ESTP Newsletter 2017 (2)

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President's column

Dear ESTP members,

Again, some months are passed and things are going on. As already written in the last President's Column, ESTP stepped out of the IFSTP. Nevertheless international collaboration is going on during the President's meeting and with high engagement of some colleagues.

In February, the 24th Classic Examples took place in the Department of Pathology at the University of Veterinary Medicine in Hannover. As always, the organizers put together a great program. The scientific exchange was great, especially on Friday evening during the reception, which was held for the first time. Also the SEND Workshop on Friday morning was very well received.

The Cutting Edge Pathology Meeting (ESTP/ECVP/SFPT Joint Meeting) in Lyon (August 30-Sept 02, 2017) moves closer and the registration is already open on the ESTP homepage. The SOC informs the ESTP Board about the progress on a regular basis.

The city for the next ESTP Meeting in 2018 will be Copenhagen in Denmark at 11th -14th September 2018. We are very happy that our colleagues from NovoNordisk offered their support and Ingrid Sjögren is the head of the Scientific Organizing Committee (SOC).

During our February Board Meeting, Christine Rühl-Fehlert was assigned as new ESTP Representative for the GESC Committee as the follower of Wolfgang Kaufmann, who retired. Many thanks to Christine for her willingness and good luck! Many thanks to Wolfgang for his tremendous work in the past years not only in the GESC committee but also for his work for our society especially as our President between 2004 and 2006 and the co-organizer for the Adversity Workshops and numerous other jobs he did!

The publication of the last ESTP Adversity Workshop, held in Barcelona, is also on its way and will be published within the next months. During the STP Meeting in Montreal a poster will be shown. The organizers are planning already the next workshop with the topic "Thyroid gland".

These are the most important issues happened during the last months and I hope I could inform you a little bit about the work the ESTP Board is doing.

I'm always happy to receive direct feedback from the membership and I'm glad to answer your questions! I wish you a nice spring time and a sunny summer and hope to see most of you in Lyon!

Best regards

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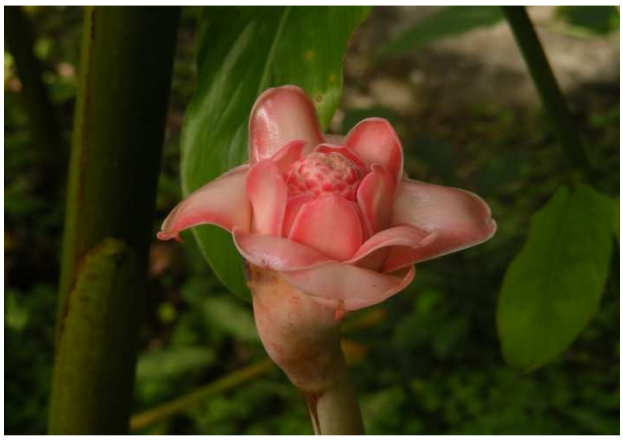

XXIV Classic Examples in Toxicologic Pathology
February 3rd & 4th 2017, Hannover

Similar to last year, the "Classical examples in Toxicologic Pathology" was preceded by a morning workshop **"Toxicopathology Data and SEND"** on the 3rd February, 2017. The attendance was great. When arriving around lunch time to the Institute of Veterinary Pathology in Hannover, the participants were trickling in and found their way to the coffee and sandwiches served at the first floor, or when arriving somewhat later they went directly to the Main Lecture Room where the microscopes were already waiting to be used for the slides accompanying the presentations. Upon entering the lecture room, many of the pathologists were greeting each other and trying to catch up before the start of the program. This illustrates the informal character of the meeting which is highly appreciated by all of us. This year there were 118 participants and ten speakers from the industry that were responsible for the very interesting program and lively discussions. As last year, digital slides were available for examination two weeks before the meeting accessing via the ESTP-website. For some presentations glass-slides and microscopes were available during the meeting in the lecture.

Before going into more detail on the different speakers and presentations, I would like to start by thanking the scientific organizers (Thomas Nolte, Florian Colbatzky, Wolfgang Baumgärtner, Ulrich Deschl) for their recurrent commitment every year. Year in, year out they manage to provide us with ten new inspiring subjects and speakers. We also would like to thank the students of the Hannover Veterinary Pathology Department for their great help in organizing this meeting and taking care of everything runs smoothly.

At 13.15h the program of the Classical Examples started with a short introduction and welcome by Thomas Nolte followed by Florian Colbatzky who also introduced the first speaker.

The first speaker, Kevin Keane from Novo Nordisk, presented a case of a glucagon-like peptide 1 agonist. In a carcinogenicity study, this GLP-1 agonist induced proliferative changes (focal hyperplasia) and tumors of C-cells (C-cell adenoma and C-cell carcinoma) in the thyroid glands of Sprague-Dawley rats and CD-1 mice. In non-humane primates that were exposed to high doses of GLP-1 agonists, thyroid gland findings were not examined. It is believed that the thyroid findings were caused by an activation of the GLP-1 receptor which is abundantly present on C-cells in in rats and mice, with subsequent persistent increased calcitonin levels and C-cell proliferation and tumor formation. As chronic exposure to GLP-1 agonists is not associated with changes in calcitonin levels in human and non-human primates, the relevance for human seems limited but are contraindicated for human with a family history of some thyroid gland tumors or syndromes.

