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Translational PK/PD modeling to increase probability of success in drug discovery and early development

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In this review we present ways in which translational PK/PD modeling can address opportunities to enhance probability of success in drug discovery and early development. This is achieved by impacting efficacy and safety-driven attrition rates, through increased focus on the quantitative understanding and modeling of translational PK/PD. Application of the proposed principles early in the discovery and development phases is anticipated to bolster confidence of successfully evaluating proof of mechanism in humans and ultimately improve Phase II success. The present review is centered on the application of predictive modeling and simulation approaches during drug discovery and early development, and more specifically of mechanism-based PK/PD modeling. Case studies are presented, focused on the relevance of M&S contributions to real-world questions and the impact on decision making.

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Introduction

Inherent to Pharma R&D is that more projects fail than succeed. Currently, a Phase II success rate of ~10% mandates delivery of 10 molecules into the preclinical development pipeline to achieve 1 successful Phase III transition per year. Selecting indications with higher historical probability of success is a straightforward approach to reduce attrition. Increasing the quality of molecules entering the development pipeline, including the associated confidence in the target and the predicted human efficacy and safety, is a major driver for reducing attrition rates.

A thorough characterization of the target and compound is key for turning drug candidates into successful medicines. Building up on the understanding of disease and therapeutic approach, translational pharmacokinetics/pharmacodynamics (PK/PD) uses modeling and simulation (M&S) to integrate information on the target, pathway modulation, compound properties, pharmacology and safety. Throughout the conceptual and early experimental phase, M&S aids in addressing key questions that are crucial for downstream development success (Fig. 1).

How can we better influence Phase II survival?

In a recent analysis of the Pfizer portfolio, Morgan *et al.* investigated 44 small molecule programmes that reached Phase II decision points [1]. This work revealed that the principal reason for Phase II attrition was insufficient clinical efficacy. A detailed assessment showed that objectively evaluating the following 3 simple criteria could be used to

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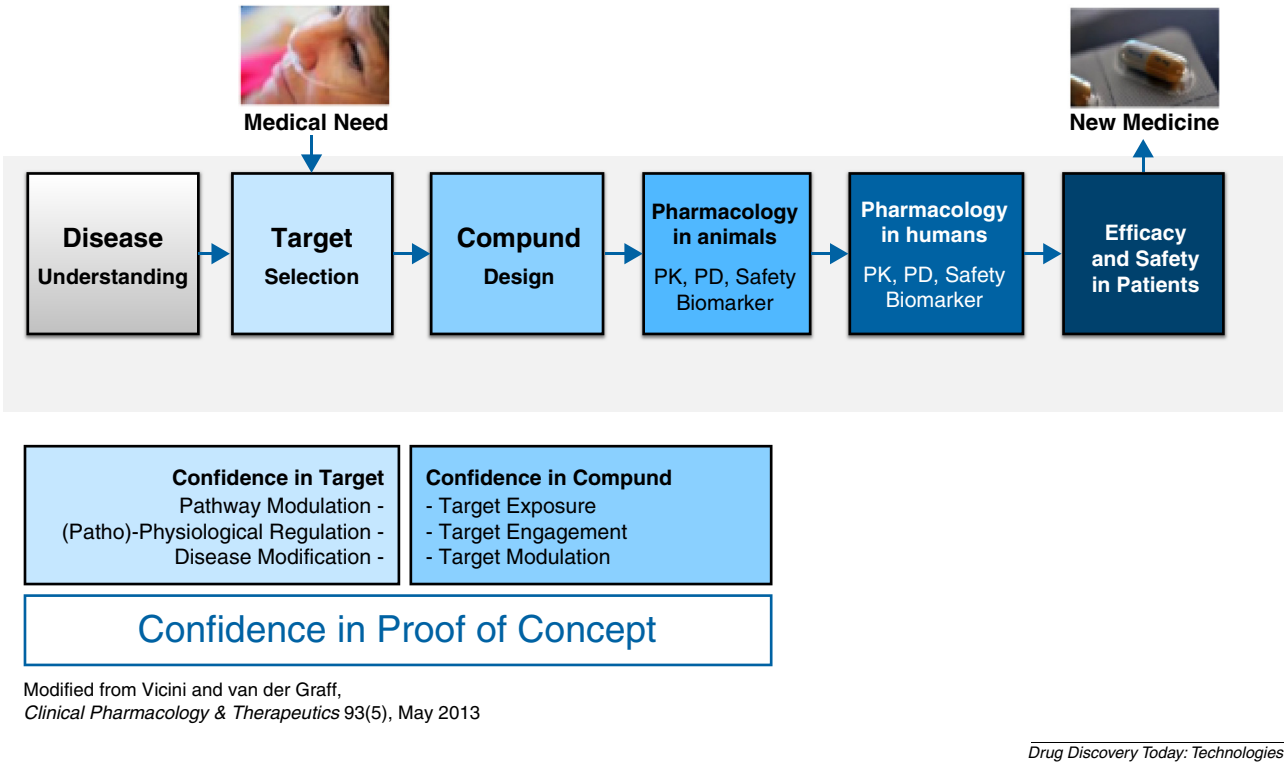

