EUROPEAN CONGRESS OF
TOXICOLOGIC PATHOLOGY
PRECEDED BY IATP SYMPOSIUM

23-26 SEPTEMBER 2025
MANCHESTER UK

2ND JOINT CONGRESS OF BSTP & ESTP

PROCEEDINGS BOOK

BSTP

European Society of Toxicologic Pathology
estp

BSTP-ESTP-CONGRESS.EU

23-26 SEPTEMBER 2025

MANCHESTER UK

2ND JOINT CONGRESS OF BSTP & ESTP

WELCOME

Dear colleagues and friends

Welcome to the 2nd joint BSTP/ESTP congress in the city of Manchester. This is also the 22nd congress of the ESTP and the 40th of the BSTP. Manchester, located in northwest England, has a rich and dynamic history. Originally a Roman settlement called Mamucium in 79 A.D., it grew modestly through the medieval period as a market town. Its transformation began during the Industrial Revolution in the late 18th century, when it became a global hub for textile manufacturing, earning the nickname "Cottonopolis." The city was at the forefront of technological innovation, with the world's first industrialized cityscape and the opening of the Manchester Ship Canal in 1894, connecting it to the sea.

Today, Manchester has transitioned into a diverse and modern city. Key industries include advanced manufacturing where Manchester is a leader in advanced materials including graphene, digital and creative industries, as well as life science and healthcare. The city is home to world-class institutions like the University of Manchester and Manchester University NHS Foundation Trust, fostering cutting-edge advancements in biotechnology, pharmaceuticals, and medical technologies. Manchester's Health Innovation initiative HInM integrates academia, healthcare, and industry to accelerate the adoption of innovative solutions. The city also boasts a strong focus on precision medicine, digital health, and clinical trials, supported by its extensive healthcare infrastructure and skilled workforce.

The topic of our congress, "**Carcinogenicity in the 21st century**", may be considered well suited for Manchester, as it spans from the well-established process of carcinogenicity testing with the 2-yr bioassay to recent developments including in silico assessment, in vitro methods, omics technologies, and Weight of Evidence Assessments. The role of the pathologist in the evolving process of carcinogenicity risk assessment will be highlighted. We will present the current state of the 2-year bioassay together with pointing to the shortcomings of this way of carcinogenicity risk assessment and the controversial debate of its usefulness.

Evolving technologies that are already now, or will in the future, inform the carcinogenic potential of a molecular entity, will be presented next. We will continue highlighting the challenges associated with drug candidates belonging to new modalities like protein degraders or gene therapy. The new and still evolving approach of "Weight of Evidence Assessment of carcinogenic potential" will conclude the scientific program. This final part will compare the procedure and status for agrochemicals and pharmaceuticals. Interactive case presentations will be interspaced throughout the program, representing the applied science aspect. Distinguished work will be recognised with the IATP Maronpot Guest Lecture Award, the ESTP Science Award, the BSTP Chirukandath Gopinath Lecture Award, the ESTP publication award, and the SFTP poster award.

An industry exhibition and sponsored presentations will communicate recent developments made by your key suppliers. We encourage you to also attend the satellite meetings. These are an ESTP Expert Workshop on adversity and human relevance of effects to the female reproductive tract on Monday and an IATP symposium on Pathology Working Groups on Tuesday morning before congress opening.

We acknowledge the dedication and voluntary efforts of the ESTP and BSTP members serving on the Scientific Organizing Committee and the service of our professional congress organizer (PCO – Partner in Congress Organization). Furthermore, we are grateful to our sponsors and exhibitors for supporting this congress so generously. Finally, we welcome you to meet and exchange with colleagues and friends during breaks, the poster and industry exhibition, the welcome reception at the Skybar of the Manchester Deansgate Hotel, and the congress dinner at the Science and Industry Museum.

On behalf of the organizing committee, we thank you for joining us and contributing to the success of this event. Welcome to Manchester, and welcome to the 2nd Joint ESTP/BSTP congress!

Sincerely,

Ute Bach, Jonathan Carter, Zuhal Dincer, and Thomas Nolte (co-chairs)
On behalf of the Scientific Organizing Committee

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Organization

Chairs Scientific Organizing Committee | BSTP representatives
Jon Carter, *Head of Pathology, Labcorp, United Kingdom*
Zuhal Dincer, *Head of Pathology Sciences, Sequani, United Kingdom*
Chairs Scientific Organizing Committee | ESTP representatives
Thomas Nolte, *NonClinical Safety and DMPK, Boehringer-Ingelheim, Germany*
Ute Bach, *Head of Pathology and Clinical Pathology, Bayer AG, Germany*

Scientific Organizing Committee
Antonia Morey Matamalas, *Charles River Laboratories, UK*
Barbara Lenz, *Roche, Switzerland*
Cécile Sobry, *Labo-Novaxia, France*
Charlotte Dalsgaard, *Novonordisk, Denmark*
Dirk Schaudien, *Fraunhofer ITEM, Germany*
Emily Meseck, *Novartis, USA*
Fabienne Lien, *Royal Veterinary College, UK*
Frederic Schorsch, *Bayer, France*
Heike Marxfeld, *Basf, Germany*
Jacqui Stewart, *Labcorp, UK*
Laetitia Elies, *Charles River Laboratories, France*
Maike Huisinga, *Basf, Germany*
Matthew Jacobsen, *AstraZeneca, UK*
Sandra De Jonghe, *Johnson&Johnson, Belgium*
Sébastien Laurent, *Sanofi, France*
Shelley Patrick, *Alnylam, USA*
Xavier Palazzi, *AstraZeneca, USA*

Session Leads
Shelley Patrick, *Carcinogenesis / Best Practice*
Frederic Schorsch, *New Approach Methodologies for Carcinogenicity Evaluation*
Emily Meseck, *New Modalities and Carcinogenicity Assessment*
Sandra De Jonghe, *Data Interpretation*
Xavier Palazzi, *Carcinogenicity Risk Assessment*

Representatives for the IATP Satellite Symposium
Ramesh Kovi
Heike-Antje Markfeld

Congress Organisers
Partners in Congress Organisation
Mrs. Mirel Kostons, m.kostons@pcopartners.nl, T +31(0)43 321 84 80
Avenue Ceramique 222, 6221 KX Maastricht, The Netherlands

Useful information

The Manchester Deansgate Hotel

303 Deansgate, Manchester M3 4LQ, United Kingdom

We are excited to host this year's congress at the The Manchester Deansgate Hotel, located in the heart of Manchester's city center. Set within the iconic Beetham Tower, this venue offers exceptional facilities, breathtaking views, and an ideal location for both local and international attendees. Making it an excellent choice for hosting congresses. Easily accessible by train, tram, and just a short drive from Manchester Airport, the venue is perfectly situated for seamless travel. The congress will take place in the hotel's versatile event spaces, including the Deansgate Suite for scientific lectures and it's foyer that houses the poster and exhibition area.

Registration Desk

The registration area in the conference centre will be open for registration and questions on:
Monday 22 September: 07.30-17.30
Tuesday 23 September: 08.00-18.00
Wednesday 24 September: 07.30-18.00
Thursday 25 September: 08.00-17.00
Friday 26 September: 08.00-11.00

Please note that the official currency at the congress is the Euro. At the registration desk cash, cheques and foreign currencies are not accepted.

The registration fee includes

- Admission to all scientific sessions (separate registration required for IATP Satellite Symposium & Expert Workshop)
- Admission to the exhibition area
- Lunch on all days
- Daily coffee breaks
- Final Program booklet
- Welcome reception
- Congress dinner

WIFI
You will have free WIFI access on-site in the congress venue.
Network: **Deansgate Hotel**, Password: **Conf2025**

Congress badges
All participants, accompanying persons and exhibitors must wear the identification badges. Entrance to meeting halls and exhibition area will not be permitted to any person without badge.

Certificate of attendance
A certificate of attendance can be downloaded after submission of the online evaluation which will be requested to be filled in after the congress. You will receive an invitation via email after the congress.

Congress rooms
The plenary lecture room is in Deansgate Suite 2 & 3. The exhibition hall, posters and catering are located in the surrounding Deansgate foyer and Deansgate Suite 1.

Interactive Slides
For the interactive presentations we kindly ask you to download the App Slido on your smart phone.

GET IT ON Google Play

Download on the App Store

Poster Presentations
Posters will be exhibited during the entire congress in the Deansgate Foyer. Authors are kindly requested to be at their posters on Wednesday during the afternoon coffee break and on Thursday during the morning coffee break to answer potential questions.

Anything lost?
Please go to the registration desk.

Language
The official language of the congress is English.

Mobile phones
Please silence your mobile phones during the lectures.

Photography, Videotaping, Recording Policies
Photography of poster presentations is prohibited without the specific consent of the presenter(s)/author(s). Photography of exhibitor booths and/or equipment is prohibited without the specific consent of the exhibitor. Photography, videotaping, or recording of the Scientific Sessions is not permitted.

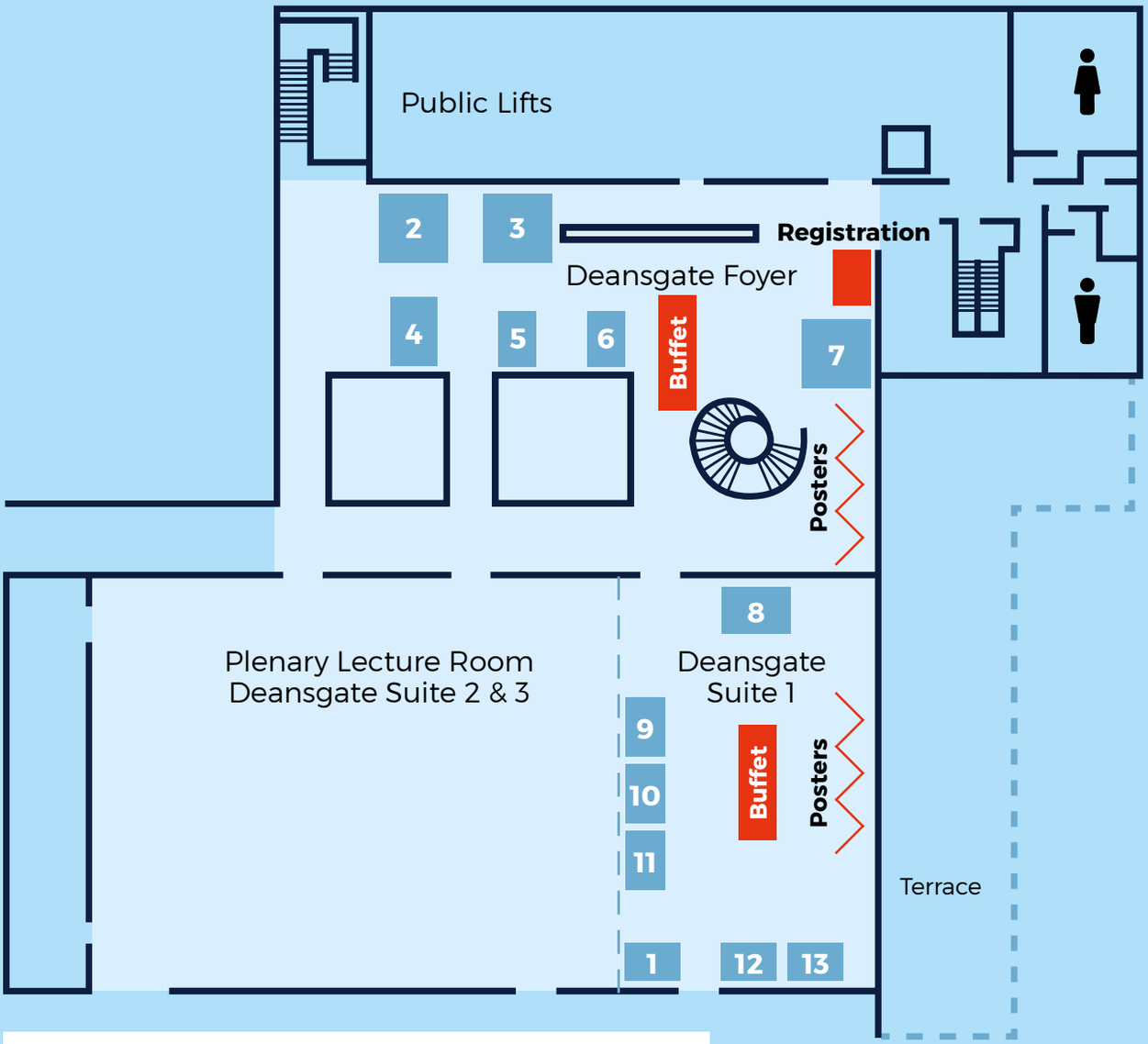
City Map

A **The Manchester Deansgate Hotel**
Congress Venue & Welcome Reception

B **Museum of Science & Industry**
Congress Dinner

- Exchange Square & New Cathedral Street
- Northern Quarter
- Petersfield
- Manchester Arndale & Market Street
- Deansgate, King Street & St Ann's Square
- Spinningfields
- Castlefield
- The Gay Village
- Oxford Road
- Chinatown

Exhibition Floor Plan



1. Histofy
2. Pathology Experts
3. 3D Histech
4. INSTEM
5. Resero Analytics
6. BSTP
7. Hamamatsu
8. Standard Bio
9. Deciphex
10. Aiforia
11. ERBC
12. PathQA
13. Biomed Linkage

Awards

BSTP Gopinath Lecture Award

The award, instigated by the British Society of Toxicological Pathology in 2008, was due in part to the BSTP's involvement in the organization of the scientific program of the 2008 Annual ESTP Congress held in Edinburgh. To mark the occasion, the BSTP sponsored the keynote lecture and since then this sponsorship has become a tradition at the ESTP Congresses. The sponsored lecture was called the BSTP Chirukandath Gopinath Lecture in tribute to one of the founder members of the BSTP whose name is recognized by toxicological pathologists all over the world. The lecture is to be on a topic in pathology relevant to practicing toxicological pathologists. The speaker is an internationally recognized scientist and is chosen by the scientific organizing committee and approved by the BSTP council.

Maronpot Guest Lecture

This award recognizes Dr. Robert Maronpot for his significant contributions to the field of toxicologic pathology and the advancement of the IATP. This lecture award is sponsored through an educational grant provided by The Telikicherla Higher Education Foundation.

Poster Award

Award for the Best Poster sponsored by the French Society of Toxicologic Pathology (SFPT)

Société Française de Pathologie Toxicologique

ESTP Science Award

The ESTP science award honors an individual who has significantly advanced the field of toxicology through his/her work in education, research, practice and/or actively supported the work of the ESTP.

IATP Satellite Symposium

Tuesday 23 September 2025 | The Manchester Deansgate Hotel
303 Deansgate, Manchester M3 4LQ, United Kingdom

Registration fee

IATP Satellite Symposium €205 (Prices are incl. 20% UK VAT). The registration fee includes admission to the IATP scientific sessions, Coffee break and Lunch

Pathology Working Groups (PWG) in Toxicologic Pathology

Pathology Working Groups (PWG) are specialized panels of expert pathologists convened to provide independent, unbiased assessments of specific questions that arise during pathology peer review or presented by regulatory authorities. PWGs play a crucial role in establishing appropriate nomenclature and diagnostic criteria for pathology findings of interest or novel findings, as well as addressing issues that may result in a clinical hold on candidate compounds. PWGs are routinely conducted by the U.S. National Toxicology Program (NTP) for rodent carcinogenicity studies in environmental chemical hazard identification and risk assessment. The 2025 International Academy of Toxicologic Pathology (IATP) Satellite Symposium will provide historical perspectives and context with current applications of PWGs and modified PWGs in risk assessment for environmental chemicals and pharmaceuticals. Key topics will include:

- Background and historical perspectives of PWGs at NTP/DTT/NIEHS
- A comparison of PWGs in the chemical industry and pharmaceutical sector.
- The evolution and application of Expert Working Panel (EWP)
- Regulatory perspectives from FDA and other regulatory agencies.
- Panel discussion featuring experts from pharmaceutical and chemical industry, academia/government organizations, contract research organizations (CROs), and regulatory agencies.