Sameh Youssef from Janssen R&D continued with his key-note lecture and gave an excellent overview of the different animal models of neurodegenerative diseases. The presentation included disease-specific morphological features such as atrophy, various pigmentations, calcification, different inclusions or vacuoles. Also some specific staining methods were mentioned that could be useful for the diagnosis. Some more details were given for Alzheimer disease, Parkinson's disease and Amyotrophic lateral sclerosis.

After a short break, Hironobu Yasuno from Takeda Pharmaceutical Company presented a case of pyridoxine-induced sensory neuropathy in dogs. From human studies it is already known that mega doses (up to 6000 mg) of vitamin B6 for a year or more, can lead to sensory neuropathy. However, the mechanism is not completely clear yet, but the message in this presentation was that dog neuronal toxicity (dorsal/trigeminal/nodose ganglion, spinal tract, trigeminal nerve, spinal cord, peripheral and/or optic nerve) could already be found at doses of 150 and 300 mg/kg/day and after 7 days of treatment.

The next presentation was covered by Erio Barale-Thomas from Janssen R&D and he showed an interesting case of the neurotoxic NMDA antagonist dizocilpine (MK-801). The presentation illustrated how difficult and time-consuming it is to prepare an optimized histo-processing workflow using HE- and Fluoro-Jade B-stained slides, to better localize neuropathologic lesions such as is known from NMDA antagonists (e.g. neuronal vacuolation and necrosis in the posterior cingulate gyrus and retrosplenial cortex). The presentation was a successful attempt to match the reproducible procedure of Bolon (2013) with stereotactic documentation of Paxinos (2014) so it should be possible to make a comparison with other animal data.

After another short break, Silvia Guionaud and Jean-Martin LaPointe from AstraZeneca and MedImmune presented the histopathological aspects of immuno-enhancing drugs that are used as therapeutic drugs in the area of oncology. The toxicologic profile with a human recombinant fusion protein given to cynomolgus monkeys for 2-4 weeks were mainly related to activation of the immune system (increased T-cells in lymph nodes; and increased circulating inflammatory cells in the liver) and the formation of immune complexes (vascular changes and increased mesangial matrix in glomeruli kidney together with mononuclear infiltrates). Both were not considered relevant for human. The adverse events in human with these kinds of drugs are mainly related to the immune-modulatory mechanisms of these drugs.

For the first time this year a “Get together” was organized in the Hall. Drinks were served together with a large variety of very tasty snacks and dishes. This was an excellent opportunity for everyone to talk to each other and exchange both professional and personal information. This “Get together” was very much appreciated by everyone and hopefully it will continue in the following years.

At 8.15 h on Saturday morning (4th of February) the meeting continued with a presentation of Stephanie Czasch and Angele Breithaupt from Merck KGaA on CDK8/CD19 inhibitors. These compounds are used in the area of cancers such as colorectal cancer, gastric adenocarcinoma, melanoma and breast cancer. Histopathology results of a 14-day rat study showed early deaths and a large variety of histopathology changes in many organs (bone, bone marrow, lungs, liver, pancreas, lymph nodes, thymus, spleen, mammary gland, female and male reproductive tract, brain, heart, GI-tract, adrenal glands). Some of the changes were attributed to the mode of action, but for other changes the mode of action was unclear. The presentation was followed by Florian Colbatzky from Boehringer with a short overview of the changes in gene-expression after a mechanistic study with CDK8/CD19 using toxicogenomics.

Alfonso da Costa from Boehringer continued the meeting with a presentation on Cathepsin C inhibitors. This drug is used for treatment of COPD and is believed to inactivate neutrophil-derived serine proteases and by a better balance between protease/ant-protease activity, reduce lung tissue destruction. Side-effects in rats and minipigs were seen in many organs and were considered to be related to lysosomal storage and/or phospholipidosis. For some of the organs this was confirmed by electron microscopic evaluation.

After the coffee break, Aswin Menke from Triskelion presented the Zebrafish as another useful animal model to study toxicity. Firstly the normal histology, background histopathology and main differences with other species was shown which is a prerequisite to recognize drug-related changes. This was followed by examples of drug-induced toxicity in kidney and liver of the adult zebrafish. In addition, it was discussed how embryonal/larval fish could be used in toxicity studies, what genetically modified models of zebrafish are available and what the relevance could be for the predictability of toxicity in human.

Klaus Weber from AnaPath continued with a presentation on transcriptase inhibitors. At histopathology, main adverse side effects in rats were observed in kidneys in the proximal tubules and this was related with increased KIM-1, cystatin C and albumin levels. The changes in other organs were not considered to be adverse. The mechanism of this toxicity is believed to be related to oxidative damage of the mitochondria in the proximal tubules by uptake of the drug by the brush border.

