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WHITE PAPER

Applications of Quantitative Systems Pharmacology in Model-Informed Drug Discovery: Perspective on Impact and Opportunities

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Quantitative systems pharmacology (QSP) approaches have been increasingly applied in the pharmaceutical since the landmark white paper published in 2011 by a National Institutes of Health working group brought attention to the discipline. In this perspective, we discuss QSP in the context of other modeling approaches and highlight the impact of QSP across various stages of drug development and therapeutic areas. We discuss challenges to the field as well as future opportunities.

BACKGROUND/MOTIVATION

During the past decade, quantitative systems pharmacology (QSP) has gained traction within the pharmaceutical industry as a modeling method to quantitatively and mechanistically describe diseases and the complexity of drug action. The preclinical QSP working group, within the Translational and ADME Sciences Leadership Group (TA LG), as part of the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ), was formed in 2016 to bring together representatives across the pharmaceutical industry with objectives to share knowledge, assess the current landscape of QSP modeling in the preclinical space of research and development, and discuss/align on best practices. The goals of this white paper are to (i) discuss and highlight how QSP modeling has impacted drug discovery efforts across multiple therapeutic areas; (ii) examine similarities and differences between various modeling approaches and gain alignment within the modeling and simulation community on definitions and terminology; (iii) discuss some of the challenges and barriers to more widespread use of QSP in industry, underscoring the strengths and limitations of QSP modeling; and (iv) provide recommendations for its use in preclinical research as well as future opportunities.

In 2011, a National Institutes of Health (NIH) Workshop hite Paper was published that brought widespread attention to QSP.[1] In that white paper, QSP was defined as "an approach to translational medicine that combines computational and experimental methods to elucidate, validate and apply new pharmacological concepts to the development and use of small molecule and biologic drugs," with a purpose of understanding "in a precise, predictive manner, how drugs modulate cellular networks in space and time and how they impact human pathophysiology."[1] In practice, this broad scope suggests that QSP may include several disciplines, methodologies, and applications. Thus, this presents a challenge in alignment, communication, and general understanding of what QSP is (and is not) both within and outside of the modeling and simulation community. In this paper, we expand on this, discussing similarities and differences between various modeling approaches and put forth a recommendation to clarify the definition of QSP modeling by stipulating certain model structural requirements.

BASIC PRINCIPLES

QSP is a discipline that integrates computational modeling of biological systems with that of pharmacologic systems. With advances in high throughput -*omic* technologies (genomics, transcriptomics, proteomics, and metabolomics) and increasing computational power and bioinformatic methodologies, there has been a surge in experimental data availability across several biological scales, time scales, and species. A quantitative framework, which requires the integration of diverse computational methodologies, is necessary to leverage this "big data" to enable understanding of disease pathophysiology and identify and test therapeutic strategies. QSP modeling can be used to integrate data across scales to understand the interacting network elements and bridge molecular to systems level scales. Further discussion of big data and model integration in QSP is covered elsewhere.[2–4]

The ultimate goal of QSP is to mechanistically and quantitatively understand a biological, toxicological, or disease

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process in response to therapeutic modulation. Typically, formal mathematical models are developed that incorporate data at several temporal and spatial scales and include sufficient biological information to allow for extrapolation beyond the data used to develop and/or qualify the model. Furthermore, to be maximally impactful within preclinical drug discovery, QSP models should be fit for purpose to address specific questions, be actionable, and built within a time frame that accommodates the rapid pace of decision making. Although a detailed discussion of the technical aspects of QSP modeling is beyond the scope of this work, several reviews and technical papers on QSP modeling are available.[5–11]

QSP modeling has been leveraged throughout preclinical drug discovery to interrogate both therapeutic and toxic actions of drugs across therapeutic areas including metabolism, autoimmunity, oncology, and neuroscience as well as several others. As indicated in the 2011 NIH Workshop White Paper, a role for both industry and academia was envisioned for the development and implementation of QSP, whereby the pharmacokinetic-pharmacodynamic (PKPD) experience in the former would integrate with the systems biology interests of the latter. This coming together has occurred in different ways including publication of models by academia that can then be used in industry, in partnership between academia and industry, through third-party vendors to build QSP models[12] that use industry-generated PKPD and/or mechanistic data and through precompetitive consortia (e.g., DILIsym, QSP Immunogenicity Consortium, etc.). Several examples of these published models are captured here (see **Table 1**).

DEFINITION AND TERMINOLOGY

Well-defined terminology provides direction, focus, and branding for a scientific discipline. In a corporate environment, it may also contribute to resourcing discussions as well as assessments of return on investment. Admittedly, it is a challenge to define in practice the broad discipline that is QSP. This was evident from the preclinical QSP modeling survey that identified that QSP modeling lacks a clear definition.[12] Here we compare QSP with two potentially overlapping modeling approaches: mechanistic PKPD and physiologically-based pharmacokinetic (PBPK) and attempt to add clarity to QSP's existing definition by defining the structural elements that are inherent to QSP models.

It is important to emphasize that quantitative systems pharmacology essentially developed from and still benefits from existing, complementary modeling approaches, including systems biology, PKPD, and PBPK modeling methods. With advances in computational methods, access to new data and greater biological knowledge, a natural progression for some drug discovery questions is to move toward more mechanistic (and perhaps holistic) descriptions of the system, thereby permitting extrapolations beyond collected data sets and addressing new questions through QSP modeling. It is also important to emphasize that these modeling approaches are not exclusive, and the appropriate model should be implemented to address the question at hand. In the future, a more seamless connection between a variety of different modeling approaches may be realized as demonstrated later in the modeling approach by Wu *et al*.[13]

Comparing PKPD and QSP

Through years of implementation in drug development, PKPD modeling has demonstrated tremendous value in elucidating the relationship between the pharmacokinetics (PK) of a therapeutic intervention and the resulting pharmacodynamic (PD) effect.[14,15] This is especially true in the translational space, where estimated PKPD parameters, derived from relevant preclinical studies and appropriately adjusted for the clinical scenario, enabled prospective simulations to evaluate key drug development questions such as clinical dose level and frequency.[15,16] Over the years, translational PKPD modeling has evolved beyond empirical models to incorporate more mechanistic components to establish mechanism-based PKPD models, which facilitate biologic driven translations across species and/or between different patient populations. Although the value of PKPD modeling has been widely recognized, its main focus is to establish relationship between drug PK and selected elements of the biological system that are perturbed by a particular drug treatment. The focus on select PD end points in PKPD models, albeit parsimonious, could potentially miss other intermediate or parallel signals that are equally important because the interaction between a drug molecule and its target(s) will likely elicit a whole host of changes for multiple biosignals. As such, PKPD models may have limited capacity to extrapolate beyond collected data sets. Moreover, there could be causal linkages between these biosignals within a network of signaling pathways that cannot be ignored or dismissed. Although the degree of mechanistic detail and scientific questions addressed by PKPD and QSP models may differ, the two approaches also differ in technical aspects, such as data requirements, model implementation (e.g., data fitting vs. the use of virtual subject simulations) and model evaluation/qualification methods. These topics are addressed in greater detail elsewhere.[6,7,17–19]

It can be appreciated that a natural evolution from empirical PKPD to mechanistic PKPD to QSP occurred with a recent concerted effort to consider approaches from top-down (PKPD) and bottom-up (systems biology) perspectives. This blending of complementary perspectives was highlighted in the original QSP white paper.[1] QSP was developed to address the desire to incorporate additional biological mechanism with the potential to characterize these important biosignals together simultaneously. Although empirical PKPD and QSP are more easily differentiated from one another, in some cases, the separation of mechanistic PKPD from QSP models is less obvious, especially in scenarios where the underlying biological mechanism can be described with sufficient mechanistic detail using a parsimonious model that can subsequently extrapolate beyond existing data sets to address future questions.

