Society of Toxicologic Pathology
33rd Annual Symposium

Washington, DC

TRANSLATIONAL PATHOLOGY:
Relevance of Toxicologic Pathology to Human Health

June 22–26, 2014

TRANSLATIONAL PATHOLOGY:
Relevance of Toxicologic Pathology to Human Health

Scientific Co-Chairs: *Sabine Francke, DVM, PhD, FIATP, US FDA/CFSAN, Silver Spring, MD; Mark Hoenerhoff, DVM, PhD, DACVP, NIEHS, Research Triangle Park, NC; and Lee Silverman, DVM, PhD, DACVP, Agios Pharmaceuticals, Cambridge, MA*

Toxicologic pathologists work in diverse settings studying changes elicited by pharmacological, chemical, and environmental agents, and factors that modify these responses. This work involves the integration of pathology data into hazard identification, risk assessment, and risk communication frameworks that guide safety decisions for potentially toxic substances. A central part of this process is the translation of pathologic effects in animal models to address specific issues in public health.

This symposium will focus on translational science and the relevance of toxicologic pathology to human health. Topics will include the predictive value of nonclinical models and how animal model and human endpoints inform each other. Progress in the development of new nonclinical animal models and other types of models will be discussed, highlighting areas where models are highly predictive of human endpoints and areas where alternative models are needed. Emerging technologies which have the potential to improve translational capabilities will also be presented, with an emphasis on advancements that will impact regulatory decision making in coming years. As the field of epigenetics is rapidly advancing, the role and utility of epigenetic endpoints in toxicologic pathology and their relevance to human health will be addressed. Environmental toxicologic pathology plays a critical role in understanding health impacts of environmental exposures; therefore, how pathology outcomes inform human health assessments and regulatory decisions will be discussed. Finally, as the incidence of comorbidities in the human population increases, there is a greater need to develop translational models that provide useful information on human populations with comorbidities; the challenges of developing such relevant animal models will be addressed. By the end of this symposium, the audience will have a better understanding of current trends and data needs in translational pathology and how the field of toxicologic pathology can leverage expertise and tools to meet these needs.

Monday, June 23

Session 1: Toxicity Concordance from Animals to Humans: How Predictive are Traditional Preclinical Studies of Adverse Effects or Toxicities in Clinical Studies?
Co-Chairs: Jeff Engelhardt, DVM, PhD, DACVP, FIATP, EPL, Inc., Camarillo, CA; Daniela Ennulat, DVM, PhD, DACVP, GlaxoSmithKline, King of Prussia, PA; and Sabine Francke, DVM, PhD, FIATP, US FDA/CFSAN, Silver Spring, MD

Testing of xenobiotics in animals prior to human use has been a regulatory requirement since 1939. Since that time, safety testing has been an integral part of the development of regulated compounds such as pharmaceuticals, food additives, and environmental chemicals. As new chemicals or biologics and their targets have become more sophisticated or specialized, so have the questions regarding the reliability of the animal models. As translational toxicologic pathology relies on the predictive value of target organ toxicities identified in animal studies for responses in humans, robustness of the concordance between target organ toxicities identified as morphologic or biochemical changes in preclinical species and humans will be highlighted in this session. Limitations and advantages of animal models and traditional or non-traditional biomarkers for successful translation of preclinical study findings

for clinical use will also be explored. For example, questions to be addressed are: do routine safety studies identify the safety information needed by clinical investigators or are specific, hypothesis-driven studies needed? Are there better ways to interrogate toxicity data through the use of shared databases? What have we learned of early biomarkers and their concordance with tissue morphologic changes and their translational utility?

Overview: Setting the Stage for Translational Pathology
Jeff Engelhardt, DVM, PhD, DACVP, FIATP, EPL, Inc., Camarillo, CA

Nonclinical Safety Testing: Considerations of Current and Future Performance Characteristics
Thomas Jones, PhD, Eli Lilly, Indianapolis, IN

IQ-PSLG Nonclinical Translational Safety Database Initiative
Thomas Monticello, DVM, PhD, DACVP, Amgen, Inc., Thousand Oaks, CA

Biomarker Development: "Burning Down the Haystack" to Find, Develop, and Qualify Translational Biomarkers
Daniela Ennulat, DVM, PhD, DACVP, GlaxoSmithKline, King of Prussia, PA

