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BRIEF REPORT

Quantitative Systems Pharmacology Model of Chimeric Antigen Receptor T-Cell Therapy

Deni Hardiansyah¹ and Chee Meng Ng^{1*}

Chimeric antigen receptor T-cell (CART) therapy is a new and promising cancer therapy. However, severe toxicity due to cytokine release syndrome (CRS) in CART-treated patients highlighted the possible danger of this new therapy. Disease burden and CART doses are the potential factors associated with CRS but the detail relationships between these factors and the severity of the CRS remain largely unknown. In this study, the quantitative systems pharmacology (QSP) approach is used to quantify the complex relationships among CART doses, disease burden, and pro inflammatory cytokines in human subjects and to gain relevant insights into the determinant of clinical toxicity/efficacy in development of CART therapy. The expansion of CART and elimination of B cells are more highly correlated with disease burden than the administered CART doses. To our best knowledge, this is the first QSP model that can describe the observed clinical data from CART-treated patients with cancer. This QSP model is a valuable tool for deepening our understanding of how the mechanism of action connects to the clinical outcomes and, therefore, may serve as an important model-based platform to guide the development and personalized dosing of the CART therapy.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Chimeric antigen receptor T cell (CART) therapy is a new and promising therapy for cancer. However, unexpected toxicity, such as cytokine release syndrome (CRS), following CART therapy can cause significant organ dysfunction and death. The disease burden and CART doses have been proposed to be associated with the CRS, but the quantitative relationships between these factors and the CRS associated with CART therapy remain largely unknown.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ We built the first quantitative systems pharmacology (QSP) model that can describe the complex relationships of CART and pro inflammatory cytokines associated with CRS for CART therapy. By using this model, we have quantified relationships among CART dose, disease burden, and CRS associated with CART therapy.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ This study shows that CART is a “living drug” that exhibits unique target-mediated drug disposition characteristics (i.e., the CART cells “live and grow” in the presence of the target cells), which is in contrast to most drugs that accelerate the elimination from the body after binding to the targeted receptors. Furthermore, the magnitude of the inflammatory cytokine (e.g., interleukin (IL-6), IL-10, and interferon_γ) elevation is more related with baseline disease burden than the administered doses.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCES?

☑ This QSP model is a valuable tool for deepening our understanding of how the mechanism of action connects to the clinical outcomes and, therefore, may serve as an important model-based platform to guide the development and personalized dosing of the CART therapy.

Chimeric antigen receptor T cells (CART) are engineered T cells with a single-chain variable fragment on the cell membrane that recognizes the tumor antigen and intracellular signaling domain that can promote T cells' antitumor function.^{1,2} CART therapy demonstrates remarkable efficacy in some blood cancers and represents a paradigm shift in oncology treatment.^{2–6} Currently, two anti-CD19 CART therapies have been approved by the US Food and Drug Administration: tisagenlecleucel-T (Kymriah; Novartis) for pediatric and young adults (up to 25 years) with relapsed or refractory B-cell acute lymphoblastic leukemia (ALL)

and axicabtagene ciloleucel (Yescarta; Kite Pharma/Gilead Sciences) for adults with relapsed or refractory B-cells lymphoma, including diffuse large B-cell lymphoma.^{2–4} The CART therapy pipeline is rapidly expanding and is expected to capture the largest share of drug sales in pediatric and young adult patients with ALL and diffuse large B-cell lymphoma.² However, unexpected organ damage and deaths following CART therapy have been reported and, thus, highlight the possible danger of this new treatment.¹ Cytokine release syndrome (CRS), a systemic inflammatory response caused by pro inflammatory cytokines released by infused

