in human immune system and the factors governing their expansion 
may be instrumental in optimizing CAR design and *ex vivo* expansion of CAR T-cells. There is also an 
immense need for better understanding of the downstream signaling networks in receptor modified CAR 
T-cells in order to extend the CAR T-cell therapies beyond hematological malignancies.

The CAR containing the signaling domain CD3ζ has six tyrosine phosphorylation sites arranged in pairs on 
three immunoreceptor tyrosine-based activation motifs (ITAMs), which when doubly phosphorylated, 
become activated, bind to the signaling proteins and perpetuate downstream signaling. Several modeling 
studies have attempted to better understand ITAM activation and subsequent downstream signaling. One 
study used CD3ζ phospho-tyrosine specific antibodies (29) while another study used synthetic peptides, 
each containing one ITAM tyrosine to measure the preference of lymphocyte-specific protein tyrosine 
kinase (LCK) for each site (30). The third study experimentally measured the total protein phosphorylation 
for CD3ζ with individual ITAM mutations (31, 32). However, these studies did not account for the 
competitive factors that influence site-specific phosphorylation and are not validated with site-specific 
phosphorylation data.

Second-generation CAR T-cells have shown improved expansion and persistence *in vivo* (33). The 
mechanism of recruitment and competition for LCK by CD28 can alter the phosphorylation of CD3ζ 
affecting the downstream signaling. This downstream signaling controls T-cell activation responses 
including cytotoxicity, cytokine production, proliferation and persistence. All of these should be better 
understood. Rohrs et al. (34) studied the kinetics of CD3ζ and CD28 phosphorylation in detail by 
quantitatively measuring the site-specific phosphorylation of CAR proteins by LCK over time, using 
phospho-proteomic mass spectrometry and quantifying the differences between the phosphorylation 
kinetics of the 10 tyrosine sites. Their ODE-based mechanistic model is experimentally parametrized and 
validated on the upstream portion of the CAR T intracellular signaling network using an *in vitro* liposomal 
system quantified with mass spectrometry. The authors found that LCK phosphorylates CD3ζ through a 
competitive inhibition mechanism, and that CD28 sites are phosphorylated by LCK at a slower rate than 
those of CD3ζ. Phenomenologically, the best representative model was selected out of four candidate 
models aiming to explain the tyrosine phosphorylation sites of the CD3ζ-CD28 construct. These candidate
models are publicly available. With the selected model, Rohr's group generated and tested new predictions regarding the mechanisms by which LCK phosphorylates CD3ζ ITAMs and identified the mechanism of competitive inhibition by which the phosphorylated and unphosphorylated tyrosine sites could interact while competing with each other. Overall, the mechanisms generated using this model may help to better engineer quicker phosphorylating CARs, for optimal activation of T-cells.

Cess and Finley (35) investigated the impact of intracellular protein expression level heterogeneity on the CAR T-cell activation and the efficacy of CAR T-cell therapy. The team applied partial least-squares (PLS) technique to encode the Monte Carlo simulation results of their previously-developed nonlinear ODE-based mechanistic model of chimeric antigen receptor (CAR) T-cell signaling. Their simulation pipeline uses a set of initial concentrations of 23 proteins, allowing for unphosphorylated proteins, e.g., extracellular-signal-regulated kinase (ERK), proteins with varying levels of phosphorylation, free proteins, and various protein complex species. The researchers were able to find that only the expressions of proteins relating directly to the receptor and the mitogen-activated protein kinase (MAPK) cascade, the upstream and downstream of the reaction network, respectively, are relevant to a T-cell's response. Also, they predicted that increasing the number of available receptors can inhibit a cell's ability to respond due to increasing strength of negative feedback from phosphatases.

Additionally, Cess and Finley demonstrated the influence of cell-to-cell heterogeneity in protein expression levels on the activation of CAR T-cells, in their article. Their predictions can be validated against ex vivo data and used to help select and develop the “best” CAR T-cells for patient treatment. On the other hand, the type of modeling in (35) might have limitations such as overfitting due to high number of parameters, and the PLS technique assumes linear relationships between inputs and outputs. The authors claim, there was a reasonable approximation of linear relationship because of their PLS model’s high accuracy, although collinearity tests are typically necessary to demonstrate and ascertain such a result.

In another article, Rohrs and colleagues generated an experimentally testable hypothesis, and developed a larger mechanistic mathematical model of a CAR T-cell activation signaling cascade to better understand the system (36). This is one of the first, detailed (23 proteins), experimentally-parametrized, and validated mechanistic models of the CAR T intracellular signaling network. By combining different models from the literature which study the various signaling networks, the authors predicted that CD28 primarily influences ERK activation by way of recruitment of LCK, which increases the kinetics of CD3ζ activation. Since these models are based only on part of the intracellular signaling network, we do not know the extent of the impact of other relevant proteins that were not included in the model, but which may play important roles in T-cell activation. Also, from the ensemble model, it is not immediately clear how having alternative CAR constructs would alter the cellular activation. The models were not validated with in vivo data, which makes knowing their predictive power in real-world patient treatment scenarios difficult.

Harris et al. (37) employed ODE-based mathematical modeling to better understand and contrast the sensitivity and signaling capacity of T-cells with CARs and T-cells with TCRs in mouse cells. The research team found that although CAR cell membrane surface expression was 10-fold higher than that of ordinary TCRs, they were 10–100-fold less sensitive than TCRs. Mathematically modeling demonstrated that lower CAR sensitivity could be attributed to less efficient signaling kinetics, including reduced kinetic proofreading rate, reduced activation rate, or a combination of both mechanisms. Furthermore, reduced cytokine secretion observed at high antigen density for both TCRs and CARs suggested a role for negative regulators in both systems. Interestingly, at high antigen density, CARs compared to TCRs lead to secretion of 1.5 to 2-fold higher levels of IL-6. The use of modeling alongside in vitro experiments makes this article
compelling. However, we do not know how the model predictions change for the human T-cells binding therapeutically relevant antigen targets (e.g., CD19).

2.1.2. Modeling the Impact of CAR T-cell Characteristics on In Vivo Expansion and Persistence:
Studies of cellular kinetics play an important role in understanding the expansion and persistence of the cells and in optimizing a safe and efficacious dose. Although the cellular kinetics of CAR T-cells targeted against cells in peripheral blood have been studied, the CAR T-cell kinetics targeted against cells in extranodal/extramedullary sites require further study.

