SATURDAY, JUNE 13

9:00 AM–4:30 PM

NTP Satellite Symposium: Pathology Potpourri

Chair: Susan A. Elmore, MS, DVM, DABT, FIATP, DACVP, NTP/NIEHS, Research Triangle Park, NC

The objective of this interactive symposium is to provide continuing education on interpreting pathology slides, to generate lively and productive conversation, and to have a good time. During each talk, the speakers will project a series of images of lesions on one screen with a choice of diagnoses/answers on a separate screen. The members of the audience will then vote using wireless keypads and the results will be displayed on the screen. Time is allowed for discussion after each voting session.

SUNDAY, JUNE 14

Career Development Workshop (Sunday AM)

8:00 AM–12:00 Noon

CE1 (Sunday AM)

8:00 AM–12:00 Noon

Vaccine Development from the Pathologist Perspective

Co-Chairs: Rani Sellers, DVM, PhD, DACVP, Pfizer Inc., Pearl River, NY; and Cynthia M. Rohde, PhD, DABT, Pfizer Inc., Pearl River, NY

The design and execution of toxicology studies supporting vaccine development have several unique elements relative to the conduct of traditional small molecule- or monoclonal antibody-supporting studies. This course is designed to give an overview of vaccine development, with emphasis on the regulatory guidances and special considerations in vaccine development (prophylactic and therapeutic), study design (including species selection), unique technical considerations, and anatomic and clinical pathology findings.

8:00 AM–8:05 AM
Introduction

8:05 AM–8:40 AM
Introduction to Vaccine Development
Cynthia M. Rohde, PhD, DABT, Pfizer Inc., Pearl River, NY

8:40 AM–9:05 AM
Animal Models to Support Vaccine Development
Rani Sellers, DVM, PhD, DACVP, Pfizer Inc., Pearl River, NY

9:05 AM–9:35 AM
Points to Consider in Vaccine Study Design and Implementation
Keith G. Nelson, DVM, PhD, DACVP, Charles River Laboratories, Mattawan, MI

9:35 AM–10:05 AM
Break

10:05 AM–10:55 AM
Anatomic and Clinical Pathology Interpretation and Correlations
Niraj K. Tripathi, BVSc, MVSc, PhD, DACVP, Covance, Madison, WI; and Bindu Bennet, DVM, MSc, MS, PhD, Voyager Therapeutics, Cambridge, MA

10:55 AM–11:25 AM
Determining Adversity: Contributions of Local Tolerance, Acute Phase Reactants, and Systemic Reactivity
Panel Presentation

11:25 AM–12:00 Noon
Panel Discussion

CE2 (Sunday AM)

8:00 AM–12:00 Noon

No Bones About It: Considerations for Bone Toxicity, Healing, and Remodeling Studies

Co-Chairs: Kathleen A. Funk, DVM, PhD, DACVP, EPL, Inc., Sterling, VA; and Maralee McVean, PhD, DABT, Inotiv, Fort Collins, CO

This course will focus on bone toxicity as a potential off-target effect based on the class of compound or an early and unexpected pathology signal rather than on drugs specifically designed to affect bone. The first presentation will cover normal anatomy and histology of the various bones which may be affected by drug administration and introduce animal models as a strategy to elucidate bone issues. A discussion of the various tools used to monitor bone toxicity, healing, and remodeling will be considered as they relate or drive the study design including model, species selection, and age followed by a regulatory perspective on strategies to de-risk compounds with potential bone effects. Finally, a synopsis of the type of pathologic changes seen in bone together with various histopathologic techniques for processing and evaluating bone and integrating these pathologic changes with the other tools for measuring bone toxicity will be discussed. Pathology characteristic of certain drug classes will be covered.
8:05 AM–8:50 AM
More Than a Framework: Understanding Bone Biology and Histology
Corinne Metzger, PhD, Indiana University Medical School, Indianapolis, IN

8:50 AM–9:35 AM
Considerations for Study Design and Tools Used to Evaluate Changes to Bone
Aurore Varela, DVM, MSc, DABT, Charles River Laboratories, Senneville, Quebec, Canada

9:35 AM–10:05 AM
Break

10:05 AM–10:50 AM
Regulatory Approaches to the Nonclinical Evaluation of Drug-Related Bone Toxicity
Gemma Kuijpers, PhD, CDER, US FDA, Silver Spring, MD

