

ESTP Newsletter 2020 (1)



Editor Emmanuelle Balme
(emmanuelle.balme@boehringer-ingelheim.com)

President's Column

Dear ESTP members,

It has been a very turbulent spring for all of us due to the Coronavirus pandemic, which has dramatically changed our everyday life. The lockdown, social distancing, home schooling, and home office with the thousands Zoom, Skype or Microsoft teams meetings of varying quality have been stressful for most of us. However, my thoughts go to those who have been ill with COVID-19, those who have lost family and friends, as well as those who work hard to keep our health system and essential social sectors running. I think we all have to work now to limit further spread of the SARS-CoV-2 virus. The need for continued collaboration globally across the borders for a healthier and safer world and a better climate has never been greater.

As communicated in April, we had to take the decision to postpone the CEP Meeting to 2021, so we will be looking forward to welcoming you in Torino, Italy next year. We are working hard to find a solution to hold the AGA virtually, enabling active participation of our members including voting, questions, and answers. Furthermore, we are also working on setting up some further educational online seminars.

Some highlights to look forward to: The 7th ESTP International Expert Workshop "Towards Regulatory Acceptance of Digital Toxicologic Pathology" organized by Vanessa Schumacher, Erio Barale, Xavier Palazzi and Pierluigi Fant, will publish their results in the Toxicology Pathology special issue on Digital Pathology, Tissue Image Analysis, Artificial Intelligence, and Machine Learning. I am also excited to announce that we have already started the work on the next 8th ESTP International Expert Workshop focusing on IT- and QA-related issues in digital pathology. The workshop will be organized by

Vanessa Schumacher, Julie Boisclair, Erio Barale and Thorsten Schlüter.

At the Global Toxicologic Pathology President Group Meeting in Japan in February, prior to the 36th JSTP annual meeting, Charlotte Keenan gave an update on the progress of The International Harmonization of Nomenclature and Diagnostic Criteria (INHAND) efforts. Each society gave an overview of their planned congresses most of which now have been postponed. As always, you can find the links on our homepage <https://www.eurotoxpath.org/calendar/index.php>. John Foster reported that the IATP will be offering two Maronpot guest lecturers grant awards per year to different societies. Erio Barale gave a short introduction to the IMI 18.2 Big Picture project. The goal of this European grant is to create a repository of three million clinical and non-clinical digital whole slide images. It will primarily be used for research purposes and to develop AI models in clinical diagnosis, preclinical development, and translational sciences, but training and education in veterinary schools could potentially also be a purpose of the project. The final EU approval for the project will hopefully be granted in June 2020.

This is my last president column and I would like to thank all of you for your support during the last two years, it has been an honor to serve as chairman for the ESTP. Finally, I would like to encourage everyone to volunteer and to support our Society.

Stay safe and healthy.
Best regards,

Anna-Lena Frisk
ESTP Chairman
Afrisk@its.inj.com

Information about ESTP Annual General Assembly

Dear ESTP Members,

Around the globe, we are currently facing a never seen and very challenging situation with the Corona pandemic. Under these circumstances, ESTP, ESVP and ECVF chairs and their Scientific and Local Organizing Committees, had to make the difficult decision to postpone our joint Cutting Edge Pathology congress.

Consequently, we will organize the ESTP Annual General Assembly as a virtual meeting, maintaining it at the originally planned date, Thursday 27th August, 14:00 – 16:00 CET. We currently evaluate various options and tools to organize this virtual event, so that it mimics as closely as possible a face-to-face meeting with true interaction while conforming with legal and constitutional requirements. It will be new and exciting exercise for us!

You will receive the official invitation and preparatory documents in due time, by email to the membership.

Best regards,

Gabriele Pohlmeier-Esch
ESTP Secretary
Gabriele.pohlmeier-esch@boehringer-ingenheim.com

Electronic voting for ESTP Executive Committee

Dear ESTP Members,

According to our constitution, this year we have the biannual elections for positions in the ESTP Executive Committee. The electronic voting procedure is now open for a 6-week period from 11th of May to 20th of June, 2020.

The positions to be filled in the Executive Committee, together with candidates, are as follows:

POSITION	CANDIDATE
ESTP Designated Chairman	Dr. Silvia Guionaud
ESTP Vice-Chairman	Dr. Lars Mecklenburg
ESTP Secretary	Dr. Gabriele Pohlmeier-Esch
ESTP Treasurer	Dr. Kuno Würsch
Councillor for International Collaboration	Dr. Erio Barale-Thomas
Councillor for Digital Pathology	Dr. Vanessa Schumacher

Councillor to represent University Teachers	Prof. Wolfgang Baumgärtner
Councillor for the Younger Generation	Dr. Emmanuelle Balme
Councillor for Electronic Communication	Dr. Rupert Kellner
Councillor for Classic Examples in Toxicologic Pathology	Dr. Thomas Nolte
Councillor for Nomenclature	Dr. Susanne Rittinghausen

According to our constitution, the present designated chairman, Dr. Franck Chanut, will automatically take over the chairman position from Dr. Anna-Lena Frisk. Access to the electronic voting procedure is through the following link in the members' only area of the ESTP website (username and password required): http://www.eurotoxpath.org/members/form_election2020.php

Candidate sheets providing information on those candidates who have not yet been part of the Executive Board/or have not yet been elected officially (Silvia Guionaud, Emmanuelle Balme) can be found under the same link.

