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PHARMACOMETRICS AND SYSTEMS PHARMACOLOGY OF ANTI-CANCER DRUGS

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Most pharmacodynamic (PD) models of anti-cancer drugs integrate the time-course of drug exposure (pharmacokinetics or PK), the growth kinetics of cancer cells (*in vitro*) or tumor volume (*in vivo*), and a rate constant associated with the temporal delay between PK and the action of the drug [1]. Such models have been adapted to include several molecular biomarkers of drug-target interactions and signal transduction, describe anti-cancer drug combinations, and incorporate intrinsic and acquired drug resistance. These *pharmacometric* models have been used during all phases of drug development to describe anti-cancer drug action in cell and murine xenograft systems and effects on disease progression in patients. Although providing insights into pharmacological aspects that translate across phases of drug development, semi-mechanistic PD models are rarely sufficiently robust (regardless of model performance) to prospectively predict combinatorial drug responses, complex genotype-phenotype relationships, off target toxicity, implications of tumor heterogeneity, and approaches to circumventing drug resistance. In contrast, systems biology is an emerging field that represents a diverse array of computational approaches to predict and understand the complex interactions within biological systems that underlie emergent properties of cells, tissues, and whole organisms [2]. Network-based methods are prominently featured and are showing utility for identifying novel drug targets and repositioning of existing agents [3]. There is a consensus that an effective integration of these disciplines is needed in order to fully realize the promise of each in bringing new therapeutic molecules and combination regimens to the bedside [4]. Both drugs and disease processes give rise to complex and dynamic clinical phenotypes by altering natural interconnected biochemical networks and support the emergence of *systems pharmacology* models of drug action [5, 6]. Multi-scale models that combine PD principles and signaling networks might eventually serve as a platform for integrating genomic/proteomic factors that regulate drug effects and clinical outcomes – so called enhanced PD models [7]. Network analysis tools, such as logic-based modeling, can provide a global perspective of system properties in the absence of kinetic parameters, as well as guidance for multi-scale model construction and evaluation [8]. This presentation will review *pharmacometric* and *systems pharmacology* approaches to providing a quantitative framework for testing confidence in early drug targets, projecting inter-individual variability and patient subpopulations likely to respond to new drugs or drug combinations, and ultimately achieving precision medicine.

References

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