

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

## Presenters Abstracts

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### Jane Bai, Ph.D.

Food & Drug Administration, FDA

**Title:** *Systems Pharmacology Modeling for Predictive Assessment of Drug Safety*

**Abstract:** Advances in omics, in-vitro phenotypic assays, and medical informatics accelerate use of big data for predictive assessment of clinical efficacy and safety. We have integrated transcriptomic, proteomic and genomic data with clinical incidence of specific drug-induced adverse reaction to analyze and construct predictive modeling of drug safety. My talk will cover our systems pharmacology modeling and analysis of rhabdomyolysis, peripheral neuropathy, lung injury, Steven Johnson Syndrome/toxic epidermal necrolysis, and cardiomyopathy. Most recently, predictive modeling of cardiomyopathy identifies a set of genes/proteins as predictors. These predictors are reportedly regulated by microRNAs that have been shown by independent studies to be of diagnostic value for heart failure patients. Biomarkers and the key biochemical/pharmacological network identified by systems pharmacology approaches along with physiologically meaningful model parameters in the context of clinical variability will be crucial for quantitative modeling of exposure/drug safety.

### James Baurley, Ph.D.

BioRealm

**Title:** *Predicting molecular phenotypes using statistical learning*

**Abstract:** During this talk, we'll review statistical learning approaches for predicting molecular phenotypes. We'll review strategies in building these models, and how to apply them in disease association studies and clinical trials. We'll discuss penalized regression and Bayesian approaches, and how to leverage evidence from existing studies and knowledge-bases. We'll motivate and demonstrate these approaches in predicting nicotine metabolism, an important biomarker for smoking cessation.

**Gerome Breen, Ph.D.**

King's College London

**Title:** *The Psychiatric Genomics Consortium: using psychiatric genetics to find drug targets and new drug indications*

**Abstract:** Genome-wide association studies (GWAS) in psychiatry, once they reach sufficient sample size and power, have been enormously successful. The Psychiatric Genomics Consortium (PGC) aims for mega-analyses with sample sizes that will grow to >1 million individuals in the next 5 years. This should lead to hundreds of new findings for common genetic variants across nine psychiatric disorders studied by the PGC. The new targets discovered by GWAS have the potential to restart largely stalled psychiatric drug development pipelines, and the translation of GWAS findings into the clinic is a key aim of the recently funded phase 3 of the PGC. This is not without considerable technical challenges. These approaches complement the other main aim of GWAS studies, risk prediction approaches for improving detection, differential diagnosis, and clinical trial design. I will outline the motivations, technical and analytical issues, and the plans for translating PGC phase 3 findings into new therapeutics.

**Owen Carmichael, Ph.D.**

Pennington Biomedical Research Center

**Title:** *Current status of functional MRI as a neuroimaging biomarker for neurotherapeutics development*

**Abstract:** Functional magnetic resonance imaging (fMRI) has been known for well over a decade to have the potential to serve as a useful biomarker in the process of developing novel neurotherapeutics. However, the use of fMRI in drug development continues to be relatively limited, due to a variety of technical, biological, and strategic barriers that limit progress. This talk will briefly review the roles that fMRI can play in neurotherapeutics development and the requirements fMRI must meet to be useful in this setting. It will then provide a summary of current strengths and limitations of fMRI as a tool for neurotherapeutics developers, and provides recommended activities to enhance its utility.

**Rima Kaddurah-Daouk, Ph.D.**

Duke University Medical Center

**Title:** *Pharmacometabolomics, Pharmacogenomics - Enabling Tools for Quantitative Systems Pharmacology*

**Abstract:** Metabolomics, the study of metabolism at an “omic” level, has the potential to transform our understanding of mechanisms of drug action and the molecular basis for variation

in drug response. It is now possible to define metabolic signatures of drug exposure that can identify pathways involved in both drug efficacy and adverse drug reactions. In addition, the “metabotype,” the metabolic “signature” of a patient, is a unique identity that contains information about drug response and disease heterogeneity. The application of metabolomics for the study of drug effects and variation in drug response is creating “pharmacometabolomics,” a discipline that will contribute to personalized drug therapy and will complement pharmacogenomics by capturing environmental and microbiome-level influences on response to drug therapy. Pharmacogenomics and pharmacometabolomics are enabling tools for “Quantitative Systems Pharmacology” (QSP). We will highlight large initiatives funded by NIGMS that helped established foundations for QSP.