On behalf of the Executive Committee I would like to encourage all of you to make use of your right to vote, in order to achieve representative participation in these elections. Please don't hesitate to use the facility on the website or contact me in case you need to obtain your login information.

Best regards,

Gabriele Pohlmeier-Esch
ESTP Secretary
Gabriele.pohlmeier-esch@boehringer-ingenheim.com



7th ESTP International Expert Workshop: “Towards regulatory acceptance of digital toxicologic pathology”

The ESTP organized an expert international workshop to discuss the future regulatory acceptance of the use of digital toxicologic pathology. Participants in the

workshop were veterinary and medical pathologists, scientists and regulators from Europe, the United States, and Japan who were involved in research (including Contract Research Organizations [CROs]) and regulatory affairs for industrial chemical, pharmaceutical, medical device and diagnostic companies. The goal of the expert workshop was to align on minimum requirements for primary or peer review evaluation of whole slide images. Focus areas included the validation of whole slide scanners; acceptable data and metadata formats; transfer of whole slide images; processing, evaluation, storage, viewing, annotating and archiving processes; comparison with current practices in diagnostic medical pathology; practical aspects of digital pathology (e.g., resolution, technical requirements, archiving costs); considerations for remote pathology; and pathologist acceptance. This effort is complementary to those ongoing in other societies, such as the Society of Toxicologic Pathology (STP) Digital Pathology and Image Analysis special interest group and the Scientific Regulatory and Policy (SRPC) working group on Digital Peer Review. A paper documenting the key discussions and outcomes of the workshop is in preparation to target the Toxicologic Pathology Special Issue on Digital Pathology.

Organizing Committee:

Vanessa Schumacher

Vanessa.schumacher@roche.com

Erio Barale-Thomas

Ebarale@its.inj.com

Pierluigi Fant

Pierluigi.fant@crl.com

Xavier Palazzi

Xavier.palazzi@pfizer.com



8th ESTP Workshop

The 8th ESTP Expert Workshop has officially kicked off in a fully virtual format, with the goal of bringing together experts from toxicologic pathology, quality assurance and IT to share and define the IT technical and security requirements as a prerequisite to digitization of pathology and provide guidelines that outline the basic principles for the validation of digital primary read and digital peer review.

Each subgroup (IT/QA/Path) is in the process of meeting to define specific requirements. Lists will be concatenated and presented in subsequent meetings with all attendees and topics will be voted for presentation and discussion at the final workshop, scheduled to take place in the fall.

Organizing Committee:

Julie Boisclair

Julie.boisclair@novartis.com

Erio Barale-Thomas

Ebarale@its.inj.com

Thorsten Schlueter

Thorsten.schlueter@bayer.com

Vanessa Schumacher

Vanessa.schumacher@roche.com

Pathology 2.0

The Pathology 2.0 Committee is kicking off again on May 28 at 2pm CET. If you have an interest to join the kickoff and take part in the committee, please reach out to Dirk and Vanessa.

The agenda of the first meeting will focus on introducing the members to each other, defining the scope of the committee and key focus areas for 2020. Areas we will discuss are member outreach, presence at ESTP meetings, and publication efforts. We will also define scope of technologies covered by the committee. We envision this could be a committee to discuss topics related to new developments in toxicologic pathology like spatial omics, microphysiological systems, multiplexing, and virtual control groups. If you are interested to shape the future of this committee, please join us!

Best regards,

Vanessa Schumacher

Vanessa.schumacher@roche.com

Dirk Schaudien

Dirk.schaudien@item.fraunhofer.de

XXVII Classic Examples in Toxicologic Pathology February 21-22, 2020 – Hannover, Germany

Friday morning the 21th February around half past eight, we started our car trip to attend the 27th edition of the Classic Examples in Toxicologic Pathology to be held (as usual) at the University of Veterinary Medicine at Hannover. Although we could follow the road with our eyes closed, being regular visitors of this excellent meeting, it was better to keep our eyes open to pick up the nearly hidden details, such as speed cameras and police cars.

To give the attendees the possibility to prepare themselves for the meeting, case-related digital slides were provided before the meeting.

