

ESTP Newsletter 2012 (2)



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President's column



Dear ESTP members,

My first duty as your new chairman is to thank our past chairman. Annette Romeike did a great job as our representative and I am sure she will stay involved further. I hope you enjoyed, as I did, our last annual meeting in Stresa with the warm welcome of our Italian colleagues on the bank of the Lake Maggiore. The scientific program was great and the session on topics of special interest for us was stimulating. If you were not in Stresa, the member section of our website informs you about the presentations and our discussions. The minutes of our Annual General Assembly are also available. Thanks Rupert!

1. From Stresa back to the bench!

The time to remember our lovely and fruitful event in Italy was short. On September 19th, Food and Chemical

Toxicology published an article by Seralini *et al.* The article reported erroneous interpretations of a 2-year feeding study in rats investigating the health effects of genetically modified maize NK603 with and without Roundup WeatherMAX® and Roundup® GT Plus alone. The main author, clearly identified as an anti-GMO activist, is a French Professor of molecular biology from the University in Caen. He openly claims his political wishes: a ban of GM crops and pesticides. In France, the debate is quite hot at the moment, as the study was sponsored by a French non-governmental organization chaired by a member of the European Parliament from the EELV (Europe Ecologie/ Les Verts) Party.

Therefore, the past president of SFPT – a little ashamed for his country – and the first French elected ESTP chairman – very proud to serve – had to wear quickly the equipment of a fire chief to calm down the outcry. On behalf of the ESTP executive committee, a letter summarizing our comments and written and signed by 10 ESTP volunteers – thanks to all of them for their involvement – was sent to the editor of F&CT on October 15th. We clearly highlighted the major shortcomings on pathology in this study and point out the responsibility of the editor and his review committee to have accepted such a paper. Our letter will be published in the same issue as the original paper, if ever published! We can be proud about our reactivity. It was necessary to stand up and defend our field of expertise: toxicologic pathology!

Earlier, upon request by the European Commission, the European Food and Safety Authority (EFSA) reviewed the study and concluded that the design, reporting and analysis of the study were inadequate. Therefore this contribution is of insufficient scientific quality to be relevant in the safety assessment process. Later on, for the first time in France, the six Academia of Sciences (amongst them the Veterinary and Medicine ones) gathered a common statement and qualified in a press release on October 19th Seralini's paper as a scientific "non-event". On October 22nd, the French High Commission on Biotechnology (HCB) and the French

Food Safety Agency (Anses) confirmed the EFSA's preliminary statement. Nevertheless, both organizations called for a public debate on the current practice of toxicology and risk assessment of GM crops.

Have we ever read, in all these comments, about the wrong assertions on pathology findings? Never! For us, as toxicologic pathologists, our opinion is crystal clear: this work was not correctly supervised, interpreted and displayed with a lot of misinterpretations of tumors, with a misuse of diagnostic terminology, with non-informative pictures and erroneous narrative! I thank my friends from the SFPT who reacted in a similar way.

2. Hard times for pathologists and toxicologic pathology

The environment is clearly challenging for us. The difficulties depend first on the general European socio-economic context. Like the whole population, we have to face a major economic crisis with a delocalization of the European industry towards the BRIC countries. We felt it clearly in Stresa. Our sponsors were less numerous. Colleagues had difficulties to join. Some of us have lost recently their jobs in industry and have to find a new position. In Stresa Lars Mecklenburg led a round table discussion on the future of toxicologic pathology in Europe: How do Toxicologic Pathologists respond to R&D downsizing in the European Pharmaceutical Industry? We have to adapt ourselves to this new environment. Thanks Lars for your initiative done in a timely manner!

Simultaneously, severe criticisms hit not only industry (mainly pharmaceuticals, agrochemicals, chemicals) but also the regulatory agencies, in a time where consumers strive for more health and safety standards. The credibility of these organizations has to be restored by better information and transparency of their contributions.

In addition, some activists and even scientists – insincere and incompetent but gifted in communicating – develop their attacks against the usefulness of research with laboratory animals. They try to oppose different approaches (*in silico*, *in vitro*, -omics, *in vivo*). They don't understand that they are all essential and complementary, but we do.

And last but not least, the role of our discipline - toxicologic pathology - remains underestimated and sometimes ambiguous. We elaborate most of the critical data in the evaluation of new compounds. We are seen as experts of morphological pathology. But our input cannot be limited to generate only pathology data! Generally we have to be more associated in the risk assessment process. We have difficulties to be stakeholders or leaders in the development of new techniques like molecular tools.

