Mechanisms of Toxicity

Scientific Co-Chairs: Carl Alden, DVM, Millennium Pharmaceuticals Inc, Lawrenceburg, IN, Daniel Rudman, 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) Non-Traditional 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.

The symposium will be held in Boston, Massachusetts, a “hub” of biotechnology and basic research, not to mention of early American history. We hope you will join us for this exciting program.

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, Dan Rudman, 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.

9:00 AM–9:05 AM

9:05 AM–10:00 AM

Introduction

Genetic Basis of the Response to Drugs and Chemicals

Jeff French, PhD, NIEHS, Research Triangle Park, NC

10:00 AM–10:30 AM

Break
### Career Development Lunchtime Series

**12:30 PM–1:30 PM**

**Careers in Environmental Toxicology**

*Presented by the STP Career Development and Outreach Committee*

(Free Event, registration required)

Panelists and audience members will discuss a variety of careers in which toxicologic pathologists play an important role in the field of environmental toxicology. The session will allow attendees to become more familiar with this area of toxicologic pathology by direct interaction with a panel encompassing multiple subspecialties in the field. This topic is timely for the 2012 lunchtime series given the initiation of an interest group and scientific session focused on Environmental Toxicologic Pathology at the 2011 STP meeting.

**Panelists for the Lunchtime Session include:**

- **Chemical Industry**
  - David L. Eisenbrandt, DVM, PhD, DACVP, Dow AgroSciences LLC, Parker, CO

- **Industrial Exposure**
  - Ann Hubbs, DVM, PhD, DACVP, NIOSH, Centers for Disease Control and Prevention, Morgantown, WV

- **Aquatic Species and Wildlife**
  - Jeffrey Wolf, DVM, DACVP, EPL, Inc, Sterling, VA

- **Academia/Respiratory**
  - Dennis Wilson DVM, PhD, DACVP, UC Davis, Davis, CA

- **National Toxicology Program**
  - David E. Malarkey, DVM, PhD, DACVP, National Institute of Environmental Health Sciences, Research Triangle Park, NC

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### Monday Afternoon

**Session 2**

1:30 PM–5:00 PM

**Organelle Toxicity: Pharmacologic and Chemotype Mechanisms**

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

Many xenobiotics have direct toxic effects on cellular organelles. Often, commonalities exist in the injury expressed among agents with a common specific subcellular organelle target. Important target organelles include mitochondria (e.g., NRTI), phagolysosomes, endoplasmic reticulum (e.g., ER stress), and the ubiquitin/proteasome system. Organelar toxicity can lead to adverse effects on cellular energetics, transport mechanisms, degradation pathways, or initiate autophagic mechanisms (e.g., mitophagy) and cellular apoptosis homeostasis (i.e., mitochondria and ER Stress). In some cases, organelar toxicity may be secondary; oxidative stress may initiate mitochondrial toxicity (e.g., reperfusion injury). This session will review the myriad mechanisms and expression of specific organelar toxic effects. Examples of classic organelar toxicants as well as pertinent examples encountered in the current drug development paradigm will be used to review the main pathways/modes of action of organelar toxicity.

1:30 PM–1:35 PM

**Introduction**

Norman Cheville, DVM, PhD, DACVP, Iowa State University, Ames, IA

1:35 PM–2:15 PM

**Broad Overview (Morphology and Mechanism)**

Gerald Dorn, MD, Washington University in St. Louis School of Medicine, St. Louis, MO

2:15 PM–3:05 PM

**SR and Mitochondria in Cardiac Myocytes/Apoptosis in the Heart**

Gerald Dorn, MD, Washington University in St. Louis School of Medicine, St. Louis, MO

3:05 PM–3:35 PM

**Break**

3:35 PM–4:20 PM

**Autophagy**

Natalie Ron D’Amore, PhD, Millennium: The Takeda Oncology Company, Cambridge, MA
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
8:30 AM–9:10 AM  Strategies in Defining On- and Off-Target Based Toxicologic Effects

Tuesday Afternoon  Free Time

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 chemotherapy). 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

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  
Nuclear Receptors, Ligand Activated Transcription Factors: Role in Cell Injury  
Andrew Patterson, PhD, Pennsylvania State University, University Park, PA

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

10:00 AM–10:40 AM  
Break

10:40 AM–11:20 AM  
DNA Reactivity/Genetic Toxicity  
Julian Preston, PhD, NIEHS, US EPA, Durham, NC

11:20 AM–12:00 NOON  
Student Speaker

Wednesday Afternoon

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

4:00 PM–4:45 PM  
The Toxicity and Pathology of Dietary Herbals/Botanicals and Supplements  
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

4:45 PM–5:00 PM  
Wrap Up

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, Dupont, Wilmington, DE

9:00 AM–9:40 AM    Nanotechnology: Toxicologic Pathology
                    Ann Hubbs, DVM, PhD, DACVP, NIOSH, Center for Disease Control and Prevention, Morgantown, WV

9:40 AM–10:00 AM   Student Presentation
10:00 AM–10:30 AM  Break
10:30 AM–11:15 AM  Nonclinical Safety Evaluation of Immunoconjugates
                    Melissa Schutten, DVM, PhD, DACVP, Genentech, South San Francisco, CA

11:15 AM–12:00 NOON RNA-Based Therapies: Toxicology and Current Clinical Status
                    Scott Barros, PhD, DABT, Alnylam Pharmaceuticals, Cambridge, MA