08.00-09.00	**Registration**
	Chairs: *Heike-Antje Markfeld & Douglas Wolf*
09.00-09.10	**Welcome and Introduction** *IATP Education Committee*
09.10-09.55	**The peer review process in the Division of Translational Toxicology (DTT) and the U.S. National Toxicology Program (NTP)** *Mark Cesta*
09.55-10.40	**Pathology Working Groups: Reviews to address specific scientific and/or regulatory issues** *Paul Snyder*
10.40-11.10	**Coffee break**
11.10-11.40	**Expert Working Panel (EWP) - a modified PWG: Confirming the morphologic diagnosis is only the first step** *Maurice Cary*
11.40-12.10	**PWG - Perspectives from the agrochemical realm** *Frederic Schorsch*
12.10-12.55	**Panel discussion**
12.55–13.00	**Closing remarks** *IATP Education Committee*
13.00-14.00	**Networking lunch - Exhibition**

Tuesday 23 September 2025

BSTP-ESTP CONGRESS

12.30-14.00 **Networking lunch - Exhibition - Registration BSTP-ESTP Congress**

14.00-14.15 **Welcome BSTP-ESTP** Chairs: *Vanessa Schumacher & Peter Clements*

Keynote lecture

Chairs: *Jacqui Stewart & Shelley Patrick*

14.15-15.00 **Keynote lecture: The two-year bioassay: What we have learned** *Samuel Cohen*

Carcinogenesis / Best Practice

Chairs: *Jacqui Stewart & Shelley Patrick*

15.00-15.30 **Navigating the complexity of carcinogenicity testing: a toxicologist's perspective** *Helen-Marie Dunmore*

15.30-16.00 **Coffee break - Posters - Exhibition**

Chairs: *Antonia Morey Matamalas & Ute Bach*

16.00-16.15 **Case Study: Hepatocellular foci in rodents: Lowering the threshold for recording** *Leslie Bosseler*

16.15-17.00 **Just another study type? Challenges and pitfalls with the histopathological evaluation of carcinogenicity studies** *Matthias Rinke*

17.00-17.30 **Carcinogenicity studies: A CRO's unique perspective of peer review and beyond** *Torrie Crabbs*

17.30-18.00 **Open discussion of topic** *Samuel Cohen, Matthias Rinke, Helen-Marie Dunmore & Torrie Crabbs*

18.15-19.30 **Welcome reception** | CLOUD 23

Wednesday 24 September 2025

BSTP-ESTP CONGRESS

07.30-08.30 **Registration**

08.15-08.30 Resero Analytics sponsored session: ChatFDA: Unlocking drug safety insights AI *Taylor Scott*

Keynote lecture

Chair: *Barbara Lenz*

08.30-09.00 Keynote lecture: Molecular mechanisms of genome instability in carcinogenesis *Sven Rottenberg*

New Approach Methodologies for Carcinogenicity Evaluation

Chairs: *Barbara Lenz & Heike Marxfeld*

09.00-09.45 EPAA Initiative on NAMS for carcinogenicity of agrochemicals *Mirjam Luijten*

09.45-10.30 In silico approaches to predict carcinogenicity *Mark Cronin*

10.30-11.00 **Coffee break - Posters - Exhibition**

Chairs: *Frederic Schorsch & Maike Huisinga*

11.00-11.45 Genomics-Based NAMs for classification of carcinogens in pharma *Heidrun Ellinger-Ziegelbauer*

11.45-12.30 Advanced cellular models for carcinogenicity assessment *Kelly Evans*

12.30-14.00 **Lunch - Posters - Exhibition**

13.45-14.00 Deciphex sponsored sessions Patholytix: Beyond drug safety *Colin Doolan*

Chairs: *Emily Meseck & Dirk Schaudien*

14.00-14.30 Identifying potential carcinogenicity risks through innovative genetic toxicology methods and target safety assessments *Joanne Elloway*

New Modalities and Carcinogenicity Assessment

14.30-15.15 AAV Gene Therapy: Insertional mutagenesis and cancer risk *Paul Batty*

15.15-15.45 **Coffee break - Posters - Exhibition**

Chairs: *Dirk Schaudien & Barbara Lenz*

15.45-16.30 Oligonucleotides: Evolution of carcinogenicity and risk *Tae-Won Kim*

16.30-17.15 Case Study: Is evaluation of cell proliferation in rat mammary glands a useful tool for evaluation of the carcinogenic potential of insulin? *Anne-Marie Mølck & Vivi Jensen*

17.15-18.00 Carcinogenicity risk assessment of protein degraders *James Sidaway*

18.00-19.30 **BSTP Anniversary reception** | Deansgate Foyer - Booth 6

Thursday 25 September 2025

BSTP-ESTP CONGRESS

08.00-08.30 **Registration**

08.15-08.30 **Standard Bio sponsored session: Hyperion XTi: The gold standard for spatial proteomics-at scale, in detail, beyond limits** *Filomena Spada*

New Modalities and Carcinogenicity Assessment

Chairs: *Sandra De Jonghe & Jonathan Carter*

08.30-09.15 **Carcinogenic risks of CAR-T cell therapy** *Ronnie Chamanza*
Maronpot Guest Lecture, Sponsored by IATP and the Telikicherla Higher Education Foundation (THE)

Data Interpretation

Chairs: *Sandra De Jonghe & Jonathan Carter*

09.15-09.45 **Peer review of rodent carcinogenicity studies: Things to consider?** *Matt Jacobsen*

09.45-10.15 **Carcinogenicity statistics – Part 1 (Basics)** *Jim Saul*

10.15-10.30 **A guide to combining primary tumors for statistical analysis in carcinogenicity studies** *Alys Bradley*

10.30-11.00 **Coffee break - Posters – Exhibition**

Chairs: *Matt Jacobsen & Laetitia Elies*

11.00-11.40 **Carcinogenicity statistics – Part 2 (Advanced)** *Jim Saul*

11.40-12.00 **Navigating the pathology minefield: Harnessing the value of historical background data** *John Foster*
The Chirukandath Gopinath Award (sponsored by BSTP) will be awarded to John Foster

12.00-12.30 **Case Study: Human relevance and risk assessment of endocrine and reproductive system tumours in a rat carcinogenicity study of a small molecule** *Zuhal Dincer*

12.30-14.00 **Lunch - Posters - Exhibition**

13.45-14.100 **AiraMatrix sponsored session: The role of digital pathology as a service in streamlining preclinical workflows: a case study** *Tijo Thomas*

Chairs: *Heike Marxfeld & Charlotte Dalsgaard*

14.00-14.45 **Challenges of applying INHAND nomenclature for carcinogenicity studies – Case Presentations** *Ute Bach & Tanasa Osborne*
The ESTP Science Award will be awarded to Ute Bach

14.45-15.00 **Poster award session & ESTP Best paper award & presentation**

15.00-15.15 **INHAND updates** *Emily Meseck,*
Chair: *Emily Meseck*

Thursday 25 September 2025

15.15-15.30 **Interactive case presentation: AI-Assisted purkinje cell density baseline in 54 control cynomolgus macaques and sex comparison** *Brieuc Cossic*

15.30-16.15 **Coffee break - Posters - Exhibition**

16.00-16.15 **Histofy sponsored session: Beagle: your tox path study companion** *Nasir Rajpoot*
Chair: *Thomas Nolte*

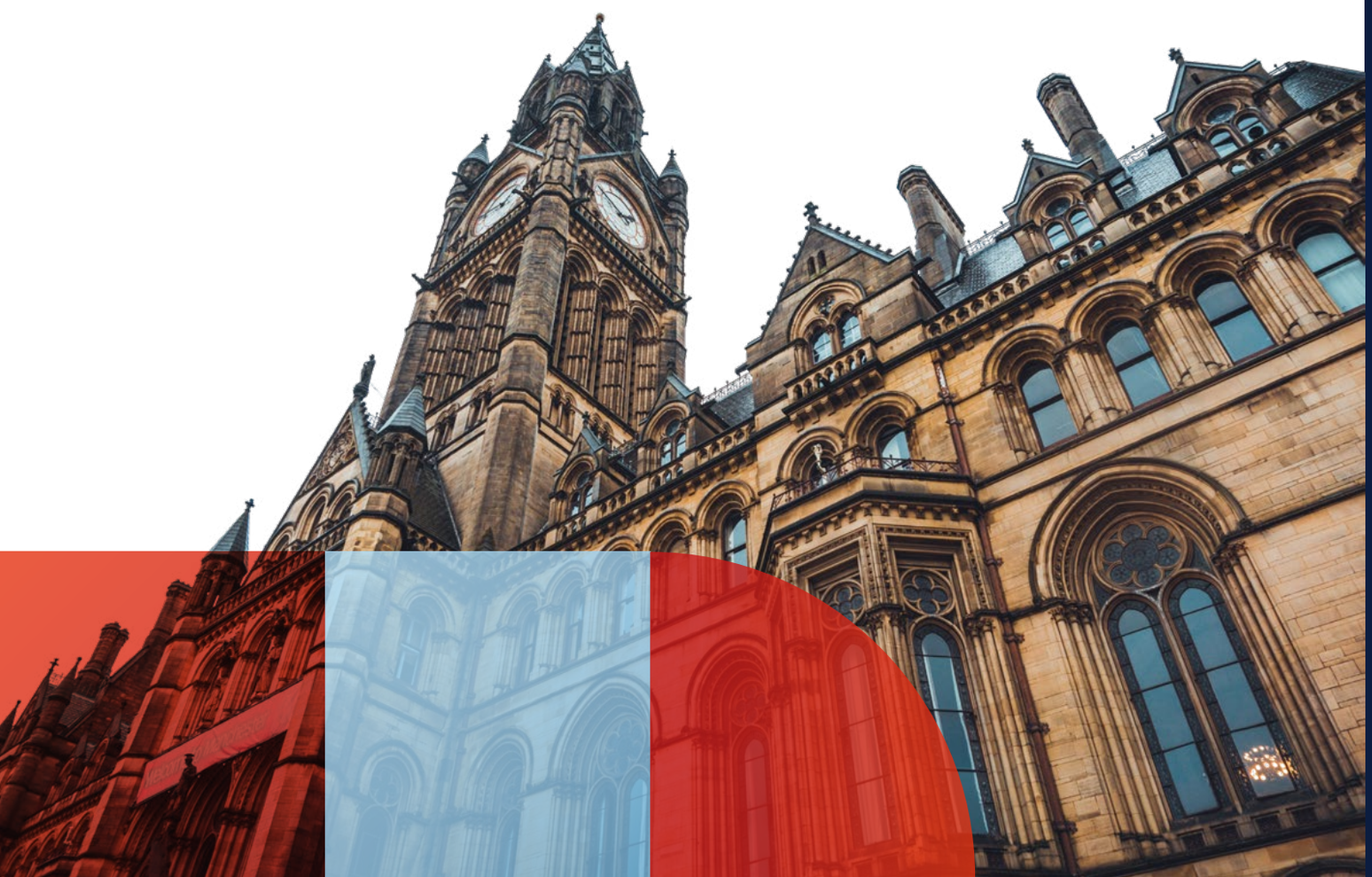
16.15-16.30 **Interactive Case Presentation: A nasal bone finding in CD1 mice** *Marcia Pereira Bacares*

16.30-16.45 **Interactive Case Presentation: Findings in cynomolgus monkeys following long-term exposure to an immunomodulatory biotherapeutic,** *Sébastien Laurent & Svenja Hartung*

16.45-17.00 **Interactive Case Presentation: Retrospective review of the pathological findings in diagnostic necropsy submissions of laboratory Grey Short-tailed opossums (Monodelphis domestica)** *Henry Miller*

17.00-18.00 **Annual General Assembly ESTP** - Hybrid

19.30-01.00 **Congress Dinner & dance |** Science & Industry Museum



Friday 26 September 2025

BSTP-ESTP CONGRESS

Carcinogenicity Risk Assessment
Chairs: *Xavier Palazzi & Thomas Nolte*

08.30-09.15 **New approaches for screening for carcinogenicity** *Samuel Cohen*

09.15-10.15 **Carcinogenicity WOE assessment in pharmaceutical and agrochemical industry: A regulatory perspective** *Stephanie Melching-Kollmuss & Kris Siezen*

10.15-10.30 **Case Study: Subcutaneous route of administration in rodent carcinogenicity bioassay: A review of rodent specific injection site tumors and relevance to humans** *Bhanu Singh*

10.30-11.00 **Coffee break - Posters**
Chairs: *Xavier Palazzi & Jacqui Stewart*

11.00-12.00 **Carcinogenicity WOE assessment in pharmaceutical and agrochemical industry: An industry perspective** *Lindsay Wright & Douglas Wolf*

12.00-12.15 **Case Study: No preneoplastic precursor lesion of thymomas induced by a RORγt inhibitor?** *Thomas Nolte*

12.15-12.30 **Case Study: Continuum between preneoplastic lesions and hepatocellular tumors induced by CAR/PXR nuclear receptor activation** *Frederic Schorsch*

12.30-12.45 **Case Study: Rat-tical misjudgement: Tumors in disguise** *Xavier Palazzi*

12.45-13.00 **Closing Ceremony**

13.00-14.00 **Farewell lunch**

Side Meetings

Early Career Meeting – open meeting
Wednesday 24 September 2025 | 10.30-11.00
The Boardroom
Chair: *Davide Corbetta*

ESTP Board Meeting – on invitation only
Thursday 25 September 2025 | 07.00-08.00
The Boardroom
Chair: *Vanessa Schumacher*

SOC 2026 Meeting – on invitation only
Thursday 25 September 2025 | 10.30-11.00
The Boardroom
Chair: *Anna-Lena Frisk*

ESTP Pathology 2.0 Committee Meeting – open meeting
Thursday 25 September 2025 | 15.30-16.00
The Boardroom
Chair: *Dirk Schaudien*

Social Program

Welcome reception

Tuesday 23 September 2025 | 18.15-19.30
Cloud 23 | Beetham Tower 303 Deansgate, Manchester M3 4LQ
Located in the same building as The Manchester Deansgate Hotel
The welcome reception will take place at Cloud23. Cloud23 is a skybar, located on the 23rd floor at the Manchester Deansgate Hotel. Cloud23 offers spectacular panoramic views over the city. As one of the most beautiful rooftop bars in Manchester and one of the best bars in Manchester, Cloud23 offers a unique ambience to meet your fellow congress participants!

Registration fee
Included in the registration fee, but registration is required

BSTP Anniversary reception

Wednesday 24 September 2025 | 18.00-19.30
The Manchester Deansgate Hotel | Deansgate Foyer – Booth 6
Beetham Tower, 303 Deansgate, Manchester M3 4LQ
2025 marks the 40th year of the British Society of Toxicological Pathology (BSTP). BSTP would like to invite all congress participants from the joint BSTP-ESTP Congress to celebrate this milestone. Join the BSTP on Wednesday at the end of the day at their booth in the exhibition area, to raise a glass and celebrate this special occasion. Beverages will be provided.

Congress Dinner and dance

Thursday 25 September 2025 | 19.30-01.00
Science & Industry Museum | Liverpool Rd, Manchester M3 4FP
The congress dinner will take place at the Science and Industry Museum, only a few minutes by foot from the Manchester Deansgate Hotel. The museum opened its doors in 1983 and is located on the original terminus of the world's first inter-city railway. This unique venue is the perfect backdrop to dine amongst some of the world's oldest exhibits from the world of science and engineering including the world's first stored computer.

Registration fee
Included in the registration fee, but registration is required
Accompanying Persons: EUR 75.00 + VAT

Speaker Abstracts

IATP Satellite Symposium | Tuesday 23 September 2025

- The peer review process in the Division of Translational Toxicology (DTT) and the U.S. National Toxicology Program (NTP)
- Pathology Working Group: An overview of their conduct and utility
- Expert Working Panel (EWP)- a modified PWG: confirming the morphologic diagnosis is only the first step
- PWG - Perspectives from the Agrochemical realm

BSTP-ESTP Congress | Tuesday 23 September 2025

- Keynote Lecture: The 2-Year bioassay: What we have learned
- Navigating the complexities of carcinogenicity testing: a toxicologist's perspective
- Case Study - Hepatocellular foci in rodents: Lowering the threshold for recording
- Just another study type? Challenges and pitfalls with the histopathological evaluation of carcinogenicity studies
- Carcinogenicity studies: a CRO's unique perspective of peer review and beyond

IATP Satellite Symposium | Speaker Abstract

Tuesday 23 September 2025 | 09.10-09.55

The peer review process in the Division of Translational Toxicology (DTT) and the U.S. National Toxicology Program (NTP).

Mark Cesta
NIEHS, Research Triangle Park, United States

The National Toxicology Program (NTP), now the Division of Translational Toxicology (DTT) at the National Institute of Environmental Health Sciences (NIEHS) was established from the NCI Bioassay Program in 1978. The NCI Bioassay Program was established in 1962. Problems were identified with many of the bioassays in the NCI Bioassay Program the U. S. Government Accounting Office identified many bioassays that were so deficient that their results could not be published. As a result, the bioassay program was moved to NIEHS as the NTP. Pathologists at the NTP developed a peer review system to ensure those problems never occurred again. There are four steps in the DTT pathology peer review process, the audit of pathology specimens (APS), the pathology data review (PDR), the quality assessment (QA), and the pathology working group (PWG).

In this process, all the data and materials are reviewed to ensure accuracy and consistency. The QA and PWG are done by different contract labs, and the PWG is conducted in a blinded fashion (with the participants having no knowledge of the dose groups) to avoid bias and conflicts of interest. The goals of the PWG are to provide a consensus opinion on the toxicologically significant findings and to verify their accuracy, resolve diagnostic differences, recommend additional reviews if needed, and ensure the findings are correctly interpreted. This process ensures the accuracy of the data from NTP/DTT studies, and for the last 45 years, the pathology peer review process used by the DTT/NTP has been considered the gold standard by regulatory agencies in the U.S., Europe, and Japan.

IATP Satellite Symposium | Speaker Abstract

Tuesday 23 September 2025 | 09.55-10.40

Pathology Working Groups: Reviews to address specific scientific and/or regulatory Issues

Paul Snyder
Experimental Pathology Laboratories, Inc.

The Pathology Working Group (PWG) is a specialized type of review. Unlike the routine peer reviews described previously, PWGs are convened to answer specific questions regarding study results. They may be convened by study sponsors, consortiums or government agencies. PWGs are generally conducted after a study (or studies) have been finalized and thus require full documentation.

The panel for a PWG is composed of a group of expert pathologists who are assembled to discuss a specific question regarding study results. Since the purpose of the PWG is to provide an independent unbiased opinion, members of the PWG may come from academia, government or industry. Panel members are selected based on their experience in toxicologic pathology, as well as their expertise in the area or organ being discussed. Both veterinary and medical pathologists with appropriate expertise may serve as members of a PWG.

Pathology Working Groups may be convened to answer any number of specific questions. This talk will cover the conduct and application of PWGs.

