

# **NIH Workshop: Quantitative Systems Pharmacology and Drug Discovery: Filling the Gaps in Current Models of the R&D Process for Neurotherapeutics**

***An NIH Workshop Sponsored by NINDS in collaboration with NIA, NIMH, NIDA and NCATS***

**July 26-27, 2017**

**Bethesda North Marriott Hotel & Conference Center**

**Conference Room: Salon C**

**5701 Marinelli Road**

**Bethesda, MD 20852**

## **Introduction**

Systems Biology has been defined as the study of biological systems by systematically perturbing them (biologically, genetically or chemically) and monitoring informational pathway responses. These data are then integrated, ultimately formulating mathematical models that describe the structure of the system and its response to individual perturbations. Defined in this manner, systems biology shares many concepts with the field of classical pharmacology, where information is gained on a molecular level in simple biological settings and utilized to predict physiological effects, which are comprised of multi-organ system responses to a perturbation (usually a drug). Systems Pharmacology is an extension of classical pharmacology, where data and concepts are integrated in a vertical fashion from the level of molecules to the levels of cells, tissues and whole organisms, allowing the development of models that could predict the relationship between pharmacokinetics and pharmacodynamics (PK/PD). All of these disciplines utilize precise, mathematical relationships between perturbations and physiological consequences.

An NIH White Paper written by participants in an NIGMS Workshop on the topic of Quantitative Systems Pharmacology (2011) proposed that merging systems biology and systems pharmacology approaches could greatly facilitate drug discovery and development for complex diseases that have not been defined by a single molecular target. Thus, the systems biology approach could be used to elucidate a network of genes, proteins or neural pathways and then model the responses of that network to environmental, chemical or genomic perturbations. Information gained from this approach could be crucial to the identification of therapeutic targets and biomarkers for disease. In turn, a systems pharmacology approach would allow the vertical integration of systems biology data from molecular to physiological levels. Information gained from a merged systems biology and pharmacology approach would allow not only drug

target identification, but would also allow more efficient prediction of PK/PD relationships that would lead to more accurate human dose projections. In addition, this merged discipline would allow better prediction of toxicity, translating “omic” or phenotypic screening data to animal models. Finally, a merged systems biology and pharmacology approach could facilitate better identification of biomarkers used to better select and stratify patients in clinical trials.

A merged systems biology and pharmacology approach, otherwise known as a Quantitative Systems Pharmacology (QSP) approach, could be a particularly useful one in CNS drug discovery and development, which has been plagued by low rates of success, high drug development costs and relatively stagnant progress in understanding the basis for complex neurological diseases. The recent impressive advances in mapping functional neural networks even on a cell to cell basis, may provide the groundwork for a QSP approach to drug discovery in this therapeutic area. *Therefore, the purpose of this workshop is threefold: 1) Assess the impact of QSP approaches on CNS drug discovery and development, 2) Identify roadblocks and gaps in the application of QSP to CNS drug discovery/development and 3) Identify opportunities to address roadblocks and gaps.*

### **Workshop Goals**

- To assess the impact of a QSP approach on CNS drug discovery and development by evaluating the effects of this approach on the following:
  - Discovery of new therapeutic targets
  - Identification of therapeutics through screening
  - Accuracy and efficiency of PK/PD correlations
  - Predictive value of toxicology
  - Clinical study design
  - Biomarker discovery and validation
- To identify roadblocks and gaps in the application of merged systems biology and pharmacology approaches to CNS Drug Discovery and Development
- To identify opportunities to address these roadblocks and gaps

### **Deliverables of Workshop**

- White Paper: Merged Systems Biology and Pharmacology as an approach to CNS Drug Discovery: Filling the Gaps in Current Models of the R&D Process for Neurotherapeutics: NINDS/NIH Workshop, Summer, 2017
- Recommendations regarding the utility of this approach to CNS Drug Discovery and Development
- Posted WS summary on [ADDS website](#) to foster collaborations between data science and systems biology PI's (post → advertisement of WS to [ADDS blog](#) and its participants)

## **Organizing Committee:**

### **Co-chairs:**

Mary Ann Pellemounter (NINDS) Co-chair

Suzana Petanceska (NIA) Co-chair

Piet van der Graaf (Certara) Co-chair

Oreisa O'Neil-Mathurin (NINDS)

Timothy Lyden (NINDS)

Victoria Smith (NINDS)

Pascal Laeng (NINDS)

Margaret Sutherland (NINDS)

Vicky Whitemore (NINDS)

Jill Morris (NINDS)

Michael Oshinsky (NINDS)

Laura Mamounas (NINDS)

Jim Gnadt (NINDS)

Amir Tamiz (NINDS)

Shamsi Raeissi (NINDS)