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CART, is the major and most common source of toxicity that can cause widespread significant organ dysfunction and death.^{1,3,7} As a result, both tisagenlecleucel-T and axicabtagene ciloleucel are available through a restricted program that includes a risk evaluation mitigation strategy to address the severe and life-threatening toxicity of CRS.² Although potential risk factors, such as disease burden (DB), CART doses, and T-cell expansion levels after CART infusion, are expected to be associated with the severity of the CRS, the quantitative relationships between these factors and the severity of the CRS reported in CART-treated patients remains largely unknown.¹ Therefore, further investigation is needed to elucidate the quantitative relationship of CRS and the DB/CART dose in order to design an optimal dosing strategy for the prevention of the CRS. Recently, several mathematical models have been developed to provide theoretical speculation for the biologic of CART therapy, but none of these models has been used to describe the kinetic profiles of pro inflammatory cytokine and CART observed in patients with cancer treated with CART.⁸⁻¹⁰ Hence, in this study, we develop the first quantitative systems pharmacology (QSP) model that can describe the observed kinetic profiles of CART, DB, and pro inflammatory cytokines in a patient with advanced chronic lymphocytic leukemia (CLL) treated with anti-CD19 CART therapy.

METHODS

Distinct kinetic profiles of the CART and inflammatory cytokines (interleukin-6 (IL-6), IL-10, and interferon gamma (IFN_γ)) in peripheral blood (PB) from two patients with CLL were used to develop the QSP model (**Figure 1a**). Kinetic data of pro inflammatory cytokines were obtained from the supplemental tables in Kalos *et al.*,⁷ and the kinetic data of CART were obtained from the same study using software WebPlotDigitizer (version 3.8; <https://automeris.io/WebPlotDigitizer/>). The clinical study was conducted according to the guidelines described in the Declaration of Helsinki, and detailed information about the study design has been reported previously.⁷ In brief, three patients with advanced, chemotherapy-resistant CLL were enrolled in the study and the treatments were scheduled as an i.v. dose of CART cells with 3-day split dose regimen (10%, 30%, and 60%). Corticosteroid therapy can inhibit the expression and action of most cytokine.¹¹ UPN2 was excluded from the analysis because this patient had a different and subdued CART and cytokine kinetic profile compared with the other two subjects (UPN1 and UPN3),⁷ which was possibly due to the cytokine-masking effects of concurrent corticosteroid

