

EUROPEAN CONGRESS OF
TOXICOLOGIC PATHOLOGY
PRECEDED BY IATP SYMPOSIUM



23RD ESTP ANNUAL CONGRESS
KRAKOW-POLAND
29 SEPTEMBER - 2 OCTOBER 2026
PROCEEDINGS BOOK



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Welcome

Dear colleagues and friends,

The [European Society of Toxicologic Pathology \(ESTP\)](#) is pleased to invite you to the **23rd ESTP Annual Congress** entitled '**Beyond Morphology: The Pathologist's New Toolbox In A Data-Driven Era**'.

The Scientific Organizing Committee (SOC) comprising internationally recognized experts is preparing a very interesting and diversified program showcasing new tools and approaches that are reshaping our profession - within and beyond morphologic examination. Invited speakers will address cutting-edge molecular technologies like spatial proteomics, metabolomics and MS imaging, new approach methodologies (NAMs), and the different applications of AI in toxicopathology. In addition, advances in the areas of genetically engineered animal models, alternatives to NHPs, group housing and virtual controls will be covered. The program will be balanced between brief introductions into selected methods, reviews of regulatory aspects and requirements for a strategic implementation in discovery and risk assessment, and ample core examples illustrating successes and limitations, predictability and translatability, and the pathologist's role in the development and application of new tools and approaches.

The lectures, oral presentations and posters will be accompanied by a trade exhibition introducing new equipment, technologies, and services. The social program will include the welcome reception (29th September 2026), and a congress dinner (01st October 2026).

In conjunction, an **IATP Satellite Symposium** is planned to take place immediately before the congress, for which a separate registration will be needed.

The congress takes place in Krakow from the 29th of September to the 2nd of October 2026. Located in southern Poland, Krakow is the second largest and one of the oldest cities in Poland. The official capitol and the seat of Polish Monarchs from the 11th to the 16th century, the city boasts an architectural legacy ranging from the early Romanesque to the Modernist periods. In the well-preserved historic Old Town, one of the first UNESCO World heritage sites, you can visit the Wawel Hill complex with the Cathedral and Royal Castle, the Jagiellonian University founded in 1364, one of the world's oldest universities, and Europe's largest medieval town square with St. Mary's Basilica and the Renaissance cloth hall Sukiennice. You also shouldn't miss the historic Jewish quarter of Kazimierz - an important center of creativity, cultural life, and gastronomic delights - or the nearby Wieliczka Salt Mine - a one-of-its-kind, hidden place of mystery and legends. In the evenings, you will fall in love with mouthwatering Polish culinary specialties and the unique atmosphere in the historical cellar bars dedicated to live music. We look forward to seeing you in Krakow!

With kind regards

Chairs of Scientific Organizing Committee on behalf of the ESTP

Anna-Lena Frisk

Distinguished Scientist Pathobio PSTS , Johnson & Johnson, Innovative Medicine, Belgium

Bhanu Singh

Head of Toxicology and Pathology, Drug Discovery, Calico Life Sciences LLC, USA

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Organization

Chairs of Scientific Organizing Committee on behalf of the ESTP

Anna-Lena Frisk

Distinguished Scientist Pathobio PSTS , Johnson & Johnson, Innovative Medicine, Belgium

Bhanu Singh

Head of Toxicology and Pathology, Drug Discovery, Calico Life Sciences LLC, USA

Scientific Organizing Committee Members

Scientific Organizing Committee Members

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Sabina Soldati, Pathology Experts GmbH, Switzerland

Sebastien Monette, Novartis Pharma AG, Switzerland

Thomas Lemarchand, StageBio GmbH, Germany

Awards

Bob Maronpot Guest Lecture Award – kindly sponsored by the IATP and the Telikicherla Higher Education Foundation

The award recognizes a new Toxicology pathology area topic. The IATP Bob Maronpot 2026 Guest Lecture Award will be awarded to *Brian Berridge*.

BSTP Gopinath Award

Awarded to a speaker with outstanding contributions to education, training, and mentoring. The Gopinath 2026 Award will be awarded to *Alys Bradley*.

ESTP Science Award – awarded by ESTP SOC/Congress Council

Granted for an outstanding scientific contribution to the field of toxicologic pathology.

ESTP Publication Award – awarded by ESTP/Award Committee Chair**ESTP Best Poster Award – awarded by SFPT representative (sponsored by SFPT)****ESTP Achievement Award – awarded by ESTP/Award Committee Chair****ESTP Poster Award – awarded by ESTP/SOC**

Side Meetings

Monday 28 September 2026

ESTP Board Meeting 16.00-18.00 | Epsilon Room (1st floor), Park Inn Hotel

By invitation only

Organizer: Amy Narewski | Chair: Vanessa Schumacher

Wednesday 30 September 2026

EFPIA Pathologists Meeting 13.00-13.45, Room 12

Thursday 1 October 2026

CEP SOC Meeting + Breakfast (hybrid) 07.15-08.15, Room 12

Organizer: Anna-Lena Frisk

Early Career Pathologists Meeting 12.45-13.45 (during lunch break), Press room

Organizer: Laura Polledo

ESTP Pathology 2.0 Meeting 12.45-13.45, Room 12

Organizer: Josep Monné & Dirk Schaudien

ESTP AGA (hybrid) 14.15-15.15, Room S3

INHAND Workshop

On Monday 28 September, INHAND Rodent working group chairs, co-chairs and designated representatives will join GESC committee members in a premeeting workshop to review the progress to date on the global rodent terminology review that was begun in August 2024, working towards alignment and finalization of recommended changes to the INHAND terminology.

Plan to meet 8am - 4pm with colleagues to reach alignment and finalize recommended changes with the goals of cross system alignment as well as updates to meet current toxicologic pathology nomenclature needs.

Please note that invitations and arrangements will be shared via the Rodent WG Chairs Email Distribution list. Those wishing to observe the discussions can reach out to the GESC INHAND Chair (emily.meseck@novartis.com) and we will accommodate if feasible, based on the limits of the accommodations.

Venue:

Park Inn by Radisson Kraków

Monte Cassino 2, 30-337 Kraków, Poland

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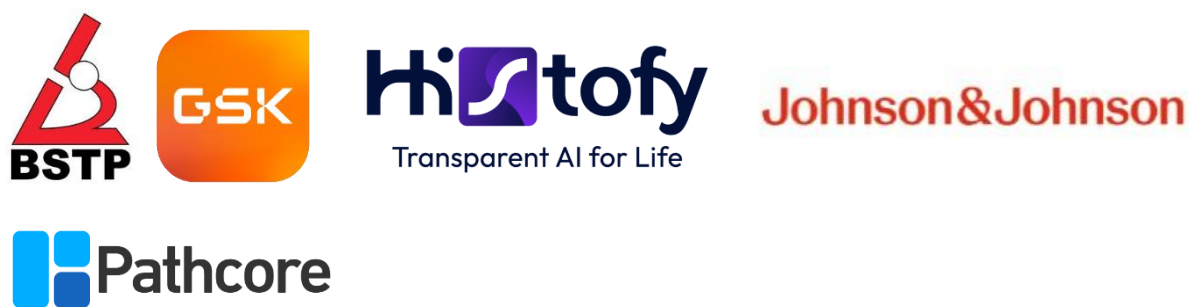
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Tuesday 29 September - Speaker Abstracts

TUESDAY 29 SEPTEMBER 2026 | 08:40-09:30

Translational Safety Challenges in the Early Development of GLP-1 Receptor Agonists: Addressing Signals for Thyroid and Pancreatic Safety

John L. Vahle

Translational Safety Challenges in the Early Development of GLP-1 Receptor Agonists: Addressing Signals for Thyroid and Pancreatic Safety

John Vahle¹

¹ Lilly Research Laboratories, Indianapolis, United States

Translational safety challenges frequently emerge when nonclinical findings require assessment of their clinical relevance. Conversely, clinical safety signals may surface that require nonclinical data to establish biological plausibility and inform risk. Both scenarios were encountered during the development of incretin-based therapies — a therapeutic class highly effective in treating cardiometabolic diseases, including type 2 diabetes and obesity. Despite being widely perceived as a recent breakthrough, the scientific study of incretins spans decades, during which substantial challenges in both basic research and clinical development had to be overcome. Among the most consequential during early development of GLP-1 receptor agonists were thyroid C-cell tumors, identified through traditional rodent carcinogenicity studies, and pancreatic toxicity concerns, initially prompted by clinical observations and investigator-initiated rodent studies. This presentation uses a case study approach to illustrate how both traditional and mechanistic investigative nonclinical studies were employed to evaluate the clinical significance of these findings and support the safe development of this important therapeutic class.

TUESDAY 29 SEPTEMBER 2026 | 09:30-10:10

Emerging Challenges and Safety Considerations in T-cell Engager and CAR-T in Oncology Therapeutics

Anna-Lena Frisk

Emerging Challenges and Safety Considerations in T-cell Engager and CAR-T Cellin Oncology Therapeutics

Anna-Lena Frisk ^{1, 2}

Ronnie Chamanza ², Michaël Maes ², Simone Buraschi ³, Tynisha Glover ³, Molly Morgan ⁴

¹ Johnson & Johnson, Beerse, Belgium

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Immune-based modalities such as T-cell engagers (TCEs) and chimeric antigen receptor T- (CAR-T) cell therapies are transforming oncology, but introduce safety risks that require integrated, mechanism-informed pathology evaluation and diligent nonclinical safety assessment strategies.

Understanding these complex safety liabilities requires a framework that integrates real word clinical outcomes with underlying pathologic mechanisms. This presentation will review key safety signals and their pathologic correlates across immune effector cell therapies, with emphasis on the clinical presentation and underlying pathogenesis of cytokine release syndrome (CRS), immune-effector-cell associated neurotoxicity syndrome (ICANS), on-target/off-tumor tissue injury, and immune-effector cell-associated hemophagocytic syndromes (IEC-HS).

The presentation will also highlight key gaps in preclinical and translational pathology for these modalities and outline fit-for-purpose best practices for pathology and safety endpoints in nonclinical studies. Collectively, these approaches aim to enable the safe and efficient development of efficacious next-generation TCEs and CAR-Ts while balancing scientific rigor, development speed, quality expectations, and the 3Rs where applicable.

TUESDAY 29 SEPTEMBER 2026 | 10:40-11:20

Adversity Calls in Oncology Nonclinical Development: Are we asking the Right Questions?

Franck Chanut

Adversity Calls in Oncology Nonclinical Development: Are We Asking the Right Questions?

Franck Chanut¹

¹ Sanofi, Paris, France

Nonclinical safety assessment in oncology drug development presents distinct challenges that demand careful evaluation of risk-benefit profiles. While traditional adversity assessment in pathology provides scientific rigor, they may not fully capture the nuanced decision-making required for oncology therapeutics, where acceptable safety thresholds differ substantially from other therapeutic areas.

This discussion examines the alignment between preclinical safety evaluation criteria and the ultimate objective of achieving clinical proof-of-concept with acceptable safety profiles. Key considerations include:

Are we applying appropriate evaluation standards that reflect the unique risk tolerance in oncology versus other therapeutic areas?

How do we maintain scientific rigor while enabling the thoughtful risk-taking essential to oncology development?

Is our adversity assessment aligned with regulatory expectations and clinical translatability?

How can we refine our processes to avoid both overly conservative and insufficiently protective approaches?

Conclusion

Effective adversity assessment in oncology nonclinical development requires a framework that extends beyond traditional toxicology endpoints. By refocusing our evaluation on clinical relevance, back-translation, mechanistic understanding, and patient-centric risk-benefit analysis, we can enhance decision-making quality and accelerate the development of transformative oncology therapeutics while upholding appropriate safety standards.

TUESDAY 29 SEPTEMBER 2026 | 11:20-12:00**CRO Perspectives on Current Trends and Challenges in Nonclinical Safety Assessment***Sarah Gould & Annette Romeike***CRO Perspectives on current trends and challenges in Nonclinical Safety Assessment – Pathology Perspective**Annette Romeike ¹¹ Labcorp Early Development Services GmbH, Münster , Germany

Over the last two to three decades, the business model for the development of medicinal products and chemical compounds has profoundly shifted. Since the early 2000s, industry started to consolidate nonclinical safety assessment inhouse capabilities and mid/big pharma and chemical companies began to outsource entire project submission packages. In parallel, new modalities and approaches evolved with a steadily increasing portion of biopharmaceuticals, genetic medicines, cell therapies, vectors & viral platforms, next generation/chemical modalities, hybrid conjugates, and new delivery technologies compared to classic small molecules. A quick snapshot at those modalities will be presented, including figures of trends in a large global CRO, along with consequences on species selection, 3Rs and challenges for toxicologic pathologists.

CRO perspectives on current trends and challenges in nonclinical safety assessment**Sarah Gould ¹**¹ **Charles River Laboratories, Saint Germain Les Nuelles, France**

While the future cannot be predicted with certainty, examining current trends offers insight into how it may evolve. Contract Research Organizations (CROs) are built on 'what the customer wants' and provide practical/efficient solutions to an ever-changing pharmaceutical industry. They are well positioned to see trends and consistently deliver practical, efficient solutions in an ever-changing environment. There is a drive to accelerate development, reduce costs, improve scientific quality and support the 3Rs. The latter is gaining more regulatory momentum: reflected in the updated FDA Modernization Act and recent published papers by both FDA and EMA.

Completely replacing in vivo testing remains a significant challenge. New alternative in vitro methods are being developed that are becoming increasingly sophisticated, including organoids and organ-on-chip systems. Combined with RNA sequencing or omics technologies, these models could be successful both as screening and ultimately validated safety assessment tools. Machine learning tools are enabling large datasets to be analyzed and can identify patterns, which may provide answers to key safety questions in the future. In parallel, more weight-of-evidence approaches are being encouraged e.g. carcinogenicity (ICH S1); juvenile testing (ICH S11) and this trend will continue in a wider context. There is also a move away from traditional safety testing paradigms and a shift toward tailored assessments. Emerging trends also suggest that future safety assessments will adopt a more integrated approach, incorporating alternative species models to address specific questions (e.g. *C. elegans*, zebrafish, or transgenic models), and considering alternatives for general toxicology, such as the rabbit.

TUESDAY 29 SEPTEMBER 2026 | 13:45-14:45

Highly multiplexed imaging in the omics era: understanding tissue structures in health and disease

Bernd Bodenmiller

Highly multiplexed imaging of tissues with subcellular resolution by imaging mass cytometry.

Bernd Bodenmiller

Cancer is a tissue disease. Heterogeneous cancer cells and normal stromal and immune cells form a dynamic ecosystem that evolves to support tumor expansion and ultimately tumor spread. The complexity of this dynamic system is the main obstacle in our attempts to treat and heal the disease. The study of the tumor ecosystem and its cell-to-cell communications is thus essential to enable an understanding of tumor biology, to define new biomarkers to improve patient care, and ultimately to identify new therapeutic routes and targets.

To study and understand the workings of the tumor ecosystem, highly multiplexed image information of tumor tissues is essential. Such multiplexed images will reveal which cell types are present in a tumor, their functional state, and which cell-cell interactions are present. To enable multiplexed tissue imaging, we developed imaging mass cytometry (IMC). IMC is a novel imaging modality that uses metal isotopes of defined mass as reporters and currently allows to visualize over 50 antibodies simultaneously on tissues with subcellular resolution. In the near future we expect that over 100 markers can be visualized.

We applied IMC for the analysis of breast cancer samples in a quantitative manner. To extract biological meaningful data and potential biomarkers from this dataset, we developed a novel computational pipeline geared for the interactive and automated analysis of large scale, highly multiplexed tissues image datasets. Our analysis reveals a surprising level of inter and intra-tumor heterogeneity and identify new diversity within known human breast cancer subtypes as well as a variety of stromal cell types that interact with them.

In summary, our results show that IMC provides targeted, high-dimensional analysis of cell type, cell state and cell-to-cell interactions within the TME at subcellular resolution. Spatial relationships of complex cell states of cellular assemblies can be inferred and potentially used as biomarkers. We envision that IMC will enable a systems biology approach to understand and diagnose disease and to guide treatment.