After a short introduction by Thomas Nolte, Marielle Odin from Hoffmann-La Roche kicked off the scientific part of the afternoon meeting with a presentation on drug-induced small intestinal pathology in minipigs. The drug on test induced goblet cell hyperplasia, nicely demonstrated using the Alcian-Blue staining method. Following Marielle Odin, Ingrid Pardo from Pfizer presented liver findings induced in non-human primates by a novel adeno-associated virus serotype gene therapy vector. Next to obvious liver cell degeneration/necrosis also hyaline eosinophilic intracytoplasmic inclusions were noted. Several techniques were used to reveal the nature of these inclusions. Michael Winter from the Roche Innovation Centre then presented a case of hematotoxicity in dogs following oral treatment with a small molecule drug candidate. Only after a certain treatment period, severe (regenerative) neutropenia developed in a subgroup of treated dogs. Affected dogs showed apoptosis and phagocytosis of neutrophils by Kupffer's cells in the liver. Based on the present data, this case was believed to represent an example of drug-induced immune mediated neutropenia with no proven relevance to human. A completely different case was presented by Dirk Nehrbass from the AO Research Institute Davos Switzerland. Dirk showed us the unique characteristics of Nitinol, a nickel-titanium alloy used for orthopedic devices in a premature sheep model of leg length discrepancy. Nitinol is a super-elastic metal with shape memory and can as such be used to modulate skeletal deformities by pressure force, resulting in temporary growth reduction of the treated leg. Morphologically, the changes induced by the pressure force were growth plate thinning and discontinuation. As a side-effect, temporarily shape changes however were also noted after removal of the device. For toxicologic pathologists (often not for others), it is always nice to be confronted with unexpected findings in studies or models. Such an unexpected finding was the subject of the last speaker of the afternoon session, Silke Treumann from BASF. Silke presented the unexpected finding in the kidneys and livers of androstane receptor/ pregnane X receptor (CAR/PXR) double knock-out rats (CARKO/PXRKO) used in a 7-days dietary study with phenobarbital (PB). Unexpectedly, few CARKO/PXRKO rats exposed to PB had enlarged polycystic kidneys and showed biliary cysts in the liver, suggesting a relationship to the knocked-out genes. Nevertheless, based on information of the breeder that the affected CARKO/PXRKO animals were found to be siblings, it was assumed that the combination of kidney and liver cysts most likely was the result of a spontaneous mutation, also known to occur in human (autosomal recessive polycystic kidney disease, Caroli's disease). After the last speaker we enjoyed the informal talk with colleagues while enjoying a drink and some finger food.

Saturday morning Andreas Popp from AbbVie woke us up with a presentation on changes in the inner ear, a subject not very familiar to most of us. In a breeding colony of a transgenic mouse line, few mice exhibited an unexpected phenotype: a.o. circling and thrown off balance. When histopathologic investigation of the brain did not unravel possible underlying changes, the inner ear was examined. It was discovered that, compared to WT mice, the otoliths on top of the sensory hair cell within the vestibular system had an abnormal shape and size. The phenotype consisting of otoconial dysgenesis however was found not to be related to the introduction of the transgene. A nice example of nearly concealed details! The next presentation on Myeloid cell leukemia 1 (MCL1) inhibitors was given by Florian Colbatzky from Boehringer Ingelheim. MCL-1, a key regulator of mitochondrial homeostasis, is a prosurvival member of the Bcl-2 family and thus involved in the regulation of apoptosis. MCL-1 often is overexpressed in various types of cancer. A small molecule that was found to be a promising candidate to inhibit Mcl-1 was tested in an explorative intravenous toxicity study in beagle dogs. Apoptotic/necrotic change and related changes in hematology and clinical chemistry were observed in a wide range of organs (pancreas, liver, gastrointestinal tract, lymphoid organs and bone marrow, and testes) after short high dose exposure. Anja Knippel from Merck KGaA then presented the results of a 4-week dose range finding study and investigative study with a monovalent fibroblast growth factor receptor 1 (FGFR1) antagonist in rats. The compound induced multifocal ectopic mineralization in aorta, bone, spinal meninges, fundus mucosa of the stomach, kidney, lung, heart and eye by interfering with the mineral homeostasis most likely due to decreased signaling of FGF23 resulting in hyperphosphatemia. Johannes Zellmer from the department of Nuclear Medicine, Munich presented the results related to the kidney in a 16-week toxicity study with everolimus, a mTOR inhibitor in combination with radiolabeled ¹⁷⁷Lu-DOTATATE, a combination that is expected to increase the radiosensitivity in neuroendocrine tumors in man. The data did not indicate an increased renal toxicity profile using the combination compared to control. Finally, we could listen for the second time to Florian Colbatzky who summarized the adverse effects of three mutation-specific drugs, potentially interfering targets involved in specific upregulated signaling pathways in tumor cells observed in exploratory studies using male rats and mice.

Thanks to the organizers Wolfgang Baumgärtner, Ulrich Deschl, Florian Colbatzky and Thomas Nolte, the assisting students and supporting companies for the excellent organization. I look forward to the meeting of next year.

Eric van Esch
Eric.vanesch@insightpathology.com