Model-informed target identification and validation through combining quantitative systems pharmacology with network-based analysis

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PERSPECTIVE

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One of the main areas where quantitative systems pharmacology (QSP) can impact drug discovery and development is target identification and validation. However, due to the multiscale nature and complexity of typical QSP models, the target space that can be explored is still significantly constrained. Therefore, we propose to combine QSP with network-based analysis (NBA) to increase the efficiency and effectiveness of in silico (model-informed) target identification and validation.

The majority of drug development projects fail in phase II and phase III clinical trials, mainly due to the lack of efficacy and unacceptable safety profiles.[1] One of the notable contributing factors contributing to this failure is an inadequate understanding of the underlying disease biology and target-disease linkage. This results in poor target choice, suboptimal target modulation, unanticipated structure-based or mechanism-based toxicity, inappropriate patient-population selection, and the absence of decision-making biomarkers.[2] Therefore, finding novel, drugable targets associated with high confidence in rationale for therapeutic efficacy and safety remains a major challenge. Adoption of a discovery pipeline based on in-depth understanding of disease biology and mechanisms is an absolute need for identifying potential targets for clinical success. Indeed, AstraZeneca reported that the implementation of their revised research and development (R&D) strategy based on the so-called 5R framework (which includes "the right target") increased the trial success rate from 4% to 19%,[3] whereas Pfizer recently disclosed their phase II survival is now above 50% while maintaining phase III success.[1]

Clinical trials initiated based on preclinical studies in models with unknown translational value has more often than not led to disappointing results in patients. For example, in a recent study, Lin et al. investigated a set of cancer drugs and their targets that are in various stages of clinical or late-stage preclinical development using clustered regularly interspaced short palindromic repeats-associated protein 9 (CRISPR/Cas9)-mediated mutagenesis and found that most of these drugs work through off-target interaction to kill cancer cells.[4] The loss of these putative targets did not affect the efficacy of these drugs, proving that these targets are nonessential for cancer cell proliferation. Hence, misidentification of targets would lead to misconception of a drug's mechanism of action, which could, for example, hamper identifying effective biomarkers that are used for predicting therapeutic response.

With target identification and validation being such a formidable challenge, companies continue to invest significant time and resources in identifying novel approaches, such as in silico technologies. For example, it has been proposed that target identification and validation is one of the main areas where QSP can impact drug discovery and development.[5] The strength of QSP models lies in the incorporation of the underlying disease biology at the molecular level and its propagation to a higher level organization. Hence, developing QSP models is a significant task requiring a considerable amount of background information on target mechanisms at multiple biological scales to be implemented at the required level of details. Currently, the mechanistic details to be included in the QSP models are largely driven by expert opinion and traditional literature survey. This process is extremely laborious and constrained with limited capability to explore multiple targets and associated mechanisms in a cell-specific or tissue-specific manner.

Therefore, in silico screening of an entire molecular network in the context of the whole genome may be more effective in identifying potential targets that simultaneously modulate multiple disease genes. However, given their time-consuming nature, this approach is currently not practically feasible with the current QSP methods discussed previously. In contrast, high-throughput,

data-driven in silico screening methods of multi-omics data (typically referred to as network-based analysis [NBA]) have been developed and applied for many years in the field of systems biology and bio-informatics but to date have not been linked to QSP.[6] In recent years, NBA has gained significant interest in drug discovery and development for analyzing and making meaningful hypothesis out of the rapidly growing high-throughput multi-omics data. Although the generation of high-throughput clinical multi-omics data has provided a great opportunity to understand the complex relationship between molecular layers, integration and translation of these multilayered networks to extract mechanistic insights remains a challenge. Recently, several publications used various multi-omics data integration strategies and extracted key functional insights connecting it to clinical outcomes at a cellular level for individual patients (see Material S1). For example, our group recently developed an NBA pipeline that generates a patient-specific disease network by integrating multifaceted data sets, including patient-specific transcriptomic data, and identified key molecules and pathways that were then used to prioritize drug candidates (see references 21–22 in the Material S1). Not surprisingly, the most recent approaches focus on the application of machine-learning (ML) and deep-learning (DL) principles. For example, Dugourd et al. developed Causal Orientated Search of Multi-Omics Space (COSMOS), a network-based method using ML principles that extracts mechanistic hypothesis by integrating prior-knowledge network and multi-omics data.[7]

