ESTP Newsletter 2016 (2)

Editor Zuhal Dincer (zuhal.dincer@novartis.com)

President's column

Dear ESTP members,

Welcome everyone to our Spring Newsletter. After a very successful Classic Examples Meeting in February, we can now look forward to the STP conference in June at which some members of your ESTP Committee will be present. Another important message for you at this time of the year concerns the upcoming elections for the Executive Committee. We would like to inform you that, according to our constitution, elections for the ESTP Executive Committee will be conducted soon (between May and July) by means of an electronic voting procedure. We would like to call for candidates for the following positions (EC members volunteering to continue in their position are given in brackets):

- ESTP Designated Chairman
- ESTP Vice-Chairman (Lars Mecklenburg)
- ESTP Treasurer
- ESTP Secretary (Gabriele Pohlmeyer-Esch)
- Councillor for IFSTP (Johannes Harleman)
- Councillor for the Younger Generation (Annabelle Heier)
- Councillor for the University Teachers (Wolfgang Baumgärtner)
- Councillor for Electronic Communication (Rupert Kellner)
- Councillor for Classic Examples (Thomas Nolte)
- Councillor for Digital Pathology (Thierry Flandre)

The opening of the voting period will be announced with a message to the membership. At our next Annual General Assembly in Barcelona, we will endorse the results of the elections.

Regarding the commitment required to be a committee member, the ESTP Executive Committee has a monthly 1.5 hour teleconference and we aim to have to have two face to face meetings per year, after the Classic Examples Meeting in February and of course at our Annual General Meeting. The commitment required certainly peaks coming up to the AGM where all committee members and Councillors provide their reports for the society. However, the main attribute is dedication to the society and its constitution and it is a great privilege to work with so many dedicated people willing to devote some spare time to the organization.

If you are willing to commit to an active contribution to the ESTP in any of these roles, or wish to receive further information on work involved, please contact the ESTP Secretary (gpe@kaleidis-consultancy.com) and Chairman (jenny-mckay@idexx.com) until 30th April 2016 latest. We look forward to receiving your applications!

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XXIIIrd CLASSICAL EXAMPLES IN TOXICOLOGIC PATHOLOGY: 19th & 20th February 2016, Hannover

After a morning workshop entitled "Toxicopathology data and SEND", the XXIIIrd Edition of the Classical Examples seminar took place at the Institute of Veterinary Pathology in Hannover.

This year's program included 10 presentations highlighting class effects of compounds in various test species and organs, and for the first time, a keynote lecture on "Therapeutic concepts in oncology". For the second year, over 100 participants could access digital slides 2 weeks before and 4 weeks after the seminar, and this innovation was again approved at a large majority.

Matthias Rinke quite humorously awarded the two fastest registered participants of this year among the large audience.

Jürgen Funk from Roche started the Friday afternoon session by presenting striking antibody-induced renal lesions in monkeys: endocapillary glomerulonephritis was demonstrated by immunohistochemistry and transmission electron microscopy to result from the formation and deposition of immune complexes after administration of a humanized monoclonal IgG antibody. Next, as useful introduction to the discussion on mechanistic steps of carcinogenesis, morphological key features of hepatic foci of cellular alteration were reviewed by Ulrich Deschl from Boehringer Ingelheim. Then, Christine Rühl-Fehlert from Bayer and Harald Enzmann from the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) continued on by presenting the relationship between occurrence of hepatic foci of cellular alteration, degeneration or hypertrophy of hepatocytes and hepatocellular tumors, based on the NTP database. In addition, results of an initiation/promotion assay were presented to highlight the two main steps of carcinogenesis. Following a short break, Eric Borges from Boehringer Ingelheim gave an enthusiastic keynote lecture on "Therapeutic concepts in oncology: past, presence and future". This centered on chemotherapy, targeted therapy and immunotherapy. Cancer therapies for the future as cell based therapies and therapies using nanotechnology were also discussed. Another excellent presentation was proposed by Franck Chanut from Sanofi, who stressed the expected therapeutic benefit of fibroblast growth factor receptor 4 (FGFR4) antagonism in the treatment of hepatic cancer carcinoma and detailed the toxicologic profile of a FGFR4 antagonist in a short term study performed in monkeys. Finally, Florian Colbatzky from Boehringer Ingelheim capped off the first day with a presentation on Syk inhibitors. Syk is regarded as an interesting pharmaceutical target in a variety of indications, including neoplastic, inflammatory, allergic and autoimmune diseases, due to its manifold physiological functions.

