Published OnlineFirst March 26, 2018; DOI: 10.1158/1078-0432.CCR-18-0580

CCR Translations

Clinical Cancer Research

The Long Neglected Player: Modeling Tumor Uptake to Guide Optimal Dosing

Leire Ruiz-Cerdá[1,2], Eduardo Asín-Prieto[1,2], Zinnia P. Parra-Guillen[1,2], and Iñaki F. Trocóniz[1,2]

Pharmacokinetic modeling, traditionally using drug exposure, is widely used to support decision-making in translational medicine and patient care. The development of mechanistic computational models that integrate drug concentrations at the site of action making use of existing knowledge opens a new paradigm in optimal dosing. *Clin Cancer Res; 24(14); 3236–8. ©2018 AACR.*

See related article by Ribba et al., p. 3325

In this issue of *Clinical Cancer Research*, Ribba and colleagues (1) applied the Model Informed Drug Discovery & Development (MID3) paradigm to optimize dosing regimens of cergutuzumab amunaleukin (CEA-IL2v), a bivalent carcinoembryonic antigen (CEA)–specific antibody fused to a modified IL2 capable of activating the immune response in the tumor microenvironment. Their contribution, which relies on the fundamental premise that drug exposure represents the major driver of a patient's response (at least at early stages of disease progression), goes far beyond the MID3 standards.

In this commentary, we aim to bring attention to the concepts of tumor exposure, mechanistic conceptualization of the system to treat, data integration, knowledge reusability, and virtual scenarios. These concepts are key to understand and predict a patient's response in the tight frames of decision-making during drug development, as illustrated by Ribba and colleagues (1).

The use of models to establish dosage regimens has been present in drug development and patient care during the past three decades. With the arrival of biologics, specifically mAbs, these models have gained mechanistic insights leading to the term "target-mediated drug disposition" (TMDD; ref. 2), accounting among other phenomena for time-dependent pharmacokinetics. Indeed, the TMDD framework has been used by Ribba and colleagues (1) to characterize the reduction of circulating drug exposure during treatment triggered by the increasing target levels.

On the other hand, there is an arsenal of models linking systemic circulating drug exposure to response. One drawback of these approaches comes from the fact that tumor exposure is inferred from the time course of systemic drug levels and response, and therefore, variability in response due to target bioavailability cannot be accounted for (Fig. 1A). Gathering tumor exposure appears as an obvious solution to overcome this important limitation; however, accessing tumor biopsies or intratumor microdialysis is not always possible. In the article by Ribba and colleagues (1), CEA-IL2v longitudinal tumor uptake was assessed through imaging data, which likely implied a significant amount of resources, as indicated by the fact that a small cohort of 14 patients received 89Zr-labeled CEA-IL2, and only three measurements up to 8 hours postdose were obtained per subject. The additional costs may pay off in the long term if this methodology proves to be more precise to select the "optimal dosing regimen" for efficacy studies, therefore maximizing the chances of clinical success and reducing the alarming rates of late-phase failure—one of the major hurdles in current oncology drug development.

It should be highlighted that those raw data would have been sufficient to simply confirm tumor access, but certainly, it would have not permitted the prediction of exposure at the site of action in untested dosing scenarios (Fig. 1B). How to deal with that type of information to get robust and trustworthy exposure predictions is a very relevant and nontrivial question to answer related to extrapolation. We need scientifically sound tools to constrain prediction outcomes within reliable bounds, which can be achieved considering the system (tumor) as an entity with a dynamism governed by physiologic processes rather than a black box. This mechanistic perspective is not exempted from complexities though, as it is quite data and computationally demanding.

Interestingly, the strategy followed by Ribba and colleagues (1) minimized data and computation requirements upon the adaptation of a mechanistic computational model publicly available (Fig. 1C). One fundamental property of mechanistic models is that processes (and their corresponding parameters) inherent to the system are isolated from those that are treatment specific, therefore enabling the integration of physicochemical characteristics of the compound, which are independent from the type of disease and its progression and frequently available from early stages of the discovery phase. This approach ensures and promotes model reusability in other therapeutics and reduces the data acquisition needs permitting the use of sparse measurements in the target tissue.

[1]Pharmacometrics & Systems Pharmacology Research Unit, Department of Pharmacy and Pharmaceutical Technology, School of Pharmacy and Nutrition, University of Navarra, Pamplona, Spain. [2]IdiSNA, Navarra Institute for Health Research, Pamplona, Spain.

