PERSPECTIVE

Transforming Translation Through Quantitative Pharmacology for High-Impact Decision Making in Drug Discovery and Development

Neeraj Gupta[1,*], Dean Bottino[1], Ulrika S.H. Simonsson[2], Cynthia J. Musante[3], Tjerk Bueters[4], Theodore R. Rieger[3], Sreeraj Macha[5], Marylore Chenel[6], Craig Fancourt[4], Jitendra Kanodia[7] and Satyaprakash Nayak[3]

This perspective emphasizes the role of quantitative translational pharmacology to bridge science and practice to make better, faster, and efficient decisions in drug discovery and development. Case studies crowdsourced from the American Society for Clinical Pharmacology and Therapeutics (ASCPT) Impact and Influence Initiative demonstrate improved efficiency, increased confidence in biomarkers or demonstrate the potential for time and resource savings, including timely program terminations.

Despite promising advances in our understanding of disease biology, drug target discovery, and innovations in therapeutic modalities, the likelihood of success in drug development remains low. Lack of robust translation from preclinical pharmacology to clinical efficacy or failure to establish proof of concept at phase II to III decision point can lead to expensive late-phase failures while consuming vital patient resources. To overcome some of these challenges, model-informed drug discovery and development has gained substantial attention across the pharmaceutical industry, and a pilot program to explore its applications has also been started by the US Food and Drug Administration (FDA).[1,2] Quantitative models built upon biologically plausible hypotheses offer a powerful framework for translation across mechanisms, species, patient populations, and clinical contexts of use.

The *Impact and Influence Initiative* of the Quantitative Pharmacology (QP) Network of the ASCPT aims to highlight the most impactful examples of QP application. As a part of this initiative, we crowdsourced a compendium of case examples demonstrating the innovative applications of QP throughout the drug development process. Thirty-seven case examples were received in 2017, and case studies related to rational dose selection for pivotal trials, reduced trial burden for vulnerable populations, or simplified posology have been reported previously.[3] Herein, we showcase selected examples identified across the preclinical discovery to clinical development continuum, in which QP played a transformational role that resulted in increased confidence in biomarker-driven decisions, or improved efficiency, or helped save resources by early program terminations (**Figure 1**).

TRANSLATIONAL APPROACHES TO INCREASE CONFIDENCE IN BIOMARKER-DRIVEN DECISIONS

Precision medicine development has traditionally relied on establishing statistical associations between predictive biomarkers and clinical outcomes.[4] Confidence in hypotheses and trial designs for investigations in select patient populations can be enhanced through formal incorporation of molecular profiling data in a population pharmacokinetic/pharmacodynamic (PK/PD) analytical framework. Bottino *et al*. developed a longitudinal kinetic model to assess relationships between exposure and tumor size accounting for exposure variability and baseline target single nucleotide polymorphism status (biomarker) as drivers of antitumor effect for an investigational Aurora A kinase inhibitor. Viewed from a broader perspective, such a holistic approach provides a more accurate estimate of effect size for quantifying the relationship between biomarker status and response. Such integrative pharmacometric models that incorporate PK and

[1]Millennium Pharmaceuticals, Inc. (a wholly owned subsidiary of Takeda Pharmaceutical Company Limited), Cambridge, Massachusetts, USA; [2]Uppsala University, Uppsala, Sweden; [3]Pfizer Inc, Cambridge, Massachusetts, USA; [4]Merck & Co., Inc, Kenilworth, New Jersey, USA; [5]Sanofi, Bridgewater, New Jersey, USA; [6]Servier, Suresnes, France; [7]Theravance Biopharma US, Inc., South San Francisco, California, USA. *Correspondence: Neeraj Gupta (Neeraj.Gupta@takeda.com)