Starting on the second day, Afonso Da Costa from Boehringer Ingelheim nicely reported the skin lesions observed in Beagle dogs treated with a GLP-1R/GCGR dual agonist which displayed typical features of the Superficial Necrolytic Dermatitis. The second lecturer, Klaus Weber from AnaPath, discussed the key histopathological lesions observed in acute and chronic dextran-sulfate-sodium (DSS)-induced colitis in mice, compared with the bacteria-induced colitis model and discussed the relevance of both models for reflecting the human ulcerative colitis. From Bayer Pharma, Sabrina Heinz and Bettina Lawrenz gave an extensive overview on Complex I Inhibitors which, by acting on the mitochondrial electron transport chain, induce ATP depletion and broad metabolic changes in several target tissues.

The audience could listen for a second time to Klaus Weber who discussed chemically-induced sperm granulomas in epididymides. The use of laser scanning microscopy on sperm smears revealed a subtle change which was the absence of the cytoplasmic droplet in a large part of the sperm cells. It was deemed that stasis and subsequent granuloma formation was a direct consequence of the droplet absence.

To close the 2016 Edition of the Classical Examples, a multidisciplinary team from Janssen, consisting of Marjolein van Heerden (Preclinical Development and Safety) and Nicolas Darville (Clinical pharmacology and Pharmacometrics) presented the time course modeling of the tissue responses to intramuscular long-acting drug suspension by means of an elegant pharmacokinetic study in the rat, supported by qualitative histopathology. Long-acting injectable (LAI) drug nano-/ microsuspensions constitute a relatively new class of formulations that enable prolonged and stable therapeutic drug exposure from 2 weeks to several months.

The success story of the Classical Examples at the great benefit of the European scientific community is made possible by the continuous commitment of the scientific organizers (Wolfgang Baumgärtner, Ulrich Deschl, Florian Colbatzky and Thomas Nolte), the thoughtful students from the Hannover Veterinary Pathology Department, and finally the large audience of scientists triggering lively and interesting discussions. Please, keep on being part of this success story and already note in your calendar the dates of the next Classical Examples Meeting, which will be slightly anticipated in 2017, on 3rd and 4th of February.

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TOXICOPATHOLOGY DATA & SEND WORKSHOP

I attended this workshop held at the Department of Pathology at the University of Veterinary Medicine in Hannover, Germany just before the XXIIIrd Classic Examples in Toxicologic Pathology the 19th of February. As ever in Hannover, the local organization was very good. This aim of the workshop was to address pathology related issues when submitting data packages using the SEND format. I thought it was a great idea to have such a meeting now, considering that we will all have to use SEND very soon. Being able to exchange with people from various companies was also very promising.

SEND is the Standard for Exchange of Nonclinical Data based upon the Clinical Data Interchange Standards Consortium (CDISC) Study Tabulation Model. The aim is to create a consistent format of standard nonclinical

tabulation datasets for interchange between organizations and, importantly, for submission to the US Food and Drug Administration (FDA). Raw data of toxicology animal studies started at the end of 2016 to support submission of new drugs to the US Food and Drug Administration will have to be submitted to the agency using SEND. Earlier studies submission using the SEND format is encouraged. The current production version (3.0) supports single-dose general toxicology, repeat-dose general toxicology, and carcinogenicity studies.

The meeting started with an introduction on SEND (by Gitte Frausing), explaining what it is, the regulatory recommendations and the upcoming changes in the new version. We all had a lot of questions on how the system works, how it will convert the pathology findings, if we would lose some of the modifiers or locators. To be completely reassured more time spent on a "real life" demo of the system would have been great and very useful. Unfortunately, because we discussed so much on this part, we did not have enough time to really talk about the implementation issues that we can face, pathologists from various companies only briefly presented what they were doing.

So, this was definitely a workshop worth attending to, but I feel that another one allowing more time for discussions and feedback from experience on the implementation will be very well received. I don't know if they will repeat the workshop but I have the feeling that, after the discussions we had (unfinished really) a new one will be more than welcome.

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5th ESTP INTERNATIONAL EXPERT WORKSHOP: 23-24th September 2016 "Adversity of Lysosomal Accumulation"

Dear ESTP members,
Our 4th ESTP International Expert Workshop on the general definition and use of "adversity" has been successfully closed with the acceptance of our paper for publication in *Toxicologic Pathology*.