10:50 AM–11:35 AM
Pathology of Bone: Changes Associated with Different Classes of Compounds
Kathryn E. Gropp, DVM, PhD, DACVP, Pfizer Inc., Groton, CT

11:35 AM–12:00 Noon
Panel Discussion

CE3 (Sunday PM)

1:30 PM–5:30 PM
Antibody Drug Conjugates (ADCs) as Cancer Therapies
Co-Chairs: William O. Iverson, DVM, AstraZeneca, Faber, VA; and Nancy E. Eversd, DVM, DACVP, Seattle Genetics, Bothell, WA

Antibody-drug conjugates (ADCs), which use a specific antibody to deliver a toxic payload to target cells, hold great promise to increase efficacy and reduce adverse side effects, especially for oncology drugs. Six ADC molecules have received marketing approval in the US over the past 18 years. Nonclinical safety assessment has proven challenging as many ADCs still have steep dose-response curves and low therapeutic indices. Toxicities in many different organs and tissues have been seen, including bone marrow, skin, liver, kidney, eye, gastrointestinal tract, and nervous system. ADC-related toxicities may be more challenging to predict and manage than those seen with small molecules or unconjugated antibodies. This has led to more sophisticated engineering of antibodies, linkers, and drugs to increase internalization of drug by target cells, decrease off-target toxicity, and decrease bystander effects. This course will give an overview of synthesis and mechanisms of representative ADCs, and the clinical and anatomic pathology findings associated with different classes of agents, including immunomodulatory molecules and PROTACs.

1:30 PM–1:35 PM
Introduction

1:35 PM–2:25 PM
Immune Modulatory Activity of Traditional and Nontraditional ADCs
Shyra J. Gardai, PhD, Seattle Genetics, Bothell, WA

2:25 PM–3:15 PM
Recent Progress in Antibody Drug Conjugates and PROTACs as New Modalities: Application to Oncology
Drug Discovery
Lakshmaiah Gingipalli, PhD, AstraZeneca, Waltham, MA

3:15 PM–3:45 PM
Break

3:45 PM–4:35 PM
Clinical Pathology Effects of Antibody Drug Conjugates in Toxicology Studies
Niraj K. Tripathi, BVSc, MVSc, PhD, DACVP, Covance, Madison, WI

3:45 PM–4:35 PM
Anatomic Pathology Associated with Antibody Drug Conjugates
Matthew D. Smith, DVM, PhD, DACVP, Charles River Laboratories, Reno, NV

CE4 (Sunday PM)

1:30 PM–5:30 PM
Sponsored by the American College of Toxicology (ACT)
Co-Chairs: Michael K. Pugsley, PhD, FBPhS, DSP, Cytokinetics, South San Francisco, CA; and Steve Tichenor, PhD, Charles River Laboratories, Reno, NV

This continuing education course will include lectures that describe fundamental areas of safety pharmacology studies (CNS, Respiratory, Cardiovascular systems) for both new chemical entities (NCE) as well as biotechnology-derived products. It will also include some discussion of clinical issues (and methods) as well as novel non-clinical methods and approaches that may be added to the core ‘battery’ of tests used to explore the safety of novel therapeutic agents. Attendees will be introduced to discussion regarding the role safety pharmacology has as an integral component within the safety program for drug development. We will also introduce the Comprehensive In Vitro Proarrhythmia Assay (CIPA) cardiovascular paradigm being developed for hazard identification, elimination and risk assessment that would help to obviate conduct of the clinical “Through QT” (TQT) study. Furthermore, this course will provide attendees with a crucial resource that explains the important role safety pharmacology has in the overall pharmaceutical drug development process.