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Figure 1. Schematic of a typical drug discovery pipeline showing how and when translational PK/PD can be applied for bolstering confidence in drug discovery and early development. Modeling and simulation applied to translational PK/PD enables to integrate information pertaining to the target, pathway modulation, compound properties, pharmacology and safety to maximize downstream development success.

determine chances of Phase II success and prioritize drug development programmes:

1. Drug exposure at the site of action is necessary to elicit a pharmacological response over a desired period of time.
2. Occupancy by binding to the pharmacological target is required for expression of pharmacology and target modulation.
3. Functional modulation of the target is a pre-requisite for expression of pharmacological activity to test the mechanism.

These simple yet fundamental principles can be used in both clinical and preclinical settings as objective, data-driven criteria for assessing programmes/molecules for confidence in delivering decisive proof of mechanism readouts, and ultimately confidence in Phase II outcome. Formally driving these evaluations into early discovery programmes (e.g. at target assessment/lead identification phase) provides solid foundations upon which confidence in clinical success can be built. Starting this evaluation early in discovery also allows for development of a plan to address gaps before the final compound is selected.

These findings advocate a systematic application of integrative and quantitative PK/PD principles throughout the drug discovery and development value chain, and selection of targets and candidates with stronger confidence to demonstrate the therapeutic hypothesis in clinical development.

Quantitative translational approaches

Quantitative translational approaches include physiologically based pharmacokinetic (PBPK) models as well as mechanism-based PK/PD models. An essential characteristic of these mechanism-based translational models is the separation of system-specific parameters from compound-specific parameters. System parameters are related to specific pharmacology or disease processes and can be used to model different compounds. This is very relevant, considering the challenge of translating research from animal models to human efficacy and safety.

PBPK models represent a very powerful example of the successful application and implementation of translational approaches in drug discovery and development. PBPK models have been increasingly included in regulatory submissions, for example, for the prediction of drug–drug interactions, formulation effects, drug-exposure predictions in pediatric and organ-impaired populations [2]. Applications of PBPK specific to decision-making in industry include lead optimization and candidate selection leading to prediction of first-in-human pharmacokinetics (PK) and can play a supportive

role in enabling decision making in later phases [2]. These more mechanistic models provide a quantitative framework for prediction of systemic and tissue exposures with the distinct separation of physiology and drug-dependent information. PBPK models enable the extrapolation from *in vitro* to *in vivo* [3], from animal to human [4], from healthy volunteers to patient or special populations [2], and are applied at all stages of drug development [5].