Comparing PBPK and QSP

PBPK models are another type of model often debated as to whether it falls within the definition of a QSP model. Similar

Table 1 Examples of QSP impact in drug discovery

Title	Disease	Impact (focus: short description)	Company	References
Replication Vesicles Are Load- and Choke-Points in the Hepatitis C Virus Lifecycle	Antiviral	Target identification/prioritization: The model described the biology of the viral replication cycle, identified sensitive processes in the pathway	Heidelberg University/ Technische Universität Dresden	65
Development and Application of a Quantitative Systems Pharmacology (QSP) Model of Complement Pathway to Evaluate Treatments for Autoimmune Diseases	Autoimmune	Target validation and modality selection: A comprehensive QSP model of the complement pathway was developed and dosing tractability of several complement proteins were estimated by combining pharmacokinetics for small/large molecule modalities within the QSP model	GlaxoSmithKline	20
A Physiologically-Based Mathematical Model of Integrated Calcium Homeostasis and Bone Remodeling	Bone	Mechanism of action: Integrated calcium homeostasis and bone remodeling; utility to describe a range of therapeutics and disease states	Amgen	66
A Strategy for Developing New Treatment Paradigms for Neuropsychiatric and Neurocognitive Symptoms in Alzheimer's Disease	Neuroscience	Understanding disease pathogenesis and target validation: A combined QSP, phenotypic screening, and preclinical model strategy for progressing drug discovery and development for Alzheimer's disease	In Silico Biosciences/ University of Pennsylvania/ Oregon Health & Science University	67,68
A Translational Systems Pharmacology Model for Aβ Kinetics in Mouse, Monkey, and Human	Neuroscience	Understanding mechanism of compound and translation from preclinical species: A mechanistic model of Aβ production, degradation, and distribution to predict $A\beta_{42}$ inhibition for various avagacestat dosing regimens across species	Institute for Systems Biology, Moscow/Pfizer	69
A Computer-Based Quantitative Systems Pharmacology Model of Negative Symptoms in Schizophrenia: Exploring Glycine Modulation of Excitation-Inhibition Balance	Neuroscience	Combined preclinical neurophysiological network, predicted biomarker modulation in clinical trials, which is helpful to understand human neurophysiology of negative symptoms, especially with targets that show nonmonotonic dose responses	In Silico Biosciences/Oregon Health & Science University/ University of Pennsylvania	70
Systems Pharmacology Analysis of the Amyloid Cascade After β-Secretase Inhibition Enables the Identification of an Aβ42 Oligomer Pool	Neuroscience	Mechanism of action: β-secretase 1 (BACE1) inhibitor pathway modulation (amyloid precursor protein)	Leiden University	71
Mathematical Model on Alzheimer's Disease	Neuroscience	Mechanism of action: Understanding Alzheimer's disease pathogenesis; identification of combination therapies	Penn State University	72
Cross-Membrane Signal Transduction of Receptor Tyrosine Kinases (RTKs): From Systems Biology to Systems Pharmacology	Neuroscience	A systems pharmacology model based on the local physiology of receptor tyrosine kinases to characterize its dynamics and study the effects of drug intervention	Pfizer	73
A Mathematical Model of Multisite Phosphorylation of Tau Protein	Neuroscience	The development of a mathematical model of multisite phosphorylation of tau for identifying targets and biomarkers	Pfizer	74
QSP Modeling for the Identification of Key Drug Targets	Neuroscience	Target validation: Suggested a druggable target (TrkA), and predicted the necessary Ki of TrkA inhibitor for efficacy	Xenologiq/Astellas/Pfizer	75
A Humanized Clinically Calibrated Quantitative Systems Pharmacology Model for Hypokinetic Motor Symptoms in Parkinson's Disease	Neuroscience	Understanding mechanism of action and efficacy of drugs for Parkinson's; model also correctly recapitulates the lack of clinical benefit for many approved therapies, e.g., perampanel, MK-0567, and flupirtine	In Silico Biosciences/ Washington State University/University of Pennsylvania	76
Systems Pharmacology Modeling in Neuroscience: Prediction and Outcome of PF-04995274, a 5-HT4 Partial Agonist, in a Clinical Scopolamine Impairment Trial	Neuroscience	Compound efficacy prediction: Model for cognitive brain function resulting from with description of cortical neural network and neurotransmitter signaling and evaluation of 5-HT4 modulation as treatment for Alzheimer's disease	Pfizer	77
In Silico Modeling of the Effects of Alpha-Synuclein Oligomerization on Dopaminergic Neuronal Homeostasis	Neuroscience	Target identification: Homeostasis model included aggregation and degradation of the protein, exploration of possible points of drug intervention	National and Kapodistrian University of Athens	78

(Continues)

Table 1 (Continued)

Title	Disease	Impact (focus: short description)	Company	References
A Multiscale Model of Interleukin-6–Mediated Immune Regulation in Crohn's Disease and Its Application in Drug Discovery and Development	Crohn's disease	Target validation and compound efficacy prediction: Comparative study of biotherapeutic strategies targeting IL-6–mediated signaling in Crohn's disease such as IL-6, IL-6Rα, or the IL-6/sIL-6Rα complex	Pfizer	[79]
A Systems Pharmacology Model for Inflammatory Bowel Disease	Inflammatory bowel disease	Literature-based Boolean network for therapeutic target identification/validation for inflammatory bowel disease	University of Navarra/Janssen	[80]
Benefits and Challenges of a QSP Approach Through Case Study: Evaluation of a Hypothetical GLP-1/GIP Dual Agonist Therapy	Metabolic	A type II diabetes model (in PhysioLab) used to evaluate the efficacy of a hypothetical GLP-1/GIP dual agonist therapeutic	Pfizer	[81]
Systems Pharmacology Modeling of Drug-Induced Modulation of Thyroid Hormones in Dogs and Translation to Human	Metabolic	Prediction of compound efficacy and translation from preclinical species: A model of hormone physiology was developed based on *in vitro* and animal studies and used for prediction of drug-induced effects on plasma thyroid hormones concentrations in humans due to TPO inhibition	AstraZeneca	[82]
Preexisting Autoantibodies Predict Efficacy of Oral Insulin to Cure Autoimmune Diabetes in Combination with Anti-CD3	Metabolic	For type 1 diabetes to rapidly identify candidate biomarkers, which were confirmed in subsequent preclinical studies	Entelos	[83]
Virtual Optimization of Nasal Insulin Therapy Predicts Immunization Frequency to Be Crucial for Diabetes Protection	Metabolic	Model proposed optimal dose regimen and identified time frame at which biomarkers associated with disease protection were induced	La Jolla Institute for Allergy and Immunology	[84]
Model-Based Interspecies Scaling of Glucose Homeostasis	Metabolic	Model described human glucose homeostasis scaled for different preclinical species and can be applied toward translation of exposure/response	Uppsala University	[85]
Effects of IL-1β–Blocking Therapies in Type 2 Diabetes Mellitus: A Quantitative Systems Pharmacology Modeling Approach to Explore Underlying Mechanisms	Metabolic	Used *ex vivo* data of IL-1β effects on β-cell function and turnover with a disease progression model of the long-term interactions between insulin, glucose, and β-cell mass in type 2 diabetes mellitus	AstraZeneca/MedImmune	[86]
Radiation and PD-(L)1 Treatment Combinations: Immune Response and Dose Optimization via a Predictive Systems Model	Oncology	Mechanism of action: tumor dynamics of radiation and immuno-oncology (anti PD-(L)1) and optimization of the combinations and dose regimens	AstraZeneca	[87]
Therapeutically Targeting ErbB3: A Key Node in Ligand-Induced Activation of the ErbB Receptor–PI3K Axis	Oncology	Describes a computational model of ErbB signaling network. Sensitivity analysis is used to identify ErbB3 as the key node. Model predicts the effects of MM-121, an antibody inhibiting ErbB3 phosphorylation, on halting growth of tumor xenografts in mice. Particularly, model predicted that an ErbB3 antagonist would inhibit combinatorial, ligand-induced activation of ErbB-PI3K network more potently than current marketed therapeutics	Merrimack	[88]
A General Network Pharmacodynamic Model–Based Design Pipeline for Customized Cancer Therapy Applied to VEGFR Pathway	Oncology	Described a computational workflow for development of pharmacokinetic/enhanced pharmacodynamic models that can aid in new target identification and combination therapy identification	Icahn School of Medicine, Mount Sinai	[89]
Clinical Responses to ERK Inhibition in BRAF V600E-Mutant Colorectal Cancer Predicted Using a Computation Model	Oncology	Model linking pathway signaling and activation to tumor growth inhibition predicted phase I drug combination efficacy and biomarker-based patient stratification strategy	Genentech	[90]
Computational Modeling of ERBB2-Amplified Breast Cancer Identifies Combined ErbB2/3 Blockade as Superior to the Combination of MEK and AKT Inhibitors	Oncology	Mechanism of action: ErbB signaling network; optimization of dose regimen and combinations of herceptin and lapatinib	Merrimack	[91]