TUESDAY 29 SEPTEMBER 2026 | 14:45-15:15

Tissue based Mass Spectrometry beyond morphology, there is more to see behind nice picture

Bogdan Munteanu

Tissue based Mass Spectrometry beyond morphology, there is more to see behind nice picture:

Bogdan Munteanu ¹

¹: Center of Excellence for tMSI-Laboratory Sciences Germany-TMU-Sanofi

Tissue based Mass Spectrometry beyond morphology, there is more to see behind nice picture: A Methodological Assessment for Drug Distribution (NCE & NBE) and untargeted Biomarker Discovery in biomedical research and toxicologic pathology

Matrix-Assisted Laser Desorption Ionization (MALDI) Mass Spectrometry Imaging (MSI) is a powerful technique that enables **label-free detection** of a wide range of molecules (*e.g., lipids, metabolites, peptides, proteins, and pharmaceutical drugs/metabolites*) together with their **spatial distribution** in target tissues and organs. In the context of drug development, untargeted multi-omics analysis can contribute to **understanding therapeutic and toxicity mechanisms** of a drug or **identifying novel disease biomarkers**. During this presentation the technological background of MALDI-MSI in the context of (safety) biomarker evaluation in pre-clinical industry research shown exemplary for the cross-species analysis of fialuridine in human liver spheroids will be introduced.

Drug-Induced Liver Injuries (DILI) are a critical safety concern in drug development and their prevention or prediction is of critical importance, therefore customized in vitro assays and high content biomarker discovery analytical workflows are required.

Background and Purpose: Fialuridine, a nucleoside analog that was being developed for the treatment of hepatitis B, did not demonstrate any hepatotoxicity in pre-clinical species (rat, dog, monkey) but led to fatal hepatotoxicity in clinical trials. The exact mechanism for this interspecies difference is not clear but previous data suggests that human-specific fialuridine toxicity resulted from mitochondrial damage and lactic acidosis. Herein, we used liver spheroids from human, dog, and rat coupled with tissue mass spectrometry imaging (tMSI), a fast, automated, and specific screening technology based on ultrahigh-resolution matrix-assisted laser desorption ionization (UHR-MALDI) MSI to characterize and differentiate the mechanism of fialuridine hepatotoxicity in these species.

Conclusions: tMSI indicated some early signs of mitochondrial toxicity in human liver spheroids while minimal to no changes were observed in rat or dog liver spheroids after fialuridine treatment suggesting human specific fialuridine toxicity could at least in part be related to mitochondrial damage.

TUESDAY 29 SEPTEMBER 2026 | 15:15-15:45

Beyond Morphology: Leveraging Spatialomics for Precision Drug Development in a Data-Driven Era

Kerstin Hahn

Beyond Morphology: Leveraging Spatialomics for Precision Drug Development in a Data-Driven Era

Kerstin Hahn¹

Johanna Schaffenrath^{1, 2}, Jia Le Lee², Benedek Pesti¹, Roberta Lauria¹, Nadine Kumpesa¹, Sven Rottenberg^{3, 4}, Sizun Jiang², Marc Sultan¹, Markus Britschgi¹, Alberto Valdeolivas Urbelz⁵

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³ Institute of Animal Pathology, Vetsuisse Faculty, University of Bern, Bern, Switzerland

⁴ Bern Center for Precision Medicine, Department for BioMedical Research, University of Bern, Bern, Switzerland

⁵ Computational Sciences Center of Excellence, Roche Innovation Center Basel, Basel, Switzerland

Spatial transcriptomics and proteomics fundamentally alter pathology by enabling the mapping of molecular heterogeneity within the native histological context. This presentation explores the "spatial toolbox" through preclinical use cases, demonstrating how these technologies deconvolve complex therapeutic responses.

A primary challenge in spatial proteomics is the lack of standardized protocols for Formalin-Fixed Paraffin-Embedded tissues. We addressed this through a systematic evaluation of 24 combinatorial protocols, identifying conditions that optimize reproducibility and signal-to-noise ratios across different spatial proteomics platforms. To further validate these parameters, we utilized the Akoya PhenoCycler platform with specialized antibody panels to map mouse and non-human primate tissues. This approach enabled the precise assessment of cell-type-specific distribution patterns for gene therapy vectors across the DNA, RNA, and protein levels.

The utility of sequencing- and imaging-based spatial multi-omics is exemplified by a case study detailing the dissection of Alzheimer's Disease in a mouse model treated with a therapeutic antibody. Combining Visium ST with Xenium spatially deconvolved the multicellular response, revealing specific interferon-responsive states across microglia, astrocytes, and oligodendrocytes in proximity to infiltrated T cells. These findings underscore that multi-resolution spatial tools can uncover localized immune programs and subtle therapeutic effects, establishing a robust framework for identifying novel biomarkers and accelerating targeted therapy development in modern pathology.

TUESDAY 29 SEPTEMBER 2026 | 16:30-17:00**Spatial Multi-Omics in Inflammatory Bowel Disease: Advancing Pathobiology and Drug Target Discovery***Sunish Mohanan***Spatial Multi-Omics in Inflammatory Bowel Disease: Advancing Pathobiology and Drug Target Discovery**Sunish Mohanan ¹¹ Gilead Sciences, Foster City, United States

Spatial biology has moved from a specialized method to a practical engine for evaluating tissue, and inflammatory bowel disease (IBD) has become one of its most productive proving grounds. This presentation reviews how spatial omics technologies, used as hypothesis-generating platforms, are changing how we interpret inflamed and fibrotic intestine. Crohn's disease and ulcerative colitis are heterogeneous at every scale, and Crohn's separates into inflammatory, stricturing, and penetrating behaviors that look alike yet diverge in biology. When heterogeneity is the rule, the useful question is not only which cells are present, but where they sit and which neighbors they signal to. Modern interrogation of intestinal tissue rests on a pipeline built on archival formalin-fixed, paraffin-embedded (FFPE) blocks. Much of the value is decided before sequencing: fixation, storage, and RNA integrity (DV200) gate whether a block yields interpretable data. A disciplined workflow then layers complementary readouts on the same or serial sections, combining capture-based spatial transcriptomics for unbiased discovery, high-order multiplexed immunofluorescence for single-cell validation, and single-nucleus RNA-seq for cell identity. Every layer is read back against the H&E; the pathologist defines regions of interest and separates real biology from artifact, turning a data matrix into a disease narrative.

Applied this way, spatial profiling surfaces biology that dissociated suspensions miss. The epithelium reveals transitional, wound-associated states that are neither fully inflamed nor fully healed, and because cells are mapped in place, the analysis extends to tissue neighborhoods and inferred ligand-receptor signaling. Immune zonation and fibroblast niches organize disease along anatomical lines, and effective therapy reorganizes these communities rather than depleting a target. Inflammation and fibrosis come into view as multicellular circuits with a geography.

The wider field now applies spatial and single-cell omics across IBD research and clinical trials. Foundational atlases established the cellular taxonomy of the inflamed colon and linked inflammatory fibroblast populations to treatment resistance. Spatially resolved studies defined treatment-refractory disease around an interleukin-1-driven stromal-neutrophil axis, and single-cell spatial profiling has mapped macrophage and neutrophil heterogeneity together with macrophage-fibroblast communication networks. Recent work concentrates on the stricturing phenotype, where spatial programs connect to inherited (GWAS) risk loci and where fibroblast and mesenchymal programs lay down the collagen that narrows the bowel. Longitudinally, these signatures track therapy response, and the field is maturing from discovery toward predictive, stratifying readouts.

For toxicologic and discovery pathologists, the value of this work is methodological rather than a direct mapping of disease biology onto safety findings. IBD is immune-mediated, and its programs should not be transposed onto drug-induced lesions; what transfers is the discipline of tissue selection, fixation and RNA-quality control, and tight molecular-morphologic correlation, all of which generalize to any tissue. Feasibility turns on species and platform coverage; cost and the need for a multidisciplinary team keep spatial multi-omics a selective, question-driven tool. Spatial biology does not displace the pathologist's eye; it extends

TUESDAY 29 SEPTEMBER 2026 | 17:00-17:45

Acceleration of drug discovery through multi-omics imaging data analysis in our new AI-era

Richard Goodwin

Acceleration of Drug Discovery Through Multi-Omics Imaging Data Analysis in Our New AI Era

Richard Goodwin ¹

¹ Unknown, Unknown, Netherlands

Advances in imaging, spatial biology and multi-omics technologies have transformed our ability to measure complex biological systems. In parallel, developments in artificial intelligence are creating new opportunities to integrate these rich datasets and extract insights at a scale previously impossible. Together, these innovations are redefining how new medicines are discovered, developed and translated to new medicines.

This presentation will describe how integrated analysis of multi-omics and imaging data is being applied across the discovery-to-clinic continuum. We will consider emerging foundation models and AI-driven approaches that connect molecular, cellular and tissue-level information within a continuously learning scientific ecosystem.

By combining deep biological data with modern AI, the pharmaceutical industry is moving from largely descriptive experimentation towards predictive, data-driven decision making. This shift has the potential to accelerate drug discovery and ultimately improve the delivery of effective medicines to patients.

Wednesday 30 September - Speaker Abstracts

Topic 4: Virtual Controls and Group Housing

WEDNESDAY 30 SEPTEMBER 2026 | 08:30-09:00

Development and characterization of a novel rat colony cage for refinement and remote behavior tracking in toxicity studies

Christian Brenneis

Development and characterization of a novel rat colony cage for refinement and remote behavior tracking in toxicity studies

Christian Brenneis¹

Jan Paul Weidenbusch¹, Sigrid Johannes¹, Michael Wilhelm Schmitt¹, Sven Jaeckel¹, Anja Knippel¹

¹ Merck Healthcare KGaA, Darmstadt, Germany

For refinement in rat toxicity studies, we developed a novel, customized housing system that provides a more species-appropriate environment, allowing social behavior and the establishment of functional areas across different levels in a larger space. To leverage information from more complex spontaneous behaviors, we integrated a tracking system that remotely monitors the locomotion of individual rats.

In 4-week (+ 4-week recovery) general toxicity studies using methotrexate or cisplatin as reference treatments, we conducted a head-to-head comparison of study feasibility, data variability and animal stress levels after study execution in regular Type-IV and novel colony cages. While colony housed animals showed much higher activity in their home cage, they were cooperative when handled and settled more quickly when transferred to a novel test environment. Clinical chemistry, hematology and toxicokinetic parameters showed comparable levels and variability across groups. Histopathological analysis identified the same target organs with comparable incidence and severity of findings. Reduced corticosteroid levels, increased IgA levels, and an improved granulocyte/lymphocyte ratio in colony housed rats indicated less stress response with a positive consequence on the immune status. Finally, a reduction in spontaneous daily activity, as indicated by “cage-level changes”, correlated with treatment and symptoms most relevant to the individual animal’s general condition.

In conclusion, the novel colony cages proved suitable for conducting standard toxicity studies within a more rat-appropriate housing environment. All toxicology data can be reliably collected, a welfare benefit for rats is suggested by decreased stress markers, and health monitoring is enhanced by continuous remote behavior tracking.

WEDNESDAY 30 SEPTEMBER 2026 | 09:00-09:30**Group housing of nonhuman primates from a pathologist's perspective***Ann-Kathrin Haverkamp***Group housing of nonhuman primates from a pathologist's perspective**Ann-Kathrin Haverkamp ¹Annette Romeike ¹, Matthias Mietsch ¹¹ Labcorp, 48163 Münster, Germany

In recent years, the development of new drug modalities has underlined the importance of nonhuman primates (NHP) in biomedical research. However, the use of NHP in research is ethically controversial and highly regulated. Housing and husbandry procedures are complex and key for exhibition of species-typical behavior and animal welfare. The high need for housing strategies which allow social interaction and best possible conditions without negative influence on research results has led to several modifications and improvements over the past decades.

During the session, we will introduce modern group housing concepts of different NHP species (cynomolgus monkey and marmoset monkey) according to EU directives and describe handling, veterinary treatment, systematic cage mate selection, and enrichment strategies which allow dynamic and safe animal activities. We will further discuss potential infectious and non-infectious health issues and analyze risks and chances of NHP group housing from a veterinary pathologist's perspective in the scope of toxicologic pathology.

WEDNESDAY 30 SEPTEMBER 2026 | 09:30-10:00

Virtual Controls in Toxicologic Pathology: Turning Challenges into Opportunities

Julie Boisclair & Armelle Grevot

Virtual Controls in Toxicologic Pathology: Turning Challenges into Opportunities

Julie Boisclair¹

Armelle Grevot¹

¹ Novartis Pharma AG, Basel, Switzerland

The use of virtual controls in toxicologic pathology is gaining momentum as part of efforts to reduce animal use while maintaining scientific rigor in nonclinical safety studies. Virtual control approaches, derived from curated historical control data and increasingly supported by digital pathology, may complement or replace traditional concurrent controls by broadening context for interpretation and supporting robust reproducible assessments.

Bringing virtual controls from concept into routine use presents important scientific, operational, and regulatory challenges. These include building well-annotated, fit-for-purpose historical control databases, accounting for covariates and study-specific factors, and ensuring traceability, transparency, and auditability.

These challenges can also be viewed as opportunities to modernize toxicologic pathology assessment by shifting from implicit, experience-based use of individual knowledge toward a more explicit, harmonized, and data-driven approach. Digital pathology is a key enabler, providing scalable access to slide repositories and supporting more consistent comparative evaluation, and facilitating reproducible decision-making across pathologists and institutions.

A pragmatic path forward is likely to involve hybrid strategies that combine concurrent and virtual controls according to context. Advances in data science and artificial intelligence may further refine control selection and interpretation, provided they remain anchored in pathologist expertise. Virtual controls are not a substitute for expert judgment, and their successful adoption will depend on collaboration across industry stakeholders, including CROs and regulators. At the frontier of NAMs, virtual controls are less about replacing biological systems than about rethinking how existing data can be leveraged to advance toxicologic pathology.

WEDNESDAY 30 SEPTEMBER 2026 | 10:30-11:00

Leveraging Historical Control Data and Whole Slide Images for Virtual Control Groups: The VICT3R Approach

Frank Bringezu

Leveraging Historical Control Data and Whole Slide Images for Virtual Control Groups: The VICT3R Approach

Frank Bringezu ¹

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⁶ Bayer AG, Leverkusen, Germany

In September 2024, the IHI consortium VICT3R (www.vict3r.eu) was established to develop an approach for replacing concurrent control animals or control groups with appropriately matched historical control animals / groups in nonclinical safety studies. The tasks to achieve these goals include the creation of a shared database of curated single animal data for the generation of virtual control animals / groups (VCGs), best practices including computer system validation and data integrity assessments, AI tools, and regulatory guidance for implementing VCGs.

The presentation will highlight the recent advancements in virtual controls aimed at replacing concurrent control animals in *in vivo* studies including the integration of Whole Slide Images (WSI) for anatomic pathology to support the retrospective and prospective application of VCGs.

To reach the VICT3R objectives, single animal data from *in vivo* studies from different sponsors have been collected, thoroughly curated and populated in the VICT3R database. This repository contains data from rodent studies but also from large animals including dogs, minipigs and monkeys. The study types are focused on repeated dose toxicity studies but also include other study designs relevant for preclinical assessments, e.g. carcinogenicity and developmental toxicity. In total, data from 139 940 animals across approximately 8 500 studies contributed by more than 20 industry sponsors have been processed and collected for release 2.3 of the VICT3R DB. To fully support the application of VCGs, ways to integrate WSI repositories by linking animals stored in the VICT3R DB with their respective WSIs have been explored in different use cases.

The presentation will introduce the VICT3R initiative emphasizing the development of the curated VICT3R Database and the current procedures for VCG generation. Emphasis will be put on the current EMA qualification of VCGs for their use in repeated dose toxicity studies.