These PBPK models provide the opportunity to understand pharmacokinetics (PK) at the target or site of action, which is a prerequisite to unravel the relationship between drug concentration and pharmacology. For many peripheral drug targets, unbound drug concentration in plasma will reflect the unbound drug concentration at the target site under equilibrium conditions. When this is the case, the plasma exposure can be linked to efficacy parameters measured *in vitro* and can be reliably used to estimate the target receptor occupancy which provides the link between the exposure and effect. However, together with a lack of solid understanding of pharmacology, the lack of solid understanding of target exposure can invalidate this PK/PD modeling and reduce our ability to understand the properties required for discovery or development compounds to become medicines for the patient. Target exposure can be challenging to estimate when active transport processes are involved in tissue uptake but recently, improved estimation of active and passive transport parameters in the *in vitro* assay has opened the door for the possibility of incorporating transporter kinetics in a PBPK model for improved quantitative predictions of transporter dynamics *in vivo* [6]. Key drivers for development and increased application of PBPK have been the developments around physiologic models incorporating physicochemical and *in vitro* human drug data to predict elimination, distribution and absorption. The availability of user-friendly, commercially available PBPK software platforms, incorporating all physiological, biochemical and other data has been key as well. A more recent key driver came from the increased acceptance by regulators. However, PBPK models are increasingly used in the Pharmaceutical Industry mainly in support to small molecule portfolio. PBPK models still need further developments in their potential to account quantitatively for active transport processes for example that is limiting their predictive power and possibility to predict concentrations at target sites as mentioned above. PBPK models need also further development in the field of biologics where their application is relatively limited to exploratory questions so far.

Translational PK/PD modeling of both efficacy and safety provides a robust support to drug development programs when implemented in early stage development [7,8]. It offers the potential to extrapolate the pharmacological response in humans based on the exposure-response relationship in the animal species, after accounting for species differences [9].

Translational PK/PD modeling enables the extrapolation and prediction of the PK, safety, and efficacy of a clinical candidate in human. Its utility in the context of drug development is exemplified in the case studies presented herein (Boxes 1–3). For instance Figs 2 and 3 integrate and visually summarize the PK/PD characteristics of two Roche drug candidates (Compounds 1 and 2, respectively). Such graphs are useful tools to promote the understanding of efficacy in the context of safety and to facilitate decision making for development and clinical teams as well as management.

In the early clinical development phase it predicts the range of efficacious and tolerable target exposure, supports the selection of the most favorable dosage regimen and study design elements such as selection of predictive PD biomarkers and PK sampling time points. Many anticancer drugs have, for example, a narrow therapeutic window. Profiling the therapeutic window in preclinical species and its extrapolation to humans are crucial steps. A third case study is presented describing how a translational PK/PD model for efficacy (Fig. 4a,b) and safety (Fig. 5a,b) was applied to select the most favorable dosing regimen in humans (Box 3). The translational PK/PD model revealed that the dosing regimen is a determinant of the therapeutic window. Modeling enabled the optimization of the dosing regimen for the EIH trial and maximized the chances of success in clinical development.

Leveraging quantitative translational approaches during early phases of R&D

Quantitative translational approaches are key to build confidence in the target and compound. These model based approaches applied across the discovery and development value chain help to characterize mechanistically the concentration-effect relationship, understand the PK/PD relationship required to turn a compound into a medicine, and assess the translatability of PK/PD from preclinical to clinical.

During the discovery and development process PK/PD is fundamental to address questions such as:

- Do we have a druggable target?
- What degree of target engagement is needed for the MOA (stimulus, continuous, partial)?
- How can effective drug concentrations be achieved at the site of action?
- Will the target interaction lead to the desired pharmacological activity?
- What PK and PK/PD properties would be ideal for the drug to optimize the target interaction?

These approaches are also very informative to understand pathway modulation, disease, biomarkers and help to address questions such as:

- How will the MOA change the pathophysiology in absence and presence of other drugs?
- What biomarkers can be explored to support drug development and patient selection?

Three case studies shared in more detail in Boxes 1–3 illustrate how translational PK/PD has helped projects increase the likelihood of technical success at Roche.

Examples

Box 1. Integrated description of PK, safety, and efficacy in human to guide clinical development

According to the amyloid hypothesis, aggregation of amyloid β (Aβ) peptides in the brain with plaque formation plays a pivotal role in the pathogenesis of Alzheimer's disease and the onset of cognitive impairment. Aβ is generated through cleavage of the amyloid precursor protein (APP) by the β-site APP cleaving enzyme 1 (BACE1). Inhibition of BACE1 cleavage activity is therefore believed to be a meaningful therapeutic strategy for preventing Alzheimer's disease and delaying its progression.

