Mechanisms of Toxicity

Scientific Co-Chairs: Carl Alden, DVM, Millennium Pharmaceuticals Inc, Lawrenceburg, IN, Daniel Rudmann, DVM, PhD, Eli Lilly and Company, Indianapolis, IN, and Richard Peterson, DVM, PhD, DACVP, GlaxoSmithKline, Research Triangle Park, NC

The global regulatory agencies and the general public require outstanding scientific rigor and quality in the human risk assessment of xenobiotics. To meet these demands, the toxicology and pathology professions are positioned to take advantage of key learnings captured from major advances in the molecular understanding of host defense, disease, and toxicity processes. The purpose of the 2012 Annual Symposium of the Society of Toxicologic Pathology will be to examine mechanisms of toxicity in six general sessions covering tissue injury related to the following: 1) host factors, 2) chemical structure, 3) xenobiotic cellular targets (on- and off-target), 4) new technologies (e.g., nanotechnology, siRNA therapy and immunoconjugates), 5) cellular organelle specific effects, and 6) high-profile environmental chemicals and consumer products.

Five continuing education sessions will be held on Sunday before the general sessions begin including: 1) Mechanism-Based Approaches to Cardiovascular Safety Assessment, 2) Nontraditional Applications of Clinical Pathology in Drug Discovery and Preclinical Toxicology, 3) the ACT-sponsored Drug Development 101 course, 4) “The Placenta As an Immune Organ and Its Relevance in Toxicological Studies,” and 5) A half-day Career Development Workshop: Presentation Skills and Scientific Advocacy.

A Career Development Lunchtime Series held on Monday will provide participants guidance on careers in environmental toxicology.

Scientific Sessions

Monday Morning

8:00 AM–8:05 AM

Welcome
Thomas Monticello, DVM, PhD, DACVP, Amgen, Thousand Oaks, CA, STP President

8:05 AM–8:10 AM

Introduction
Carl Alden, DVM, Millennium Pharmaceuticals Inc, Lawrenceburg, IN, Daniel Rudmann, DVM, PhD, Eli Lilly and Company, Indianapolis, IN, and Richard Peterson, DVM, PhD, DACVP, GlaxoSmithKline, Research Triangle Park, NC

8:10 AM–9:00 AM

Keynote Address:
The Mechanisms of Formaldehyde Toxicity: State of Research 30 Years and Counting
James A. Swenberg, DVM, PhD, DACVP, University of North Carolina at Chapel Hill, Chapel Hill, NC

Session 1
9:00 AM–12:00 Noon

Host Factors and the Expression of Toxicologic Effects

Co-Chairs: Harm HogenEsch, DVM, PhD, DACVP, Purdue University, West Lafayette, IN, and Marlon Rebelatto, DVM, PhD, DACVP, MedImmune, Inc., Gaithersburg, MD

Even though the genomes of individuals are 99.9% identical, the small 0.1% difference predicts millions of polymorphisms, some of which will affect protein expression and function, resulting in toxicologic response phenotypes. Likely every immunologic response to injury as well as every pathway involved in xenobiotic metabolism and transport will have variations due to different patient group’s genetic profile. Environmental agents may result in alterations in gene expression that might ultimately lead to a toxicity phenotype via epigenetic mechanisms. In addition, factors such as metabolic disease and nutritional status may impact the individual response to xenobiotic exposure. An understanding of host-specific toxicologic responses is important in the refined risk assessment. This session will examine some of these host specific factors that can lead to an injury phenotype.
Monday Afternoon

Session 2
1:30 PM–5:00 PM

Morphologic and Molecular Underpinnings of Organelle Toxicity

Co-Chairs: Charles W. Qualls Jr., DVM, PhD, DACVP, Amgen, Thousand Oaks, CA, and Lee Silverman DVM, PhD, DACVP, Agios Pharmaceuticals, Cambridge, MA

Organelle toxicity has historically been evaluated by morphologic criteria primarily, transmission electron microscopy. More specific understanding of molecular mechanisms of organelle-based toxicity is quickly expanding. During this session we will bring classic and cutting-edge methods of evaluation together. There will be an overview of classic ultrastructural organelular toxicologic manifestations that will include information related to molecular mechanisms. We will then delve into more in-depth discussions exploring the emerging understanding of the molecular mechanisms that define autophagy, ER stress, and the differentiation of apoptosis from programmed necrosis. In addition, the relation of these molecular mechanisms to pathologic processes will be discussed.