1:30 PM–1:35 PM
Introduction

1:35 PM–2:25 PM
An Introduction to the Principles and Practice of Safety Pharmacology
Michael K. Pugsley, FBPhS, PhD, DSP, Cytokinetics, South San Francisco, CA
The bone marrow is the soft, supple, highly vascular tissue found within bone cavities. There are two types of bone marrow tissues. The yellow marrow, consisting predominantly of adipose cells, and the red marrow, where the hematopoietic stem cells reside and where blood cell production (i.e., hematopoiesis) primarily occurs. The major function of the bone marrow is to generate blood cells and, on average, bone marrow can generate billions of new blood cells daily. Bone marrow contains two main types of stem cells. Hematopoietic stem cells (HSC), found in red marrow, are responsible for the production of blood cells. Bone marrow mesenchymal stem cells (multipotent stromal cells) produce the non-blood cell components of marrow, including fat, cartilage, fibrous connective tissue, stromal cells that support blood formation, and bone cells. This morning session is planned to examine certain functions of the bone marrow, hematopoietic stem cells and hematopoiesis. First, an introductory presentation will provide an expanded description of bone marrow structure and function. The second presentation delves into an exploration of the hematopoietic process outside the confines of the bone marrow (e.g., extramedullary hematopoiesis). Following a brief break, the third presentation will focus on the role of the nervous system in the regulation of the HSC niche in the bone marrow. This effort is based on observations suggesting a critical function of adrenergic signals emerging from the sympathetic nervous system in HSC egress. Finally, focusing on stem cell niche interactions in skeletal muscle and bone marrow in the context of exercise and obesity, this session will end with a presentation looking at the external cues that regulate the cellular composition of the stem cell niche and how the changes in cellular composition of the stem cell niche regulate stem cell function.

**Session 1**

9:00 AM–12:00 Noon

**Bone Marrow Structure, Function, and Cell Biology—More Than Just the Basics**

*Co-Chairs: Gregory S. Travlos, DVM, DACVP, NIEHS/NTP, Research Triangle Park, NC; and Anne Provencher, DVM, MSc, DACVP, DECVP, FIATP, Charles River Laboratories, Sherbrooke, Quebec, Canada*

Hematology and bone marrow analysis is central to our understanding of the hematopoietic system and how it responds to insults, and this session will provide a review of current and novel approaches for the evaluation of the hematopoietic system in the context of nonclinical investigations. The session will begin with a discussion on histological and cytological bone marrow evaluations, providing information around their similarities and differences as well as guidance on what types of interpretations, correlations, and attributions can be made using each method. This will be followed by information on novel approaches for evaluation of the hematopoietic system using automated hematology analyzers, including details around the quantitative assessment of bone marrow cell suspensions as well as introducing several newly available hematology parameters. Several exciting emerging technologies will also be covered, beginning with the application of *in vitro* screening assays to detect hematopoietic cytotoxicity and elucidate certain mechanisms of toxicity. This will be followed by a discussion on intravital microscopy and live cell imaging and how
these methods can assist with de-risking hematopoiesis-associated safety concerns. The session will conclude with a presentation on the application of cellular barcoding to hematopoietic stem and progenitor cells in nonhuman primate models.

1:30 PM–1:35 PM
Introduction

1:35 PM–2:05 PM
Bone Marrow Cytological and Histological Evaluations: Close or Distant Relatives?
Anne Provencher, DVM, MSc, DACVP, DECVP, FIATP, Charles River Laboratories, Sherbrooke, Quebec, Canada

2:05 PM–2:35 PM
Allison Vitsky, DVM, DACVP, Pfizer Inc., San Diego, CA; and Florence Poitout-Belissent, DVM, DACVP, DECVP, Charles River Laboratories, Senneville, Quebec, Canada

2:35 PM–3:10 PM
In Vitro Hematopoietic Cells Toxicity Assays
Wendy Hu, PhD, Pfizer Inc., San Diego, CA

3:10 PM–3:40 PM
Break

3:40 PM–4:15 PM
Intra Vital Microscopic and Live Cell Imaging—Neutrophils, Extracellular Traps, and Cellular Toxicity
Madhu Sirivelu, BVSc, PhD, DACVP, Pfizer Inc., Andover, MA

4:15 PM–5:00 PM
Hematopoietic Stem and Progenitor Cells Barcoding
Cynthia E. Dunbar, MD, NHLBI, NIH, Bethesda, MD

Annual Business Meeting and Town Hall
5:30 PM–7:00 PM

Mystery Slide Session: Hematopoietic Pathology
7:30 PM–9:30 PM
Co-Chairs: Tara P. Arndt, DVM, DACVP, Covance, Madison, WI; and Kyathanahalli Janardhan, BVSc, MVSc, PhD, DACVP, AbbVie, North Chicago, IL

TUESDAY, JUNE 16

Session 3
8:00 AM–12:00 Noon
Mechanisms of Decreased Erythropoiesis and Erythroid Cell Injury
Co-Chairs: Lila Ramaiah, DVM, PhD, DACVP, Pfizer Inc., Pearl City, NJ; and A. Eric Schultze, DVM, PhD, DACVP, FIATP, Eli Lilly and Company, Indianapolis, IN

Deleterious effects on erythrocytes are among the most commonly observed in preclinical animal toxicity studies. Despite their apparent simplicity and ease of analysis, there is more to erythrocytes than meets the eye. Mechanisms of erythrotoxicity extend beyond blood loss and cytotoxicity and are discerned using a complex array of endpoints beyond hematocrit and bone marrow histopathology.