IATP Satellite Symposium | Speaker Abstract

Tuesday 23 September 2025 | 11.10-11.40

Expert Working Panel (EWP)- a modified PWG: confirming the morphologic diagnosis is only the first step

Maurice Cary
Pathology Experts GmbH, Witterswil, Switzerland

Pathology Working Groups (PWGs) mostly serve to resolve disagreements between the study pathologist and peer review pathologist; or to confirm findings that may be borderline statistically significant and may sometimes include mode of action, relation to treatment and toxicological significance in the PWG report. Pathology Experts GmbH has been organizing modified PWGs, Expert Working Panels (EWPs), for many years to resolve issues for its clients for compounds that may have been placed on hold in the clinics by a regulatory agency or to facilitate internal GO/NO GO decisions regarding the continued development of a compound. Whereas, in PWGs blind slide evaluation is employed, the slide evaluation in our EWPs is not blinded. The major difference is in EWPs we may include expert toxicologists or DMPK specialists, as well as any other specialty deemed necessary to address the issues in line with the challenges faced by the client. Thus, the EWP report will include some of the same points discussed in a classic PWG report but will also include discussion of the pathology finding(s) in question with the added perspective of significant in-life findings, exposure and any other point deemed necessary to properly address the issue.

IATP Satellite Symposium | Speaker Abstract

Tuesday 23 September 2025 | 11.40-12.10

PWG - Perspectives from the agrochemical realm

Frederic Schorsch
Bayer, Sophia Antipolis, France

The presentation will provide an in-depth analysis of three recent cases selected amongst agrochemicals where a Pathology Working Group (PWG) was instrumental to conclude about their potential carcinogenicity.

In case 1, a fungicide acting as a succinate dehydrogenase inhibitor, the PWG examined findings from a 2-year carcinogenicity study in Wistar rats. Despite some regulatory authorities suggesting a link between observed tumors and treatment, the PWG affirmed that there was no evidence of treatment-related increases in histiocytic sarcomas, brain astrocytoma, and ovarian tubulostromal neoplasms. The statement made by the panelist members of the PWG confirmed the conclusion made by the study pathologist.

The second case focused on an insecticide affecting the ryanodine receptor. The PWG reviewed a chronic toxicity and carcinogenicity study that indicated an increased incidence of uterine tumors in high-dose female rats. The PWG confirmed the presence of proliferative findings in the uterus. Again, the PWG was supportive to reinforce the original statement found in the pathology report.

Lastly, the third PWG was convened to evaluate proliferative changes in the thymus gland observed in the course of a rat 2 year study to test carcinogenicity of a fungicide from the thiazolylpiperidine family. The panel unanimously concluded that the observed non-neoplastic and neoplastic findings were not related to dietary administration of the active ingredient, reinforcing the absence of treatment-related carcinogenic findings.

This talk will highlight the methodologies employed during those PWGs. Emphasis will be made on the simplification brought by digital pathology during the panel discussion, the value related to the application of current diagnostic criteria, and the implications of these findings for human risk assessment in the context of agrochemical safety. Attendees will gain insights into the complexities of evaluating carcinogenic potential in chronic toxicity studies and the importance of expert pathologic review in regulatory decision-making.

BSTP-ESTP Congress | Speaker Abstract

Tuesday 23 September 2025 | 14.15-15.00

Keynote lecture: The 2-Year bioassay: What we have learned

Samuel Cohen
University of Nebraska Medical Center, Omaha, United States

The two-year rodent bioassay evolved from animal studies in the 1950s and 1960s, with standardization in the 1970s and continuing to the present. Standardization has included husbandry issues, diet, and statistical approaches, but most importantly, histopathology classification. The results of the bioassay have greatly enhanced our understanding of carcinogenesis and have led to identification of several key molecular events, including identification of several nuclear receptors involved with carcinogenesis, at least in rodents, such as CAR, PPAR, AHR, and ER, PR, and AR. Delineation of carcinogenesis as a multi-step process also occurred from animal studies. Distinction between genotoxic and non-genotoxic carcinogens began with studies by Ames in the 1970s. Non-genotoxic carcinogens rely on increased cell proliferation as their mode of action. Insights into metabolism and toxicokinetics have also been gained from animal studies. The 2-year bioassay uses the maximum tolerated dose (MTD) as the highest dose. However, this results in toxicity, which can be important in contributing to development of tumors, which may not be relevant to human exposures. Detailed mechanistic research has identified numerous modes of action responsible for carcinogenesis in rodents, many that are not relevant to human cancer risk. The two-year bioassay has provided the foundation for considerable progress in our understanding of carcinogenesis, but it is time to discontinue its use.

BSTP-ESTP Congress | Speaker Abstract

Tuesday 23 September 2025 | 15.00-15.30

Navigating the complexities of carcinogenicity testing: a toxicologist's perspective

Helen-Marie Dunmore
Certara, Sheffield, United Kingdom

The objectives of carcinogenicity testing are to identify a tumorigenic potential in animals and to assess the translational risk to humans. Any cause for concern derived from laboratory investigations, animal toxicology studies, and data in humans may lead to a need for carcinogenicity studies. The practice of requiring carcinogenicity studies in rodents was instituted for pharmaceuticals and other products that were expected to be administered regularly/exposure over a substantial part of a subject's lifetime. The design and interpretation of the results from these studies preceded much of the available current technology to test for genotoxic potential and the more recent advances in technologies to assess systemic exposure. These studies also preceded our current understanding of tumorigenesis with non-genotoxic agents. Results from genotoxicity studies, toxicokinetics, and mechanistic studies can now be routinely applied in preclinical safety assessment. These additional data are important not only in considering whether to perform carcinogenicity studies but for interpreting study outcomes with respect to relevance for human safety. Since carcinogenicity studies are time consuming and resource intensive they should only be performed when human exposure warrants the need for information from lifetime studies in rodents in order to assess carcinogenic potential. 1 This talk will cover the practical aspects of designing GLP compliant carcinogenicity assays in rodents to meet regulatory expectations (medicines and chemicals) for product approval and when carcinogenicity study waivers may be appropriate.

BSTP-ESTP Congress | Speaker Abstract

Tuesday 23 September 2025 | 16.00-16.15

Case Study - Hepatocellular foci in rodents: lowering the threshold for recording

Leslie Bosseler
Johnson & Johnson, Beerse, Belgium

All cases show rat livers from rat toxicity studies.
Case 1: 1 month tox study,
Case 2 & 3 : 3 month tox studies. Would you record the shown lesions as foci of cellular alteration or not?

Hepatocellular foci of cellular alteration (FCA) in rodents are putative preneoplastic lesions that are sporadically encountered in (sub)chronic toxicology studies. The morphology of FCA can vary depending on their predominant staining characteristic (basophilic, eosinophilic or clear cell) on H&E staining, their reactivity to IHC cell markers (eg: γGT, GSTP), and their size. While large FCA are easily recognizable, smaller ones tend to be overlooked or not recorded. Also, recording criteria, especially for the lower threshold are not defined. Yet, not recording FCA in shorter term studies may lead to missed opportunities to flag potentially carcinogenetic compounds early. We present 3 cases where small FCA were present in 1-3-month rat studies. In the first case, very small foci were seen after 1 month, which developed to numerous foci after 6 months and carcinomas after 1 year. In the second case, small foci were seen after 3 months, which developed to a 100% incidence of foci after 6 months. In both these cases, the FCA were originally not recorded by the study pathologist during the 1- or 3-month study. The third case shows a spectrum of FCA morphologies during a 3-month study of a known carcinogen (TCDD). Using these cases as examples, we advocate for the recording of all FCA, even in studies

BSTP-ESTP Congress | Speaker Abstract

Tuesday 23 September 2025 | 16.15-17.00

Just another study type? Challenges and pitfalls with the histopathological evaluation of carcinogenicity studies

Matthias Rinke
Retiree from Bayer AG, Wuelfrath, Germany

Carcinogenicity studies are performed in laboratory rodents to determine whether the “life-long” exposure to a substance, usually a chemical or drug, bears a carcinogenic potential for humans. Various international guidelines regulate their execution, but there are still distinct differences between the assessment of agrochemicals and pharmaceuticals, e.g. concerning study duration and international acceptance. While the TG rasH2 mouse model is now accepted as second species for pharmaceuticals, genetically engineered mice are not yet accepted for other chemicals. In general, carcinogenicity studies are performed at the end of a development phase and might be conducted after the registration of a compound. Thus, the outcome of their assessment is often on the critical path to registration.

Several factors may have an impact on the histopathologic evaluation of a carcinogenicity study some of which will be addressed in the presentation. They are not meant to be comprehensive but rather to trigger discussion.

While in former years many companies performed and evaluated their studies inhouse, they are now, especially in the pharmaceutical world, mostly entirely sourced out to a CRO. This, however, results in a lack of experience of the pharmaceutical companies’ pathologists with reliance on the qualifications of CRO pathologist colleagues. A thorough peer-review by a company’s pathologist is highly recommended not only to prove the quality, but also to learn and gain experience on species and strain specific lesions. Good communication between the company and CRO pathologists with knowledge of the compound profile is imperative.

Harmonization progress has been made with the introduction of commonly accepted organ trimming guides and internationally standardized nomenclature with the use of common diagnostic criteria (INHAND). Nevertheless, the distinction between hyperplastic and neoplastic lesions, benign or malignant classifications and appropriate grading systems can be difficult. Special techniques such as immunohistochemistry may be necessary for neoplasm classification to avoid the

use of terms such as carcinoma, sarcoma or even tumor NOS (not otherwise specified). The application of an appropriate grading system for preneoplastic lesions is another topic to be discussed.

Reading a carcinogenicity study can be a daunting task because of the large numbers of animals. Tissues may be evaluated animal-by-animal which affords an encompassing overview of an animal's complete health status. An organ-by-organ technique allows more focused attention to changes and helps for grading consistency. To make both methods applicable requires special preparation. Diagnostic drift is possible and alternating evaluation of animals from different treatment groups is therefore necessary. Decedent animals may be examined in advance to determine causes of death.

Assessment and interpretation of the results from a carcinogenicity study can be challenging for both the study and peer-reviewing pathologist. Statistical analysis is typically not available prior to the peer review, but may be essential for data interpretation. Historical control data finally may be fundamental for data interpretation justification.

BSTP-ESTP Congress | Speaker Abstract

Tuesday 23 September 2025 | 17.00-17.30

Carcinogenicity studies: a CRO's unique perspective of peer review and beyond

Torrie Crabbs
EPL, Inc., Morrisville, United States

This seminar will provide a unique perspective on the evolving landscape of pathology peer review, focusing on carcinogenicity studies. Drawing from decades of Contract Research Organization (CRO) experience, attendees will explore the historical development of the peer review process and emergence of pathology working groups (PWGs), including the shift from traditional to digital review formats. The session will highlight key differences between peer review of carcinogenicity and subchronic studies, common pitfalls encountered during the review process, and lessons learned over time. Participants will gain insight into how peer review practices have adapted to technological advancements and regulatory expectations, with case-based examples illustrating trends, best practices, and areas for continued improvement in toxicologic pathology to enhance scientific rigor, transparency, and regulatory confidence in study outcomes.

Speaker Abstracts

BSTP-ESTP Congress | Wednesday 24 September 2025

- Keynote lecture: Molecular mechanisms of genome instability in carcinogenesis
- EPAA initiative on NAMS for carcinogenicity of agrochemicals
- In silico approaches to predict carcinogenicity
- Genomics-Based NAMs for classification of carcinogens in pharma
- Advanced cellular models for carcinogenicity assessment
- Identifying potential carcinogenicity risks through innovative genetic toxicology methods and target safety assessments
- AAV gene therapy: Insertional mutagenesis and cancer risk
- Oligonucleotides: Evolution of carcinogenicity and risk
- Case Study - Is evaluation of cell proliferation in rat mammary glands a useful tool for evaluation of the carcinogenic potential of insulin?
- Carcinogenicity risk assessment of protein degraders

BSTP-ESTP Congress | Speaker Abstract

Wednesday 24 September 2025 | 08.30-09.00

Keynote lecture: Molecular mechanisms of genome instability in carcinogenesis

Sven Rottenberg
University of Bern, Bern, Switzerland

Genome instability is a defining hallmark of cancer, driving clonal evolution, therapeutic resistance, and phenotypic diversification. While initially viewed as the consequence of random mutational events, emerging evidence challenges this paradigm and suggests that mutagenesis can be an adaptive, regulated response to cellular stress. In my lecture, I will explore stress-induced mutagenic DNA repair as a process that cells may harness under genotoxic pressure, which adds to our knowledge on how genome instability arises during carcinogenesis.

A central focus will be placed on endogenous sources of DNA damage, particularly mitochondrial reactive oxygen species (ROS) and oxidative DNA damage. I will present recent data from our laboratory on ECHDC2, a previously poorly characterized mitochondrial enzyme. Our findings demonstrate that ECHDC2 contributes to mitochondrial ROS production and, indirectly, to genomic DNA damage. Remarkably, loss of ECHDC2 confers resistance to DNA-damaging chemotherapeutics and radiotherapy, which underscores its potential role as a modulator of cancer cell vulnerability and a novel therapeutic target.

My lecture will integrate molecular mechanisms, systems biology insights, and toxicologic pathology perspectives, spanning from DNA damage sensing to repair pathway choice. I will also discuss how the tumor microenvironment and chronic inflammation might exacerbate mutational processes through sustained oxidative stress and impaired repair fidelity.

By dissecting these intertwined mechanisms, I aim to provide a comprehensive framework linking endogenous genome instability to cancer development, with implications for biomarker discovery and therapeutic intervention.

BSTP-ESTP Congress | Speaker Abstract

Wednesday 24 September 2025 | 09.00-09.45

EPAA Initiative on new approach methodologies for carcinogenicity assessment of agrochemicals

Mirjam Luijten
National Institute for Public Health and the Environment (RIVM), Bilthoven, Netherlands

In human health risk assessment of agrochemicals the two-year rodent cancer bioassay is currently the standard method for assessing the carcinogenic potential. However, this method has prominent weaknesses and is subject to ethical and scientific debate. Multiple initiatives are underway to modernize carcinogenicity assessment, by incorporating weight of evidence (WoE)-based methodologies that utilize new approach methodologies (NAMs). A WoE approach to carcinogenicity assessment should be based on modes of action (MOAs) relevant for carcinogenesis in humans. Funded by the European Partnership on Alternative Approaches to Animal Testing (EPAA) we previously analyzed 170 unique agrochemicals to identify the MOAs involved in tumors observed in rodent cancer bioassays. For two-third of the tumor cases an underlying MOA (network) could be identified, while the MOA involved was unclear for the remainder of the tumor cases. As a next step we further investigated these 'unknowns'. Patterns in tumor incidences and underlying MOAs were explored in a stepwise fashion. Our analysis yielded additional MOAs that should be included in WoE-based carcinogenicity assessment. At the same time, we also identified tumor cases for which the underlying MOA could not yet be unraveled. The resulting overview of the MOA (networks) underlying non-genotoxic carcinogenicity of agrochemicals will greatly facilitate the selection of NAMs for the development of a WoE approach to carcinogenicity assessment.

References

Heusinkveld et al. 2020. doi: 10.1080/10408444.2020.1841732

BSTP-ESTP Congress | Speaker Abstract

Wednesday 24 September 2025 | 09.45-10.30

In silico approaches to predict carcinogenicity

Mark Cronin
Liverpool John Moores University, Liverpool, United Kingdom

Computational tools for toxicity prediction include, but are not limited to, (quantitative) structure-activity relationships (QSARs), structural alerts, read-across, machine learning and artificial intelligence (AI). These varied approaches have in common that they are attempting to relate some feature(s) of chemical structure and / or physico-chemical properties to toxicological activity. They have a number of uses, ranging from identifying structures with potential toxicity, e.g. for screening and prioritisation of large inventories, or as part of a testing strategy, or weight of evidence to perform hazard identification of a substance. With regard to predicting carcinogenicity (as with all endpoints), they are viewed as valuable to reduce time, cost and the numbers of animals involved in testing. A lot is known about their strengths and weaknesses. Technologies as simple as structural alerts (which have been available for over three decades) are very powerful to identify compounds with the potential for genotoxic carcinogenicity. Alerts, and many other computational techniques, work well for the prediction of genotoxic carcinogenicity as the molecular initiating event (MIE), covalent interactions with DNA is readily, and easily, modelled. In contrast, modelling non-genotoxic carcinogenicity is much more difficult, often resulting in less robust predictions. There are a number of reasons for the lower quality of non-carcinogenic models, but key amongst them are the number and complexity of mechanisms, lack of definitive MIEs on which to base a model, and the paucity of suitable data for modelling. Integrating such computational tools into carcinogenicity assessment should include an assessment of the uncertainty in the approaches and whether a prediction is acceptable on its own or will require other information, which may include “big” data from New Approach Methodologies (NAMs) and in vivo bioassays.

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BSTP-ESTP Congress | Speaker Abstract

Wednesday 24 September 2025 | 11.00-11.45

Genomics-Based NAMs for classification of carcinogens in pharma

Heidrun Ellinger-Ziegelbauer[1], Keith Tanis[2], Scott Auerbach[3], Kaitlyn Venneman[4], Udayan Apte[4], Connie Mitchell[5]

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In 1999, when Spencer Farr suggested that all toxicologically relevant effects are accompanied by gene expression changes with potential connection to mechanisms, the expectations were high to predict carcinogenicity from short term animal studies in combination with gene expression analysis. Yet, analysis of the transcriptomics data available at that time dampened this initial hype.
In the following evaluation of case studies, including transcriptomics, increased mechanistic insight into mechanisms of carcinogenicity. Furthermore, systematic collection of gene expression data to build up transcriptomics databases after treatment of rodents with hepatocarcinogens allowed for reconsideration of the prediction of long-term carcinogenicity outcome with short term studies, at least for rodent liver. Although still using animals, the number of animals would be greatly reduced, and the mechanistic knowledge gained would allow evaluation of human relevance, thus overall representing a new approach methodology (NAM). Much of this research was or currently is being conducted within collaborative projects like the IMI Marcar consortium and the HESI eSTAR Carcinogenomic Project. The aim of the ongoing HESI project is to further the use transcriptomics-based carcinogenicity prediction in Pharma as weight of evidence consideration to waive 2-year rat bioassays, and for improved safety assessment of industrial and environmental chemicals.