1:30 PM–1:35 PM

Introduction

Ultrastructural Pathology and Interorganelle Crosstalk in Hepatoxicity

Norman Cheville, DVM, PhD, DACVP, DHontC, Iowa State University, Ames, IA
Tuesday, June 26

Session 3

8:00 AM–12:00 Noon

Target-Related and Off-Target Based Toxicologic Effects

Co-Chairs: Dominique Brees, DVM, PhD, DACVP, Novartis Pharma AG, Basel, Switzerland, and Daniel Rudmann, DVM, PhD, DACVP, Eli Lilly and Company, Indianapolis, IN

The vast majority of adverse toxicologic effects can be placed into one of three categories including chemical-based, target-related or off-target effects (the latter two mainly in the case of chemotherapeutics). Target-related refers to exaggerated and adverse pharmacologic effects at the target of interest in the test system. Off-target refers to adverse effects as a result of modulation of other targets; these may be related biologically or totally unrelated to the target of interest. Both the decision to develop and the risk assessment of a xenobiotics are influenced by this understanding. It is imperative that the toxicologic pathologist use the toxicologic and biologic data at hand and literature information on the target to form testable hypotheses related to target vs. off-target mechanisms or even chemical-based mechanisms of toxicity. The objective of this session will be to examine specific examples of target and off-target based effects and strategies for differentiating these three possibilities in human risk assessment.

8:00 AM–8:30 AM

Introduction and Panel

5:30 PM–5:35 PM

Introduction and Overview of the NEG CARC Rat Paradigm

Carl Alden, DVM,
Millennium Pharmaceuticals Inc, Lawrenceburg, IN

5:35 PM–5:40 PM

Regulatory Status Update

Todd Bourcier, PhD,
Division of Metabolic & Endocrine Products, CDER, US FDA

5:40 PM–6:30 PM

Q&A

Dan Morton, Todd Bourcier, and Carl Alden

www.toxpath.org
Wednesday, June 27

Wednesday Morning

Session 4
8:00 AM–12:00 Noon

Chemical-Based Tissue Reactivity

Co-Chairs: James Klaunig, PhD, ATS, Indiana University, Bloomington, IN, and Richard Peterson, DVM, PhD, DACVP, GlaxoSmithKline, Research Triangle Park, NC

Xenobiotics have chemical structures that are foreign to living organisms, though they are sometimes produced to mimic endogenous molecules. Chemicals interact with cells, biochemical pathways and physiologic systems by virtue of their chemical structure. Recognizing that effects may be dependent on individual susceptibility, the majority of adverse effects can be placed into one of three categories including chemical-based, target-related, or off-target effects (the latter two mainly in the case of chemotherapeutics). Chemical-based reactivity is dependent on xenobiotic absorption, distribution, metabolism, transport, target tissue concentration and secretion leading to molecular processes such as covalent binding, lipid peroxidation, mitochondrial dysfunction, and/or redox cycling. This session will examine various toxicologic mechanisms of chemical-based tissue reactivity.

8:00 AM–8:10 AM
Introduction
Mechanisms of Oxidant Injury and Oxidant Defense
Jim Klaunig, PhD, ATS, Indiana University, Bloomington, IN

8:10 AM–8:50 AM
Mechanisms of Oxidant Injury and Oxidant Defense
Jim Klaunig, PhD, ATS, Indiana University, Bloomington, IN

8:50 AM–9:30 AM
DNA Reactivity/Genetic Toxicity
Julian Preston, PhD, NIEHS, US EPA, Durham, NC

9:30 AM–10:00 AM
Reactive Intermediates
Terrence Monks, PhD, The University of Arizona, Tucson, AZ

10:00 AM–10:40 AM
Break

10:40 AM–11:20 AM
Nuclear Receptors, Ligand-Activated Transcription Factors: Role in Cell Injury
Andrew Patterson, PhD, Pennsylvania State University, University Park, PA

8:00 AM–8:10 AM
Introduction
Mechanisms of Oxidant Injury and Oxidant Defense
Jim Klaunig, PhD, ATS, Indiana University, Bloomington, IN

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Andrew Patterson, PhD, Pennsylvania State University, University Park, PA

11:20 AM–12:00 Noon
Student Presentation
Wednesday Afternoon

**Ethical Figure Adjustments for Publication**

**Part 2 of Responsible Authorship and Publication Practices**

* Sponsored by IATP and STP

Electronic images of graphs, charts, blots, photomicrographs, etc. are typically provided as part of manuscript submissions to journals. With the currently available image adjustment programs, it is relatively easy to modify any of the various figures submitted along with manuscript text for publication in scientific journals. Photomicrographs captured with electronic cameras often need adjustment for white balance and require some sharpening. While global image adjustment changes are generally accepted, other electronic image adjustments are considered unethical. The purpose of this workshop is to present practical approaches and techniques for image adjustment, with emphasis on photomicrographs. Following the 90-minutes presentation, individuals may bring specific questions and problem images for one-on-one interaction with imaging experts.