Using data from the JULIET phase 2 clinical study (NCT02445248), Awasthi et al. (38) performed correlation analysis of the cellular kinetics of tisa-cel in peripheral blood, to the safety/efficacy endpoints in adult patients with r/r DLBCL, where the primary locations of tumor cells are in lymph nodes or the extranodal/extramedullary sites. The data from the JULIET study demonstrated that patients with sustained responses showed longer persistence of CAR T-cells compared to non-responders. It is important to understand factors that influence this varied CAR T expansion and persistence among patients. Awasthi et al. (38) analyzed the correlations between in vivo cellular kinetics and product characteristics, intrinsic/extrinsic factors, and tumor characteristics (CD19 expression, baseline tumor burden). Their analysis has shown that the geometric mean of tisa-cel expansion in the peripheral blood is nearly 6-fold lower in DLBCL compared to B cell acute lymphoblastic leukemia (ALL) based on data from ELIANA clinical study. This could be due to the CAR T-cell trafficking to target tissues in DLBCL that may result in a longer half-life compared to B-ALL, in which the target cells are present predominantly in the blood. Additionally, to understand dose-response for efficacy or safety, correlation analysis of tisa-cel dose and exposure (i.e., AUC) was performed and no relationship was found between the dose and the peak expansion, or exposure of CAR T-cells; as CAR T-cells could undergo rapid multilog expansion beyond the initial infused dose. Moreover, they found no association between the baseline tumor burden and the CAR T-cell kinetics. This finding may be due to CAR T-cells possibly trafficking to the loci of target cells. Target accessibility and accessible antigen amount may also play a role in the differential CAR T-cell expansion. Also, the transgene levels measured in the blood may not actually represent the overall CAR T-cell expansion and may not fully reflect the CAR T-cell interaction with the target at the tumor site. After adjusting the baseline tumor burden, there was no significant correlation between dose and severe cytokine release syndrome (sCRS).

In another study, Finney et al. (9) analyzed the relationship between therapeutic outcomes (such as duration of leukemia-free survival and B cell aplasia) and product features (e.g., phenotype, function, and expansion of CAR T-cell) using Cox Regression and classification tree models. Their analysis showed that the initial failures of therapy were associated with reduced CAR T-cell expansion and/or rapid attenuation of functional CAR effector cells after adoptive transfer. This suggests that treatment outcome may be predictable based on measurable CAR T kinetics, thus patient management can be adjusted accordingly; however, Finney, et al. did not provide adequate results from their analysis.

2.2. Models for evaluating CAR T-cell therapy safety and efficacy

CAR T-cell therapy has yielded unprecedented efficacy with sustained remissions in patients with refractory cancers. Two-year follow-up data from the international single-arm, multicenter ZUMA-1 clinical trial showed 58% (n = 59/101) of patients had a complete response, suggesting that axi-cel can induce a median overall survival of more than two years (39). A phase-2 clinical trial of tisa-cel in pediatric patients showed an overall response rate of 81.3% (n = 61/75) (39). In addition, a meta-analysis of 38
published clinical studies including 665 patients treated with CAR T-cells for ALL, chronic lymphocytic leukemia (CLL), and B cell lymphomas showed an overall pooled response rate (RR) of 72%. The response rate for ALL, CLL, and lymphoma was 81%, 70% and 68%, respectively (40).

Unfortunately, common life-threatening, immune-mediated adverse events are associated with CAR T therapy. Cytokine release syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) (41) are two such adverse events; however, they may be controlled by anti-inflammatory treatments, such as IL-6 inhibitors and corticosteroids. Another serious adverse event attributable to CAR T therapy is the on-target, off-tumor toxicity (OTOT), which depletes healthy cells that express the target surface antigen. Manifestation of OTOT in patients with successful anti-CD19+ CAR T therapies is B cell aplasia, which significantly increases the risk of developing such fatal infections as hepatitis B (42). Intravenous or subcutaneous administration of immunoglobulins is the standard treatment for B cell aplasia. These adverse events may be linked to a CAR T-cell mechanism of action; however, development of CAR T toxicity management algorithms and risk mitigation strategies have significantly decreased the number of deaths due to CAR T therapy (21, 43, 44). Anti-CD19+ CAR T-cell therapy is not uniformly effective for disease remission, and relapse was observed after a short period in a significant proportion of treated patients. Several factors may impede CAR T therapy efficacy, such as tumor antigen escape and the heterogeneity in tumor antigen expression profile. CAR T-cells are designed to be fully functional and have antitumor activity, although their short-term active state is among many other barriers to successful CAR T therapy, and their poor persistence is inversely correlated to the effective antitumor immune response.

The regulatory assessment of CAR T therapies remains challenging since CAR T-cells are a living drug with therapeutic outcomes that are variable and highly patient-specific. Although, CAR T-cell therapy has yielded unprecedented efficacy with sustained remissions in cancer patients with refractory diseases, there are several factors which may impede CAR T therapy efficacy or increase the risk of life-threatening immune-mediated adverse events. Utilizing mathematical predictive models, it may be possible to identify the factors that govern non-uniform CAR T-cell therapy efficacy and safety. Also, those models may be able to identify patients who are more likely to have successful therapeutic outcomes with tolerable toxicities, or those who may be at a risk of relapse or sCRS, so that risk mitigation strategies can be planned, possibly reducing the complications related to CRS symptoms and mortality rate. Though CAR T-cell therapy has demonstrated remarkable antitumor efficacy in treating B cell malignancies, its use in treating solid tumors remains in early stages of clinical development. The variety of CARs for treating different types of solid tumors, different target patient populations, and different preconditioning regimens makes determining the factors critical for CAR T-cell efficacy challenging (20). In this section, we summarized mathematical or pharmacokinetic models (using data either from animal models or clinical studies) focused on studying the interplay between tumor cells and CAR T-cells and/or the cytokines to help predict the efficacy and safety outcomes of CAR T-cell therapy.

Sahoo et al. (19) developed a simple ODE-based predator-prey mathematical model describing the temporal interplay of glioma and CAR T-cells by using in vitro assays and in vivo patient data, enabling better understanding of the relative impacts of cell proliferation, killing and exhaustion on the outcomes of CAR T therapies. This study is a valuable one, as the model validation and parametrization were performed using both in vitro cell-killing assays and in vivo clinical trial data from a glioblastoma multiforme (GBM) patient. Use of a simple mathematical model built using knowledge of CAR T was helpful in this application to describe and understand CAR T-cell therapy dynamics. The authors’ mathematical analysis showed that the model can simulate three scenarios: (1) successful CAR T-cell
treatment, (2) CAR T-cell treatment failure, and (3) pseudo-failure or pseudo-response (i.e., model-predicted coexistence of CAR T and target cells). This prediction is consistent with clinical observations in which the cancer initially progressed during therapy before finally responding. The model results suggest that the balance between proliferation and exhaustion of CAR T-cells may contribute more to treatment success or the failure than the rate of CAR T-cell-mediated cancer cell killing. Nevertheless, their model is a variation of the classic Lotka-Volterra predator-prey model. It only captured the simple dynamics observed from the data in their experiment, and parameter estimates are uniquely determined by their experiment. This model may not work in other in vitro assay conditions or when the model incorporates more complex dynamics. Moreover, the change in the electrical impedance to non-invasively quantify the adherent cell densities, measured as cell index, cannot differentiate cell detachment from cell killing, and this system is not a direct measurement of CAR T-cell dynamics. The intracavitary and intraventricular injections potentially result in spatially heterogeneous densities of CAR T-cells. Therefore, using the modeling assumption of well-mixed cell populations and tumor spheroids might not be easily justified. Application of spatial methods can be a more suitable modeling direction. Last, this model does not include cytokines, stromal cells, or additional immune cells (e.g., myeloid cells which contribute to CAR T-cell activity in vivo).