This presentation will give an overview on the evaluation and development of omics methods for characterization of carcinogenic mechanisms with the goal to reach a classification of carcinogens. Limitation of current in vitro models being able to emulate most of the relevant carcinogenic mechanisms, and how increasing knowledge derived from omics methods applied in vivo may improve in vitro model development, will also be discussed.

BSTP-ESTP Congress | Speaker Abstract

Wednesday 24 September 2025 | 11.45-12.30

Advanced cellular models for carcinogenicity assessment

Kelly Evans
Safety Sciences, Clinical Pharmacology and Safety Sciences, R&D, AstraZeneca, Cambridge, United Kingdom

Assessing pre-clinical drug safety is essential in the drug development pipeline but can be associated with several challenges, one of which is translatability to clinical findings. Many current *in vitro* pre-clinical safety models utilise either 2D-cell cultures or cancer cell lines, neither of which accurately represent the patient population due to their simplified nature or cancer background. Therefore, there is often a translational disconnect between safety findings found in a dish and those observed in animal *in vivo* studies or in the clinic. In the context of complex, multi-stage processes such as carcinogenicity, there is a clear need for more human-relevant, advanced cell models that can better recapitulate the complex structure and mechanisms of human tissues. To this end, advanced human cell models, including organoids and organ-on-a-chip systems, are currently under development to help overcome these issues. Due to their three-dimensional arrangement and increased complexity through inclusion of multiple cell types, they provide the opportunity to assess carcinogenicity within a physiologically relevant, human-appropriate system. Such systems have the advantage of being generally long-lived, allowing assessment of repeat dosing or carcinogenicity that may only be detected over an extended period. This talk will outline the recent developments in the advanced cell models space and how these models can be used to predict carcinogenicity *in vitro*. These predictions are crucial to ensure patient safety.

BSTP-ESTP Congress | Speaker Abstract

Wednesday 24 September 2025 | 14.00-14.30

Identifying potential carcinogenicity risks through innovative genetic toxicology methods and target safety assessments

Joanna Elloway
AstraZeneca, Cambridge, United Kingdom

Predicting carcinogenicity is a pivotal requirement for drug development and regulatory toxicology. Accuracy in these predictions is crucial to ensure patient safety and meet regulatory standards. In this talk, I will provide an overview of how target safety assessments, along with advancements in genetic toxicology and sequencing methodologies, can offer increasingly accurate predictions of the carcinogenic potential of compounds. Target safety reviews for carcinogenicity prediction focus on evaluating compounds for potential cancer risks early in development. These reviews assess biological pathways and molecular targets to identify potential oncogenic pathways and genetic markers, utilising published and data repositories. Error-corrected next-generation sequencing (ecNGS) is under extensive investigation for the use in genetic toxicology and has the potential to transform our understanding of compound effects on the genome, improving risk assessment of carcinogenic potential. I will describe ecNGS, explaining how it enables the sensitive detection of low-frequency mutations and where it can be applied. I will also include examples of its utilisation to understand mutagenic carcinogens. Both these methodologies have the potential to be performed without the use of animals, facilitating the early identification of carcinogenic potential to support informed decision-making and aid in developing earlier testing strategies to better assess these risks.

BSTP-ESTP Congress | Speaker Abstract

Wednesday 24 September 2025 | 14.30-15.15

AAV Gene Therapy: Insertional mutagenesis and cancer risk

Paul Batty
University College London, London, United Kingdom

Adeno-associated viral (AAV) gene therapy has emerged as a promising strategy for the treatment of monogenic disorders. This approach has been successfully trialled for treatment of the inherited bleeding disorders haemophilia A and B, where long-term expression of Factor or Factor IX has resulted in a significant reduction in bleeding events. These pivotal studies led to EMA and FDA approvals of Etranacogene dezaparvovec for haemophilia B and Valoctocogene roxaparvovec for haemophilia A. Despite these advances there are questions on the cellular mechanisms via which AAV vectors persist and whether this treatment could lead to long-term safety concerns.

Wild-type AAV (wt-AAV) is a replication-deficient single stranded DNA virus, with a genome consisting of Rep and Cap coding regions, flanked by inverted terminal repeats. Although wt-AAV primarily persists in extrachromosomal episomal forms, site specific integration mediated by the Rep78/68 complex has been characterised. wt-AAV is considered to be non-pathogenic based on a high seroprevalence of AAV antibodies in the population. These assumptions have been challenged in a recent study which reported wt-AAV integration in a small number of hepatocellular carcinoma biopsies. There are conflicting findings in this area and further research is required to evaluate whether wt-AAV integration may play a minor role in this process.

Recombinant AAV (rAAV) vectors are produced by replacing the viral coding regions with a promoter/enhancer and gene of interest. These fundamental differences limit translatability of studies of wt-AAV. Early murine studies demonstrated that rAAV predominantly persists in an episomal form. In these studies; however, rAAV integration was seen following both local and systemic delivery. In some, but not all murine studies, there has been evidence of insertional mutagenesis associated with recurrent integration events into the murine Rian locus. Where these events were seen, this was in the context of neonatal treatment, high vector doses and/or stronger promoter/enhancer elements. These findings have not been seen in other rodent or large animal models.

To gain greater understanding of the mechanisms of rAAV vector persistence, studies have been conducted in large animal models. These have demonstrated long term therapeutic expression with no evidence of tumorigenesis. One study in the haemophilia dog model demonstrated predominant episomal persistence, with low integration frequencies in areas of chromatin accessibility. Detailed analyses using long-read sequencing demonstrated only fragmented integrated forms, supporting the hypothesis that transgene expression is derived from episomal forms. A similar study demonstrated hepatic integration with clonal expansion of hepatocytes containing rAAV vectors, albeit without tumorigenesis. A recent study has challenged the concept of transgene expression being derived from episomal rAAV, demonstrating full-length integrated forms in samples from non-human primates treated with different rAAV constructs.

Data has been reported from a small number of human biopsies from individuals treated with rAAV. Similar to large animal models these have shown the presence of both episomal and integrated rAAV. Integration events in these samples occurred at low frequencies with no evidence of recurrent integration sites, insertional mutagenesis, or clonal expansion. With demonstration of integration in pre-clinical and clinical samples, this has led to theoretical concerns that integration could result in insertional mutagenesis. Integration site analysis has been conducted on biopsy tissue as part of the investigation of seven malignancies reported in clinical gene therapy trials. These studies have identified no evidence of insertional mutagenesis.

In summary, data from pre-clinical and clinical studies of rAAV vectors have shown that although AAV vectors predominantly persist in episomal extrachromosomal forms, that rAAV integrates into the host genome at low frequencies. Integrations site analysis in large animal models and clinical biopsies has shown no evidence of insertional mutagenesis to date. Although these results are reassuring, there is a need for further research into the relevance of rAAV integration to help inform long-term outcomes.

BSTP-ESTP Congress | Speaker Abstract

Wednesday 24 September 2025 | 15.45-16.30

Oligonucleotides: Evolution of carcinogenicity and risk

Tae-Won Kim
Ionis Pharmaceuticals, Carlsbad, United States

The potential for oligonucleotides to cause cancer has historically been assessed via 2-year bioassays in rats and/or mice. No human-relevant findings have been observed to date. More recent oligonucleotide programs have successfully leveraged data from approved products to streamline carcinogenicity assessment, such as by replacing the 2-year mouse bioassay with a 6-month transgenic mouse assay. Recent draft guidance for nonclinical safety assessment of oligonucleotide-based therapeutics and for platform technologies may provide further opportunities to streamline carcinogenicity assessment of oligonucleotides in the near term. This presentation will provide an overview of carcinogenicity assessment approaches and findings in rodents followed by a discussion of proposed opportunities to limit carcinogenicity assessment of future oligonucleotide-based therapeutics when it is scientifically justified.

BSTP-ESTP Congress | Speaker Abstract

Wednesday 24 September 2025 | 16.30-17.15

Case Study - Is evaluation of cell proliferation in rat mammary glands a useful tool for evaluation of the carcinogenic potential of insulin?

Anne-Marie Mølck, Vivi Jensen
Novo Nordisk, Maaloev, Denmark

Introduction: In the 90s, publication of a study showing carcinogenic effect of the insulin analogue, insulin X10, in rat mammary glands raised concerns regarding increased cell proliferative effect of modified insulin analogues in vivo. Consequently, Health Authorities started to recommend assessment of cell proliferation (CP) (1-4). Therefore, assessment of CP in mammary gland has often been included in nonclinical studies evaluating the carcinogenic effects of new insulin analogues using X10 as a positive control(5). However, growing knowledge on human insulin and insulin analogues challenges the value of this assessment, particularly since histopathologic examination of mammary gland tissue and identified macroscopic changes are included.

Methods: We compared results from four nonclinical rat studies evaluating the effects of repeated dosing with insulin detemir or degludec in mammary glands. Studies included human insulin and/or X10-dosed groups as comparators, CP of mammary glands, and histopathologic evaluation.
Results: Neither human insulin, insulin detemir, degludec, nor X10 induced mammary tumors or increased CP in the studies. In agreement with publish data, CP fluctuated during the estrous cycle and thus the applied methods were able to identify changes, if present(6-8).

Conclusions: Based on the four studies evaluated, we find the mitogenic effect of insulin in rat mammary glands weak and that in vivo CP evaluation in nonclinical studies is not predictive of the carcinogenic potential of insulin, thus, the value of including this endpoint is debatable as is the inclusion of X10 as a positive control.

BSTP-ESTP Congress | Speaker Abstract

Wednesday 24 September 2025 | 17.15-18.00

Carcinogenicity risk assessment of protein degraders

James Sidaway
ApconiX, Alderley Edge, United Kingdom

Targeted protein degraders (TPDs) have recently emerged as a novel drug class. Their mode of action utilises E3 ubiquitin ligases to degrade therapeutic proteins of interest selectively. This modality offers excellent potential for targeting previously intractable drug targets. There are two main TPD classes: the molecular glue degraders, which have drug-like properties similar to conventional small molecules, and proteolysis targeting chimeras (PROTACs; also termed heterobifunctional targeted protein degraders) that are typically higher molecular weight. The cereblon E3 ligase complex is the most widely employed in drug discovery, and several cereblon-based TPDs are in late-stage clinical development for oncology indications. A significant safety consideration for cereblon-based TPDs is the degradation of unintended neosubstrates, in light of the teratogenicity findings associated with thalidomide and other immunomodulatory imide drugs, which is thought to be mediated, at least in part, through a cereblon-neosubstrate mechanism. Due to the inherent complexity of TPD-mediated cereblon: neosubstrate binding, unintended neosubstrates are varied and challenging to predict. As cereblon and other E3 ubiquitin ligase complexes are employed in drug discovery for non-life-threatening indications, carcinogenicity risk assessment will be required. There is no regulatory requirement to treat this new drug class differently from conventional small molecules in carcinogenesis assessment. However, several properties of TPDs could influence weight of evidence assessments and carcinogenicity study design. For weight of evidence assessments, the association of both the primary target and the E3 ligase with cancer biology should be evaluated, as the latter may be hijacked from its normal cellular function. For cereblon-based TPDs, several potential neosubstrates are associated with cancer pathways, indicating potential off-target effects that will not be assessed in standard secondary pharmacology assays. Compared to functional small molecule inhibitors, toxicodynamics may be different for TPDs due to their catalytic degradation properties, and drug metabolism may be more complex for PROTACs, which may influence the design of toxicology studies and risk assessment. Furthermore, species differences in TPD interactions with cereblon and neosubstrates can complicate translational safety, including rodent carcinogenicity studies. In summary, TPDs offer an exciting prospect for new drug discovery, but their differing properties from conventional small molecules should be taken into account in carcinogenicity risk assessment.

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Speaker Abstracts

BSTP-ESTP Congress | Thursday 25 September 2025

- Carcinogenic risk of CAR-T cell therapy
- Peer review of rodent carcinogenicity studies: Things to consider?
- Carcinogenicity statistics
- A guide to combining primary tumors for statistical analysis in carcinogenicity studies
- Navigating the pathology minefield: Harnessing the value of historical background data
- Case Study - Human relevance and risk assessment of endocrine and reproductive system tumours in a rat carcinogenicity study of a small molecule
- Challenges of applying INHAND nomenclature for carcinogenicity studies - Case Presentations
- International Harmonization of Nomenclature and Diagnostic criteria in 2025 - a brief update

BSTP-ESTP Congress | Speaker Abstract

Thursday 25 September 2025 | 08.30-09.15

Carcinogenic risk of CAR-T cell therapy

Ronnie Chamanza
Johnson & Johnson Innovative Medicine, High Wycombe, United Kingdom

Chimeric antigen receptor (CAR)-T cells are human gene therapy products in which T cells are genetically modified to recognize a desired (mostly oncology) target for therapeutic purposes. Presently, there are 3 platforms, autologous and allogeneic (also called ex vivo), which share relatively similar costs and safety challenges, and in vivo CAR-Ts, which share similar off-target transduction concerns as gene therapy products. To date, only autologous CAR-T cell products have been approved, and the requirement for a robust carcinogenicity assessment of these products has been heightened by the perceived potential risks of second primary malignancies (SPMs), thought to be linked to insertional mutagenesis. Although there is very limited data to support this association in the post–CAR-T setting, evidence-based solutions and scientific strategies for risk mitigation are expected by regulators. Regulators recommend that a case-by-case nonclinical testing strategy based on in silico, in vitro and in vivo pharmacology or toxicology models be applied, as appropriate, in conjunction with available nonclinical and clinical data from related products. This weight of evidence evaluation should include an assessment of individual components of the CAR-T cell products, process and engineering strategies that may be linked to a potential carcinogenic risk. These include the biology of the CAR construct (specificity, signalling, additional modification or 'armouring'), vector characteristics (integration, self-inactivating, cell specific promoters), donor-related risks (high-fidelity genomic tests e.g. whole genome sequence analysis or karyotyping), and implementation of a clinical program that includes site integration analysis or baseline screening for clonal haematopoiesis. Although there is no scientific consensus on which in vivo models to use, studies in murine xenografts or pigtail macaques (for in vivo CAR-T) with pathology and molecular pathology endpoints can also provide valuable evidence of transduction specificity and T cell trafficking and proliferation profile, that can be used in the overall carcinogenic risk assessment.

BSTP-ESTP Congress | Speaker Abstract

Thursday 25 September 2025 | 09.15-09.45

Peer review of rodent carcinogenicity studies: Things to consider?

Matt Jacobsen
Astrazeneca, Cambridge, United Kingdom

Regulatory authority review of submitted carcinogenicity data may generate unanticipated questions for sponsors, particularly where a weak or equivocal carcinogenicity signal is present. By attempting to anticipate how an agency might view a draft carcinogenicity study data set, the author suggests how this approach might influence the need for additional scrutiny when reviewing both neoplastic and non-neoplastic study findings. Considerations might include: review of Sponsor request for special protocol assessment documentation (FDA Carcinogenicity Advisory Committee) to understand rationale for dose selection and FDA stipulations around study adequacy; precedents from existing carcinogenicity studies with a similar mechanism or action (MOA); awareness of publications that may align the test item's MOA with carcinogenicity risk in rodents; study toxicokinetic data to understand how a potential carcinogenicity signal (effect and no effect level) will dictate safety margins at the maximum recommended human dose; relevant historical control data (HCD) to determine if numerical imbalances in histopathology findings will fall within HCD ranges, and whether tumor types will be classified as common or rare for statistical analysis; and tumour combinations when summed, that may produce a statistically positive result that may not be apparent when comparing incidence data from the individual tumor types alone.

BSTP-ESTP Congress | Speaker Abstract

Thursday 25 September 2025 | 09.45-10.15 & 11.00-11.40

Carcinogenicity statistics

Jim Saul
Labcorp, Harrogate, United Kingdom

Carcinogenicity studies are unique among in-vivo toxicology studies in that microscopic findings are routinely statistically analyzed. Study strategy and design, double control groups, early removal of groups, classification of tumours as fatal or non-fatal, tumour combinations, palpable tumors, and interpretation of results will be discussed. The use of alternative statistical methods will also be presented, along with thoughts on digital pathology and the use of virtual control groups to reduce animal use.

