SUNDAY, JUNE 16

CE1 (AM)

8:00 AM–12:00 Noon

Immunotoxicology from a Pathology Perspective

Co-Chairs: Tracey L. Papenfuss, DVM, MS, PhD, DACVP, *StageBio and* ***Daniel Weinstock, DVM, PhD, DACVP,*** *Self-Employed*

The field of immunotoxicology originated in the early 1970s when it was recognized that therapeutics and chemicals can affect the function of the immune system. While immunosuppression was a primary endpoint evaluated in early immunotoxicology evaluation, the field has evolved over time. With an increased understanding the role that the immune response plays in numerous diseases and the development of numerous therapies that are designed to modulate the immune system, the field of immunotoxicology looks very different than its beginnings half a century ago. In this course, we intend to provide pathologists with a better understanding of the current considerations pertaining to the pathologic evaluation of the immune system, clinical and anatomic pathology findings indicative of immunotoxic changes (as well as background or incidental findings), factors to consider in adversity determination, relevant toxicologic species and translational aspects relating to the immune system. The goal is to enable a holistic interpretation and provide concepts important for a weight-of-evidence (WOE) approach to be used during the development and regulatory review of therapeutics..

8:00 AM–8:05 AM	**Introduction**
8:05 AM–8:55 AM	**The Changing Landscape of Immune System Evaluation: From Immunotoxicology and How to Navigate in the Brave New Work of Immunotherapies.** *Tracey L. Papenfuss, DVM, MS, PhD, DACVP, StageBio*
8:55 AM–9:45 AM	**Relevant Tox Species and Translational Aspects Relating to Immune System** *Ashwini Phadnis Moghe, MS, PhD, DABT, Takeda*
9:45 AM–10:15 AM	**Break**
10:15 AM–11:05 AM	**Clinical and Anatomic Pathology Findings Indicative of Immunotoxicity with Common Background or Incidental Findings** *Lauren E. Himmel, DVM, PhD, DACVP, AbbVie*
11:05 AM–11:55 AM	**WOE (Weight of Evidence), Holistic Interpretation, Regulatory Guidances: Practical Approaches for Various Therapeutics** *Ana Goyos, PhD, The Janssen Pharmaceutical Companies of Johnson & Johnson*
11:55 AM–12:00 Noon	**Panel Discussion**

DTT Satellite Symposium: Pathology Potpourri (AM)

9:00 AM–12:00 Noon

Co-Chairs: Erin M. Quist, DVM, MS, PhD, DACVP, *Charles River Laboratories;* ***Mark F. Cesta, DVM, PhD, DACVP,*** *NIEHS; and* ***Robert Sills, DVM, PhD, DACVP,*** *NIEHS*

The objective of this interactive symposium is to provide continuing education on interpreting pathology slides and data, 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, and the results will be displayed on the screen. Time is allowed for discussion after each voting session.

Note: DTT is the NIEHS Division of Translational Toxicology.

CE2 (PM)

1:30 PM–5:30 PM

Nonclinical Safety Evaluation of Long-Acting Injectables (LAI) in Animal Models

Co-Chairs: ***Bhanu P. Singh, BVSc, MS, DACVP, DABT, FIATP,*** *Gilead Sciences, Inc. and* ***Keith G. Nelson, DVM, PhD, DACVP,*** *Inotiv*

Many pharmaceuticals are administered through short-acting formulations, necessitating frequent dosing. This can compromise patient compliance and elevate the risks of treatment failure due to irregular usage. The use of long-acting injectables (LAI) for consistent dosing of pharmaceuticals is an ever-growing field. The use of these long-lasting injectables is valuable in maintaining consistent dosing, ensuring patient compliance with dosing, and providing long-term pharmaceutical therapy with a single injectable treatment. This CE course will focus on nonclinical study design of long-term injectable compounds, with specific discussion of best practices for in-life evaluation and potential issues; best practices for sample collection and submission; and post-life evaluation and recommendations for pathology evaluation in non-clinical safety studies. The course will also cover nonclinical strategy for developing a long-acting Injectable drug product and clinical risk communication with some case studies.