The session presentations will be held from 12:00 noon to 1:30 pm. A charge of $50 at the time of registration will cover the cost of a box lunch. Following the presentation, individuals may interact with imaging experts at work stations. Appointments must be made in advance. If you wish to make an appointment, select appropriate choice when registering. You will be contacted for scheduling. Adobe PhotoShop will be the primary image adjustment software used to this interactive workshop.

**Session 5**

1:30 PM–5:00 PM

**Mechanisms of Toxicity: High-Profile Environmental Chemicals and Consumer Products**

* Co-Chairs: Jack Harkema, DVM, PhD, DACVP, Michigan State University, East Lansing, MI, and David Malarkey, DVM, PhD, DACVP, NIEHS, Research Triangle Park, NC

Multinationals reach around the world providing products to populations that can total in the billions. Products are increasingly developed by the least cost producer sometimes in countries without well-established consumer protection institutions. Often, products that have extensive distribution and utilization for decades continue to be controversial, sometimes because modern testing methodology has not been applied or because risks have been identified more recently. Products with extensive human exposure as well as heightened recognition and concern include medicinals, construction materials, manufacturing/plastics, food/water storage containers, food adulterants and contaminants, and persisting environmental pollutants. This session will address these important toxicants including review the source, toxicologic effects, and pathogenesis.

1:30 PM–1:35 PM  Introduction  
1:35 PM–2:15 PM  Mechanistic Studies of Carcinogenic Activity of Hexavalent Chromium  
Michele Hooth, PhD, NIEHS, NTP, Research Triangle Park, NC

2:15 PM–2:55 PM  TASH (Toxin-Associated Steatohepatitis) and Liver Cancer  
Matthew cave, MD, University of Louisville, Louisville, KY

2:55 PM–3:25 PM  Break

3:30 PM–4:00 PM  Air Pollution and the Cardiometabolic Syndrome  
Sanjay Rajagopalan, MD, The Ohio State University, Columbus, OH
# Society of Toxicologic Pathology

## Mechanisms of Toxicity

### 31st Annual Symposium

**Boston**

**Marriott Copley Place**

**June 24–28, 2012**

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<th>Session</th>
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<tr>
<td>4:00 PM–4:45 PM</td>
<td>The Toxicity and Pathology of Dietary Herbals/ Botanicals and Supplements</td>
<td>June Dunnick, PhD, National Toxicology Program, Division of the NIEHS, Research Triangle Park, NC, and Abraham Nyska, DVM, DECVP, FIATP, Consultant in Toxicologic Pathology, Timrat, Israel</td>
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<tr>
<td>4:45 PM–5:00 PM</td>
<td>Wrap Up</td>
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<td>5:30 PM–5:50 PM</td>
<td>Awards Ceremony</td>
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<td>5:50 PM–6:30 PM</td>
<td>Annual Business Meeting</td>
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<td>7:00 PM–9:00 PM</td>
<td>President’s Reception</td>
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<td>9:00 AM–9:40 AM</td>
<td>Nanotechnology: Toxicologic Pathology</td>
<td>Ann Hubbs, DVM, PhD, DACVP, National Institute for Occupational Safety, Centers for Disease Control and Prevention, Morgantown, WV</td>
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<td>9:40 AM–10:00 AM</td>
<td>Student Presentation</td>
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<td>10:00 AM–10:30 AM</td>
<td>Break</td>
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<td>10:30 AM–11:15 AM</td>
<td>Nonclinical Safety Evaluation of Immunoconjugates</td>
<td>Melissa Schutten, DVM, PhD, DACVP, Genentech, South San Francisco, CA</td>
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<td>11:15 AM–12:00 Noon</td>
<td>RNA-Based Therapies: Toxicology and Current Clinical Status</td>
<td>Scott Barros, PhD, DABT, Alnylam Pharmaceuticals, Cambridge, MA</td>
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**Thursday, June 28**

**Thursday Morning**

**Session 6**

8:00 AM–12:00 Noon

### Technology-Related Toxicologic Effects

**Co-Chairs: John Vahle, DVM, PhD, DACVP,**

**Eli Lilly and Company, Indianapolis, IN, and David Hutto,**

**DVM, PhD, DACVP, Eisai, Inc., Hopkinton, MA**

There are several potentially transformational technologic approaches to develop and deliver biotherapeutics and optimize agricultural and chemical products. These approaches include methods to directly or indirectly manipulate gene transcription and translation pathways and access cellular or tissue compartments generally difficult to reach. The methods may lead to toxicologic effects which require evaluation by toxicologic pathologists and inclusion in our risk assessment and value proposition for the regulatory agencies and public. The objective of this session will be to review several of these technology-based approaches, their potential toxicologic effects, and the approaches to risk assessment.

8:00 AM–8:10 AM  **Introduction**

8:10 AM–9:00 AM  **Nanotechnology: Overview and Public Health Implications**

David Warheit, PhD, DABT, DATS, DuPont Haskell Global Centers, Newark, DE