The small molecule Compound 1 was developed at Roche as a BACE1 inhibitor and progressed into early clinical trials. During nonclinical development the compound exhibited adequate Aβ inhibition in numerous animal models while eliciting undesired QT_c prolongation in cynomolgus monkey. Measurements of Aβ40 concentration in plasma and QT_c interval duration were collected in a first-in-human SAD study to test its efficacy and safety, respectively. The data were used to develop PK/PD models and support further clinical development. Human PK was described with a PBPK model, Aβ40 data with an inhibitory indirect response model, and QT_c prolongation with a direct effect model (hockey stick threshold model) [10].

Fig. 2 shows the modeled dose–response curves for efficacy and safety under pharmacokinetic steady state conditions. The plot indicates that the efficacious dose delivering the target 50% Aβ40 inhibition at trough at steady state is not associated with significant QT effects in terms of both mean and maximum ΔQT_c (corresponding to the ΔQT_c associated with C_{max}).

This graphical representation provided a succinct yet comprehensive picture of the compound's pharmacology. It supported communication of results and efficient decision making in clinical development. Of particular benefit to the team was the possibility to draw an immediate relation between dose, efficacy and safety. Even if they are not explicitely depicted, such representations integrate also the impact of further variables, such as time or drug concentration at the site of action, as well as nonlinearities in PK and PD. As a consequence, such PKPD model can be used to explore the possibility of having dosing regimens that would enable to achieve the desired pharmacological effect with no significant QT effects.

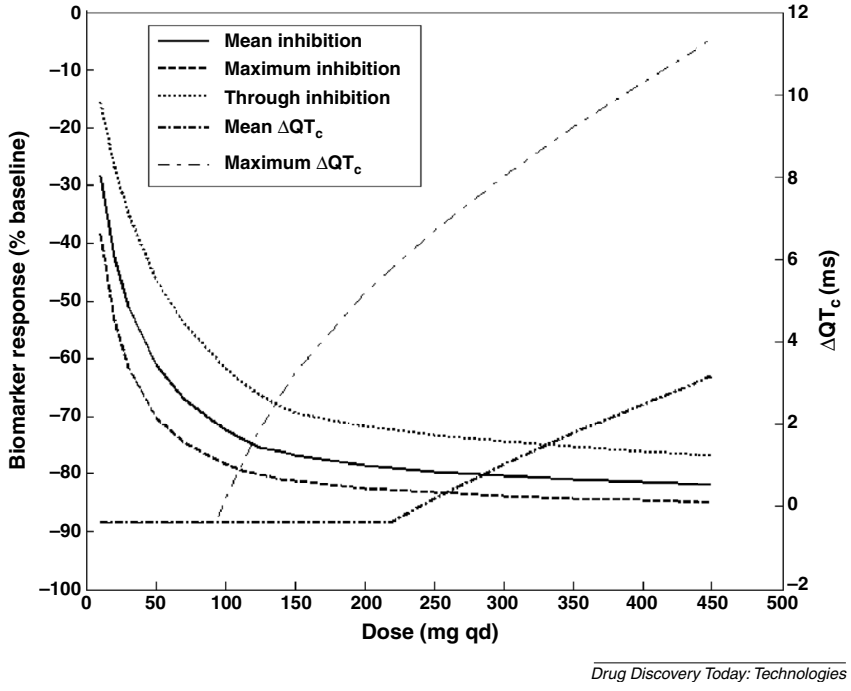

Figure 2. Steady state dose–response relationships of Compound 1 for efficacy and safety in human based on modeling of SAD study results. Solid, dashed, and dotted lines: mean, maximum, and trough Aβ40 inhibition over 24 h in plasma expressed as a percentage of baseline, respectively. Dash-dotted lines: mean and maximum ΔQT_c over 24 h as a function of administered dose.
Figure modified from [10].

