Course Faculty

Rebecca A. Clewell, Ph.D.
Dr. Clewell has over 10 years experience developing life-stage specific physiologically based pharmacokinetic (PBPK) models. Her current research maps the structure of cellular signaling pathways affected by chemical exposures and models the dose response behaviors of these pathways in order to develop new strategies for understanding low dose risks of environmental chemicals.

Patrick D. McMullen, Ph.D.
Dr. McMullen has 10 years of experience in research-driven computational biology model development and using high-content data streams to extend our understanding of molecular biology. He uses gene expression microarray, ChIP-seq, and metabolomics data to map toxicity pathways with to aid in the development of more informative *in vitro* assays.

Miyoung Yoon, Ph.D.
Dr. Yoon's research has coupled biologically based kinetic modeling with targeted *in vitro* studies to improve risk assessment for sensitive sub-populations. In her current research, she works to improve *in vitro* to *in vivo* extrapolation modeling in order to estimate safe human exposures for various environmental compounds of human health concern.

Qiang Zhang, Ph.D., M.D.
Starting as a biomedical scientist, Dr. Zhang is interested in using computer simulations to understand the dynamic and steady-state behaviors of biological systems in response to perturbations. His research has focused on nonlinear dose responses arising from cellular homeostatic control and gene circuit underlying binary cell fate decisions.

Salil N. Pendse, M.S.
Mr. Pendse's expertise in scientific computing and management of large data sets has led the development of new tools and models of cellular signaling at the Hamner. He specializes in developing visualization strategies for understanding toxicogenomics and other high-content data streams.

Harvey J. Clewell III, Ph.D., D.A.B.T.
Over the past 35 years, Dr. Clewell has played a major role in the first uses of PBPK modeling in regulatory decision-making at several federal agencies including FDA, ATSDR, OSHA, and EPA. His research interests today include computer simulation of drug-induced liver injury and the integration of *in vitro* data with pharmacokinetic modeling to perform *in vitro* to *in vivo* extrapolations.

Melvin E. Andersen, Ph.D., D.A.B.T., FATS
Dr. Andersen pioneered the use of PBPK modeling in toxicology and in risk assessments in the 1980's. His current research uses computational models of cell signaling networks to understand the molecular perturbations giving rise to dose-response curves and then applies this information to guide regulatory decision making.

General Information

Workshop fee includes:
- Tuition
- Comprehensive take-home course materials
- Continental breakfasts and daily lunches
- Refreshment breaks
- Wednesday evening dinner
- Certificate of attendance

Laptop Requirement

Students will be required to bring a PC laptop computer each day to the course for hands-on computer modeling exercises.

Registration and Payment

Class size is limited to 40 attendees. Reservations will be accepted on a first-come, first-served basis, upon receipt of the registration form with full payment. Please register for the course and submit payment online at **www.thehamner.org/systemstoxicology** no later than **September 25, 2015**.

All requests for substitutions or cancellations must be made in writing (by email) and received by **September 25, 2015**. Substitutions may be made with additional charge. Cancellations received after September 25, 2015 will be issued a refund of 30%. Please contact LaShuane Allen at (919) 558-1388 or **pbpkcourse@thehamner.org** for questions regarding registration and payment policy.

Workshop Fee

General $2,500, Students/Post-docs $1,500
For more information on the workshop fee, please visit **www.thehamner.org/systemstoxicology**.

Suggested accommodations w/ free shuttle service to The Hamner

Hilton Garden Inn Durham, (919) 941-6066
Cambria Suites RDU Airport Morrisville, (919) 361-3311
Holiday Inn Express & Suites Durham, (919) 474-9800

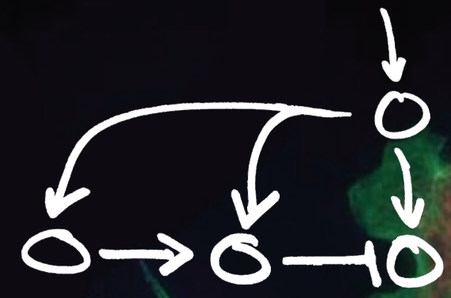
The Hamner Institutes for Health Sciences
6 Davis Drive • PO Box 12137
Research Triangle Park, NC 27709

TT21C

From cell-based assays to safety assessments

October 5 – 9, 2015

Use computational modeling, bioinformatics, and IVIVE tools to inform fit-for-purpose toxicity assay development and interpretation



Institute for Chemical Safety Sciences
The Hamner Institutes for Health Sciences
Research Triangle Park, North Carolina, USA

Course Details

TT21C: From cell-based assays to safety assessments

Course Description

This one-week course will cover the fit-for-purpose paradigm for in vitro toxicity testing. We will cover principles of physiologically based pharmacokinetic modeling and computational biology, with an emphasis on applications for toxicological safety assessment. The course features comprehensive lectures and extensive hands-on computer modeling exercises.