This session will delve into the mechanisms of erythrotoxicity, with emphasis on decreased erythropoiesis and erythroid cell injury. An introductory description of erythropoiesis will be followed by an example of deep transcriptomics and chromatin profiling to characterize erythrocyte differentiation using functional studies of GATA1, a specific master regulator. The second presentation will discuss investigations characterizing p38 MAP kinase inhibitor-induced disruption of erythroid maturation. Immediately prior to the break, we welcome a guest presentation by a student member/trainee. We hope that all meeting attendees will participate and provide an attentive audience for our potential future colleagues. Immediately after the preplanned break, the fourth presentation will discuss mechanisms and detection of erythrocyte injury, with focus on osmotic fragility due to dyslipidemia. The session will conclude with a case presentation of morphologic, numeric and functional erythrocyte abnormalities caused by the dietary supplement, black cohosh.

8:00 AM–8:10 AM
Introduction
Lila Ramaiah, DVM, PhD, DACVP, Pfizer Inc., Pearl City, NJ; and A. Eric Schultze, DVM, PhD, DACVP, FIATP, Eli Lilly and Company, Indianapolis, IN

8:10 AM–9:00 AM
Mechanisms of Physiologic and Pathologic Erythropoiesis and Functional Studies of GATA1
Leif Ludwig, MD, PhD, Boston Children’s Hospital and Harvard Medical School, Cambridge, MA

9:00 AM–9:45 AM
Effects of p38 MAP Kinase Inhibitors on the Differentiation and Maturation of Erythroid Progenitors
Deidre A. Dalmas, MS, PhD, GlaxoSmithKline, Collegeville, PA

9:45 AM–10:00 AM
Student Speaker

10:00 AM–10:30 AM
Break
### Session 4

8:00 AM–12:00 Noon

**To Clot or Not to Clot: Deepening Our Understanding of Alterations in the Hemostatic System**

**Co-Chairs:** Karrie A. Brenneman, DVM, PhD, DACVP, Pfizer Inc., Cambridge, MA; and William J. Reagan, PhD, DACVP, Pfizer Inc., Groton, CT

In response to vascular injury, there is a delicate balance between the formation of clots that keep hemorrhage in check and fibrinolysis that prevents deleterious formation of thrombi/emboli. Administration of proposed therapeutic or toxic substances can disrupt this homeostatic equilibrium directly or indirectly resulting in hemorrhage, thrombosis, or both. Evaluation of these perturbations and understanding their mechanism of toxicity can be challenging for the clinical and anatomic pathologist alike. This session discusses these challenges in the context of development of pro-coagulants, anti-coagulants, lipogenesis inhibitors, gene therapies for hemophilia, and antibody-drug conjugates as well as recent advances in platelet biology and preclinical biomarkers of hypercoagulable states.

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<td>Introduction</td>
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<td>8:05 AM–8:40 AM</td>
<td>Anatomic Pathologist’s View on the Development of Pro- and Anti-Coagulants</td>
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<td>8:40 AM–9:20 AM</td>
<td>The Sweet Side of Platelet Clearance</td>
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<td>9:20 AM–9:50 AM</td>
<td>The Effects of Lipogenesis Inhibitors on Platelet Production in Humans and Nonclinical Species</td>
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### Wednesday, June 17

#### Session 5

1:30 PM–5:00 PM

**Understanding Off-Target and Idiosyncratic Hematologic Effects in Toxicology Studies**

**Co-Chairs:** Nancy E. Everds, DVM, DACVP, Seattle Genetics, Bothell, WA; and Adam Aulbach, DVM, DACVP, Charles River Laboratories, Galesburg, MI

A variety of therapeutic modalities have the potential for off-target/unanticipated adverse effects on blood cell counts and/or hematologic function in nonclinical species and in humans. These effects are often indirectly related to the therapeutic agent and can be the result of aberrant cell activation, autoimmunity/immunogenicity, drug-dependent and independent immune responses, and/or downstream sequelae of cytokine and complement activation. This session will review key concepts related to the pathophysiology of off-target hematotoxicity including contemporary investigational approaches using case examples to emphasize key concepts.