**Steve Finkbeiner, MD, Ph.D.**

Gladstone Institutes and the University of California, San Francisco.

**Title:** *Ex Vivo phenotypic model systems in target ID for motor neuron disorders*

**Abstract:** In this talk, we will describe efforts to establish high throughput deep phenotypic screening methods and model systems for motor neuron disorders and their applications to target identification and therapeutics development. For example, we will describe new methods to generate a functional human neuromuscular junction with a differentiation protocol that instructs induced pluripotent stem cells to generate co-cultures of motor neurons and skeletal muscle. We will also describe high throughput longitudinal single cell analysis platforms and an array of over 270 biosensors to collect multiplexed deep phenotypic data from different cell types relevant to motor neuron disorders. Finally, we will briefly describe how the integration of deep learning methods is significantly expanding the phenotypic information we can extract, beyond what the human eye can see, and leading to new ways to do phenotypic screening for target identification and therapeutics development.

**Hugo Geerts, Ph.D.**

In Silico Biosciences, Inc.

**Title:** *From Big Data to Smart Data in CNS Quantitative Systems Pharmacology Provides Concrete and Actionable Knowledge for Improving Drug Discovery and Development*

**Abstract:** Quantitative Systems Pharmacology (QSP) modeling approach is a powerful computational method that integrates domain expertise and pharmacology for generating actionable knowledge in CNS R&D. That is, mechanism-based and biophysically realistic QSP models integrate preclinical neurophysiology with human imaging and clinical data and simulates action firing dynamics in relevant neuronal networks that are driving human behavior.

The model currently is based on formalized representations of relevant cortico-striatal-thalamo-cortical circuits, has over 30 targets with their appropriate location and neurophysiology in addition to common human genotypes (COMT Val158Met, the 5-HTTLPR s/l rs23351, and

D2DR1A1 genotype derived from human imaging studies) and has the complete pharmacology of all CNS active drugs, including PK profile and metabolites. Specific pathologies (Alzheimer's Disease, Parkinson's and Huntington's disease and schizophrenia) are introduced using human imaging studies and the platform is calibrated by retrospectively 'predicting' the clinical outcome of historical clinical trials. In terms of predictive validation, examples will be presented where blind platform predictions were superior to animal studies in accurately predicting an unexpected clinical outcome.

A major application are virtual patient trials, where pharmacodynamic interactions of a new investigative drug with existing comedications and common genotypes can be simulated, allowing to improve clinical trial design. Conversely, by addressing the variability of clinical responses, the platform can provide better understanding on the reasons for clinical trial failure, in order to avoid making the same mistakes. A recent example where QSP approaches beats Big Data analytics in optimizing individualized polypharmacy in clinical practice will also be presented.

Disease modification approaches include a model of the relationships between amyloid modulation and cognitive readouts in Alzheimer's Disease and the recently launched MAPTA, the **Modeling Alliance for Systems Pharmacology of Tauopathies**.

**Nancy Klimas, MD**

NOVA Southeastern University

**Title:** *Biomarkers, modeling and therapeutic targets: The CFS/ME and GWI Story*

**Abstract:** The Nova Southeastern University's Institute for Neuro-Immune Medicine is a group of 62 scientists, clinicians, and support staff with an ambitious goal: to cure ME/CFS and a related condition, Gulf War Illness. We believe that in order to cure an illness that that is as complex as ME/CFS, you have to take the "big picture" approach, connecting the knowledge gained through studies of immune, neuroendocrine, autonomic, genomics, neuroimaging, exercise physiology and bioenergetics. Using a systems biology approach, research subjects are challenged with exercise and, then the team maps out the cascade of events across immune, neuroendocrine, autonomic and bioenergetic domains to create a firm understanding of the underlying homeostatic networks. The computational team used this approach to map out the mediators of relapse, then taking the knowledge to the next step, created a virtual model of illness persistence and relapse. This model was then used to design clinical trials "*in silico*" discovering new targets, understanding the balance between the systems and attempting to force a "reset" or "reboot" by treating multiple targets in set time courses to create a new homeostatic balance.

