

National Institute of Environmental Health Science

GENOTYPE-TO-PHENOTYPE CORRELATIONS IN HEALTH AND DISEASE

- * All meetings, unless otherwise noted, will be held in St. Andrews 'A' on floor 2 of the main building.
- * All meals and poster sessions will be held in St. Andrews B, C, D.
- * Posters should be set up upon arrival in St. Andrews B, C, D and will be displayed throughout the meeting. Push-pins will be provided.
- * Registration booth is open from 8:00 a.m. to 5:00 p.m. for information and assistance.

AGENDA

December 4

4:00-9:00 Registration begins in The Resort lobby

December 5

7:00- Registration continues in The Resort lobby

8:00-9:00 Continental Breakfast (provided with registration)

9:00-9:05 **Welcome and Introduction**
Dr. Peter Spencer, Oregon Health & Science University

9:05-10:00 **OPENING ADDRESS - Building on a genomic infrastructure to understand environmentally induced human disease**
Dr. David Schwartz, National Institute of Environmental Health Sciences

10:00-10:15 Coffee Break

Session 1: **Creation and Manipulation of Model Genotypes**
Chair: Peter Spencer, OHSU

10:15-10:45 **Generation of mouse models carrying human missense mutations**
Winifred Edelmann, Albert Einstein College of Medicine

10:45-11:15 **Multi-strain analysis for identifying determinants of susceptibility**
David Threadgill, University of North Carolina

- 11:15-11:45 **Applications of posttranscriptional gene silencing technologies, including RNAi, to *in vitro* and *in vivo* toxicogenomics studies**
Helmut Zarbl, Fred Hutchinson Cancer Research Center
- 11:45-1:00 Lunch (provided with registration)
- Session 2:** ***DNA Repair as a Model for Genotypic Analyses***
Chair: Peter Stambrook, University of Cincinnati Medical Center
- 11:00-1:45 **BRCA2 and the maintenance of genome stability: From bench to bedside**
Steven West, Cancer Research UK
- 1:45-2:15 **Genomic response to environmental stress**
Jon Freedman, National Institute of Environmental Health Sciences
- 2:15-2:45 **Creation and function of 3D microscale models of liver**
Linda Griffith, Massachusetts Institute of Technology
- 2:45-3:00 Coffee Break
- 3:00-3:30 **High-throughput screening in genetically altered mouse cells**
Paul Hasty, University of Texas Health Science Center, San Antonio
- 3:30-4:00 **ATF3 models: From gene expression to mice**
Mike MacLeod, University of Texas M.D. Anderson Cancer Center
- 4:30-6:30 **Poster Viewing and Reception** (all posters attended)
- 6:30-8:00 Dinner (provided with registration)
- 8:00-11:00 **CMGCC Steering Committee meeting**, Robert Burns Rooms B& C.
- 8:00-10:00 **TRC Standardization Experiment 3**, St. Andrews A
- 10:00-11:00 **TRC Steering Committee meeting**, TBA

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- 8:00-9:00 Continental Breakfast (provided with registration)

- Session 3:** ***Integrated Approaches to Evaluation of the Phenotype***
Chair: David Johnson, University of Texas M.D. Anderson Cancer Center

- 9:00-9:45 **Keynote lecture - Metabonomic and global systems approaches to understanding metabotype variation in relation to disease development**
Jeremy Nicholson, Imperial College, London
- 9:45-10:15 **Toxicogenomics and environmental health research**
Ray Tennant, National Institute of Environmental Health Sciences
- 10:15-10:30 Coffee Break
- 10:30-11:00 **The search for disease pathways in integrated biochemical and omics data**
Joel Pounds, Pacific Northwest National Laboratory
- 11:00-11:30 **Spatial learning assessment in mitochondrial catalase transgenic mice using a modified Barnes maze**
Warren Ladiges, University of Washington
- 11:30-12:00 **High-throughput phenotyping of knockout mice for drug discovery**
Alex Abuin, Lexicon Genomics
- 12:00-1:00 Lunch (provided with registration)
- Session 4:** **Tools for Linking Genotype with Phenotype**
Chair: David Balshaw, National Institute of Environmental Health Sciences
- 1:00-1:45 **Understanding gene-gene interactions underlying complex traits in a segregating mouse population**
Pek Yee Lum, Rosetta/Merck
- 1:45-2:15 **Tools and approaches for comparative genomics-based analyses of Transcriptome and Variantome in health and disease**
Bruce Aronow, Cincinnati Children's Hospital Medical Center
- 2:15-2:30 Coffee Break
- 2:30-3:00 **The Chemical Effects in Biological Systems knowledgebase**
Mike Waters, National Institute of Environmental Health Sciences
- 3:00-3:45 **Genetic diversity to improve the predictive power of preclinical safety and toxicogenomic studies**
Richard Roman, Medical College of Wisconsin and PhysioGenix