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<td>1:30 PM–1:35 PM</td>
<td>Introduction</td>
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<td>1:35 PM–2:05 PM</td>
<td>Overview of Pathophysiologic Mechanisms Involved in Off-Target Hematologic Effects</td>
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<td>2:05 PM–2:55 PM</td>
<td>Idiosyncratic Drug-Induced Immune Neutropenia</td>
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<td>2:55 PM–3:10 PM</td>
<td>Student Speaker</td>
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3:10 PM–3:40 PM
Break

3:40 PM–4:00 PM
Case Presentation: Platelet Decreases in Cynomolgus Monkeys During Administration of ISIS 104838, a 2’-MOE-Modified Antisense Oligonucleotide
Padma K. Narayanan, DVM, MS, PhD, Ionis Pharmaceuticals, Carlsbad, CA

4:00 PM–4:40 PM
Hematologic Changes as Secondary Effects: Iron-ing Out the Impact of Inflammation, Stress, and Other Factors
William Siska, DVM, MS, DACVP, Amgen Inc., Sparks, NV

4:40 PM–5:00 PM
Case Presentation: Bone Marrow Toxicity of Palbociclib
Stephane Thibault, DVM, DACVP, DABT, Pfizer Inc., San Diego, CA

Award and Recognition Ceremony
5:30 PM–6:30 PM

President’s Reception
7:00 PM–9:00 PM

THURSDAY, JUNE 18

Session 6
8:00 AM–12:00 Noon

Hematopoietic Neoplasms and Clonal Hematopoiesis in the Setting of Drug Development

Co-Chairs: Michelle L. Lepherd, BVSc, PhD, DACVP, Genentech, South San Francisco, CA; and Dana B. Walker, DVM, DACVP, MS, PhD, Novartis Institute of Biomedical Research, Cambridge, MA

Hematopoietic neoplasia and clonal hematopoiesis are human disorders that have a high degree of unmet medical need. Research and drug development in these areas is rapidly evolving and becoming increasingly complicated as more is understood about the genomics and molecular biology of these conditions. This session will focus on hematolymphoid clonal conditions with emphasis on myeloproliferative and myelodysplastic disorders. The session will cover comparative classification of hematolymphoid neoplasia and dysplasia in laboratory animals and humans, including aspects of clinical pathology, anatomic pathology, molecular pathology, and genetics, as well as relevant animal models of the human conditions. Presentations will include that from an invited speaker from Duke University School of Medicine on the epigenetic mechanisms and role of X-chromosome inactivation (XCI) maintenance in regulation of transcription and chromatin structure in hematopoietic cells and the causal role of XCI loss in myeloproliferative neoplasia and myelodysplastic syndromes in mice. Presentations on the prevalence, and a practical approach to evaluation and interpretation of hematopoietic neoplasia in aging rodents in non-clinical carcinogenicity studies, and on the role of immunomodulatory drugs in promoting tumorigenesis, particularly hematological malignancies with consideration of immunologic components implicated, and for future drug development will be included.

8:00 AM–8:05 AM
Introduction

8:05 AM–8:50 AM
Tumors of the Hematolymphoid System
TBD

8:50 AM–9:25 AM
Animal Models of Hematopoietic Neoplasia
David Caudell, DVM, PhD, Wake Forest University, Winston-Salem, NC

9:25 AM–10:10 AM
Balancing X-Chromosome Dosage in Hematopoietic Cells: Mechanistic Insights and Impact on Cancer
Eda Yildirim, PhD, Duke University School of Medicine, Durham, NC

10:10 AM–10:40 AM
Break

10:40 AM–11:15 AM
Perspectives on Hematopoietic Neoplasia in Carcinogenicity Toxicology Studies
David A. Rehagen, DVM, DACVP, Charles River Laboratories, Mattawan, MI

11:15 AM–12:00 Noon
Immunomodulators and Cancer Risk Assessment
Hervé N. Lebrec, PharmD, PhD, DABT, Amgen Inc., South San Francisco, CA

12:00 Noon
Meeting Adjourned