WEDNESDAY 30 SEPTEMBER 2026 | 11:00-11:30**Virtual Control Groups: Pathology Promises, Problems, and Practical Reality in Rat Studies***Laura Boone & Alok Sharma***Virtual Control Groups: Pathology Promises, Problems, and Practical Reality in Rat Studies**Laura Boone¹Kelly Ashcroft-Hawley², Brian Chanas¹, James Saul², Alok Sharma¹¹ Labcorp Drug Development Laboratories, Madison, Wisconsin, United States² Labcorp Drug Development Laboratories, Harrogate, United Kingdom

Virtual control groups (VCGs) are derived from a well-curated historical control database (HCD) using predefined, study-specific selection criteria based on the test system population within a nonclinical study, with the goal of reducing or replacing concurrent control animals. This session presents the results of a retrospective comparison of data interpretation for body weight, clinical pathology, organ weights, and anatomical pathology endpoints from a selected 4-week rat study (index study), using VCGs as comparators versus the original data interpretation based on concurrent control groups. Twenty-six 4-week repeat-dose oral gavage rat studies conducted at the Labcorp test facility in Madison, Wisconsin, USA, between 2019 and 2024 were included. One study was designated as the index study, while data from the remaining 25 studies were integrated into a curated HCD. From this database, 10,000 VCGs were generated, and several VCGs were selected for comparison of test article-treated groups in the index study. Data for the comparison of test article-treated groups to each VCG and concurrent control group were presented to representative scientists for independent review and interpretation. These interpretations were then compared with the original interpretation and conclusions drawn using concurrent controls. Overall, this work underscores the importance of a well-curated HCD, clearly defined selection criteria to ensure comparability with test study animals, and demonstrates the impact of using VCGs on data interpretation relative to traditional concurrent control groups.

Topic 5: AI-empowered toxicologic pathology

Block 1: Introduction - what's in it for me?

WEDNESDAY 30 SEPTEMBER 2026 | 14:00-14:30

Keynote - Making AI Accessible to Pathologists as End Users: Understanding the Promise, Pitfalls, and Path to Clinical Adoption

Andrew Janowczyk

Making AI Accessible to Pathologists as End Users: Understanding the Promise, Pitfalls, and Path to Clinical Adoption

Andrew Janowczyk^{1, 2}

¹ Emory University, Atlanta, United States

² Geneva University Hospitals, Geneva, Switzerland

Artificial intelligence (AI) is increasingly presented as a transformative technology for pathology, yet many practicing pathologists are left wondering a simpler question: What should I actually know to judge whether an AI tool is trustworthy and clinically useful? This keynote is designed for pathologists as end users rather than AI developers, providing a practical framework for understanding both the promise and the current limitations of computational pathology.

The lecture will begin with why pathology is a uniquely challenging domain for AI, emphasizing the enormous size of whole-slide images, biological heterogeneity, technical variability, and the often-imperfect nature of diagnostic ground truth. It will then discuss differences between hand-crafted feature engineering and more recent end-to-end deep learning and foundation models. We will discuss that while these newer approaches have achieved impressive research performance, they have also become increasingly opaque, making it difficult to understand what information a model is truly using to reach a prediction.

A central theme of the talk is that high benchmark performance does not automatically translate into clinical readiness. Particular attention will be paid to confounders and batch effects arising from differences in staining, tissue processing, scanner hardware, and institutional practices and biases. These hidden sources of variation can lead models to learn shortcuts unrelated to disease biology, raising important concerns about generalizability and safety. The discussion will cover the types of validation pathologists should look for, including external validation, benchmarking, and clinically meaningful performance metrics.

The keynote will also address the practical realities of deploying AI in a diagnostic laboratory, including accreditation, quality management, and laboratory-developed test (LDT) approaches within the Swiss regulatory context. Rather than viewing AI as an autonomous replacement for pathologists, the lecture will argue that current systems are best understood as decision-support tools that require continuous oversight, monitoring, and expert interpretation.

Finally, the talk will consider how precision medicine is pushing pathology toward increasingly rare molecular subtypes and individualized therapeutic decisions. This emerging “ $n = 1$ ” paradigm creates a paradox: the clinical questions becoming most important are often those for which large, homogeneous training datasets are least available. Understanding this tension is essential for evaluating the future role of AI in pathology.

The goal is to equip pathologists with the vocabulary, concepts, and critical perspective needed to engage confidently with AI, collaborate effectively with computational scientists, and make informed decisions about clinical adoption.

WEDNESDAY 30 SEPTEMBER 2026 | 14:30-14:50

Explainable AI: what has my algorithm really learned?

Heike Marxfeld

Explainable AI: what has my algorithm really learned?

Heike MARXFELD ¹

¹ BASF SE, Frankenthal, Germany

Expanding on recent publications, ways of explaining computer vision algorithms will be presented.

Block 2: Case examples AI in histopathology

WEDNESDAY 30 SEPTEMBER 2026 | 14:50-15:10

Towards AI Models for Preclinical Drug Safety Assessment

Simone De Brot & Guillaume Jaume

Towards AI Models for Preclinical Drug Safety Assessment

Guillaume Jaume ¹

Simone De Brot ²

¹ University of Lausanne, Lausanne, Switzerland

² University of Bern, Bern, Switzerland

Assessing drug toxicity remains a major bottleneck in preclinical development, as it depends on labor-intensive histopathological review by expert pathologists. To address this, we developed TRACE, a foundation model for toxicologic liver histopathology trained on 15 million images from 46,734 tissue sections collected across 157 rat studies. TRACE enables a broad set of applications, from lesion assessment and severity scoring to morphological retrieval and automated dose-response analysis, including in low-label settings. In an independent reader study, it showed stronger agreement with the consensus diagnosis than the average of ten board-certified veterinary pathologists. We also adapted TRACE with vision-language and instruction-based fine-tuning, allowing the model to be queried directly about toxicology-relevant morphologies and lesions. TRACE points toward a new generation of AI systems for faster, more consistent, and more interactive toxicologic pathology.

WEDNESDAY 30 SEPTEMBER 2026 | 15:10-15:30

**From Credibility Framework to Practical Implementation:
Operationalizing AI-Based Image Analysis in Toxicologic Pathology**

Frederic Gervais

**From Credibility Framework to Practical Implementation: Operationalizing AI-
Based Image Analysis in Toxicologic Pathology**

Frédéric Gervais ¹

¹ Charles River Laboratories , Evreux, France

Artificial intelligence (AI)-based image analysis is increasingly applied in toxicologic pathology to support quantitative evaluation of histological endpoints in both regulatory and non-regulatory studies. While recent regulatory guidance or publications, including the 2025 FDA draft guidance on AI credibility, provide a structured framework for algorithm qualification, its practical implementation remains challenging in routine preclinical workflows.

This presentation focuses on the operationalization of AI validation in toxicologic pathology, emphasizing real-world decision-making rather than theoretical considerations. Through representative use cases (including Ki67 proliferation indices, ovarian follicle quantification, immune cell detection, and morphometric analysis) we describe common implementation scenarios and associated technical and documentation challenges.

Key aspects addressed include dataset selection, risk-based validation strategies, performance metric selection, revalidation triggers, and documentation approaches. Particular attention is given to frequent pitfalls observed in practice, such as biological confounders, staining variability, and misalignment between validation effort and context of use.

We propose a pragmatic framework positioning AI algorithms as analytical tools, analogous to immunohistochemical assays, requiring defined context of use, proportionate validation, and lifecycle governance. This perspective aims to support toxicologic pathologists in integrating AI into study workflows in a scientifically robust and regulatorily defensible manner.

WEDNESDAY 30 SEPTEMBER 2026 | 15:30-15:50**Pathology Reimagined: When AI Joins the Workflow***Lise Bertrand***Pathology Reimagined: When AI Joins the Workflow**Lise Bertrand ¹¹ Charles River Laboratories, Saint Germain-Nuelles, France

Toxicologic pathology is a cornerstone of drug safety assessment, providing critical insights into target organ toxicity. However, the discipline is increasingly challenged by growing study complexity and the demand for accelerated decision-making. Artificial intelligence (AI) offers an opportunity to transform the pathology continuum—from tissue processing to translational interpretation. This presentation explores how AI can enhance the post-mortem evaluation of toxicity and carcinogenicity studies.

In early workflow stages, AI-supported histological processing and intelligent quality control improves standardization, throughput, and reproducibility. At the interpretative level, anomaly detection enables efficient triaging of large datasets, while advanced models can assist with lesion identification and endpoint quantification. These tools have the potential to reduce observer variability and shift the pathologist's role from exhaustive visual screening toward higher-level data interpretation and biological insight. A key paradigm shift lies in multimodal data integration, whereby histopathology data can be combined with other study data to uncover relationships between morphological and molecular changes, further supported by advanced visualization tools. Generative AI introduces new efficiencies in reporting, enabling structured, consistent documentation while reducing administrative burden under appropriate human oversight.

Despite these opportunities, challenges remain, including data standardization, model validation, interpretability, and integration into regulated environments. Addressing these factors will be critical for successful adoption.

In conclusion, AI is poised to augment—not replace—the toxicologic pathologist and redefine their role. By embedding AI across the pathology workflow, the field can transition toward a more integrated, reproducible, and insight-driven discipline, enhancing its impact on nonclinical drug development.

Block 3: From Pixels to Paragraphs: Expanding AI's Role in Pathology

WEDNESDAY 30 SEPTEMBER 2026 | 16:20-16:35

LLMs in Pathology Practice: A Practitioner's Tour from Scientific Writing to Whole Slide Images

Aleksandra Zuraw

LLMs in Pathology Practice: A Practitioner's Tour from Scientific Writing to Whole Slide Images

Aleksandra Zuraw¹

¹ Charles River Laboratories, Fairfield, United States

Large language models (LLMs) introduced a transformer-based architecture that now also underlies vision models, multimodal systems, agentic frameworks, and retrieval-augmented generation (RAG) pipelines. Several of these technologies, individually and in combination, are in routine use across multiple areas of pathology practice. This talk presents a practitioner's tour of those applications, from text-only writing assistance to multimodal agentic image analysis.

Scientific writing benefits from LLM-assisted workflows: specific prompt patterns, source-handling discipline, and review steps that catch fabricated references and factual errors. Coding and scripting assistance, including agents specialized for biomedical model development, enables non-programmer pathologists to perform image and data analysis. Structured data extraction from data tables and study reports, performed by agent-based pipelines, accelerates the curation of historical findings databases. Toxicologic pathology study reporting is supported by domain-specific agentic systems, which interrogate complex datasets, integrate internal and external sources, and assist in drafting narratives with the pathologist in the loop. Whole-slide image analysis uses multimodal agents that coordinate language models with vision models to navigate slides and produce reasoning trajectories pathologists can audit.

Limitations are addressed for each application: hallucination, sensitivity to prompt formulation, and the gap between benchmark performance and real-world data.

WEDNESDAY 30 SEPTEMBER 2026 | 16:35-16:50

Use of AI in manuscript preparation – an editor's perspective

Kevin Keane

Use of AI in manuscript preparation - an editor's perspective

Kevin Keane¹

¹ Toxicologic Pathology, Cambridge, MA, United States

The use of artificial intelligence is infiltrating and overtaking many workplace activities, and publishing is certainly no different. Our scientific discipline and the scholarly work that flows from it will need to confront what is and is not an appropriate use of this new and powerful technology. This short presentation will discuss how the editorial team of Toxicologic Pathology handles this issue and will pose questions to our readership to ponder and solicit feedback on where we are headed with AI.

Block 4: Collaborative Science: Aligning Data and Standards for Innovation

WEDNESDAY 30 SEPTEMBER 2026 | 16:50-17:05

IMI BigPicture: From Consortium Build to Sustainable Impact in Pathology

Julie Boisclair

IMI BigPicture: From Consortium Build to Sustainable Impact in Pathology

Julie Boisclair¹

¹ Novartis Pharma AG, Basel, Switzerland

The IMI Bigpicture initiative is a major European public–private collaboration advancing digital and computational pathology through a publicly available repository of clinical and non-clinical whole slide images with associated metadata. As the project moves through its extension phase, priorities include consolidating data contributions, completing key deliverables, and ensuring the resource remains scientifically relevant in a rapidly evolving AI landscape.

Looking beyond the funded period, the focus is on sustainability and implementation: maintaining high-quality datasets, enabling continued model development, and translating outputs into workflows relevant to drug development and regulatory engagement. Continued cross-industry collaboration will be essential to maximize the value of the resource and support emerging applications such as virtual controls.

For the pharmaceutical industry, Bigpicture is an important step toward developing and validating AI-driven tools for clinical trials and toxicologic pathology, including lesion detection, scoring, foundation model development, and data-driven decision-making. Integration with complementary initiatives such as IHI VICT3R may further support virtual and synthetic control approaches.

This presentation will summarize project achievements, current progress, and the role pharmaceutical stakeholders can play in shaping Bigpicture into a sustainable, high-impact resource for collaborative innovation and more predictive, data-driven safety assessment.

WEDNESDAY 30 SEPTEMBER 2026 | 17:05-17:20

IQ DruSafe working Group: use of AI in Regulatory Pathology

Thomas Forest

IQ DruSafe working Group: use of AI in Regulatory Pathology

Thomas Forest ¹

¹ Merck & Co, West Point, United States

Artificial intelligence (AI) is rapidly advancing and is increasingly close to practical application in regulatory pathology, with the potential to enhance efficiency, consistency, and decision support in toxicologic studies. However, the field currently lacks widely accepted guidance on the appropriate context of use, validation expectations, traceability requirements, and supervision standards for AI-powered tools in this setting. To address this gap, the IQ DruSafe working group proposes to establish best practices for integrating AI capabilities into regulatory pathology workflows.

The working group will focus on defining the scope of AI use cases relevant to toxicologic pathology, including the distinction between supervised detection-based approaches and unsupervised normal/abnormal discrimination systems. Key objectives include developing recommendations for validation and compliance, outlining record-keeping and traceability expectations, and clarifying the level of human oversight needed for safe and effective implementation. The group will also engage with compliance stakeholders and global regulatory authorities to align proposed practices with emerging regulatory expectations and to support future acceptance of these technologies.

Planned outputs include use-case definitions, validation and compliance best practices, engagement activities with regulators, and a final publication summarizing recommended best practices and lessons learned. By promoting alignment across industry experts, AI specialists, and regulatory stakeholders, this initiative aims to accelerate responsible adoption of AI in regulatory pathology, improve quality and traceability, and support more efficient drug development.

Block 5: Townhall

WEDNESDAY 30 SEPTEMBER 2026 | 17:35-18:35

Deployment of AI tools in regulatory toxicologic pathology - are we there yet?

Gabriele Pohlmeyer-Esch & Charles Halsey

Deployment of AI tools in regulatory toxicologic pathology - are we there yet?

Charles Halsey ¹

Gabriele Pohlmeyer-Esch ²

¹ Pfizer, Inc., Groton, CT, United States

² Boehringer Ingelheim, Biberach, Germany

While AI tools promise improved efficiency, sensitivity, and consistency in toxicologic pathology, their readiness for validation, auditability, and regulatory acceptance remains uncertain. This town hall will focus on regulatory readiness, featuring three brief perspectives: AI GLP readiness, AI GLP uncertainty, and a regulatory viewpoint. We invite you to contribute your experience and perspective to an open discussion on the requirements for translating AI innovation into regulatory practice.

Thursday 1 October Speaker Abstracts

Topic 3: Advancements in Genetically Engineered Animal Models for Nonclinical Safety

THURSDAY 1 OCTOBER 2026 | 08:30-09:15

Introductory talk on genetically engineered animal models

Roland Rad

Deciphering Cancer Mechanisms through Functional Genomics in Mice

Roland Rad¹

¹ Technical University of Munich, Munich, Germany

Gene targeting in mice has revolutionized the study of complex diseases that are often shaped by interactions between multiple genes, cell types, and organ systems. I will highlight advances in germline and somatic engineering of the mouse genome as well as key discoveries enabled by these approaches. The expanding genetic toolbox has greatly accelerated and diversified model generation, while large-scale resources such as the Mouse Cancer Cell Atlas (MCCA) extend these approaches and their applications across a broad spectrum of cancer types, including applications in preclinical modeling and therapeutic discovery. In parallel, scalable in vivo screening using transposons and CRISPR enables systematic discovery of cancer genes, genetic dependencies, and mechanisms of tumor evolution. Together, these advances are driving a new era of in vivo functional cancer genomics.

