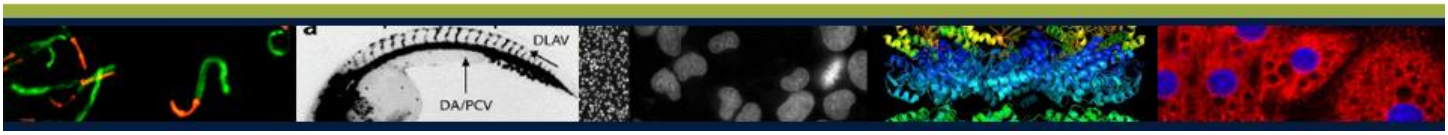
PITTSBURGH WORKSHOP ON QUANTITATIVE SYSTEMS PHARMACOLOGY IN PERSONALIZED MEDICINE



We would like to acknowledge and thank the following supporters of this workshop:

- **University of Pittsburgh**
  - **Clinical and Translational Science Institute**
  - **Drug Discovery Institute**
  - **Institute for Personalized Medicine**
- **Carnegie Mellon University**
- **UPMC**

6:00 PM-9:00 PM **Hospitality Suite, Monday evening, November 18, for those who get in early**
Lounge Area, Bridges Restaurant, Wyndham Hotel

DAY 1-TUESDAY, NOVEMBER 19, 2013

Upper Ballroom-University Club

7:30 AM **Coffee and Workshop Check-In**

8:00 AM **BREAKFAST AND WELCOME FROM THE UNIVERSITY OF PITTSBURGH AND CARNEGIE MELLON UNIVERSITY**

Arthur S. Levine, MD, Senior Vice Chancellor for the Health Sciences and Petersen Dean of Medicine, University of Pittsburgh

Steven D. Shapiro, MD, Executive Vice President and Chief Medical and Scientific Officer, UPMC

Subra Suresh, **ScD,** President, Carnegie Mellon University

Randy P. Juhl, PhD, Vice Chancellor for Research Conduct and Compliance, University of Pittsburgh

8:30 AM **WORKSHOP GOALS**

D. Lansing Taylor, PhD
Allegheny Foundation Professor of Computational and Systems Biology
Director, University of Pittsburgh Drug Discovery Institute

Jeremy M. Berg, PhD
Pittsburgh Foundation Professor and Director, University of Pittsburgh Institute for Personalized Medicine
Associate Senior Vice Chancellor for Science Strategy and Planning, Health Sciences

9:00 AM **SESSION 1—QUANTITATIVE SYSTEMS PHARMACOLOGY**

Session Chair: Ivet Bahar, PhD
John K. Vries Professor and Chair of Computational and Systems Biology
Distinguished Professor of Computational and Systems Biology
University of Pittsburgh School of Medicine

9:00 AM **QSP—The Academic Perspective (20')**
Brian Shoichet, PhD
Professor of Pharmaceutical Chemistry
University of California, San Francisco

9:30 AM **QSP—The Industry Perspective (20')**
James Stevens, PhD
Senior Research Fellow
Eli Lilly Research Laboratory

10:00 AM **An NIH Perspective on Quantitative and Systems Pharmacology (20')**
Michael Rogers, PhD
Director, Division of Pharmacology, Physiology, and Biological Chemistry
National Institute of General Medical Sciences

10:30 AM **Break**

11:00 AM **SESSION 2—ADDITIONAL PERSPECTIVES ON QSP**

Session Chair: Bruce A. Freeman, PhD
UPMC-Irwin Fridovich Professor and Chair of Pharmacology and Chemical Biology
University of Pittsburgh School of Medicine

11:00 AM **Talk 1 (15')**
Trey Ideker, PhD
Director, San Diego Center for Systems Biology
Director, National Resource for Network Biology
University of California, San Diego

11:20 AM **Talk 2 (15')**
Gary J. Nabel, MD
Senior Vice President and Chief Scientific Officer
Sanofi

11:40 AM **Talk 3 (15'): "Reconstructing Dynamic Regulatory Networks for Studying Disease Response"**
Ziv Bar-Joseph, PhD
Associate Professor of Machine Learning
Lane Center for Computational Biology
Carnegie Mellon University School of Computer Science

12:00 NOON **Talk 4 (15')**

Ivet Bahar, PhD
John K. Vries Professor and Chair of Computational and Systems Biology
Distinguished Professor of Computational and Systems Biology
University of Pittsburgh School of Medicine

