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EDITORIAL

Systems Approaches Evolve Clinical Pharmacology

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THE WHOLE IS GREATER THAN THE SUM OF ITS PARTS: ARISTOTLE

The May 2013 issue of *Clinical Pharmacology and Therapeutics (CPT)*,[1] coincident with the recent launch of the new journal *CPT: Pharmacometrics and Systems Pharmacology (CPT:PSP)*,[2] highlights systems approaches in pharmacology. These publications underscore the concept that we have reached a critical juncture in the discipline of clinical pharmacology.[3] Until recently, the field was driven by a reductionistic perspective of biology, comprising piecemeal dissection of individual molecules and pathways, and their unique functions to provide a view of normal physiology associated with health, and the corruption of those biomolecules and circuits producing pathophysiology underlying disease.[4] Using this approach, our rudimentary models predicted the impact of small molecule drugs on these individual components that were aligned with their behavior under controlled laboratory conditions in the test tube.[5] However, more often than not, these drugs failed to behave "appropriately" in preclinical *in vivo* models, in normal individuals, or in patients, reflecting a lack of efficacy and/or intolerable adverse effects that could not be predicted by a reductionistic approach.[6] Rather, individual biomolecules are part of a much larger complex network whose integrated functions extend beyond individual components and pathways.[7] In that context, the cover image of the May 2013 issue of CPT is a profound metaphor, in which blind monks describe an elephant by the individual "components" they feel with their hands.[1] The monk probing the tail of the elephant describes a serpent, the one feeling the pachyderm's broad back describes a tortoise, the monk feeling a tusk describes a rhinoceros, and so on. Each monk accurately describes what they feel, and their conclusion is based on a combination of their individual experiences and context. And while their instantaneous descriptions of structure are correct, each fails to accurately describe the elephant. Indeed, the true nature of the elephant only emerges when the individual observations of the monks are integrated to provide a systems-level view, creating a complete "picture." Like the blind monks, our description of structure and function for individual component molecules has been accurate. However, like the elephant, the true nature of physiology, its corruption in disease, and its remediation in therapy is emergent, only revealed by understanding the individual molecular functions within the context of the entire integrated system.

Therefore, the critical juncture confronting the discipline of clinical pharmacology is the move from a reductionistic approach to a systems-level view to "see the whole picture."[2,8] Our ability to move beyond descriptions of single molecules and their functions reflects parallel evolution in enabling platform technologies and quantitative modeling.[9] Indeed, there has been an exponential explosion in the ability to simultaneously interrogate the structure and function of the biology of cells, organs, and organisms, through omic technologies describing the genome, proteome, and metabolome, just to name a few, in health and disease.[10] In turn, resulting high-dimensional datasets produced by these platform technologies can only be reduced by understanding of (patho) physiology through the integration of biomedical informatics approaches and modeling.[11] In that context, quantitative model building provides an opportunity to incorporate biological mechanisms underlying normal and abnormal physiology at multiple levels.[2] These models continuously incorporate new data as they become available, to provide the most complete picture of the entire integrated system.[12] Here, resolution of the structure and function of the integrated system is only limited by the richness of data generated by platform technologies and the dimensionality of the models generated.

These systems-level approaches offer a capacity to generate novel insights across the orthogonal dimensions of (patho)physiology and drug development.[8] Indeed, they provide an opportunity to integrate emerging understanding of the circuitry of subcellular molecular pathways with the structure and function of organs and organisms, a gap that was previously difficult to span, essentially linking biochemical, cellular, and organismal pharmacology for the first time.[13] Similarly, these approaches permit expansion of insights in biology and physiology into identifying new disease targets and novel molecularly directed therapies that cure disease.[14] In that context, systems pharmacology provides an important bridge that links the foundational clinical pharmacology discipline of pharmacokinetic and pharmacodynamic modeling, in which the primary focus is drug exposure, target engagement, and target modulation, with disease-relevant functional modeling focused on pathway modulation, (patho)physiological regulation, and disease modification.[15] In turn, this integration across the continuum of cellular, organ-based, and organismal pharmacology provides a unique opportunity to accelerate the drug development enterprise.[8] Indeed, the "whole picture" provided by systems approaches improves the predictability of the pharmacokinetic behavior of new molecular entities, their adverse effects, and their disease-modifying activities, increasing the success rate across the discovery-development-application continuum.

The discipline of clinical pharmacology is poised on the advancing edge of a revolution in technologies and algorithms that will permit deconvolution of biology in service to advancing the science and practice of therapeutics, enabled by systems approaches in omic technologies and informatics and advanced modeling techniques. These paradigms essentially integrate the observations of the individual blind monks to provide a complete picture of the elephant, in which the whole is clearly greater than the mere sum of the individual parts. The central importance of these systems

approaches to the discipline of clinical pharmacology was the engine driving the creation of *CPT:PSP*. We look forward to the remarkable evolution of this field and its potentiation of human therapeutics that will be reported in future issues of *CPT:PSP*.

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