Corresponding Author: Iñaki F. Trocóniz, Department of Pharmacy and Pharmaceutical Technology, School of Pharmacy and Nutrition, University of Navarra, Irunlarrea 1, Pamplona 31008, Spain. Phone: 349-4842-5600, ext. 806507; Fax: 349-4842-5740; E-mail: itroconiz@unav.es

doi: 10.1158/1078-0432.CCR-18-0580

Published OnlineFirst March 26, 2018; DOI: 10.1158/1078-0432.CCR-18-0580

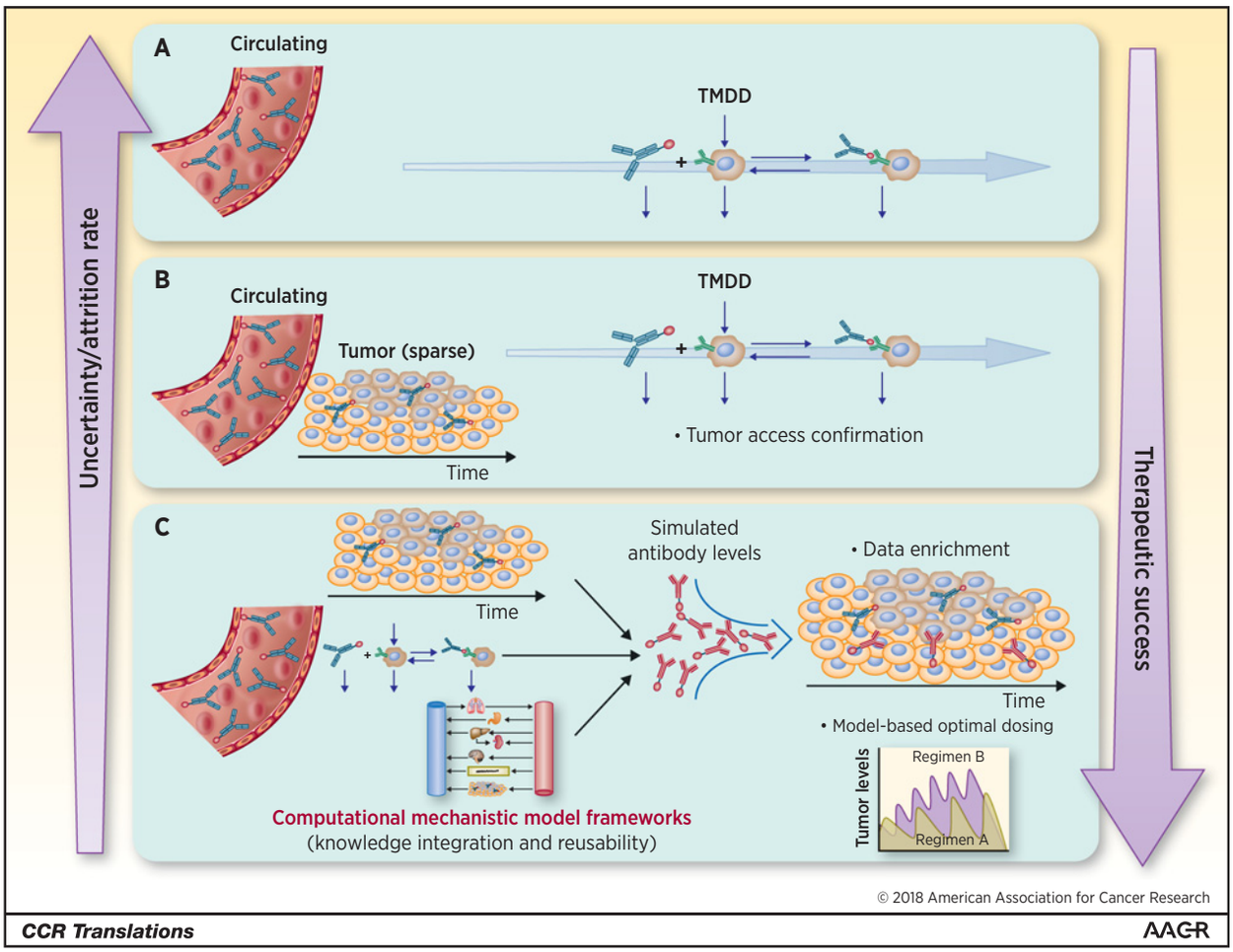

Figure 1.

Expected impact of study design driving data availability and data processing approaches on attrition rates and therapeutic success in oncology drug development and patient care. **A,** Circulating antibody measurements coupled with semimechanistic modeling efforts. **B,** Circulating antibodies and sparse tumor measurements coupled with semimechanistic modeling efforts using tumor uptake information to confirm target uptake. **C,** Circulating antibody and sparse tumor measurements coupled with mechanistic modeling efforts using publicly available computational tools and Bayesian modeling.

