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Short Communication

Quantitative Systems Pharmacology Uses in Drug Development

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INTRODUCTION

QSP is a computational model that examines the interface between discrete experimental data (studies of the drug/compound) and the system. The system can be any biological process related to the disease such as the physiological consequences of a disease, a specific disease pathway (signal transduction or up/down regulation of a pathway, increased heart rate), or any of the omics (genomics, proteomics, metabolomics).

ABOUT THE STUDY

Tapping into the omics generates substantial opportunity to learn from big data systems by looking for intersecting themes. While omics data are not likely to lead to definitive directions during drug development on their own, their coupling with QSP can result in powerful insights that decrease uncertainty at key decision points in the development process. QSP can help guide appropriate study design or suggest what additional experiments might be needed to make more informed choices. Similarly, QSP can greatly reduce missteps that might prolong the drug development process or even result in an unnecessary failure. For example, one way that utilizing big data in QSP can glean powerful insights into drug development is by integrating regulative and metabolic biological pathways with novel drug compound mechanisms to accelerate the pace of innovation with the identification of overlapping moieties. These insights can aid in exploiting possible additive or synergistic effects, planning around potential set-backs and redesigning experimental direction at critical times during early stages of the drug development process to help thwart unnecessary failures.

As previously unknown and intersecting disease pathways are discovered, QSP can be leveraged to identify new targets, verify current targets, understand potential adverse effects of novel pathways, and repurpose existing drugs to new targets. QSP has built on the insights gained in developing physiological based pharmacokinetic models (blood flow rates, organ volumes, transporter expression) and has truly taken the power of understanding drug action to a new level.

QSP can be employed at all stages of drug development. Given the amount of experimental data generated for diseases, genetics, drug binding, metabolism, polymorphisms, biological pathways, inter-relationships between systems, information from big data, and more, coupled with the availability of necessary computational power, QSP is primed to change the landscape of drug development.

Mechanism of action: new and old drugs, possible repurposing; simplifying pathways: distinguishing between relevant and irrelevant pathways in complex biological systems; important determinants of exposure: pharmacogenomics (rapid/normal or reduced metabolizer of various drug-metabolizing enzymes; transporter expression) drug-drug and drug-gene interactions. Efficacy: define interspecies differences in the expression levels and characteristics of biological targets leading to improved translational understanding of PK/PD responses across species, for better prediction of clinical outcomes from preclinical models. Comorbidity: impact and implications on the PD response such as liver disease, kidney disease, heart failure, gastrointestinal variations, etc. Special populations: forecasting results of perturbations to the system (such as in pediatrics where receptor expression or endogenous pathways may still is developing relative to adult populations) in a population of *in silico* patients: verifying actions of responses to novel targets and therapeutic agents.

Dosing regimen: choosing doses, rational selection of combination therapies, and dose frequency for different patient populations. QSP can save valuable resources during drug development, and importantly, reduce the time to getting therapies to the patients in need. QSP can facilitate the decision-making process in order to get the right drug, to the right patient, for the right disease, at the right time, and in the right dose. In programs where the first clinical study will be in a patient population such as in a rare disease or in cell and gene therapies, the need to predict a therapeutic dose for the first in human dose is crucial. QSP offers the ability to help make these critical and ethical decisions with more confidence. Having an early understanding of what QSP can provide can guide the design of therapeutics from the very beginning of the drug discovery process.

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Examples of when to use QSP

Predicting drug response: One major use of QSP is to forecast drug responses resulting from perturbations in the system in populations of *in silico* patients before running clinical trials. For example, perturbations might include deteriorating liver function or the biological effects of pregnancy. Responses to these pertubations might include alterations in drug metabolizing enzyme expression or receptor occupancy needed for therapeutic effect, causing possible alterations in outcomes on clinical trial endpoints. This can be proactively analyzed using computer models to predict pd responses and verify predictions in animal models of disease to predict outcomes in healthy volunteers and other patient populations. Confirmation of clincial responses to biomarkers in healthy volunteers further improves predictions and study design for Phase II trials, in special populations or in selecting appropriate target populations.

Integrative models: QSP has also been shown to be useful in intergrative drug-disease models within academia, the pharmaceutical industry, and the FDA for disease areas such as oncology, metabolic disorders, neurology, cardiology, pulmonary, and auto-immune diseases, to name a few. The scope and application of QSP, specifically within oncology ranges from specific combination of regimens.

Efficacy and safety: Another capability of QSP is to highlight efficacy and safety concerns through the interactive evolution of a QSP model. This has been used to predict cardiovascular effects using blood pressure and heart rate, identify peripheral resistance, predict herg mediated qtc prolongation, linking biomarkers to cell injury and renal dysfunction, or explaining drug-induced liver injury and how to avoid it.

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