(Continues)

Table 1 (Continued)

Title	Disease	Impact (focus: short description)	Company	References
Computational Modeling of Sphingolipid Metabolism	Oncology/ CNS	A comprehensive model for lipid metabolism and to Alzheimer's disease (although not embedded within a physiological framework)	University of Warsaw	92
A Computational Analysis of Proangiogenic Therapies for Peripheral Artery Disease	Peripheral artery disease	Mechanism of action: Molecular signaling similarities and key differences in several classes of proangiogenic strategies	Johns Hopkins University	93
Systems Pharmacology-Based Approach for Dissecting the Active Ingredients and Potential Targets of the Chinese Herbal BJF for the Treatment of COPD	Pulmonary disease	Dissected the molecular mechanism of BJF for the treatment of chronic obstructive pulmonary disease and predicted the potential targets of the multicomponent BJF, illustrated the synergetic mechanism of the complex prescription and discovered more effective drugs against chronic obstructive pulmonary disease	Henan University of Traditional Chinese Medicine	94
Systems Pharmacology-Based Dissection of Mechanisms of Chinese Medicinal Formula Bufei Yishen as an Effective Treatment for Chronic Obstructive Pulmonary Disease	Pulmonary disease	Mechanism of action of Bufei Yishen formula to prevent COPD and its comorbidities, such as ventricular hypertrophy; by inhibiting the inflammatory cytokine, hypertrophic factors expression, protease-antiprotease imbalance, and the collagen deposition	Henan University of Traditional Chinese Medicine	95
QSP Toolbox: Computational Implementation of Integrated Workflow Components for Deploying Multi-Scale Mechanistic Models	QSP workflow	QSP workflows based on Matlab and Simbiology with capabilities in data integration, model calibration, and variability exploration using an antibody drug conjugate QSP model	Bristol-Myers Squibb	96
Systems Biology for battling Rheumatoid Arthritis: Application of the Entelos PhysioLab Platform	Rheumatoid arthritis	Describes a QSP model for rheumatoid arthritis and application to rank putative drug targets using the Entelos PhysioLab platform	Organon/Entelos	97
Identification of CXCL13 as a Marker for Rheumatoid Arthritis Outcome Using an In Silico Model of the Rheumatic Joint	Rheumatoid Arthritis	QSP model used to predict candidate biomarkers for bone erosion. One of the markers, CXCL13, was validated with clinical data	Merck	98
Alternate Virtual Populations Elucidate the Type I Interferon Signature Predictive of the Response to Rituximab in Rheumatoid Arthritis	Rheumatoid arthritis	Mechanism of action: To understand how the interferon signature may predict response to rituximab	Entelos	17
Quantitative Pharmacokinetic-Pharmacodynamic Modeling of Baclofen-Mediated Cardiovascular Effects Using BP and Heart Rate in Rats	Safety	Mechanism of action: Baclofen-mediated cardiovascular changes in rats	AstraZeneca	30
A Systems Pharmacology Model of Erythropoiesis in Mice Induced by Small Molecule Inhibitor of Prolyl Hydroxylase Enzymes	Safety	Mechanism of action: *In vivo* description of erythropoiesis regulation via the inhibition of prolyl-hydroxylase-2 (PHD2) enzyme by PHI-1 in mice	University at Buffalo/Pfizer/ Amgen	99
Multiscale Mathematical Model of Drug-Induced Proximal Tubule Injury: Linking Urinary Biomarkers to Epithelial Cell Injury and Renal Dysfunction	Safety	A systems pharmacology model for identification of biomarkers for proximal tubule (PT) epithelial cell injury and organ-level functional changes	University of Georgia/ AstraZeneca	34
Characterization and Prediction of Cardiovascular Effects of Fingolimod and Siponimod Using QSP	Safety	A QSP CVS model to identify total peripheral resistance and heart rate as the site of action for fingolimod using *in vitro* binding assays	Novartis/Leiden Academic Centre for Drug Research	32
Application of A Systems Pharmacology Model for Translational Prediction of hERG-Mediated QTc Prolongation	Safety	Integrated preclinical *in vitro* (hERG binding) and *in vivo* (conscious dog ΔQTc) data of three hERG blockers (dofetilide, sotalol, moxifloxacin) to compare the *in vivo* efficacy of the three drugs	Leiden University/Janssen/ Merck	33
The Role of Quantitative Systems Pharmacology Modeling in the Prediction and Explanation of Idiosyncratic Drug-Induced Liver Injury	Safety	Describes the application of DILISym	DILISym	23

(Continues)

Table 1 (Continued)

Title	Disease	Impact (focus: short description)	Company	References
A Mechanistic, Multiscale Mathematical Model of Immunogenicity for Therapeutic Proteins: Part 1—Theoretical Model	Safety	By recapitulating key biological mechanisms, the model suggested mechanistic understanding of immunogenicity, helpful for immunogenicity risk assessment and ultimately aid in immunogenicity prediction	Pfizer	[100]
A Mechanistic, Multiscale Mathematical Model of Immunogenicity for Therapeutic Proteins: Part 2—Model Applications	Safety	This is a first attempt at modeling immunogenicity of biologics to help understand the immunogenicity mechanisms and impacting factors potentially set up the starting framework to integrate various *in silico*, *in vitro*, *in vivo*, and clinical immunogenicity assessment results to help meet the challenge of immunogenicity prediction	Pfizer	[101]
Systems Pharmacology Model of Gastrointestinal Damage Predicts Species Differences and Optimizes Clinical Dosing Schedules	Safety	A QSP model with rat and human variants to predict a dosing schedule for irinotecan that would minimize gastrointestinal adverse events	AstraZeneca	[36]
Evaluating DILIsym for Pre-clinical Drug Development	Safety	Prediction of compound toxicity: The DILIsym model was used to predict the likelihood of toxicity of a lead compound at expected human therapeutic exposures that led to the decision to terminate the lead compound and provided crucial insights on the mechanism of hepatotoxicity	GlaxoSmithKline	[25]

