President’s Message Winter 2014

Hello members of the Society of Toxicology, Ocular Toxicology Specialty Section (OTSS).

I hope everyone is involved in making plans to attend the 53rd Annual Meeting of the Society of Toxicology in Phoenix, Arizona. Tuesday, March 25 will be a special day for ocular toxicology. The OTSS Program Committee has put together a wonderful Workshop entitled, "Ocular Immunotoxicology: A Privileged View" to be held at 9:00 am to 11:45 pm. Then, in the evening, the OTSS Meeting/Reception will be at 6:00 to 7:30 pm. More information about the Reception is enclosed.

The Workshop will be chaired by Drs. Brian Christian and JoAnn Schuh. Dr. Schuh will also be the lead speaker with a presentation entitled, "Ocular Oversight: Immune Privilege, and Immune Regulation and Dysregulation. Her talk will be followed by a presentation entitled, "Innate and Adaptive Immune Responses to Ocular Insult". The presenter of this talk will be Dr. Brian Gilger, who's book, "Ocular Pharmacology and Toxicology", was recently released. The third presentation is, "Compliment as a Target for Ocular Disease" by Dr. Damon Demady and this presentation will be followed by a presentation entitled, "Innate and Acquired Immune Responses to Ocular Viral Gene Delivery Vectors in Primate Eyes", and will be presented by Dr. Curtis Brandt. To wrap up the session, Dr Frederick Fraunfelder will present , "Clinical Implications of Ocular Immunotoxicology". As you can see, the Workshop is an event not to miss.

After the SOT meeting my term in office as President of the OTSS will be nearly complete and the current OTSS Vice President, Dr. Edward Chow will be taking over as President. I will move into the Past President position on the OTSS Executive Committee and assume the duties of that office. It has been a great experience as OTSS President and I encourage all OTSS members to find ways of getting involved with the OTSS. The current members of the OTSS Executive Committee want the OTSS to be an active organization and are open to ways of making the OTSS a useful part of your professional life.

Best wishes to all.
See you at the SOT meeting.

Jim Render
Mark your Calendar

Society of Toxicology
Ocular Toxicology Specialty Section (OTSS) Reception

WHAT: Ocular Toxicology Specialty Section (OTSS) Reception
WHEN: Tuesday, March 25, 6-7:30pm
WHO: Open to all OTSS members as well as SOT members interested in Ocular Toxicology
WHERE: The SOT Program Event Calendar will have a listing of locations and times.

Workshop Entitled “Ocular Immunotoxicology: A Privileged View”
9:00am-11:45am

ABSTRACT: Vision is achieved through highly specialized ocular tissue structures and processes which refract and transmit light to the photosensitive cells of the retina. Optimal visual function depends on maintaining the integrity and transparency of cornea, aqueous, lens and vitreous, which can be compromised by unchecked immune reactions. The eye is considered to be an “immune privileged “organ because of its capacity to moderate intraocular inflammatory responses and protect tissues of the visual axis through anatomic barriers, as well as through local and systemic immunoregulatory mechanisms, particularly immunosuppression. Breakdown or dysregulation of ocular immune privilege can lead to inflammatory disorders such as uveitis, and progression of intraocular neoplasms, and has been implicated in age-related macular degeneration and glaucoma. In addition, ocular inflammation is a commonly encountered response to intentional breach of immune privilege via intraocular administration of therapeutics.

This session will highlight the unique aspects of the immunology of the eye and the associated implications for ocular toxicology and the development of ocular therapeutics. The audience will gain current understanding of structural barriers and active mechanisms of ocular immune privilege. The current understanding of innate and acquired immune responses to ocular insult, including allergens, microorganisms, as well as ocular administration of small molecule drugs, biotherapeutics and viral vector based gene therapies will be presented. Routine and specialized techniques for evaluating ocular immune responses will also be described. The session will include a presentation describing a current immunomodulatory approach to treat ocular disease involving the complement pathway and possible mechanisms for toxicities in preclinical studies. The final presentation will provide clinical examples of and mechanisms of drug-induced immunotoxicity.

Co-chaired by Drs. Brian Christian and JoAnn Schuh
**Sponsorship**

We sincerely thank our sponsors for their generous support!!

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We need continued support for your Specialty Section in 2014!!