Box 2. Impact of formulation on the therapeutic index of Compound 2

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have demonstrated potent antidepressant effects. In fact several these pharmaceuticals have received approvals and are on the market today. As an extension of SSRIs and SNRIs, several triple (serotonin, norepinephrine, dopamine) reuptake inhibitors (TRIs) are currently under development with the expectation that adding the dopaminergic action would enhance the therapeutic benefit. Compound 2 was developed at Roche as an investigational agent in this new pharmaceutical class and tested in early clinical trials. PBPK/PD modeling was applied to relate the efficacy and safety of Compound 2 and to predict the influence of formulation on its therapeutic index. Plasma exposure data from a first-in-human SAD study were used to develop a PBPK model describing human pharmacokinetics [10]. Receptor occupancy was considered a surrogate for efficacy and it was modeled with a direct effect E_{max} model based on *in vitro* binding and human PET data. The efficacious dose was selected based on the steady state trough plasma concentration leading to the desired receptor occupancy, as determined in preclinical efficacy models. Drugs targeting monoamine transporters have been reported to exhibit cardiovascular side effects in human including increases in blood pressure [11]. Thus, an indirect response model previously developed to describe blood pressure changes in the beagle dog was modified to predict the response in human. The system-specific parameters (baseline systolic and diastolic blood pressure, SBP and DBP respectively, turnover rate) were adjusted, whereas the pharmacological potency was assumed comparable between species [9].

The model was used to predict the transient SBP changes associated with the efficacious dose. It was also employed to simulate the impact of different formulations on the therapeutic index. A similar approach aiming to minimize drug-induced SBP changes was successfully explored by Stroh *et al.* (reference: Stroh) for a different investigational compound. Assuming a 40 mg qd dose is required for efficacy, it was found that a controlled release (CR) formulation characterized by 90% release after 10 hours would lead to a peak SBP increase 5 mmHg smaller than the one predicted with an immediate release formulation. The integrated illustration of Compound 2 efficacy and safety in human shown in Fig. 3 was instrumental in discussions of the development team and management around the opportunity to develop a modified release formulation. The CR paradigm remains to be tested in the clinic. The PBPK/PD approach provides the opportunity to address such question prospectively and in the absence of clinical data and on the basis of predicted human pharmacokinetic profiles with PBPK.