12:20 **Bio Break/Set Tables for Lunch**

12:30 **LUNCH AND FOCUSED DISCUSSIONS**

Discussion Leaders

1) Steven Altschuler, PhD
Associate Professor of Pharmacology
Green Center for Systems Biology
University of Texas Southwestern Medical Center

2) Dan Gallahan, PhD
Deputy Director, Division of Cancer Biology
National Cancer Institute

3) Cecilia Schott, PhD
Head, Personalized Healthcare
Corporate Development & Ventures
AstraZeneca

4) Dietrich Stephan, PhD
Professor and Chair of Human Genetics
University of Pittsburgh Graduate School of Public Health

5) John P. Wikswo, PhD
Gordon A. Cain University Professor
A.B. Learned Professor of Living State Physics
Director, Vanderbilt Institute for Integrative Biosystems Research and Education

6) Sean Xie, PhD, MBA
Professor of Pharmaceutical Sciences
University of Pittsburgh School of Pharmacy

Jeffrey Brodsky, PhD
Avinoff Professor of Biological Sciences
University of Pittsburgh Dietrich School of Arts and Sciences

2:00 PM **SESSION 3—PERSONALIZED MEDICINE**

Session Chair: **Rebecca Crowley, MD, MS**
Associate Professor of Biomedical Informatics and of Pathology
University of Pittsburgh School of Medicine

2:00 PM **PM—The Academic Perspective (20')**
Steven Shapiro, MD
Executive Vice President & Chief Medical and Scientific Officer
UPMC

2:30 PM **PM—The Industry Perspective (20')**
Andrew S. Plump, MD, PhD
Vice President, Research and Translational Medicine and
Deputy to the President of Global R&D
Sanofi

3:00 PM **Break**

3:30 PM **SESSION 4—ADDITIONAL PERSPECTIVES ON PM**
Session Chair: James R. Faeder, PhD
Associate Professor of Computational and Systems Biology
University of Pittsburgh School of Medicine

3:30 PM **Talk 4 (15'): "Applying QSP to Breast Cancer Research and Personalized Medicine"**
Adrian Lee, PhD
Professor of Pharmacology and Chemical Biology
University of Pittsburgh School of Medicine

3:50 PM **Talk 5 (15')**
Srinivas (Ravi) Iyengar, PhD
Professor and Chair of Pharmacology and Systems Therapeutics
Icahn School of Medicine at Mt. Sinai Hospital

4:10 PM **Talk 6 (15'): "Analytics and Precision Medicine"**
Kathleen Bove, PhD
Molecular Diagnostic Platforms
GE Healthcare Medical Diagnostics

4:40 PM **Talk 7 (15') "Bringing the Genome to the Point of Care"**
Dietrich A. Stephan, PhD
Chair, Department of Human Genetics
University of Pittsburgh Graduate School of Public Health

5:00 PM **Talk 8 (15')**
Christopher P. Austin, MD
Director, National Center for Advancing Translational Sciences

5:30 PM **COCKTAIL HOUR AND POSTER SESSION FEATURING PITT AND CARNEGIE MELLON SCIENTISTS**
Lower Ballroom-University Club

6:45 PM **DINNER**
Lower Lounge, William-Pitt Union

After-Dinner Speaker
Ashley Dombkowski, PhD
Managing Director
Bay City Capital

DAY 2—NOVEMBER 20, 2013

Upper Ballroom –University Club

8:00 AM **Breakfast**

8:30 AM **SUMMARIES AND SUGGESTED NEXT STEPS FROM DAY 1 LUNCH DISCUSSIONS**

9:20 **Response**
The Honorable Michael Wolf
Secretary of Health
Commonwealth of Pennsylvania

9:30 AM **PANEL DISCUSSION 1**
Moderator—Cecilia Schott, PhD
Choose 2-3 topics from previous day lunch discussions—one to two panelists selected from each table

10:30 AM **PANEL DISCUSSION 2**
Moderator—Dan Gallahan, PhD
Choose 2-3 topics from previous day lunch discussions—one to two panelists selected from each table