BSTP-ESTP Congress | Speaker Abstract

Thursday 25 September 2025 | 10.15-10.30

A guide to combining primary tumors for statistical analysis in carcinogenicity studies

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The Tumor Combination guide was created at the request of the U. S. Food and Drug Administration (FDA) by a Working Group of biopharmaceutical experts from the international societies of toxicologic pathology, FDA, and members of the Standard for Exchange of Nonclinical Data (SEND) initiative, with a primary goal of assisting pharmacology/toxicology reviewers and biostatisticians in statistical analysis of nonclinical tumor data. The published guide was also intended to be used by both Study and Peer Review pathologists in interpreting the tumor data when evaluating carcinogenicity studies. The guide excel files provide the tumor nomenclature from the International Harmonization of Nomenclature and Diagnostic Criteria (INHAND) publications and correlates them with those in the NEOPLASM controlled terminology (CT) code list in SEND for electronic submissions to the FDA. The tumor combination guide was prepared in a tabular format to assist the pathologist to make informed decisions for combining tumor data for statistical analysis in their studies. The strategy for combining tumor types for statistical analysis is based on scientific criteria gleaned from the current scientific literature regarding cell type of origin of each tumor type. The standard analysis would be to (1) Analyze each tumor type separately by site in the body (2) Combine benign tumors of the same cell type by site for analysis (3) Combine malignant tumors of the same cell type by site for analysis (4) Combine benign and malignant tumors of the same cell type by site for analysis. For systemic tumors such as the Hematopoietic tumors, then the incidence of tumors of the same cell type should be determined on a whole animal basis i.e. number of animals in which the tumor was observed at any site, rather than the total number of tumors. Vascular tumors may be recorded by the specific organ where they occur and/or under a ‘designated organ name’ such as ‘Whole Body’. Therefore, also analyze combined benign and malignant vascular tumors on an animal basis as well as in the individual organs. The key take home message is to only combine tumors of the same cell of origin.

BSTP-ESTP Congress | Speaker Abstract

Thursday 25 September 2025 | 11.40-12.00

Navigating the pathology minefield: Harnessing the value of historical background data

John Foster
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Toxicologic pathology is governed by the principles of dose response where increasing dose of a test item will normally result in the appearance of pathology either not normally observed in control animals, or that is increased in incidence and/or severity, of a pathology finding present in controls. The rigid adherence to these broad principles is dependent upon many factors, not the least of which is the presence of background histopathology in the concurrent control animals used on the study. Both the incidence and severity of spontaneous pathology in controls can be variable and is known to be affected by a number of factors that include the species, strain, age, gender, duration and dose route for the animal under test. Changes in the spontaneous pathology in control animals are commonplace such that a simple comparison of concurrent control parameters to those present in treated animals can compromise the correct interpretation of the safety, or otherwise, of a given product. While these factors are present in toxicity studies of all durations, they are especially relevant in rodent lifetime carcinogenicity bioassays where rare neoplasms can arise following treatment whose incidences appear outside of that of the concurrent control group. To help interpret such findings the use of secondary data, from control animals from previously conducted bioassays of similar duration and in the same gender and species, has become a mainstay. Such data has been referred to as “historical background”. Since not every laboratory carrying out carcinogenicity bioassays will have a sufficient number of suitable studies to constitute a useful historical database, the existence of such a reliable database for the main rodent strains used has become a valuable resource sought after by clients.
The current presentation will illustrate the variables that affect the spontaneous incidences of both neoplastic, and non-neoplastic, histopathological findings and suggest ways in which these can be ameliorated. It will also suggest ways in which perceived inadequacies in available databases can be corrected and how to avoid these. Finally, the presentation will show how HCD can be used, alongside other factors such as statistics, information regarding pharmacological target, concurrent, and preceding, organ specific toxicity, to formulate a weight of evidence approach to interpreting the likelihood of a particular chemical being carcinogenic in the test species and if this could subsequently translate to a risk to human exposure.

BSTP-ESTP Congress | Speaker Abstract

Thursday 25 September 2025 | 12.00-12.30

Case Study - Human relevance and risk assessment of endocrine and reproductive system tumours in a rat carcinogenicity study of a small molecule

Zuhal Dincer, Svetlana Markova, Pamela Mullins, Lorraine Britton
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A 2-year carcinogenicity study was performed in Wistar Han Rats on a novel small molecule for the treatment of a rare genetic disease. The carcinogenicity study was considered appropriate based on weight of evidence (WoE) criteria (as specified in Addendum to ICH S1B) due to macroscopic and microscopic changes in the endocrine and reproductive organs in the repeat dose toxicity studies.

In the 2-year rat carcinogenicity study, a test article-related increased incidence of neoplastic changes was observed in the liver (hepatocellular adenomas in females; statistically significant), thyroid gland (follicular cell adenomas in males; not statistically significant), pituitary gland (adenomas in males; statistically significant), testis (benign Leydig cell tumours; statistically significant), and ovary (benign and malignant granulosa cell tumours; not statistically significant). Non-neoplastic microscopic findings in these tissues were as follows: increased incidence of centrilobular hepatocellular hypertrophy in the liver; increased incidence of focal follicular cell hyperplasia in the thyroid glands; increased incidence/severity of focal hypertrophy and vacuolation of the pars distalis of the pituitary in males; and increased incidence/severity of interstitial cell hyperplasia in the ovary. Hyperplastic changes were not present in the Leydig cells of the testis.

Rat toxicity studies showed a similar pattern of pathology to that seen in the 2-year carcinogenicity study with the addition of lobular atrophy in the mammary gland of males and cortical hypertrophy in the adrenal gland. There were no microscopic changes in the testis or pituitary gland. There were no effects on male or female fertility or on sperm analysis in a rat fertility study and no adverse effects of maternal administration on pup survival, growth, development, or behaviour in a rat pre- and post-natal development study. Maternal and embryo-foetal toxicity (major and minor abnormalities) were seen at the high dose in the rat embryo foetal development study, but not in the rabbit. Similar target organs to adult rats were identified in the juvenile rat toxicity study, together with minimal oestrous cycle changes, some growth retardation, and delays in sexual maturity.

The cytology and architecture of the tumors (liver, pituitary gland, and testes) in the treated groups were generally the same as those present in the control rats, suggesting augmentation (promotion) of spontaneous tumors, rather than a de novo carcinogenic mechanism. These observations, together with the corresponding non-neoplastic findings, are suggestive of an adaptive response in the liver resulting in mild hormonal perturbation, through disruption of normal homeostatic feedback mechanisms on the hypothalamic-pituitary-gonadal axis (HPGA). HPGA dysregulation has the potential to impact a variety of organs due to altered homeostasis of hormones such as adrenocorticotropic hormone, gonadotrophin, luteinizing hormone, and estrogen (Harvey and Sutcliffe, 2010). No endocrine related changes were seen in chronic toxicity studies with non-human primates (up to 26-weeks duration), despite the inclusion of additional hormone-related endpoints in the 13-week repeat dose study. These data suggest that the hormonal perturbation signals, seen in the initial rat studies, are specific to this species and therefore not relevant to humans.

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BSTP-ESTP Congress | Speaker Abstract

Thursday 25 September 2025 | 14.00-14.45

Challenges of applying INHAND nomenclature for carcinogenicity studies – Case Presentations

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The International Harmonization of Nomenclature and Diagnostic Criteria for Lesions in Rats and Mice (INHAND) is a global project that aims to establish harmonized criteria for both proliferative and nonproliferative changes in laboratory animals. This nomenclature, compiled by experts from the societies of toxicologic pathology of the UK (British (BSTP), Europe (ESTP), Japan (JSTP) and the US (STP), is the basis of diagnostic terminology for pathologists worldwide and is used e.g. by the Standard for Exchange of Nonclinical Data (SEND) system of the US Food and Drug Administration (FDA) and by the Registry of Industrial Toxicology Animal Data (RITA) member companies in Europe. The original documents for each organ system in the rodent were published between 2009 and 2019. The main focus of this initiative was predominantly on the definition of a harmonized nomenclature for the nonproliferative lesions which have not been established until that point in time whereas the nomenclature for proliferative lesions was mainly available and based on the classification of the World Health Organization/International Agency for Research on Cancer International Classification of Rodent Tumors as well as from databases, and the collective authors' experience.
Over the years, however, it has become apparent that there is a need for improvement regarding the description of some proliferative changes. In daily diagnostics, especially of long term and carcinogenicity studies, the use of INHAND terminology can be challenging, particularly for younger pathologists or pathologists without many years of experience in the field of toxicopathology.
In the first part of the presentation, two cases are presented that illustrate the difficulties in applying the existing INHAND criteria for individual diagnoses. The second part of the presentation will focus on a case from a rat carcinogenicity study that demonstrates the application of the new and revised INHAND terms for rat and mouse ovarian sex cord stromal findings. This segment will detail the methodologies used, highlighting the differences encountered when using historical control databases that rely on former diagnostic criteria and/or terminology. The presentation provides an example of the practical implications of applying the updated INHAND diagnostic criteria/terms and the adjustments needed to align historical control databases with current diagnostic standards.

BSTP-ESTP Congress | Speaker Abstract

Thursday 25 September 2025 | 15.00-15.15

International harmonization of nomenclature and diagnostic criteria in 2025 – a brief update

Emily Meseck
Novartis, East Hanover, United States

The INHAND Proposal (International Harmonization of Nomenclature and Diagnostic Criteria for Lesions in Rats and Mice) has been operational since 2005. As the new chair of the Global Editorial Steering Committee (GESC), I would update the congress on upcoming publication of the Fish INHAND nomenclature in 2025 and recent publications including 2024 publication of the Non-rodent Ocular system. All rodent organ systems have been published as well as the non-rodent nomenclatures for Mini-pig, Dog, Non-human primate and Rabbit. A newly formed working group for Medical Device nomenclature has been established in 2025 as well. goRENI.org is the most up to date source for INHAND terminology, diagnostic criteria, differential diagnoses, images, and guidelines for recording lesions in toxicity and carcinogenicity studies, including ongoing change control results. INHAND GESC representatives work with Clinical Data Interchange Standards Consortium (CDISC) to incorporate terminology as preferred terminology for Standard for Exchange of Nonclinical Data (SEND) submissions to the FDA. Beginning in August 2024, the rodent organ working groups began a systematic review of the published terminology with cross reference to other rodent organ systems and the non-rodent terminology to identify areas for updates and harmonization. Several focused INHAND publications are expected to result from these efforts, with the female reproductive working group leading the field with publication of sex cord stromal tumor nomenclature later this year.

Speaker Abstracts

BSTP-ESTP Congress | Friday 26 September 2025

- New approaches for screening for carcinogenicity
- Carcinogenicity WOE assessment in pharmaceutical and agrochemical industry: A regulatory perspective
- Case Study - Subcutaneous route of administration in rodent carcinogenicity bioassay: a review of rodent specific injection site tumors and relevance to humans
- Carcinogenicity WOE assessment in pharmaceutical and agrochemical industry: a pharmaceutical industry perspective
- Case Study - No preneoplastic precursor lesion of thymomas induced by a RORγt inhibitor?
- Case Study - Continuum between preneoplastic lesions and tumors in the rat induced by CAR/PXR nuclear receptor activation
- Case Study - Rat-tical misjudgement: tumors in disguise

BSTP-ESTP Congress | Speaker Abstract

Friday 26 September 2025 | 08.30-09.15

New approaches for screening for carcinogenicity

Samuel Cohen
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The problems with the 2-year bioassay have been well delineated, but most importantly, is the issue of a large percentage of the results not being relevant to predicting human cancer risk, especially for non-genotoxic carcinogens.
The modes of action can be identified based on basic principles of carcinogenesis, including genetic alterations, spontaneous errors, clonality, and probabilistic events. For human carcinogens, the known modes of action include DNA reactivity, immunosuppression, increased estrogen activity, and cytotoxicity with consequent regenerative proliferation. Focusing on new approach methods, short-term in vivo, in vitro and in silico investigations can be used as the basis for screening for human carcinogens in place of the two-year bioassay, actually with greater sensitivity and specificity. Incorporation of threshold of toxicologic concern in addition to considerations of exposure and dose becomes critical in the evaluations. Most of these approaches in a regulatory setting will require changes in guidelines and possibly legal issues.

BSTP-ESTP Congress | Speaker Abstract

Friday 26 September 2025 | 09.15-10.15

Carcinogenicity WOE assessment in pharmaceutical and agrochemical industry: A regulatory perspective

Stephanie Melching-Kollmuss[1], Kris Siezen[2]
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Regulatory perspective on WOE Assessment for Carcinogenicity Study Outcomes conducted with Agrochemicals.
Rodent carcinogenicity studies are available for almost all agrochemicals, as required by the European EU legislations (EC 1107/2009 and EC 283/2013). As – according to study guidelines (e.g. OECD TG 451, 453) – top doses up to toxic doses are required, quite a number of animals develop tumors over the life time exposure period (rat 2-year / mouse 18-months studies). The regulatory background of carcinogenicity testing and assessment for agrochemicals will be laid out, as well as approaches to conduct comprehensive carcinogenicity and human relevance assessments will be presented. Further, an overview of the relevant classification and labelling aspects following CLP Regulation (EC 1272/2008) will be provided; especially on criteria differentiating between Carcinogenicity Categories 1 (known or presumed human carcinogen), 2 (suspected human carcinogen), and no classification.
Aspects of the prevalence, and biological relevance of tumors occurring in specific animal strains will be covered as well as crucial elements of dose selection and high dose testing. Using practical examples, it will be shown, how the treatment-relationship of observed tumor incidences is assessed, how historical control data could be used, and how mechanistic studies can help to identify the mode of action, the sequence of events for a tumor outcome (AOP – adverse outcome pathway), and eventual species differences (between rats, mice and humans).

Implementation of ICH S1B (R1), a regulatory point of view.
Since the revision of ICH S1B has come into effect in 2022, several Weight of Evidence documents have been submitted to regulatory authorities, to establish the risk of a carcinogenic effect of a medicinal product, and the need for a 2-year rat study to further investigate this risk. In this presentation, an overview will be provided, illustrating how many and to which authorities WoE approaches are submitted, and what proportion is accepted or denied. Further an analysis of reasons why such decisions were made is presented. Any discrepancies between regulatory agencies on the decision of accepting or denying the WoE will be presented and discussed further.

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Case Study - Subcutaneous route of administration in rodent carcinogenicity bioassay: a review of rodent specific injection site tumors and relevance to humans

Bhanu Singh
Gilead Sciences Inc., Foster city, United States

The two-year rodent carcinogenicity bioassay has been the regulatory standard to determine the carcinogenic potential of new drugs. As per guidelines, a therapeutic agent should be tested in a manner comparable with the route of intended human application. Generally, the subcutaneous route is preferred for carcinogenicity evaluation of the drugs intended for parenteral administration. This presentation reviews the injection site neoplastic findings in rodents with subcutaneous administration of injectable drugs and their relevance to humans. A review of marketed long-acting injectable drugs (Mipomersen, Liraglutide, Insulin glargine, Lanreotide acetate, Octreotide acetate, Pegvisomant) shows that injection site neoplasms (fibrosarcomas, malignant fibrous histiocytoma) have been reported via the subcutaneous administration of these drugs in rodent carcinogenicity studies. Although tumor findings were mentioned in the U.S. labels for these compounds, injection-site neoplasms were not mentioned in the warnings and Precaution section. There is no evidence of local malignancy at injection sites in patients associated with these injectables based on available literature or product label information. Similar to injectables drugs, many nongenotoxic food colorants with unrelated chemical structures, inert biomaterials, and plant extracts can also produce mesenchymal neoplasms in rats at the site of subcutaneous injection or implantation. Since these is little or no concern for human cancer associated with these compounds, these findings highlight the unique susceptibility of rodents to develop injection site sarcomas from the method of administration (subcutaneous injection) and associated inflammation and does not represent a cancer risk to humans.

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Friday 26 September 2025 | 11.00-12.00

Carcinogenicity WOE assessment in pharmaceutical and agrochemical industry: An industry perspective

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Carcinogenicity WOE Assessment in Pharmaceutical and Agrochemical Industry: A Pharmaceutical Industry Perspective.
In 2022, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) adopted the ICH S1B(R1) guideline. This guideline utilises a weight of evidence approach to provide pharmaceutical companies with a framework for conducting thorough scientific assessments to evaluate the carcinogenic potential of compounds, as outlined in ICH S1A. Ensuring the robustness of these assessments is crucial to ensure patient safety and provide appropriate information for product labelling. If it can be proven that a 2-year rat carcinogenicity study does not contribute additional value to the human carcinogenicity risk assessment, and this conclusion is accepted by health authorities, the assessment can replace the need for the 2-year study. The guideline's successful acceptance was driven by collaboration between health authorities and the industry. While it holds significant potential to advance carcinogenicity risk assessment science and reduce animal use in line with the 3Rs principles, the implementation presents challenges for the pharmaceutical industry. These challenges include integrating novel in vitro and computational approaches with traditional data, ensuring global regulatory alignment, and managing regulatory procedures without delaying patient access to medicines. Addressing these challenges is vital for optimising the carcinogenicity testing framework and ensuring the safe, effective development of therapeutic agents in today's rapidly evolving scientific environment.

Modernizing carcinogenicity evaluation for agrochemicals.
The long-term rodent bioassay is neither appropriate nor efficient to evaluate carcinogenic potential for humans and to inform risk management decisions. Cancer is the consequence of DNA coding errors that arise either directly from mutagenic events or indirectly from sustained cell proliferation. Developments in the understanding of the etiology of cancer have profound implications for the way the carcinogenicity of chemicals can now be addressed. This knowledge has implications for testing chemicals for carcinogenic potential and risk management.