The virtual platform has predicted specific subgroups in each illness, differences in treatment strategies based on gender and HPG cycle, and clearly predicts that single drug treatments focused on a single system are unlikely to sustain a remission of symptoms. Running thousands

of virtual trials in various combinations and time courses, the computational team led by Drs. Gordon Broderick and Travis Craddock have provided clinical trial designs to move forward to phase 1 studies. Using a similar approach in Gulf War Illness, the predicted strategies for that illness did indeed “reboot” the mouse model and are moving forward to human trial this fall. ME/CFS modeling is near completion, we anticipate moving to human phase 1 trial this winter. In this presentation, Dr Klimas will discuss the use of biomarkers in modeling efforts, and their role in defining targeted therapeutic approaches by biologic subgroup.

**Peter Lansbury, Ph.D.**

Lysosomal Therapeutics, Inc

**Title:** *Metabolic modeling of a glucocerebrosidase activator for a genetic subtype of Parkinson’s disease*

**Abstract:** Glucocerebrosidase (GCase; encoded by GBA) catalyzes the hydrolysis of lysosomal glucosylceramide (GluCer) to produce ceramide. In Gaucher disease, where GCase function is typically less than 20% of healthy controls, GluCer accumulates in circulating macrophages (hence “lysosomal storage”). But in the case of the subtype of Parkinson’s disease in GBA carriers (50-80% GCase activity as compared to controls), GluCer accumulation does not clearly occur in brain. It is unclear whether GluCer or another substrate of GCase, or a combination, drives PD pathogenesis. Lysosomal Therapeutics, Inc. is developing a small molecule GCase activator that is designed to normalize GCase activity in the brain and reduce the rate of disease progression. However, in advance of an expensive clinical trial, it is critical to demonstrate target engagement, that is GCase activation, in human brain. A systems approach to measuring GCase activation, where the entire GSL catabolic pathway is measured, will be discussed.

**Lara Mangravite, Ph.D.**

Sage Bionetworks

**Title:** *Open ecosystems for systems biology applications in target discovery*

**Abstract:** Systems-level evaluations hold great potential to advance pharmaceutical discovery and development by providing an integrated view of the impact on disease of targeted perturbations. Several barriers to successful application of these emerging approaches exist. First, such approaches are highly data intense, requiring multi-modal data characterizing disease across numerous scales. In addition, they utilize emerging approaches for which standard methodologies do not exist and that are not well understood by scientists traditionally involved in the drug development process. These issues are universal – faced across the field – and can be addressed in a systematic manner through coordinated efforts across a research community. The concerted and interactive efforts of three NIA-sponsored consortia focused on the application of systems biology for AD target and biomarker discovery provides one example. The AMP-AD and M<sup>2</sup>OVE-AD programs test the application of systems biology approaches to quantify network-

based human AD states in support of target prioritization and biomarker discovery. MODEL-AD generates rodent models of late onset AD selected based on genetic and genomic observations including those arising from AMP-AD and M<sup>2</sup>OVE-AD. The consortia interact to provide shared resources, formalized evaluations of methods and outputs, interactive collaborations, and opportunities to educate and translate findings across researchers with complementary but diverse expertise. Coordinated integration and public dissemination of data and evidence across these projects provides a powerful way to increase the reproducibility and translatability of discovery research, enabling rapid advancement of systems biology concepts in AD drug development.

**Kalpana Merchant, Ph.D.**

TransThera Consulting Co.

