Workshop on the Concept and Tools for Pathways of Toxicity

Mt. Washington Conference Center, Baltimore MDOctober 10-12, 2012

Within the NIH Director's Transformative Research Projects Program on "Mapping the Human Toxome by Systems Toxicology" and cosponsored by Unilever

In 2007 the US National Academy of Sciences publication, Toxicity Testing in the 21st Century: A Vision and a Strategy (TT21C), proposed a paradigm shift in toxicology from current animal-based testing towards the application of emerging technologies, including genomics, metabolomics, and proteomics, as well as systems biology, and has strongly endorsed the concept of Pathways of Toxicity (PoT). This new paradigm would provide greater mechanistic insight into the ways in which many compounds, including pharmaceuticals, affect human health. These PoTs are simply normal cellular pathways that lead to adverse health effects when perturbed to a sufficient degree. The explosion of scientific knowledge on mode of action in target cells, tissues, and organs, driven by advances in molecular and computational tools and coupled with high-throughput and high-content screening assays, enables interrogation of these PoT and provides a means to study and evaluate the effects of thousands of chemicals. A number of PoT are already well-established. However, most PoT are only partially known, and no common annotation exists. Mapping the entirety of these pathways, a project we call the Human Toxome, will be a large-scale interdisciplinary effort.

The 2-1/2 days workshop brings together a group of about 30 invited experts from academia, industry and regulatory agencies representing content providers, front-line researchers, end-users of toxicity studies and software tool developers from systems biology/systems toxicology disciplines. The PoT workshop will include the following areas for discussion with a focus on defining pathways and developing tools for annotation and analysis.

- Data content, data sources (e.g., from transcriptomics, proteomics, transcription factor-DNA binding, metabolomics) and tools
- Analysis strategies and challenges associated with mapping and modeling PoTs
- Databases that can provide relevant PoT information to the diverse user communities
- Working definition and annotation of PoT, including current challenges in Systems Toxicology for assisting these activities

Participants

Yeyejide Adeleye
Unilever

Melvin Andersen*
The Hamner Institutes for Health Sciences

Stephan Albaum
University of Bielefeld

Scott Auerbach
NIH/NIEHS

Richard Brennan
Thomson Reuters

Mounir Bouhifd
Johns Hopkins

Paul Carmichael
Unilever

Kevin Crofton
US EPA

Michelle Embry
ILSI Health & Environmental Sciences Institute

Suzanne Fitzpatrick
US FDA

Albert Fornace
Georgetown University

Kevin Gaido
US FDA

David Gerhold
NIH

Ben Gordon
Agilent

Thomas Hartung*
Johns Hopkins

Robin Haw
Ontario Institute for Cancer Research

Adriano Henney
Virtual Liver Germany

Helena Hogberg
Johns Hopkins

Minoru Kanehisa
KEGG

Andre Kleensang
Johns Hopkins

Justin Lamb
Genometry

Avi Ma'ayan
Systems Biology Center New York

Alexandra Maertens
Johns Hopkins

Mary McBride
Agilent

Stefano Monti
Boston University

Michael Ochs
Johns Hopkins

Akhilesh Pandey
Johns Hopkins

Michael Rosenberg*
Agilent

Roded Sharan
Tel-Aviv University

Lena Smirnova
Johns Hopkins

Rob Stierum
TNO

Michael Trush
Johns Hopkins

James Yager
Johns Hopkins

Kate Willett
HSUS

Clemens Wittwehr
European Commission

Jeff Xia
University of Alberta

Liang Zhao
Johns Hopkins

Joanne Zurlo
Johns Hopkins

Agenda

Wednesday, 10 Oct. 2012—Mount Washington Room

10:00-10:15
Welcome
Andre Kleensang, Johns Hopkins CAAT

10:15-11:00
Around the table: Introduction of workshop participants

11:00-11:30
Introduction
Pathways of Toxicity: Where we are now, where would we like to go?
Thomas Hartung, CAAT

11:45-12:15
Introduction to PoT definition problems by examples: Endocrine disruptors—known genomic and non-genomic signaling pathways of estrogen responses
Melvin Andersen, The Hamner Institutes for Health Science

Examples of relevant databases and implementations

12:15-12:45
Kyoto Encyclopedia of Genes and Genomes—metabolomics, transcriptomics and other omics connection to pathways
Minoru Kanehisa, University of Tokyo, NPO Bioinformatics Japan, KEGG

1:45-2:15
Reactome: A Comprehensive View Of The Human Toxome
Robin Haw, Ontario Institute for Cancer Research Community Outreach Manager - Reactome

2:15-2:45
OECD Adverse Outcome Pathways, Harmonized Templates and eChemPortal
Clemens Wittwehr, European Commission, Systems Toxicology Unit

2:45-3:15
Drugbank, Toxin-Target Database (T3DB) and metabolomics tools
Jeff Xia, University of Alberta

3:30-4:00
Wikipathways, Applications in Systems Toxicology
Rob Stierum, European Registered Toxicologist

Brainstorming session and discussion as preparation for the breakout groups

4:15-5:00
From the example databases towards a database of PoT:

- What do we need?
- Where should we start?
- Information that are needed to define a PoT
- Connections to other databases
- Current challenges in Systems Toxicology for assisting these activities
- Databases that can provide relevant PoT information to the diverse user communities
- What should be discussed in addition to the agenda tomorrow in the breakout groups?

5-5:30
Summary of the first day

Thursday, 11 Oct. 2012

9:00-12:30
Breakout groups including small presentations by the participants

Group I: Translational group: definitions of PoT
Leader: Thomas Hartung, CAAT

- Information that is needed to define a PoT (continued)
- From signaling pathways to PoT
- The molecular members of the PoT and their links, including possible branches of the PoT
- The link to metabolic changes and where possible to hazard manifestation
- The (known) targets of toxicants in the PoT
- Collection of examples
- Current challenges in Systems Toxicology for assisting these activities
- Databases that can provide relevant PoT information to the diverse user communities
- Comparison PoT to OECD AOP
- Working definition and annotation of PoT

Group II: Application group: data content, databases and data analysis for PoT
Leader: Andre Kleensang, Johns Hopkins CAAT

- Data content, data sources (e.g. from transcriptomics, proteomics, transcription factor, DNA binding, metabolomics, etc.)
- Analysis Tools (systems biology, pathway enrichment, systems toxicology)
- How to combine transcriptomics and metabolo-

mics or other omics data

- Data sharing and databases
- Available technical implementations, wiki
- Graphical presentations
- Connections to other databases

1:30-3:30
Breakout group summaries and discussion

- Try to come up with a common proposal of a formal working definition of PoT

4:00-5:00

- What have we learned today?
- What should be discussed tomorrow (define Agenda for the third day)

Thomas Hartung, Johns Hopkins CAAT

Friday, 12 Oct. 2012

9:00-10:30
Agenda and discussion to be defined

11-12:00
Round table: what are the next steps and summary