1:30 PM–1:35 PM	**Introduction**
1:35 PM–2:00 PM	**Practical Considerations in Evaluating LAI Injection Site Reactions in Animal Models: Study Design and In-Life Evaluations** *Tyler Plachta, MS, Charles River Laboratories*
2:00 PM–2:30 PM	**Practical Considerations in Evaluating LAI Injection Site Reactions in Animal Models: Post-Life Considerations and Evaluation** *Keith G. Nelson, DVM, PhD, DACVP, Inotiv*
2:30 PM–3:15 PM	**Nonclinical Strategy for Developing a Long-Acting Injectable Drug Product** *Doris Zane, MS, PhD, DABT, Gilead Sciences, Inc., and Bhanu P. Singh, BVSc, MS, DACVP, DABT, FIATP, Gilead Sciences, Inc.*
3:15 PM–3:45 PM	**Break**
3:45 PM–4:30 PM	**Communicating the Clinical Risk of Injection Site Reactions (ISR) from LAI Drugs** *John L. Vahle, DVM, PhD, DACVP, Eli Lilly and Company*
4:30 PM–5:15 PM	**The Temporal Evolution and Characterization of Histopathology and Immunological Changes Associated with Five Different LAI Drug Nanosuspensions** *Ronnie Chamanza, BVSc, MSc, FRCPath, MRCVS, FIATP, Johnson & Johnson Innovative Medicine*
5:15 PM–5:30 PM	**Panel Discussion**

Career Development Workshop (PM)

1:30 PM–5:30 PM

US FDA Modernization ACT 2.0

Co-Chairs: Alycia Fratzke, DVM, PhD, DACVP, *Charles River Laboratories and* ***Leah Schutt, DVM, PhD, DACVP,*** *Genentech*

The US FDA Modernization ACT 2.0 was signed into law in December 2022 with overwhelming bipartisan support in Congress. Passage of the act resulted numerous popular news articles suggesting that animal testing is no longer required for new drugs. In reality, the law recognizes the many non-animal methods for novel drug assessment that may be used concertedly with animal testing and provides researchers the opportunity to use the most rigorous scientific methods available to bring safe and effective treatments to patients. In this session, the US FDA Modernization Act 2.0 and its impacts on drug development will be outlined and approaches for reducing animal testing, such as virtual control groups, *in vitro* modeling systems, and new approach methodologies, will be discussed.

Welcome Reception

5:30 PM–7:00 PM

MONDAY, JUNE 17

STP 43nd Annual Symposium Welcome

8:00 AM–8:10 AM

Keynote Presentation

8:10 AM–9:00 AM

James M. Wilson, MD, PhD, University of Pennsylvania

Session 1

9:00 AM–12:00 Noon

AAV-Based Therapies

Co-Chairs: Juliette Hordeaux, DVM, PhD, DECVP, *University of Pennsylvania and* ***Laurence O. Whiteley, DVM, PhD, DACVP,*** *Dyne Therapeutics*

Gene therapies hold great promise to treat diseases for which there are no available therapies or as improvements over currently available options. Several gene therapies have been approved by the US Food and Drug Administration (US FDA) and the European Medicines Agency (EMA) in recent years as the field progresses, and many more are in late-stage development. As more nonclinical and clinical data are collated, the understanding of AAV toxicities keeps on growing.

The AAV-Based Therapies session will begin with an overview of innate and adaptive immune responses to AAV vectors. This will then be followed by individual presentations focused on AAV toxicities in nonclinical studies and translational relevance. AAV toxicities observed in the eye, CNS, cardiovascular system, and those observed with systemic administration will be covered.

9:00 AM–9:30 AM	**AAV Immunology** *Ying Kai Chen, PhD, Harvard University*

9:30 AM–10:00 AM **AAV Eye Toxicity**
Helen S. Booler, BSc (Hons), BVetMed, DECVP, PhD, MRCVS, Novartis

10:00 AM–10:30 AM **AAV CNS Toxicity**
Brad Bolon, DVM, MS, PhD, DACVP, DABT, FATS, FIATP, FRCPath, GEMpath, Inc.

10:30 AM–11:00 AM **Break**

11:00 AM–11:30 AM **AAV Cardiovascular Toxicity**
Juliette Hordeaux, DVM, PhD, DECVP, University of Pennsylvania.