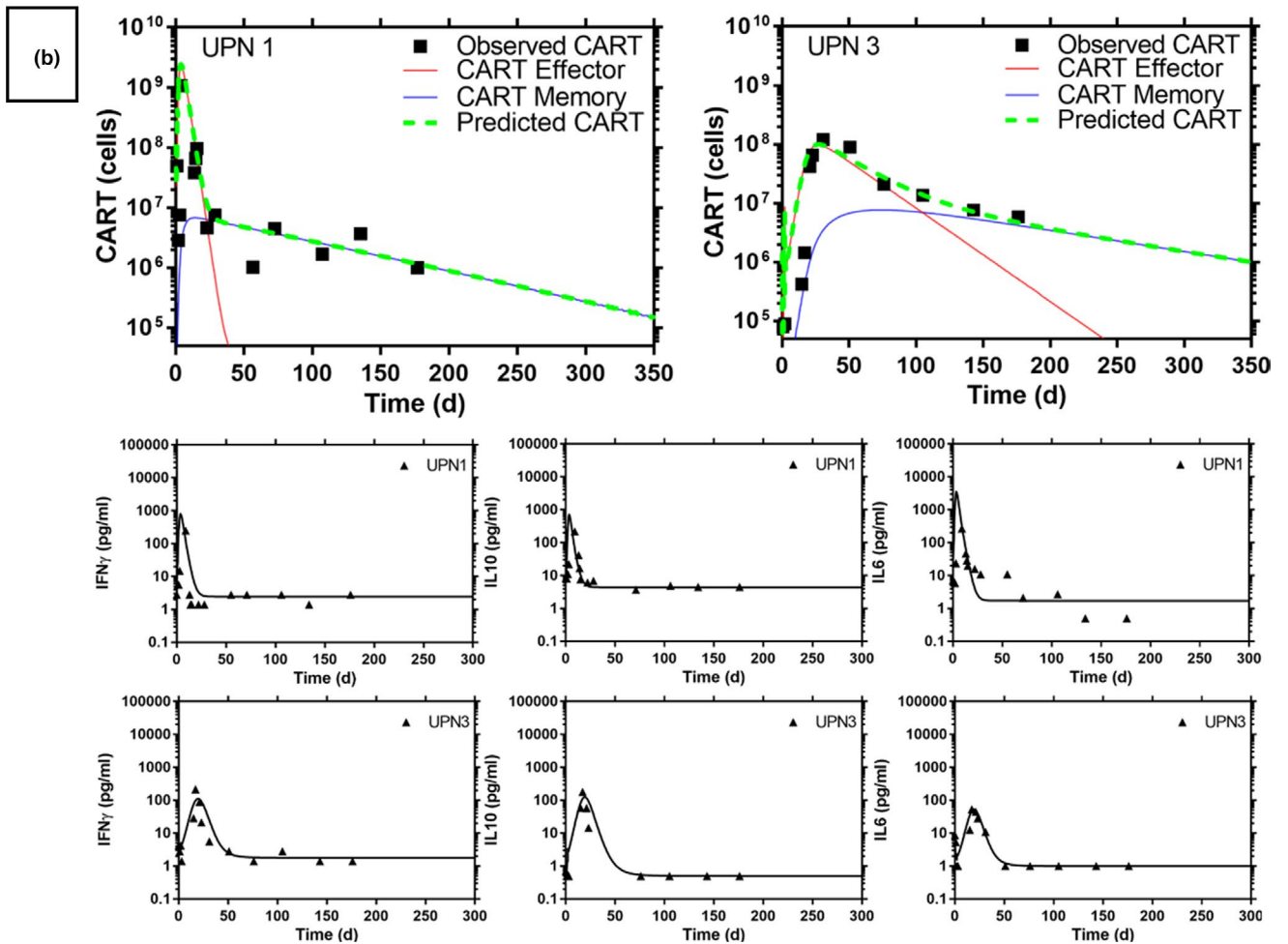
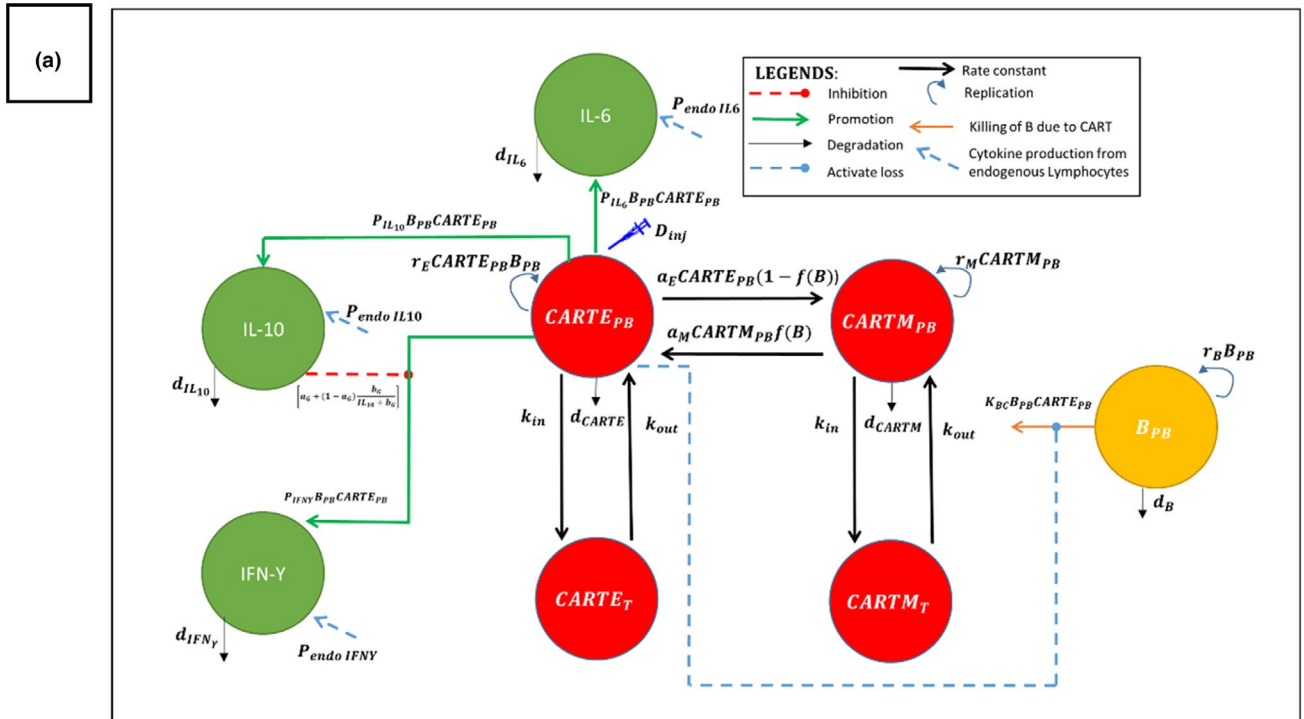
treatment. As a result, only two subjects (UPN1 and UPN3) were included in the QSP model development in this study.