5-HT4, 5-hydroxytryptamine receptor 4; AKT, protein kinase B; BJF, Bufei Jianpi Formula; BP, blood pressure; BRAF, gene that encodes serine/threonine-protein kinase B-raf; CD3, cluster of differentiation 3; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; CVS, cardio vascular safety; CXCL13, chemokine ligand 13; ErbB3, human epidermal growth factor receptor 3; ERBB2, gene that encodes human epidermal growth factor receptor 2; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; hERG, human ether-a-go-go-related gene; IL-6, interleukin-6; IL-6Rα, interleukin-6 receptor alpha; IL-1β, interleukin-1 beta; Ki, equilibrium binding constant; MEK, mitogen-activated protein kinase kinase; PD-(L)1, programmed death-ligand 1; PI3K, phosphatidylinositol 3-kinase; QSP, quantitative systems pharmacology; QTc, corrected QT; sIL-6Rα, soluble interleukin-6 receptor alpha; TPO, thyroid peroxidase; TrkA, tropomyosin receptor kinase A; VEGFR, vascular endothelial growth factor receptor.

to the PKPD evolution to QSP, mechanistic PBPK models demonstrated that highly mechanistic models could provide predictive biological insights and deliver value to the pharmaceutical industry, laying the groundwork for QSP models. Although PBPK models can have significant mechanistic detail and rely on system and drug-dependent parameters, it is the focus on PD and disease biology/(patho)physiology components that separates the two modeling approaches. PBPK models are focused predominantly on absorption, distribution, metabolism, excretion, and PK questions, whereas QSP models are focused on modulation of a given target and the subsequent impact on the underlying biology and/or disease pathology. Thus, mechanistic PBPK models may be more aptly called quantitative systems PK models rather than QSP models. This distinction is not meant to diminish the value of either approach but, rather, to provide clarity regarding model focus, required data, deliverables, potential resourcing, and impact. Although the primary focus of the two modeling approaches may be different, it is important to emphasize that these approaches are not exclusive, and it could be desirable to connect a PBPK model to a QSP model to drive target tissue-specific drug concentrations for example. This integrated approach will be demonstrated later in the example by Wu *et al*.[13]

Proposed QSP model structural requirements

The initial scope and aim of QSP modeling, "to develop formal mathematical and computational models that incorporate data at several temporal and spatial scales; these models will focus on interactions among multiple elements (biomolecules, cells, tissues, etc.) as a means to understand and predict therapeutic and toxic effects of drugs" was provided in the 2011 NIH Workshop White Paper.[1] However, as stated earlier, this broad scope has led to a lack of alignment across the modeling and simulation community as to what type of modeling qualifies as QSP. To understand and distinguish the impact of QSP from these other methods, we propose that the following structural requirements should be met for the modeling approach to be classified as QSP: (i) pharmacologic action of an agent, either an endogenous biomolecule or exogenously delivered molecule must be incorporated; (ii) the model contains spatial and temporal components; (iii) the underlying biologic and/or (patho)physiologic details are quantitatively and mechanistically described.

IMPACT

Through discussion within the IQ TA LG QSP Working Group, results from an industry-wide survey, and evaluation of the literature (**Table 1**), it is evident that QSP modeling has had a significant impact in preclinical drug discovery across multiple therapeutic areas. Here we demonstrate the areas of impact with a few examples considering only models that include the action of a molecule (therapeutic or toxicant) within the context of a comprehensive mechanistic model of a disease process with outputs that are relevant to decision making in drug discovery. The applications are

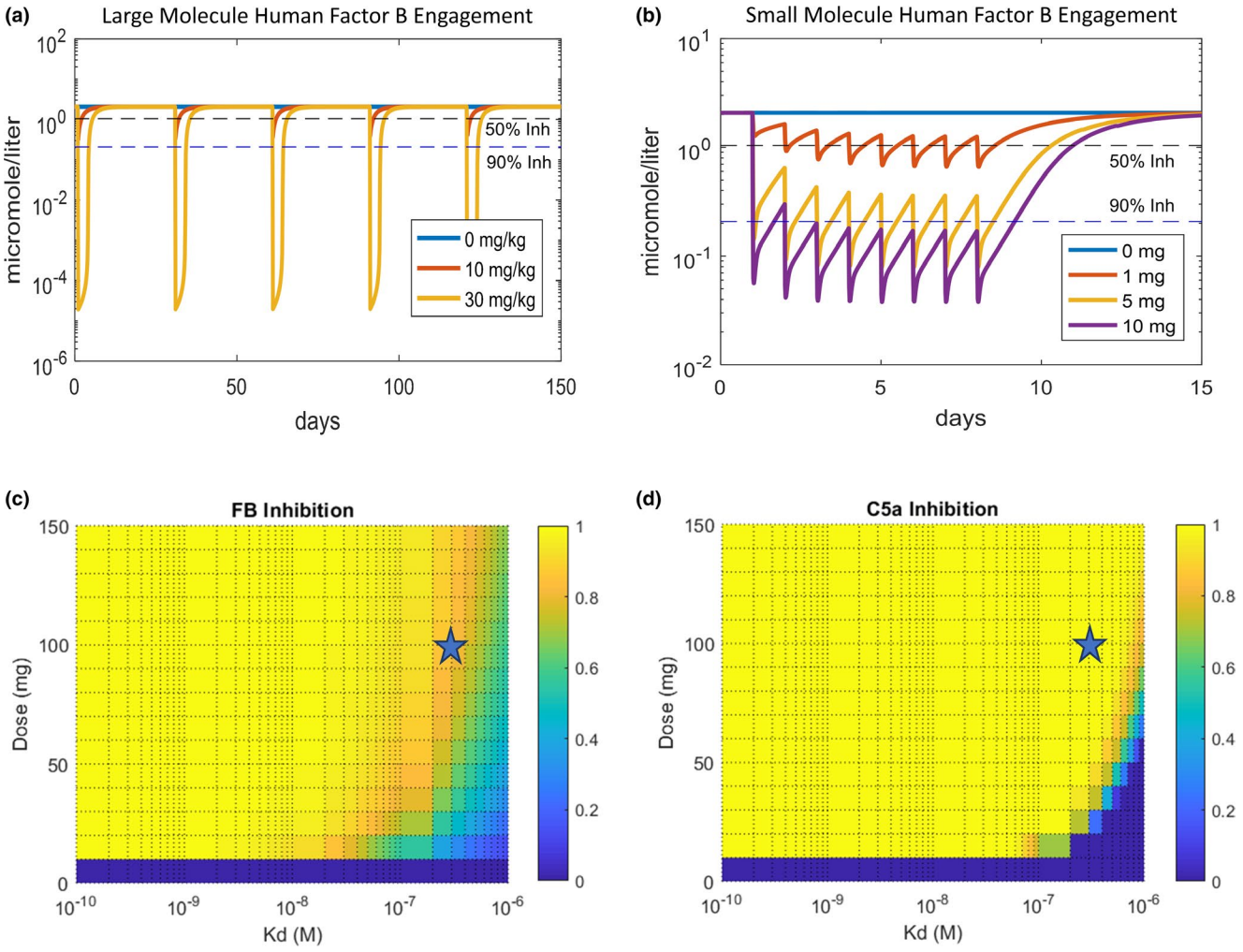

Figure 1 Application of quantitative systems pharmacology model for modality selection. (**a**) Human dose prediction for engagement of Factor B (FB) with a large molecule modality (Kd = 10 pM, half life = 28 days) with monthly dosing. (**b**) FB engagement with a small molecule (Kd = 10 nM) with single daily dose (assuming no protein binding and bioavailability of 95%). (**c**) Fractional engagement FB with a small molecule at different affinities and doses. (**d**) Corresponding effect of FB inhibition on a downstream biomarker – C5a. The star denotes the minimum potency (~0.3 μM) required to keep small molecule dose under 100 mg. Inh, Inhibition.

varied and demonstrate the utility of QSP models in all phases of discovery and highlight the flexibility of these models to address multiple research questions. In addition, the strengths of QSP modeling to *a priori* simulate complex biological information, to integrate data from multiple sources and simulate beyond the data sets used to generate models, and to interrogate biological mechanisms and generate hypothesis are exemplified in the examples below and provide illustrative scenarios that differentiate QSP approaches from other modeling methods.

