Toxicologic Pathology of the Digestive Tract and Pancreas

Scientific Co-Chairs: Dimitry M. Danilenko, DVM, PhD, DACVP, Genentech, Inc., South San Francisco, CA, Mark F. Cesta, DVM, PhD, DACVP, National Institute of Environmental Health Sciences, Research Triangle Park, NC, and Prashant R. Nambiar, BVSc&AH, MS, PhD, DACVP, DABT, Pfizer Inc., Groton, CT

The 2013 STP Scientific Symposium will cover fundamental biology and recent innovations in the toxicologic pathology of the digestive tract and pancreas.

The focus of this international meeting is to correlate advances in the morphologic evaluation and integration of findings in the digestive tract and pancreas with functional, cellular, and molecular knowledge in a series of plenary and poster sessions. The meeting will provide a venue for interactive discussion of the current state of knowledge in both conventional and specialized nonclinical safety studies of the digestive tract and pancreas. Core sessions will include Normal Digestive Tract Functional Anatomy and Physiology, Inflammatory Bowel Disease, Digestive Tract Toxicity and Risk Assessment, Digestive Tract Carcinogenesis, Biomarkers of Digestive Tract and Pancreatic Injury and Disease, and Pancreatic Toxicity and Carcinogenesis. The symposium keynote address will focus on the gut microbiome and its critical interactions with the digestive tract epithelium and the mucosal immune system during health and disease.

Individual presentations will focus on a mix of traditional and contemporary strategies for the pathophysiologic and toxicologic evaluation of the digestive tract and pancreas. The meeting will also provide a unique forum for reviewing recent progress in developing and optimizing best practices for routine and specialized toxicologic pathology evaluation of digestive tract and pancreas across academia and the pharmaceutical and chemical industries. The symposium will also feature practical case study presentations as part of two scientific sessions: the session on Digestive Tract Toxicity and Risk Assessment and the session on Pancreatic Toxicity and Carcinogenesis.

The digestive tract and pancreas are rapidly growing areas of toxicologic inquiry and regulatory concern, and this symposium promises to be a great opportunity to review and expand your knowledge in this important field.

Monday, June 17

Scientific Sessions

Monday Morning
- 8:00 AM–8:05 AM Symposium Welcome
- 8:05 AM–8:10 AM Introduction
- 8:10 AM–9:00 AM Keynote Address
  - Andrew Gewirtz, PhD, Georgia State University, Atlanta, GA

Session 1
- 9:00 AM–12:00 Noon Normal Digestive Tract Functional Anatomy and Physiology
  - Co-Chairs: Arlin Rogers, DVM, PhD, University of North Carolina at Chapel Hill, Chapel Hill, NC, and Piper Treuting, DVM, MS, DACVP, University of Washington, Seattle, WA

Meaningful interpretation and translation of results from animal models of digestive disease must be rooted in an understanding of the similarities and differences of normal structure and function of the gastrointestinal tract in different species. The esophagus, stomach, and small intestine are critical sites of food transport, enzymatic digestion, and nutrient absorption. Disruption of one of these compartments often has effects on adjacent ones (i.e., acid reflux and Barrett’s esophagus). An overview of the comparative morphology and physiology of each segment in small and large animals will be presented in order to provide meaningful context for the translation of experimental outcomes to human health. The role of the colon in physiology goes well beyond simple absorption of salt and water from ingesta prior to excretion from the body. The colon also has a systemic effect on energy homeostasis, lipid processing, and immune function. Because xenobiotics can alter mucosal signaling pathways, microfloral composition and immune responses, a review of the complex activities of the colon in health and disease will be presented to aid comparative pathologists engaged in drug development. Regenerative medicine is an emerging industry requiring understanding by toxicologic pathologists. The ability to regenerate tubular organs, including the digestive tract, requires an ability to distinguish tissue changes associated with regeneration from those that may be interpreted as abnormal or of a safety concern. Morphological changes associated with tubular organ (e.g., intestine) regeneration, and native-like tissue structures, will be discussed along with mechanisms of the regenerative process.
### Monday Afternoon