The modes of action that lead to the induction of tumors are already considered under other hazardous property categories (Mutagenicity/Genotoxicity and Target Organ Toxicity). A rapid transition to a decision-tree matrix can now be applied with better prediction and in step with our growing knowledge of the process of cancer formation. In silico and in vitro evaluation can be performed to look for effects associated with the precursors to the carcinogenic process. Protection of human health is achieved by limiting exposures to below NOAELs for these precursor effects. A systematic approach that evaluates and integrates mechanism-based knowledge with exposure consideration allows for hazard characterization that is scientifically defensible and appropriate for regulatory decision-making of crop protection products. As part of a collaborative effort, the Rethinking Carcinogenicity Assessment for Agrochemicals Project (ReCAAP) developed a reporting framework to guide a weight of evidence (WOE)-based carcinogenicity assessment that demonstrates how to fulfill the regulatory requirements for chronic risk estimation without the need to conduct lifetime rodent bioassays. The framework is the result of a multi-stakeholder collaboration that worked through an iterative process of writing case studies (in the form of waivers), technical peer reviews of waivers, and an incorporation of key learnings back into the framework to be tested in subsequent case study development. The evaluation of new agrochemicals followed this framework that considers ADME, potential exposure, subchronic toxicity, genotoxicity, immunosuppression, hormone perturbation, mode of action (MOA), and all relevant information available from similar agrochemicals using read-across and WOE assessment. The point of departure was estimated from the available data, excluding the cancer bioassay results, with a proposed agricultural use to estimate the chronic dietary risk assessment. The read-across assessments compared data from reliable registered chemical analogues to strengthen the prediction of chronic toxicity and/or tumorigenic potential. The presentation will provide the current state of the art which has evolved rapidly over the last few years and includes a published OECD IATA. The challenges to move away from the cancer bioassay will also be addressed.

BSTP-ESTP Congress | Speaker Abstract

Friday 26 September 2025 | 12.00-12.15

Case Study - No preneoplastic precursor lesion of thymomas induced by a RORγt inhibitor?

Thomas Nolte[1], *Birgit Fogal*[2], *Leila Eslamizar*[2], *Katja Matheis*[1], *Madeline Stuetzle*[1], *Katja Hempel*[1]

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The retinoid-related orphan receptor γt (RORγt) is a nuclear receptor and transcription factor that is important for regular development of lymphoid organs. Specifically, it is essential for the maturation of double positive thymocytes into single positive thymocytes and IL-17 producing T helper 17 (T_h17) cells. Several IL-17 directed therapies are effective in treating autoimmune disease conditions like psoriasis and rheumatoid arthritis. As T_h17 cells express other inflammatory mediators in addition to IL-17, their inhibition by targeting ROR t gained attractiveness as a new therapeutic concept with the potential of therapeutic superiority over solely inhibiting IL-17.

We tested the small molecule ROR t antagonist (compound X) in repeat-dose toxicity studies with up to 26 weeks duration in rats as well as in a 2-year carcinogenicity study in rats and a 6-month carcinogenicity study in rasH2 Tg mice. In the carcinogenicity studies, compound X induced thymomas in both rats and mice. Well-differentiated thymomas were lymphocyte rich and showed a gradual transition to atypical lymphoid hyperplasia. Lymphoid hyperplasia originated from an enlarged cortex, while the medulla appeared unaffected or depleted from lymphocytes. Thymomas progressed to malignancy by an increase of the epithelial component with epithelial cells attaining cellular and nuclear atypia. Retrospective immunostaining of thymi from repeat-dose toxicity studies confirmed the absence of atypical hyperplasia as preneoplasia. While it seems not straight forward that thymomas developed from atypical hyperplasia, we hypothesize that the inhibition of the maturation of thymic CD4+ lymphocytes may have triggered a regenerative response, an effect known to involve not only lymphoid but also epithelial cells. The sequel of events resulting in thymomas is indicative of a ROR t-mediated effect.

In repeat dose toxicity studies with daily oral gavage administration of compound X to rats for up to 26 weeks, no proliferative thymic lesion was detected in histopathology.

However, there was a minor increase of cortical lymphocyte apoptosis, despite lack of thymus weight reduction. Immune phenotyping by flow cytometry revealed an increase of certain T-cell subpopulations in the thymus after 13-week dosing, but not after 26 weeks. The only change after 26 weeks consisted in an increase of apoptotic DP-T lymphocytes and apoptotic Th-cells. In light of constant thymus weight in males and even an increase to 1.5X Control in females, this increase in apoptosis obviously must have been over-compensated by an – undetected – proliferative response.

It is concluded that thymomas induced by a ROR t inhibitor in rats have been preceded by increased T cell turnover in the thymic cortex. Detection of this effect was possible only indirectly by the combination of increased apoptosis and increased organ weight.

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Friday 26 September 2025 | 12.15-12.30

Case Study - Continuum between preneoplastic lesions and tumors in the rat induced by CAR/PXR nuclear receptor activation

Frederic Schorsch
Bayer, Sophia Antipolis, France

Examples will be deciphered where hepatocellular tumors but also follicular cell tumors of the thyroid gland can be predicted from preneoplastic or proliferative data observed after repeated exposure in the 90 day or one year rat toxicity studies. Real cases will be selected from agrochemicals, either already published or not. Car/Pxr activation will be taken as a classical mode of action where such modeling of hepatocellular tumors but also thyroid follicular cell tumors is possible. More complex cases where direct thyroid toxicant mechanisms can lead to thyroid follicular cell tumors will serve to illustrate the same continuum between preneoplastic lesions and tumors.

BSTP-ESTP Congress | Speaker Abstract

Friday 26 September 2025 | 12.30-12.45

Case Study - Rat-tical misjudgement: tumors in disguise

Xavier Palazzi
AstraZeneca, Waltham, United States

Compound X is a small molecule developed for oncology. Hyperplastic and neoplastic findings from a 6-month oral toxicity and a 2-year carcinogenicity study in Han Wistar rats will be presented and discussed in relationship with INHAND guidelines. Compound X caused hemangiomas and angiomatous hyperplasia in the mesenteric lymph node of the 2-year carcinogenicity study, as evidenced by microscopic incidence tables. However, questionable changes were present in the 6-month study. This presentation will highlight the difficulty of interpreting minimal incidence variations of hyperplasic findings in chronic studies.

Interactive Case Presentations

Thursday 25 September 2025

- AI-assisted Purkinje cell density baseline in 54 control cynomolgus macaques and sex comparison
- A nasal bone finding in CD1 mice
- Findings in cynomolgus monkeys following long-term exposure to an immunomodulatory biotherapeutic
- Retrospective review of the pathological findings in diagnostic necropsy submissions of laboratory Grey Short-tailed opossums (Monodelphis domestica)

BSTP-ESTP Congress | Interactive Case Presentations

Thursday 25 September 2025 | 15.15-15.30

AI-assisted Purkinje cell density baseline in 54 control cynomolgus macaques and sex comparison

Brieuc Cossic, Xavi Langa Oliva, Mar Hernández-Obiols, Laura Polledo, Pierre Maliver, Marco Tecilla
Hoffman-La Roche, Basel, Switzerland

Introduction

Purkinje cells are crucial for cerebellar function and accurately counting them is essential for assessing neurotoxicity in toxicologic pathology studies. Despite their significance, there is a lack of existing data on Purkinje cell (PC) density in healthy cynomolgus macaques (Macaca fascicularis). This study aims to fill this gap using AI-assisted image analysis of hematoxylin and eosin (H&E) stained images.

Methods

Standard coronal cerebellar sections stained with H&E from 54 control cynomolgus macaques (21 females, 33 males) were analyzed. AI-assisted image analysis was performed using Halo AI software (Indica Labs®) to generate annotations identifying the PC, the granular, and molecular layers. These annotations were expanded and intersected in QuPath to determine the length of the PC layer. Subsequently, the density of PCs was quantified as the number of PCs per 100 µm length of PC layer. Differences in PC densities between sexes were assessed using an independent t-test.

Results

Average PC density was 1.15 cells/100 µm (range: 0.80-1.54). Comparison between sexes revealed no statistically significant difference in mean density (females: mean ≈ 1.20; males: mean ≈ 1.13; p=0.226).

Conclusion

This study establishes a baseline PC density of 1.15 cells per 100 µm of PC layer (range 0.80-1.54) in the cerebellum of healthy control cynomolgus macaques. No statistically significant difference in PC density was observed between males and females. The effect of age and geographical origin remain to be studied. These benchmark values will enhance the sensitivity and interpretability of PC quantification in future neurotoxicity and safety assessment studies.

BSTP-ESTP Congress | Interactive Case Presentations

Thursday 25 September 2025 | 16.15-16.30

A nasal bone finding in CD1 mice

Marcia Pereira Bacares
Labcorp, Chantilly Va, United States

CD-1 (ICR) - (Crl:CD1[ICR]) (NA or UK) mice, five females from water or vehicle control groups, from 104-week carcinogenicity studies (oral or subcutaneous route), either moribund or terminal sacrificed, were noted with an incidental finding in the bone /marrow of the nasal turbinates, but not in the femoral and/or sternum bone/marrow. Tissue samples were stained with Hematoxylin and Eosin. No clinical or macroscopic observations related to this finding were noted in the nose or head. The macroscopic observation “cyst” was noted in the ovary of all affected females.

Fibro-osseous lesion (FOL) was noted in nasal bone and marrow but not in the femur or sternum in 13 out of 204 CD-1 female mice from control groups administered either sterile saline (subcutaneous), purified water (oral) or Methylcellulose/Tween 80 in purified water (oral) in two different carcinogenicity studies. Five of these cases were selected for this case presentation. Animals were supplied by Charles River Laboratories from two different vendor barrier facilities. Two to four sections of nasal turbinates were examined microscopically for each animal per study protocol. FOL was noted in the nasal bone and marrow and characterized by partial or complete replacement of bony trabeculae and marrow cavity by fibrovascular stroma containing fibroblasts, osteoclasts, and osteoblasts embedded in eosinophilic matrix. Severity ranged from minimal to moderate, with some bone distortion in the moderately affected animal. In addition to nasal FOL, microscopic findings observed in all five cases included ovarian cyst and uterine cystic endometrial hyperplasia. FOL can occur in all bones in mice but has been reported most frequently in the sternebrae, long bones, and vertebrae particularly in aging females and it is limited to some strains, with B6C3F1 female mice having higher incidence of FOL than C57BL/6 or CD1 mice. FOL has not been reported in rats yet. FOL has been associated with hyperestrogenism (suggested by the presence of ovarian cyst, cystic endometrial hyperplasia, vaginal epithelial cell hyperplasia and hyperkeratosis) and increased serum alkaline phosphatase activity, but not with primary or secondary hyperparathyroidism. Development is hastened and lesions are more severe in females given estrogen. Furthermore, incidence and severity of FOL may be influenced by treatment with compounds with estrogenic effects. Therefore, this lesion should be diagnosed and given a

severity grade. Considerable histologic variation is observed for FOL. This variability has led to diagnosis of this condition as hyperostosis, myelofibrosis, osteoporosis, osteofibrosis, and osteosclerosis in the past. Advanced FOL is indistinguishable histologically from fibrous osteodystrophy (FOD), and diagnosis is by excluding advanced renal disease (generally marked chronic progressive nephropathy) or other causes of increased parathyroid hormone (PTH) production, which were not appreciated in any of these five cases.

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Thursday 25 September 2025 | 16.30-16.45

Findings in cynomolgus monkeys following long-term exposure to an immunomodulatory biotherapeutic

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A 6-month subcutaneous repeat-dose GLP toxicity study was conducted in cynomolgus monkeys (Macaca fascicularis) with an immunomodulatory biotherapeutic at two dose levels (high and low). The study also included a 12-week recovery period. A few days before the scheduled sacrifice, two high dose animals had to be euthanized due to constant body weight reduction, poor general condition, and moderate anemia. Both animals presented at necropsy with enlargement of the spleen, mesenteric lymph node and adrenal glands, as well as beige, firm nodules in several non-lymphoid organs (e.g., liver, lung, heart). One high dose animal without clinical symptoms was noted some days later with enlarged spleen and adrenals and a beige, firm nodule in the liver at terminal necropsy. The histological and immunohistochemical characteristics of the findings, the different investigations conducted, as well as the diagnosis and pathogenesis will be presented and discussed in an interactive way with the audience.

Microscopically, affected tissues were infiltrated by a monomorphic population of round to polygonal neoplastic cells arranged in closely packed sheets, measuring 15 to 25 µm in diameter, and displaying significant anisocytosis and anisokaryosis, starry sky pattern, a high mitotic ratio, and atypical mitoses. Immunohistochemistry of tumor sections indicated that the majority of neoplastic cells were positive for CD20 and negative for CD3 and iba-1. The histological and immunohistochemical characteristics of the tumors were consistent with B-cell lymphomas. While neoplastic cells were negative for macaque lymphocryptovirus (LCV) by immunohistochemistry (EBNA2) and RNAscope in situ hybridization, a very strong signal was detected in multiple tumor sections by RNAscope in situ hybridization using a probe designed to specifically target macaque rhadinovirus (RV). In addition, qPCR performed on longitudinally-collected blood samples showed prominent increases in circulating viral loads of RV (but no test articlerelated changes in LCV loads) in all three animals from Week 16 or Week 24. The full set of data supported the diagnosis of macaque RVassociated B-cell lymphomas, following a profound immunosuppression induced by the chronic administration of the test article. While lymphoproliferative disease in old world

NHPs has most often been reported to be associated with the primate LCV in an immunocompromised context, this report demonstrates that RV can be involved in B cell lymphomagenesis in animals chronically dosed with an immunomodulatory drug. Opportunistic rhadinoviral infection should be considered as a differential etiological diagnosis of B-cell lymphomas encountered in safety studies conducted in the NHP.

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BSTP-ESTP Congress | Interactive Case Presentations

Thursday 25 September 2025 | 16.45-17.00

Retrospective review of the pathological findings in diagnostic necropsy submissions of laboratory grey short-tailed opossums (Monodelphis domestica)

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Introduction

Monodelphis domestica, the grey short-tailed opossum, is a South American tropical small marsupial and well established as a laboratory animal, featuring in experimental research articles dating back to 1969. M. domestica is valuable as a marsupial model because it breeds readily in captivity and does not bear its young in a pouch therefore neonates are easily accessible. Despite a long history in experimental research, including as disease model, there is strikingly little published on spontaneous pathologies of M. domestica.

Methods

This poster provides a retrospective review of the gross and histological findings across the main organ systems of laboratory short-tailed opossums submitted to the diagnostic service at the Royal Veterinary College, U.K..

Results

Across the approximately 20 post mortem examinations conducted common indications for euthanasia, or causes of death, were endocarditis, cellulitis and pneumonia with a full breakdown of lesion frequency provided in the table below.

Conclusion

Interestingly, in contrast with a previous similar report, there was minimal digestive tract pathology. These findings complement the one previous published study on spontaneous pathology of laboratory opossums and aids the interpretation and contextualisation of histological lesions noted during experimental studies involving this species.

Poster Presentations

- P01 | Preclinical safety evaluation of a 1940 nm Tm:YAP Laser for fractional skin ablation in a swine model
- P02 | Spontaneous neoplasms in laboratory Beagle dogs: 11 cases (2014-2024)
- P03 | INHAND: International Harmonization of Nomenclature and Diagnostic criteria for lesions - Update 2025
- P04 | Lens fiber degeneration - a novel background finding in Göttingen minipigs?
- P05 | Historical control data of neoplastic lesions in CD-1 Mice carcinogenicity bioassays
- P06 | Radiation-induced chronic nephropathy occurring as late toxicity in an orthotopic xenograft pancreatic tumor mouse model
- P07 | Macaque rhadinovirus (RV)-associated B-cell lymphomas in cynomolgus monkeys following long-term exposure to an immunomodulatory biotherapeutic
- P08 | A case of carcinogenicity evaluation of eye drops during development in Japan: motugivatrep, a TRPV1 antagonist for dry eye disease.
- P09 | Thyroid proliferative findings in the Crl:WI (Han) Rat in 2-Year carcinogenicity studies – an update
- P10 | Long-term tissue preservation: comparative study of slide quality across decades in formalin-fixed tissues, paraffin blocks, and stained-glass slides
- P11 | Degenerative joint lesions in Cynomolgus monkeys (Macaca fascicularis)

Poster Presentations

P01 | Preclinical safety evaluation of a 1940 nm Tm:YAP Laser for fractional skin ablation in a swine model

Abraham Nyska[1], Yuval Ramot[2], Michal Steiner[3], Udi Vazana[4], Rotem Nahear[5], Neria Suliman[5], David Friedma[5,6], Salman Noac[6,7]

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Introduction | Fractional laser ablation is widely used for dermatologic applications, offering precise tissue removal with controlled healing responses. The 1940 nm Thulium-doped Yttrium Aluminum Perovskite (Tm:YAP) laser (Epicare) is a novel system designed for skin resurfacing. This study evaluates its safety and histopathological effects in a swine model to support its potential clinical use.

Methods | Two female domestic swine underwent fractional skin ablation at 52 marked abdominal sites with varying energy settings. Macroscopic assessments were performed immediately and at 1, 3, 7, 14, 22, and 29 days post-ablation. Histopathological evaluations were conducted at 1, 7, and 29 days, focusing on epidermal regeneration, inflammation, dermal remodeling, and collagen deposition.

Results | Macroscopic observations showed immediate erythema and edema, resolving by day 14. Histopathology revealed focal epidermal necrosis with early regeneration by day 7 and advanced collagen deposition by day 29. No infections, ulcerations, or scarring were observed. The laser produced well-defined ablation zones, with differences in lesion width correlating with energy settings, demonstrating precise depth control.

Conclusion | The Epicare 1940 nm Tm:YAP laser demonstrated a favorable safety profile with effective tissue ablation and rapid healing in a swine model. These findings suggest its potential for dermatologic applications, warranting further clinical evaluation to optimize treatment parameters and confirm efficacy in human skin resurfacing.

P02 | Spontaneous neoplasms in laboratory Beagle dogs: 11 cases (2014-2024)

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Labcorp, Harrogate, United Kingdom

Introduction | There is scarcity of literature on spontaneous neoplasia in laboratory-kept beagle dogs, with most information limited to case reports. The International Harmonization of Nomenclature and Diagnostic Criteria (INHAND): Nonproliferative and Proliferative Lesions of the Dog states that neoplasms are rare in toxicity studies, but no data on incidence is available. The authors describe the incidence of spontaneous neoplasms in control beagle dogs kept in a research facility over a 10-year interval and list spontaneous occurring neoplasms in test article treated beagle dogs for the same time interval.