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**Repeat Call for Student and Post Doc Representatives**

The OTSS is looking for an undergraduate student and a postdoctoral student to serve on the OTSS Executive Committee. Serving as Student or Postdoc representative to the OTSS will provide a valuable experience to young scientists interested in developing their leadership and service skills beyond the lab. Serving in a leadership role in the society of Toxicology also makes a notable addition to your resume or CV. For further information please contact Evan Thackaberry, chair of the OTSS membership committee.
OTSS Committee Updates

Program Committee

The program committee has been actively developing program ideas for the next few years. For 2015, a symposium proposal on “Retinal Toxicology” will be submitted to SOT in the next few months to cover subtopics such as mammalian retinal anatomy and physiology, mechanism of toxicity for retinal pigment epithelium, mechanism of toxicity for photoreceptor cells, pharmacokinetic factors affecting retinal toxicity, and stem cells in retina repair and regeneration. For 2016, the committee is exploring the possibility of holding a SOT-sponsored “Contemporary Concept in Toxicology” whole day symposium either adjacent to SOT or ARVO. The committee has also been working on other topics such as “In Vitro Methods for Evaluating Ocular Toxicity” and “Biomarkers of Ocular Injury” as upcoming symposia or continuing educational courses. Please provide your program suggestions, if any, to the committee chairperson, Edward Chow, or any of its members listed as follows: Brian Christian, Craig Crosson, Don Fox, Melva Rios-Blanco, JoAnn Schuh, and Evan Thackaberry.

Membership Committee

The membership committee is responsible for outreach to new prospective members of the OTSS. In 2013, this has included direct e-mails to new SOT members, and an effort to encourage student membership in collaboration with current student members and the post doctoral assembly. In addition, the membership committee works with other committees to promote initiatives that encourage membership, including new student awards (via the awards committee) and sponsoring scientific sessions at the annual meeting (via the program committee).

Book of Interest

Ocular Pharmacology and Toxicology
Editor(s): Brian C. Gilger
Affiliation(s): (1)Department of Clinical Sciences College of Veterinary Medicine, North Carolina State University, Raleigh NC USA
Series: Methods in Pharmacology and Toxicology
Print ISBN: 978-1-62703-744-0

Springer Methods in Pharmacology and Toxicology has a new book from Humana Press, "Ocular Pharmacology and Toxicology" that is edited by Dr. Brian Gilger. The book’s subject is ocular pharmacokinetics, pharmacodynamics and toxicology and contains detailed chapters on study design, analysis and routes to regulatory approval for various types and routes of ophthalmic drugs. The book is intended to assist ophthalmologists, toxicologists and pharmacologists in the development of ocular therapeutics from preclinical study design to regulatory approval.
Papers of Interest

Summaries Provided by Ryan Hamilton:

**Early safety assessment of human oculotoxic drugs using the zebrafish visualmotor response.**
Sudhakar Deeti, Sean O’Farrell, Breandán N. Kennedy.

Due to the high influence of ocular toxicity on drug development and the difficulty in managing adverse effects in the visual system, assays that can screen compounds with predictive toxicology are of high value. In addition, the push to implement 3R methodology in terms of animal usage is also a high priority. Here, zebrafish visual behavior was studied in the presence of known oculotoxic (digoxin, gentamicin, ibuprofen, minoxidil and quinine) as well as several non-oculotoxic agents.

Drug solutions were added directly to the zebrafish environment and optokinetic response (OKR), visualmotor response (VMR) and touch response assays were analyzed. Overall VMR results had a sensitivity of 83%, a specificity of 90% and a positive predictive value of 83%, and would be an appropriate alternative to screen for possible visual system toxicity in unknown compounds.

Implications for this type of rapid, non-labor intensive, low animal usage method of screening large numbers of potential drugs or toxins is key for a more efficient development process. The process can conceivably be applied to ocular-specific drugs as part of an early toxicity profile or non-ocular drugs which need to satisfy ocular toxicity as part of a regulatory submission package.

**Circulating microRNAs as biomarkers of retinal toxicity.**
Qinghai Peng, Wenhu Huang and Annette John-Baptiste
J Appl Toxicol 30 Sep, 2013 DOI: 10.1002/jat.2930

Here for the first time, analysis of specific micro-RNA (miR) expression has been studied as a biomarker for retinal toxicity. Very recently, researchers have had success linking the increase in specific miRs to either organs or in response to certain agents, similar a toxicity fingerprint, such as miR-122 and -192 upregulation in acetaminophen-induced hepatotoxicity. Several retinal tissue-specific miRs (miR-96, -124a, -181a, -182 and -183) have been identified and linked to the retinal degenerative disease RP and specifically in the regulation of photoreceptor cell apoptosis. In response to apoptosis, these miRs have been found not only localized to ocular tissue, but circulating in the bloodstream as well.