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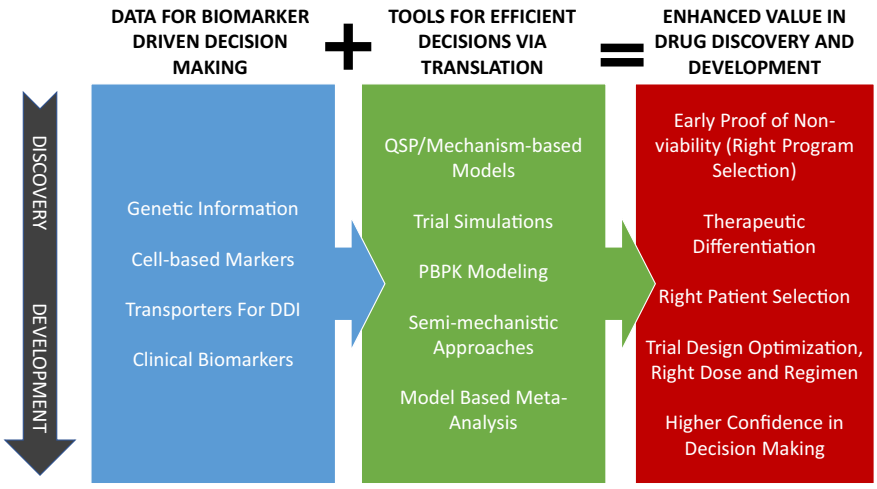

Figure 1 Transforming translation through quantitative pharmacology. DDI, drug–drug interaction; PBPK, physiologically-based pharmacokinetics; QSP, quantitative systems pharmacology.

biological variability, developed from data collected in early clinical development, can serve as powerful priors to inform simulations and performance characteristics of pivotal clinical study designs and increase confidence in decision making.

Drug development for neurodegenerative disorders can be particularly challenging due to the lack of confidence in translation from preclinical pharmacology models of human pathophysiology. In early clinical development, experimental clinical pharmacology models used to evaluate proof of mechanism do not replicate clinical disease pathology. One such example is the scopolamine challenge test that is used for development of agents to treat cognitive dysfunction, a pharmacotherapeutic class associated with high rates of late-phase failure.[5] Traditional protocols for conducting the scopolamine challenge test in healthy subjects are typically based on historical design elements (e.g., scopolamine dose). Macha *et al.* developed an indirect response PK/PD model to characterize the effect of donepezil on scopolamine-induced cognitive impairment demonstrating superior performance characteristics with the use of 0.8 mg scopolamine as compared with the standard dose of 0.5 mg. This example illustrates the power of PK/PD modeling to enhance the design of experimental medicine studies and improve the fidelity of PD biomarker-based decision making. Along similar lines, Fancourt *et al.* describe application of a joint PK/PD mechanistic model-based meta-analysis (MBMA) to explain insulin PK and action during a glucose clamp in both nondiabetics and type 1 diabetics, thereby enabling efficient translation and design of multiglycemic clamp studies.

PRECLINICAL TO CLINICAL TRANSLATION FOR EFFICIENT DECISIONS

Physiologically-based pharmacokinetic (PBPK) and quantitative systems pharmacology (QSP) models are particularly valuable in translating the results of preclinical studies to clinical effects where species differences can be captured through differences in biological system parameters and incorporation of on-target and off-target (systemic) drug effects. One such example is in the prediction of human PK and drug–drug interactions at the level of transporter-mediated clearance. Chenel *et al.* illustrate application of a PBPK framework for predicting interactions between an investigational agent and probe substrates for renal transporters, thereby laying the groundwork for obviating the need for clinical drug–drug interaction studies. Furthermore, a QSP framework for drug–target interactions can be particularly valuable for engineering molecules in drug discovery settings when dealing with complex modalities such as bispecific antibodies or drug delivery systems. Kanodia *et al.* describe the optimization of bispecific antibody affinity to transferrin receptors for enhancing brain penetration and thus potentiating the desired therapeutic response. A notable advantage of PBPK and QSP models is their ability to predict drug effects on endpoints that may be inaccessible for direct measurement in the clinical setting. Musante *et al.* describe a QSP model of nonalcoholic fatty liver disease calibrated for performance using preclinical data in a rat model, thereby providing a valuable translational framework for predicting relationships between drug exposure, proximal PD biomarkers, and reduction in liver fat. Models of this nature hold promise for *in silico* simulation of alternative clinical trial designs aimed at selection of appropriate design elements (e.g., dose and regimen) that would maximize probability of clinical success for achieving outcomes (e.g., liver fat reduction) not otherwise readily measurable in studies seeking signs of clinical activity.

Combination therapy is increasingly becoming the norm in oncology drug development, necessitating the need for objective analytical frameworks that can help define optimal dose combinations. Bottino *et al.* describe combined modeling of clinical exposure–safety relationships and exposure–efficacy relationships for antitumor activity in preclinical xenograft models to inform the dose escalation strategy and determination of the optimal recommended phase II dose for a novel drug combination. A key lesson learned from this example is that although multiple dose pair combinations may be equivalent from a safety standpoint and represent alternative maximum tolerable doses, not all the combination dose pairs would be expected to be comparable in their efficacy, thus requiring careful discrimination to "pick the winner" for proof of concept trials.