Methods | The authors interrogated the Historical Control Data (HCD) for all beagle dog studies at the Harrogate Labcorp site and searched for canine tumors in test article-treated groups considered not test article-related in a 10-year interval (2014-2024).

Results | A total of 11 tumors were identified, with 3 from control dogs and 8 from test article-treated dogs. The mean age of the dogs was 10.8 months, and most tumors occurred in females. The most common tumors were skin histiocytomas (6 cases) and squamous cell papillomas (3 cases). Other rare tumors included a vaginal stromal polyp and a submandibular salivary gland adenocarcinoma. The histological appearance of all tumours was consistent with descriptions found in the literature. The incidence of histiocytomas, squamous cell papillomas and salivary gland adenocarcinomas in control dogs was less than 0.2 %.

Conclusion | Neoplasms are uncommon in laboratory beagle dogs. Skin histiocytomas and squamous cell papillomas were the most frequently identified tumors, with locations consistent with previous literature.

P03 | INHAND: International Harmonization of Nomenclature and Diagnostic criteria for lesions - Update – 2025

Emily Meseck[1], Ute Bach[2], A Bradley[3], Stacey Fossey[4], Shim-mo Hayashi[5], Matt Jacobsen[6], Rupert Kellner[7], Victoria Laast[8], Thomas Nolte[9], Susanne Rittenhausen[7], Junko Sato[10], John Vahle[11], Katsuhiko Yoshizawa[12]

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Introduction | The INHAND Proposal has been operational since 2005. A Global Editorial Steering Committee (GESC) coordinates objectives of the project.

Methods | Development of terminology for rodent organ systems and non-rodent species is the responsibility of Working Groups, with experts from North America, Europe, and Japan.

Results | All rodent organ systems have been published – Respiratory, Hepatobiliary, Urinary, Nervous Systems, Male Reproductive and Mammary, Zymbals, Clitoral and Preputial Glands and Hematolymphoid System in Toxicologic Pathology and the Integument and Soft Tissue, Female Reproductive System, Digestive System, Cardiovascular System, Skeletal System, Special Senses and Endocrine System in the Journal of Toxicologic Pathology as supplements and on a web site – www.goReni.org. Mini-pig and Dog were published in Toxicologic Pathology in 2021 and Non-human primate and Rabbit were published in the Journal of Toxicologic Pathology in 2021. Non-rodent ocular toxicity manuscript was published by Toxicologic Pathology in late 2024 and the Fish INHAND manuscript is targeted for publication in Journal of Toxicologic Pathology in 2025.

Conclusion | INHAND guides offer terminology, diagnostic criteria, differential diagnoses, images, and guidelines for recording lesions in toxicity and carcinogenicity studies. INHAND GESC representatives work with Clinical Data Interchange Standards Consortium (CDISC) to incorporate INHAND terminology as preferred terminology for the Standard for Exchange of Nonclinical Data (SEND) submissions to the FDA. Interest in INHAND nomenclature, based on input from industry and government scientists, is encouraging wide acceptance of this nomenclature.

P04 | Lens fiber degeneration - a novel background finding in Göttingen minipigs?

Theresa C Broemel[1], Fernando Romero-Palomo[1], Kerstin Hahn[1], Annamaria Brändli-Baiocco[1], Sean McKeag[2], Barbara Lenz[1]
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Introduction | Göttingen minipigs are an increasingly popular alternative to the use of nonhuman primates in preclinical studies. This species is known to exhibit particular spontaneous findings across various organ systems, and the number of published background findings in Göttingen Minipigs is still evolving. In three independent preclinical studies, several control and treated Göttingen minipigs presented with uni- or bilateral lens opacity in the routine pre-dose and pre-termination ocular examination.

Methods | Histopathological evaluation of the eyes was performed as part of the predefined readouts in these studies. To identify potential underlying causes for the in-life findings, we investigated several factors including the age, sex and pedigree of affected and unaffected animals. Additionally, we retrospectively reviewed studies using Göttingen minipigs performed between 2014 and 2023 in which ocular examinations and histopathology were reported as unremarkable.

Results
The in-life observations correlated microscopically with subcapsular lens fiber degeneration at the posterior lens in the majority of affected animals. A relation with the sex or pedigree of the animals could not be detected, however, the incidence of affected animals increased during the duration of the studies suggesting an age-related effect. We could not detect this finding in any of the retrospectively evaluated animals.

Conclusion | Our investigations suggest that subcapsular lens fiber degeneration is a novel spontaneous background finding in Göttingen minipigs, with higher incidence as the animals become older, particularly in chronic studies. While being rare, this finding should be kept in mind especially when using Göttingen minipigs in preclinical ocular safety assessments.

P05 | Historical control data of neoplastic lesions in CD-1 Mice carcinogenicity bioassays

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Introduction | Carcinogenicity testing in rodent species is required by regulatory agencies for the evaluation of potential toxic or carcinogenic effects of a substance. CD-1 mice are regularly implemented for this purpose but up-to-date information on the incidence of spontaneous neoplastic findings is not currently available. Thus, a retrospective study was performed to determine the incidences of spontaneous tumors in CD-1 mice from carcinogenicity studies.

Methods | Historical control data (HCD) of spontaneous tumors were collected from 1791 male and female CD-1 mice from 78-, 80-weeks, and 2-year studies evaluated between 2010 and 2025.

Results | A total of 1164 benign and 660 malignant tumors were recorded in males. The most common tumor in males was bronchioalveolar adenoma (N=438, 24.46%), followed by bronchioalveolar carcinoma (N=279, 15.58%); hepatocellular adenoma (N=216, 12.06%), Harderian gland adenoma (N=186, 10.39%), lymphoma (N=98, 7.71%), adrenal subcapsular cell adenoma (N=87, 4.95 %) and hepatocellular carcinoma (N=83, 4.63 %).
A total of 807 benign and 723 malignant tumors were recorded in females. The most common neoplasm in females was lymphoma (N=254, 20.00%), followed by bronchioalveolar adenoma (N=220, 12.30%), uterine polyp (N=120, 3.69%), bronchioalveolar carcinoma (N=111, 6.20%), Harderian gland adenoma (N=64, 3.58%) and uterine leiomyoma (N=63, 3.53%).

Conclusion | Carcinogenicity studies are essential in preclinical drug development and knowledge of spontaneous neoplasms is crucial to identify any potential drift which can occur due to genetic or non-genetic causes. This HCD will assist both the interpretation of neoplastic findings in CD1 mice carcinogenicity studies and the differentiation of background findings from test article-related effects.

P06 | Radiation-induced chronic nephropathy occurring as late toxicity in an orthotopic xenograft pancreatic tumor mouse model

Leona Arps[1, 2, 3], *Severin Kampfer*[4, 5], *Christopher Kessler*[4, 6], *Janne Schoening*[7], *Daniela Schilling*[4, 8], *Robert Klopfleisch*[3], *Carolin Mogler*[1, 2, 6], *Jan Jakob Wilkens*[4], *Stephanie E. Combs*[4, 6, 8], *Katja Steiger*[1, 2, 6], *Sophie Dobiasch*[4, 6, 8]

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Introduction | High-precision irradiation (RT) devices for preclinical animal models simulate cancer treatments *in vivo*. The kidney is prone to radiation-induced nephropathy, characterized by tubular atrophy, interstitial fibrosis and glomerulosclerosis. This study investigates chronic renal toxicities in an orthotopic xenograft pancreatic tumor mouse model.

Methods | Image-guided RT was performed in 22 nude mice bearing orthotopic implanted tumors from the human pancreatic cancer cell line MiaPaCa-2. The cohort included five unirradiated controls and 17 irradiated mice. Weekly cone beam computed tomography (CBCT) was conducted. At the end of the follow-up period, creatinine and blood urea nitrogen (BUN) levels were measured. Histopathological examination of the kidneys was performed with semiquantitative scoring of glomeruli, tubules and interstitium.

Results | Atrophy was detected in 59 % (10/17) of the left kidneys of irradiated mice by CBCT after an average of 79 days. The dose distribution showed the proximity of the left caudal kidney to the high-dose region. Mice with CBCT-based kidney atrophy received higher mean doses (42.2 Gy) than those without (33.9 Gy) and exhibited elevated serum BUN and creatinine levels. Microscopically, the left atrophied kidneys showed significantly more pronounced chronic progressive nephropathy than the right kidneys of the same mice, characterized by

glomerular and tubular atrophy, interstitial fibrosis and interstitial mononuclear cell infiltrates.

Conclusion | Our preclinical high-precision irradiation setup in a pancreatic tumor mouse model demonstrates chronic renal RT side effects comparable to patient observations. Our findings highlight the importance of integrating clinically established dose constraints into preclinical tumor models to minimize tissue toxicity and enhance translational relevance.

P07 | Macaque rhadinovirus (RV)-associated B-cell lymphomas in cynomolgus monkeys following long-term exposure to an immunomodulatory biotherapeutic

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Introduction | Rhadinovirus (RV), a gamma-2 herpesvirus, is frequently found in non-human primates (NHPs), the natural infection being usually asymptomatic in immunocompetent animals. In contrast, animals coinfected with SIV can develop B cell lymphocytosis with an activated phenotype. Repeat dosing of NHPs with immunomodulatory drugs may be associated with opportunistic infections.

Methods | A 6-month subcutaneous repeat-dose toxicity study was conducted in cynomolgus monkeys with an immunomodulatory biotherapeutic at two dose levels. The study also included a 12-week recovery period.

Results | At necropsy, three high dose animals showed enlargement of the spleen, mesenteric lymph node and adrenal glands, as well as beige, firm nodules in several non-lymphoid organs. Microscopically, affected tissues were infiltrated by a monomorphic population of round neoplastic cells arranged in closely packed sheets. Significant anisocytosis and anisokaryosis, starry sky pattern and high mitotic ratio were noted. Immunohistochemical investigations indicated that the majority of neoplastic cells were positive for CD20 and negative for CD3 and iba-1. While neoplastic cells were negative for macaque lymphocryptovirus (LCV) by immunohistochemistry and RNAscope *in situ* hybridization, a very strong signal was detected in multiple tumor sections by RNAscope *in situ* hybridization using a probe against macaque RV. In addition, real-time quantitative polymerase chain reaction (qPCR) showed prominent increases in circulating viral loads of RV in those animals from Week 16 or Week 24.

Conclusion | The set of data supported the diagnosis of RV-associated B-cell lymphomas, following immunosuppression induced by the chronic administration of the test article. While lymphoproliferative disease in old world NHPs has most often been reported to be associated with LCV in an immunocompromised context,

this report demonstrates that RV can be involved in B cell lymphomagenesis in animals chronically dosed with an immunomodulatory drug. Opportunistic rhadinoviral infection should be considered as a differential etiological diagnosis of lymphomas encountered in safety studies conducted in the NHP.

P08 | A case of carcinogenicity evaluation of eye drops during development in Japan: motugivatrep, a TRPV1 antagonist for dry eye disease.

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Introduction | Motugivatrep, a selective antagonist of transient receptor potential cation channel subfamily V member 1 (TRPV1), is under development as a novel ophthalmic product for the treatment of dry eye disease. The ICH S1A guideline states that pharmaceuticals administered by the ocular route may not require carcinogenicity studies unless there is cause for concern or significant systemic exposure. However, the guideline does not specify a threshold for systemic exposure level. During the consultations with the FDA and PMDA regarding carcinogenicity evaluation of motugivatrep, we received different opinions. This presentation summarizes a case of the carcinogenicity evaluation of eye drops and communication with regulatory authorities.

Methods | Based on general toxicity and genotoxicity studies, we consulted with the FDA and PMDA regarding the necessity of carcinogenicity studies for the motugivatrep ophthalmic suspension.

Results | Following the PMDA's opinion that carcinogenicity studies are necessary, a 26-week oral dosing study in rasH2-Tg mice and a 2-year oral dosing study in rats were conducted as part of the carcinogenicity evaluation. In both studies, there were no increases in tumor development following the oral administration of motugivatrep.

Conclusion | Although the threshold remains unclear, the necessity of carcinogenicity studies for eye drops may vary among regulatory authorities. Therefore, carcinogenicity evaluation programs should be prepared even in eye drops development in case regulatory authorities require them.

P09 | Thyroid proliferative findings in the Crl:WI (Han) Rat in 2-Year carcinogenicity studies – an update

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Introduction | The thyroid gland is an important target in carcinogenicity studies for the inducibility of follicular tumors secondary to liver changes. Historical control data (HCD) are helpful for differentiating spontaneous and test item–related findings.

Methods | HCD were provided for thyroid proliferative findings in control Han Wistar rats (1189 males and 1085 females) in 21 2-year carcinogenicity studies conducted at Labcorp, Huntingdon/Eye, UK, between 2012 and 2025. Incidence over time, supplier, route of administration, diet and pathologist were surveyed to investigate any association with the findings.

Results | Focal follicular cells (FC) hyperplasia was observed in 3% of males [0-18% range of incidence (RI)], and 1.5 % of females (0-8% RI), FC adenomas were observed in 8% of males (0-18% RI), and 3% of females (0-10% RI), FC carcinomas were observed in 1.4% of males (0-9% RI), and 0.5% (0-2% RI) of females. Focal C cell (CC) hyperplasia was observed in 14% of males (0-40% RI), and 14% of females (0-33%RI), CC adenomas were observed in 11% of males (2-24% RI), and 9% of females (4-20% RI), CC carcinomas were observed in 0.7% of males [0-5.5% RI], and 0.5% of females (0-2% RI). Marked differences in the incidence of several findings were noted, however no clear association with any factor could be drawn.

Conclusion | High variability in the incidence of thyroid proliferative findings, particularly of C cells, was observed in control Han Wistar rats which was considered likely related to the genetic heterogenicity of outbred stocks or threshold variation between pathologists/studies.

P10 | Long-term tissue preservation: comparative study of slide quality across decades in formalin-fixed tissues, paraffin blocks, and stained-glass slides

Raquel Vallejo[1], *Ricardo De Miguel*[1], *Klaus Weber*[1], *Yoshimasa Okazaki*[1], *Cristina Soriano*[2], *Alba Navarra*[2], *Samuel Rodriguez*[2], *Paula Mendoza*[2], *Albert Sandoval*[2], *Francisco Jose Mayoral*[2], *Robert Kreutzer*[1], *Kristel Kegler*[1], *Paula Ortega*[1]

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Introduction | Formalin-fixed tissues, paraffin blocks, and glass slides are widely utilized for preservation of samples in pathology. Despite the widespread use, there is limited documentation on the long-term impact of prolonged storage on histological quality.

Methods | For this study, samples from rodents (Wistar and SD Rats) and non-rodents (Cynomolgus macaques and Beagle dogs) were retrieved from the AnaPath Research S.A.U. tissue archive. The materials included formalin-fixed tissues, paraffin blocks and tissue sections on glass slides that had been stored at room temperature under controlled conditions for periods ranging from 1.5 to over 30 years. Histopathological evaluation was performed by two pathologists in newly hematoxylin and eosin-stained slides and original glass slides.

Results | Macroscopically, pale yellow discoloration, friability, and hardness increased with prolonged storage of tissues in formalin, but they still remained suitable for processing. Histologically, tissues stored for longer periods revealed a series of changes including the presence of crystalline structures, formalin pigment deposition, loss of basophilic staining, deterioration in overall staining quality, and progressive morphological quality loss. These changes were more severe in formalin preserved tissues compared with paraffin blocks and glass slides, with variations depending on the organ type.

Conclusion | Histopathological evaluation remained feasible in tissues stored for extended periods (from 1.5 to over 30 years) in formalin, paraffin blocks and glass slides. However, long-term storage triggers various artifacts that may complicate histopathological evaluation. Tissues stored in glass slides and paraffin blocks demonstrated the best overall preservation, staining quality and tissue integrity.

P11 | Degenerative joint lesions in Cynomolgus monkeys (Macaca fascicularis)

Svenja Regina Hartung, Vivien Lindner, Annette Romeike
Labcorp, Muenster, Germany

Introduction | Cynomolgus monkeys are used in toxicity studies due to their physiological similarity to humans. Older animals are used in studies in which sexual maturity is a prerequisite. Spontaneous degenerative joint disease is known in adult and advanced age monkeys, but detailed descriptions and publications are rare. Herewith the authors present an overview of spontaneous degenerative joint disease from the stock colony at the Labcorp facility in Münster, Germany (Jan 2021 to Apr 2025).

Methods | 124 necropsies (animal welfare) have been reviewed. HE stained standard sections of the joints with macroscopic lesions or preliminary X-ray findings were examined microscopically.

Results | 16 Animals (10 males/6 females; median age: 71 months; range: 42 - 296 months) displayed degenerative lesions at the knee (75%), vertebra (tail: 56%; lumbar: 50%; thoracic: 25%), tarsus (19%), hips (12.5%), shoulder (6%), and/or elbow (6%). Microscopic findings comprised arthrosis in the knee (75%), tarsal joint (19%), and hip (12.5%) with cartilage thinning, fibrillations, synovial hyperplasia; spondylosis/ankylosis in lumbar (44%) or thoracic vertebra (12.5%), and disc degeneration in the tail (56%) with cartilage proliferation and woven bone formation.

