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PERSPECTIVE

NIH Support for the Emergence of Quantitative and Systems Pharmacology

M Rogers[1], P Lyster[1] and R Okita[1]

The National Institute of General Medical Sciences (NIGMS) of the National Institutes of Health (NIH) sponsored two workshops and the development of a white paper on the emergence of quantitative and systems pharmacology (QSP) as a discipline. In subsequent efforts to encourage this area, NIGMS modified existing research and training offerings. We highlight these changes and point out other new and existing initiatives at NIH that provide avenues for support of research and training in QSP.
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In recent years, the National Institute of General Medical Sciences (NIGMS) of the National Institutes of Health (NIH) has sought to explore the integration between systems biology and pharmacology, believing that systems approaches are needed to understand the complexity of drug action and that studies of drug action will yield new insights into systems biology. To this end, NIGMS sponsored the first quantitative and systems pharmacology (QSP) workshop in October 2008, followed by a second workshop in October 2010 (reported in ref. 1). A working group from the second workshop composed a white paper, "Quantitative and Systems Pharmacology in the Post-Genomic Era: New Approaches to Discovering Drugs and Understanding Therapeutic Mechanisms," that presented background and recommendations for research and research training for the emerging discipline of QSP.[2] The authors present a summary of programmatic offerings that have occurred at NIGMS and NIH in response to these efforts and provide an overview of NIH-wide interest in QSP.

WHY QUANTITATIVE?

The link between systems pharmacology and systems biology is perhaps obvious, but it might be asked why NIGMS chose to include "quantitative" in the title for the workshops and white paper. At NIGMS, we view systems biology research as relating to complex biomedical problems characterized by emergent behavior that cannot easily be inferred from studies of components in isolation. Systems biology relies on mathematical methods and computational models to generate hypotheses and to design new experiments. Iteration between theory and experiment is crucial, with the critical link being provided through quantitative analysis and modeling. It seems to us that pharmacologists, clinical pharmacologists, and pharmacokineticists have entered an era in which systems approaches are essential for understanding global behavior. For example, as a key tool for drug discovery, clinical pharmacologists are now performing whole-body modeling of the distribution of drugs in humans and animals. In broad terms in the field of pharmacology, one sees frequent attempts to model events between vertical levels of integration, i.e., cells, tissues, and organisms, whereas systems biologists are often attempting to model events horizontally within the cell, linking pathways, and gene circuits. Both approaches are critical to understanding drug action. The analogy comes to mind that we have two railroad companies attempting to span a continent, beginning at different ends and meeting in the middle. It is obviously necessary to arrive at the same place with the same gauge tracks. Systems biology increasingly demands more data, such as images, binding affinities, rate constants, and genomic information. It also demands new computing algorithms. Similarly, pharmacokineticists are pushing quantitatively into pharmacodynamics and other systems approaches to improve the drug discovery pipeline. We believe it is important to support the development of new tools for data acquisition and storage as well as new computational analytical tools designed to seamlessly couple both directions through their quantitative integration.

ENCOURAGING RESEARCH IN TODAY'S BUDGET CLIMATE

We decided to consider what steps we might take to encourage QSP research in the absence of an influx of new funds to support a large-scale effort. These include highlighting existing and new NIH efforts and making changes in NIGMS training and research programs.

QSP-RELATED NIH RESEARCH PROGRAMS

Some of the ongoing and new activities at NIH institutes and centers include:

1. The National Cancer Institute's Integrative Cancer Biology Program[3] explicitly requires computational, quantitative, and experimental elements in the discovery of complex phenomena relating to cancer.
2. An NIGMS program for National Centers for Systems Biology[4] currently funds 15 centers at a total budget of ~$45 million per year. The majority of work in these

[1]National Institute of General Medical Sciences, National Institutes of Health, Bethesda, Maryland, USA. Correspondence: M Rogers (RogersM@nigms.nih.gov)
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centers focuses on basic cellular and molecular biological processes, areas that are mainstays of research at NIGMS. In recent years, the program has extended to multiple scales, and in 2011, it funded the Center for the Study of the Virtual Physiological Rat at the Medical College of Wisconsin. One of the areas of study is how multiple genes and environmental factors interact to determine the cardiovascular phenotype. The current funding opportunity announcement for the National Centers for Systems Biology (PAR-12-187)[5] is bolstered with specific language to encourage applications in QSP.