#### Session 2
**1:30 PM–5:00 PM**

**Inflammatory Bowel Diseases**

*Co-Chairs: Lauri Diehl, DVM, PhD, DACVP, Genentech, South San Francisco, CA, and Brad Bolon, DVM, MS, PhD, DACVP, DABT, FATS, FIATP, The Ohio State University, Columbus, OH*

Inflammatory bowel disease (IBD) afflicts as many as 1 in every 200 people in Europe and as many as 1 in every 300 in North America. The underlying pathogenesis is a complex mix of genetic and environmental factors which result in the loss of tolerance to commensal gut flora and poorly-controlled mucosal inflammation. The mechanisms influencing whether or not IBD is limited to the colon (e.g., ulcerative colitis) or has a broader distribution (e.g., Crohn’s disease, which can affect any part of the gastrointestinal tract) have yet to be defined. One major paradigm of growing importance to IBD is the interaction between immune cells, the mucosal epithelium, and the intestinal microbiome. This session will begin with a discussion of pathogenesis, current treatments and unmet medical needs for IBD. The next two talks will examine the innate immune system and its role in gastrointestinal health, particularly its relationship with the gut commensal organisms. The final speaker will explore animal models of IBD, emphasizing their biology and pathology as they apply to the discovery and development of new anti-IBD therapies.

<table>
<thead>
<tr>
<th>Time</th>
<th>Event Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:30 PM–1:35 PM</td>
<td>Introduction</td>
</tr>
<tr>
<td>1:35 PM–2:15 PM</td>
<td>Overview of IBD and Evolving T Cell-based Therapy: An Old Player in the Current Understanding and Treatment of IBD</td>
</tr>
<tr>
<td>Zili Zhang, MD, PhD, Case Western Reserve University, Cleveland, OH</td>
<td></td>
</tr>
<tr>
<td>2:15 PM–3:05 PM</td>
<td>Innate Immune System Interactions with the Gastrointestinal Microbiome</td>
</tr>
<tr>
<td>David Underhill, PhD, Cedars Sinai, Los Angeles, CA</td>
<td></td>
</tr>
<tr>
<td>3:05 PM–3:35 PM</td>
<td>Innate Immune System in Mucosal Immunity</td>
</tr>
<tr>
<td>Charles A. Parkos, MD, PhD, Emory University, Atlanta, GA</td>
<td></td>
</tr>
<tr>
<td>3:35 PM–4:20 PM</td>
<td>Break</td>
</tr>
</tbody>
</table>

---

**Career Development Lunchtime Series**

**12:30 PM–1:30 PM**

**Career Paths to Nontraditional Roles in Toxicologic Pathology**

*Presented by the STP Career Development and Outreach Committee*  
*(Free Event, registration required)*
<table>
<thead>
<tr>
<th>Time</th>
<th>Session 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00 AM–12:00 Noon</td>
<td><strong>Digestive Tract Toxicity and Risk Assessment</strong></td>
</tr>
<tr>
<td><strong>Co-Chairs:</strong> Zaheer A. Radi, DVM, MBA, PhD, DABT, DACVP, Pfizer Worldwide R&amp;D, Cambridge, MA, and Mehrdad Ameri, DVM, MS, PhD, DACVP, Amgen, Thousand Oaks, CA</td>
<td></td>
</tr>
</tbody>
</table>

Drug toxicity is one of the major causes of costly late-stage development failures and market withdrawals. Xenobiotics-induced toxic effects on the gastrointestinal (GI) tract can be one of the liabilities associated with novel therapeutics. GI toxicity preclinical to clinical translation, in vitro derisking strategies, and sympathetic neuroimmune interactions will be discussed in this session. Appropriate preclinical toxicology approaches to detect adverse GI events and to evaluate the relevance of preclinical findings to the clinical setting is critical to reduce attrition due to GI toxicity. Speakers from academia and pharmaceutical industries will review the GI system in health and disease, GI neural circuits, neurotransmitters, and receptors involved in the sympathetic regulation of GI tract pathophysiology, derisking small molecule receptor targets, and GI tract risk assessment strategies. The session will conclude with a few practical case studies and pertinent examples of drug-induced GI tract toxicities encountered in drug development of novel therapeutics.