Ilyas Singec (NCATS)

Lorenzo Refolo (NIA)

Laurie Ryan (NIA)

Eliezer Masliah (NIA)

Lois Winsky (NIMH)

Margaret Grabb (NIMH)

Kris Bough (NIDA)

Craig Hopp (NCCIH)

Avi Maayan (Mount Sinai School of Medicine)

Pankaj Agarwal (Glaxo Smith-Kline)

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## Agenda

8:30 AM	<b>Welcome</b>	Amir Tamiz, PhD, Associate Director, Division of Translational Research, NINDS
8:30-8:40 AM	<b>Introduction (NINDS)</b>	Walter Koroshetz, MD, Institute Director, NINDS
8:40-8:50 AM	<b>Introduction (NIA)</b>	Richard Hodes, MD, Institute Director, NIA
8:50-9:00 AM	<b>Meeting Overview (Goals and Logistics)</b>	Mary Ann Pelleymounter, PhD, NINDS, Workshop Organizer
<b>9:00-10:15 AM</b>	<b>Context for Quantitative Systems Pharmacology (QSP) and NIH Involvement</b>	<b>Chair: Piet van der Graaf, PhD, Certara, Workshop Co-Chair</b>
9:00-9:20 AM	QSP: History, Relationship to Systems Biology and Applications to CNS Drug Discovery	Piet van der Graaf, PhD, Certara, Workshop Co-Chair
9:20-9:40 AM	Topic: Evolution of Systems Biology to Pharmacology in Drug Discovery and Systems Medicine	Eric Schadt, PhD, Icahn School of Medicine, Mount Sinai
9:40-9:50 AM	NIH Initiatives in Systems Biology and QSP: Accelerated Medicines Partnership (NIA)	Suzana Petanceska, PhD, NIA, Workshop Co-Chair

9:50-10:05 AM	NIH Initiatives in Systems Biology and Pharmacology: NINDS/LYNCS	Margaret Sutherland, PhD, NINDS
10:05-10:15 AM	NIH Initiatives in Systems Biology and Pharmacology: NCATS	Ilyas Singec, MD PhD, NCATS
<b>10:15-10:30 AM</b>	<b>Break</b>	
<b>10:30-12:30 PM</b>	<b>Systems Pharmacology Approaches to CNS Disease</b>	<b>Chair: Roberta Brinton, PhD, University of Arizona</b>
10:30-10:45 AM	Overview	Roberta Brinton, PhD, University of Arizona
10:45-11:00 AM	Alzheimer's Disease (Academic Perspective)	David A Bennet, MD, Rush Medical College, Rush University
11:00-11:15 AM	Systems Pharmacology Approaches in Alzheimer's Disease: Industry Perspective	Kapil Gadkar, PhD, Genentech
11:15-11:30 AM	Parkinson's Disease (Academic Perspective)	Clemens Scherzer, MD, Harvard Medical School
11:30-11:45 AM	Metabolic modeling of a glucocerebrosidase activator for a genetic subtype of Parkinson's Disease	Peter Lansbury, PhD, Lysosomal Therapeutics
11:45-12:00 PM	Multi-Omics, Multi-Center Data Integration to Dissect Subtypes and Causal Networks in ALS	Karen Sachs, PhD, Stanford University School of Medicine
12:00-12:15 PM	The Psychiatric Genomics Consortium: using psychiatric genetics to find drug targets and new drug indications	Gerome Breen, PhD, Kings College of London
12:15-12:30 PM	How Biomarker Discovery has informed Systems Pharmacology for Migraine	Michael Oshinsky, PhD, NINDS
<b>12:30-1:30 PM</b>	<b>Lunch</b>	
<b>1:30-3:00 PM</b>	<b>Neurotherapeutic Target Identification and Deconvolution</b>	<b>Chair: Kalpana Merchant, PhD, TransThera Consulting Co.</b>
1:30-1:45 PM	De-risking therapeutic target identification and validation through human translational studies	Kalpana Merchant, PhD, TransThera Consulting Co.