Through the lens of mouse models, de Jesus Rodrigues and colleagues (13) developed a simple ODE-based mathematical model that describes the temporal interplay of mouse cancer cells and CAR T-cells by using in vivo data in order to better understand the relative impacts of cell proliferation, killing, and tumor immunosuppressive environment on the outcomes of CAR T therapies. Their proposed model can represent the three phases of the therapy: tumor elimination, equilibrium, and escape. It provides an in silico tool for assessing tumor burden-dependent CAR T-cell dosing, CAR T-cell infusion protocols, and immunosuppressive tumor mechanism. Their model is built not only on known biological mechanisms (dynamics of the tumor, CAR T effector, and memory T-cells), but also on mouse data presented (45, 46) for different receptor types (CART 4-1BB or CART 123), and different tumor targets such as HDLM-2 and RAJI. In general, their model can be adapted to different treatment and tumor scenarios and can help predict therapy efficacy. However, this model does not include cytokines and concurrent therapeutics such as tocilizumab, corticosteroids, or checkpoint inhibitors and parametrization was performed on mouse model data.

Kimmel et al. 2019 (15) developed a hybrid ODE-based mathematical model that describes the interplay of malignant CD19+ B cells and CAR T-cells in order to better understand the relative impacts of cell proliferation and killing of malignant cells on overall CAR T therapy efficacy. With their model, they predict that clinical interventions before CAR T therapy could improve the likelihood and timing of durable responses in decreasing tumor mass. Another model prediction was an increase in memory CAR T-cell fractions (fraction of CCR7+ cells), leading to lower progression-free survival (PFS) rates. This deterministic mathematical model is well described and easy to understand. One limitation, however, is the lack of clinical trial validation, even though the parametrization was performed on clinical trial data. The focus is on CAR T efficacy, but cytokines are not included in the model. Code for the simulations is not available, which makes replication of the results challenging. Finally, the phenomenon of immune evasion of cancer cells was not considered.

The most frequently-seen adverse effect of CAR T-cell therapy is CRS; however, little is known about the underlying biology of this syndrome. An increased understanding could help to better predict risk and improve mitigation strategies so the associated serious complications can be prevented. Two such studies
were conducted by Teachey et al. (21) and Hopkins et al. (14), in which these authors identified the cytokines associated with CRS and the cytokine inhibitor targets to alleviate it.

Teachey et al. measured cytokines and clinical biomarkers in 51 patients, including 39 children (5–23 years) and 12 adults (25–72 years) with r/r ALL treated with tisa-cel, and identified that the peak levels of 24 cytokines in the first month after CAR T-cell infusion were associated with sCRS (21). Although these cytokines were associated with CRS, their levels are not predictors of which patients will develop CRS. The authors developed and analyzed 16 predictive models using either regression or decision tree modeling and were able to predict which patients developed grade 4–5 CRS. Using their top regression model, they accurately predicted which patients would develop sCRS using a signature composed of three cytokines, including IFNγ, sgp130 and sIL1RA. These predictions could help in early interventions, thus decreasing morbidity and mortality in CAR T-treated patients. Teachey et al. tested the predictive accuracy of their models both with cytokines alone and cytokines along with initial tumor burden measured from bone marrow aspirates of pediatric cohorts immediately prior to CAR T-cell infusion. They found that incorporating the initial tumor burden into their regression model did not increase predictive accuracy; however, the tumor burden was identified as an important predictive variance in their decision tree model. Model accuracy was validated using 12 additional pediatric patients. The authors also characterized the effects of tocilizumab on CRS, showing that CRS is mediated by trans-IL-6 signaling, which is abrogated after tocilizumab treatment. The findings in this study provide a step forward in predicting severity of CRS and the general cytokine dynamics, even though patient-level cytokine kinetic data was not made available to readers.

Hopkins et al. (14), on the other hand, used a set of ODEs to better understand the inhibitor/inductor mechanisms of nine cytokines important in CRS and to propose optimized CRS treatment strategies. The authors advanced a model of cytokine dynamics during CRS, published earlier by Yiu et al. (47), and analyzed the model parameter sensitivities. They were able to design a novel CRS grading system that facilitated the selection of targets for inhibitors to lessen CRS. This grade reduction was achieved with insight obtained from the local sensitivity analysis showing the best targets. The clinical trial dataset used to train the model is based on a “passive” medication (i.e., an antibody drug). The model cannot be readily applicable to a cell therapy such as CAR T because the cells are alive and proliferating, unlike the cytokine network studied in this article.

Although the CAR T-cell dose, tumor burden, and T-cell expansion kinetics were thought to be associated with the severity of CRS, the quantitative relationship between these factors and occurrence of CRS had not been studied until recently. In 2019, Hardiansyah and Ng (48) established the first Quantitative Systems Pharmacology (QSP) model that used clinical data to quantify the complex relationships among CAR T doses, disease burden, and cytokines in human subjects and to gain relevant insight into the determinants of clinical toxicity/efficacy in the development of CAR T-cell therapy. This model included CAR T-cell subsets (i.e., effector and memory), B cells, and inflammatory cytokine (IL-6, IL-10 and IFNγ) components. It predicted that the expansion of CAR T-cells and the elimination of B cells are more correlated with disease burden than is the administered CAR T dose. This is the first mechanistic model of its kind to study the relationship between CAR T dose, tumor burden, and CRS using clinical data. It can be a good prototype on which to build a more comprehensive CAR T model and can be reproduced using the ODE published in the paper; however, data from only two patients was used to develop the model.

An ODE-based mathematical model was developed by Hanson et al. (11, 18) that describes the interplay of malignant CD19+ B cells and CAR T-cells in order to better understand the relative impacts of cell
proliferation, killing of malignant cells, and cytokine secretion rates on overall CAR T therapy outcomes. This model made it possible to conduct an in silico randomized controlled trial (sRCT) to help understand why inter-patient variation can give rise to a range of clinical responses observed in CAR T-cell therapy and to develop treatment protocols possibly having a higher likelihood of success in different patient populations. These in silico trials identified a patient subgroup which might not have been ideal candidates for CAR T therapy. They also demonstrated mechanistically that small differences in initial tumor burden and other patient-specific parameters can result in large differences in therapeutic outcomes and showed correlation between toxicity and initial tumor burden but not with CAR T-cell dose. Also, when no memory cells were in infused CAR T-cells, toxicity is lower on average, but could result in earlier malignancy relapse. However, the predictions of the model were not validated using clinical trial data, and only a single cytokine was modeled.