Conclusion | Degenerative joint disease in cynomolgus monkeys is rare and mainly occurs in adult and advanced age animals (knee, tail and lumbar vertebrae), similarly to elderly humans. Given the age range of cynomolgus monkeys in standard toxicity studies (adolescent to young adult) and a thorough selection process, degenerative joint disease in toxicity studies is a rare event but may occur in studies with animals of advanced age (ePPnD; sexually maturity endpoints).

P12 | Articular inflammation in Cynomolgus monkeys (Macaca fascicularis)

Svenja Regina Hartung, Vivien Lindner, Annette Romeike
Labcorp, Muenster, Germany

Introduction | Cynomolgus monkeys are widely used in preclinical toxicity studies due to their physiologic similarities with humans. While degenerative joint disease is comparatively frequent in cynomolgus monkeys, articular inflammation is rather rare and often described to be caused by bacterial infection. Herewith the authors present an overview of spontaneous articular inflammations from Jan 2021 to Apr 2025 (animal welfare necropsies) from the Labcorp test facility in Münster, Germany.

Methods | Animals underwent a macroscopic examination with weighing following full necropsy. Decalcified and HE stained standard sections of the joints with macroscopic lesions or preliminary X-ray findings were examined microscopically.

Results | 8 female animals (6.4%; median age: 60 months; range: 17 – 84 months) displayed articular inflammation in the knee joint (100%), tarsal joint (37.5%), and lumbar vertebra (12.5%). Fibrinosuppurative (100%) to pyogranulomatous (37.5%) inflammation was observed in the joint (100%), with osteophyte formation (25%) and involvement of the bone and bone marrow (75%), tendons (100%), adjacent musculature and connective tissue (87.5%), and tributary lymph nodes (25%).

Conclusion | Articular inflammation must be considered as a differential diagnosis in case of clinical observations of lameness and articular swellings. Articular inflammation is rather rare in cynomolgus monkeys but can impact the animals' wellbeing considerably. In the cases reviewed in this cohort, inflammation was also noted in the surrounding tissues (e.g. tendons, muscle, connective tissues) and was considered to be of infectious origin.

P13 | Evaluating adrenal cortex hyperplasia in rats using foundational and weakly supervised deep learning models

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Introduction | This study aims to develop and qualify a method to assist pathologists in evaluating adrenal cortex hyperplasia in rat carcinogenicity studies. Data from four studies, comprising 330 whole slide images (WSIs), 69 negatives and 261 positives were used.

Methods | An organ recognition model was used to identify adrenal tissue on WSIs. From these regions, tiles were extracted for model training using three approaches:

1. Supervised Learning: A ResNet50 tile-level classifier was pretrained on ImageNet and domain-specific histopathology data. Due to limited annotated tiles, performance was weak and unsuitable for reliable slide-level predictions.
2. Weakly Supervised Learning (Multiple Instance Learning - MIL): MIL assigns labels to sets of tiles (bags) rather than individual tiles. However, co-occurring lesion patterns in the training data led to model confusion.
3. Foundational Model Approach: A model trained on ~800 tiles from 16 slides showed promising results. Future improvements include incorporating multi-magnification (20x and 5x) and additional annotations to improve localisation.

Results | NA

Conclusion | The foundational model approach that is under development has shown encouraging preliminary results for identifying cortical hyperplasia. In contrast, the MIL method struggled with mixed lesion patterns—common in carcinogenicity studies. When qualified, this approach will be extended to detect of alteration proliferative lesions in other organs evaluated in rodent carcinogenicity studies.

P14 | Beagle: An AI agent for integrated toxicologic pathology reporting

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Introduction | Toxicologic pathology reporting requires integration of data on various study endpoints, related literature, and information sources into a clear narrative with well-founded conclusions. We introduce Beagle, the first-of-its-kind AI agent to empower expert toxicologic pathologists with tools that streamline data integration and interpretation, enabling their insights to drive faster, more consistent decisions in drug development. Beagle is designed to interrogate and aggregate data, information and knowledge across company siloes, literature and in databases. Here we evaluate Beagle's capabilities using a subchronic toxicity study involving Enalapril.

Methods | Beagle-v0.5 was tested on data from a 13-week rat study evaluating Enalapril. It was asked, in plain English terms, to analyse the study pathology data, to accurately describe morphologic findings, link them to study metadata (dose, sex, timepoint), provide mechanistic interpretations consistent with expert pathologist Conclusions, and draft the toxicologic pathology study report.

Results | Beagle-v0.5 successfully identified and described dose-dependent renal lesions, including tubular basophilia, dilation, and interstitial fibrosis, predominantly in high-dose male rats. It contextualized these findings with known pharmacologic effects of ACE inhibitors, including altered renal perfusion and compensatory changes in nephron architecture. Importantly, the agent offered transparent references to underlying data fields and maintained alignment with original SEND dataset annotations.

Conclusion | This work demonstrates Beagle's potential as an agentic AI companion for toxicologic pathology studies, capable of increasing reporting efficiency and accuracy through integrating clinical chemistry, morphologic and mechanistic data with external literature and related sources for real-time decision support. Future work will focus on extensive testing and expanding domain coverage.

P15 | Comparative general toxicity and thyroid effects of PFOA and its substitute GenX in sprague-dawley rats

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Introduction | Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS), the most well-known perfluoroalkyl substances (PFASs), have been restricted in production and use as persistent organic pollutants (POPs). Undecafluoro-2-methyl-3-oxahexanoic acid (GenX) has been introduced as a substitute for these PFASs; however, it also raises similar toxicological concerns. This study aimed to evaluate the oral toxicity and thyroid hormone alterations induced by GenX in comparison with PFOA and a short-chain PFAS, perfluoroheptanoic acid (PFHpA), in Sprague-Dawley rats.

Methods | GenX was orally administered once daily at dose levels of 0, 5, 20, 50, 150, and 500 mg/kg in male and female SD rats for 14 days; PFOA and PFHpA at 5 and 20 mg/kg. General toxicity was assessed by evaluating mortality, clinical symptoms, clinical pathology, organ weights, and macroscopic and microscopic findings. Thyroid function was assessed by measuring serum levels of T3, T4, and TSH using the Immulite 2000 Xpi immunoassay.

Results | GenX-related effects included decreased red blood cell parameters, increased reticulocyte counts, elevated ALT levels, increased liver weight, hepatocellular hypertrophy in the liver, and follicular cell hypertrophy in the thyroid. T3 and T4 levels were significantly decreased only in males, accompanied by a trend toward increased TSH. These changes were similar to those observed with PFOA.

Conclusion | These findings indicate that GenX exhibits a toxicological profile comparable to that of PFOA and further support the endocrine-disrupting potential of PFAS substitutes. The results highlight the need for rigorous toxicological evaluation before designating such alternatives as safer options and underscore the importance of continued research in this field.

P16 | Immunodetection of lipid droplets by targeting adipophilin (PLIN2) in tissues of rats, mice, dogs, minipigs and non-human primates

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Introduction | Drug-induced cytoplasmic vacuolation is commonly observed in preclinical toxicology and can arise from various mechanisms. Differentiating non-phosphorylated lipid accumulation from phospholipidosis is challenging using standard H&E staining. While histochemical stains (e.g., Oil Red O) and transmission electron microscopy can distinguish these conditions, they are limited by sensitivity, throughput, or accessibility. Immunohistochemistry (IHC) targeting adipophilin (PLIN2), a lipid droplet-specific protein, offers a sensitive and efficient alternative. This work aimed to develop and validate an IHC protocol for adipophilin detection in formalin-fixed paraffin-embedded (FFPE) tissues from rats, mice, dogs, minipigs, and non-human primates.

Methods | FFPE tissues from adrenal glands, skin, liver, and kidneys of control animals from an internal biobank were used. IHC was performed using the Ventana Ultra platform. Four protocols were validated, each using a species-specific primary antibody: one for rodents and one each for dogs, minipigs, and non-human primates.

Results | Adipophilin staining consistently highlighted lipid droplets, particularly in the adrenal cortex and sebaceous glands across all species. Variable expression was observed in kidneys and liver, with rodents showing prominent lipid droplets in hepatic stellate cells. Minimal background staining did not interfere with interpretation.

Conclusion | The present work successfully validated IHC for detecting lipid droplets in five species commonly used in nonclinical safety studies. The adrenal gland proved to be a reliable positive control. These findings support the use of adipophilin IHC as a practical and sensitive method for distinguishing lipid accumulation types in preclinical toxicological assessments.

P17 | Colour standardization in whole slide imaging: a method to reduce colour variability

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Introduction | Whilst the uptake of digital microscopy and whole slide imaging has brought numerous advantages to the field of pathology, it has also introduced the need for colour management for consistent diagnosis. This condition for reliable colour imaging is likely to be compounded by the development of Artificial Intelligence (AI) algorithms. Colour variability can be introduced by Whole Slide Imaging (WSI) scanners, due to different manufacturers, scanner models as well as variance within the same scanner model.

Methods | Using colour data from a variety of WSI scanners of a slide containing 55 colour patches and a proprietary algorithm to generate an ICC (International Color Consortium) profile, colour standardization can be achieved by adjusting the colour values to their true spectral values. The colour data from different scanner models were compared to ground-truth colour before and after standardization and to the sRGB (standard Red Green Blue) colour gamut commonly used by display manufacturers.

Results | Data demonstrated different WSI scanners typically apply different linear or tone curves to their scanned data, as well as introducing variability in the overall white and black points. The colour standardization method used reduced the difference between the colour values collected by the scanner and their true spectral values.

Conclusion | It is possible to reduce the impact of WSI scanner colour variability using ICC profiles to provide ground-truth colour standardization. As digital pathology attempts to validate AI, these differences in the colour on a display compared to what is presented to AI, are vital to be addressed, otherwise a human user and a machine learning algorithm will be validated on different data.

P18 | Advanced technology for the preparation of biological tissues and materials in plastic (resin) embedded sections for histopathological evaluation

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Introduction | Analysis of the interaction of invasive medical implants with the surrounding tissues, is crucial for the study of the implant. We present a novel Laser based technology for the dissection of plastic (resin) embedded tissue samples that results in histological specimens of supreme quality, far above that of classical ground sections (cutting and grinding), which permit an accurate histopathological evaluation of an invasive implant.

Methods | Fixed tissue in Formaldehyde (4%) will be embedded in MMA (Methyl methacrylate) or Spurr (resin – epoxy) plastic medium. Then a cross section will be performed using a diamond saw. The section surface will be glued on a subject glass. Optical Coherence Tomography is used for measurements and a laser dissection will be performed resulting an accurate cross section. De-platinization proces and stain of the slide will take place.

Results | Two case reports of different medical devices using the novel method will be presented:
Case report #1: Bone regeneration along the implanted orthopedic device; modified Masson Goldner Trichrome stain. Here a bone replacer, titanium device in a sheep tibia anchored with a metal plate evaluation for tissue integration will be presented. The quality of the slides will be presented by colored histological pictures in high resolution.
Case report #2. Evaluation of histopathological changes in a goat vein model following Implant + Filler stent implantation; HE stain. Here a vascular embolization device, intended to control bleeding from aneurysms, vascular tumors or arteriovenous malformations will be presented. Illustrated histopictures will be presented.

Conclusion | The new method offers a Fast and easy cutting of a broad range of implants and biomaterials. Optical Coherence Tomography is leading to an accurate, thin, cross-section. There are minimal sectioning artifacts due to contact free cutting process. We achieve top-quality sections, superior to classical ground sections in particular at high magnification.

P19 | Diagnosis of one case of melanoma in Beagle dog?

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Introduction | For many tumors, a definitive diagnosis by the pathologist without immunohistochemistry or other supportive Methods is not possible. Unfortunately, getting permission to use these supportive methods under GLP compliance is not systematic due to tight timelines, extra cost, and because most tumors are incidental (not test item-related) in short term studies.

Methods | Forty Beagle dogs, allocated into one control and three dose groups, were administered three times a day via oral gavage for 4 weeks an immunomodulator or vehicle. Tissues were collected, fixed in 10% neutral buffered formalin for H&E staining and microscopic evaluation.

Results | A macroscopic raised area (about 1.0×1.0×0.6 cm) in the skin/subcutis of the ear was noted at necropsy in one female from high dose group. The tumor occupied the dermis and subcutis, ulceration was noted in the surface area.
The tumor was characterized by round, oval or polyhedral cells invaded the surrounding tissues, mitotic figures were frequently observed, multifocal necrotic areas were noted. The differential diagnoses included lymphoma, basal cell carcinoma, squamous carcinoma, histiocytic sarcoma, or mast cell tumor.
A definitive diagnosis without immunohistochemistry was not possible but unfortunately it was not accepted by the sponsor. It was decided to call malignant (amelanotic) melanoma.

Conclusion | A variety of morphology can be observed in one kind of tumor or similar morphology can be observed in different tumors, so diagnoses of tumors can be challenging when special staining is not allowed.

P20 | Comparation of spontaneous blood vessel neoplasms in different strains of rats from subchronic, chronic and carcinogenicity studies.

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Introduction | This abstract presents and compares the incidence of spontaneous blood vessel tumors in three rat strains. Tumor incidences are important considerations when interpreting histopathologic data and useful when selecting a suitable animal model, especially for drugs with potential tumorigenic effect.

Methods | The incidences of hemangioma and hemangiosarcoma in control Wistar Han IGS (Crl:WI(Han)) (2974 males/3110 females), Hsd:Sprague Dawley® SD® (1379 males/1456 females) and Sprague Dawley (CD® IGS) (Crl:CD(SD)) (6202 males/6192 females) rats, were reviewed for 13, 26 and 104-week studies conducted at Labcorp (USA), between January 1, 2015 and December 31, 2024 (10 years). Neoplasms with incidence rate greater than 1% were considered common, lesser than 1% were considered rare.

Results | Blood vessel tumors occurred spontaneously in the three strains of rats. In Wistar Han, hemangioma and hemangiosarcoma were rare and noted only in the mesenteric lymph nodes of males in 13- and 26-week studies, but common in the mesenteric lymph node in 104-week studies, rare in other tissues. In SD (CD® IGS), blood vessel tumors were absent in 13-week studies and rare in 26- and 104-week studies. In Hsd:SD, no blood vessel tumors were noted in 13- and 26-week studies; hemangioma and hemangiosarcoma were rare in 104-week studies, except for mesenteric lymph node in males.

Conclusion | Blood vessel tumors did not occur or were rare in rats from 13-week or 26-week studies, were rare in Hsd:SD and SD(CD® IGS) rats from 104-week studies but were common in Wistar Han rats. The mesenteric lymph node was a common site for blood vessel tumors among all strains.

P21 | Scanner color drift corrected by color calibration: real-time quality assurance for artificial intelligence on whole slide images

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Introduction | A peer-reviewed study demonstrated standardizing whole slide image (WSI) color by calibration increases artificial intelligence (AI) robustness and reliability. Concerns exist that as scanners change color over time, AI performance potentially compromises safety and reliability.

Methods | We employed a color calibration technology that corrects WSI to ground truth color of real glass slides using International Color Consortium (ICC) profiles. To assess impacts of temporal color variation, 119 prostate cores with balanced cancer grade distribution were scanned alongside the color calibration slide on one scanner every 14 days for one year. Tissue color was measured for change. Scanner-induced temporal variance on pathologist concordance and AI performance was evaluated on a deep-learning prostate cancer model trained on 46,000 WSI.

Results | The color stability of the scanner degraded over short timepoints, discernable by humans and revealing events that caused sudden changes. Timepoint ICC profiles recovered to stable, accurate color resulting in better AI concordance with pathologist grading, and actual tissue did not change color. With only scanner color uncontrolled AI performance changed, which ICC color calibration rescued to intended consistency.

Conclusion | Frequent color calibration provides a universal solution to the variation introduced by scanners drifting, making AI-based tissue diagnostics in pre-clinical or clinical applications more reliable in the real world. Introducing more scanners, tissue types and algorithms such as those used in preclinical studies, will demonstrate exponential impacts on AI reliability. This study pioneers real-time quality assurance and GLP for stable and scalable performance of scanners and AI over time, to enhance pre-clinical efficacy and consistency.

P22 | Spontaneous multicentric lymphoma in a young New Zealand White rabbit

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Introduction | Lymphoma is described as an uncommon proliferative neoplastic finding that can affect the laboratory rabbit according to the International Harmonization of Nomenclature and Diagnostic Criteria: Nonproliferative and Proliferative Lesions of the Rabbit (INHAND). However, it is the most common neoplasm of juvenile pet rabbits. This case report details the clinical findings, macroscopic, microscopic and immunohistochemical features of a spontaneous case of lymphoma in a 9.5-month-old, female New Zealand White rabbit.

Methods | The HCD (Historical control data) for all rabbit studies at all Labcorp sites was investigated. A total of 32 studies (269 control rabbits) were found. No malignant tumours were present.

Results | On dosing day 23 of a regulatory 4-week (intramuscular) toxicity study, a rabbit from the low dose group (age of rabbits at study start was 27-37 weeks) presented with body weight loss and inappetence. A solid, painful mass was detected in the cranial abdomen; therefore, on welfare grounds, the animal was euthanized. At necropsy, macroscopic observations of bilaterally enlarged kidneys, with multiple, bilateral red/tan and soft renal masses were recorded.
At microscopic examination, medium to large sized neoplastic lymphoid cells were replacing normal tissue of kidneys, ovaries, adrenals and pituitary. Less significant neoplastic infiltrates were noted in the brain, liver, spleen, eye, intestines, uterus and cervix, and bone marrow.

Conclusion | The toxicologic pathologist should be aware that lymphoma is the most common spontaneous occurring neoplasm in young rabbits and can therefore occasionally be detected in toxicity studies, where its differentiation from treatment-related effects is essential.

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