Target validation and modality selection

In early stages of discovery, QSP modeling can provide an initial assessment of the dosing tractability of target(s), i.e., the amount of dose and affinities required to engage a target using small-molecule or large-molecule compounds. This can guide modality selection as various modalities can have a specific feasible dose and affinity range. An example of evaluating this has been demonstrated by Bansal *et al.*[20] using a model of the complement pathway for the treatment of autoimmune diseases. The dosing tractability of several complement proteins was evaluated by incorporating the PK for small-molecule or large-molecule modalities within the QSP model. As an example, model simulations (**Figure 1a**) showed that 90% engagement of the target Factor B with a large molecule is infeasible because of the high concentration and turnover of Factor B. In contrast, a small-molecule modality can lead to > 90% engagement of the target with 10 mg daily dosing (**Figure 1b**). By predicting the doses needed for 90% target engagement of Factor B at several drug affinities, the optimal affinity was predicted to be ~ 0.3 μM to achieve ≤ 100 mg dose of a small molecule (**Figure 1c**). The model was also used to predict the effect of Factor B inhibition on C5a (a marker for complement activation) and predicted a strong effect (> 99% inhibition) on C5a inhibition (**Figure 1d**). The model was instrumental in guiding target validation efforts as well as modality selection during lead

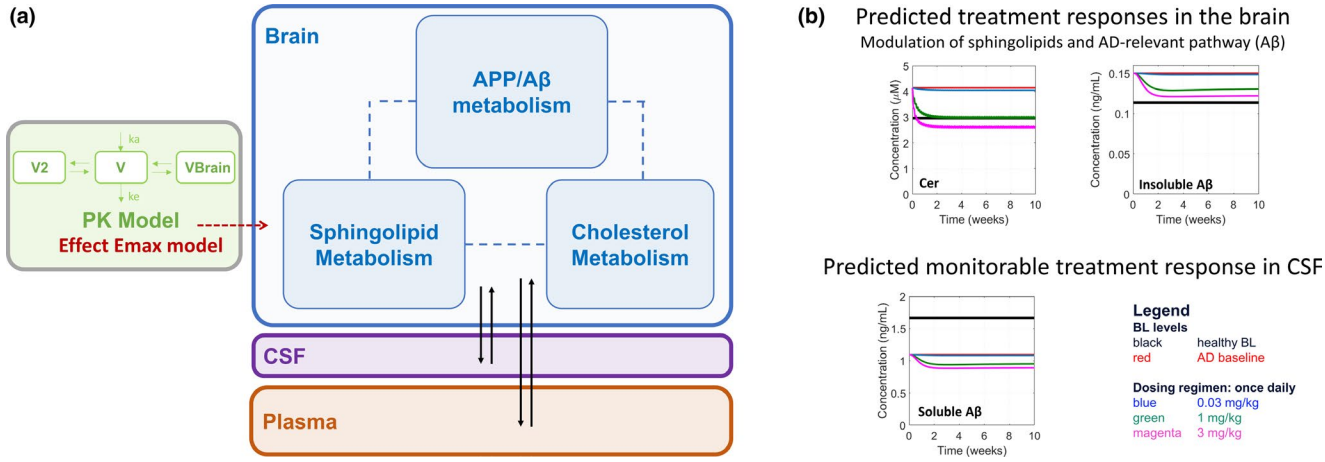

Figure 2 Application of quantitative systems pharmacology model for biomarker selection. (**a**) Schematics of the quantitative systems pharmacology model consisting of (1) physiology, including brain, CSF, and plasma and (2) the pharmacology model including pharmacokinetics and pharmacological effect. The brain model includes submodules for cholesterol and sphingolipid pathways as well as APP/Aβ metabolism. Their interrelations by molecular interactions are represented schematically by lines connecting the submodules. Transport between different compartments is included for some molecular species of interest and is indicated schematically by the directional arrows. (**b**) Predictions of the model for treatment responses to sphingosine-1-phosphate receptor 5 agonist indicate dose-dependent modulation of sphingolipids and the AD-relevant Aβ pathway in the brain and CSF. Figure reprinted from Clausznitzer *et al*. [21], licensed under CC BY-NC-ND 4.0 © 2018 The Authors. Aβ, amyloid-beta; APP, amyloid precursor protein; AD, Alzheimer's disease; BL, baseline level; Cer, ceramide; CSF, cerebrospinal fluid; E_{max}, maximal effect; Ka, absorption rate constant; Ke, elimination rate constant; PK, pharmacokinetic; V, volume of central compartment; VBrain, volume of brain compartment; V2, volume of peripheral compartment.

discovery efforts. Because of a lack of availability of compounds that can bind to several complement proteins at the target validation and lead discovery stage, the generation of animal data and PKPD modeling was not feasible. The question of target and modality selection could only be addressed using mechanistic QSP modeling, which integrated literature knowledge around the pathway dynamics with plausible PK and affinities for small-molecule and large-molecule modalities.

Biomarker identification and selection

QSP modeling can also be leveraged for biomarker identification, and its mechanistic detail can provide valuable insights to new potential targets. An example in Alzheimer's disease is the QSP model (**Figure 2**) published by Clausznitzer *et al*.[21] that includes lipid dysregulation in the brain with a focus on sphingosine-1-phosphate receptor 5 (S1PR5). The model reproduces expected baseline levels of lipids and amyloid-beta (Aβ) for healthy and Alzheimer's Disease subjects, and appropriately captured reported plasma and cerebral spinal fluid treatment responses to several therapies. This model was used to predict the treatment response for a compound targeting sphingosine-1-phosphate receptor 5 and showed modulation of sphingolipids as well as Aβ, in particular, soluble Aβ in cerebral spinal fluid. These simulations built confidence in soluble Aβ's potential utility as a clinical biomarker to monitor treatment response. Furthermore, a sensitivity analysis identified additional potential targets to modulate lipid dysregulation and Aβ in Alzheimer's disease. The QSP model was able to increase confidence in a novel disease pathway and can be used further for validation of potential new targets as well as the identification of clinical biomarkers that may be used to monitor treatment response. Although nonclinical data were also generated that demonstrated changes in brain Aβ concentration following sphingosine-1-phosphate receptor 5 treatment, the QSP model captured the complexity of dysregulation of interrelated pathways observed in human Alzheimer's disease. Therefore, it is expected that the QSP model provides a better estimate of expected timescales and size of the treatment effect compared with directly extrapolating from preclinical species through a PKPD approach.