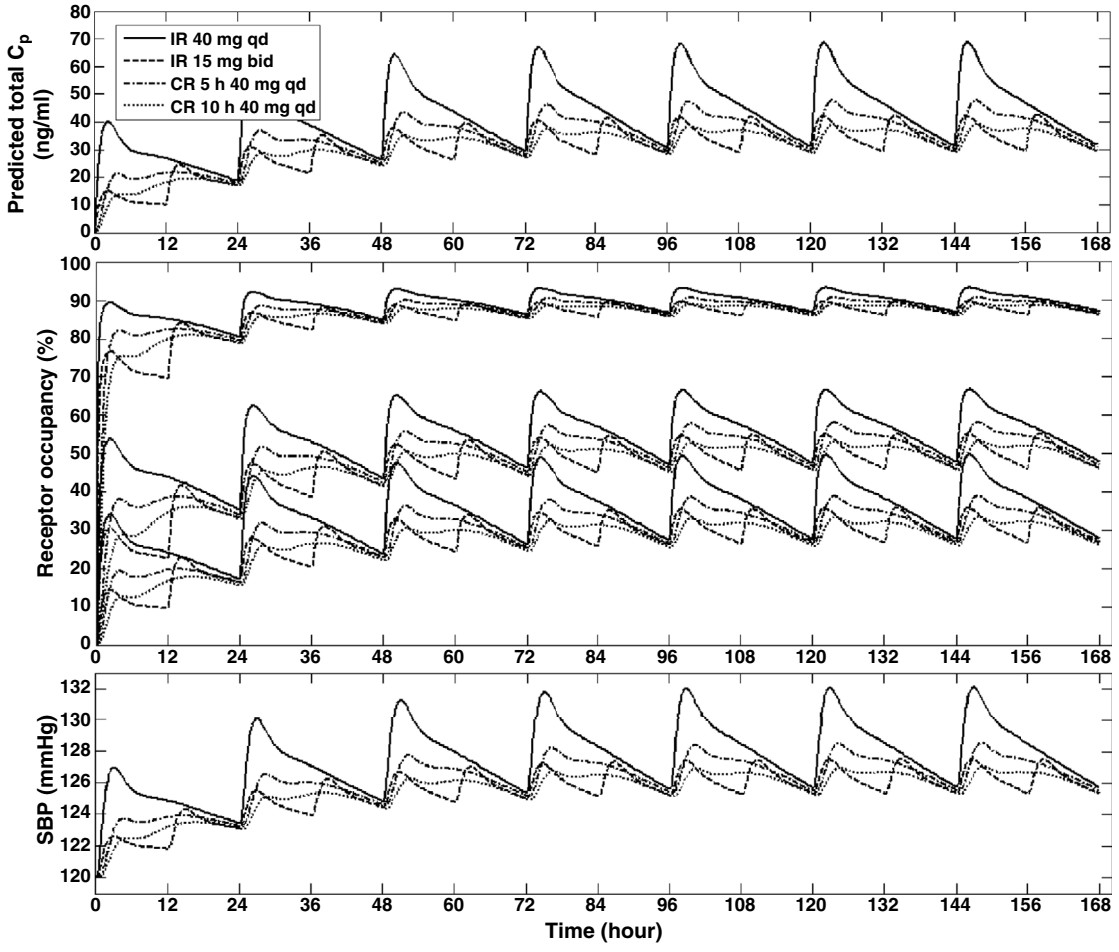

Figure 3. Simulated time course of human plasma concentration (top), occupancy of the three targeted monoamine transporters: DAT, NET and SERT (middle), and systolic blood pressure (bottom) for one week of Compound 2 administration. Solid, dash-dotted, and dotted lines: simulated administration of the therapeutic dose (40 mg qd) with immediate release (IR) and controlled release (CR) formulation. Two CR formulations were simulated, with 90% release after 5 or 10 hours. Dashed lines: simulations of 15 mg bid administration with IR formulation, achieving similar trough concentrations at steady state as 40 mg qd. The target receptor occupancy was defined at trough under pharmacokinetic steady state conditions.
Figure modified from [10].

Box 3. Impact of dosing regimen on the therapeutic window and prediction of most favorable regimen before EIH

The MDM2 antagonist RG7112 has demonstrated clinical activity in cancer patients, however daily administration was poorly tolerated with thrombocytopenia and neutropenia as dose-limiting toxicity [12]. The back-up molecule RG7388 has the same mechanism of action with improved potency and selectivity [13]. To evaluate and increase the chances of success of this back-up molecule, a model-based approach was applied to predict the most favorable dosing regimen in cancer patients based on preclinical data. First, a PK/PD model was used to describe the time-course of drug exposure and its anti-cancer effect assessed in xenograft tumor mice (Fig. 4a). The PK/PD model suggests that chronic dosing is not required for anti-cancer effects. Since hematological toxicities are typically reversible, intermittent dosing regimens are expected to have better tolerability since they allow the system to recover during drug holiday period. Simulations were conducted to identify intermittent dosing regimen with sustained anti-cancer effect [13]. A follow-up study was conducted with the proposed intermittent dosing regimens. The study confirmed the model prediction and the proposed intermittent dosing regimens resulted into tumor growth inhibition $\geq$95%. In addition, the increase in lifespan relative to control was monitored [13]. Independent of the dosing schedule, total exposure was observed to correlate with increase in life span (Fig. 4b).

For prediction of the toxicity, a translational PK/PD model was developed to describe the time-course of the drug-induced thrombocytopenia [14]. The model allows to separate system-specific (platelet baseline level, maturation time, rate of progenitor production, feedback regulation) and drug-specific (e.g. drug potency) parameters [14,15] in cynomolgus monkey after single dose. The model was verified with repeat dose data and then scaled to humans by accounting for system-specific differences while assuming drug potency to be the same across (Mager *et al.*). Human PK was predicted by a PBPK model and linked to the scaled thrombocytopenia model.