George and Levine (10) developed a stochastic modeling framework of co-evolution of the cancer cells, the immune system, and biotherapeutics (e.g., CAR T-cells) in order to evaluate several key factors (e.g., cancer cell immune evasion) impacting disease prognosis. Their model predicted immunotherapy success probabilities considering immune turnover, antigen escape, and immune adaptive repertoire. A specific prediction was that in acute myeloid leukemia (AML), CAR T therapies have a higher probability of success than cancer vaccines. They also predicted that AML incidence would increase as immunity decreases with age and with use of a chronic immunosuppressor. This simple yet high-quality modeling framework helped evaluate the interplay between cancer immunotherapies and cancer progression and immune evasion. The availability of the code and the dataset increases the reproducibility of the model’s predictions. However, assumptions about the model do not include variations of cancer subtype such as antigenicity, T-cell infiltration, and sub-clonal neoantigen landscape. A model including these variables might provide a better prediction of immunotherapy efficacy.

The inclusion of cytokines and other lymphocytes would be a critical step in modeling the CAR T-cell therapies, and Mostolizadeh et al. (16) developed an ODE-based mathematical model including these components for modeling CAR T therapy efficacy and safety. They analyzed the model to identify dosage and patient conditions that would result in the optimal therapeutic outcome. The model was analyzed with respect to its equilibrium points, which gives certain guidance on the various outcomes of the CAR T therapy, depending on the initial conditions. Authors applied optimal control theory to their model and identified the optimal dosage of anti-cytokine drug and CAR T-cells with respect to safety and efficacy. However, the model was limited by a lack of clinical and experimental validation and was not able to determine the relationship between tumor burden and CAR T-cell proliferation. Healthy and malignant B cells were killed at different rates by CAR T-cells, and no explanation was provided to justify these rates.

2.3. Pharmacokinetic models
This section reviews CAR T-cell pharmacokinetic modeling studies. These studies used either population data or individual-patient data; both are instrumental in understanding the disparities in CAR T-cell therapy outcomes, in identifying the covariates that influence variability, and in quantitatively estimating the variability commonly seen in CAR T-cell therapy. The typical pharmacokinetic components, including distribution, metabolism and excretion, are not directly applicable to CAR T-cells, as CAR T-cells proliferate in vivo after they are infused. Hence, studying the cellular kinetics of CAR T-cells refers to their in vivo characterization (49). Several studies have attempted to identify the relationships between the cellular kinetics of CAR T-cells and their efficacy and safety.
To elucidate the relationships among CRS, tumor burden/cell expansion, and response; Mueller et al. (49) for the first time characterized the in vivo cellular kinetics of CAR T-cell therapy across multiple diseases. They did this by pooling data from three different clinical trials (n=103) including pediatric B-ALL, adult ALL, and CLL patients that received either a single dose of CTL019 or two to three fractionated doses within the first 28 days, using noncompartmental analyses in Phoenix WinNonlin 6.4 (Certara, Princeton, NJ, USA). The authors observed a transient decline in circulating CAR T-cells immediately after peak infusion levels due to the distribution of the cells throughout the peripheral blood (PB), bone marrow (BM), and other tissues. Cellular kinetic analyses have shown that the patients with longer CAR T-cell persistence maintained longer event-free survival. The expansion and cellular kinetic profile in adult ALL were consistent with that of pediatric B-ALL. In pediatric B-ALL, adult ALL and CLL, CAR T-cells were present at higher levels in BM and for a longer time in responding patients compared to nonresponding patients.

Mueller evaluated the effect of tumor burden on cell expansion, CRS, and neurological events in pediatric B-ALL. The analysis showed an increased expansion in patients with higher pre-infusion tumor burden, and an association of higher CRS grade and neurological events with greater tumor burden and higher expansion. In patients with ALL, a correlation between peak CAR T-cell and cytokine levels was seen during the first 28 days. It was demonstrated that tocilizumab has not abrogated the CAR T-cell expansion, supporting its possible use in safely treating patients with sCRS. Although these analyses help in understanding the relationships between CAR T cellular kinetics and various other factors in patients with ALL and CLL, such as the association of continuation of therapeutic efficacy and with CAR T-cell persistence, these observations may not be applicable to other malignancies (e.g., non-Hodgkin lymphoma) because CAR T-cell kinetics can be disease-specific. Moreover, other factors that might affect these relationships and the T-cell mediated cell killing were not integrated into the assessment and prediction of the responses in this study. These factors include functional capacity of a patient’s own T-cells, characteristics of a patient’s tumor cells, the location of the tumor, and the tumor environment.

In a subsequent study addressing some of these factors, Mueller et al. (50) analyzed the effect of patient factors, humoral immunogenicity, manufacturing attributes, exposure-response analysis for safety, and efficacy assessment of tisa-cel in 79 pediatric B-ALL patients from two clinical studies, ELIANA and ENSIGN. The authors observed that following infusion, the pharmacokinetic profile of tisa-cel was characterized by distribution, expansion, contraction, and persistence stages. The dose-exposure analysis showed dosage is not correlated with peak plasma concentration (C_{max}) or the 28-day area under the concentration curve (AUC_{0-28d}). Tisa-cel expansion (C_{max} and AUC_{0-28d}) was positively associated with clinical response, and higher C_{max} was associated with occurrence and severity of CRS. Tisa-cel was observed to continue to expand and persist following administration of tocilizumab and corticosteroids. Preexisting anti-mCAR19 antibodies and treatment-induced/boosted anti-mCAR19 antibodies did not affect the expansion or cellular kinetics and therapeutic response. The blood to bone marrow partitioning suggested that CAR T distribution in bone marrow was 44%, 67%, and 68.8% of that present in blood on day 28, and months three and six, respectively. The type of lymphodepletion regimen did not affect expansion and persistence of the transgene. Logistic regression analysis of the relationship between tisa-cel dose and CRS showed there was no impact of CAR T dose on the probability of grade 3 or 4 CRS. The authors determined the CD4:CD8 ratio in the final product for the ELIANA study and the relationship between clinical response, safety, and in vivo expansion was evaluated. These analyses presented a similar CD4:CD8 ratio of infused CAR T between responding and non-responding patients, showing that in vivo expansion is independent of initial CD4:CD8 ratio. However, this model is an empirical one based on observed PK profile of tisa-cel and is not physiology-based.
Stein and colleagues (51) have developed the first nonlinear mixed-effect semi-mechanistic model-based approach to investigate the different peak tisa-cel levels and the impact of tocilizumab and corticosteroids on the rate of CAR T-cell expansion, based on two phase-2 clinical studies, ELIANA and ENSIGN, including pediatric and young adult r/r B cell ALL patients. Doubling time, initial decline half-life, and the terminal half-life of tisa-cel were reported to be 0.78, 4.3, and 220 days, respectively. The authors observed no impact of tocilizumab or corticosteroids on CAR T-cell expansion rate, supporting Mueller et al.’s observations (49, 50); however, the model estimated $C_{max}$ was 2-fold higher in patients who received tocilizumab. Although some patients received multiple doses of tocilizumab and corticosteroids, only impact of the first dose was modeled and the interaction term between tocilizumab and corticosteroids was not included in the model. Furthermore, the effect of corticosteroids at higher doses before or without tocilizumab were not modeled. Yet, this model can be adapted to characterize the expansion and persistence of different types of CAR T-cells manufactured for different indications.