In another example, Schuck *et al*.[22] developed and used a QSP model to identify biomarkers predictive of tumor growth inhibition for a cancer immunotherapeutic, E7046. The model, initially developed in mice, was intended to be translated to human to aid in the selection of efficacy biomarkers in clinical development and to identify combination therapies hypothesized to provide the highest possibility of improved response. Through sensitivity analyses of the various system parameters, the following three markers were identified as predictors of tumor growth inhibition by E7046: (i) tumor CD8 T cell infiltration, (ii) prostaglandin E2 serum levels, and c) tumor growth rate. The hypothesis generated by the model was tested in additional tumor models (B16F10, 4T1, SaIN, and PAN02) outside of the QSP model calibration system (CT26). Overall, the tumor growth inhibition predictions for 3 of the 4 tumors matched the experimental observations well (**Figure 3b–e**). The predictions for B16F10 and 4T1 appear to predict experimental observations closely, and although the experimental data were much more variable for the SaIN model, the predictions were able to capture the general feature of the data set, namely, that vehicle grew at a modest rate

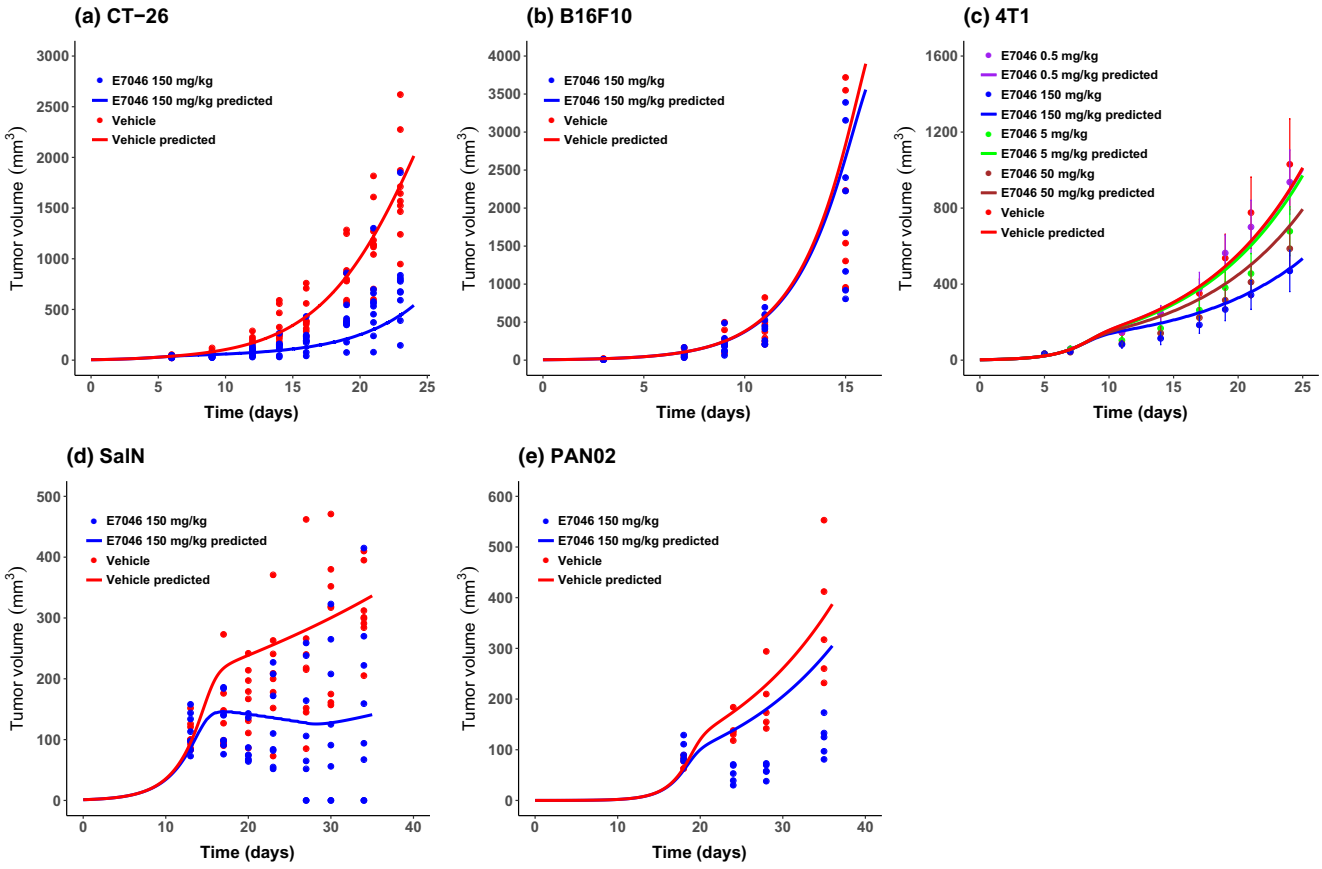

Figure 3 Prediction of E7046 dose-effect in preclinical tumors. Predicted tumor growth inhibition curves (lines) and experimental data (points) for (**a**) CT-26, (**b**) B16F10, (**c**) 4T1, (**d**) SalN, and (**e**) PAN02 tumors.

and the E7046 treatment resulted in control of that growth. The model was used to explore the tumor growth inhibition resulting from different doses of E7046 and its combination with a mouse PD-1 checkpoint inhibitor (data not shown), one of the promising potential combinations identified. Here QSP modeling was employed because of its prospective nature and ability to integrate data from multiple separate experiments. Experimental data for multiple markers were available, but understanding how they integrated to predict response was lacking. QSP modeling provided a quantitative way to assess and evaluate the impact of multiple markers together. Sensitivity analysis indicated that tumor growth inhibition was most sensitive to three different markers and that the use of a single marker could not accurately predict tumor growth inhibition following E7046 treatment. PKPD models are normally developed based on each marker independently, which would not help in this case.

Predictive toxicology

Equally important to understanding a compound's efficacy is mitigation of a compound's known toxicity risks, and there are multiple examples of QSP models developed to predict hepatic,[23–25] cardiac,[26–33] renal,[34,35]and gastrointestinal[36] toxicity (**Table 1**). These models can be extremely useful early in the drug discovery process by helping teams predict and mitigate potential risks of the toxicity associated with molecules. Michalski *et al*. leveraged DILIsym,[37] a QSP model of drug-induced liver injury (DILI), to investigate the mechanisms of hepatotoxicity observed during lead optimization of a program. The DILIsym model, developed by the DILIsym initiative (now part of Simulations Plus, Lancaster, CA, USA), is an example of a modeling effort that was in part developed through a consortium approach, where knowledge from across industry was leveraged to construct a shared model framework. In the example, the systems model was developed and employed to identify the primary mechanism of hepatotoxicity as mitochondrial toxicity. The DILIsym model was used to predict the likelihood of toxicity of the lead compound at expected human therapeutic exposures, indicating a suboptimal safety margin. This prediction led to the decision to terminate the lead compound and importantly provided crucial insight on the mechanism of toxicity allowing a discovery team to modify their lead optimization strategy to include measures of mitochondrial dysfunction in their screening cascade.

Another application of QSP modeling to translate preclinical toxicology findings to predict potential clinical impact is in cardiac safety risk assessment. Tremendous efforts have been made from both academia and industry to develop mechanistic and predictive models for drug-induced cardiac toxicity.[26–29] Wu *et al*.[13] developed a model that integrated

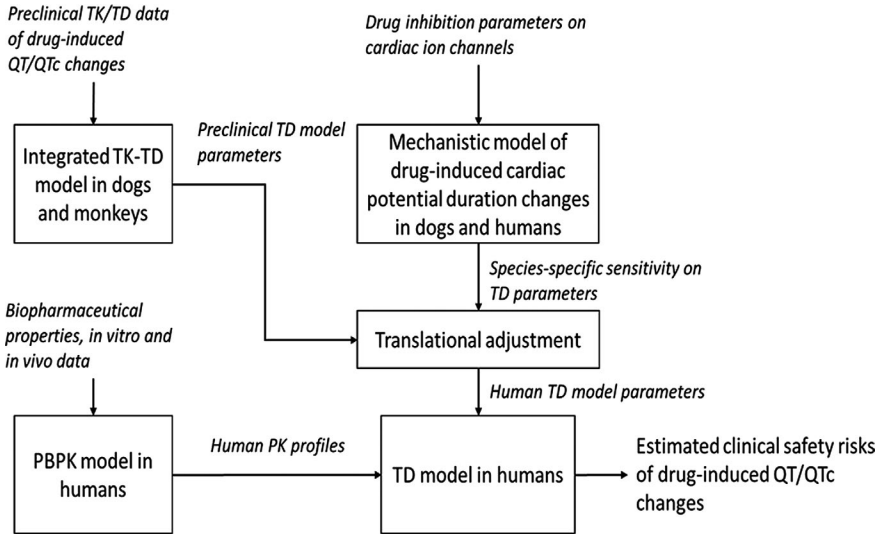

Figure 4 A diagram illustrating the work flow for the integrated quantitative systems pharmacology–PBPK/pharmacodynamic modeling approach to predict the clinical safety risks of drug-induced QT/QTc changes using the preclinical safety data. PBPK, physiologically-based pharmacokinetic; PK, pharmacokinetic; QTc, corrected QT; TD, toxicodynamic; TK, toxicokinetic.

