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EDITORIAL

CPT: Pharmacometrics and Systems Pharmacology

Welcome to the first issue of *CPT: Pharmacometrics and Systems Pharmacology* (*CPT:PSP*), a new journal from the American Society for Clinical Pharmacology and Therapeutics. *CPT:PSP* is a cross-disciplinary journal devoted to publishing advances in quantitative, model-based approaches as applied in pharmacology, (patho)physiology, and disease to aid the discovery, development, and utilization of human therapeutics. The emphasis of *CPT:PSP* will be on the application of modeling and simulation and the impact of Pharmacometrics and Systems Pharmacology on the discovery and development of innovative therapies.
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PHARMACOMETRICS AND SYSTEMS PHARMACOLOGY

Pharmacometrics has been defined as "*the science of developing and applying mathematical and statistical methods to: (a) characterize, understand, and predict a drug's pharmacokinetic and pharmacodynamic behavior, (b) quantify uncertainty of information about that behavior, and (c) rationalize data-driven decision making in the drug development process and pharmacotherapy. In effect, Pharmacometrics is the science of quantitative pharmacology*".[1] Another more biologically oriented definition of Pharmacometrics is "*the branch of science concerned with mathematical models of biology, pharmacology, disease, and physiology used to describe and quantify interactions between xenobiotics and patients, including beneficial effects and side effects resultant from such interfaces*".[2] Approaches related to Pharmacometrics, in particular pharmacokinetic–pharmacodynamic (PKPD) modeling and simulation, are increasingly being applied in the development of novel therapeutics, and the impact of these investments is being highlighted and advocated by both pharmaceutical research organizations[3] and regulatory agencies.[4,5] The "coming of age" of Pharmacometrics as a global discipline was underscored by the recent establishment of the International Society of Pharmacometrics. As an official journal of this society, *CPT:PSP* shares its mission of "*promotion and advancement of the discipline of Pharmacometrics, through Integration, Innovation, and Impact: quantitative integration of multisource data and knowledge of clinical, biomedical, biological, engineering, statistical, and mathematical concepts, resulting in continuous methodological and technological innovation enhancing scientific understanding and knowledge, which in turn has an impact on discovery, research, development, approval, and utilization of new therapies*" (http://go-isop.org/).

Systems Pharmacology, on the other hand, is more of an emerging concept[6] that has yet to be fully defined. The term first appeared in the literature under the banner of a National Institute of General Medical Sciences initiative "Integrative and Organ Systems Pharmacology"[7] and later in the context of drug discovery as "*...the body-system-wide, predominantly molecular, characterization of drug-perturbed state relative to the unperturbed state*".[8] More recently, Systems Pharmacology has been described as the interface between Pharmacometrics and Systems Biology,[9] wherein the latter can be defined as the "*quantitative analysis (through application of concepts of systems engineering and iteration between computational and/or mathematical modeling and experimentation) of the dynamic interactions between several components of a biological system and aims to understand the behavior of the system as a whole, as opposed to the behavior of its individual constituents*".[10] The growing interest in Systems Pharmacology across academic, regulatory, and industrial partners is outlined in a recent White Paper by the National Institutes of Health Quantitative Systems Pharmacology workshop group,[11] which defines Quantitative Systems Pharmacology 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 .... to determining mechanisms of action of new and existing drugs in preclinical and animal models and in patients*".