A mechanism-based translational PK-PD model developed by Singh et al. (52) integrated key drug-specific and system-specific parameters into a quantitative framework in order to understand the PK-PD determinants of CAR T-cells. Those authors employed a stepwise, bottom-up approach. In the first step, a cell-level PD model was developed integrating the effects of CAR affinity, CAR-densities, antigen densities, and E:T ratios (to compute the rate and determine the extent of saturable tumor cell killing), as well as CAR T expansion, cytokine release, and data from comprehensive set of in vitro experiments used to account for the dynamic E:T ratio due to T-cell expansion, key drug-specific determinants like CAR-affinity, CAR-density and system-specific determinants like antigen density. This cell-level model captured the quantitative impact of the drug-specific parameters on the overall CAR T-cell activities in vitro.

In the second step, the authors developed a PBPK model to characterize the biodistribution of untransduced T cells, anti-EGFR CAR T-cells, and anti-CD19 CAR T-cells in all major tissues, including spleen, liver, and lungs. In the third and final step, an integrated PBPK-PD model was developed to characterize the rapid expansion of CAR T-cells in blood and the observed inhibition of tumor growth. Using this translational modeling framework, based on overall comparison of potency parameters across different CAR constructs, authors established an in vitro to in vivo correlation, and that the in vitro potency values were consistently 10–20-fold higher than in vivo potency values. These model simulations suggested that CAR T-cells may have a steep dose-exposure relationship, and the apparent $C_{max}$ upon CAR T-cell expansion in blood may be more sensitive to patient tumor burden than to CAR T dose levels. Simulations also suggested that upon formation of threshold CAR-target complexes per tumor cell, there is increased expansion of CAR T-cells, leading to increased tumor cell eradication. This comprehensive physiologically-based, pharmacokinetic-pharmacodynamic (PBPK-PD) model developed using in vitro and in vivo data can be used to evaluate efficacy/safety in anti-EGFR, anti-HER2, anti-BCMA, and anti-CD19 CAR T-cells. The model simulations were performed using Stochastic Approximation Expectation Maximization (SAEM) algorithm of Monolix version 8 (Lixoft) and the authors have made the model code available in their paper. However, the model was not validated on clinical (human studies) data, and by itself is limited by the value of its training in vitro and in vivo data.

2.4. Statistical survival models for patients undergoing CAR T therapy
To estimate the long-term overall survival of patients with DLBCL treated with axi-cel, Bansal et al. (8) compared the standard parametric models to mixture cure models. This study demonstrated that the traditional parametric survival models can underestimate the overall survival with CAR T-cell therapy because there is a substantial variability in the extent and timing of patient responses to CAR T. Although both the standard and mixture cure models showed successful fitting to the currently available data (up
to about two years’ follow-up), the two models differed substantially in their extrapolated survival outcomes beyond two years. For example, the 10-year survival probability predicted by the mixture cure models was 0.5, while standard models predicted probability of less than 0.2. As this is a statistical model, the model parameters were estimated using clinical trial data. However, the model forecasts currently cannot be validated due to small sample size and short follow-up periods in the clinical trials of CAR T therapies, and long-term survival/efficacy/safety of the patients are unknown. Also, they focused only on one study, which raised concerns that the predictions may not be easily reproduced. The code for their model was not made available, but implementation of the model using the equations in the article is straightforward.

Grant et al. (53) provided a detailed analysis on the fitness of cure models when predicting patient survival data. The authors simulated a case study of virtual patients based on actual disease progression rates reported in the literature. They simulated CAR T therapy survival data and analyzed the goodness of fit of non-mixture and mixture cure models to evaluate the usefulness of cure modeling in cancer survival prediction. The authors showed how real-life data could affect survival predictions made by cure modeling. Particularly, their results suggest that cure modeling techniques should not be used if the real-life survival data is immature (i.e., early phase in a clinical trial with insufficient follow-up). On the other hand, unnecessarily long follow-up periods in a dataset may involve age-related mortality as a potential confounder for the model. The optimal time point to use cure modeling is disease-specific, and clinician input is necessary in finding that time point. However, the conclusions of this study are specific to the data generated in it, and applying the techniques used in this paper to immature data could result in inaccuracy of the cure fraction.

2.5. Pharmacoeconomic models
Often, the information pertaining to long-term benefits and risks of CAR T-cell therapies is limited, which makes determining cost-effectiveness of CAR T therapy difficult. More importantly, the clinical trials that led to CAR T-cell therapy approvals, and many ongoing trials, are single-arm trials. Pharmacoeconomic models are important evidence-based tools in forecasting and evaluation of CAR T-cell therapy outcomes and are a means of justifying therapeutic cost-effectiveness. Pharmacoeconomic models can be used to simulate single-arm clinical trials to evaluate the efficacy and safety of CAR T with respect to standard line of therapy. Results of these model simulations provided long-term projections on product benefit and risk, along with treatment costs. The long-term clinical outcomes are not readily available from clinical trials with limited follow up periods. Here, we summarize the pharmacoeconomic studies developed to determine the cost-effectiveness of CAR T-cell therapy and their advantages and disadvantages.

Using Markov cure/survival modeling, Lin et al. (54) determined the cost-effectiveness of tisa-cel for pediatric B cell ALL patients versus the standard line of therapy. This model provided a sequence of important milestones in the outcomes of pediatric r/r ALL patient populations that receive CAR T therapy or chemotherapies using detailed patient and product attributes informed by clinical trials. The cost-effectiveness analysis of tisa-cel was conducted for multiple scenarios using a well-informed model. Based on their analysis, the authors recommended a reduction in the price of tisa-cel (from $475,000) to $200,000 or $350,000, allowing the therapy to meet a $100,000/quality-adjusted life year (QALY) or $150,000/QALY willingness-to-pay threshold in all outcome scenarios. One limitation similar to other models is lack of high-quality long-term clinical outcomes data. Another issue was that all trials for relapsed or refractory pediatric ALL were single-arm studies, which limit a direct comparison between tisa-cel and standard-line therapy. Additionally, the authors did not account for tisa-cel’s non-health care
benefits, such as future productivity, which may be substantial given the young age at which patients are treated.

Using a multi-state survival model, Furzer et al. (55), using data of 192 patients from three pooled clinical trials and 118 patients from the cancer registry of Canada, quantified the value of tisa-cel compared with current standard care for eligible pediatric patients with relapsed ALL. Even though the authors were unable to use a randomized clinical trial dataset due to unavailability, they incorporated sensitivity analyses to demonstrate the robustness of their cost utility analytic results. They found an incremental cost per QALY gain of tisa-cel over standard care (US $53,933–$213,453) based on assumed cure rates of 40%–10%. Like similar models, this type of modeling would provide higher estimating precision as long-term outcomes data becomes available.