PBPK with population PKPD and a mechanistic cardiac action potential model (**Figure 4**) to reveal the mechanisms underlying the observed species-specific drug-induced toxicity for a lead molecule (NVS001) and further predict potential clinical safety risks. The distinct dose-QT/corrected QT (QTc) relationships for NVS001 observed in dogs and monkeys lead to challenges in translating preclinical cardiotoxicity findings to clinical risk. The authors show that the integrated QSP and PBPK-PD modeling approach successfully predicted the clinical exposure–safety risk relationships by incorporating the QSP-model-derived, species-specific PD sensitivity and PBPK-derived clinical PK variability. The model predictions were verified with clinical thorough QT results and further applied to guide future clinical studies.

Other applications

A strength of QSP modeling is the incorporation of the underlying biological information of a disease (network of signaling pathways, feedback or compensatory control, and redundancy, etc.) beyond simplified empirical relationships describing the target modulation and impact on disease (e.g., traditional PKPD), which allows for extrapolations beyond a given data set or patient population. Take the QSP model of bone remodeling with integrated calcium homeostasis as an example; the motivation was to address questions that could not be practically answered either by clinical trials or traditional PKPD modeling for denosumab.[38] A decade later, this model was used by the US Food and Drug Administration (FDA) to address a safety concern of hypercalciuria for a drug, parathyroid hormone (NATPARA), in an entirely different indication (hypoparathyroidism). Similarly, the Alzheimer's disease QSP model presented earlier was used to identify new targets in the lipid regulation pathway that were not previously studied in the clinic.[21]

Furthermore, the integrated biological mechanisms within QSP models can reveal key processes or parameters that are important but not readily obvious otherwise. For example, the human epidermal growth factor receptor 2 (HER2) targeted liposome encapsulating doxorubicin (MM-302), where it seemed obvious that the first and foremost important determinant for *in vivo* efficacy should be the HER2 expression level of a given cancer type. However, the QSP model indicated the two most important parameters for efficacy are the liposome PK and tumor leakiness followed by the HER2 expression level. The model performance was validated in murine xenograft models and later verified in humans via positron emission tomography imaging studies.[39,40]

CHALLENGES AND CONTROVERSIES

Data availability for model construction and qualification

Preclinical QSP modeling has the potential to leverage existing knowledge of known targets and pathways to aid in the selection and development of novel targets that have not yet been tested in the clinical setting. The aforementioned QSP model of the complement pathway serves as a perfect example of this. In fact, when reflecting on many of the examples presented here, it is evident that additional insights beyond the initial question asked of the model frequently arose from the QSP model, creating collateral benefits and insights.

However, it must be acknowledged that the clinical data used to develop and constrain these models can vary widely across the spectrum of disease areas for which QSP models have been developed (**Table 1**), and one of the challenges the modeling community faces is limited availability of well-annotated data. For example, in rheumatoid arthritis there are many large trials that span diverse mechanisms of action and well-established clinical measures used across these studies that can be used for model calibration and qualification.[41–51] By contrast, in Alzheimer's disease there are fewer trials with none thus far showing efficacy.[52–54] Nonetheless, neuroscience has been identified as a key

disease area for investment in QSP models,[2] and examples of successful QSP impact in this therapeutic area are available, such as the one presented above by Clausznitzer *et al*.[21] Although the availability of clinical data does not preclude the development and use of QSP models, it can influence how simulation results are interpreted. Models built on copious amounts of clinical data are likely to be more predictive, whereas models built with sparse clinical data are likely better suited for hypothesis generation.

In contrast to clinical data, which are used to assess high level behavior of the model, preclinical data are essential to establish the underlying pathway connections representative of the biology. One of the challenges for QSP model building is defining the scope of biology necessary to answer the research question. Typically, this is driven by subject matter experts but can also be informed by insights gained from bioinformatic analyses of omics data and the use of databases and software tools such as Metacore (Clarivate Analytics, Boston, MA, USA), Ingenuity (QIAGEN bioinformatics, Redwood City, CA, USA), database for annotation, visualization and integrated discovery (Laboratory of Human Retrovirology & Immunoinformatics, Frederick Nataional Laboratory for Cancer Research, Frederick, MD, USA), Kyoto Encyclopedia of Genes and Genomes (Kanehisa Laboratories, Institute for Chemical Research, Kyoto University, Kyoto, Japan), and Reactome (http://www.reactome.org). However, the major gap is a database of well-annotated biological parameters that the community can access and refer to during model development. The development and use of resources such as BioNumbers (http://bionumbers.hms.harvard.edu) and the Merck Manual (Merck & Co., Inc., Kenilworth, NJ, USA) would accelerate model building and bring consistency to models that address specific therapeutic areas.

Purposeful complexity

Each case study presented here and the examples in **Table 1** provide critical and insightful answers to project problems, and each QSP model must be able to demonstrate a sufficient degree of validity such that its guidance is accepted and acted on. For more conventional (population) PKPD models built entirely on data from one or more trials and answering questions from a descriptive (covariate identification), interpolative (optimal dose), or a limited extrapolative analysis, validation can be achieved by confirming the adequacy of the model fit. This is not true for QSP models[55]: The model structure is purposefully complex to connect disparate data sets and then inform on novel situations, and in doing so it is accepted that the model will contain parameters and assumptions that may not be uniquely confirmed by a validation data set. Indeed, the objective of informing novel situations typically means such validation data sets will not exist. The case studies herein instead achieve an appropriate model qualification by testing their predictive ability against scenarios that are distinct from those of the partial data sets used to create them. The ability to predict results without the originating data demonstrates that a model has been constructed to describe adequately the behavior of the underlying pharmacological system being modeled over and above a recapitulation of the data and as such may make valid predictions for further scenarios in which the system is involved. Note that even with such independent validation, model predictions can still be affected by unidentifiability. Although the impact of this may be limited because parameters in the QSP model are typically based on physiological quantities and thus are bounded by observed physiological data as opposed to parameters in empirical models that are estimated to achieve best fit, it can nonetheless be assessed via sensitivity analyses and the exploration of parameter uncertainty used to understand the robustness of simulation results.[56] Importantly, the studies given here also provide both an answer to the research question and a mechanistic rationale from which a further assessment of the model validity may be made. For example, proposing biomarkers of the response of the complement system or DILIsym identifying the mechanism of toxicity may allow for an independent test of the QSP model predictions.