In the meantime, the next workshop, on "adversity of lysosomal accumulation" has entered its preparatory phase, and three teleconferences were already held. The group comprises 22 members, approximately half of which have participated in the last workshop, therefore ensuring continuity and efficiency of this new endeavour. We feel proud that all four participants from international regulatory agencies have stayed on board and that we could win an additional expert toxicologist from FDA to take part. In addition, the participation of a chemist and an investigational toxicologist will help us to shed light on biochemical and mechanistic questions.

The goal of this new workshop is to provide criteria for pathologists to assess adversity of histopathologic findings associated with lysosomal accumulation.
To achieve this, the group decided it will be necessary to 1) understand the mode of action and functional consequences of lysosomal accumulation, 2) to categorize (if possible) test item types according to their properties to induce lysosomal accumulation and 3) to describe analytical methods appropriate to assess adversity of lysosomal accumulation. Exemplarily, we expect to be able to discuss case examples of compounds causing phospholipidosis, iron accumulation and alpha2u-globulin accumulation as well as of oligonucleotides, pegylated drugs and various other chemical entities. A certain number of contributions will already be made during preparatory TC's.

The **face-to-face workshop** with a summary of TC contributions, the remainder of contributions and expert discussion will take place immediately after this year's ESTP congress, at the congress venue in Barcelona (Avenida Palace Hotel, **Friday 23rd September pm and Saturday 24th September am/pm**). The room facilities allow accepting an additional audience of up to 50 interested pathologists/toxicologists for this event.
Online registration is possible via the ESTP website and will close on August 15, 2016:
http://www.eurotoxpath.org/meetings/index.php?id=workshop5

Due to the limited places available, registrations will be accepted on a first-come-first-serve basis. Please feel invited to contact us any time in case you have suggestions or wish to receive further information.

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PATHOLOGY 2.0 GROUP: PAST, PRESENT & FUTURE

Pathology 2.0, the ESTP committee dedicated to novel techniques and tools used in pathology, has been created two and a half years ago, with the aim to bring useful information to the ESTP community. For the first 2 years, it was kicked off and successfully led by Franck Chanut until ESTP 2015 in Guildford. It is now pursued by Thomas Lemarchand, who is continuing the effort for the next 2 years. After a period where we tried to understand the need, it was decided to focus first on

immunohistochemistry, in-situ hybridization and image analysis.

The committee organized a session at the last ESTP meeting in Guildford with presentations by Jennifer Cann (*Fundamentals of Histopathologic Image Analysis*) and Jurgen Funk (*Automated ISH, ISH/IHC double stain and ISH image analysis*). Another activity of the committee, led by Silvia Guionaud, was the creation and organization of a series of webinars on the same main topic, image analysis. The committee is continuing to contribute to the scientific content of the upcoming ESTP meeting in Barcelona, and has selected speakers who will emphasize the role of special techniques and approaches in better defining adversity and impact in drug/compound development. Many members of the group actively contributed. Likewise, there is an ongoing effort to organize 3 more webinars in 2016, and 3 are currently scheduled: one on statistics, the next one on stereology and the last one on imaging. Please watch our website and most importantly the messages in your mailbox sent by Gabi Pohlmeyer-Esch.

The group would like to continue, accelerate and further drive the evolution of the "21st century pathologists", to be more involved in what remains the best added value of pathologists: mechanisms of disease development, mechanisms of compound-related lesion development, target distribution/characterization, target validation, prediction of models and disease model development, activities. These tasks should be more and more undertaken by Vet and Human Tox Pathologists altogether in the future, using the adequate modern toolboxes, it be fluid biomarker measurements, imaging, in situ molecular techniques, including novel approaches like MALDI MS, *in silico* tools, molecular biology and other "omics" approaches etc. etc.

To that end, the Group will continue to entertain the European and now Global Toxicologic Pathologists with emerging or well established tools, webinars and presentations as well as be an opinion leader in the arena of the added value of toxicologic pathologists, following the seminal paper of Ettlin RA in 2013 (Etllin, Robert A 2013. Toxicologic Pathology of the 21st Century. *Tox Path*, 41: 689-708). We welcome members with ideas and energy to accelerate and complement the actions of the group! More Discovery and Investigative Pathologists wanted!