Using a very detailed microsimulation cure/survival modeling framework, Sarkar et al. (56) determined the cost effectiveness of tisa-cel for pediatric B cell ALL patients with regard to the standard line of therapy. The model produced outcomes of progression, survival, and toxicity similar to estimates in the literature. Cost-effect analysis was most sensitive to assumptions of long-term CAR T survival, proportion of CAR T patients achieving complete remission, and health utility of post-treatment patients. Their probabilistic sensitivity analysis found that CAR T was cost-effective in 94.8% of iterations at a willingness to pay $100,000/QALY. Also, if one-year survival was decreased to 57.8%, then CAR T was predicted to no longer be cost-effective. This type of modeling has limitations. First, due to lack of long-term data on survival, cost, role of hematopoietic stem cell transplantation (HSCT) after CAR T, and complications, the findings in this article could vary as more data becomes available. Second, the quality of data used to inform this model of cost-effectiveness should be from a randomized phase 3 trial comparing CAR T therapy to the standard of care. This research was based on the available data without information about how patients not responding to CAR T would respond to chemotherapy afterward, as the authors assumed that patients had similar responses to chemotherapy as those who initially did not receive CAR T therapy.

Whittington and colleagues (12) estimated the long-term survival of r/r leukemia patients younger than 25 who used tisa-cel, and then estimated the actual value of tisa-cel based on long-term survival rates using a mixture cure model and a decision analytic model including a short-term decision tree and a long-term semi-Markov partitioned survival model. They parametrized the model using published literature on therapeutic (CAR T and clofarabine) safety and efficacy outcomes and the pertinent economic parameters. The study suggests that tisa-cel in pediatric patients with B-ALL provides clinical benefits in quality-adjusted and overall survival compared with clofarabine, and that tisa-cel seems to be priced in alignment with its clinical benefits.

In their recent study, Whittington and colleagues (57), estimated the long-term survival of adult r/r non-Hodgkin lymphoma patients who used axi-cel, and then estimated the actual value of axi-cel based on long-term survival rates with respect to standard chemotherapy. Treatment with axi-cel appeared to be associated with positive, yet uncertain, gains in survival compared with chemotherapy, and more cost-effectiveness because of better long-term survival. However, the predictions from this model cannot currently be validated, as not enough patients with sufficiently long follow-up periods are available. Also, there is no data from randomized controlled trials directly comparing CAR T therapies against chemotherapies. However, when building and parametrizing their model, the authors assumed that their data came from a single RCT. Plus, the authors compared CAR against a single alternative treatment only and no other context-relevant therapy (e.g., blinatumomab in leukemia). Because of the uncertainty in long-term survival extrapolations and corresponding assumptions, the authors claimed that it is important
to generate and present the results from multiple potential survival models that have differing but plausible assumptions. Therefore, they fitted five different survival models to the published survival curves, by which the variation in long-term survival assumptions were captured and a range of long-term survival estimates were generated.

Roth et al. (58) using cure/survival modeling, determined the cost-effectiveness of axi-cel for U.S. adult r/r B cell lymphoma patients compared to the standard line of therapy. The authors determined that the cost of axi-cel was $58,146 per QALY gained. This prediction was most sensitive to the long-term remission rate, drug price discounts, and axi-cel price. The current data of ZUMA-1 is limited at a median patient follow-up of 15.4 months, and longer-term outcomes should be considered for model validity. They modeled the R-DHAP regimen as a comparator treatment strategy, a common guideline-recommended treatment, but alternative regimens could be considered.

| Article | Model Scope | CAR Construct Focus | Model Type and Algorithms Used | Simulation and Analysis Tools | Data Provided | Code Provided | Model Fitting and Validation |
|---------|-------------|---------------------|--------------------------------|-------------------------------|---------------|---------------|------------------------------|
| Cess & Finley 2020 and Rohrs et al. 2018/2019 (34-36) | Single cell level with intracellular signaling detail | CD28-CD3ζ CAR | ODE-based Mechanistic, MC Sampling, PSO, eFAST, PLS | MATLAB, Prism, BioNetGen | No | Yes | Fitted/validated with in vitro data |
| Harris et al. 2018 (37) | Single cell level with intracellular signaling detail | CD3ζ and CD28-CD3ζ CAR | ODE-based Mechanistic | Not reported | No | No | No |
| de Jesus et al. 2019 (13) | Population of cells | Anti-CD19 and anti-CD123 CAR | ODE-based Mechanistic, MCMC | QUESO Library | No | No | Fitted with in vivo mouse data |
| George and Levine 2018 (10) | Population of cells and patients | No | Therapeutic outcome modeling, Stochastic and deterministic variants | MATLAB | Yes | Yes | No |
| Hanson et al. 2016-2019 (11, 18) | Population of cytokines, cells and cohort of patients | No | QSP, ODE-based Mechanistic | MATLAB | No | No | No |
| Hardiansyah and Ng 2019 (48) | Population of cytokines, cells and cohort of patients | CD3ζ-4BB | QSP, ODE-based Mechanistic | MATLAB, Simbiology and SAAMII | No | No | Fitted with patient-level clinical trial data |
| Hopkins et al. 2019 (14) | Cellular Cells, cytokines | No | ODE-based Mechanistic | Not reported | No | No | No |
| Kimmel et al. 2019 (15) | Population of cells and cohort of patients | CD28-CD3ζ CAR | Hybrid (stochastic and deterministic), Gillespie Algorithm | Julia | No | No | Fitted with ZUMA-1 trial data |