3. The role of the ESTP in shaping the future of toxicologic pathology

I am convinced – and you with me – that we are still key players in toxicology and risk assessment. We benefit

from our background in medical training and from our knowledge and experience of comparative pathology. The recent events and regulations – REACH, GM plants and criteria for the definition of endocrine disruptors as examples – show that the society demands higher safety standards for compounds / chemicals / technologies. Scientifically we are at the heart of this evaluation.

On the technical side we have to look for positions beyond morphological pathology. We have to interact with colleagues who develop modern molecular / digital technologies like computational toxicology and molecular pathology. We have to resume our relationships with clinical pathologists and biologists working on biomarkers.

On the professional side we have to look for positions outside our comfort zone, in risk assessment and in regulatory toxicology. We have to commit ourselves in regulatory agencies to explain better the input of toxicology pathologists. The ESTP executive committee and I want to develop those complementary skills and networks.

Hopefully for most of us, as bench pathologists, we are still involved in standard toxicologic pathology. ESTP is willing to serve in this direction as our society did it in the past. We will continue to co-operate intensively with other international societies in the INHAND initiative (International Harmonization of Nomenclature and Diagnostic Criteria for Lesions in Rats and Mice). I am very keen to follow the development of the recent collaboration with the FDA on SEND (Standard for the Exchange of Nonclinical Data). I am sure that it will have consequences and applications in our daily work. Colleagues willing to cooperate in the development of intelligent data systems for computational toxicology should find synergies with this project.

Training in toxicologic pathology remains our main duty and we will continue to organize symposia. Our yearly meetings are the occasion to get access to excellent continuing education programs, to learn and exchange. I encourage you to participate to the 20th Classic Examples of Toxicologic Pathology Course which will take place in February 22 and 23, 2013 in Hannover. Yes, it will be already the 20th anniversary of this event! Thanks to the organizers, and in particular Prof Karbe, for his continuous effort.

Further conclusive thanks

I would like to thank you again for your trust. I will try and be pleased to do my best! We have to continue the success story of our organization and to expand it with new initiatives in order to make ESTP more visible. Despite the difficulties we are and remain key players in toxicology.

I want to thank all the colleagues working in the INHAND initiative for their hard and dedicated work. A special thank for Susanne Rittinghausen and all our colleagues at the Fraunhofer Institute who support our activities. Thanks Rupert for maintaining our website which is now our main tool for increasing our visibility! I

am grateful to the chairs and members of all our committees (Award Committee, Guideline Committee, Membership Committee, Guess What Committee, and Newsletter Committee) for their continuous and important work. Is there a need for new ones? I may suggest two new one: communication with the scientific journalists and relationship with authorities?

I would like to congratulate again our Italian colleagues for the successful meeting in Stresa. Already I want to encourage our colleagues working in the scientific committee and the local organizing committee of our upcoming 11th ESTP congress in Ghent, Belgium, on September 7-11, 2013. I will end with a special thought to my colleagues of the Executive Committee and especially Francesco for his efficient support as our secretary.

I ENCOURAGE ALL OF YOU, FRIENDS & COLLEAGUES OF ESTP TO PARTICIPATE IN THE DEBATE. WE WELCOME YOUR IDEAS AND YOUR PROPOSALS. WE NEED YOUR HELP AND YOUR INVOLVMENT.

Thanks for reading.

Frédéric SCHORSCH
Your Chairman

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31st Annual Symposium of Society of Toxicologic Pathologists (STP), 24-28th June 2012, Boston-USA: Mechanisms of Toxicity

31st Annual Symposium of STP was focusing on “Mechanisms of Toxicity” this year. The topic was examined in six general sessions covering tissue injury related to the following: 1) host factors, 2) chemical structure, 3) xenobiotic cellular targets (on- and off-target), 4) new technologies (e.g., nanotechnology, siRNA therapy and immunoconjugates), 5) cellular organelle specific effects, and 6) high-profile environmental chemicals and consumer products.

As always, the first day of the symposium started with NTP Satellite Pathology Potpourri which I enjoyed the most: great cases, educational, lively and very productive conversations between colleagues and friends!

On Sunday, we had ‘Continuing Education Courses’. I joined the ‘Mechanism-based approaches to cardiovascular safety assessment’. Speakers (M. Boyle, T. Force, H. Thomas, I. Pruijboom-Brees, M. Quaile, and E. Schultze) did a fantastic job on exploring the current understanding of toxicity in the cardiovascular system and put that understanding in the context of how

we do our non-clinical assessments, and offering biomarker recommendations.