Simulations were conducted to predict the time-course of drug-induced thrombocytopenia in humans [14] for two cycles (2×28 days). Different dosing regimens were compared (Fig. 5b) such as 5 days on/23 days off, $3\times$ weekly followed by a 1-week drug holiday period ($3\times$ qw/7 off) and 21 son/7 off targeting the same total exposure per cycle with $\leq$ grade 3 thrombocytopenia ($\geq 25 \times 10^9$/L). Dosing regimen was predicted with $\leq$ grade 3 thrombocytopenia. As a result, the more dose intense regimen (5 days on/2 days off) was assumed to be better tolerated as the less intense dosing regimen at the same total exposure. In this case study, translational PK/PD of both efficacy and safety allowed to understand the impact of dosing regimen on the therapeutic and enabled to select an optimal dosing regimen for EIH trial and increase the chance of success in clinical trial.

The clinical information (PK and thrombocytopenia) obtained for RG7112 was key to build confidence in the model and simulations performed for RG7388. This gave confidence that RG7388 was clearly differentiated from RG7112 and offered a more favorable risk benefit for the patient.

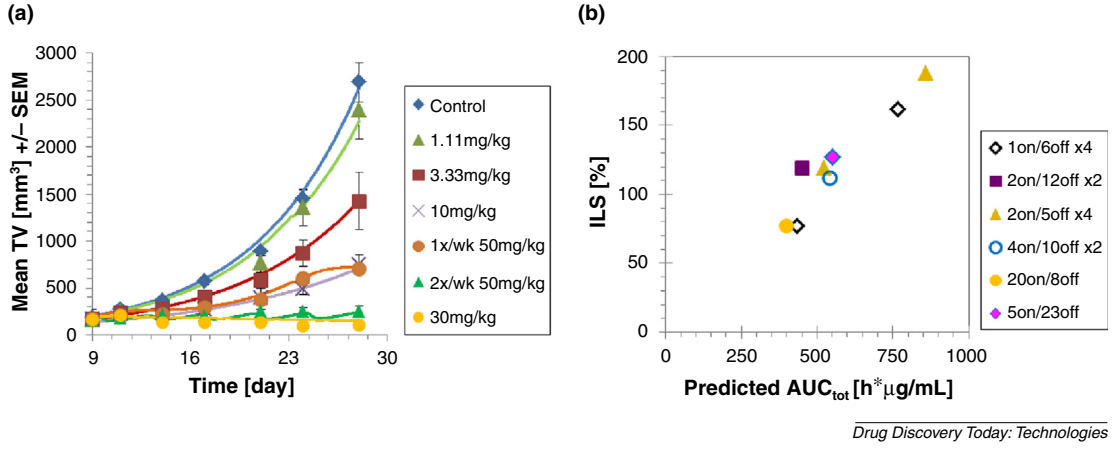

Figure 4. PK/PD relationship of anti-cancer effect with RG7388. **(a)** Tumor growth inhibition profiles in SJSA xenograft mice. Mean observed tumor volumes (symbols, $\pm$standard error of the mean (SEM)) and model predicted tumor volume (solid lines) over time. **(b)** Increased life span (ILS) relative to control group versus total exposure (AUCtot).

