Toxicologic Pathology of the Digestive Tract and Pancreas

The 2013 STP Scientific Symposium, to be held on June 16–20 in Portland, Oregon, 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

Keynote Address: Andrew Gewirtz, PhD, Georgia State University, Atlanta, GA

Session 1: Normal Digestive Tract Functional Anatomy and Physiology
Co-Chairs: Arlin Rogers, DVM, PhD, DCVP, University of North Carolina, 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 (for example, 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.

Functional Anatomy (Including basic histomorphology)

Upper Digestive Tract  
Howard Gelberg, DVM, PhD, DACVP, Oregon State University, Corvallis, OR

Lower Digestive Tract  
Rani Sellers, DVM, PhD, Albert Einstein College of Medicine, Bronx, NY

Regenerative Medicine  
Timothy A. Bertram, DVM, PhD, Tengion Labs, Winston-Salem, NC

Session 2: Inflammatory Bowel Diseases  
Co-Chairs: Lauri Diehl, DVM, PhD, DACVP, Genentech, South San Francisco, CA, and Brad Bolon, DVM, MS, PhD, DACVP, 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.

Clinical Overview/Current Therapies/Unmet Need  
Zili Zhang, MD, PhD, Oregon Health and Science University, Portland, OR

Innate Immune System Interactions with the GI microbiome  
David Underhill, PhD, Cedars Sinai, Los Angeles, CA

Innate Immune System in Mucosal Immunity  
Charles A. Parkos, MD, PhD, Emory University, Atlanta, GA

Animal Models: Challenges of Modeling Human Disease  
Lauri Diehl, DVM, PhD, DACVP, Genentech, South San Francisco, CA
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 de-risking 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 industry will review the GI system in health and disease, GI neural circuits, neurotransmitters and receptors involved in the sympathetic regulation of GI tract pathophysiology, de-risking small molecule receptor targets and GI tract risk assessment strategies. The session will conclude with few practical case studies and pertinent examples of drug-induced GI tract toxicities encountered in drug development of novel therapeutics.

**Digestive Tract Toxicity: Adverse Events and Preclinical to Clinical Translation**
Judit E. Markovits, DVM, PhD, Novartis Institutes for Biomedical Research, Cambridge, MA

**Digestive Tract Toxicity In Vitro: Small Molecule Receptor Target Associated Digestive Tract Toxicity and Derisking Strategies**
Richard A. Westhouse, DVM, PhD, Bristol-Myers Squibb, Princeton, NJ

**Digestive Tract Neuroimmune Interactions in Health and Disease**
Alan E. Lomax, DVM, PhD, Queens University, Ontario, Canada

**Case Studies of Digestive Tract Toxicity:**
Zaher A. Radi, PhD, DACVP, Pfizer, Cambridge, MA, Mehrdad Ameri, DVM, MS, PhD, DACVP, Amgen, Thousand Oaks, CA, and Prashant Nambiar, BVSc&AH, MS, PhD, DACVP, Pfizer, Groton, CT

*Free Afternoon for Attendees*
Session 4: Digestive Tract Carcinogenesis

Co-Chairs: Jerry 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 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, pre-clinical animal models to study the etiology, pathogenesis, methods of prevention and therapy with goals of applications to humans will be presented.

Biomarkers and the Pathogenesis of Gastrointestinal Cancer
William M. Grady, MD, Fred Hutchinson Cancer Center, Seattle, WA

Targeting Mutated Pathways for Colon Cancer Therapy
Zhenghe John Wang, PhD, Case Western Comprehensive Cancer Center, Cleveland, OH

Rodent Intestinal Carcinogenesis: Pathology and Evaluation Methods for Preclinical Models
Jerrold M. Ward, DVM, PhD, DACVP, Global Vet Pathology, Montgomery Village, MD

Animal Models of Helicobacter-associated Gastric Cancer
James G. Fox, DVM, Massachusetts Institute of Technology, Cambridge, MA

Diet, Genes and Microbes: Complexities of Colon Cancer Prevention
Diane F. Birt, PhD, Iowa State University Dept. of Food Science and Human Nutrition, Ames, IA

Session 5: 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.

Review of Commonly Used Clinical Pathology Parameters for General GI Disease
Jörg Steiner, DVM, PhD, DACVIM, DECVIM-CA, Texas A&M University, College Station, TX

GI Biomarkers in Nonclinical Safety Studies: Following Lesions at Different Levels of the GI Tract
Allison Vitsky, DVM, DACVP, Pfizer, La Jolla, CA

miRNAs and Their Usefulness in Biomarker Evaluations
Amy H. Yang, PhD, DABT, Pfizer, La Jolla, CA

Peptide Biomarkers of Exocrine Pancreatic Injury
Jennie L. Walgren, PhD, Lilly, Indianapolis, IN
Session 6 Pancreatic Toxicity and Carcinogenesis
Co-Chairs: Arun Pandiri, BVSc&AH, MS, PhD, National Institute of Environmental Health Sciences/National Toxicology Program, Research Triangle Park, NC, and Eric Schultze, DVM, PhD, DACVP, 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 non-neoplastic 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 pancreas as a target organ in toxicological studies.

Overview of Pancreatic Function with Respect to Pharmacology/Toxicology
Arun Pandiri, BVSc&AH, MS, PhD, National Institute of Environmental Health Sciences/National Toxicology Program, Research Triangle Park, NC

Pathogenesis of Pancreatic Cancer: Lessons Learnt from Animal Models
Charles L. Murtaugh, PhD, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT

Pancreatic Toxicity at the Exocrine-Endocrine Interface
Karrie A. Brenneman, DVM, PhD, DACVP, Pfizer, Andover, MA

Animal Models of Non-Neoplastic Pancreatic Diseases
John R. Foster, BSc, PhD, FRCPath, FIATP, HonFBTS, Astra Zeneca, Macclesfield, Cheshire, United Kingdom

Case Examples of Pancreatic Toxicities as Liabilities and Derisking Activities
Chandikumar S. Elangbam, BVSc, PhD, GlaxoSmithKline, Research Triangle Park, NC