Clinical Perspective on Biomarker Utilization
Scott Adler, MD, AstraZeneca, Wilmington, DE

Successful Integration of Nonclinical and Clinical Findings in Interpreting Clinical Relevance of Rodent Neoplasia with a New Chemical Entity
Kirk Ways, MD, PhD, Janssen Research and Development, LLC, Raritan, NJ

Session 2: Progress in Preclinical Testing for Translational Science
Co-Chairs: Glenn H. Cantor, DVM, PhD, DACVP, Bristol-Myers Squibb Company, Princeton, NJ; Jerrold M. Ward, DVM, PhD, DACVP, FIATP, Global Vet Pathology, Montgomery Village, MD; and Cory Brayton, DVM, DACLAM, DACVP, John Hopkins University School of Medicine, Baltimore, MD

Nonhuman animals used as human surrogates in preclinical testing and hypothesis-driven translational science have led to important medical and scientific breakthroughs. Preclinical (aka nonclinical) research in animals also has received scrutiny and criticism for insufficient relevance to human conditions. Current issues in the development of pharmaceuticals and biopharmaceuticals, and some new approaches in mouse models, will be presented. This session will focus on new findings and strategies to optimize preclinical translational research.

The Future of Preclinical Animal Models in Pharmaceutical Discovery and Development: A Need to Bring *In Cerebro* to the *In Vivo* Discussions
Jeffrey Everitt, DVM, DACVP, DACLAM, FIATP, GlaxoSmithKline, Research Triangle Park, NC

Using Mouse Genetic Diversity for Better Translation to Human Diseases and Toxicities
Alison Harrill, PhD, University of Arkansas Medical School, Little Rock, AR

Mice with Humanized Livers
Markus Grompe, MD, Oregon Health and Science University, Portland, OR

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Opportunities for Pathology in the Changing World of Translational Sciences and Biologic Modalities
Emanuel Schenck, DVM, PhD, MedImmune, LLC, Gaithersburg, MD

Tuesday, June 24

Session 3: Emerging Technologies
Co-Chairs: Eric Blomme, DVM, PhD, DACVP, AbbVie, Inc., North Chicago, IL; and Gary Boorman, DVM, PhD, DACVP, FIATP, Covance Laboratories, Inc., Chapel Hill, NC

Emerging technologies offer exciting promise to address many diseases that have been refractory to traditional therapies, but also to improve toxicological assessment and human risk assessment. An increasing number of novel therapeutic approaches, such as oligonucleotide-based agents, antibody-drug conjugates, or new delivery systems, are in preclinical and clinical studies with some already approved by regulatory agencies. Likewise, a multitude of analytical technologies based on recent advances in molecular biology or engineering are available to evaluate exploratory compounds *in vitro* or *in vivo*. Discovery pathologists need to become familiar enough with these potentially useful technologies to offer salient advice on utility, data interpretation, or experimental designs. Pathologists involved in preclinical safety assessment also face new challenges associated with the interpretation of frequently complex toxic changes of poorly characterized mechanism and of unknown relevance to humans. This session will discuss the role that pathologists in the pharmaceutical industry can play in the identification, application and development of emerging technologies to improve toxicity prediction and characterization, but also in the assessment of the safety of novel treatment modalities. This session is designed to provide a framework for pathologists to expand their contribution to this exciting but increasingly complex area of therapeutic development and safety assessment.

Evaluation of Potential and Utility of New Technologies for Early Compound Characterization
Yvonne Will, PhD, Pfizer, Inc., Groton, CT

How Discovery Technologies Have Impacted Toxicology-related Attrition and Influenced Regulatory Preclinical Assessment
Eric Blomme, DVM, PhD, DACVP, AbbVie, Inc., North Chicago, IL

Evaluation of the Promise and the Potential Toxicities of Antisense Oligonucleotides
Kendall Frazier, DVM, PhD, DACVP, DABT, GlaxoSmithKline, King of Prussia, PA

Recent Efforts in Prediction and Characterization of Adverse Immune Reactions
Ellen Evans, DVM, PhD, DACVP, Pfizer, Inc., Groton, CT