Transparency and reuse of QSP models

The transferability of QSP models remains an issue. Most of the examples referenced here are "one-time" models—used at a discrete time and place to provide an answer to a specific question and then shelved. In part, this is because of the time and cost of developing QSP models: It is more pragmatic to build a "fit for purpose" model than to design one intended for multiple projects because of time and cost (including access to an appropriate budget). Furthermore, although the originating modeling team will have gained experience and understanding of their QSP model during its derivation, the choice of structure, discussion of data applicability/parameter values, and understanding of system behavior is often not adequately documented. Such detailed consideration can rarely be expressed in the model write-up or publication, making it difficult for other parties to adopt their models with confidence. Consequently, it is often easier to build models from scratch, as illustrated by the commentaries of Chelliah *et al.,*[57,58] which noted that there are some 160 models of type 1 diabetes mellitus in the literature. The QSP community has recognized this shortcoming and has begun to recommend reporting methods to facilitate transparency and model reuse.[59,60]

The DILIsym and QTc examples presented here illustrate that transferable models are possible. It is notable that these examples relate to issues common to therapeutics largely irrespective of their target or modality. This provides the benefit of enabling precompetitive data sharing and a way for third parties to evaluate the utility of the model without requiring an in-depth knowledge of the model workings, as they can test the model against in-house data with known outcomes to qualify the model for their chemical space. However, this necessitates significant resource to be spent on data management, model curation, documentation, and updates. Such models are inevitably developed within consortia that can afford the dedicated modeling team and budget significantly in excess of any QSP resource within the largest pharmaceutical companies.[12,37,61] A limitation of the consortium approach is that it is often difficult to adopt outside of safety or other shared concerns such as immunogenicity[62] as leveraging

this approach to build standard disease-specific models typically requires that partners reveal the targets that they are interested in, which can put competitive advantages at risk. Despite this, Certara (Certara USA, Inc., Princeton, NJ, USA) recently launched a consortium to develop a QSP model for immuno-oncology with the purpose of identifying biomarkers, optimal therapeutic combinations, and dosing regimens in virtual patient populations.

Communication

Communication is another key challenge that can often impede understanding of the purpose and utility of QSP models as well as analysis and interpretation of simulation results, which can limit wider use in preclinical drug discovery. This is important as organizational buy-in is necessary for resource allocation both in terms of budget and full-time employees to support model development. In addition, QSP model development requires a cross-functional, multidisciplinary effort to ensure that the appropriate components of the biology are being incorporated and that the data necessary for model parameterization and qualification/validation are identified or generated, necessitating proper communication of the modeling approach and its impact. The effective communication of simulation outputs, results, and how to best leverage the model is paramount to maximizing the impact of QSP modeling efforts to influence program strategy. Learning how to describe the models, how they are used, how data are incorporated, how outputs are represented, and how to draw appropriate conclusions from simulations to nonmodeling and simulation stakeholders is a necessary skill that often takes modeling and simulation experts years to refine or can require multiple iterations of communication of the information to help teams digest the messaging.

RECOMMENDATIONS

Although the challenges to the broader adoption of QSP described here can and have led to suboptimal uptake at times in industry during the past few years, none of these issues are insurmountable. As we continue to live in a world that is generating new data exponentially (i.e., "omics" data), approaches such as QSP can be used to gain insights from these seemingly disconnected data, and vice versa, the vast data generated by multi-omic approaches can be leveraged to evolve QSP modeling. The following recommendations to standardize documentation of model design and construction, promote model publication, and improve publication process, leverage consortium or consensus model-building approaches, and advocate for inclusion of model-based approaches in internal documents and governance materials can serve as initial guidelines to set the foundation so that QSP conducted today can be prepared to take on the needs of tomorrow.

A lack of model transparency can be addressed via standardization of reporting practices.[60] Although models may start as fit for purpose, we advocate reusing and building on these models where possible such that they move toward "platform" status and indeed serve as a means of institutional learning and knowledge retention. Integral to this would be standard operating procedures for project teams to document design decisions, sources for parameter values, clinical data used, relevant literature, and so on. Ideally software would be leveraged to do this and perhaps the QSP community can look to the software industry and adopt tools such as GitHub (San Francisco, CA, USA) and Jira (Atlassian, Sydney, Australia), which are effective at maintaining version control and tracking issues, respectively. Ultimately, transparency can likely only be truly achieved through publication of models. Given the complexity of these models, it is presently difficult for a reviewer to properly assess them. A flexible approach may be required given the variety of models that can be considered QSP and, importantly, the context of use.[56] In addition, practices should be adopted to ensure model reproducibility.[59]

Many QSP models have been developed behind the firewalls of small consulting or large pharma companies. Although some of the models/methods/applications have been published, the industry lacks standard pathway and/or disease-related QSP models, which could facilitate their uptake. Precompetitive consortiums that include pharmaceutical companies, academic thought leaders, and FDA experts in both mathematical modeling and the pertinent physiology should be leveraged to define standard models where possible. As mentioned previously, the consortium approach can be applied to shared concerns such as safety but faces more challenges for disease areas where the consortia members would be competitors. Nonetheless, consensus models may be a viable approach for some therapeutic areas where the pathophysiology is well understood, such as type II diabetes. For these models, the community will likely need to rely on publication for dissemination. In the spirit of standardization, these models should be published with all equations and parameters written in a standard format such that they can be coded in any software of choice. We recommend this path as there are many software options for building and applying QSP models, but no clear frontrunner.[63]

For QSP modeling to reach its full impact within pharma it needs to move from an ad hoc, nice-to-have activity to a standard method for addressing early mechanistic questions across programs and disease areas. In the fast-paced pharmaceutical environment, it is paramount that QSP modeling activities demonstrate impact on a portfolio in a timely manner by addressing well-defined, specific questions with short-term deliverables that provide quick wins for the discipline and demonstrate the benefit of a sustained investment. To achieve this timely implementation of QSP models, researchers can leverage existing models by incorporating new biological knowledge to address new questions. As such, learnings from prior projects with the original model will be carried forward. QSP models should be updated to reflect new learnings, especially as knowledge around the fundamental biology in the model changes and as new clinical data emerge. Furthermore, as QSP modeling demonstrates its utility, it is expected that it will become integrated into internal documents and governance meetings. For example, preclinical target validation could include *in vitro*, *in vivo*, and *in silico* assessments. Finally, when appropriate, it is encouraged that QSP

modeling results be included in regulatory documents and that companies actively engage with regulators in planning and implementing proposed models. Based on the outcome of the QSP survey,[12] QSP models are rarely or never included in regulatory documents. However, recent data suggest that this is changing, with most regulatory examples occurring in investigational new drug submissions.[64] This is perhaps not too surprising because the mechanistic nature of QSP models lends itself to potential inclusion as part of the supporting knowledge defining the proposed mechanism(s) and its role in the pathophysiology of the disease as well as initial trial design considerations. The details of when and how QSP models should be shared with the FDA are still developing and may require different regulatory engagement depending on the intent of the QSP modeling results.[64] One aspirational goal is that, similar to internal documentation, QSP model results could be included in target validation/mechanism of action sections of FDA documents (*in vitro*, *in vivo*, *in silico*). This will necessitate greater transparency of QSP models through publications or direct engagement with the FDA through their model-informed drug development program.

ANTICIPATED OUTCOMES

As QSP has become a regular topic of education sessions, symposiums, round tables, discussion groups, and so on at national and international conferences, it is expected that QSP as a discipline will continue to develop and will be leveraged more broadly across academia and industry. However, as a modeling community we need to be cautious of overselling QSP modeling and maintain the mind-set of generating the right-sized and right type of model to address program questions and industry needs. This paper highlights the growing use of QSP modeling in preclinical drug discovery to evaluate the tractability of targets, identify new targets, guide modality selection, influence compound design, aid in biomarker identification and selection, elucidate biological mechanisms, and generate new testable hypotheses. It is our hope that as an industry and community we can see an even greater penetration of QSP modeling in this critical space of new drug design and development.

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