Monday’s topics were ‘Host factors and the expression of toxicologic effects’ and ‘Morphologic and molecular underpinnings of organelle toxicity’. The discussion topic of the Town Hall Meeting was ‘New paradigm needed for carcinogenicity risk assessment’. Dr Carl Alden, Dr Todd Bourcier, and Dr Dan Morten reviewed the new ‘NEG CARC Rat’ proposal briefly and asked the audience to make recommendations for a new strategy.

Tuesday topic was my favourite: Target-related and off-target based toxicologic effects. The speakers were Dr R. Thomas (application of genomic dose-response analysis to chemical risk assessment), Dr J. Sagartz (the species-specific mechanism-based challenge), Dr S. Levin (unexpected prostate effect in dogs with the aldosterone receptor blocker, Eplerenone), Dr N. Everds (unexpected effects of large molecules on peripheral blood cells), and Dr T. Rosol (on-target GLP-1 agonist effects on thyroid C-cell proliferation). The speakers gave specific examples of target and off-target based effects and strategies for differentiating these possibilities in human risk assessment (adverse? monitorable? reversible?) by using chemical, bioformatic, ADME, formulation and drug delivery tools, and animal models.

The afternoon was ‘enjoy the rest of the day’ session. It was a fantastic afternoon spent with Novartis colleagues and ended-up in a fish restaurant by the harbour.

Wednesday morning started with ‘Chemical-based tissue reactivity’ session chaired by Dr J. Klaunig and Dr R. Peterson. In the afternoon, we continued with the ‘mechanisms of toxicity: high-profile environmental chemicals and consumer products’ session. The speakers addressed important toxicants (products with extensive human exposure as well as heightened recognition and concern include medicinals, construction materials, manufacturing/plastics, food/water, storage containers, food adulterants and contaminants, and persisting environmental pollutants) including review the source, toxicologic effects, and pathogenesis.

Thursday, final day! The subject of the session was ‘Technology-related toxicologic effects’. The topics were covered by Dr D. Warheit, Dr A. Hubbs, Dr B. Walling, Dr M. Schutten, and Dr S. Barros. They reviewed several of these technology-based approaches, their potential toxicologic effects, and the approaches to risk assessment.

At the breaks, I was overwhelmed with those great posters and exhibits.

Catching up with friends and colleagues were also very nice parts of the Symposium. Boston was a beautiful city; stunning scenery, many historical sites, famous Harvard University, great variety of restaurants to go to

at lunch hours, and most importantly (for me of course) a great shopping centre near to the hotel!

I had a great time in every way! Hope to meet you all again in another STP.

With best wishes
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XIXth Classical Examples in Toxicologic Pathology: 24-25th February 2012, Hannover-GERMANY

Once again, the organizers succeeded in putting together a very interesting program of examples in toxicologic pathology, ranging from very classic examples to topics covering the latest technologies. Despite the recent shocks of site closure announcements hitting our field and others hanging over our heads, many of us were able to make our way to Hannover and the seminar was well attended.

On the first day, Sivert Bjurström started the program with a lecture on trypsin inhibitors inducing pancreatic acinar cell hyperplasia and adenomas in rats. Jürgen Funk introduced the puromycin aminonucleoside model, a model for acute glomerular and tubular kidney damage in rats, and discussed the use of novel kidney biomarkers. Cécile Sobry presented her work on antisense nucleotides and the observed toxicity in different animal species and relevance for humans. Thomas Nolte gave a summary about the toxicity induced by β_2 -adrenergic agonists, presenting glass slides to the attendants with examples of lesions in the female reproductive system. Replacing Hans Harleman, Jayne Harris talked about compounds causing vascular lesions. Saturday morning started with a joint presentation about in vitro assays, which include histopathology as an endpoint, used in the safety assessment of chemicals: Maria Cecilia Rey Moreno gave an overview of the Bovine Corneal Opacity and Permeability Assay used to test ocular irritation, followed by her colleague Heike Marxfeld, who presented the Amphibian Metamorphosis Assay for evaluation of endocrine disruption. Then we had the honor to listen to Jerry Hardisty, presenting a study about brain tumors in rats, caused by chronic dosing of acrylonitrile. Based on the immunohistochemical characterization, he suggested that rat tumors so far diagnosed as astrocytomas should be called microgliomas. Matthias Rinke and Elke Hartmann gave an overview on mouse and rabbit models in atherosclerosis research, showing examples of the different typical histopathological findings. Klaus Weber did not merely give his scheduled presentation about engineered heart valve grafts, focusing on quality of the

tissue-engineered valves assessed by histopathology, but went on to give an ad-hoc talk on compounds inducing neurotoxicity.