11:30 AM **SUMMARY OF MEETING AND PROPOSED ACTION STEPS**

Lans Taylor, PhD

Jeremy Berg, PhD

QUANTITATIVE SYSTEMS PHARMACOLOGY

Quantitative systems pharmacology (QSP) offers a new paradigm in the development of therapeutics that promises to make personalized medicine a reality. The last 30 years of drug discovery and development have been guided by a "target-centric" method that succeeded in producing "blockbuster" medications based on the one-gene, one-protein, one-drug paradigm. Increasingly, though, this reductionist approach has experienced a high failure rate due to low efficacy in the transition from preclinical to clinical trials or serious side effects discovered late in the development process. However, these undesirable outcomes often reflect only the averaged population-level results: some drug candidates that failed in the trial cohort as a whole showed positive results in sub-populations of patients, while other agents that were successful in most patients produced serious adverse effects, including death, in others. These results suggest that a new paradigm is required to identify those patients who will benefit from "failed" drugs and those who could be injured by "successful" ones.

QSP has emerged as an alternative to the reductionist approach through its ability to model and classify patients by predicted response to therapy. QSP starts with the understanding that all disease is complex, including simple Mendelian disorders, and that the disease phenotype is expressed based on defective molecular network(s) that are also modulated by variable environmental factors. QSP is the merging of what have traditionally been two distinct fields: pharmacology and systems biology.

Pharmacology has always been a highly quantitative measurement of the effects of chemicals/biologics and the mechanism of these effects on living organisms (pharmacodynamics) coupled to the effect of the living organism on the chemicals/biologics (pharmacokinetics). Pharmacology is deeply rooted in physiology, the study of the functions of living systems from the level of component molecules up through the whole organism.

Systems biology is the integration of experimental data with computational models to create quantitative representations of complex biological processes. System biology data reflect the measurement and analyses of data from DNA, RNA, proteins, metabolites, cells, tissue, organs, integrated organ systems, microbiome and the whole organism, including humans; the role of noise in signaling networks; and the principles of biological design. The systems biology approach can also identify "emergent" properties of the "system" that are not evident from the study of individual components.

In **QSP**, integrating systems biology allows classical pharmacology to move beyond the whole-population, reductionist approach to identifying and validating novel drug targets. A key goal of QSP is to mathematically predict how drugs – both existing and under development – modulate cellular networks and to define how the drugs influence disease pathophysiology itself. QSP generates computational models by incorporating data both from multiple time points and from increasingly complex experimental platforms (component molecules, cells, tissues, experimental organisms, and humans) to characterize and then predict the therapeutic effects and toxic liabilities of drugs and drug candidates. QSP harnesses knowledge of the temporal-spatial connections in signaling, transcriptional, and metabolic networks while taking into account heterogeneity in the output of these networks arising from differences in genetic and environmental factors.

PERSONALIZED MEDICINE

Although the practice of medicine has always focused on the individual patient, solutions have generally been derived from population averages. These solutions have targeted a pathology that looks the same in most patients at the tissue level. However, not all patients share the same pathway to this pathology and therefore may not respond to preventive or therapeutic interventions in the same manner.

We now have the technology and computational capacity to target etiology rather than pathology and thus personalize treatment to the causative agents in each patient. These agents could include any combination of genetic variants, epigenetic changes, post-transcriptional alterations in gene expression, microbiome metabolites, and other contributions to our molecular phenotype. Systems biology provides the means for integrating these diverse data through interactive networks and identifying the modules most likely to be causative of the observed dysfunction. Quantitative systems pharmacology goes a step further to include the impact of drugs that target components of one or more modules not only on the observed pathology but also on the rest of the system, to discover other networks that might be perturbed.

Such a personalized medicine approach has demonstrated value in several disciplines, such as oncology, complex chronic diseases, and pharmacogenomics. Rapid advances in understanding the genomic and other parameters of tumor biology, through The Cancer Genome Atlas and thousands of individual studies, have highlighted the importance of tumor heterogeneity and the evolution of resistance to therapy. Treatment personalized to exploit vulnerable pathways in a patient's own tumor have produced remarkable remissions even in late-stage cancer as well as some population-level improvements due to refined therapeutic strategies. Our understanding of the genetic variants that can contribute to complex chronic diseases has increased, providing clues about the networks and pathways that underlie disease pathobiology. Finally, in pharmacogenomics, we are expanding our knowledge of known genes variants that affect overall drug efficacy, optimal dosing, or susceptibility to adverse events for an ever-growing number of drugs. The challenges for personalized medicine are using this information in the context of routine clinical workflow and prescribing practices and capturing the data needed to