A main driver behind the growing investments in Systems Pharmacology is the recognition that novel, innovative approaches are required to improve productivity in pharmaceutical research and development, specifically tackling attrition due to insufficient efficacy in proof-of-concept/phase II studies, which is increasingly seen as the main bottleneck.[12] Although it has been shown that a more consistent and integrated application of "traditional" PKPD principles across all stages of discovery and development should result in a significant improvement of phase II survival,[13] this may not be sufficient to address the (arguably) bigger challenge of improving our ability to select the right biological target in the right patient population and validate medical hypotheses using optimal pharmacological modalities (**Figure 1**). Systems Pharmacology is a response to the growing awareness that to reverse the decline in research and development productivity, there is a need to better characterize, understand, and predict pharmacological modulation of biological targets in a quantitative manner. For instance, although there is an increased realization that the traditional "one-drug for one-target" approach to pharmacological treatment may be intrinsically flawed for many diseases and complex, synergistic interactions are well established even at the level of relatively simple biochemical networks,[14] we are currently lacking a practical and testable framework to translate these

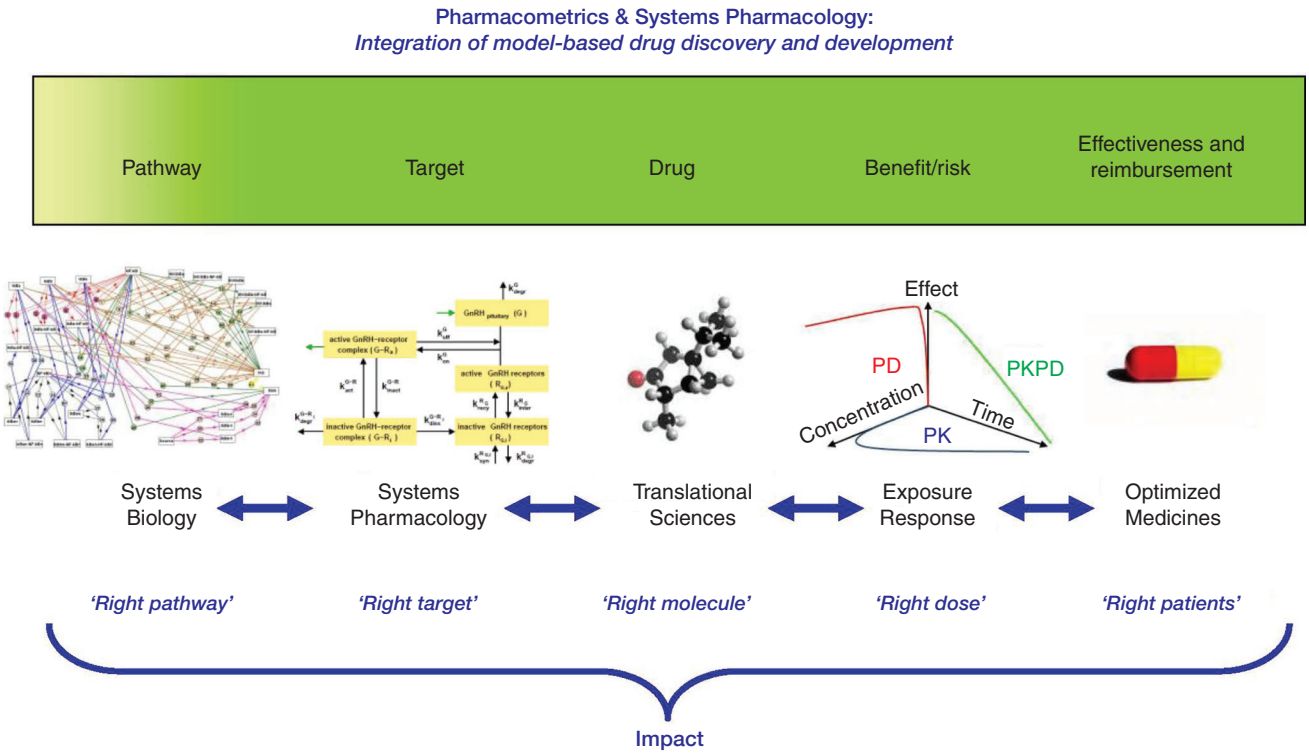

Figure 1 An integrated view of model-based drug discovery and development. *CPT: Pharmacometrics and Systems Pharmacology* **(***CPT:PSP***)** welcomes contributions of research across the whole spectrum of Pharmacometrics and Systems Pharmacology, with emphasis on application and impact on innovation of therapeutics. The common focus will be on quantitative methods that improve our understanding of pharmacology and therapeutics in humans. This is based on Figure 3 in the work of van der Graaf and Benson,[9] which was further developed with input from Peter Milligan (Pfizer) and redrawn with permission from *Pharmaceutical Research.* PD, pharmacodynamics; PK, pharmacokinetics; PKPD, pharmacokinetics–pharmacodynamics.