NBA predicts the mechanistic relationship between drugs, their targets, disease-causing genes, and differentially expressed genes and proteins from multi-omics data sets by taking into account the entire target interactome extracted from large-scale, protein–protein interaction databases. Hence, it facilitates exploring "multiple drugs, multiple targets, multiple pathways operating in multiple tissues" aiming at identifying optimal nodes for intervention to have maximum therapeutic effect. Moreover, accounting for genetic variants and differentially expressed genes in individual patients or a subset of patients, NBA may provide pharmacogenomics insights in the influence of these genetic markers on drug response. Therefore, NBA can help with deciding whether a particular drug would work for an individual or a subset of patients based on their genetic makeup. Hence, depending on the data that are fed into an NBA framework, it can be used to connect tissue, cell, pathway, and target data at the level of an individual patient to drug response, as illustrated in Figure 1 (see Material S1 for more details).

Although NBA methodologies that integrate diverse multifaceted biological data have brought a unique opportunity to understand disease processes, discover novel targets and drug mechanisms, and design therapeutic strategies tailored to individual patients, they have limited capability to quantitatively investigate the degree of efficacy of drug action at the system level, design dosing regimens, and predict longitudinal outcomes. Therefore, we propose to combine QSP with NBA to increase the efficiency and effectiveness of in silico (model-informed) target identification and validation. In this "QSP 2.0" paradigm, the initial target identification step is driven by NBA and the subsequent target validation by QSP (Figure 1), arguably in the spirit of the original National Institutes of Health White Paper where QSP was defined as quantitative and systems pharmacology (see reference 23 in the Material S1).

Historically, a broad spectrum of computational and modeling methods that aim to understand how drugs affect the physiological system under consideration have been referred to as "Systems Pharmacology." Thus, *systems pharmacology* is an umbrella term that spans the entire spectrum from qualitative to quantitative modeling approaches, that is, from biological NBA to QSP models typically used in pharmaceutical R&D. Although static NBA methods exploit the entire target interactome and provide insights on key pathways and targets, current QSP approaches are based on multiscale, physiology-based pharmacodynamic models to predict the effects of therapeutic interventions over time.[8] In our proposed new paradigm, the systems-level propagation of the target mechanism in the cell-specific and tissue-specific manner first identified by NBA ("target identification") can subsequently be investigated through QSP models to understand if modulating the target would provide a potential therapeutic benefit ("target validation"). Cell-specific molecular mechanisms identified from multi-omic data sets can be converted into simpler ordinary differential equation models via logic-modeling approaches, as demonstrated recently by Nanavati et al.[9] to achieve a well-structured, fit-for-purpose QSP model. To facilitate implementation of such an approach at scale, standardized and semiautomated methods and protocols need to be developed and implemented. In the current Perspective, we have outlined a roadmap for using the high-throughput clinical data sets to inform a QSP modeling framework through NBA. The NBA approaches and tools listed in the supplementary materials are developed for various purposes and hence are of different granularity. A more collective thinking and development of standard pipelines depending on data availability and purpose is an immediate need to answer several biological and drug discovery questions.