THURSDAY 1 OCTOBER 2026 | 09:15-09:50

Genetically engineered mouse models in preclinical research: Challenges and considerations for pathologists

Sebastien Monette

Genetically engineered mouse models in preclinical research: Challenges and considerations for pathologists

Sebastien Monette¹

¹ Novartis Pharma AG, Basel, Switzerland

Over the past four decades, genetically engineered mice (GEM) have become indispensable tools in preclinical biomedical research. Their use has advanced our understanding of disease biology and supported the development of novel therapies. Technological innovations in genetic engineering have enabled the creation of increasingly sophisticated models. However, this growing complexity has also introduced substantial challenges that researchers, and particularly pathologists, must address to ensure that studies using these models answer key scientific questions in an accurate and reproducible manner.

Phenotypes observed in GEM are shaped by the interplay of multiple factors, including genotype, genetic background, microbiome composition, and environmental conditions. Each of these variables can profoundly influence study outcomes, making it essential to account for their effects during experimental design and when interpreting results. Based on their training in animal health and disease biology, veterinary pathologists play a critical role in validating new GEM models and safeguarding the integrity of data generated from established models. Their expertise in anatomic and clinical pathology underpins comparative pathology; however, evaluating GEM also requires additional specialized knowledge. This presentation reviews key considerations in this field, with an emphasis on recent advances in GEM technologies. Topics include standardized mouse strain nomenclature, resources providing historical phenotypic data, the influence of genetic engineering strategies and genetic background on disease phenotypes, and approaches to investigate and manage unanticipated findings in these models.

One of the major objectives in mouse genetic engineering has been to modify the immune system to investigate immunological pathways across diseases and to generate immunodeficient hosts for engraftment of human cells and tissues, including neoplastic and immune cells. Although these models offer valuable insights into human biology, the resulting chimerism adds complexity and can produce distinctive pathological manifestations. In addition, the development of models with increasingly severe immunodeficiencies, together with the exchange of cells, tissues, and other biologics between laboratories, has amplified the impact of infectious agents. Previously unrecognized pathogens—and organisms once considered harmless commensals in mice—have emerged as important confounders. Several recently identified pathogens threaten research outcomes by modulating phenotypes or, in more severe cases, causing clinical disease and mortality in mouse colonies.

The discussion emphasizes the practical implications of these challenges for pathologists evaluating GEM models in preclinical studies. Some of these topics will be explored further through case examples presented by other speakers later in this session.

Keywords: genetically engineered mouse models; comparative pathology; model validation; immunodeficient mouse models; infectious confounders.

THURSDAY 1 OCTOBER 2026 | 09:50-10:10

MALT1 Highlights the Complexity of Interpreting Engineered Mouse Models for Translational Immunology

Alessandro Piaia

MALT1 Highlights the Complexity of Interpreting Engineered Mouse Models for Translational Immunology

Alessandro Piaia¹

¹ Novartis Pharma, Basel, Switzerland

Genetically engineered mouse models are widely used to understand target biology and help guide decisions in translational research. However, different types of genetic manipulations do not necessarily recapitulate the effects of pharmacological inhibition, particularly for multifunctional signaling proteins.

MALT1, a central component of the CARD11–BCL10–MALT1 complex for which several genetically engineered mouse models have been developed, serves as a clear example. MALT1 regulates T- and B-cells immune receptor-driven responses through both a scaffold function and a protease activity driving NF- κ B activation. Engineered mouse models targeting these distinct functions display divergent phenotypes. Both MALT1 knockout and MALT1 protease-dead mice exhibit impaired lymphocyte activation consistent with immunodeficiency, with immune defects more pronounced in MALT1 knockout animals. MALT1 protease-dead mice, expressing a catalytically inactive MALT1 that retain scaffold-mediated signaling, develop immune dysregulation, including regulatory T cell deficiency and multiorgan inflammatory pathology.

While pharmacological MALT1 protease inhibition can suppress inflammatory responses in preclinical pharmacology models, sustained inhibition is associated with dose-dependent reductions in regulatory T cells and emergence of progressive inflammatory pathology in rat and dog toxicology studies

Together, these findings demonstrate that knocking out the gene, or genetically/pharmacologically inactivating the catalytic site, highlights distinct functional aspects of the same target. MALT1 therefore exemplifies the challenges of translating engineered mouse model data into predictions of drug effects, emphasizing the need to integrate complementary approaches to accurately assess efficacy and safety.

The presentation will include representative histopathological pictures of MALT1 knockout and protease dead mouse characterization, as well as key findings from rat and dog toxicology studies with potent and selective MALT1 protease inhibitor.

THURSDAY 1 OCTOBER 2026 | 10:55-11:25

The practical advantages, disadvantages, and challenges of using GEMMs in Drug Discovery and Carcinogenicity Studies

Alys Bradley

The practical advantages, disadvantages, and challenges of using GEMMs in Drug Discovery and Carcinogenicity Studies.

Alys Bradley ¹

Shawna Jackman ²

¹ Charles River Laboratories, Edinburgh, United Kingdom

² Charles River Laboratories, Shrewsbury, United States

The mouse is an excellent experimental model for defining human gene function because of the genetic similarity to humans and ease of manipulation by molecular means. As well as defining molecular mechanisms and/or efficacy of therapeutic candidates, Genetically engineered mouse models (GEMMs) can predict the impact of chronic therapy, investigate molecular mechanisms of disease, evaluate innovative therapeutic targets, and identify efficacy and/or toxicity/potential side effects.

Advantages include: high specificity and accuracy; faster and more efficient production with rapid development; reduction of animal numbers as the models are more accurate so require smaller group sizes; model complex human diseases in a natural immunocompetent environment that are difficult/impossible to replicate in cell cultures; closely mimic the histopathological and molecular features of human diseases, making them superior for validating drug targets and evaluating mechanisms of drug resistance.

Disadvantages and Limitations include: lack/limited historical control for some models; heterogeneity in disease expression; limited life span and confounding physical effects of the disease; gene modification not resulting in the anticipated phenotype; high initial costs and specialized facilities/veterinary expertise; cost and availability of humanised animals; unintended Off-Target effects; incomplete disease replication; species differences; patents on GEMMs can restrict data and animal sharing among researchers.

GEMMs have been produced with an induced mutation of the oncogene *Ha-ras* which spontaneously occurs quite frequently in human neoplasms, and so TgrasH2 GEMs are slowly taking over the mouse arm for the evaluation of compound genotoxicity in carcinogenicity studies. TgrasH2 mice are more susceptible to genotoxic carcinogens than wild-type mice, supporting a reduction in both animal group size (250-400 vs 500-600 animals per study) and project timelines (26 – 40 rather than 80 weeks). There is now also a substantial amount of HCD in the CROs to fully support carcinogenicity tests in this GEMM.

GEMMs of human cancer have been successfully used to validate candidate drug targets, assess therapy efficacy, and evaluate mechanisms of drug resistance. Mouse models based on xenografting human cancer cell lines or allografting mouse tumor cells are the most commonly used *in vivo* tumor models in cancer research.

Patient-derived tumor xenografts (PDX) are derived from fresh human tumor biopsies that are transplanted into immunodeficient mice and then passaged *in vivo* directly from mouse to mouse, maintaining the cellular and histological structure of the original tumor. The introduction of a patient-derived tumor in a humanised mouse model gives you a mouse with a human immune system and a human tumor, and a model in which to evaluate PD-1 inhibitors, CTLA-4 inhibitors, IDO1 inhibitors, and other drugs involved in T-cell recognition and response to the tumor. Large-scale studies can now be carried out using PDX models to predict responses of clinical drug candidates. When promising preclinical results are obtained, the tolerability and anti-cancer efficacy of these drugs are evaluated in human patients in phase I–III clinical trials. A proportion of patients will show poor response due to intrinsic or acquired resistance, which may be studied

mechanistically in preclinical mouse models to identify response biomarkers and combination therapies to prevent or overcome resistance.

GEMMs are essential for studying musculoskeletal diseases such as Duchenne Muscular Dystrophy (DMD), and neurodegenerative diseases such as Alzheimer's (APP, PS1, Tau), Motor Neurone Disease (Amyotrophic lateral sclerosis) ALS (SOD1, SMN), Huntington's Disease (Q175KI, R6/2) and Parkinson's Disease.

This presentation will include case studies from two disease models, Duchenne Muscular Dystrophy (MDX) and Huntington's Disease (HET Q175 KI and R6/2) mice.

Muscular deficiencies are often associated with central and peripheral neuronal diseases. The X-linked muscular dystrophy (MDX) mouse (C57BL/10ScSn-Dmdmdx/J) models Duchenne Muscular Dystrophy. End-point measurements include basic monitoring and behavioural testing, as well as histopathology and imaging to assess neuromuscular degeneration and metabolic changes. A study design will be described to investigate the effects of a Test Item on a progressive muscular dystrophy MDX mouse model and histopathological samples (gastrocnemius, tibialis anterior and diaphragm) demonstrated. Pathological alterations in the muscles of MDX mice include: centralisation of nuclei within otherwise normal muscle fibres, infiltration of mononuclear cells, myonecrosis, and degeneration/regeneration causing variation in fibre size.

Huntington's disease (HD) is a rare, fatal, neurodegenerative genetic disorder that affects motor function and leads to behavioural symptoms and cognitive decline in young adults, resulting in total physical and mental deterioration over a 12 to 15-year period. HD is characterized by selective loss of striatal medium spiny neurons, forebrain atrophy, progressive motor and cognitive decline and psychiatric disturbance. Despite the clear aetiology, there are currently no disease modifying therapies to delay onset, or slow progression of a patient's decline.

B6CBAF1 transgenic R6/2 mouse (B6CBA-Tg(HDexon1)62Gpb/1J) is the most commonly used animal model of Huntington's disease and is a fast-progressing model. The objective of GEMM studies is to investigate the effects of single and/or repeated intracerebroventricular (ICV) injections with a novel Test Item. A study design will be described to investigate the effects of a Test Item on Behavior, Survival and Magnetic Resonance Imaging and Spectroscopy in R6/2 Huntington's Mice. Histopathology endpoints will be demonstrated from two studies in which the fore and mid brains were examined at eight levels between Bregma +1.10 mm and - 2.4 mm.

The Q175 knock-in (B6J.zQ175 KI ; Q175 Knock-In (wt x het)) mouse model closely mirrors the human genetic makeup of Huntington's disease, as the zQ175 knock-in allele replaces mouse Htt exon 1 by human HTT exon 1 sequence with ~180 CAG repeats. A Single Dose, Dose-Response Study of Test Item by Intra-striatal Injection with a 3-Month Investigation Period will be described and histopathology endpoints demonstrated.

THURSDAY 1 OCTOBER 2026 | 11:25-11:50

Humanized Mouse Models for Cell and Gene Therapy Safety: Power, Pitfalls, and the Pathologist's Perspective

Giovanni Pelligrini

Humanized Mouse Models for Cell and Gene Therapy Safety: Power, Pitfalls, and the Pathologist's Perspective

Giovanni Pellegrini¹

¹ Evotec, Verona, Italy

Humanized mice (Hu-mice) have emerged as one of the most ambitious attempts to bridge the long-standing translational gap between preclinical models and human biology in the development of cell and gene therapies. By incorporating functional human cells—most notably components of the human immune system—into immunodeficient murine hosts, these models promise a level of biological relevance that conventional animal systems often fail to deliver. In principle, Hu-mice offer a unique opportunity to interrogate human-specific pharmacology, biodistribution, efficacy, and immunotoxicity before first-in-human exposure, positioning them as powerful tools for regulatory decision-making in an increasingly complex therapeutic landscape.

However, the promise of Hu-mice comes with substantial caveats that challenge their widespread and uncritical adoption. Human immune reconstitution remains incomplete and highly variable, influenced by donor characteristics, conditioning regimens, engraftment strategies, and host strain. Key elements of immune complexity—such as robust myeloid function, fully functional antigen presentation, and sustained cytokine signaling—are only partially recapitulated, while xenogeneic graft-versus-host disease, limited lifespan, and lack of historical control data constrain long-term safety assessment.

A series of practical examples is presented to illustrate how the intrinsic limitations of Hu-mouse models may influence study interpretation, and to highlight the critical role of pathologists in navigating these complexities. In these chimeric systems, pathological assessment is essential not only to characterize biodistribution, engraftment, and target versus off-target effects, but also to distinguish treatment-related findings from model-related background changes, conditioning effects, or transplant-related pathology. The limitations of Hu-mice do not negate their value; rather, they highlight the importance of careful model selection, rigorous experimental design, and transparent communication of model boundaries when data are generated and used in a regulatory context.

Overall, Hu-mice represent a powerful complementary tool within an integrated nonclinical strategy. When applied in a purpose-driven and question-oriented manner, they can enhance the interpretability and human relevance of preclinical data, supporting more informed, biology-driven decision-making in the development of advanced therapies.

Keywords: humanized mice, immunodeficient models, cell and gene therapy, immunotoxicity, nonclinical safety, pathology

THURSDAY 1 OCTOBER 2026 | 11:50-12:15

Humanized Mouse Model for Nonclinical Safety Assessment of an Immunotherapeutic Monoclonal Antibody: Challenges and Lessons Learned

Deven Dandekar

Humanized Mouse Model for Nonclinical Safety Assessment of an Immunotherapeutic Monoclonal Antibody: Challenges and Lessons Learned

Deven Dandekar¹

¹ Eli Lilly and Company, Indianapolis, United States

When conventional nonclinical species lack pharmacological relevance, ICH S6(R1) directs sponsors toward transgenic or humanized animal models. For monoclonal antibodies targeting human-specific immune mediators, this is not uncommon; however, the biological challenges and logistics required to qualify humanized models are often underestimated.

Following regulatory feedback, a CD34⁺ human hematopoietic stem cells (huHSCs) of umbilical cord blood origin-engrafted BRGSF humanized immune system mouse was selected for a 3-month toxicology study with 1-month reversibility. Model selection hinged on confirmed reconstitution of human B cells, T cells, NK cells, and the myeloid compartment, including basophils expressing the relevant human target receptor — verified by flow cytometry and tissue immunophenotyping before the study began.

Practical challenges were considerable; in our experience, female BRGSF mice consistently achieved higher CD34⁺ huHSCs reconstitution than males following engraftment, reflecting a well-documented estrogen-driven advantage in HSC self-renewal and bone marrow niche support. To ensure all dose groups met the pre-specified humanization threshold, the study was designed with a sex-imbalanced group structure. Donor-to-donor variability in huHSCs engraftment required deliberate group allocation to avoid confounding factors in evaluating humanized mouse tissues. Blood volume constraints necessitated validated microsampling for toxicokinetics alongside prioritized clinical pathology endpoints. No historical control data existed for this model in our laboratory, requiring non-dosed surplus animals from all six donors to be carried throughout the study to generate concurrent background reference data.

For the pathologist, evaluating humanized mouse tissues demands familiarity with model-inherent observations — extramedullary hematopoiesis, disrupted lymphoid architecture, and variable human cell engraftment — that must be distinguished from test article effects. Species-specific immunohistochemistry (IHC) was essential and assigning the same pathologist across the range-finding and pivotal studies proved critical for interpretive consistency. On-target safety findings were identified that could not have been characterized in any conventional species, supporting the value of this approach when entered into with thorough prospective planning.

THURSDAY 1 OCTOBER 2026 | 16:16-17:00**Genetically engineered pigs for translational biomedical research and toxicological assessment: The NHPig Consortium and beyond***Tatiana Flisikowska***Genetically engineered pigs for biomedical research and toxicological assessment: The NHPig consortium and beyond.**Tatiana Flisikowska^{1, 2}Laura Beltran Sangüesa², Beate Rieblinger², Daniela Kalla², Wei Liang², Thomas Winogrodzki^{2, 3}, Krzysztof Flisikowski^{1, 2}¹ Poznan University of Life Sciences, Poznan, Poland² Technical University of Munich, School of Life Sciences, Freising, Germany³ Columbia University, New York, United States

Genetically engineered animal models are essential tools for understanding disease mechanisms, validating therapeutic concepts, and evaluating novel diagnostic, preventive, and therapeutic strategies. While rodent models remain widely used, their translational limitations frequently restrict their predictive value for human biology and disease. Pigs offer important advantages as large-animal models because of their closer similarity to humans in anatomy, physiology, metabolism, immune responses, and organ size. In particular, genetically engineered minipigs provide new opportunities for translational biomedical research, preclinical testing, and toxicological assessment. This presentation will provide an overview of genetically engineered animal models in pigs, with a focus on their development, characterisation, and potential applications in biomedical research. Examples will include porcine models for oncology and inflammatory diseases, as well as humanised models designed to improve the assessment of therapeutic efficacy, safety, and pharmacological responses. Particular attention will be given to the value of minipigs for studies requiring clinically relevant routes of administration, longitudinal monitoring, repeated sampling, imaging, biomarker analysis, and tissue-level validation.