The IL-6, IL-10, and IFN_γ were selected because these cytokines played an important role in the inflammatory responses. Elevation of these pro inflammatory cytokines was associated with the severity of CRS and other toxicities after CART infusion.^{1,12} **Figure 1a** shows the developed QSP model based on the current understanding of the complex interactions among CART, B cells, IL-6, IL-10, and IFN_γ in human subjects. The detailed description of the QSP model implementation is included in the **Supplementary File**. In brief, CART was divided into two phenotypes of T cells (i.e., activated/effector (CARTE) and memory T cells (CARTM)). Injected CART were assumed to be activated after interacting with CLL B-cells and were expanded via growth rate r_E . CARTE was eliminated from the body with death rate d_{CARTE} . Activated CART were converted into long-life CARTM via activation rate a_E , which related to the CLL B-cells saturation function $f(B)$. On the other hand, during the fast expansion of CARTE, CARTM were converted into short-life CARTE to kill the CLL cancer via activation rate a_M . CARTM were expanded via natural growth rate r_M and were eliminated from the body with death rate d_{CARTM} . Distribution of both CARTE and CARTM between PB and tissue was described by the rate constants k_{in} and k_{out} .

The B cells in patients with CLL were assumed to have exponential growth with production rate r_B and natural death rate d_B in PB. Activated CARTE cells killed the B cells via killing rate K_{BC} and secreted IL-6, IL-10, and IFN_γ into the blood to induce the inflammatory responses and CRS. The baseline cytokine levels in patients with CLL before anti-CD19 CART therapy were maintained with the endogenous synthesis rate of $P_{endo\ IL6}$, $P_{endo\ IL10}$, and $P_{endo\ IFN\gamma}$, and natural death rate of d_{IL6} , d_{IL10} , and $d_{IFN\gamma}$ for IL-6, IL-10, and IFN_γ, respectively. Known inhibitory effects of IL-10 on the secretion of IFN_γ by activated T cells was included in the model. Most model parameters were obtained from the published literature (**Table S1**) except for several CART-related parameters that had never been reported in the literature and, therefore, had to be estimated by fitting the QSP model to all observed data simultaneously. These CART-related parameters included CART-induced IL-6, IL-10, and IFN_γ secretion (P_{IL6} , P_{IL10} , and $P_{IFN\gamma}$), growth rate of CARTE cells (r_E), the killing rate of CARTE cells to B cell CLL in PB (K_{BC}), activation rate a_M , and CARTE death rate d_{CARTE} .

The ability of the final QSP model in describing the relationships between disease burden/CART doses and CART/cytokine kinetic profiles in PB was examined with two external validation data sets that consisted of (i) maximal CART