<table>
<thead>
<tr>
<th>Time</th>
<th>Tuesday Afternoon</th>
</tr>
</thead>
<tbody>
<tr>
<td>11:10 AM–12:00 Noon</td>
<td><strong>Case Studies of Digestive Tract Toxicity</strong></td>
</tr>
<tr>
<td>Zaheer A. Radi, DVM, MBA, PhD, DABT, DACVP, Pfizer Worldwide R&amp;D, Cambridge, MA, Mehrdad Ameri, DVM, MS, PhD, DACVP, Amgen, Thousand Oaks, CA, and Prashant R. Nambiar, BVSc&amp;AH, MS, PhD, DACVP, DABT, Pfizer, Groton, CT</td>
<td></td>
</tr>
</tbody>
</table>

**Tuesday Afternoon** | **Free Time**

**Tuesday, June 18**
### Wednesday, June 19

#### Wednesday Morning

**Session 4**

8:00 AM–12:00 Noon

**Digestive Tract Carcinogenesis**

Co-Chairs: Jerrold M. Ward, DVM, PhD, DACVP, Global Vet Pathology, Montgomery Village, MD, and Kishore Guda, DVM, PhD, Case Western Comprehensive Cancer Center, Cleveland, OH

The session covers comprehensive aspects of digestive tract carcinogenesis in humans and laboratory animals. The pathology and molecular aspects of carcinogenesis in the esophagus, stomach, and colon will be reviewed with the aim of targeting key molecular pathways for cancer chemoprevention, and developing novel molecular biomarkers for early detection of cancer. Since both genetics and environment play an equally important role in gastrointestinal cancer predisposition, the effect of diet in modulating cancer risk will be discussed. Furthermore, preclinical animal models to study the etiology, pathogenesis, methods of prevention and therapy with goals of applications to humans will be presented.

<table>
<thead>
<tr>
<th>Time</th>
<th>Title</th>
<th>Speaker</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00 AM–8:05 AM</td>
<td>Introduction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8:05 AM–8:50 AM</td>
<td>Biomarkers and the Pathogenesis of Gastrointestinal Cancer</td>
<td>William M. Grady, MD, Fred Hutchinson Cancer Center, Seattle, WA</td>
<td></td>
</tr>
<tr>
<td>8:50 AM–9:35 AM</td>
<td>Targeting Mutated Pathways for Colon Cancer Therapy</td>
<td>Zhenghe John Wang, PhD, Case Western Comprehensive Cancer Center, OH</td>
<td></td>
</tr>
<tr>
<td>9:35 AM–10:10 AM</td>
<td>Rodent Intestinal Carcinogenesis: Pathology and Evaluation Methods for Nondclinical Models</td>
<td>Jerrold M. Ward, DVM, PhD, DACVP, Global Vet Pathology, Montgomery Village, MD</td>
<td></td>
</tr>
<tr>
<td>10:10 AM–10:30 AM</td>
<td>Break</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Wednesday Afternoon

**Practical Application of MRI Histology in Toxicologic Pathology**

12:00 Noon–1:30 PM

Sponsored by IATP and STP (Free Event, advance registration required*)

Isotropic 3-D in vivo MRI images of rats and mice as well as images of formalin-fixed whole tissue specimens are possible with compact scanners that can now be safely used in an animal room, a histology laboratory, or a pathologist’s office. Compact MRI in vivo imaging provides an opportunity for longitudinal evaluation of tissue changes and tumor development in experimental animal models. Imaging of whole fixed tissue samples permits a thorough examination of multiple digital slices with subsequent volumetric measurement of 3-dimensional structures while leaving the specimen intact for subsequent conventional H&E histology. This session will provide examples of major organ system pathologies encountered in rodent toxicity and carcinogenicity studies with emphasis on how MRI imaging technology can serve as an important adjunct to conventional pathology evaluation. The objective will be to use rodent animal models and show live animal images followed by images of the fixed specimens from the same animal model and comparison with conventional H&E-stained sections.

*Session is limited to the first 75 attendees who preregister. Lunch will be provided.