The results obtained by Ribba and colleagues (1) using the above mechanistic approach and integrating data from different sources (intrinsic drug properties, temporal profiles of drug levels in peripheral blood and tumor, and immune cell counts) are impressive if one compares the lack of meaningful trends shown in their Fig. 2E with the predictions generated and shown in the bottom panels of their Fig. 3. Given those results, it will not be surprising that the same modeling paradigm can be applied by others in the case of different antibodies and cancer indications.

So far, this commentary has been focused on the drug development arena; however, this approach opens the avenue of translating MID3 efforts to model-informed drug use in patient care. Ribba and colleagues (1) made use of a powerful modeling technique, the Bayesian approach (3). In brief, given a population model and individual (sparse) patient data, individual exposure profiles can be generated. Therefore, the modeling framework that Ribba and colleagues present should not be diluted in time, and we highly encourage to carry forward and reuse those computational tools at the time when patient data are gathered and the therapeutic is available for medicine personalization.

Consequently, the end product of the modeling effort we are discussing is the simulation outcome showing how a change in the dosing schema can overcome the reduced availability of circulating CEA-IL2v, a result of the model-predicted peripheral target expansion. Focusing on drug exposure and leaving efficacy and toxicity apart, at least two variables need to be taken into consideration for dose optimization for the typical patient: dose level and dosing interval. The pharmacometric discipline provides tools to find, from a formal perspective, optimal dosing and design scenarios to extract the most from clinical trials. Nevertheless, publicly available information on these therapies indicates that one of the main obstacles in clinical phases of drug development of these compounds is dose selection and optimization, which are still mainly driven by classical MTD schemas and noncompartmental analysis (4). To the best of our knowledge, there is only one publication where pharmacokinetic/pharmacodynamic modeling efforts were undertaken to develop a

Published OnlineFirst March 26, 2018; DOI: 10.1158/1078-0432.CCR-18-0580

translation model integrating information across the different phases of drug development to finally support decision-making (5) in the immuno-oncology arena.

To summarize, Ribba and colleagues (1) have applied the MID3 paradigm during the clinical development program of a new immune modulator in oncology therapy. In their work, circulating levels of CEA-IL2v and imaging data were embedded in a computational modeling framework using publicly available information. This strategy, based on sparse data, allowed for an *in silico* optimization of dosing schedules, with focus on tumor uptake as an alternate/complementary paradigm to MTD. It should not be ignored that selection of the right dosage regimen is ultimately driven by the balance between efficacy and toxicity. Remarkably, the authors found a strong positive correlation between predicted target levels and IL2R-positive cells, supporting drug mechanism of action and adding robustness to the developed model. Therefore, we are eager to see how tumor uptake drives a CEA-IL2v patient's response.

In conclusion, the contribution of Ribba and colleagues (1) highlights the enormous potential of modeling and simulation as a pillar in drug development and translational medicine, supporting dosing optimization and decision-making.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: E. Asín-Prieto, Z.P. Parra-Guillen, I.F. Trocóniz
Writing, review, and/or revision of the manuscript: L. Ruiz-Cerdá, E. Asín-Prieto, Z.P. Parra-Guillen, I.F. Trocóniz
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): I.F. Trocóniz
Study supervision: I.F. Trocóniz

Received March 8, 2018; revised March 14, 2018; accepted March 22, 2018; published first March 26, 2018.

References

1. Ribba B, Boetsch C, Nayak T, Grimm HP, Charo J, Evers S, et al. Prediction of the optimal dosing regimen using a mathematical model of tumour uptake for immunocytokine-based cancer immunotherapy. Clin Cancer Res 2018;24:3325–33.
2. Levy G. Pharmacologic target-mediated drug disposition. Clin Pharmacol Ther 1994;56:248–52.
3. Barbolosi D, Ciccolini J, Lacarelle B, Barlési F, André N. Computational oncology-mathematical modelling of drug regimens for precision medicine. Nat Rev Clin Oncol 2016;13:242–54.
4. Mathijssen RHJ, Sparreboom A, Verweij J. Determining the optimal dose in the development of anticancer agents. Nat Rev Clin Oncol 2014; 11:272–81.
5. Lindauer A, Valiathan CR, Mehta K, Sriram V, de Greef R, Elassaiss-Schaap J, et al. Translational pharmacokinetic/pharmacodynamic modeling of tumor growth inhibition supports dose-range selection of the anti-PD-1 antibody pembrolizumab. CPT Pharmacometrics Syst Pharmacol 2017;6:11–20.

Published OnlineFirst March 26, 2018; DOI: 10.1158/1078-0432.CCR-18-0580

Clinical Cancer Research

The Long Neglected Player: Modeling Tumor Uptake to Guide Optimal Dosing

Leire Ruiz-Cerdá, Eduardo Asín-Prieto, Zinnia P. Parra-Guillen, et al.

Clin Cancer Res 2018;24:3236-3238. Published OnlineFirst March 26, 2018.