1:45-2:00 PM	A molecular network map of the aging brain: a framework with which to integrate genetics and multi-omic data to deconstruct immune responses involved in neurodegeneration	Phillip DeJager, MD PhD, Harvard Medical School
2:00-2:15 PM	Treating the Network: A systems approach to neurotherapies	James Schwaber, PhD, Jefferson University
2:15-2:30 PM	Models spanning Genes, Cells and Brains in Alzheimer's disease - progress and a proposal	Chris Gaiteri, PhD, Rush Medical College, Rush University
2:30-2:45 PM	Ex Vivo phenotypic model systems in target ID for motor neuron disorders	Steve Finkbeiner, MD PhD, Gladstone Institute of Neurological Disease
2:45-3:00 PM	Perspectives on phenotypic screening and target identification	Susanne Swalley, PhD Biogen
<b>3:00-3:15 PM</b>	<b>Break</b>	
<b>3:15-4:15 PM</b>	<b>Application of Systems Pharmacology to PK/PD, Prediction of Adverse Events and Systems Medicine</b>	<b>Chair: Katya Tsaion, PhD, Johns Hopkins School of Public Health</b>
3:15-3:30 PM	Systems Medicine and Biomedical Informatics	Joel Dudley, PhD, Icahn School of Medicine, Mount Sinai
3:30-3:45 PM	Strategies to minimize the risk of failure in the clinic due to insufficient brain exposure	Katya Tsaion, PhD, Johns Hopkins School of Public Health
3:45-4:00 PM	From Big Data to Smart Data in CNS: QSP provides concrete and actionable knowledge for improving drug discovery and development	Hugo Geerts, PhD, In Silico Biosciences
4:00-4:15 PM	Systems pharmacology and modeling for predictive assessment of drug safety	Jane Bai, PhD, Food and Drug Administration
<b>4:15-5:30 PM</b>	<b>Biomarker Discovery and Validation</b>	<b>Chair: Allan Levey, MD, PhD, Emory University</b>
4:15-4:30 PM	Pharmacometabolomics Pharmacogenomics Enabling Tools for Quantitative Systems Pharmacology	Rima Kaddurah-Daouk, PhD, Duke University
4:30-4:45 PM	Proteomics and systems biology discovery of biomarkers for neurodegenerative disorders	Allan Levey, MD, PhD, Emory University
4:45-5:00 PM	Current status of functional MRI as a neuroimaging biomarker for neurotherapeutics development	Owen Carmichael, PhD, Pennington Biomedical Research Center

5:00-5:15 PM	Can imaging biomarkers inform medications development for nicotine withdrawal, craving and relapse?	Elliott Stein, PhD, NIDA
5:15-5:30 PM	Biomarkers, modeling and therapeutic targets: The CFS/ME and GWI Story	Nancy Klimas, MD, Nova Southeastern University
<b>5:30-5:45 PM</b>	<b>Day 1 Summary/Next Steps</b>	<b>Piet van der Graaf, PhD, Certara, Workshop Co-Chair, MA Pelleymounter, PhD, NINDS, Workshop Organizer</b>
<b>5:45-7:00 PM</b>	<b>Poster Session/Wine and Cheese</b>	

### Day 2 Agenda

<b>8:30-8:45 AM</b>	<b>Overview of Day 2 Goals and Logistics</b>	Suzana Petanceska, PhD, NIA, Workshop Co-Chair
<b>8:45-10:05 AM</b>	<b>Technical Advances, Tools and Data Resources</b>	<b>Chair: John Wiksw, PhD, Vanderbilt University</b>
8:45-9:00 AM	Organs-on-chips and microphysiological systems as models for quantitative systems pharmacology and the development of neurotherapeutics	John Wiksw, PhD, Vanderbilt University
9:00-9:15 AM	Making a case for the role of tissue-engineered models of the neurovasculature in systems pharmacology	Peter Searson, PhD, Johns Hopkins School of Medicine
9:15-9:30 AM	Predicting molecular phenotypes using statistical learning	James Baurley, PhD, Biorealm Research
9:30-9:45 AM	Combining cell biology with micro-engineered environments	Chris Hinojosa, Emulate, Inc.
9:45-10:00 AM	Open ecosystems for systems biology applications in target discovery	Lara Mangravite, PhD, Sage Bionetworks

10:00-10:20 AM	<b>BREAK</b>	
10:20-11:20 AM	<b>Panel Discussions</b>	Panels with Audience Participation
10:20-10:50 AM	Where is a Systems Approach Working and Where are the Gaps?	<b>Chair: Roberta Brinton, PhD, University of Arizona</b> Panel: Session Chairs
10:50-11:20 AM	Panel Recommendations: Importance and Feasibility of QSP to Neurotherapeutics	<b>Chair: Piet van der Graaf, PhD, Certera</b> Panel: Kapil Gadkar, Hugo Geerts, Joel Dudley, Peter Lansbury, Rima Kaddurah-Daouk, Susanne Swalley, Session Chairs
11:20-11:50 PM	<i>Workshop Summary/Final Participant Comments</i>	<i>Piet van der Graaf, Mary Ann Pellemounter and Suzana Petanceska</i>
	<b>End of Workshop</b>	<b>Mary Ann Pellemounter, PhD, NINDS</b>
12:10-1:00 PM	<i>White Paper organization/planning</i>	Piet, Suzana and Mary Ann: Workshop Planning Committee