11:30 AM–12:00 Noon **Systemic AAV Toxicity**
Basel T. Assaf, BVSc, PhD, DACVP, Sanofi

Career Development Roundtable

12:30 PM–1:30 PM

Artificial Intelligence (AI) in the Workplace

***Co-Chairs: Elizabeth Clark, DVM, PhD, DACVP**, Boehringer-Ingelheim and **Jessica Grieves, DVM, PhD, DACVP**, Ionis Pharmaceuticals*

Artificial intelligence (AI) is the ability of computer software to mimic human judgement. Applications of AI in society and in the drug development and pathology fields are rapidly expanding. In this session, we will discuss how AI is currently being used and how it may be used in the future in pathology and nonclinical safety workflows. We will also discuss the impact of AI including how it has and will change the role and responsibilities of pathologists and other nonclinical safety scientists and training for these positions. Careers in computational pathology will also be discussed.

Session 2

1:30 PM–5:00 PM

Adoptive Cell Therapies

***Co-Chairs: Ingrid Cornax, DVM, PhD, MS, DACVP**, Altos Labs and **Brian E. McIntosh, PhD**, Labcorp*

Adoptive cell therapy is an exciting and rapidly growing area of drug development with indications including immuno-oncology, immunology, and regenerative medicine. The role of the Toxicologic Pathologist in support of this modality is unique due to the relative paucity of relevant *in vivo* model systems. This session will cover topics such as the pathogenesis of the most common platform-related safety issues: on- and off-target toxicity, cytokine-release syndrome (CRS), immune cell associated neurotoxicity (ICANS), and tumorigenicity, and how the pathologist uniquely adds value to assess these platform considerations in the preclinical space.

1:30 PM–1:35 PM **Introduction**

1:35 PM–2:15 PM **Role of Pathologist in Cell Therapy Safety Assessment**
Alessandra Piersigilli, DVM, PhD, DECVP, Takeda

2:15 PM–2:40 PM **Target Expression Profiling as Part of Cell Therapy Safety Assessment**
Vinicius S. Carreira, DVM, PhD, DACVP, DABT, Johnson and Johnson Innovative Medicines

2:40 PM–3:05 PM **Off-Target Screening of Biologics**
Frédéric Gervais, DVM, DECVP, Charles River Laboratories

3:05 PM–3:35 PM Break

3:35 PM–4:05 PM **Pathogenesis and Preclinical Assessment of Cytokine Release Syndrome**
Keith Mansfield, DVM, DACVP, Novartis BioMedical Research

4:05 PM–4:35 PM **Pathogenesis and Preclinical Assessment of ICANS**
Ingrid Cornax, DVM, PhD, MS, DACVP, Altos Labs

4:35 PM–5:00 PM **Panel Discussion**

Annual Business Meeting and Town Hall: Adversity 2.0

5:30 PM–7:00 PM

TUESDAY, JUNE 18

Session 3

8:00 AM–12:00 Noon

Targeted Delivery of siRNA and ASO-Based Therapies

Co-Chairs: Jessica Grieves, DVM, PhD, DACVP, *Ionis Pharmaceuticals and* ***Adam O. Michel, DVM, MVSc, DVSc, DACVP,*** *Regeneron*

The concept of utilizing oligonucleotides for therapeutic purposes was first proposed over 30 years ago. Today, more than a dozen antisense oligonucleotides (ASOs) and small interfering RNA (siRNA) products have been approved for human use, with numerous others in various stages of clinical development. Challenges such as short half-life and the proinflammatory nature of unmodified oligonucleotides have been largely mitigated through advancements in medicinal chemistry. While the issue of limited biodistribution persists, rapid innovations in targeted delivery are addressing this concern. Direct delivery and conjugation are two highly successful, organ-specific strategies that are transforming the field of oligonucleotide therapeutics and increasing the number of diseases that can be treated with ASOs and siRNAs. In this session, following an overview of the field, speakers will focus on organ systems where targeted delivery of oligonucleotides is most advanced, including liver, CNS, lung, and muscle. Topics addressed will include toxicology findings, unique aspects of nonclinical development, and regulatory considerations. The session will conclude with an inspiring overview of nonprofit efforts to bring individualized oligonucleotide therapies to patients lacking other treatment options.