Looking forward,

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SURVEY ON WORKING ENVIRONMENT

In September 2015 the ESTP together with the French Society of Toxicologic Pathologists contracted P.N. Lee Statistics and Computing Ltd. to run a survey of their members related to diverse aspects of the working environment. The survey started in November 2015 with an initial mailshot to 308 members of the ESTP. 6 members were retired and therefore did not fill in the survey. A further 16 members had email addresses that did not manage to reach the members of interest. There were further requests to fill in the questionnaire on the beginning of January and the beginning of February, with the final date for the survey given as 19th February 2016. In all there have been 189 completed surveys and 39 incomplete surveys out of a possible 329 who received invitations and were not retired – thus we have 57% completed responses with a further 12% partial responses. This is a great success rate. Thank you very much to everyone who responded!

Questions had been divided into the following segments:

A. Personal information
B. Position and work content
C. Remuneration and gratuity
D. Continuing education
E. People management
F. Survey experience

We are currently in the process of analysing the responses and writing up a summary that will be published soon. Below is a first extract from the responses we got:
There was a slight majority of males (53%). Most pathologists (61%) were in the age range 45 to 64 years, with 6% older and 33% younger. Of 200 respondents, 58 (29%) had qualified earlier than 1985, 98 (49%) from 1985 to 2000, and 44 (22%) later than 2000.

The great majority of the pathologists were veterinarians (86%). About 63% of respondents are holding a national certificate in pathology, 35% are Diplomates of ECVP and 16% of ACVP. 16 respondents were Fellows of IATP. 42 members are holding a certificate in toxicology (ERT, Diplomate ABT or national certificate). Twenty-six respondents were not holding any specialization, and 12 respondents were holding certificates in areas outside of pathology and toxicology (e.g. laboratory animal science).

Most respondents worked in Germany (23%) and France (21%), followed by Switzerland (15%) and United Kingdom (11%).

We also asked about the experience made with filling in the survey. 88% of respondents felt that the survey had taken less time and effort than they had expected. Only 5% felt that it was too long.

The full survey will be published soon and further information will be provided in an upcoming newsletter.

Figure 1: Age ranges of respondents

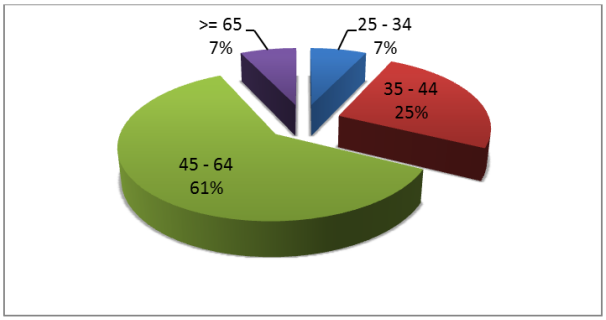


Figure 2: Primary education

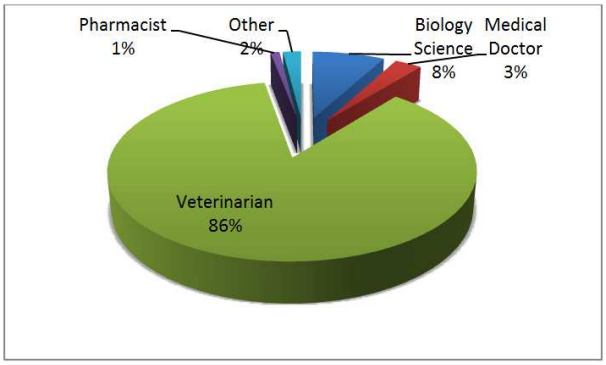
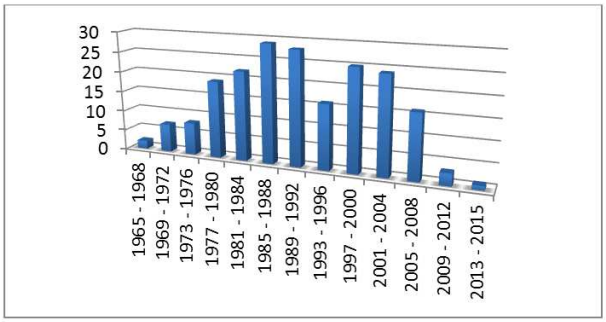


Figure 3: Year of graduation



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