The presentation will also introduce the NHPig consortium, which aims to establish and characterise next-generation minipig models for biomedical and pharmaceutical research. By combining genetic engineering, deep phenotyping, immunological profiling, multi-omics approaches, and biobanking, the consortium seeks to generate robust reference datasets and validated models that can support more predictive preclinical studies.

Finally, the talk will discuss future perspectives beyond NHPig, including the use of genome editing to generate disease-specific and humanised pig models, their integration into drug discovery pipelines, and their potential to reduce translational failure. Together, these developments highlight genetically engineered minipigs as a powerful and increasingly relevant platform for bridging the gap between experimental research and clinical application.

Keywords: genetically engineered pigs; minipigs; biomedical research; preclinical models; toxicological assessment; genome editing; NHPig consortium.

THURSDAY 1 OCTOBER 2026 | 17:00-17:45**New Strategies for Generating Rabbit and Non-Human Primate Models of Human Disease Using Pluripotent Stem Cells***Pierre Savatier***New Strategies for Generating Rabbit and Non-Human Primate Models of Human Disease Using Pluripotent Stem Cells**Pierre Savatier¹¹ INSERM, Lyon, France

For more than three decades, mouse pluripotent stem cells (PSCs), including embryonic stem cells (ESCs), have been instrumental in advancing our understanding of mammalian development and in generating models of human genetic disease. In combination with genome editing technologies, mouse PSCs have enabled precise genetic manipulation and mechanistic dissection of developmental processes. However, accumulating evidence highlights substantial differences between rodents and primates in developmental timing, gene regulatory networks, and lineage specification. As a result, many mouse models fail to faithfully recapitulate key aspects of human pathophysiology. This limitation has led to a growing consensus that non-human primates (NHPs) are required to model human development and disease more accurately, particularly for complex neurological, metabolic, and behavioral disorders.

Genome editing in NHP embryos has already demonstrated its potential. Initial studies using TALENs in rhesus and cynomolgus monkeys successfully targeted the *MECP2* gene, generating animals with phenotypes resembling Rett syndrome. Subsequent applications of CRISPR/Cas9 have enabled the disruption of genes such as *BMAL1*, *PINK1*, *SHANK3*, and *LDLR*, producing models for depression, Parkinson's disease, autism spectrum disorders, and familial hypercholesterolemia, respectively. Despite these advances, current strategies based on direct embryo editing remain inefficient and ethically challenging. They require large numbers of zygotes to obtain a single founder animal and rely on embryo transfer prior to genotyping, preventing pre-selection of correctly edited embryos. As a consequence, many animals are generated with unwanted genotypes, including mosaic or off-target mutations, leading to inefficient use of resources and ethical concerns regarding numbers of animals required in such studies. Furthermore, once founder animals are obtained, expanding cohorts remains a major bottleneck. Sexual reproduction in macaques is slow, with sexual maturity reached only after several years, meaning that generating experimental cohorts can take a decade or more. Somatic cell nuclear transfer (SCNT) offers an alternative route to rapidly expand genetically defined lines, but its efficiency in NHPs is extremely low. These limitations—low efficiency, delayed genotyping, long generation times, and poor cloning success—represent major barriers to use of genetically engineered NHP models.

To address these challenges, we aim to develop new PSC-based strategies for generating genetically modified rabbits and cynomolgus monkeys. Rabbits represent a valuable intermediate model due to their developmental and physiological similarities with primates and the availability of large numbers of embryos. Importantly, rabbit and NHP induced PSCs (iPSCs) share key molecular features, making the rabbit a relevant platform for methodological development. Our approach builds on multidisciplinary expertise in PSC biology, embryo manipulation, epigenetics, cloning, and reproductive technologies. We pursue two complementary strategies: (1) PSC-based germline chimeras, and (2) PSC nuclear transfer cloning (PSCNT).

The first strategy relies on the generation of germline chimeras through the introduction of naïve PSCs into pre-implantation embryos. These cells can integrate into the host embryo's stem cells and contribute to all somatic lineages, including the germline, enabling transmission of genetic modifications to subsequent generations. In rabbits, we have recently demonstrated the feasibility of this approach using genetically reprogrammed naïve-like iPSCs, leading to germline contribution. We now seek to extend this strategy using wild-type rabbit ESCs and iPSCs, in both male and female contexts, to establish robust and reproducible germline chimera systems. Building on these advances in rabbits, we will implement a similar strategy in cynomolgus monkeys. This represents a major technical challenge and requires several enabling advances, including the development of non-animal models to assess embryonic chimerism before large scale experiments with surrogate females, and *in vitro* gametogenesis systems to reduce generation time.

The second major strategy involves PSC nuclear transfer cloning (PSCNT). In this approach, naïve PSCs are fused with enucleated oocytes, allowing extensive epigenetic reprogramming and the generation of cloned embryos. Some of these embryos can develop to term following transfer into surrogate females. We seek to establish PSCNT in cynomolgus monkeys, building on our expertise in naïve pluripotency and nuclear reprogramming. To improve efficiency, we develop a "serial PSCNT" strategy, combining the use of bovine and primate oocytes with optimized epigenetic modifier treatments. This approach is expected to enhance nuclear reprogramming and increase the yield of viable cloned embryos.

Together, these complementary strategies are designed to resolve the key limitations of current NHP genome editing approaches. First, they will enable precise genetic modification at the PSC level, allowing rigorous genotypic validation prior to embryo generation and reducing the number of animals required. Second, they will facilitate the rapid production of cohorts of genetically identical animals, bypassing the need for prolonged breeding schemes. Third, they will allow the generation of mutant and control animals with identical genetic backgrounds, thereby reducing phenotypic variability and improving experimental robustness.

Friday 2 October Speaker Abstracts

Topic 2: NAMs – From Predictivity to Transability

FRIDAY 2 OCTOBER 2026 | 08:45-09:30

Keynote - A pathologist's role in the adoption of NAMs: Should we lead, follow, or get out of the way?

Brian R. Berridge

Bob Maronpot Guest Lecture Award - Keynote lecture is kindly sponsored by the IATP and the Telikicherla Higher Education Foundation

A pathologist's role in the adoption of NAMs: Should we lead, follow, or get out of the way?

Brian Berridge¹

¹ B2 Pathology Solutions LLC, Cary, North Carolina, United States

Animal studies have long served as a primary means of protecting patients and the public from the potential risks associated with pharmaceuticals and environmental exposures. Within their current context of use, they remain the most biologically and human-relevant modeling systems available. Toxicologic pathologists play a critical role in supporting animal studies by identifying and characterizing adverse effects across the many organ systems evaluated. However, like all model systems, animal models are imperfect and may be improved or, in some cases replaced by alternative approaches. As veterinary pathologists, we are committed to the responsible and judicious use of animals in biomedical research and reducing that use whenever scientifically appropriate.

A rapidly growing portfolio of New Approach Methodologies (NAMs) that include in vitro, in silico, and enhanced animal modeling capabilities is providing opportunity to gain better mechanistic insights into human-relevant responses to xenobiotics, to increase throughput, to be more predictive, and to reduce our use of animals. That portfolio of opportunity can be complemented by increasing acceptance of novel approaches that could improve the efficiency and effectiveness of preclinical drug safety and chemical hazard assessments.

Many have advocated that animal studies can and should be replaced by non-animal NAMs, prompting debate about whether such an approach can adequately protect patients and the public. Accordingly, our current approach to adopting new approaches is more competitive than complementary and NAMs have become more additive than subtractive capabilities. This significantly adds to the challenges we already have with the time, cost, and efficiency of drug development and chemical hazard assessment. As we are trying to explore how to best leverage these opportunities, the technology continues to progress at a rapid pace. Accordingly, we are at risk of relying too much on fragmented datasets generated in technological silos which could sabotage the clinical translatability and safety of compounds developed solely with non-animal models. We lack an aligned vision for the future of hazard and risk assessment, whether NAMs will be complements or superior replacements to usual animal-based approaches, and a roadmap for how to get there. Regulatory and societal expectations for human risk assessment of pharmaceuticals and environmental chemicals (e.g. agrochemicals) are varied and rapidly evolving. Pathologists, as primary contributors to animal studies, have an important role to play in designing and executing a roadmap defining the future of toxicology. It is up to us to define that role as "leading, following, or getting out of the

way”.

This presentation will provide an overview of our foundational rationale for using animal studies to predict human responses, the challenges to our current approaches, and opportunities to address those challenges with new capabilities. It will reference the growing number of opportunities to complement and even replace some current approaches. Lastly, it will propose a future state for safety and hazard assessment, an overview of evidence-based frameworks that may help us get there, and the critical role of pathologists in supporting the evolution to that future state.

The aims of this presentation are to:

- Acknowledge opportunities to improve drug safety and environmental hazard assessment through the use of NAMs.
- Advocate that the near-term opportunity is complementary rather than competitive.
- Demonstrate that pathologists are uniquely positioned to lead the evolution in our approaches that are more efficient, more informative, and more translationally predictive.

FRIDAY 2 OCTOBER 2026 | 09:30-09:50**Modernizing Nonclinical Safety Assessment: Weight of Evidence and NAMs***Nadine Stokar-Regenscheit***Modernizing Nonclinical Safety Assessment: Weight of Evidence and NAMs**Nadine Stokar-Regenscheit ¹Imein Bousnina ²¹ F. Hoffmann-La Roche Ltd, Basel, Switzerland² Genentech, US Regulatory Policy, Washington, DC, United States

The growing need for human-relevant translational models has accelerated adoption of new approach methodologies (NAMs), including organoids and microphysiological systems (MPS), in the early drug discovery process. Unlike conventional animal models, which often incompletely recapitulate human barrier biology, immune signaling, and pharmacologic responses, these platforms incorporate human-derived multicellular architecture, tissue mechanics, and physiologically relevant microenvironments enabling more predictive assessment of tissue responses, toxicity mechanisms, and therapeutic efficacy in humans.

Among NAM technologies, lung, intestinal, and skin systems are among the most mature epithelial platforms currently deployed in pharmaceutical research. Lung MPS models integrating air-liquid interface culture, perfusion, and cyclic stretch are increasingly used to study respiratory infection, fibrosis, inflammatory signaling, and inhaled therapeutics, offering improved human relevance over murine pulmonary models. Intestinal organoids and gut-on-chip systems enable investigation of oral absorption, transporter biology, microbiome interactions, and inflammatory bowel disease while overcoming species-specific limitations in gastrointestinal metabolism and immune responses observed in preclinical animal studies. Similarly, skin equivalents and skin-on-chip systems support translational studies of barrier function, inflammatory skin disease, wound healing, and safety pharmacology with greater physiological fidelity than traditional rodent or porcine models.

Current applications of these platforms include translational target validation, mechanistic biomarker discovery, phenotypic screening, and early-stage efficacy and safety de-risking. Although challenges remain in scalability, reproducibility, and standardization, mature epithelial NAM platforms are rapidly evolving from exploratory tools toward integrated components of modern drug discovery workflows.

FRIDAY 2 OCTOBER 2026 | 10:00-10:30**Pathologist's toolbox for in vitro model characterization and toxicologic pathology evaluation***Nadine Stokar-Regenscheit***Pathologist's toolbox for in vitro model characterization and toxicologic pathology evaluation**Nadine Stokar-Regenscheit ¹¹ F. Hoffmann-La Roche Ltd, Basel, Switzerland

To bring life-saving drugs to patients, health authorities require rigorous and mandatory safety testing following regulatory guidelines. Major global health authorities are currently revising guidelines to embrace non-standard testing approaches. This will open the door for future applications of non-standard approaches, for example the use of Complex in vitro models (CIVMs) in preclinical drug development. Veterinary pathologists are trained in comparative animal medicine which enhances their understanding of mechanisms underlying both human and animal diseases. This expertise enables them to bridge between animal models and human diseases. This skill set is important for CIVM development, validation, and data interpretation. Ideally, diverse teams of scientists, including engineers, biologists, pathologists, and others, should collaboratively develop and characterize novel CIVMs, and collectively assess their precise use cases (context of use). Implementing a morphological CIVM evaluation should be essential in this process. This requires robust histological technique workflows, image analysis techniques, and needs correlation with translational biomarkers. This session will focus on the pathologist's toolbox such as image-based tissue methods including hematoxylin and eosin staining (HE), immunohistochemistry (IHC), multiplex immunofluorescence (mIF), in situ hybridization (ISH) and Matrix Assisted Laser Desorption/Ionization Mass Spectrometry Imaging (MALDI-MSI) and AI/Digital Pathology methods to characterize and evaluate CIVM studies for drug toxicity assessments. Case examples will highlight the similarities and differences between CIVMs or "mini organs" and their in vivo tissue counterparts. The session also aims to lower the barrier for pathologists to become actively involved in in vitro safety assessment.

FRIDAY 2 OCTOBER 2026 | 11:00-11:30**Example 1: From Animal Models to Human Biology: Lung, Intestinal, and Skin NAMs in Drug Discovery***Dinesh Bangari***From Animal Models to Human Biology: Lung, Intestinal, and Skin NAMs in Drug Discovery**Dinesh Bangari¹¹ Sanofi, Cambridge, United States

The growing need for human-relevant translational models has accelerated adoption of new approach methodologies (NAMs), including organoids and microphysiological systems (MPS), in the early drug discovery process. Unlike conventional animal models, which often incompletely recapitulate human barrier biology, immune signaling, and pharmacologic responses, these platforms incorporate human-derived multicellular architecture, tissue mechanics, and physiologically relevant microenvironments enabling more predictive assessment of tissue responses, toxicity mechanisms, and therapeutic efficacy in humans.

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FRIDAY 2 OCTOBER 2026 | 11:30-11:55

Example 2: Leveraging Pathology to Advance New Approach Methodologies for Respiratory Toxicity Testing

James Baily

Leveraging Pathology to Advance New Approach Methodologies for Respiratory Toxicity Testing

James Baily¹

¹ Charles River Laboratories, Edinburgh, United Kingdom

In an effort to advance the use of New Approach Methodologies (NAMs) for respiratory toxicity assessment, CRL is undertaking an American Chemistry Council-funded project in collaboration with MatTek to characterise the direct toxicity of ten well defined respiratory toxicants in rat and human upper airway air-liquid interface (ALI) models. Semi quantitative pathology scoring and complementary quantitative image analysis endpoints have been developed and benchmarked against established cell permeability and viability assays. Acute and chronic exposure scenarios, as well as liquid and aerosolised test article application were compared.

This presentation will demonstrate how detailed pathology evaluation can play a critical role in assessing the performance and biological relevance of advanced in vitro airway models, guiding their refinement and supporting their progressive use—first to augment, and ultimately to selectively replace, in vivo respiratory toxicity studies.

FRIDAY 2 OCTOBER 2026 | 11:55-12:15**Example 3: Balancing Innovation and Evidence: Integrating In Silico, In Vitro, and In Vivo Approaches in Next-Generation Risk Assessment***David Rouquié***Balancing Innovation and Evidence: Integrating in silico, in vitro, and in vivo Approaches in Next-Generation Risk Assessment**David Rouquié¹Karen Tilmant², Frederic Schorsch²¹ BayerSAS, Sophia Antipolis, France² Bayer AG, Wuppertal, Germany

Next-generation risk assessment is reshaping toxicology by combining in vitro, in silico, and omics-based approaches to generate more human-relevant and mechanistically informed safety data. In this oral presentation, the promise of this framework will be discussed, while the scientific limitations that still constrain its routine application will be emphasized. The OASIS consortium will also be highlighted as an example of how multi-model and multi-omics strategies can improve our understanding of liver toxicity across different in vitro cellular systems. Currently, the most robust approach to risk assessment remains an integrated strategy in which in silico and in vitro methods are complemented, where necessary, by short-term in vivo studies enriched with omics readouts. This comprehensive and complementary framework supports a more efficient, ethical, and scientifically defensible decision-making process in next-generation risk assessment.