8:00 AM–8:10 AM	**Session Introduction** *Jessica Grieves, DVM, PhD, DACVP, Ionis Pharmaceuticals and Adam O. Michel, DVM, MVSc, DVSc, DACVP, Regeneron*
8:10 AM–8:40 AM	**Introduction to Oligonucleotides** *Martin Egli, PhD, Vanderbilt University*
8:40 AM–9:10 AM	**Nonclinical Safety of Liver-Targeting Oligonucleotides** *Maja M. Janas, PhD, DABT, Alnylam Pharmaceuticals*
9:10 AM–9:40 AM	**Nonclinical Safety of Eye-Targeting Oligonucleotides** *Adam O. Michel, DVM, MVSc, DVSc, DACVP, Regeneron*
9:40 AM–10:10 AM	**Break**
10:10 AM–10:40 AM	**Nonclinical Safety of Lung-Targeting Oligonucleotides** *Jessica Grieves, DVM, PhD, DACVP, Ionis Pharmaceuticals*
10:40 AM–11:10 AM	**Nonclinical Safety of Muscle-Targeting Oligonucleotides** *Katherine A. Knostman, DVM, PhD, DACVP, Sarepta Therapeutics*
11:10 AM–11:40 AM	**Precision Medicine—Individualized Oligonucleotide Therapies** *Julie Douville, PhD, n-Lorem Foundation*
11:40 AM–12:00 Noon	**Student Speaker**

Committee Social

12:00 Noon–1:30 PM

Session 4

1:30 PM–5:00 PM

mRNA-Based Therapies and Others

Co-Chairs: Shan K. Naidu, DVM, PhD, DACVP, *Moderna Therapeutics and* ***Rani Sellers, DVM, PhD, DACVP,*** *University of North Carolina at Chapel Hill*

The unprecedented speed of developing vaccines against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for the COVID-19 pandemic, has propelled mRNA technologies into the public eye. The versatility of mRNA technology, often referred to as "plug and play," offers immense promise for rapidly updating vaccines to address newer variants of respiratory diseases and combat emerging infectious diseases and lethal pathogens, such as the Ebolavirus. However, the potential applications of mRNA technology extend well beyond prophylactic vaccines. This session will explore the two primary mRNA platforms: non-replicating mRNA and self-amplifying RNA (saRNA). We will discuss current research efforts aimed at broadening the applications of mRNA modalities in treating cancer and respiratory diseases. This includes opportunities for delivering mRNA via intratumoral and inhalational routes. Talks will include discussions about the immunological and systemic inflammatory responses elicited by these modalities. Lastly, we will address the regulatory considerations involved in the development and licensing of these technologies.

1:30 PM–2:10 PM	**Safety and Immunogenicity of Self-Amplifying RNA Vaccines** *Sue-Jean Hong, PhD, Pfizer, Inc.*
2:10 PM–2:40 PM	**saRNA/mRNA Opportunities in Oncology** *Prashant R. Nambiar, BVSc, MS, PhD, DACVP, MBA, DABT, Strand Therapeutics*

2:40 PM–3:10 PM	**Inhaled mRNA Therapy for Cystic Fibrosis** *Eric Jacquinet, PhD, DVM, DACVP, SalioGen Therapeutics*
3:10 PM–3:25 PM	**Student Speaker**
3:25 PM–3:55 PM	Break
3:55 PM–4:30 PM	**Clinical Pathology Findings with mRNA Vaccine Compared to Relevant Vaccine Adjuvants** *Lila Ramaiah, DVM, PhD, DACVP, The Janssen Pharmaceutical Companies of Johnson & Johnson*
4:30 PM–5:00 PM	**Regulatory Considerations with mRNA Modalities—Working Without Guidelines** *Rani Sellers, DVM, PhD, DACVP, University of North Carolina at Chapel Hill*

WEDNESDAY, JUNE 19

Session 5

8:00 AM–12:00 Noon

Protein Degraders

Co-Chairs: Monica Rodrigo, PhD, *AstraZeneca;* ***Kiran S. Palyada, BVSc, MVSc, PhD, DACVP, DABT,*** *Pfizer, Inc.;and* **Clare E. Hoover, DVM, PhD, DACVP,** *AstraZeneca*

The so-called undruggable space is an exciting area of potential growth for drug development. Undruggable proteins are defined as those unable to be targeted via conventional small molecule drugs. New modalities are being developed to potentially target these proteins. Targeted protein degradation (TPD) is such a new modality, which over the last two decades has moved from academia to industry. TPD makes use of the endogenous degradation machinery present in all cells, in which E3 ubiquitin ligases mark proteins for degradation via ubiquitin attachment. To date, Cereblon is the most utilized E3 ligase for TPD. In this session, we will explore the challenges and perspectives of using protein degraders as novel therapeutic agents. The session will begin with a general introduction to this exciting modality, followed by particular considerations in evaluating their on- and off-target toxicities. We will explore the role of transgenic models in evaluating hemotoxicity associated with Cereblon-based therapies and how the unique ADME properties of degrader molecules might affect not only their development, but also their toxicity assessment. This will be followed by a regulatory perspective on the challenges of having toxicity associated with degradation. Finally, we will explore a case study where efforts to derisk dose-limiting thrombocytopenia are discussed.