Figure 1 (a) The quantitative systems pharmacology model of anti-CD19 chimeric antigen receptor T cells (CART) in a patient with chronic lymphatic leukemia (CLL). B_{PB} represent the B-cell CLL in peripheral blood (PB). CART effector (CARTE) and CART memory (CARTM) cells are distributed between PB ($CARTE_{PB}/CARTM_{PB}$) and tissue ($CARTE_T/CARTM_T$) compartments via rate constant k_{in} and k_{out} after i.v. infusion. d_{CARTE} and d_{CARTM} are the death rate constants of CART from the PB. CARTE and CARTM are activated via activation rate a_E and a_M . $P_{endo\ IL6}$, $P_{endo\ IL10}$, and $P_{endo\ IFN\gamma}$ are endogenous synthesis rate and d_{IL6} , d_{IL10} , and $d_{IFN\gamma}$ are the natural death rate of interleukin (IL)-6, IL-10, and gamma interferon (IFN_γ), respectively. P_{IL6} , P_{IL10} , and $P_{IFN\gamma}$ represent the production rate of IL-6, IL-10, and IFN_γ by the activated CART, respectively. K_{BC} is the CARTE-mediated B-cell CLL degradation rate constant in peripheral blood. a_G and b_G are the inhibitory parameters of IL10 on IFN_γ production. **(b)** Observed CART and cytokines kinetic profiles and model prediction in an anti-CD19 CART-treated CLL patient. Symbol—observed CART and cytokines. Solid line—model prediction.



peak plasma concentration (C_{\max}) and area under the curve of the time-concentration curve from $t = 0$ to $t = 28$ days (AUC_{0-28}) in patients with CLL treated with CART,¹³ and (ii) C_{\max} of IFN $_{\gamma}$ and CART observed in CART-treated adult subjects with ALL.^{13,14} The details of the external validation process is described in the **Supplementary File**. The final QSP model was then used to simulate the kinetic profiles of CART cells, B cells, and pro inflammatory cytokines in patients with CLL with different DB and CART doses. Due to the limitation of the data used for QSP model development, the DB and CART doses up to twofold differences from the actual values in UPN1 and UPN3 were used in the simulation studies.

RESULTS AND DISCUSSION

The parameters in the final QSP model are estimated with good precision (percentage of coefficient of variation < 50) and the final QSP model is able to describe the observed CART kinetic and pro inflammatory cytokine profiles in patients with CLL (**Figure 1b**, and **Table S2** and **Figure S1**). In general, CARTs differentiate and expand rapidly in the presence of the targeted B cell after infusion into patients with CLL. Then these activated CARTE target and destroy the B cell CLL, resulting in rapid decline of the DB. As the DB decline, the CARTE decay rapidly. Depending on the baseline tumor burden and administered CART doses, this model is able to describe two distinct CART and pro inflammatory cytokine profiles observed in patients with CLL (**Figure 1b**). In Subject UPN1 who had 4.5-fold higher baseline disease burden and received 79-fold higher CART doses compared with subject UPN3, more CARTE are activated and are expanded rapidly in the presence of higher DB and administered CART doses. Then the CARTE undergo a rapid decline, as many of these cells are used to destroy the large DB. This rapid formation and elimination of activated CARTE coupled with a relatively slow formation of the CARTM cells¹⁵ contribute to the observed biexponential CART kinetic profiles of subject UPN1 (**Figure 1b**). In contrast, relatively low DB and administered CART doses are associated with a slow formation and elimination of the activated CARTE that contribute to the lower and less distinct bi-exponential CART kinetic profiles observed in subject UPN3 (**Figure 1b**). CART are a “living drug” that exhibit unique target-mediated drug disposition characteristics.^{16–18} In contrast with most drugs that are eliminated from the body after administration, the CART “live and grow” in the presence of the target cells. As the disease burden remains low, the CARTE populations lose its feeding sources and continue to decline and, thus, predisposing the patient to potential relapse. The inflammatory response characterized by elevation of the cytokine IL-6, IL-10, and

IFN $_{\gamma}$ reaches its peak between 15 and 23 days postinfusion⁷ and the magnitude of the cytokine elevation is highly correlated with the baseline DB. As the DB declines, the inflammation subsides^{1,3} (**Figure 1b**).