FRIDAY 2 OCTOBER 2026 | 12:15-12:35

Example 4: Translating nonclinical renal toxicity of novel antibiotics using kidney-on-a-chip models and urinary biomarkers

Steven Laing

Translating nonclinical renal toxicity of novel antibiotics using kidney-on-a-chip models and urinary biomarkers

Steven Laing¹, Tomomi Kiyota¹

Anna Engstrom¹, Min Tseng¹, Lanlan Yu¹, Mike Reichelt¹, Colin Dimond¹, Yuan Chen¹, Ramakrishna Rachumallu¹, Tanja Zabka¹

¹ Genentech, South San Francisco, United States

Introduction: Two novel antibiotics exhibited dose-limiting kidney toxicity in rats and dogs, with no observed adverse effect levels (NOAELs) at or below projected clinical exposures. Kidney-on-a-chip (KOC) models were used to investigate the human relevance of this finding.

Materials and Methods: Histopathology findings from toxicity studies were further characterised by electron microscopy. Urinary biomarkers, including bis (monoacylglycerol)phosphate (BMP) and kidney tubular biomarkers, were assessed. Human KOC models were used to evaluate concentration-cytotoxicity and biomarker relationships. These data informed a Phase 1 escalation strategy with robust renal monitoring including urinary BMP, kidney injury molecule-1, clusterin, cystatin-C, lipocalin-2, osteopontin, N-acetyl-beta-D-glucosaminidase, albumin, and total protein.

Results: Histopathology identified renal cortical tubular epithelial cell degeneration and necrosis. Tubular phospholipidosis, confirmed by electron microscopy and urinary BMP elevations, occurred at subtoxic exposures, preceding elevations in serum and urinary kidney tubular biomarkers at overtly toxic doses. In vitro models did not demonstrate significant cytotoxicity at concentrations exceeding projected clinical levels. However, these systems did not demonstrate phospholipidosis, limiting mechanistic concordance. Phase 1 escalation beyond the rat NOAEL was successful. Elevated urinary BMP was noted without clinically significant nephrotoxicity based on intensive serum creatinine assessments.

Conclusions: Integrated nonclinical in vitro and in vivo data supported clinical progression despite narrow safety margins in animals. KOC models may be useful to rank nephrotoxic compounds, but their inability to recapitulate key pathological features of these antibiotics highlights uncertainty for their use in quantitative risk assessments. A weight-of evidence approach, anchored in pathology and clinical monitoring, remains essential.

FRIDAY 2 OCTOBER 2026 | 12:35-12:50**Example 5: Leveraging the complementary strengths of tissue cross-reactivity and cell-based protein array technologies for off-target assessment***James T Raymond***Leveraging the complementary strengths of tissue cross-reactivity and cell-based protein array technologies for off-target assessment**James Raymond¹¹ Charles River Laboratories, Reno, United States

Preclinical safety evaluation of biologics for both off-target and on-target, off-disease effects is essential for clinical development and success, as unintended binding to non-target tissues can lead to serious adverse consequences. Recent regulatory guidance recommends comprehensive strategies for off-target screening of biologics, highlighting the need for an integrated approach that combines multiple methodologies including tissue-based assays like Tissue Cross-Reactivity (TCR) studies and cell-based protein array assays like Retrogenix®. Furthermore, the FDA announcements in April and December 2025, of a plan to advance public health by replacing animal testing in the development of monoclonal antibody therapies with more effective, human-relevant methods (so-called New Approach Methodologies or NAMs) further underscores the need for a comprehensive off-target screening strategy utilizing TCR and cell-based protein array assays.

A retrospective study of TCR and Retrogenix® data at Charles River Laboratories found that from 2020 to 2025, 47 test articles were assessed with the combination of TCR and Retrogenix® assays, of which 45 test articles worked on both TCR and Retrogenix®. All test articles (100%) had matching TCR and Retrogenix® on-target results demonstrated by test article positive staining of the positive control(s), and there was a 73% correlation of TCR and Retrogenix® data for test articles that either had matching no off-target staining ("clean" TCR and Retrogenix® studies) or 1 or more matching off-target staining. Of the 45 test articles evaluated, 18 test articles had monkey, rat, mouse, and/or mini-pig toxicologic pathology reports available for review and the TCR and Retrogenix® data was predictive of the toxicologic pathology findings in 12 of 18 test articles (67% predictive rate). Specific case examples will be presented.

In conclusion, combining cell-based protein array assays such as Retrogenix® with TCR studies provides a strong comprehensive approach to off-target screening of biologics. This dual approach provides the complementing off-target with its cellular localization (the "where") and its protein identification (the "what") that is human relevant. TCR and cell-based protein array assays have low false negative rates for on-target binding and together can reduce false positive and false negative rates for off-target binding thus strengthening the preclinical safety characterization and risk assessment of biologics.

Poster Abstracts

Incidental Benign Nasal Adenoma in a NZW Rabbit: A Histopathological Case Report

Satish Panchal ¹

Vasanthi Mowat ¹, Paul Edwards ¹, Kalaiselvan Ponnusamy ¹

¹ Labcorp Huntingdon, Cambridgeshire United Kingdom

Introduction:

Nasal tumors in rabbits are rare, with most reported cases being malignant; benign nasal adenomas are exceptionally uncommon and not documented in recent case series of spontaneous intranasal tumors. During a nonclinical toxicity study in New Zealand White (NZW) rabbits, an unusual nasal lesion was identified, prompting histopathological characterization.

Methods:

The affected male NZW rabbit, 17 week old at euthanasia, was part of a 6-week study involving intramuscular dosing of vaccine on Days 1, 15, and 29, followed by intranasal and intratracheal administration on Day 43, with a 2-week recovery period. No clinical signs or gross lesions were noted. Nasal cavity sections (Levels 5 and 6) were evaluated microscopically and compared with controls and standard reference images for rabbit nasal turbinates.

Results:

Histology revealed a well-demarcated, non-invasive proliferation of well-differentiated glandular structures lined by non-ciliated cuboidal to low columnar epithelial cells with basophilic cytoplasm and centrally placed nuclei—findings consistent with a **nasal adenoma**. No features suggestive of adenocarcinoma (e.g., invasion, marked pleomorphism) or olfactory neuroblastoma (e.g., rosettes, neuroendocrine morphology) were present. This lesion occurred in only one study animal, and no comparable findings were seen in other rabbits or in literature reports under similar conditions.

Conclusion:

This case represents a rare benign nasal adenoma in an NZW rabbit. The absence of clinical, gross, or invasive features supports an incidental spontaneous lesion. This case adds to the limited documentation of benign nasal neoplasms in rabbits and highlights the value of thorough nasal cavity histopathology in nonclinical studies.

INHAND: International Harmonization of Nomenclature and Diagnostic Criteria for Lesions - An Update

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Introduction:

Since the inception of INHAND (International Harmonization of Nomenclature and Diagnostic Criteria for Lesions in Rats and Mice) in 2005, a Global Editorial Steering Committee (GESC) composed of representatives from the Japan, Europe, British and US Societies of Toxicologic Pathology has coordinated objectives and publications of the ongoing project. Development of terminology for rodent organ systems and non-rodent species is the responsibility of working groups, with globally recognized experts from North America, the United Kingdom, Europe, Japan and other regions.

Methods:

All rodent organ systems have been published in Toxicologic Pathology or the Journal of Toxicologic Pathology, including Respiratory, Hepatobiliary, Urinary, Nervous, Male and Female Reproductive, Mammary, Zymbal, Clitoral and Preputial Glands, Hematolymphoid, Integument and Soft Tissue, Digestive, Cardiovascular, Skeletal, Special Senses and Endocrine Systems. Publications are available as journal supplements and on www.goReni.org, where change control updates are uniquely available. Rabbit, Non-human Primate, Mini-pig and Dog terminology was published in 2021. Non-rodent ocular toxicity nomenclature was published in Toxicologic Pathology in 2024 and the final non-rodent species, Fish, was published in Journal of Toxicologic Pathology in 2026. The Medical Device working group is making progress as well.

Results:

INHAND offers nomenclature, diagnostic criteria, differential diagnoses, images, commentary and references to guide recording of microscopic findings in nonclinical toxicity and carcinogenicity studies. INHAND GESC representatives work with Clinical Data Interchange Standards Consortium (CDISC) to incorporate INHAND terminology as preferred terminology for SEND (Standard for Exchange of Nonclinical Data) submissions to the US FDA, with wide acceptance of this nomenclature by global health authorities.

Spatial mapping of oligonucleotide biodistribution and target knockdown in the brain using 6-plex FISH/IF

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Introduction:

Spatial profiling of oligonucleotide biodistribution and target mRNA knockdown (KD) at cellular resolution is critical for identifying new targets, safety liabilities, and delivery strategies. Image analysis from FISH/IF (Fluorescence In Situ Hybridization/Immunofluorescence) using FFPE material offers relative quantification, improves technical feasibility, and provides spatial information from accessible FFPE tissue.

Methods:

FFPE brain samples from mice (n=4/group) IV treated with brain-shuttled oligonucleotides for 16 days (5xQ3D) were compared to vehicle controls. A multiplex FISH/IF methodology detected the oligonucleotide and target mRNA by FISH, and neurons (NeuN), astrocytes (GFAP), microglia (iba1), and endothelial cells (CD34) by IF. Quantitative image analysis at single-cell resolution related cellular oligonucleotide uptake to target mRNA expression across brain regions and cell types. qPCR on RNA extracted from the same FFPE blocks was used for cross-validation.

Results:

Global brain analysis showed uniform oligonucleotide exposure with broad oligo distribution (>60% of all cells positive); and uniform uptake in neurons, astrocytes, microglia and endothelial cells. Potent target mRNA KD was confined to neurons (target expressed in neurons only), with variation across brain regions, closely matching qPCR data despite similar oligonucleotide delivery, indicating region-specific pharmacodynamics.

Conclusion:

High-plex FISH/IF on FFPE material maps the oligonucleotide "biodistribution-efficacy" relationship at cellular resolution, identifying accessible cell types and regional KD patterns undetectable by bulk analysis. This platform provides a scalable complement to bulk and sequencing-based spatial methods for CNS oligonucleotide programs, delivering multi-dimensional datasets that facilitate a holistic interpretation of the distribution of the siRNA and the subsequent cellular response.

Histopathology-triggered Mass Spectrometry Imaging (MSI): optimizing sample collection and storage to bridge morphological patterns and chemical specificity

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Introduction:

Routine histology staining provides an unparalleled morphological context but often lacks the chemical specificity required to characterize unknown morphological changes, crystals, pigments, and other deposits, such as parent compounds or their metabolites. Mass Spectrometry Imaging (MSI) can bridge this gap, acting as a "molecular microscope" to enable label-free visualization of drugs and metabolites in situ, overlaid on histological sections. An integrated workflow, in which initial histopathological findings trigger targeted MSI analysis, is described.

Methods:

We evaluated critical pre-analytical variables, freezing methods (slow- vs snap-freezing), embedding media, and storage conditions, to propose standardized operative procedures.

Results:

Pre-analytical variables significantly impacted data quality. Slow freezing at -80°C induced ice crystal artifacts and molecular delocalization (in case of crystals); standard Optimal Cutting Temperature (OCT) embedding media caused severe signal suppression due to polymer interference. In contrast, snap-freezing in pre-cooled isopentane or Carboxymethyl cellulose (CMC)/Gelatin mixture preserved both morphology and molecular localization. An integrated workflow resolves diagnostic ambiguities beyond the reach of standard histochemical stains, as proven by several cases (e.g. MSI successfully differentiated drug-induced renal crystals from endogenous molecules and identified drug metabolites within hepatic Kupffer cell pigments).

Conclusion:

Analytical success in MSI is determined at the necropsy table: a "garbage in, garbage out" principle applies. Pathologist-driven region of interest selection maximizes efficiency, while a standardized protocol - immediate snap-freezing, avoiding OCT, and generally maintaining a cold chain - is essential. This collaborative approach enables definitive chemical identification of lesions, confirming cause-and-effect relationships, for an informed decision-making process in drug research and development.

Similarity Search-Based AI for Lesion Detection and Grading Support in Toxicologic Pathology Evaluation

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Introduction:

AI-assisted diagnostic tools are increasingly implemented in the field of pathology in human medicine. However, the scalability of supervised AI models in toxicologic pathology is limited by the vast combinations of organs, species, and lesion types required to detect diverse lesions and findings. We therefore explored AI-based similarity search using toxicologic pathology whole slide images (WSIs) with diagnoses. Existing similarity search methods have mainly focused on human pathology, whereas their applicability to toxicologic pathology for lesion detection and grading support is under development.

Methods:

WSIs of rat hearts with cardiomyopathy (n=10, 10 WSIs) and non-human primate livers with or without cholangitis (n=14, 28 WSIs) were analyzed. Feature vectors were extracted from tiled WSIs using H-optimus-0. Mean vectors of representative lesion tiles annotated by pathologists were used as queries to retrieve similar tiles from WSIs. Retrieved regions were evaluated by pathologists. In cholangitis, normalized lesion tile counts were compared with histopathologic grades.

Results:

Lesions were successfully identified across WSIs. In cardiomyopathy slides, we can detect the lesions in the atria using the query from ventricle, indicating robustness to tissue heterogeneity. In cholangitis slides, lesions with varying severity were captured. Retrieved tile extent showed good agreement with pathology grades. Although some false positive and negative occurred, overall concordance with pathologist evaluation was high.

Conclusion:

Similarity search effectively identified lesions and showed potential for semi-quantitative grading. This approach enables efficient retrieval and visualization of lesions, supporting diagnosis without extensive supervised training. Further optimization and evaluation are ongoing to expand applicability

QuPath workflows in digital pathology: expectations vs. reality

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Introduction:

Open-source digital pathology tools such as QuPath can be used by anyone for quantitative tissue analysis. However, applying the same workflow across different research projects remains challenging, and reproducibility is often limited. We retrospectively evaluated a standardized QuPath workflow across collaborative projects processed in our comparative experimental pathology core facility to identify recurrent problems and practical limitations.

Methods:

Four projects were analyzed, including lymphoid tissue from an endogenous mouse model, human colorectal cancer xenografts in mouse tissue, murine intestinal organoids, and mouse lung tumor syngrafts, all immunohistochemically stained. A uniform workflow was applied consisting of stain vector estimation, thresholding, cell detection, positive cell detection, object classification, and data export. Project-specific classifiers were trained to distinguish relevant structures (e.g., tumor, normal tissue, necrosis, epithelial cells, debris, tissue folds). Workflow performance and recurring problems were documented.

Results:

Our workflow was applicable across all datasets, provided that image quality was optimal. Reliable performance required project-specific optimization and manual adjustments. Recurrent limitations included inaccurate watershed-based cell segmentation, especially for membranous staining, staining gradients, background signals, and false-positive detections caused by folds or debris. Small or complex structures, such as organoids, required manual annotation.

Conclusion:

QuPath is a powerful software for digital pathology and standardized workflows enhance data consistency. However, reliable tissue quantification depends on optimal image quality and project-specific pathological expertise for validation of cell segmentation and classification outputs. Hence, full automation remains difficult in practice, highlighting the gap between expected and practical performance of QuPath workflows in heterogeneous experimental pathology settings.

Influence of Fixative Type and Fixation Duration on Protein and Nucleic Acid Labeling

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Introduction:

The ESTP Pathology 2.0 Molecular Pathology subgroup is currently evaluating the pre-analytical variables that influence protein and nucleic acid labelling. Among these, the type of fixative and the duration of fixation are critical factors. Standard practice typically involves fixation in 10% neutral buffered formalin for 24-48 hours in. However, in some cases, the fixation time extends to several months, or other fixatives may be used. Such variations can significantly affect the labelling.

Methods:

Different protein labelling assays were performed after different fixation times and using different fixatives, including cytokeratin immunohistochemistry (IHC) following a one-year formalin fixation period in different species (rats and dogs). In addition, the effect of using Davidson's solution on RNA preservation for *in situ hybridization* (ISH) was evaluated.