ENHANCING VALUE THROUGH DRUG DISCOVERY AND DEVELOPMENT

Model-informed approaches can enhance value, beginning as early as drug discovery through clinical drug development. When the mechanistic underpinnings of drug action are well understood with points of reference in the clinical literature to inform biological target validation, QSP models can serve as a valuable quantitative framework for reverse translation. One example of such an application is in glucose

Table 1 Examples of strategic integration of quantitative pharmacology to inform key translational decisions across the research and development continuum

Translation category	Question	Methodology	Impact
Translational approaches to increase confidence in biomarker-driven decisions	How much do genetic information and baseline levels of biomarkers drive variability in therapeutic effect?	Dose-exposure-tumor kinetic modeling to determine strength of baseline biomarker as driver of antitumor effect	These methods have the potential to tease out the relative contributions of baseline biomarker differences (e.g., SNP status) and pharmacokinetic variability to the antitumor effect of a drug (see case example by Bottino *et al.* in **Supplementary Material**)
	Can a meta-analysis help to optimize scopolamine challenge study design to evaluate NCEs targeting cognition impairment?	An indirect effect model with effect compartment was used to describe PK/PD relationship	A higher scopolamine dose is required to obtain a more robust and consistent effect size in scopolamine challenge studies (see case example by Macha *et al.* in **Supplementary Material**)
	How does the insulin PK/PD relationship change as a function of glucose clamp target in clinical studies to enable design of multi-glycemic clamp study and dose selection for comparator arm?	A joint PK/PD mechanistic model to describe insulin PK and action during the hyperinsulinemic clamp for T1DM and ND populations and varying glycemic levels	This model was used to select dose for the comparator arm for (multi) glycemic clamp studies in both healthy subjects and T1DM patients (see case example by *Fancourt et al.* in **Supplementary Material**
Preclinical to clinical translation for efficient decisions	Can model-based approaches be used to predict renal transporter-mediated DDI?	PBPK model was used to predict renal transporter-mediated DDI	PBPK modeling approach gave a better prediction of the extent of DDI than the static predictions; therefore this can be considered a potentially valuable tool within drug development including replacing clinical studies (see case example by Chenel *et al.* in **Supplementary Material**)
	Given the observed clinical toxicity and our preclinical understanding of exposure-response, what tolerable dose pair will provide optimal antitumor effect?	Simultaneous safety/efficacy modeling to determine optimal doses for an anticancer drug combination	This is a general methodology that can be applied to any early phase oncology combination for which preclinical antitumor and clinical safety data are available (see example by Bottino *et al.* in **Supplementary Material**).
	How can we predict optimal anti-TfR affinity for human brain penetration and expected clinical activity of anti-TfR bispecific antibodies based on preclinical studies?	Mechanistic PK/PD model for bispecific anti-TfR/BACE1 antibodies that accounts for antibody-TfR interactions at the BBB as well as the pharmacodynamic (PD) effect of anti-BACE1 arm	Illustration of reverse translation where various characteristics of bispecific antibodies, transferrin kinetics, and brain targets were used to more quantitatively design novel drugs. In principle, this approach eliminates drugs that are unlikely to work in the clinic and thus helps save time and money (see case example by Kanodia *et al.* in **Supplementary Material**)
	Can we use a mechanistic model to predict efficacy for a treatment for fatty liver disease given that early clinical studies cannot directly measure changes in liver fat?	Quantitative systems pharmacology (QSP) model	The model quantified both the therapeutic potential for the novel treatment and showed some of the variability in response. The model can be used for testing questions about clinical design (e.g., inclusion/exclusion, duration, dose) in future (see case example by Rieger *et al.* in **Supplementary Material**)

(Continued)

Table 1 (Continued)