After treatment with 2 pan-CDK inhibitors (known retinal toxicants) retina-specific miR expression was upregulated in whole blood as well as ocular tissue in explant cultures. The non-retinotoxic agent, HSP90, caused no change in any tested miR expression level (in or ex vivo). The results of altered miR expression was correlated with ERG and histopathological changes which showed evidence of toxic insult after CDK inhibitor treatment.

This is the first known paper to examine what are thought to be novel retinal miRs whose expression is specifically tied to retinal insult of a toxicant. This is an important step in ocular toxicity screening in the search for biomarkers and non-invasive, early determinants of toxicity, predictive toxicology and animal usage reduction that has implications across all of toxicology.
Summary of 2013 COPS Meeting (Provided by Jim Render):

The first annual COPS meeting was successfully held in Madison, Wisconsin on September 26 to 28, 2013. Activities included invited presentations, including “Comparative Approach to Eye Pathology” by Dr. Dan Albert, “The Cell Biology of Glaucoma” by Dr. Rob Nickells and “Glaucoma Phenotypes in Humans” by Dr. Yao Liu, and numerous case presentations. In addition, attendees viewed scientific posters from the Health Sciences Learning Center on campus of the University of Wisconsin followed by a presentation by Dr. Thomas Cronin on “Incredible Eyes: The Visual World of Mantis Shrimp”. The meeting had topics on diagnostic, toxicologic, comparative and basic scientific ocular pathology and allowed time to share ideas and enjoy the beautiful campus. The next meeting is tentatively set for late September, 2014, in Denver, Colorado.

2014 COPS Meeting

We’ve set the 2014 COPS meeting dates in Fort Collins CO. Remaining details are a work in progress.

Fort Collins CO Sept 17-20

Sept 17 5pm-8pm: evening welcome reception. Drinks and appetizers. Microscopes will be available to share and discuss cases.
Sept 18-Sept 20 noon: meeting.

Please share this information with colleagues and whoever might be interested!
JSOT Workshop Summary

Summary of the workshop entitled “Scientific Viewpoints in Ocular Toxicity Assessment: Departure from Conventional Practice” in the JSOT (Japanese Society of Toxicology) 2013 meeting held in July 2013. The JSOT 2014 and the JSCVO 2014 will be held in Kobe in July and Tokyo in August, respectively.

Scientific Viewpoints in Ocular Toxicity Assessment: Departure from Conventional Practice

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Summary

Humans commonly obtain approximately 80% of external information from vision. Since quality of life markedly decreases with loss of vision, risk assessment for visual toxicity of new drugs is extremely important. However, the ICH 54 guideline for nonclinical toxicity study of new drugs only includes very limited description for ophthalmologic examinations, and data submission only according to this guideline is not always considered sufficient for risk assessment of ocular toxicity.

The eye is an assembly of many specialized sub-organisms which have specific function, and integral maintenance of homeostasis in the eye plays an important role of visual function. When only a part of integrity of function is lost, overall function of the eye might be commonly disturbed. Therefore, understanding of anatomy and physiology of these sub-organisms may help to know mechanisms of observed ocular change.

In ophthalmologic examinations in nonclinical toxicity studies, it is vital to understand principles and features of each examination. Comparisons of findings between pre and post drug treatment as well as considerations of species differences, strain differences, age differences, and location of abnormalities should be essential. In addition, many kinds of spontaneous ocular findings are well known in experimental animals. To identify treatment-related changes from spontaneous findings, measuring basic skills for ophthalmologic examinations and making advantage of collection of background data is necessary. To extrapolate to human, ocular findings obtained from animal should be evaluated based on their clinical significance.

For preparation of histopathological samples, careful sampling of organs and appropriate selection of fixatives is important. To accurately orient ocular lesions in the specimens for histopathological examinations, discussion prior to necropy among ophthalmologists, gross necropy pathologist and histopathology technician should be effective and helpful. Final diagnosis of ocular toxicity only based on histopathological findings does not always mean definitive, and comprehensive evaluation with information obtained from various examinations, mainly ophthalmologic examinations, should be made.

In conclusion, for risk assessment of ocular toxicity, integrated judgement from all examination data in nonclinical toxicity studies are required, and therefore, ophthalmologists, as well as study director (toxicologists), clinical sign investigator, histopathology technicians and pathologists should share examination results, cooperate and act even more closely one another.

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