**Table 1** A Summary of the CAR T-cell Therapy modeling and simulation articles. MLE: Maximum Likelihood Estimation, ODE: Ordinary Differential Equations, CAR: Chimeric Antigen Receptor, PL5: Partial Least Squares, MC: Monte Carlo, MCMC: Markov Chain Monte Carlo, QSP: Quantitative Systems Pharmacology, PK: Pharmacokinetics, PBPK: Physiologically-based Pharmacokinetic Model, PD: Pharmacodynamic, PSO: Particle Swarm Optimization, eFAST: Extended Fourier Amplitude Sensitivity Test, SRCT: Simulated Randomized Control Trial, PIA: Parameter Identifiability Analysis.
| Study                        | Population of patients | Population of cytokines from patient cohorts | Model Type                      | Software           | Fitted?      | Validated?  |
|------------------------------|------------------------|---------------------------------------------|---------------------------------|--------------------|--------------|-------------|
| Mostolizadeh et al. 2018 (16) | Population of cytokines and cells | No | ODE-based Mechanistic | MATLAB | No | No | No |
| Sahoo et al. 2020 (19)       | Population of cells | IL13BBζ | PDE/ODE-based Mechanistic | MATLAB, PIA | Yes | No | Fitted with in vitro data, validated on in vivo MRI data |
| Teachey et al. 2016 (21)     | Cytokine levels in cohorts of patients | CD3ζ-4-1BB | Statistical, Regression and Decision Tree analysis | R and SAS | Yes | No | Fitted with clinical trial data |
| Awasthi et al. 2020 (38)     | Population of cells from patient cohorts | CD3ζ-4-1BB | Statistical, Noncompartmental PK | Phoenix WinNonlin | No | No | PK analysis based on clinical trial data |
| Mueller et al. 2017-2018 (49, 50) | Population of cells from patient cohorts | CD3ζ-4-1BB | Statistical, Noncompartmental PK, Logistic Regression | Phoenix WinNonlin, R, and SAS | No | No | PK analysis based on clinical trial data |
| Singh et al. 2020 (52)       | Population of cells and cytokines from patient cohorts | Anti-EGFR, Anti-HER2, Anti-BCMA, Anti-CD19 | ODE-based Mechanistic, PBPK/PD | Monolix SAEM | No | Yes | Fitted and validated with clinical trial data |
| Stein et al. 2019 (51)       | Population of cells | CD3ζ-4-1BB | Statistical/empirical PK | Monolix, R, and MATLAB | Yes | Yes | Fitted with clinical trial data |
| Bansal et al. 2019 (8)       | Population of patients | CD3ζ-CD28 | Statistical cure modeling, MLE | Strata | No | No | Fitted with clinical trial data |
| Finney et al. 2019 (9)       | Population of cells | CD19CAR-T2A-EGFRt | Statistical, Classification, and Regression Tree analysis | R, SAS, Prism | No | No | Fitted with clinical trial data |
| Grant et al. 2019 (53)       | Population of patients | CD3ζ-CD28 and CD3ζ-4-1BB | Statistical cure modeling | R flexsurvcurve | Yes | No | Fitted with clinical trial data |
| Whittington et al. 2018-2019 (12, 57) | Population of patients | CD3ζ-CD28 and CD3ζ-4-1BB | Pharmacoeconomics, Statistical cure modeling, Decision Trees | MS Excel, R | No | No | Fitted with clinical trial data |
| Furzer et al. 2020 (55)      | Population of patients | CD3ζ-4-1BB | Pharmacoeconomics, Cost-utility | R | No | No | Fitted with clinical trial data |
| Lin et al. 2018 (54)         | Population of patients | CD3ζ-4-1BB | Pharmacoeconomics, Cost-utility, Markov cure/survival | TreeAge Pro, R | No | No | Fitted with clinical trial data |
| Roth et al. 2018 (58)        | Population of patients | CD3ζ-CD28 | Pharmacoeconomics, Cost-utility, Multi-state survival | MS Excel, SAS | No | No | Fitted with clinical trial data |
| Sarkar et al. 2019 (56)      | Population of patients | CD3ζ-4-1BB | Pharmacoeconomics, Cost-utility, Multi-state survival | TreeAge Pro | No | No | Fitted with clinical trial data |
3. DISCUSSION

3.1. Overview of good modeling and reporting practices
Mathematical and computational models facilitate the ability to quantitatively bridge the gap between data gathering and mechanism testing (59). Computational models can provide a set of analytical and numerical tools, complementary to laboratory experimentation, for understanding the underlying mechanisms that drive the observed biological phenomena across multiple scales, from the cellular-molecular level up to human population groups. They therefore provide new insights on key interactions within a system and demonstrate whether a hypothesized mechanism explains observed phenomenon (59). In addition, these models have the advantage of avoiding the difficult challenge of performing laboratory experiments that are currently not viable or ethical in a physical system (59). As an example, computational modeling of immune system dynamics in response to CAR T therapy provides novel insights into the complex interactions between the human immune components and CAR T-cells; helping to explain the existing observations, predict potential outcomes, and generate hypotheses that can be tested in vitro, or in vivo (60). It is well understood that all models are inherently limited, but they are useful tools if appropriately constructed and validated. Computational models can be of great use when they satisfy the good modeling practices discussed in more detail below.

First, a model is always a simplified reflection of reality. Models that deviate substantially from reality can often lead to “spherical cows,” missing required details or correct parametrization (61). In contrast, if the number of parameters is much greater than the number of observed data points, the model inference may be inappropriate and predictions might be inaccurate (19, 62). This is known as the parameter identifiability problem, or overfitting. A good model should be as simple as possible, but capable of factoring complicated data sets when needed and detailed where it matters. An initial exploratory model structure that is appropriate for specific scientific questions and scenarios of interest is critical.

Second, obtaining model parameters appropriately representing biological reality is very important. Model parameters may be obtained from literature or estimated from data; in the latter case, data fit should be examined for appropriateness of the parameter estimate. If the model simulation results are not consistent with observations in the experiment, the model must be reexamined and additional reactions/factors could be added, or irrelevant reactions/factors could be excluded. Another challenge for model parametrization is uncertainty due to lack of data or extrapolation of in vitro or animal data to humans (60). Parameter-sensitivity analyses can be performed to identify the parameters with the greatest impact on an important outcome, and hence require the most effort to reduce uncertainty. Furthermore, a parametrized model should be validated with data separate from that used to estimate model parameters. In an ideal situation, a verified and validated model could be valuable in providing outcome predictions for different potential scenarios with alternative systemic conditions.

Finally, it is essential to document model algorithms, data, information about how and from where the model parameters have been obtained, the initial values of parameters, and the assumptions used. The code for the models and simulations and the input data should be made available to the scientific community for reproducibility if possible, or at the very least, the source and detailed information about the data should be shared.

3.2 What are the added values of CAR T modeling and simulation efforts?
Regulatory approval of tisa-cel and axi-cel and demonstrated clinical effectiveness open new avenues for novel cellular immunotherapies. However, current CAR T-cell therapies face substantial challenges,
including product manufacturing issues, life-threatening adverse events, and high cost. As we continue to better understand the factors triggering therapeutic safety and efficacy issues, scientists have applied computational modeling and simulation to help link these factors to clinical outcomes.

Several computational models have been developed to investigate the aspects of CAR T-cell therapy, including mechanistic ODE-based mathematical models, as simple as the well-known Lotka-Volterra (predator-prey) model, to study the interplay between the CAR T-cells, tumor cells, and cytokines (17, 48), and to understand the mechanisms of CAR activation with models at the cellular level (34, 36). Also, PK models have been used to study CAR T-cell proliferation and the effect of tocilizumab (51). Moreover, machine learning approaches have been implemented to identify biomarkers of CRS (21); pharmacoeconomic models have been proposed for evaluating cost-effectiveness of CAR T-cell therapy (54-56, 58), and multiscale PK-PD models (52) have been developed to understand and determine the factors responsible for therapeutic outcome.