Translation category	Question	Methodology	Impact
Enhancing value through drug discovery and development	How to optimally select clinical anti-TB drug combination regimens from preclinical studies using a translational pharmacometric approach?	Multistate tuberculosis pharmacometric model and general pharmacodynamic interaction model	Translation of preclinical TB information into clinical setting (especially dose selection in phase IIA and/IIB or III) and efficient evaluation of drug combinations already in phase IIA to identify the most efficacious drug combination as early as possible (see case example by Wicha *et al*. in **Supplementary Material**)
	Does the compound have sufficient differential potential from SoC to support continuation of Ph1b POC study in patients?	A model-based meta-analysis (MBMA) of competitors and early patient data	How MBMA can be used to focus on "differentiation value" early in the development process through early data integration and make “no go” decisions (see case examples by Simonsson *et al.*, Fancourt *et al*. in **Supplementary Material**)
	Can a dual GLP-1 + GIP agonist sufficiently differentiate from existing GLP-1 agonists for the treatment of T2DM?	QSP modeling of literature data on incretin biology and their effects on both healthy volunteers and patients with T2DM	Even though several optimistic assumptions around GIP's activity in patients with diabetes were made, the hypothetical dual incretin did not sufficiently differentiate from existing GLP-1 products to justify further investment. The QSP model was a contributing piece that allowed the project team to make their recommendation with confidence to management (see example by Musante *et al*.)

BACE1, beta-secretase 1; BBB, blood-brain barrier; DDI, drug–drug interaction; GIP gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1; NCE, new chemical entity; ND, nondiabetic; PBPK, physiologically-based pharmacokinetic modeling; PhIb, phase Ib; PK/PD, pharmacokinetic/pharmacodynamic; POC, proof of concept; QSP, quantitative systems pharmacology; SNP, single nucleotide polymorphism; SoC, standard of care; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TB, tuberculosis; TfR, transferrin receptor.

regulation via incretin hormone pathways and associated drugs for type 2 diabetes mellitus. Rieger *et al*. integrated knowledge of incretin biology and the clinical effects of GLP-1 (glucagon-like peptide-1) agonists to quantify value differentiation for a hypothetical dual GLP-1/GIP-1 (gastric inhibitory polypeptide-1) agonist in a drug discovery setting. In the model, the hypothetical dual incretin did not sufficiently differentiate from existing GLP-1 products to justify further investment. Comparison of predictions with numerous marketed therapies with similar mechanism-of-action (e.g., liraglutide and sitagliptin) were key factors in providing the *in silico* proof of nonviability for differentiation, resulting in early program termination. Key focus of the work was predicting efficacy above and beyond a GLP-1 agonist alone and not effect of dual agonist on food intake and effect of body weight.

Similarly, MBMA has shown promise in making better decisions in drug development by providing a quantitative framework that can enable forecasting the probability of superiority over emerging competition and standard of care during early clinical development of investigational agents. Such analyses can enable assessment of competitiveness and potential for achieving expectations outlined in the target product profile. Bueters *et al*. used MBMA to compare the probability of superiority of an investigational agent with competitors in phase II (~100 patients) and standard of care data from various studies (>100,000 patients). Quantitative analysis enabled efficient decision making on a moderately effective drug, albeit based on limited data. Based on the limited available options to revise the clinical strategy and the competitor being substantially ahead in the development, the decision was made to discontinue the program.

A crucial step for accelerating drug development is bridging the gap between preclinical and clinical trials. QP allows for transforming the translation in an efficient way by allowing incorporation of preclinical pharmacology into clinical trial simulations and, if possible, using a disease model as the key component. Wicha *et al*. describe a preclinical model-informed translational pharmacometrics approach to predict drug effect in early tuberculosis clinical trials using the *in vitro*-based multistate tuberculosis pharmacometric model as disease model. This translational model approach can be used to predict the clinical dose–response relationships for antimycobacterial drugs and uses, multiple translational factors (e.g., target site exposures, postantibiotic effects, mycobacterial factors, minimal inhibitory concentration distribution, human PK, and PK covariates), thereby providing an objective framework for clinical trial simulations to guide design of phase II trials with dosing regimens most likely to succeed.

In principle, these types of translational paradigms can be broadly applied in drug

development with significant potential for enhancing global health using a totality of evidence mindset.[6]

SUMMARY

Realizing the potential of translational medicine in drug discovery and development demands application of an integrative approach that pivots to a culture of model-informed drug discovery and development. This perspective showcases several examples for strategic integration of modeling & simulation throughout the research & development continuum to drive informed decisions (**Table 1**). These examples illustrate impactful decisions across diverse contexts, including molecular drug design, dose optimization, biomarker qualification, patient selection, acceleration of clinical development, early proof of nonviability and therapeutic differentiation, and enhanced clinical trial design. We hope that these examples stimulate continued cross-disciplinary application of QP approaches throughout drug discovery and development.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

Supplementary Materials

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CONFLICT OF INTEREST

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