- 3:45-4:30 **Genotype to exposure susceptibility: A challenge for toxicogenomics in the context of risk estimation**
Harvey Mohrenweiser, University of California, Irvine
- 4:30-6:30 **Poster Discussion and Reception** (all posters attended)
Moderator: William Kaufmann, University of North Carolina, Chapel Hill
- 6:30-8:00 **Corporate Sponsor Presentations**
- 8:00-10:00 Conference dinner, Awards presentation (provided with registration)

December 7, 2005

**National Research Council
Committee on Emerging Issues and Data on Environmental Contaminants
Meeting #11**

APPLICATIONS OF GENOMIC SIGNATURES

AGENDA¹

- 7:30-8:30 Continental Breakfast (provided with registration)
- 8:30-8:45 **Introduction to Workshop Organization and Objectives**
Peter Spencer, Oregon Health & Science University
- 8:45-9:30 **Questions About Regulatory Use of Toxicogenomics Information**
Peter Lord, Johnson & Johnson
- 9:30-10:00 **Acetaminophen Toxicogenomics Data: Application to Other Compounds²**
Richard Paules, National Center for Toxicogenomics, NIEHS

¹ This workshop is being recorded with the intent of placing audiofiles on the committee's website
[www.http://dels.nas.edu/emergingissues/toxicogenomics_meet10.shtml](http://dels.nas.edu/emergingissues/toxicogenomics_meet10.shtml)).

² This paper will provide background for this discussion: Heinloth AN, Irwin RD, Boorman GA, Nettesheim P, Fannin RD, Sieber SO, Snell ML, Tucker CJ, Li L, Travlos GS, Vansant G, Blackshear PE, Tennant RW, Cunningham ML, Paules RS. Related Articles, Links Gene expression profiling of rat livers reveals indicators of potential adverse effects. *Toxicol Sci.* 2004 Jul;80(1):193-202. Epub 2004 Apr 14. PMID: 15084756 [PubMed - indexed for MEDLINE]

General questions to be addressed in presentation:

- What types of signatures evolve from these experiments?
- What are the limitations on the interpretation of these results?

Specific questions to be addressed in presentation:

- If these same data were generated for another chemical, would they be useful in establishing a threshold? At what time after dosing should this be tracked?
- How does a genomic threshold correlate with a phenotypic threshold, whether that phenotype be a protein, a cell, a tissue, or a behavior
- What is the genomic signature correlate of a phenotype dose-effect relationship? Are affected pathway genes simply modulated more strongly or do other pathways become involved as the dosage increases?
- If these same data were generated for a new/unknown chemical, would they be useful in establishing a NOEL?
- Are there genomic correlates of unusual dose-response profiles?

10:00-10:30 **Panel Discussion of Questions Above**

Peter Spencer, Moderator

John Leighton, FDA/CDER; Robert Kavlock, EPA; Carol Henry, ACC; Nigel Walker, National Toxicology Program; Richard Brennan, Iconix; William Mattes, Gene Logic

- Panel members' clarifying questions (10 mins)
- Panel members' debate topics raised (20 mins)

10:30-10:45 Coffee Break

10:45-11:15 **Endocrine Disrupter Toxicogenomics Data³**

George Daston, Proctor and Gamble

General questions to be addressed in presentation:

- What types of signatures evolve from these experiments?
- Does this set of experiments suggest one or more signatures reflecting attributes of policy significance? For what attributes?
- What are the limitations on the interpretation of these results?
- Are genomic data reliable adjuncts to more traditional sources of toxicology data?