As always, the organizers, Prof Eberhard Karbe, Prof Wolfgang Drommer, Prof Wolfgang Baumgärtner and Dr Ulrich Deschl did an excellent job. Also, I would like to mention that we were very well looked after by the residents of the Hannover Veterinary Pathology Department, in charge of the local organization.

Hopefully many of us will be able to attend and celebrate the XXth anniversary of the Classic Examples in Toxicologic Pathology, which will take place on the 22th and 23th of February 2013. See you in Hannover!

With best regards
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10th European Congress of Toxicologic Pathology (ESTP), 11-14th September Stresa-ITALY: Toxicopathology of Soft tissue and Musculo-Skeletal System

The 10th European Congress of Toxicologic Pathology (annual meeting of the ESTP) was held in Stresa, Italy, September 11-14, 2012. The beautiful Lake Maggiore offered a charming location frame for the meeting. The congress venue was the Palazzo dei Congressi, a beautiful conference center. Over 160 delegates from more than 15 countries (including several European nations, US, Japan, Korea, Taiwan, Thailand, Iran, India, Canada, Brazil, Israel) attended the scientific sessions. The main scientific focus of the meeting was "Toxicopathology of Soft Tissue & Musculo-Skeletal System".

The opening session of the congress in the afternoon of Tuesday 11 featured interesting lectures on the cellular and molecular pathophysiology of bone remodeling (Prof. Ermanno Bonucci) and on histomorphometric approaches to the evaluation of osteoporosis in animal models (Dr. Paola Ballanti). These were followed by an outstanding presentation on animal models of osteoarthritis (Prof. Rik Lories, University of Leuven, Belgium) and by an interesting overview of mouse models of cancer bone metastasis with insight into the cellular and molecular pathogenesis and their usefulness as platform for the investigation of therapeutic strategies (Prof. Thomas Rosol). Dr. Kumar Changan closed the first afternoon of the congress with an excellent presentation on in vivo imaging technologies and approaches for skeletal muscle in preclinical studies.

The second day of the congress, Wednesday 12, was opened by the presentation of the Stereotactic Brain Atlas of the Beagle Dog (Dr. Xavier Palazzi) a project resulting in the publication of a landmark reference for neuroanatomy and neuropathology. Additional presentations in the morning included an outstanding plenary lecture on in vivo imaging technology approaches applied to the skeletal system in the context of preclinical studies and in clinical settings (Dr. Michaela Kneissel), an excellent overview on the current state of the art and future perspectives for clinical pathology and biomarkers for the musculo-skeletal system in preclinical safety studies (Dr. David Ledieu), and an extremely interesting presentation on the local (subcutaneous connective tissue) and systemic toxicity of glatiramide compounds in chronic toxicity studies (Dr. Abraham Nyska). The Wednesday afternoon session was opened by Dr. Chirukandath Gopinath who introduced the speaker selected as recipient of the BSTP-sponsored Gopinath Lecture Award, Dr. John Vahle, who offered an overview of bone changes and tumors induced in rodents by parathyroid hormone and related peptides. After the lecture Dr. Gopinath presented the BSTP-sponsored award to Dr. Vahle. The session on compound-induced lesions in bone, skeletal muscle and soft tissues was closed by Dr. Elke Atzpodiens presentation on brown adipose tissue pathophysiology with examples of drug-induced morphological changes. The afternoon was then completed by the session focused on "Replacement Therapies" featuring Dr. Milena Fini with a lecture on preclinical models for devices/biomaterials for the skeletal system along with examples of clinical translation, Dr. Xavier Palazzi with a presentation on the preclinical safety evaluation of devices/biomaterials for the musculo-skeletal system, and by Dr. Lorenzo Moroni with an impressive presentation on 3D fabrication technologies for the generation of cell-instructive porous biomaterials for skeletal regenerative therapies. After the scientific sessions, in the late afternoon of Wednesday the main conference room also hosted the ESTP Annual General Assembly, with the communication of the results of the Elections in the ESTP Executive Committee board, and a lively discussion of the membership on the future perspectives for the journal strategy.