Cellular level models have been used to help evaluate and identify the optimal CAR T characteristics, including signaling domains, CAR affinity, CAR density, and antigen density, to select the lead CAR T candidate at the discovery stage, or to understand the intracellular signaling mechanisms responsible for the activation and expansion of CAR T-cells (36, 37), thus supporting clinicians in identifying the underlying factors for therapy failure, saving them time and resources, and helping them come up with better clinical protocols.

Although CAR T-cell therapy has shown tremendous efficacy in terms of disease remissions, the variable outcomes in patients must be studied further and be better understood in order to develop better CARs. Using a simple mathematical model of predator-prey dynamics, Sahoo et al. (19) explored the nonlinear dynamics involved in CAR T-cell therapy and explained the variations in patient-specific responses, even when the same CAR T-cell dose was given, and also proposed the factors important for the success of the therapy. This model suggests that the CAR T-cell dose can be tailored according to the patient’s tumor growth rate and antigen level to maximize therapeutic benefit, and such hypotheses can be tested in in vitro or in vivo systems to optimize the dose and CAR T-cell treatment regimen in clinical trials for personalized therapies. One of the advantages of modeling is to help reduce the number of clinical trials required to optimize treatment regimen, target patient group, test combination therapy, and to predict the possible adverse effects. Hanson, using an ODE-based mathematical model, generated virtual patients and simulated them to study the quantitative relationship between CAR T-cells, B-cells, and cytokines at different dosage regimens. Such randomized clinical trials may require long times and larger resources to conduct and may not be practical in a wider population. In such a case, simulated randomized trials of virtual patients would be of immense help in testing the virtual patient cohorts at different doses and different initial tumor burdens to optimize CAR T-cell therapy for positive benefit-risk profiles. Such randomized simulations of virtual patients also help in understanding the inter-patient variability and facilitating the extrapolation to different populations of interest, including pediatric, gender-based, and disease stage-based (60).

One of the major limitations of CAR T-cell therapy is CRS, and the ability to predict the patients who will likely have severe CRS enables early interventions that would reduce morbidity and mortality. Teachey et al. (21), using a regression modeling approach, predicted which patients would develop severe CRS, which might not otherwise be predicted using standard lab tests, as many of the cytokines peaked after the patients became ill. This study generated a hypothesis that patients who develop CRS develop clinical and biomarker profiles consistent with macrophage activation syndrome. This comparison may help bring new
insights into the biology of CRS development and help manage the risk. Another ODE-based model developed by Hopkins et al. (14) helps in understanding inhibitor mechanisms of the cytokines, which in turn helps in optimizing CRS treatment strategies.

The complicated and labor-intensive production of CAR T therapies puts them among the most expensive drugs currently available on the market. Tisa-cel currently is the most expensive cancer therapy, with a single-infusion cost of $475,000 (54) and for axi-cel, a lifetime cost of $552,921 (58). Pharmacoeconomic models are important evidence-based tools in forecasting and evaluation of therapy outcomes and a means of justifying therapeutic cost-effectiveness. Although long-term efficacy data is limited for CAR T-cell therapies, several pharmacoeconomic models were developed to evaluate CAR T-cell cost-effectiveness using Markov cure/survival modeling that have described a positive relationship between cost and quality of life in CAR T-cell-treated patients (12, 54-58).

3.3 Current Gaps in Knowledge and Future of Modeling in CAR T-Cell Therapies

Finally, we would like to discuss some of the information missing on the road to further development and better applications of CAR T-cell therapies, and how these knowledge gaps can be addressed using modeling and simulation efforts. To begin with, the CAR T landscape is evolving quickly, with many emerging CARs designed against novel antigen targets, e.g., CD20 or infectious diseases (5). It is not known to what extent current modeling approaches would be applicable to the new generation of CAR T therapies. Also, some of the current model predictions cannot be validated because of small sample sizes, short patient follow-up times and missing randomized clinical trial data, more problematic for statistical cure models and pharmacoeconomic models of CAR T therapies. A better-defined CAR T cell dose with T cell subset information and longitudinal/cellular kinetic immunophenotyping data sets will be particularly valuable in validation of PK-PD models.

Mechanistic models are promising frameworks for explaining clinical PK-PD behavior of CAR T-cells, especially for different indications (e.g., ALL vs DLBCL). To establish relationships between CAR T cellular kinetics, safety, and efficacy (51, 52), studying bone marrow, where CD19+ B cells are continually produced, may be more important than studying blood. A mathematical model studying the kinetics of CAR T-cell-mediated cancer cell killing and the dependence on CAR T-cell dose and antigen expression may be helpful in identifying factors governing the efficacy of CAR T-cell therapy and patient-specific responses. In addition to the efficacy question, tocilizumab and corticosteroids are used to alleviate adverse events attributable to CAR T therapy, but it is unknown whether such immunomodulatory drugs can be used prophylactically, and if administered too early, whether they could decrease CAR T therapy efficacy (21). Models considering different disease types, mechanisms of resistance (63), cytokines, and concurrent therapies, along with CAR T-cells, together could bring further insights into these open questions.

Due to their chimeric molecular nature, CAR T-cells have the potential to cause unwanted immunogenicity, which is both a safety and an efficacy concern (64). Successful prediction of CAR T immunogenicity in individual patients might be an exciting and important research direction for modelers. Moreover, most current adoptive immunotherapy clinical trials utilize autologous T-cells, which can be hampered by the poor quality and quantity of T-cells, as well as by the time and expense of manufacturing autologous T-cell products. Thus, using genetically engineered allogeneic “universal” CAR T-cells could circumvent the limitations of using autologous T-cells and could potentially be developed into a next-generation, highly-efficient CAR T therapy. Such off-the-shelf CAR T therapies can be generated from healthy donors to treat multiple patients. The major barrier preventing the successful use of allogeneic T-
cells is unwanted immune responses to the allogeneic T-cells by the recipients, as TCRs on allogeneic cells may recognize the alloantigen molecules of the recipient (leading to Graft vs host disease or GVHD) and the expression of HLAs on the surface of allogeneic T-cells may lead to their rapid rejection. Multiscale mechanistic models studying these adverse events may help in developing safer therapies, and pharmacoeconomic models can help evaluate the cost-effectiveness of such therapies. Variability in patients undergoing CAR T-cell therapy can arise from their previous therapies, including the precondition chemotherapy. Models should be developed incorporating these previous therapies to understand how they affect the outcome of CAR T-cell therapy and how the preconditioning therapy can be tailored to minimize the CAR T dose while attaining a positive benefit-risk profile.

New hypotheses regarding the underlying biological mechanisms can be generated through modeling and simulation. These hypotheses can be tested in vitro or in animals, in turn providing evidence and more data, which can be used in building new models or updating existing models. Increases in modeling efforts, along with state-of-the-art biological science would accelerate the advance of CAR T-cell therapies in the future.
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5. DISCLAIMER
This article reflects the views of the authors and should not be construed to represent the FDA’s views or policies. These comments do not bind or obligate FDA.

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