³ This paper will provide background for the discussion. Jorge M. Naciff,¹ Karla A. Hess, Gary J. Overmann, Suzanne M. Torontali, Gregory J. Carr, Jay P. Tiesman, Leslie M. Foertsch, Brian D. Richardson, Joel E. Martinez, and George P. Daston. Gene Expression Changes Induced in the Testis by Transplacental Exposure to High and Low Doses of 17 α -Ethinyl Estradiol, Genistein, or Bisphenol A. TOXICOLOGICAL SCIENCES 86(2), 396–416 (2005) doi:10.1093/toxsci/kfi198

- What is the genomic signature correlate of a phenotype dose-effect relationship? Are affected pathway genes simply modulated more strongly, or do other pathways become involved as the dosage increases?
- Is it possible to recognize a threshold for a genomic response? At what time after dosing should this be tracked? *How does a genomic threshold correlate with a phenotype threshold, whether that phenotype be a protein, a cell, a tissue, or a behavior?

Specific questions to be addressed in presentation:

- Is there a signature representative of estrogenically active compounds? If so, what is it? How definitive is this? For what species/time period/groups etc. would this finding be applicable?
- Is there a signature representative of a dose-response curve of a particular shape? If so, what is it?
- Can data from experiments such as these be used to get a sense of comparative toxicity or be otherwise useful in prioritizing potency?
- Is the signature of estrogenic substances enough to require or not require further animal testing?

11:15-11:45 **Panel Discussions of Questions Above**

Peter Spencer, Moderator

John Leighton, FDA/CDER; Robert Kavlock, EPA; Carol Henry, ACC; Nigel Walker, National Toxicology Program; Richard Brennan, Iconix; William Mattes, Gene Logic

- Panel members' clarifying questions (10 mins)
- Panel members' debate topics raised (20 mins)

11:45-12:45 Lunch (provided with registration)

12:45-1:15 **Antifungal Toxicogenomic Data⁴**

David Dix, Environmental Protection Agency

General questions to be addressed in presentation:

- What types of signatures evolve from these experiments?
- Does this set of experiments suggest one or more signatures reflecting attributes of policy significance? For what attributes?
- What are the limitations on the interpretation of these results?

Specific questions to be addressed in presentation:

- Do these data suggest particular modes of action/mechanisms of action?
- Do these data suggest multiple modes/mechanisms of action? If yes, how should this be interpreted?

⁴ There is no background paper for this presentation.

- Can data from experiments such as these be used to get a sense of comparative hazard or be otherwise useful to prioritize?
- Are these signatures of hepatotoxicity enough to direct further animal testing?
- Is adequate detail of these genomic signatures made available in order that they can be validated or accepted for regulatory use?

- 1:15-1:45 Panel Discussion of Questions Above
Peter Spencer, Moderator
John Leighton, FDA/CDER; Robert Kavlock, EPA; Carol Henry, ACC; Nigel Walker, National Toxicology Program; Richard Brennan, Iconix; William Mattes, Gene Logic
- Panel members' clarifying questions (10 mins)
 - Panel members' debate topics raised (20 mins)
- 1:45-2:00 **Introduction to breakout group tasks, Rooms TBA**
- 2:00-3:45 **Breakout groups to address questions at end of document**
- 3:45-4:00 Coffee Break
- 4:00-4:45 **Reports of breakout groups**
- 4:45-5:30 **Comments and discussion by the committee to the workshop findings**
Peter Spencer, Oregon Health & Science University (moderator); James Bus, The Dow Chemical Company; Joseph DeGeorge, Merck Research Laboratories; Kenneth Ramos, University of Louisville; Cheryl Walker, The University of Texas M.D. Anderson Cancer Center.
- 5:30 Adjourn