Session 4: The Role of the Toxicologic Pathologist in Informing Regulatory Decisions and Guiding the Interpretation and Application of Data from New Technologies and Tools
Co-Chairs: Shashi Amur, PhD, US FDA/CDER, Silver Spring, MD; and Douglas C. Wolf, DVM, PhD, FIATP, ATS, US EPA, Research Triangle Park, NC

The use and application of data generated through the use of emerging technologies and novel tools holds great promise in aiding drug, food, and environmental safety assessments. After scientific and analytic validation of these new methods, integration of the validated methods within safety assessments is necessary for appropriate application in regulatory decision-making. The first presentation will describe

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a new method which recapitulates the basic functions of an organ *in vitro*, organ-on-a-chip. The science behind this approach as well as some of the issues that would need to be addressed for its application in safety assessment will be described in this talk. The issue of verification and applicability of new technologies is very important to the regulatory community. The application of genomics, which is now widely used as a basic tool in science, is still in the early stages for safety assessment. Its application will be addressed in the second presentation. While new tools hold a lot of promise in aiding safety assessments, issues surrounding the application and interpretation of the classic indicators of adversity continue to be important. Evaluation of clinical chemistry, its interpretation, and translation relative to tissue responses will thus be addressed in the third talk. The second half of the session will address the development, qualification, and use of biomarkers and bioindicators for exposure, effects, clinical trial design and clinical response in drug development, clinical management, and risk management decisions from a regulatory perspective followed by a panel discussion on issues relative to identifying and establishing biomarkers and bioindicators.

Integration of Emerging Technologies into Safety Assessment – Example: Organ-on-a-Chip
Anthony Bahinski, PhD, MBA, FAHA, Harvard University, Boston, MA

Role of Toxicologic Testing in the Post-genomic Era: Validation and Application
Weida Tong, PhD, US FDA/NCTR, Jefferson, AR

Evaluation, Correlation, and Interpretation of Clinical Pathology with Histopathology in Preclinical Studies
Nancy Everds, DVM, DACVP, Amgen, Inc., Seattle, WA

FDA Perspective - Biomarkers as Drug Development Tools
Shashi Amur, PhD, US FDA, Silver Spring, MD

EPA Perspective - Exposure and Effects Prediction and Monitoring
Jon Sobus, PhD, US EPA, Research Triangle Park, NC

Panel Discussion on Issues around Biomarker Needs

Wednesday, June 25

Session 5: Epigenetic Endpoints in Toxicologic Pathology and Relevance to Human Health
Co-Chairs: Jim Hartke, DVM, PhD, DACVP, Celgene Corporation, Summit, NJ; and Mark Hoenerhoff, DVM, PhD, DACVP, NIEHS, Research Triangle Park, NC

Epigenetics is the study of heritable changes in gene expression caused by mechanisms that do not alter the underlying DNA sequence. Epigenetic alterations include histone modification, DNA methylation and acetylation, small interfering RNA (siRNA) mechanisms, and epithelial-stromal interactions, to name a few. While epigenetic mechanisms of carcinogenesis have been studied for decades, its application to drug development and discovery, risk assessment, hazard identification, and toxicologic pathology in general is relatively recent. It is becoming increasingly clear that epigenetic alterations not only play a role in cancer development, but also reproductive, developmental, and degenerative diseases in humans. How epigenetic mechanisms alter the biologic system to contribute to disease and toxicity is an area of ongoing and intense interest and research. This session will discuss the utilization of epigenetic endpoints in toxicity testing, and how they relate to human disease due to exposures in the process of reproductive,

developmental, degenerative, and neoplastic disease, and the assessment of these endpoints within the safety assessment and hazard characterization paradigms in toxicologic pathology for the study of human health.

Overview - Epigenetics and Toxicology Research
Jay Goodman, PhD, Michigan State University, East Lansing, MI

Investigating the Role of Epigenetics in Product Safety Assessment
Reza Rasoulpour, PhD, Dow Chemical Company, Midland, MI

Epigenetic Changes in Cancers, Methodologies to Detect Them, and Potential Therapies
Stephen Baylin, MD, Johns Hopkins, Baltimore, MD

Chromatin Remodeling in Development and Disease
Michael Boyle, DVM, DACVP, DABT, NIEHS, Research Triangle Park, NC

Epigenetics and the Microbiome
Theresa Alenghat, VMD, PhD, DACVP, University of Pennsylvania, Philadelphia, PA