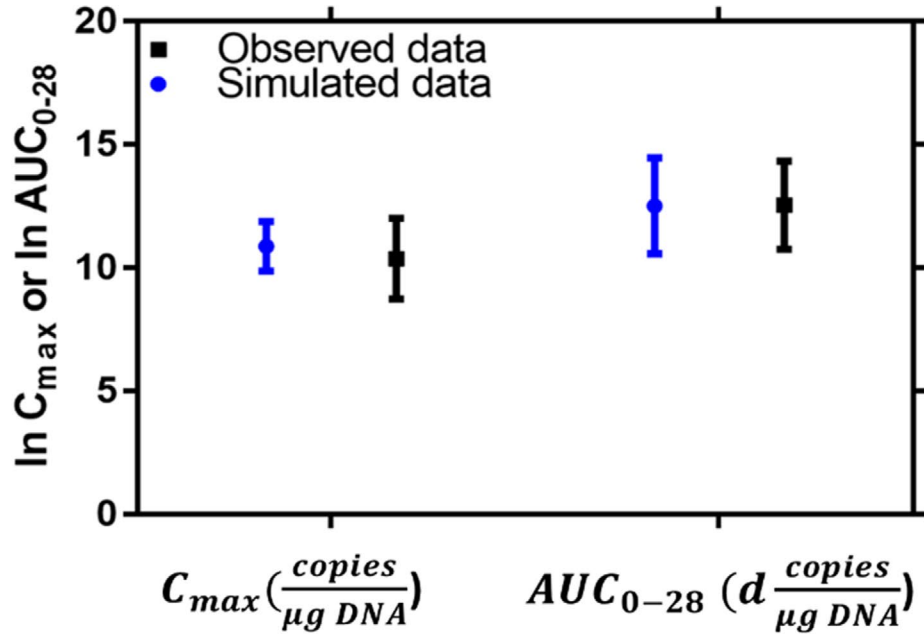
The ability of the final QSP model in describing the relationships between the DB/CART doses and CART kinetic profiles in peripheral blood of the patients with CLL is examined with the external validation data set. As clearly shown in **Figure 2a**, the log-transformed C_{\max} and AUC_{0-28} (mean \pm SD) from the simulation using our QSP model is similar to the observed values in patients with CLL treated with CART.¹³ The quantitative effect of DB on cytokine/CART kinetic profiles in the peripheral blood of patients with CLL treated with CART has never been reported in published literature. Therefore, we decided to compare the trends of the simulated relationships between blood DB and C_{\max} of the CART/pro inflammatory cytokine IFN $_{\gamma}$ in peripheral blood of patients with CLL to the reported relationships between bone marrow DB and C_{\max} of the CART/pro inflammatory cytokine IFN $_{\gamma}$ in peripheral blood of patients with ALL.^{13,14} The simulated relationships between disease burden and C_{\max} of CART and IFN $_{\gamma}$ using our QSP model in peripheral blood of patients with CLL share a similar trend with those observed in patients with ALL^{13,14} (i.e., higher DB is associated with higher C_{\max} of the CART and IFN $_{\gamma}$; **Figure S2** and **Figure S3**). Taken together, these results suggested that the ability of our QSP model in describing the relationships between the DB/CART doses and CART/cytokine kinetic profiles are relatively consistent with the observed clinical findings in cancer patients treated with CART.

Simulations are performed to investigate the effect of DB and CART dose to the cytokines level (**Figure 2b**). Patients with a higher baseline of DB are associated with higher cytokine and CART C_{\max} after infusion and, therefore, are likely to experience severe CRS toxicity (**Figure 2b** and **Figure S3**). Hence, our results demonstrate that the developed QSP model using a well-known complex mechanistic interaction between CART and the inflammatory cytokine is sufficient to support the DB-correlated toxicity observed in clinical studies.¹ Our results also support the clinical findings that the CART dose alone has a minor effect on the kinetic profile of cytokines and correlates poorly with the degree of CRS toxicity.^{1,8} The observation that toxicity is more related with baseline DB than the administered CART doses is contrary to what is observed with most cancer chemotherapy in which the administered dose is often the major factor in drug-limiting toxicity, possibly due to the unique kinetic and dynamic characteristics of the CART in patients with CLL.