**Title:** *De-risking therapeutic target identification and validation through human translational studies*

**Abstract:** Addressing unmet medical needs for CNS disorders, particularly chronic age-associated neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease, and psychiatric diseases such as schizophrenia remains one of the greatest opportunities for drug development. However, several high profile phase 2 and 3 clinical trial failures due to sub-optimal efficacy have hampered the field. Among key reasons for these failures is the selection of the wrong therapeutic target and/or patient population. Given the heterogeneous and syndromic nature of CNS disease, it is critical to develop an understanding of a drug target or target pathway to disease biology in individual patient populations. This talk will focus on translational science approaches, from human genetics to disease biomarkers identified *via* a variety of "omics" platforms and clinical pharmacology data, to garner deep insights into disease biology pathways. In turn, these studies lead to identification of therapeutic targets within the disease pathway and the potential to select patients with aberrant activity in the target pathway. Furthermore, they inform cellular and animal model systems as well as phenotypic screens that recapitulate disease biology to facilitate drug discovery solidly founded on human disease biology.

**Karen Sachs, Ph.D.**

Stanford University and MIT

**Title:** *Multi-Omics, Multi-Center Data Integration to Dissect Subtypes and Causal Networks in ALS*

**Abstract:** The Answer ALS consortium is on track to collect molecular ('omics') data from iPS derived motorneurons of 1000 patients over the next few years, with the goal of extracting underlying causal molecular networks and disease subtypes, for this relatively poorly understood, devastating disease. Data include proteomics, epigenetics, WGS, metabolomics and RNA Seq, as well as matched clinical data, generated in centers across the country. Integration

of these datatypes requires use of models sufficiently flexible to incorporate various types of data, able to leverage statistical information, yet also able to perform in underpowered, data poor realms which result from integration of multiple high dimensional datasets. We will discuss the use of Prize Collecting Steiner Forests and probabilistic graphical models for this data integration application, and show results from an initial data set of known etiology, C9ORF variant patients.

**Peter Searson, Ph.D**

John Hopkins University

**Title:** *Making a case for the role of tissue-engineered models of the neurovasculature in systems pharmacology*

**Abstract:** *In vitro* tissue-engineered models of the neurovasculature allow live cell imaging and quantitative analysis of aspects of drug and gene delivery to the brain that are difficult to obtain from studies in animal models or conventional *in vitro* models. Here we describe recent developments in tissue-engineered models of the neurovasculature and provide examples illustrating how they can be used to contribute to systems level models of drug and gene delivery to the brain. We show how real time imaging of drug transport can be used to develop quantitative kinetic models of transendothelial transport that link pharmacokinetics and pharmacodynamics. In addition, models of the neurovasculature incorporating differentiated brain microvascular endothelial cells from patients with neurodegenerative disease provide the opportunity to assess the role of disease on drug and gene delivery.

**Elliot Stein, Ph.D.**

National Institute of Drug Abuse-IRP/NIH

**Title:** *Can imaging biomarkers inform medications development for nicotine withdrawal, craving and relapse?*

**Abstract:** Drug addiction, like other psychiatric diseases, is notoriously resistant to pharmacological treatments, with recidivism rates that can approach 80-90%. Indeed, despite tremendous advances in basic neurobiological understanding of addiction, there remains a paucity of efficacious treatments for dependency on most drugs while in some instances, e.g. stimulants and cannabinoids, there are no FDA approved medications at all. While drug discovery is time consuming and financially demanding for most diseases, complex neuropsychiatric diseases are particularly problematic as it is often difficult to mimic the disease using preclinical models. Moreover, as there are no clinically useful biomarkers of the disease, it is not possible to predict a drug response without costly and time consuming clinical trials; even preclinical models have failed to be predictive of human efficacy. Using nicotine dependence as an exemplar, and varenicline and nicotine patch replacement as a model interventions, I will briefly present how

functional MRI-both 'task' based and 'resting' functional connectivity may be usefully employed to better understand in vivo drug mechanisms of action and potentially serve in therapeutic drug discovery.