3. QSP was prominently featured as a promising approach in Alzheimer's disease therapy development at the Alzheimer's disease Summit held in May 2012.[6] Later that year, the National Institute on Aging issued a request for applications (RFA AG-13-013) on novel therapeutic target identification and validation inviting the use of network-based approaches.[7]
4. For more information about government programs in quantitative sciences and systems biology, see the funding pages site of the NIH Biomedical Information Science and Technology Initiative.[8]

TRAINING IN QSP

The QSP white paper described general agreement among industry, academia, and regulatory agency attendees on the need for training in systems pharmacology to prepare the next generation of pharmacologically trained scientists to investigate and understand how drugs and drug candidates affect both target and off-target receptors and pathways, and ultimately, lead to phenotypic changes.

The white paper also described the many areas that are needed to develop a training program in QSP, as shown in **Figure 1**. It may be necessary for training in QSP to require more introductory and/or advanced courses for individuals to develop an understanding of how drugs act in terms of their therapeutic and toxic effects. The increasing emphasis on personalized medicine for better outcomes of prescribed drugs and a greater understanding of interindividual variation of drug action will require an understanding of pharmacogenomics/pharmacogenetics. The white paper noted that it is difficult to define the skill sets that are necessary to train students in QSP, but there is clearly a need for more courses and training in diverse subjects. However, there is also a move to decrease the time that predoctoral students spend in graduate training, so innovative educational approaches will be required to permit students to obtain the necessary skills in a reasonable time frame. NIGMS institutional training grants in the pharmacological sciences offer one venue for such training designs. An institutional predoctoral training program at the Mount Sinai School of Medicine run by Terry Krulwich is focused on training in systems pharmacology.[9] This program prepares its students to use systems approaches to identify therapeutic targets, study signaling systems and network integration, and study the pharmacodynamics and therapeutic effects of compounds. The program's curriculum has introduced computational

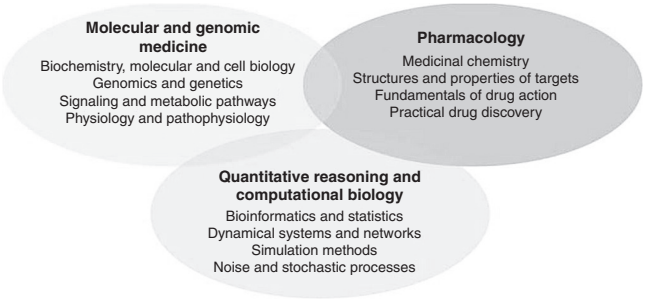

Figure 1 Concepts and application areas for a training program in quantitative and systems pharmacology.

modeling systems that permit the integration of the cellular and molecular sciences with the physiology and pathophysiology of disease states. The program states that its "problem-based learning exercises enable students from different experimental and computational backgrounds to design experiments and interpret data quantitatively."

NIGMS, the National Institute of Child Health and Human Development, and the NIH Office of Dietary Supplements support the training of PharmD students who have been accepted into joint PharmD/PhD programs in schools of pharmacy.[10] This support is intended to provide the students with additional time to take courses outside of their department to develop expertise in bioinformatics, computational biology, "omic" technologies, and other areas, beyond mastering the principles of pharmacokinetics, medicinal chemistry, pharmacology, and pharmacogenomics.

Didactic training in QSP does not stop at the predoctoral stage, and additional courses may be needed at the postdoctoral level. Postdoctoral fellows applying for Ruth L. Kirschstein National Research Service Awards for individual predoctoral fellows (F32) and Pathway to Independence Awards (K99/R00) are encouraged to take additional courses or to seek additional mentored training to improve their understanding of pharmacokinetics, physiological systems and receptor biology; bioinformatics and computational biology to better model drug effects; and various "omic" technologies to develop the expertise needed to conduct their individual research programs. NIGMS also funds institutional training (T32) grants and individual mentored clinical scientist development awards (K08, K23) in clinical pharmacology to support the research training of clinicians. Similar to the training of PhDs, clinicians (MDs and PharmDs) who plan to develop independent research careers in clinical pharmacology and personalized medicine should consider training in systems pharmacology. Finally, the NIGMS Postdoctoral Research Associate (PRA) Program, which supports postdoctoral fellows to pursue research in one of the laboratories of the NIH or Food and Drug Administration, will place special emphasis this year and next on training in QSP and computational biology.[11]

In conclusion, to advance therapeutics in the modern era, systems approaches to pharmacology are required. A greater emphasis on quantitative methods and modeling to deal with such overwhelming pharmacological complexity is essential. Training students at all levels for this future is an urgent need, and new and innovative approaches will be required

to accomplish training in an area of such scope in reasonable time frames. NIH has a strong interest in research and training efforts in QSP, and its support of this field continues to expand.

Conflict of interest. The authors declared no conflict of interest.

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