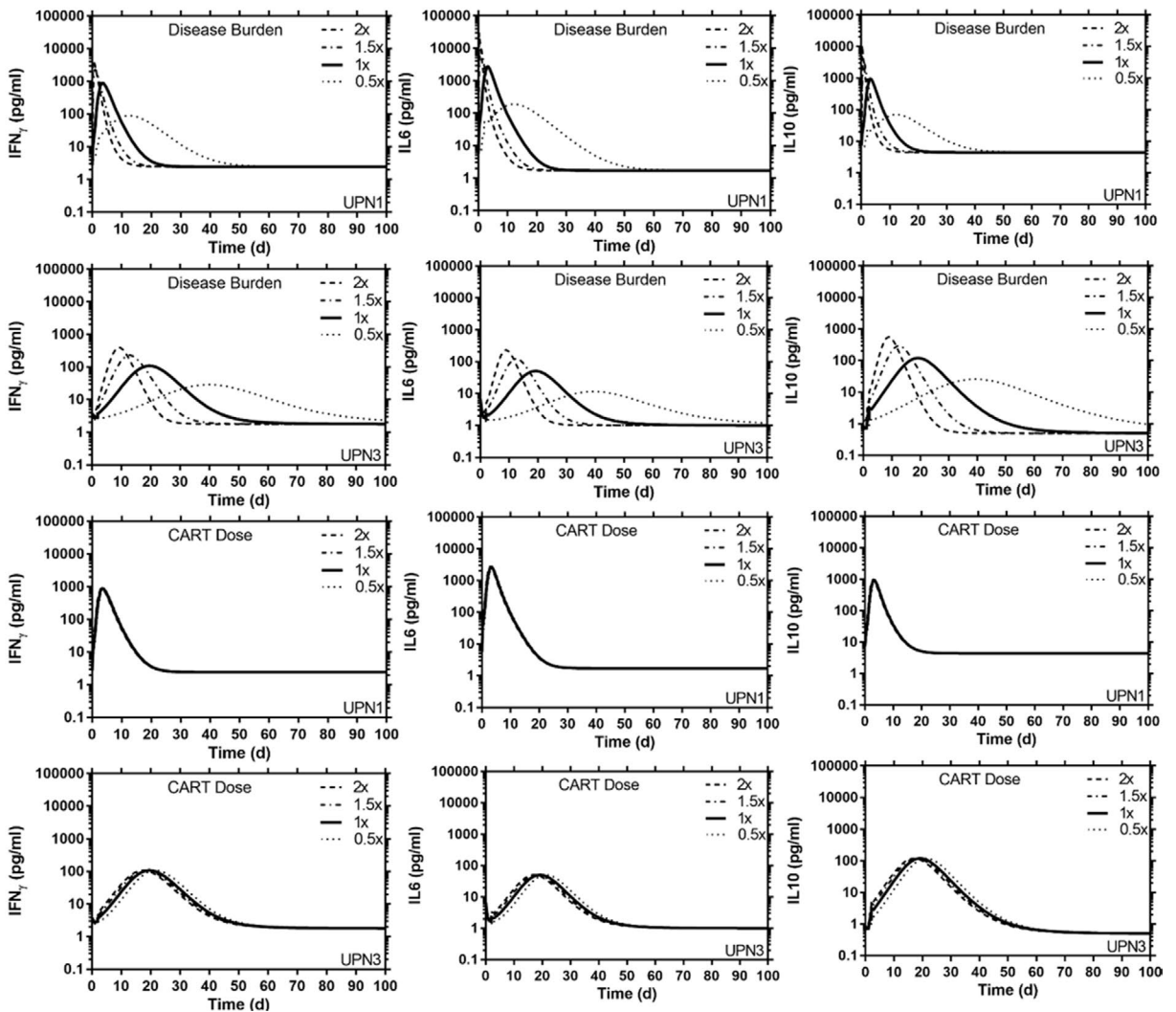
An activated macrophage is a major source of the IL-6 and can play an important role in the CRS of CART therapy.¹⁹ However, due to lack of the kinetic profiles of the activated