---

*www.toxpath.org*
Biomarkers of Digestive Tract and Pancreatic Injury and Disease

Co-Chairs: Allison Vitsky, DVM, DACVP, Pfizer, San Diego, CA, and Florence Poitout, DVM, DACVP, DECVCP, Charles River Laboratories, Senneville, Quebec, Canada

Reliable, noninvasive biomarkers of toxicity are a crucial part of both preclinical and clinical studies, enhancing compound screening and dose selection and allowing for the development of novel drugs with optimal safety profiles. Recent advances in technology, including genomic and proteomic approaches, have improved the throughput and sensitivity of existing biomarker assays and have also helped to expand the biomarker toolkit. This session will commence with a review of commonly utilized digestive biomarkers in clinical veterinary settings, then progress to discussions of the ways that these and other novel biomarkers are being utilized to successfully detect and evaluate compound-associated gastrointestinal and pancreatic lesions in exploratory toxicity studies.

1:30 PM–1:35 PM Introduction
1:35 PM–2:15 PM Review of Commonly Used Clinical Pathology Parameters for General Gastrointestinal Disease
Michele Hooth, PhD, National Institute of Environmental Health Sciences, National Toxicology Program, Research Triangle Park, NC

2:15 PM–2:35 PM Student Speaker (TBD)
2:35 PM–3:00 PM Break
3:00 PM–3:40 PM Gastrointestinal Biomarkers in Nonclinical Safety Studies: Following Lesions at Different Levels of the Gastrointestinal Tract
Allison Vitsky, DVM, DACVP, Pfizer, La Jolla, CA

3:40 PM–4:30 PM miRNAs and Their Usefulness in Biomarker Evaluations
Amy H. Yang, PhD, DABT, Pfizer, La Jolla, CA

4:30 PM–5:00 PM Peptide Biomarkers of Exocrine Pancreatic Injury
Jennie L. Walgren, PhD, Lilly, Indianapolis, IN

5:30 PM–5:50 PM Awards Ceremony
5:50 PM–6:30 PM Annual Business Meeting
7:00 PM–9:00 PM President’s Reception

Thursday, June 20

Thursday Morning

Session 6

8:00 AM–12:00 Noon

Pancreatic Toxicity and Carcinogenesis

Co-Chairs: Arun R. Pandiri, BVSc&AH, MS, PhD, DACVP, Experimental Pathology Laboratories, Inc., Durham, NC, and A. Eric Schultze, DVM, PhD, DACVP, FIATP, Eli Lilly and Company, Indianapolis, IN

The goals of this session are to provide an update on pancreatic toxicological pathology, to present novel information on responses of the pancreas to xenobiotics, and to provide a current understanding on pancreatic tumorigenesis. The session will begin with an overview of anatomy and physiology of the pancreas as well as pancreatic responses to xenobiotics. The session will highlight various rodent models used to study nonneoplastic pancreatic diseases and the molecular pathogenesis of pancreatic tumorigenesis. In addition, real case studies emphasizing associated liabilities and derisking activities will be used to illustrate the practical aspects of pancreatic toxicity. By the end of the session, the audience will develop a better appreciation for the pancreas as a target organ in toxicological studies.

8:00 AM–8:05 AM Introduction
8:05 AM–8:45 AM Overview of Pancreatic Function with Respect to Pharmacology/Toxicology
Arun R. Pandiri, BVSc&AH, MS, PhD, DACVP, Experimental Pathology Laboratories, Inc., Durham, NC
8:45 AM–9:25 AM  **Pathogenesis of Pancreatic Cancer: Lessons Learnt from Animal Models**  
Charles L. Murtaugh, PhD,  
Huntsman Cancer Institute,  
University of Utah, Salt Lake City, UT

9:25 AM–10:05 AM  **Pancreatic Toxicity at the Exocrine-Endocrine Interface**  
Karrie A. Brenneman, DVM, PhD, DACVP, Pfizer, Andover, MA

10:05 AM–10:35 AM  **Break**

10:35 AM–11:15 AM  **Animal Models of Nonneoplastic Pancreatic Diseases**  
John R. Foster, BSc, PhD, FRCPath, FIATP, HonFBTS, AstraZeneca, Macclesfield, Cheshire, UK

11:15 AM–12:00 Noon  **Case Examples of Pancreatic Toxicities as Liabilities and Derisking Activities**  
Chandikumar S. Elangbam, BVSc, PhD, DACVP, GlaxoSmithKline, Research Triangle Park, NC

12:00 Noon  **Meeting Adjourned**