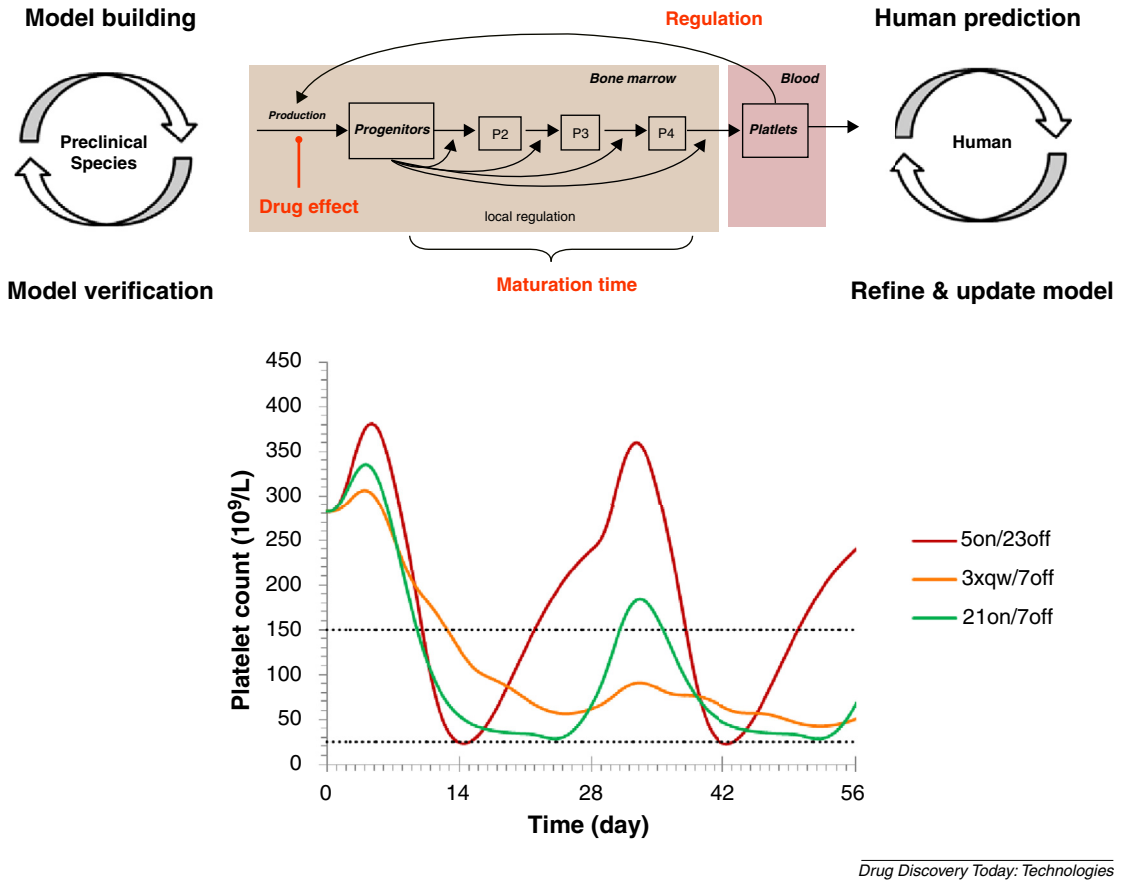

Figure 5. (a) Translational PK/PD modeling approach to predict thrombocytopenia in humans based on preclinical data. **(b)** Simulated platelet response in humans for two cycles (2 × 28 days) with different dosing regimen (5 days on/23 days off, 3× qw, 21 days on/7 off) achieving the same total exposure per cycle.

Conclusion

Translational PBPK and PK/PD modeling are used at Roche to contribute toward increasing confidence in targets and drug candidates. This review illustrates the impact of the translational paradigm with examples from drug discovery and development programs.

The need to increase probability of success in Phase II through stronger confidence in target and compound established at an early stage in discovery represent a great opportunity for further development and systematic implementation of these translational modeling approaches.

By taking advantage of pharmacokinetics, pharmacological and safety information, quantitative translational approaches help to make research more predictive. These can also guide optimization strategies by identifying relevant properties for turning drug candidates into medicines for patients.

The examples described herein demonstrate the value for project teams and impact on decision making. These case studies justify and encourage continued investment and efforts to fully leverage the potential of translational approaches in drug discovery and clinical development. These efforts need to include considerations such as continuing to build acceptance and understanding through clear project strategies that embed model based approaches; establishing strong partnership with project teams and external strategic partners; using interdisciplinary approaches to develop platform models for DMPK, disease and safety.

Conflict of interest

The authors have no conflict of interest to declare.

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