Tentative Agenda

Introduction

Welcome and introduction of faculty members and participants

Introduction to safety assessment with fit-for-purpose assays

Session I: Tools for determining mode of action with high-content data

Introduction to computational systems biology

Bioinformatic tools and mapping nuclear receptor pathways

- Exercise: Mapping PPARa pathways based on differentially expressed genes
- Exercise: Using ChIP data to uncover transcription regulatory networks

Bioinformatics and connectivity maps help determine mode-of-action

- Exercise: Connectivity maps in action

Synthesizing a model based on in vitro toxicity data

- Exercise: Demonstration of Berkeley Madonna
- Exercise: Building a model for DNA damage and repair

Session II: Toxicity pathway structure and dynamics

Network motifs – recurring components controlling biological function

Going somewhere: transitioning between states

- Exercise: MAPK signaling and ultrasensitivity

Staying put: coping with life in a changing environment

- Exercise: Maintaining cellular homeostasis through perfect adaptation

Session III: Determining safe exposure levels using toxicokinetics and pharmacodynamics

Toward a fit-for-purpose safety assessment

Constructing and parameterizing PBPK models

- Exercise: Describing individual tissue compartments
- Exercise: A PBPK model for a lipophilic compound

Application of PBPK models

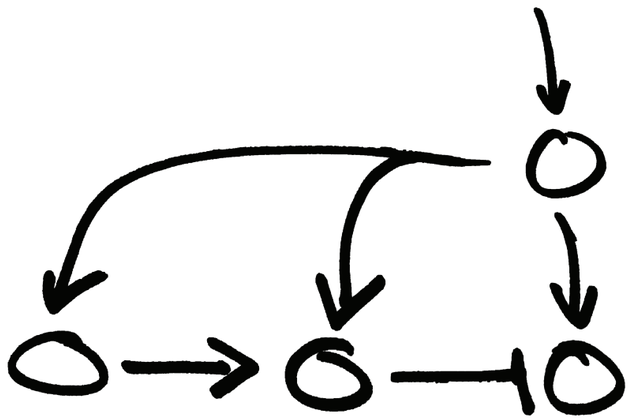
Use of PBPK models for *in vitro* to *in vivo* extrapolation (IVIVE)

- Exercise: An example of IVIVE with a PBPK model

Incorporating pharmacodynamics into PBPK models

- Exercise 1: Nonlinear pharmacodynamics response of hepatocytes to dioxins

Perspectives and close



Incoherent feed-forward motif that leads to a threshold dose response

To register, or for information on our previous offerings of the course, go to:

www.thehamner.org/systemstoxicology

Who should attend?

This course is designed to serve a variety of scientific communities.

- Anyone interested in using developing cell-based toxicity assays using pathway biology as a guide.
- Researchers and regulators wanting to develop or interpret high-throughput assays such as those used in Tox21 or ToxCast.
- Industrial, pharmaceutical and regulatory scientists desiring to interpret the results of *in vitro* or *in vivo* toxicity assays in terms of their implications for human health.
- Individuals who would like to link dosimetry models to biologically-based cellular response models.
- Individuals interested in promoting the use of alternatives to live animal testing for regulatory requirements such as REACH.

Why should you attend?

Upon completion of this course you will be able to:

- Draw from existing high-throughput datasets to help interpret your experiments.
- Understand how the structure of a signal transduction pathway shapes its behavior.
- Use Berkeley Madonna® to evaluate PBPK models and simulate intracellular signaling networks.
- Take first steps to develop cell signaling models to describe pathway perturbations.
- Understand the fundamental concepts underlying physiologically based pharmacokinetic (PBPK) modeling.
- Link PBPK models with other biologically based computational tools, such as pharmaco-dynamic modeling and cell signaling pathway modeling.

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