ILSI Health and Environmental Sciences Institute

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**Workshop: "Genetic Toxicology: Opportunities to Integrate New Approaches"**

**April 24-25, 2012**
**Crowne Plaza Silver Spring**
**Lincoln Ballroom**
**8777 Georgia Ave**
**Silver Spring, MD**

**Sponsored by:**
**ILSI Health and Environmental Sciences Institute**
**Project Committee on Relevance and Follow-up of Positive Results in In Vitro Genotoxicity Assays (IVGT)**

## Workshop Abstract

The discipline of applied genetic toxicology relies primarily on *in vitro* and *in vivo* technologies, some of which have been in use for more than 30 years. Though technological advances have led to high-throughput analyses (e.g. Ames II, flow cytometric analyses of micronuclei), development of *in vivo* assays applicable to all tissues that could be used as follow-up assays (i.e., Comet assay, gene mutations in transgenic animals), pathway analyses (genomic evaluations), and *in silico* approaches (QSAR), the regulatory testing battery remains unchanged: 1) an *in vitro* test for gene mutation in bacteria, 2) an *in vitro* cytogenetic or micronucleus assay with mammalian cells or an *in vitro* mouse lymphoma thymidine kinase (tk) assay, and in some cases, 3) an *in vivo* test for chromosomal damage using rodent hematopoietic cells. Though genetic damage is frequently assessed as a key event(s) in the progression of cancer, toxicologists recognize that a wide spectrum of human health effects may be caused by genetic damage.

Our understanding of molecular biology has increased exponentially in recent years, particularly in areas such as epigenetics, miRNA, and genetic structure. Technologies and tools are also being developed in fields outside of genetic toxicology such as 3D tissue cultures, organ cultures, stem cells, and imaging. The purpose of this workshop is to consider the impact that our improved understanding of biology and new technologies might have on our ability to perform genetic toxicology studies to yield information that is more relevant to human hazard and risk assessment for genetic damage. By bringing together expertise from both within and outside the discipline of genetic toxicology, it is hoped that productive discussions can be held to define ways of bridging

genetic toxicology to other disciplines, and to identify potential synergies that would result in new approaches to inform more accurate genotoxicity risk assessment.

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**AGENDA**

**Tuesday, April 24, 2012**

*Continental breakfast available at 8:00AM*

8:30AM Overview of ILSI Health and Environmental Sciences Institute
*Dr. James Kim (HESI)*

8:35AM Genetic Toxicology: Why thinking outside the box? Overview, rationale and objectives of the workshop
*Dr. Véronique Thybaud (Sanofi)*

9:00AM Session 1 introduction: Alternative experimental models to improve genetic toxicity testing
*Dr. Marilyn Aardema (BioReliance)*

9:15AM Overview of the use of 3-dimensional tissue constructs for genotoxicity testing
*Dr. Stefan Pfuhler (Procter & Gamble)*

9:45AM Development of in vitro toxicity tests using hepatocytes differentiated from human stem cells
*Dr. Seiichi Ishida (National Institutes of Health Science, Japan)*

10:15AM Humanized models in toxicology and their applications to hazard characterization and risk assessment
*Darrell Boverhof (The Dow Chemical Co.)*

10:45AM Break

11:15AM Session 1: discussion

12:15PM Lunch

1:30PM Session 2 introduction: Biomarkers of epigenetic changes and their applicability to genetic toxicology
*Dr. Bhaskar Gollapudi (The Dow Chemical Co.)*

1:45PM A new paradigm for epigenetic control of cell phenotype: Dynamic reprogramming of tRNA modifications and ribosomes controls selective translation of stress response proteins
*Dr. Peter Dedon (Massachusetts Institute of Technology)*

2:15PM Epigenomics and impact for drug safety sciences
*Dr. Jennifer Marlowe (Novartis)*

2:45PM Epigenetic traits as biomarkers of carcinogenesis
*Dr. Igor Pogribny (U.S. Food and Drug Administration, NCTR)*

3:15PM MIR-34 prevents in vivo lung tumor initiation and progression in the therapeutically resistant *KRAS;TRP53* mouse model
*Dr. Andrea Kasinski (Yale University)*

3:45PM Break

4:15PM Session 2: Discussion

5:15PM Adjourn

7:00PM Dinner

**Wednesday, April 25, 2012**

*Continental breakfast available at 8:00AM*

8:30AM Workshop: recap of previous day
*Dr. James Kim (HESI)*

9:00AM Session 3 introduction: New technologies and approaches
*Ms. Kristine Witt (National Institute of Environmental Health Sciences)*

9:15AM Imaging as an approach to safety assessment
*Dr. Bill Slikker (U.S. Food and Drug Administration, NCTR)*

9:45AM The Tox21 strategy for detecting genotoxicants
*Dr. Ray Tice (National Institute of Environmental Health Sciences)*

10:15AM The behavior of genomic signatures of genotoxicity: Effect of dose level and exposure duration
*Dr. Scott Auerbach (National Institute of Environmental Health Sciences)*

10:45AM Break

11:15AM Session 3: discussion

12:15PM Wrap-up: Discussion and next steps
*Dr. Bhaskar Gollapudi (The Dow Chemical Co.)*

12:45PM Adjourn

**Organizing Committee**

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| Marilyn Aardema | BioReliance (USA) |
| Laura Custer | Bristol-Myers Squibb (USA) |
| Bhaskar Gollapudi | The Dow Chemical Co. (USA) |
| Masa Honma | National Institute of Health Sciences (Japan) |
| James Kim | ILSI Health and Environmental Sciences Institute (USA) |
| Manju Manjanatha | U.S. FDA / NCTR (USA) |
| Stefan Pfuhler | Procter & Gamble (USA) |
| Leon Stankowski | BioReliance (USA) |
| Véronique Thybaud | sanofi-aventis (France) |
| Jan van Benthem | RIVM (Netherlands) |
| Paul White | Health Canada (Canada) |
| Kristine Witt | NTP / NIEHS (USA) |
| Errol Zeiger | Consultant (USA) |