The third day of the congress, Thursday 13, opened with the last item of the "compound-induced changes" session, an excellent presentation by Dr. Anke Heuser illustrating examples of histopathological effects of PDE IV inhibitors on the skeletal system of rodents (also including material contributed by Dr. Ursula Junker).

The morning of Thursday then hosted very successful interactive presentations on the INHAND nomenclature project specifically focused on proliferative lesions of bone and teeth (prepared by Dr. Heinrich Ernst, and delivered by Dr. Dirk Schaudien) and non-proliferative lesions of bone, joints and teeth (by Dr. Matthias Rinke).

After the Awards Ceremony in the mid morning, and additional INHAND interactive session, there was a presentation by Dr. Karin Küttler and Dr. Heike Marxfeld on proliferative lesions of the mammary gland. The cases and examples shared by Dr. Küttler and Dr. Marxfeld stimulated an interesting debate in the audience on the appropriate approach to classification of some controversial lesions.

The first part of the afternoon on Thursday featured very successful interactive case presentations encompassing spontaneous lesions in laboratory animal species from preclinical safety studies, challenging aspects of gestational developmental anatomy in minipigs, tumors in genetically engineered mice, and compound-induced changes in the skeletal system. The much appreciated interactive case presentations were followed by Session 6 which focused on regenerative /cell-based therapies for muscle tissue, with the presentation of Dr. Thibaut Larcher offering an overview of animal models of Duchenne Muscular Dystrophy (DMD) and Dr. Francesco Saverio Tedesco with outstanding examples of preclinical to clinical translation of stem-cell based therapeutic strategies for DMD.

At the end of the scientific sessions an extremely interesting workshop/roundtable on the "Future of toxicologic pathology" took place. Dr. Lars Mecklenburg was the driving force of this initiative, he gathered a panel of experts on the stage to initiate discussion on the current status and future perspectives for the toxicologic pathology profession in the overall challenging global financial scenario both in pharmaceutical R&D and in the preclinical outsourcing market. The themes of the roundtable were of outstanding interest and there was a substantial contribution by the audience with many comments and ideas. Dr. Mecklenburg was an excellent moderator of an interesting and thought-provoking discussion between the panel of experts and the audience.

The morning session on the last day of the congress, Friday 14, was focused on critically important items and issues for the toxicopathology profession. Dr. Ken Schafer presented an overview of global regulations applicable to pathology endpoints in repeat dose preclinical toxicity studies. Dr. Erio Barale-Thomas delivered an excellent overview of the status, current regulatory issues and challenges for Pathology Peer Review in preclinical safety studies. This presentation was followed by a concise and exhaustive summary of the situation and perspectives for Pathology Peer Review in Japan presented by Dr. Takanori Harada who was also serving as chair of the session as representative of the Japanese Society of Toxicologic Pathology. An excellent presentation on Pathology Working Groups (PWGs) along with examples was offered by Dr. Jerry Hardisty. Finally, Dr. Kathleen Funk delivered a presentation on "Industry-CROs pathology interactions – what can be improved?" (a perspective from the point of view of

CROs) that had been prepared for the congress by Dr. Jeff Engelhardt, and Dr. John Vahle offered a presentation prepared by Dr. Armando Irizarry Rovira addressing the Sponsor's perspective in the context of Industry-CRO pathology interactions.

Overall the scientific program of the meeting was interesting, varied and much appreciated by the delegates.

The social program was also successful. The welcome reception took place on the charming sky bar at the Hotel La Palma, where delegates had the opportunity to enjoy excellent food and drinks along with a breathtaking view of the Lake Maggiore at sunset and in the evening hours. The congress dinner was held in the beautiful Isola Bella, and despite a somewhat windy night attending participants enjoyed an excellent outside dinner with brilliant music entertainment.

I would take this opportunity to thank my colleagues of the Local and Scientific Organizing Committees for their great support and precious efforts, the Solution Office team (Pia Schroder, Kay Groothoff and Beate Dehning) for their tireless commitment and outstanding organization, the Italian Society of Toxicologic and Experimental Pathology (SIPTS) for kindly sponsoring the participation of one of the invited speakers, and the Sponsors and Exhibitors who kindly offered their support to the congress, and all the delegated who made this congress a success.

I hope to see many of you at the next ESTP meeting in Ghent, Belgium, September 10-13th 2013!

With best wishes and regards
Francesco Marchesi

ESTP Secretary
Chair of 2012 ESTP Scientific Organizing Committee

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