Figure 2 (a) External validation for the final quantitative systems pharmacology (QSP) model using the mean maximal concentration of chimeric antigen receptor T-cell (CART) peak plasma concentration (C_{\max}) and the mean area under the curve of the time-concentration curve from $t = 0$ to $t = 28$ days (AUC_{0-28}) of the typical kinetics of CART in chronic lymphatic leukemia (CLL). Symbols and bars represent the predicted and observed log-transformed mean and SD values. **(b)** Simulated CART and cytokine kinetic profiles with different B-cell disease burden and anti-CD19 CART doses in a patient with CLL, CART baseline in peripheral blood (PB): 1.1×10^9 cells (UPN1) and 1.4×10^7 cells (UPN3), disease burden baseline in PB: 4.14×10^9 cells (UPN1) and 9.3×10^8 cells (UPN3). IFN $_{\gamma}$, gamma interferon; IL, interleukin.

(a)



(b)



macrophage in our data, attempts to build the activated macrophages into our model are unsuccessful. Furthermore, other cytokines, such as monocyte chemo-attractant protein-1 and macrophage inflammatory protein-1 β , can play an important role in the CRS and other toxicities associated with CART therapy.²⁰ It has been shown that DB in the bone marrow compartment is correlated with the CART level in blood and, hence, can play a role in the CART kinetics.^{13,14} However, the attempt to add the bone-marrow tumor compartment in our QSP model was unsuccessful due to lack of sufficient tumor burden kinetic data in the bone marrow for this study. Therefore, further study with more experimental data and validation is needed to refine this QSP model in order to increase the confidence and precision in model prediction.

Several mathematical models have been proposed to describe the kinetics of CRS in human subjects. Yiu *et al.*²¹ developed a complex mathematical model to describe the kinetics of nine cytokines in six human volunteers experiencing CRS during the phase I clinical trial of a monoclonal antibody that was designed to simulate a regulatory T-cell response. However, 90 system parameters from a set of complex second-order ordinary differential equations are needed to be optimized in order to describe the observed kinetics of the 9 cytokines. Therefore, it is unlikely that this complex model can be supported by the limited cytokine kinetic data included in our study. Mathematical models have been developed to describe the complex interaction between the activated neutrophils/monocyte and pro inflammatory cytokines in bacteria-induced sepsis, but none of these models can be used to investigate the CRS and CART cells in human subjects without major modifications.²² Recently, several mathematical models have been developed to describe the biologics of the CART.^{8–10} However, no clinical data are used to develop and validate these models,^{8–10} and, therefore, the ability of these models in describing the observed kinetics of cytokines and CART is questionable.

To our best knowledge, this is the first proposed QSP model that can describe the observed clinical data from patients with cancer treated with CART therapy. This QSP model is a valuable tool for deepening our understanding of how the mechanism of action connects to the clinical outcomes and, therefore, may serve as an important model-based platform to guide the development and personalized dosing of the CART therapy. As shown by the well-known “learn-confirm” approach proposed by Sheiner,²³ the QSP modeling and simulation can be used to learn from experience and confirm what has been learned in order to improve the efficiency of the clinical development of CART therapy. First, the clinical data collected in the early phase I data can be used to develop the basic QSP framework (phase I QSP model) to increase our understanding of how the mechanism of action of CART therapy connects to the toxicity (safety) and possible early efficacy signals in patients. Then the modeling and simulation results with the phase I QSP model are used to design a subsequent phase II study in order to acquire new and more diverse data to refine the QSP model for predicting future clinical outcomes of safety and efficacy. This refined phase I/II population QSP model should be able to quantify the effects of specific patient

factors, such as disease and performance status, prior chemotherapy, and genetic predisposition on the QSP model parameters that govern the clinical safety and efficacy in the studied population. Hence, this population QSP model will define the exposure–response (safety and efficacy) relationships that offer insights into how the phase III study protocol may be modified based on individual patient characteristics in order to decrease toxicity, increase the persistence of CARTE population, and potentially decrease relapse rates of cancer.

Supporting Information. Supplementary information accompanies this paper on the *Clinical and Translational Science* website (www.cts-journal.com).

Supplementary Material, Tables and Figures.

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