In summary, we propose that the impact and efficiency of QSP in target identification and validation can be significantly improved through integration with
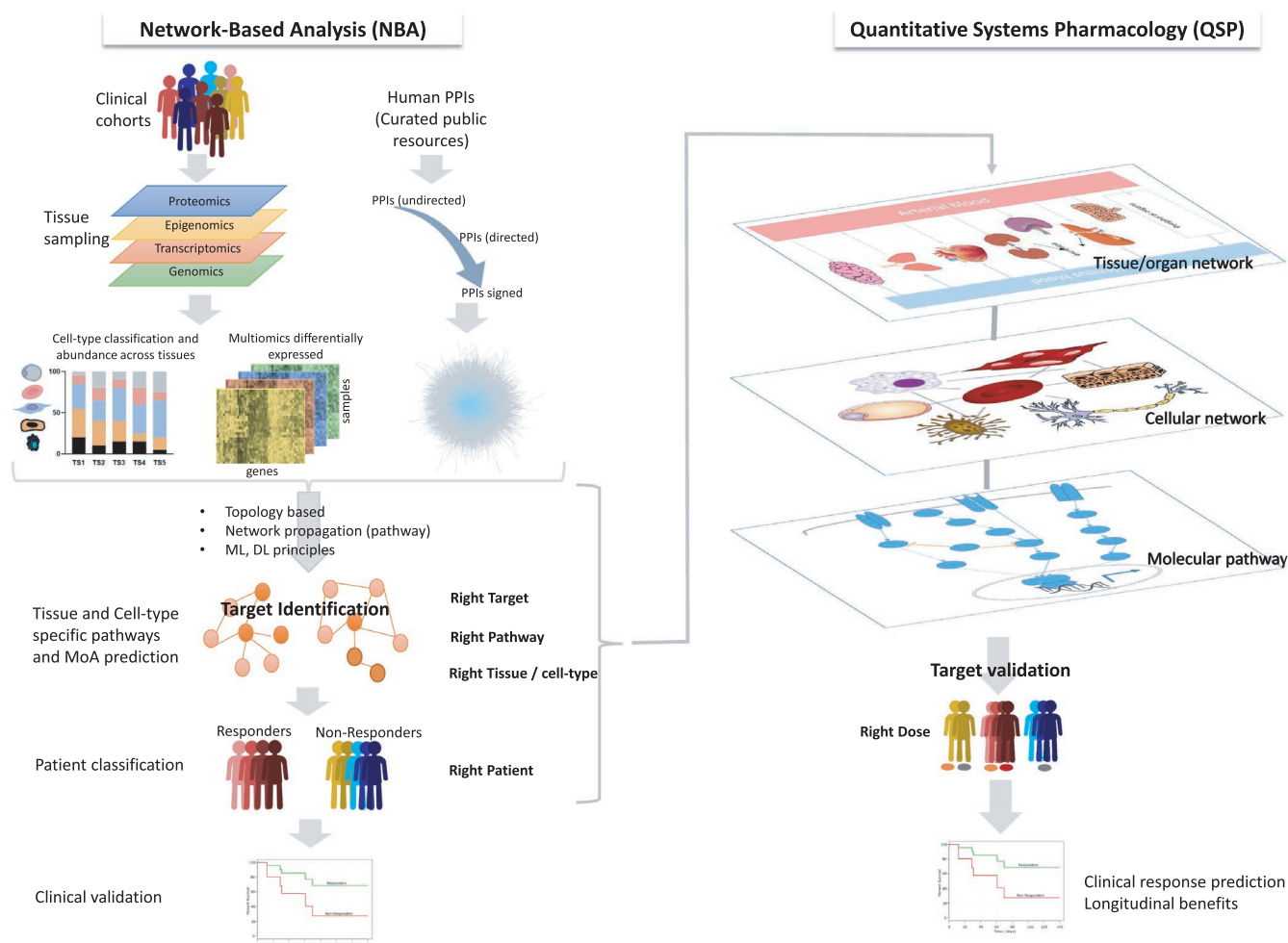
FIGURE 1 A graphical summary of the proposed network-based analysis (NBA) and quantitative systems pharmacology (QSP) integration approach in model-informed drug discovery and development. Integration and analysis of multi-omics data using an NBA framework can assist in extracting tissue/cell-specific molecular signatures and transduction mechanisms in individual patients or a subset of patients. This data-driven, qualitative hypothesis is subsequently used as the basis for the development of QSP models to predict longitudinal effects and optimize therapeutic regimens. DL, deep learning; ML, machine learning; MoA, mechanism of action; PPI, protein–protein interaction

NBA. Although we have already demonstrated how omics data can be used to parametrize QSP models in a manual and ad hoc manner,[10] a standardized, automated, and scalable approach would be a more effective way of using the full potential of both NBA and QSP together in model-informed drug discovery and development.

CONFLICT OF INTEREST
The authors declared no competing interests for this work.

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