**Susanne Swalley, Ph.D.**

Biogen

**Title:** *Perspectives on phenotypic screening and target identification.*

**Abstract:** Phenotypic screening, whether on the cell, tissue or whole animal level, has long been a powerful source of novel drugs. Historically, the greatest challenge has been in identifying targets and understanding mechanisms of action, though unbiased technologies such as chemoproteomics and functional genomics have greatly enhanced our ability to deconvolute how these molecules work. Arguably, the ideal situation is when there is high understanding of the molecular pathology of a disease, but no known small molecule targets. One such recent example is Spinal Muscular Atrophy (SMA), a monogenic disease with a well understood mechanism. In SMA, when the *SMN1* gene is mutated or missing, a single mutation in the duplicate *SMN2* gene causes exon 7 to be excluded, resulting in truncated and unstable SMN protein. Both targeted and phenotypic approaches resulted in effective molecules that correct the core splicing defect that characterizes the disease. For the targeted approach, an antisense oligonucleotide can block hnRNPA1, a splicing repressor, thus increasing exon 7 inclusion. The phenotypic approach resulted in a molecule that sequence-selectively stabilizes the binding of a core spliceosome component, U1 snRNP, to the 5' splice site, also increasing exon 7 inclusion but by a completely different mechanism. In this case, the phenotypic approach combined with successful target identification opened a new paradigm for targeting splicing diseases.

**Katya Tsaioun Ph.D**

John Hopkins University

**Title:** *What keeps us up at night: strategies to minimize the risk of failure in the clinic due to insufficient brain exposure*

**Abstract:** Pharmacokinetics/pharmacodynamics (PK/PD) relationship is a key concept in drug discovery and development and is crucial for understanding the kinetics of a disease-modifying agent in development. Lack of knowledge of brain exposure could mean a difference between a success and failure in clinical trials. In recent decade a number of *in vitro* and *in silico* prediction models have been developed and most drug-discovery programs use these tools at different stages of drug discovery and development. Strategies for incorporating the *in vitro* and computational physiologically-based pharmacokinetic (PBPK) models in drug discovery programs will be presented, with emphasis on early understanding of PK/PD and metabolism.

**John Wikswo, Ph.D.**

Vanderbilt University

**Title:** *Organs-on-chips and microphysiological systems as models for quantitative systems pharmacology and the development of neurotherapeutics*

**Abstract:** Although vast sums have been invested with the goal of understanding the brain and its disorders, much of this work has been conducted using animal and *in vitro* models that may not extrapolate directly to diseased humans. While specific models are often chosen because they are simple enough to understand, they may be either too simple or not sufficiently relevant to lead to cures of disease or treatment of disorders in humans. The successful development of neurological drugs will benefit from a detailed knowledge of both the disease in humans and the animal and *in vitro* models used to study the disease and develop therapies. One way to facilitate this is to minimize the distance required for *in vitro* to *in vivo* extrapolation (IVIVE) and maximize the information describing the range of systems being studied. Microphysiological systems (MPS) are two- and three-dimensional cellular constructs that can be used alone to recreate the function of single organs or coupled together into organ systems and even multi-organ MPS homunculi-on-a-chip. Much of the MPS research is now focused on constructing these models using human cells. For this to succeed, three general areas must be optimized: the sourcing of well-characterized human cells from healthy and diseased patients, the design of microreactor systems that support engineered organoids, tissue constructs, and biological interfaces, and the analytical tools and techniques required to record and analyze data from both the *in vitro* models and *in vivo* humans. Systems biology and multi-omics can provide data and software, but for this to be fully useful the *in vitro* model systems under study must adequately recapitulate human physiology and pathology. Many physiological functions and diseases are the product of a complex tissue microenvironment that may be controlled by tissue interfaces, with the best example being the neurovascular unit (NVU), which encompasses the blood-brain barrier (BBB) and the brain's heterogeneous population of neuronal and supporting cells that the BBB protects and supports. Other aspects of physiology and disease, particularly those involving metabolism, are governed by the distributed properties of complex organ systems, for example the gut-liver-brain axis. One of the challenges facing quantitative systems pharmacology (QSP) is the need to devise a set of human *in vitro* and *in silico* models that support such a multi-scale breadth of interactions. Simple microfluidic NVUs already demonstrate the modulation of BBB permeability with drugs and inflammatory cytokines and are now being used to study brain metabolomics and test neurological therapies. Ultimately, the NVU will have a self-organized, hierarchical vasculature and BBB that support the extravasation of cancerous and immune cells from the blood into the brain. Ongoing is the development of human MPS models of the NVU

and other organs that reflect human disease. The resulting cells and MPS systems will then provide a foundation for QSP IVIVE that should accelerate the development of neurotherapeutics.