insights into drug discovery and development. In the words of the Nobel laureate Sir James Black[15]: "*Physiological systems that are organized by chemical convergence based on potentiating interactions will need pharmacological convergence to manage them effectively. There is now a vast literature describing potentiating interactions between intercellular messenger molecules. However, I am not aware that anyone has proposed a Theory on Potentiating Interactions at the molecular level. We need to develop a conceptual base to allow us to predict the best pharmacological combination*". The hope and expectation is that Systems Pharmacology will provide the scientific foundation and tools and methodologies for the development of such quantitative concepts[16] and *CPT:PSP* aims to lead the dissemination and sharing of the best research in this area, exploiting, at the same time, the synergies and lessons that will come from the more mature science of Pharmacometrics, which is typically associated with applications during later-stage clinical development.

Systems Biology is typically associated with a "bottom–up" approach, the potential of which was very recently illustrated by the publication of the first comprehensive "whole-cell" computational model that predicts phenotype from genotype for the lifecycle of the human pathogen, *Mycoplasma genitalium*.[17] Systems Pharmacology can be based on a similar bottom–up paradigm;[18] however, the most efficient way of generating new Systems Pharmacology constructs for biological systems in drug discovery and development is not obvious as of now. "Top–down" approaches are also being used,[19] e.g., using translational bioinformatics to develop and analyze networks across large heterogeneous data sets,[20] whereas others have proposed "middle–out" approaches.[21] These start the process of integration between biology and quantitative sciences at whatever systems level there is more information available, to then branch out towards top and bottom levels of organization, adding or subtracting complexity as needed. *CPT:PSP* welcomes contributions from all these angles and aims to facilitate further integration of these approaches, thereby building bridges between Systems Pharmacology and Pharmacometrics, which to date have largely operated as unconnected disciplines.

OPEN ACCESS, OPEN MODELS, OPEN DATA, OPEN SCIENCE

CPT:PSP will be published as an online-only, open access journal. This format of the journal, supported by an Article Processing Charge, means that all articles will be made freely available for anyone to read immediately upon publication. In addition, articles will publish under the Creative Commons License, enabling readers to download the article and share it with others. This platform will allow for and encourage rapid and open discourse on published work, consistent with the position and support of a growing number of major funders

(including the National Institutes of Health in the United States, the Welcome Trust in the UK, and the European Commission) as well as governments and learned and professional societies.[22] *CPT:PSP* will therefore be freely accessible across the world and can serve as a global platform for the meeting and integration of the disciplines of Pharmacometrics and Systems Pharmacology. The open access format also provides the opportunity to reach out to members of other scientific disciplines and the wider community, who may not have access to specialized journals outside their field and therefore may be unaware of the role, impact, and potential of Pharmacometrics and Systems Pharmacology, and especially the combination of the two. A more detailed discussion of open access publishing in pharmaceutical sciences is provided in the accompanying *CPT:PSP* Perspective article by Conway.[23]

On the back of the open access debate, the next wave that will transform scientific publishing has been labeled "Open Data for Open Science", which calls for making all data freely available as part of scientific publications.[22] In its recent report on this topic,[24] the Royal Society specifically includes computational models and simulations in the first recommendation which states that "*Scientists should communicate the data they collect and the models they create, to allow free and open access, and in ways that are intelligible, assessable, and usable for other specialists in the field wherever they are in the world*". I believe this is an important principle that will facilitate the growth and development of the disciplines of Pharmacometrics and Systems Pharmacology and envisage that over time *CPT:PSP* will contribute to a framework of "Open Access Models", along the lines of examples set by other disciplines such as Systems Biology.[25] One issue related to the sharing of models is the lack of common tools and model standards across and even within disciplines. *CPT:PSP* aims to support initiatives in this area through publication of research and educational articles and facilitation of model sharing.