After the last break of the morning session, Annabelle Heier from Novartis closed the meeting with her presentation on crystal nephropathy. In this presentation two clear examples were given of compounds (detailed information on the drugs could not be provided) that induced the formation of crystal deposits within the kidneys of rats with additional degenerating, regenerating and inflammatory changes. It was demonstrated that by using MALDI-MS imaging, the nature and composition of the crystals could be identified which may be very helpful to predict at what concentrations and safety margins crystal-forming drugs could be tolerated in human.

The meeting was closed by some last words of the organizers and by an invitation to join the next “Classical Examples” which will be held the 23th and 24th of February 2018.

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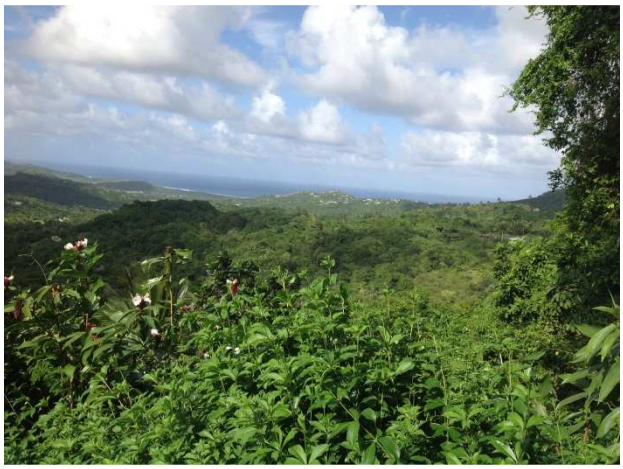


ESTP International Expert Workshops
- Update -

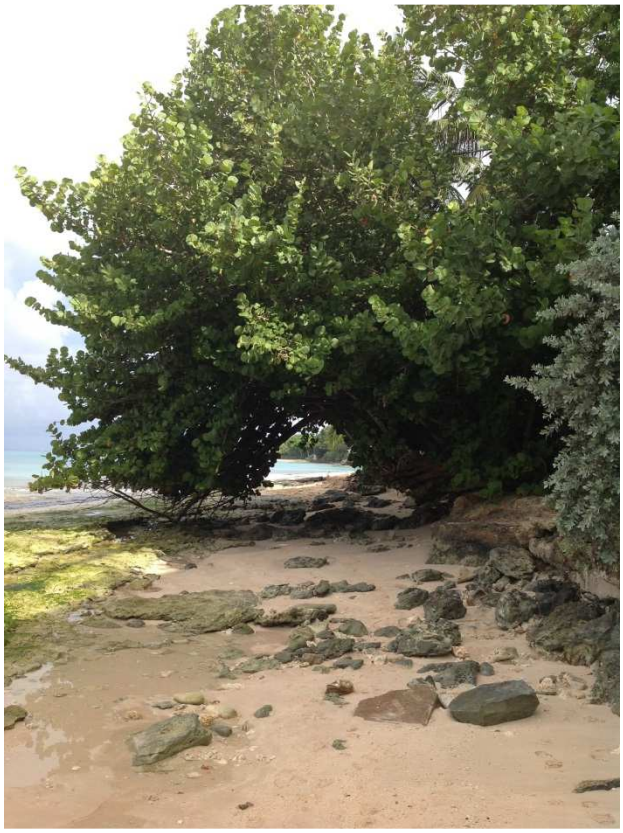
Dear ESTP Members,

As a first tangible result of our recent workshop, a poster abstract has been submitted for the upcoming STP meeting, entitled:
"Adversity of Lysosomal Accumulation" in Toxicity Studies, The Pathologists' Point of View – Results from the 5th ESTP International Expert Workshop in Barcelona, Sept. 23 – 24, 2016
A publication in *Toxicologic Pathology*, for which we will seek endorsement by all major societies in the field, will follow shortly.

For the next workshop (the 6th workshop), the ESTP Executive Committee has validated the following topic:
"Adversity of thyroid follicular epithelial hypertrophy/hyperplasia, differentiation between direct and indirect mechanisms and their implication for risk assessment"
The ambitious goals of this workshop will be:

- to summarize common mechanisms of thyroid follicular epithelial hypertrophy/hyperplasia and present example cases for direct and indirect modes of action;
- to discuss adversity considerations for thyroid follicular epithelial hypertrophy/hyperplasia, species differences/human relevance, and implications for classification as endocrine disrupting compound;
- to propose information requirements to support review and interpretation of thyroid follicular epithelial hypertrophy/hyperplasia with examples of information/testing strategies.

Practical planning for this workshop is well underway. Monthly teleconferences should start in June, and the face-to-face expert discussion will be held in Berlin, 16-17 May, 2018. We are very grateful to Bayer AG who kindly offered to host the meeting at their Berlin site



Important! New expert participants, who can contribute interesting case examples/approaches to this new workshop, are very welcome. We would therefore like to invite interested ESTP members to send us an email with a short statement about their motivation to participate in this endeavor.

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