Results:

Among presented cases, cytokeratin protein labelling remained feasible even after a one-year fixation time, and Davidson's solution appeared unsuitable for ISH resulting in absence of labelling of the positive probe control.

Conclusion:

While some proteins can still be reliably detected after prolonged fixation, labeling efficiency is target-dependent and variable. Fixative type and fixation duration can significantly impact assay performance, necessitating case-by-case validation and use of appropriately fixed controls. For ISH, inclusion of a positive control is essential to confirm RNA preservation, particularly when non-standard fixation conditions are used. Overall, optimal fixation conditions and standardized protocols are recommended when downstream protein and nucleic acid analyses are planned.

AI meets EM: Automated detection and quantification of lamellar bodies in phospholipidosis

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Introduction:

Phospholipidosis is characterized by excess phospholipid accumulation in lysosomes and can be induced by various drugs. Electron microscopy (EM) remains the gold standard for detecting characteristic intracellular membrane-bound lamellar bodies. However, these structures may deviate from their canonical morphology, complicating diagnosis.

Methods:

To support diagnostic assessment on low-magnification images, improve accuracy, and enable classification of atypical lamellar bodies, a deep learning-based workflow was developed for detection and quantification in EM images. A proof-of-concept study was conducted on images from ultra- and semithin sections from rodent kidney and liver. The model was based on the Cascade R-CNN architecture and trained on fixed-size image tiles extracted from the original images. The dataset comprised 13 images (9 training, 2 validation, and 2 held-out test images). Typical lamellar bodies were annotated as positive, while areas of normal tissue served as negative control.

Results:

Preliminary results show reliable detection of classical lamellar bodies across magnifications from 315x to 5000x. Ongoing refinements include expanding annotations to atypical forms (atypical-loose, atypical-dense) and empty lysosomes. Visual outputs will be evaluated against independent annotations made by board-certified toxicologic pathologists. An additional quantification metric will be introduced to ensure standardized, reproducible assessment.

Conclusion:

This AI-based model constitutes a promising decision-support tool for evaluating xenobiotic-induced phospholipidosis, including diagnostically challenging cases in non-clinical toxicity studies.

Generation and Use of Clinical Pathology Reference Intervals in Nonclinical Safety Assessment

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Introduction:

The generation of Reference Intervals can provide valuable added information when evaluating nonclinical safety assessment studies. These reference intervals can be used when evaluating studies with fewer animals or no concurrent control groups or to evaluate diagnostic clinical pathology data for an individual animal

Methods:

We can extract control and prestudy data from our global laboratory management system and can apply selection criteria including laboratory site, instrumentation, species, strain, animal origin, sex, age groups and experimental conditions including fasting or nonfasting. We have the ability to partition the data and generate ranges with specific inquiries including nonroutine parameters and routes of administration. After extraction of the raw data from our laboratory data system we have a defined process using Reference Value Advisor to generate statistical reports.

Results:

Following review of these reports for any outliers we use nonparametric methods to establish the central 95% of the healthy population and 90% confidence intervals of the reference limits in samples having a minimum of 120 individuals. Once scientifically reviewed the reference intervals are available for consultation in a central location and can help with data interpretation.

Conclusion:

The production and use of robust reference intervals for clinical pathology data can provide invaluable additional assistance when evaluating data from study designs with fewer animals or limited concurrent control data.

From Slide to Signal: AI-Based Detection and Quantification of α 2u-Globulin

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Introduction:

α 2u-globulin is a low-molecular-weight protein mainly present in the kidney of adult male rats. Certain drugs bind to α 2u-globulin, promoting its accumulation and resulting in hyaline droplet nephropathy, characterized by eosinophilic droplets in the proximal tubular epithelium, along with tubular necrosis, regeneration and granular casts. Consistently detecting test item-related increases in droplet number and size on routine H&E slides remains challenging, due to subtle morphological changes, staining variability, whole slide image resolution, and interobserver variability. Consequently, immunohistochemical (IHC) staining is often required, adding workload to pathology workflows.

Methods:

To support diagnosis, an artificial intelligence (AI)-based image analysis model was developed to detect and quantify α 2u-globulin-associated hyaline droplets. A proof-of-concept study used paired H&E and α 2u-globulin IHC whole-slide images (WSI), with IHC-guided annotation of H&E tiles, supplemented by H&E negative controls. 74 positive and 147 negative annotations were generated at sub-tile resolution. Tile embeddings (224 px, 0.5 μ m/px) were extracted using a pathology foundation model (Kaiko ViT-B/8). Lightweight classifiers were trained to identify droplet accumulation at 4 μ m resolution. Results were visualized as heatmaps.

Results:

The model detects renal cortical regions containing droplets and quantifies droplet burden relative to cortical area. Preliminary results demonstrate reliable detection across severities, including subtle changes, with ongoing validation against annotations by board-certified toxicologic pathologists.

Conclusion:

This AI-based model represents a promising decision-support tool for standardized and reproducible assessment of α 2u-globulin in male rat kidney H&E WSIs, supporting toxicologic pathologists in study evaluation while maintaining expert oversight.

ESTP Committee Pathology 2.0 - update of activities

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Introduction:

Pathology 2.0 is a ESTP committee that brings together toxicologic pathologists and non-pathologist scientists from industry, contract research organizations and academia/research institutions with a shared interest in classic and emerging technologies in toxicologic and investigative pathology.

Methods:

The group provides a collaborative forum to discuss scientific advances, assess their relevance for pathology practice, and support their implementation in drug discovery and development.

Results:

The goals of Pathology 2.0 are to raise awareness of state-of-the-art pathology techniques, share knowledge and experience, identify scientific and regulatory challenges, and contribute to recommendations and best practices for the pathology community. Pathology 2.0 is composed of focused subgroups covering molecular pathology, multiplexing, spatial omics, mass spectrometry imaging, complex in vitro models and pathology, and humanized mice.

Conclusion:

The objective of this poster is to update the pathology community on the current activities, progress, and priorities of Pathology 2.0 and its subgroups, while encouraging discussion and engagement with technologies shaping the future of toxicologic pathology.

Comparative microscopic anatomy of the external auditory canal of laboratory animals.

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Introduction:

The characterization of the normal microscopic anatomy of the external auditory canal in laboratory animals is important for veterinary diagnosis and toxicological evaluation of auricularly administered drugs. Although the human external auditory canal has been well described, information regarding laboratory animals remains limited.

Methods:

After intravenous euthanasia, both external auditory canals (EACs) were collected from clinically healthy 3 CD-1 mice, 3 Wistar rats, 2 New Zealand White rabbits, 2 beagle dogs and 2 cynomolgus monkeys. EACs were fixed in formalin, placed in decalcification fluid, trimmed (2 to 5 sections) and sectioned with a thickness of 6 µm. All glass slides were scanned at 40X with a NanoZoomer S360 (Hamamatsu Photonics K.K.) scanner, and uploaded to Patholytix™ viewing software, where pictures were taken at 1.25, 5, 20, or 40X.

Results:

Unlike in humans, the lateral external auditory canal of rodents and dogs contains fewer glands and hairs than the medial external auditory canal, with very small pilosebaceous units that become more numerous and larger towards the tympanic membrane. Cynomolgus macaques appear relatively similar to humans, whereas rabbits display a distinct anatomy of their own.

Conclusion:

Accurate description and knowledge of the normal microscopic anatomy of the EAC in various laboratory animal species are of particular interest to scientists involved in the development of drugs for auricular administration.

High-Throughput Ovarian Toxicology Assessment Using 3D Imaging and AI-Based Follicle Segmentation and Classification

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Introduction:

Two-dimensional (2D) histopathology is the current gold-standard for assessing toxicology in ovaries. However, it can be a time-consuming process limited by section-to-section variability, subjective interpretation and sampling bias.

To overcome these limitations, we have developed a 3D imaging platform that allows for comprehensive analysis of the whole ovary, combining high-throughput light-sheet microscopy with deep-learning AI segmentation, providing unbiased assessment of multiple ovary endpoints across different species.

Methods:

Whole mouse ovaries were processed using iDISCO whole-organ immunohistochemistry targeting CD31 (vasculature), MVH (oocytes), AMH (granulosa cells), and CC3 (apoptosis), followed by optical clearing and light-sheet fluorescence microscopy. Deep-learning AI segmentation models for mouse ovaries were developed to compute ovary endpoints in vehicle and cyclophosphamide (150 mg/kg) treated mice.

Results:

We developed an automated platform for both quantifying total follicle numbers in entire ovaries and for accurate assessment of the maturation stage of individual follicles. By applying multiple criteria based on MVH, AMH and CC3 staining as well as 3D volumetric analysis of oocyte diameter and entire follicle morphology, every follicle in the ovary could be classified into primordial, primary, secondary, antral or pre-ovulatory stages, while also detecting atretic follicles. As a proof of concept, we show the impact of cyclophosphamide treatment on reducing overall follicle number is driven by substantially depleted primordial and primary follicle reserves.

Conclusion:

Our 3D imaging platform provides accurate, unbiased and high-throughput quantification of ovarian endpoints, with scalability across multiple species. The approach has the potential to complement and enhance conventional histopathological assessment in reproductive toxicology studies.

AI-Assisted Ovarian Follicle Analysis in a Chemotherapy-Induced Primary Ovarian Insufficiency Mouse Model

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Introduction:

Classification and counting of ovarian follicles are widely used endpoints in the evaluation of animal models of reproductive disorders and reproductive toxicology. However, manual scoring is prone to inter- and intra-observer variability, which can compromise reproducibility. This study aimed to develop and validate an automated deep learning-assisted digital image analysis pipeline, termed GHOST (Gubra Histopathological Objective Scoring Technology), for objective assessment of preantral follicle staging in mouse models.

Methods:

Ovaries from mice aged 9–15 weeks were formalin-fixed, paraffin-embedded, sectioned, and stained with p63 (Abcam, Ab124762), followed by digital scanning. Whole-slide images were divided into 512×512 pixel tiles. p63-positive oocytes were annotated using the Segment Anything Model (SAM) and used to train a U-Net for oocyte detection and segmentation. For each detected oocyte, a 299×299 pixel image tile was extracted and classified by an expert histopathologist according to follicle stage. These annotated tiles were used to train an InceptionV3 convolutional neural network for follicle staging. The pipeline was implemented in Python 3.13.

Results:

A total of 400 follicles were manually classified into primordial, transitional, primary, and secondary stages. The dataset was curated to ensure variability and split into training, validation, and test sets. The model was trained using Keras for 300 epochs with an Adam optimiser, incorporating data augmentation techniques. The final model demonstrated substantial agreement with manual scoring (Cohen's kappa = 0.7) on the test set.

Conclusion:

GHOST provides a fast, unbiased, and reproducible method for automated preantral follicle detection and staging, supporting improved consistency in histopathological assessment.

Fiber optic cannulae implant-associated suppurative meningoencephalitis in Long-Evans rats

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Introduction:

Fiber optic cannulae with ceramic ferrule cranial implants are widely used in neuroscience, including fiber photometry, to record neuronal activity in freely moving rodents. Although generally well tolerated, two cases are described here where these devices were associated with mechanical injury and infectious complications.

Methods:

Two male Long-Evans rats (3-month-old) from a behavioral and cellular activity study were submitted for necropsy following the unexpected death of one animal and euthanasia of a moribund cage mate. Both animals carried cranial implants consisting of a skull-mounted polymer device secured with anchoring screws and connected to a fiber optic cannulae with ceramic ferrule, implanted one month prior to death or euthanasia. Full necropsy, histopathology, and ancillary bacteriological testing were performed.

Results:

Grossly, both rats showed implant-associated changes. Including multiple cortical depressions corresponded to screw locations. In one animal, a plastic rod extended from the implant into the cerebral parenchyma, with direct penetration. Histologically, both cases showed moderate-to-severe multifocal-to-coalescing neutrophilic meningoencephalitis extending to the cranial nerve roots (trigeminal nerve), with choroid plexus erosion, fibrinoid vasculitis, and necrosis. Implant-associated cortical injury with parenchymal rarefaction and neutrophilic infiltration was observed. *Escherichia coli* was isolated from the meninges in one case, with Gram-negative bacilli observed histologically.

Conclusion:

These cases illustrate severe suppurative meningoencephalitis associated with cranial implants used for fiber photometry, related by direct cortical trauma from anchoring screws and implant components, and bacterial infection in one of the animals. They highlight the potential for combined mechanical and secondary bacterial CNS injury in experimental animals with head implants.

Influence of including the sphenoid bone as protocol organ on pituitary gland pars distalis carcinomas incidences in rodent carcinogenicity studies

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Introduction:

Within the Registry of Industrial Toxicology Animal-data (RITA) project, incidences of pre-neoplastic and neoplastic lesions in control animals of rodent carcinogenicity studies are collected, including tumors of the pituitary gland pars distalis. As per INHAND nomenclature, pituitary carcinomas are distinguished from adenomas mainly by invasion into the meninges, brain or sphenoid bone. Assessment of sphenoid bone is, however, limited, as it is typically only captured indirectly within sections of Zymbal's gland. Because the Zymbal's gland is not a mandatory guideline organ, the adjacent sphenoid bone is not routinely evaluated.

Methods:

From the RITA database, incidences of pituitary carcinomas of the pars distalis were compared between rodent studies which did or did not include the Zymbal's gland as protocol organ. Also, the tissues infiltrated by the carcinomas were compared regarding the site and pattern of infiltration (brain, meninges, sphenoid bone).

Results:

The incidence of carcinomas was slightly higher in studies in which the sphenoid bone was present in Zymbal's gland sections compared to studies without this protocol organ. Furthermore, some tumors were, in the absence of infiltration in brain sections, diagnosed as carcinomas solely due to their infiltration into the sphenoid bone or adjacent meninges included in the Zymbal's gland section.

Conclusion:

To obtain more reliable results on the biological behavior (benign vs. malignant) of pituitary pars distalis tumors, it is recommended to include the sphenoid bone as protocol organ in rodent carcinogenicity studies. This approach would support the generation of more accurate historical control data of pars distalis carcinomas.

Quantifying the Impact of Artificial Intelligence-Driven Decision Support on Toxicologic Pathology Workflow: A Time-and-Motion Study

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Introduction:

Artificial intelligence-based decision support tools (AI-DSTs) hold the promise to support lesion detection and increase diagnostic confidence. Rigorous evaluation of their impact on pathologist experience, while controlling for learning and order effects, is essential for informed implementation.

Methods:

A randomized crossover study was conducted using two cohorts of board-certified toxicologic veterinary pathologists reviewing de-identified digital pathology study material. Cohort A completed an initial review with access to the AI-DST, followed by at least an 8-week washout period and a second review without AI support. Cohort B completed the same reviews in the reverse order. Pathologists closely tracked time spent evaluating each tissue in both instances. After each session, pathologists completed structured surveys assessing target organ identification, lesion recognition and grading, diagnostic confidence, and perceived value of the AI-DST as a second-opinion tool. Planned analyses include within-reader comparisons, cohort comparisons, and evaluation of order effects.

Results:

Preliminary data suggests a meaningful gain in review efficiency, while diagnostic performance metrics (including lesion detection, grading, and diagnostic confidence) remain stable across conditions.

Conclusion:

This randomized crossover study offers a controlled framework for evaluating the impact of AI-DST on pathologist experience. Complete results will provide a comprehensive assessment of the benefits and limitations of AI-assisted review, with implications for the responsible integration of AI-DST in toxicologic pathology.

Quantitative Pathology in pre-clinical studies: Are we there yet?

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Introduction:

In biopharmaceutical and medical device research, early nonclinical studies are often conducted as isolated, outsourced projects with substantial variability in design, endpoints, and tissues examined. Quantitative pathology offers a more granular alternative to traditional ordinal scoring by providing continuous and quantitative data in common histopathological changes, lesions and *in situ* molecular markers. However, creation of robust algorithms is hindered by low intra-study numbers of images; the variations in staining, scanning parameters and the choice of reporting systems in *in situ* assays.

The aim of this work was to analyze the outcomes of study-specific approaches of quantitative pathology with various software and study types.

Methods:

We compiled examples in which deep neural network models and other approaches from several software platforms were effectively trained on limited datasets to detect well-defined histopathological changes within small studies. Methods of validation, where used, are presented.