CPT:PSP—INTEGRATION OF QUANTITATIVE, MODEL-BASED APPROACHES

The content of *CPT:PSP* will reflect the vision that application and integration of quantitative, model-based approaches at all stages of the research and development cycle (**Figure 1**) is required for Pharmacometrics and Systems Pharmacology to reach their full potential and deliver the greatest impact.[9,26] Examples of topics in scope for the journal are Systems Pharmacology modeling of human pharmacology, physiology and pathology, computational pharmacology, physiologically based pharmacokinetic modeling applied to human pharmacology, translational mechanistic PKPD models, population-based pharmacokinetic and PKPD approaches to the analysis of clinical data, disease modeling, model-based meta-analyses, modeling and simulation as applied to the design and evaluation of clinical trials, and models of comparative efficacy, effectiveness, and cost effectiveness. As mentioned earlier, the emphasis of *CPT:PSP* will be on the application of clinical and translational value rather than the theoretical advances. The first papers published in *CPT:PSP* reflect the broad scope of the journal, ranging from physiologically based pharmacokinetics/Systems Pharmacology to population-based PKPD modeling of biomarkers and clinical outcomes.[27-31]

In addition to the original research articles, *CPT:PSP* will publish reviews and perspectives, which are shorter pieces designed to give the author's perspective on current and emerging topics of importance to the development and potential of the disciplines of Pharmacometrics and Systems Pharmacology. Tutorials form a fourth, unique article type that will focus on providing practical educational material on tools, methodologies, and approaches for modeling and simulation. The first *CPT:PSP* tutorial of this kind by Mould and Upton[32] is an introduction to population-based modeling approaches aimed at readers with little or no familiarity of the field, which fits into the journal's mission of raising awareness and understanding across and outside the disciplines of Pharmacometrics and Systems Pharmacology. More introductory tutorials of this kind on a variety of topics as well as more technical guides on specialist issues will follow. This is motivated by the fact that well-versed practitioners spanning the full range of both disciplines (**Figure 1**) are exceedingly rare.

The interdisciplinary scope of the journal is reflected in the makeup of the team of Associate Editors, who are all internationally renowned experts in the field of Pharmacometrics and Systems Pharmacology (www.nature.com/psp) and form the Editorial Leadership together with the Editor-in-Chief, supported (in partnership with our sister journal, *CPT*) by the highly experienced Editorial Office at the American Society for Clinical Pharmacology and Therapeutics and Nature Publishing Group. In addition, the distinguished members of the *CPT:PSP* Editorial Board (www.nature.com/psp) will serve as subject matter experts and work in tandem with the Editorial Leadership to maintain the scientific quality and integrity of the journal.

It is a great honor and privilege to serve as the first Editor-in-Chief of *CPT:PSP*, and I will do my best to support the development of the journal into a leading scientific publication platform for Pharmacometrics and Systems Pharmacology which will contribute to the further growth of the disciplines and a broader application and better integration of model-based approaches across the research and development spectrum. The ultimate measure of success of these efforts will be a demonstrable increased impact of model-based approaches on pharmaceutical innovation and the delivery of new medicines to patients in areas of high medical need. I would not have taken on the challenge of leading this new journal if I did not believe *CPT:PSP* can contribute towards the achievement of this ambitious goal.

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Conflict of Interest. The author is an employee of Pfizer.

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Supplementary Information accompanies this paper on the *CPT: Pharmacometrics & Systems Pharmacology* website (http://www.nature.com/psp)