Session 6: Environmental Toxicologic Pathology and Prediction of Human Health Risks
Co-Chairs: Charles Wood, DVM, PhD, DACVP, US EPA, Research Triangle Park, NC; Wanda Haschek-Hock, BVSc, PhD, DACVP, DABT, FIATP, University of Illinois, Urbana, IL; and David Malarkey, DVM, PhD, DACVP, NIEHS, Research Triangle Park, NC

Evaluating the impact of environmental factors on human health and disease is an integral part of translational science. For toxicologic pathologists, the study of environmental health effects and their mechanisms, and the use of this information in risk assessment and policy decisions, involves a range of different animal models and bioassays. Recently, there has also been increased interest in the use of higher-throughput alternative models, including *in vitro* and computational approaches, for assessing human health hazards due to environmental agents. This session will focus on translational applications of data derived from different model systems used in hazard identification and risk assessment of environmental compounds. Specific areas of focus will include current regulatory issues in chemical safety, evaluation of environmental obesogens and metabolic disruptors, emerging approaches for testing of reproductive toxicants, comparative pathology of rodent lung tumors, and health effects of phycotoxins from harmful algal blooms.

Current and Emerging Issues in Chemical Safety
Jeffrey Morris, PhD, US EPA, Research Triangle Park, NC

Interface of Air Pollution, Diabetes, and the Metabolic Syndrome: Translational Studies on Health Effects
Jack Harkema, DVM, PhD, DACVP, Michigan State University, East Lansing, MI

Comparative Pathology of Environmentally Induced Lung Tumors
Arun Pandiri, BVSc&AH, MS, PhD, DACVP, EPL, Inc./NTP, Research Triangle Park, NC; and Samuel M. Cohen, MD, PhD, University of Nebraska Medical Center, Omaha, NE

Next Generation Testing for Reproductive Toxicants
Matthew Martin, PhD, US EPA, Research Triangle Park, NC

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Health Effects of Phycotoxins from Harmful Algal Blooms
Olga M. Pulido, MD, MSc, ABPath, FIATP, University of Ottawa, Ottowa, Ontario, Canada

Thursday, June 26

Session 7: The Challenges of Safety Evaluation in Populations with Concurrent Disease
Co-Chairs: LuAnn McKinney, DVM, DACVP, US FDA/CDER/OND/DNP, Silver Spring, MD; and John E. Sagartz, DVM, PhD, DACVP, Seventh Wave Laboratories, Chesterfield, MO

Comorbidities in patient populations include overt cardiovascular disease, obesity, or diabetes, singly or in combination with other, less prominent conditions. When xenobiotics are administered, drug-related adverse events in patients with concurrent disease may be detected during clinical trials. Often adverse responses are detected by post-marketing surveillance, by meta-analysis of clinical case reports, or through data mining by regulatory agencies. The challenge is to detect, predict, or ameliorate these adverse events in nonclinical studies before patients are adversely affected. This session will explore the current methodologies applied through the translational arc: the pharmacovigilance methodologies applied to clinical and post-marketing studies followed by discussion of the safety decisions in translation from normal animal to normal humans to patient populations to patients with concurrent disease. The session will also focus on the utility of studies in normal animals to predict adverse events in patient populations and review the efficacy of animal models of human disease to detect adverse safety signals. A panel discussion of these current challenges and how nonclinical studies may meet those challenges will follow.

The Evidentiary Basis of Safety Decisions from Normal Animal to Comorbid Patient
Ellis Unger, MD, CDER, US FDA (Office of Drug Evaluation, I), Silver Spring, MD

Overview of Pharmacovigilance Methodologies to Detect Adverse Clinical Events in Comorbidities
Ajay Singh, MD, GlaxoSmithKline, Collegeville, PA

How the Early Preclinical Safety Assessment Can Identify Safety Issues and Minimize or Circumvent Adverse Safety Events
John E. Sagartz, DVM, PhD, DACVP, Seventh Wave Laboratories, Chesterfield, MO

The Utility of Animal Models of Disease in Safety Evaluation of Comorbidities
Sherry J. Morgan, DVM, PhD, DACVP, AbbVie, Inc., Alto, NM

Roundtable: What Can Preclinical Sciences Do to Meet This Clinical Challenge?