Results:

Results from selected case studies showed that model outputs align closely with pathologist assessments and fall within the range of inter-observer variability for region annotation, supporting their applicability in quantitative pathology workflows within and across similar studies. Hence, this approach and the delivery of quantitative, objective and reproducible data can complement the pathologist's visual scoring and initial assessment, not only on histological images, but also to quantitatively assess RNA or protein expression at (sub-)cellular level and in its spatial context.

Conclusion:

Despite limitations, applicability of quantitative pathology to select types of changes and lesions is shown, with performance not inferior or similar to experienced pathologists.

Spinal Cord Neuronal Mineralization in *Kcnma1*-Deficient Mice with Gait Abnormalities

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Introduction:

The large-conductance calcium-activated potassium (BK) channel, encoded by *Kcnma1*, is an important regulator of neuronal excitability and motor function. Mice lacking BK channel activity have been reported to exhibit motor deficits and impaired coordination. The present study investigated potential morphological correlates of gait abnormalities observed in a colony of *Kcnma1*-deficient mice.

Methods:

Seven mice aged 3–4 months were submitted for pathological examination, including male and female heterozygous and homozygous animals. Five mice showed an unstable gait, predominantly affecting the hind limbs, whereas two heterozygous mice appeared clinically normal. Complete necropsy was performed, followed by histological examination of the brain, spinal cord, and inner ear. Alizarin Red staining was used to confirm suspected mineralization.

Results:

Gross pathological examination revealed no significant abnormalities in any animal. Histological evaluation identified focal neuronal mineralization within the gray matter of the thoracic spinal cord. Early lesions appeared to involve the neuronal nucleus. Mineral deposits were confirmed by Alizarin Red staining in two animals, including one homozygous and one heterozygous mouse. No relevant morphological alterations were detected in the brain or inner ear. Correlation between lesion severity, genotype, and clinical phenotype is currently under investigation.

Conclusion:

These preliminary findings identify thoracic spinal cord mineralization as a potential morphological alteration in *Kcnma1*-deficient mice presenting with gait abnormalities. The localization of lesions within spinal gray matter suggests a possible contribution to the observed motor phenotype. Further studies are required to determine the relationship between BK channel deficiency, neuronal mineralization, and neurological dysfunction.

ESTP/STP Complex in vitro models & Pathology WG - Perspectives on the Evolving Regulatory Landscape on New Approach Methodologies

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Introduction:

With increasing emphasis from global regulatory bodies on reducing animal use in nonclinical research, several recent initiatives and policy frameworks have emerged, including those from the US Congress and the Food and Drug Administration (FDA). Similar efforts have been underway in Europe and other regions, although the shift remains relatively recent in the US. In this context, the ESTP/STP Complex In Vitro Model (CIVM) and Pathology working groups aim to provide a measured and scientifically grounded perspective on these evolving regulatory directions.

Methods:

New Approach Methodologies (NAMs) encompass a broad range of tools, including in vitro, in silico, and ex vivo systems, that are being explored to support nonclinical safety assessment. While these approaches are increasingly being incorporated into drug development, it is important to recognize that there is no single, uniformly accepted framework. With the exception of certain well-established use cases (e.g., skin sensitization), most NAM applications, particularly complex in vitro models (CIVMs), remain context-dependent and continue to evolve.

Results:

Accordingly, the value of these models lies not only in their potential, but in the appropriateness of how they are applied. Careful consideration must be given to the specific scientific question being asked, the context of use, and the inherent limitations of each model. At present, NAMs are best viewed as complementary tools that can inform and refine nonclinical strategies, rather than broadly replace animal studies.

Conclusion:

In addition to keeping a pulse on global regulations, the ESTP/STP CIVMs & Pathology working groups emphasize the importance of engaging pathologists and investigative scientists in the critical evaluation of CIVMs and NAMs. Pathologists are particularly well

positioned to assess biological relevance, interpret findings in context, and help define appropriate applications and limitations, ensuring that these emerging approaches are integrated thoughtfully and rigorously into safety assessment paradigms.

Immune modulation in Cynomolgus macaques and latent viral diseases: the case of Simian Parvovirus.

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Introduction:

Immunosuppression in nonclinical toxicity studies may result from primary drug-related effects while secondary factors can contribute. An impaired immune function can increase opportunistic infections or reactivate latent viruses, potentially confounding study results and adversity assessment, especially when immune modulation is the intended pharmacology. This case describes a Simian Parvovirus (SPV) infection in immunomodulated *Macaca fascicularis*.

Methods:

Data were gathered during a 13-weeks pivotal general toxicity study on *Macaca fascicularis* treated with an immunomodulatory antibody. Beyond *in vivo* toxicological endpoints, bone marrow cytology and pathogen-specific serology were performed. Histopathological investigations were complemented in selected cases by SPV *in situ* hybridization (ISH). The study was conducted in compliance with European and local animal health regulations.

Results:

Three treated juvenile females showing clinical signs suggestive of anemia underwent unscheduled euthanasia during the recovery period. Clinical pathology revealed decreased red blood cell mass and reticulocytes, anisocytosis, and hypochromasia. Bone marrow cytology showed increased myeloid:erythroid ratio, and dyserythropoiesis. At histopathology, the bone marrow showed decreased erythroid cellularity, single cell necrosis, and eosinophilic intranuclear inclusion bodies in erythroid precursors (positive to SPV with ISH). Similar findings in terminal animals were noted, albeit with milder severity.

Conclusion:

In this study, recrudescence of- or *de novo* SPV infections are believed to result from the test item's immunomodulatory action. Viral replication caused necrosis of erythroid precursors and dyserythropoiesis, leading to acute nonregenerative anemia. Since immunomodulation may similarly predispose humans to infections in clinical trials, these findings and their translation to humans should be carefully considered.

Performance of a Single-Class Unsupervised AI-Based Histology Anomaly Detector on Rat Heart from Nonclinical Toxicology Studies

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Introduction:

Introduction – A single-class, unsupervised AI-based anomaly detector trained using whole slide images (WSI) of Han Wistar rat hearts from vehicle control groups was studied to understand the utility and limitations of this method for prioritizing histology evaluations in exploratory toxicology studies.

Methods:

Methods – Studies conducted in 3 test facilities were selected including 5 treated groups with test article-related cardiac histopathology and 9 treated groups without identified test article-related findings. WSI were analyzed for anomalies. Data collected were annotation layers highlighting anomalous histology and out of distribution (OOD) score (affected tissue area/total tissue area). Annotations and OOD-scores were compared with diagnoses by Study Pathologists.

Results:

Results – Annotation layers accurately highlighted regions of cardiac histology different from vehicle controls. OOD-scores from a study conducted in 1 of the 3 test facilities were not comparable to other studies due to an increase in anomaly detections in the auricles attributable to a histology artifact in the specimens. Using a threshold based on concurrent controls, OOD-scores were insensitive for flagging WSI for review that contained small foci of myocardial degeneration, although the degenerative foci were correctly annotated as different from control. In one treated group, OOD-scores and annotations highlighted a previously unidentified cardiac histomorphology finding attributable to test article.

Conclusion:

Conclusion – Single class unsupervised anomaly detection shows promise as a screening tool for heart histology slides from nonclinical studies, however, utility depends on tight control of preanalytical variables. Moreover, simple summation metrics, such as OOD-score can be insensitive to focal histopathology findings.

Nonclinical Safety and Immunogenicity of AdCLD-CoV19-1 LP.8.1 in Sprague-Dawley Rats

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Introduction:

AdCLD-CoV19-1 LP.8.1 is a recombinant adenoviral vector-based vaccine candidate targeting the emerging SARS-CoV-2 LP.8.1 variant. This study evaluated the nonclinical safety, local tolerance, and immunogenicity of AdCLD-CoV19-1 LP.8.1 following repeated intramuscular administration in rats.

Methods:

Male and female Sprague-Dawley rats received vehicle or AdCLD-CoV19-1 LP.8.1 by intramuscular injection at 2-week intervals for a total of three administrations. Clinical observations, body weight, food consumption, body temperature, ophthalmology, hematology, clinical chemistry, urinalysis, organ weights, gross pathology, and histopathology were evaluated. A 4-week recovery period was included to assess reversibility of treatment-related findings. In addition, anti-spike IgG binding antibodies were analyzed using a non-GLP immunogenicity assay.

Results:

No mortality or treatment-related adverse clinical signs were observed throughout the study. Transient increases in body temperature post-administration were consistent with the expected vaccine response. Treatment-related findings included increased basophil counts, decreased albumin/globulin ratios, increased spleen weights, and mononuclear cell infiltration at injection sites. These findings were associated with the pharmacological action of the vaccine and generally recovered following the recovery period. Spike-specific IgG binding antibodies against SARS-CoV-2 LP.8.1 increased following repeated administration.

Conclusion:

Repeated intramuscular administration of AdCLD-CoV19-1 LP.8.1 produced treatment-related inflammatory and immune-associated changes without toxicologically significant systemic effects. All treatment-related findings showed reversibility and were consistent with the expected pharmacological response to vaccination, demonstrating a robust and favorable induction of spike-specific IgG binding antibodies.

Air–Liquid Interface Models of Human Airway Epithelium for Enhanced Drug Discovery and Safety Assessment

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Introduction:

In vitro models and new approach methodologies (NAMs) provide ethical, cost-effective, and disease-relevant complements to animal testing for drug discovery and toxicological screening. Air–liquid interface (ALI) cultures of primary human bronchial epithelial cells (HBEs) recapitulate key structural and functional features of the airway epithelium. Here, we describe the development, validation, and application of advanced ALI systems, including monoculture and multicellular co-culture models, under basal and stimulated conditions.

Methods:

Detailed methodological information will be provided in the poster.

Results:

IL-13 stimulation (1–30 ng/mL) induced a robust goblet cell hyperplasia phenotype, evidenced by concentration-dependent epithelial thickening, increased goblet cell numbers, and mucous cyst formation. These changes were supported by increased secretion of eotaxin-2/-3, upregulation of CCL24, CCL26, POSTN, FOXA3, and MUC5AC genes, and increase of MUC5AC protein level. Pharmacological validation using reference and test compounds across multiple modalities (small molecules, oligonucleotides, biologics) demonstrated the model's ability to discriminate between drugs with different levels of biological activity and potency, with some compounds exhibiting concentration-dependent reversal of morphological and molecular endpoints, whereas others only partial or no activity.

To enhance physiological relevance and investigate epithelial–mesenchymal crosstalk, an ALI co-culture model incorporating normal human lung fibroblasts was established. Following TGF- β 1 exposure, monocultures displayed epithelial disorganization, cyst-like structures, and ~3-fold induction of IL1 β , TNF α , and IL-6 expression. In contrast, co-cultures preserved epithelial architecture and showed minimal cytokine induction, indicating a modulatory, protective role of fibroblasts.

Conclusion:

Together, these complementary ALI-based models recapitulate key features of airway remodeling and intercellular interactions, providing scalable, reproducible, and mechanistically informative platforms for integrated therapeutic screening and safety assessment.

A framework for spatially resolved investigation of respiratory viral infections in the nasal cavity

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Introduction:

Many respiratory viruses initiate infection in the nasal mucosa, where early virus-host interactions shape disease progression and transmission. Despite its central role, the nasal cavity remains insufficiently characterized in infection studies due to its anatomical complexity and technical challenges of tissue processing and spatial analysis. Although advanced, spatially resolved technologies enable high-resolution investigations, they are still technically demanding, costly, and analytically complex, limiting their routine application. Consequently, most studies rely on descriptive histopathology or bulk molecular analyses, lacking the spatial context.

Methods:

Here, we present a framework for spatially resolved investigation of the nasal cavity. Using wild-type SARS-CoV-2 and two live-attenuated vaccine candidates (OTS-206, OTS-228) in the Syrian hamster model, we integrated standardized tissue sampling, histopathology, immunohistochemistry, multiplex RNA in situ hybridization, and quantitative image analysis to characterize viral distribution, tissue alterations, immune cell infiltration, and host gene expression within defined anatomical and functional compartments, infection sites, and the microenvironment, from tissue to single-cell and subcellular resolution.

Results:

Application of this framework revealed distinct infection patterns with gradually decreasing tissue damage and attenuation from wild-type to OTS-206 to OTS-228, accompanied by an early macrophage-dominated response. Infection associated gene expression indicated that, despite limited infection, the highly attenuated OTS-228 strain induced a regulatory, tissue-preserving immune response. At subcellular level, both OTS constructs, in contrast to wild-type, facilitated the nuclear export of host mRNAs encoding interferons and interferon-stimulated genes.

Conclusion:

Overall, we provide a structured, accessible, and scalable framework that integrates spatial pathology and molecular analyses to analyze the nasal cavity.

Training and Validation of an AI Model for quantitative histopathological analysis in a polyhexamethylene guanidine (PHMG)-induced murine pulmonary fibrosis model.

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Introduction:

Polyhexamethylene guanidine (PHMG)-induced pulmonary fibrosis is a devastating disease. Its toxicity may pose serious risks to human health. We aimed to develop a highly accurate AI-based model which can be used for mechanistic studies and screening potential therapeutic agents using mouse model.

Methods:

Twenty-five male mice received intratracheal PHMG (0.9 mg/kg), while 25 control mice received saline. Four weeks later, 500 lung tissue sections (10 different sections/mouse) were collected, fixed, sectioned, and stained with hematoxylin and eosin. All slides were scanned at 20× magnification. Representative lesions were categorized into 3 classes and lesion datasets were generated for macrophage aggregation, interstitial fibrosis, and epithelial hyperplasia, with 2,000 labeled images prepared for each category. DenseNet architecture with the Adam optimizer and learning rate 0.00001 was used for model training using an NVIDIA GeForce RTX4090 GPU. The trained model was used to classify representative 40 sections by each lesion. The correlation between the pathologist's lesion severity grade and the lesion area predicted by model was examined using Spearman correlation.

Results:

The model accuracy reached 97.92%. Quantification of AI-based classification and pathological grading showed strong correlations for macrophage aggregation (Spearman's $\rho = 0.91$), interstitial fibrosis (0.95), and epithelial hyperplasia (0.94).

Conclusion:

These results demonstrate that the developed AI model can serve as a reliable quantitative analysis tool for pulmonary fibrosis. Future studies will expand the analysis to the remaining all lung sections to further characterize the pathological features of pulmonary lesions.

Long-Term Safety and Biodegradation Assessment of a Coated poly(glycerol ester urethane) (PGEU)-Based Spacer Following Bilateral Sub-Acromial Implantation in Rats

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Introduction:

The safety and biodegradation of a novel coated poly(glycerol ester urethane) (PGEU)-based spacer were evaluated. The device features a highly porous bulk scaffold and a denser outer coating, aimed to create a physical buffer between the humeral head and the acromion to alleviate pain and restore function in patients with full-thickness, massive, rotator cuff tears (MRCTs).

Methods:

The poly(glycerol ester urethane) (PGEU)-based spacer was implanted bilaterally into the sub-acromial space of Sprague-Dawley rats (Test) and compared against a sham surgical procedure (Control). The safety and degradation profile were assessed over 53 weeks via in-life clinical signs, body weight measurement, clinical pathology analysis and comprehensive histopathology.

Results:

The procedure was well-tolerated; all animals survived to scheduled termination with normal weight gain and no abnormal clinical signs. Histologically, implant sites presented a well-circumscribed nodules enclosed by maturing fibrous capsules. Nodules showed peripheral compartments containing the transparent device and a central accumulation of macrophages, giant cells, and minor fibroplasia, characteristic of a localized foreign body reaction (FBR). The dense outer coating effectively reduced initial permeability, slowing surface degradation and delaying cellular infiltration relative to the porous scaffold. By study's end, only trace sequestered biomaterial and localized immune sentinel cells remained with mild fibrosis, indicating a steady state of repair. The device maintained physical integrity during the initial phases of healing, with no local or systemic toxicity noted.

Conclusion:

The coated poly(glycerol ester urethane) (PGEU)-based coated spacer demonstrates a controlled degradation profile and a non-adverse, progressively resolving FBR, consistent with complete physiological bioabsorption and localized tissue restoration.



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