8:00 AM–8:35 AM	**Protein Degraders for the Pathologists: A Primer on Hijacking the Proteasome** *Renee R. Hukkanen, DVM, MS, DACVP, Amgen*
8:35 AM–9:10 AM	**Targeted Protein Degradation (TPD): An Overview of On-Target and Off-Target Toxicity** *Richard A. Peterson, II, DVM, PhD, DACVP, AbbVie*
9:10 AM–9:45 AM	**Preclinical Safety Assessment of Cereblon-Targeting PROTAC Therapeutics** *Clare E. Hoover, DVM, PhD, DACVP, AstraZeneca*
9:45 AM–10:15 AM	**Break**
10:15 AM–10:45 AM	**Heterobifunctional Protein Degraders: Have We Seen These Same DMPK Issues Before?** *Laurie Volak, PhD, Rapport Therapeutics*
10:45 AM–11:15 AM	**Considerations for Safety Assessment of Protein Degraders** *Katie Stamp, PhD, BMS*
11:15 AM–11:45 AM	**Assessing Nonclinical Toxicity of Targeted Protein Degraders: A Regulatory Perspective** *Stephanie Leuenroth-Quinn, PhD, US FDA/CDER*
11:45 AM–12:00 Noon	**Using Protein Degrader Technology to De-Risk Dose-Limiting Thrombocytopenia: A Case Report** *Allison Vitsky, DVM, DACVP, Pfizer, Inc.*

Session 6

1:30 PM–5:00 PM

LNP and Other Delivery Systems

Co-Chairs: Dinesh Bangari, BVSc&AH, MS, PhD, DACVP, *Sanofi and* ***Nicholas A. Robinson, BVSc, PhD, DACVP,*** *Alnylam Pharmaceuticals*

With the significant growth in existing and evolution into new therapeutic modalities, lipid-based nanoparticles (LNPs) have demonstrated tremendous clinical success in delivering both hydrophobic and hydrophilic therapeutics including nucleic acids like DNA, mRNA, and siRNA due to their outstanding biocompatibility, biodegradability, and entrapment efficiency. To dig deeper into the foundation of this clinical success, this session will focus on the early stage and non-clinical aspects of LNP therapeutic development. The talks will cover basics of LNPs, toxicity encountered following LNP administration in nonclinical species including the NHP as well as non-clinical safety strategies and emerging trends in LNP development and use.

1:30 PM–2:00 PM	**Introduction to LNP/Nanomedicine** *Suzanne Hartford, PhD, Regeneron*
2:00 PM–2:30 PM	**LNP Toxicity in NHPs** *Dharani K. Ajithdoss, DVM, PhD, DACVP, DACVM, Regeneron*
2:30 PM–3:00 PM	**Toxicology and Toxicologic Pathology Approaches for LNP Therapeutics** *Jessica E. Sutherland, PhD, DABT, Alnylam Pharmaceuticals and Nicholas A. Robinson, BVSc, PhD, DACVP, Alnylam Pharmaceuticals*
3:00 PM–3:30 PM	**Break**
3:30 PM–4:15 PM	**Nonclinical Safety Strategy of LNPs with Regulator Considerations** *Prashant R. Nambiar, BVSc, MS, PhD, DACVP, MBA, DABT, Strand Therapeutics*
4:15 PM–5:00 PM	**Emerging Trends and Future Perspectives of LNP Drug Developments** *Dinesh Bangari, BVSc&AH, MS, PhD, DACVP, Sanofi and Nicholas A. Robinson, BVSc, PhD, DACVP, Alnylam Pharmaceuticals*

Awards and Recognition Ceremony

5:30 PM–6:30 PM

President's Reception

7:00 PM–9:00 PM

Meeting Adjournment