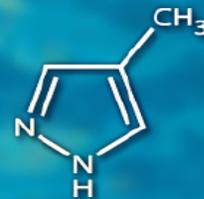


Clinical and Translational Toxicology Specialty Section



Spring 2015 Newsletter

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Message from the President

Dear Members:

Spring has arrived here in Louisiana, although you wouldn't know it from the photo that I took last week from my office. Bostonians would be rolling over in their graves if they knew that our university was closed that day for 3" of white stuff. Spring is the season when our fancy turns to the annual meeting. Even here in LA, we are looking forward to the sunny climes of San Diego. The details are elsewhere in this newsletter, but it will be an exciting meeting for our section. Our members organized and are some of the major speakers in two timely symposia, one on metal toxicity from hip

implants and the other on new treatments for nerve agent toxicity. We also have an exciting reception planned for the members – we hope that you will be able to join us to acknowledge our student and postdoctoral travel award winners and to listen to Dr. Rick Paules explain transcriptomics as a translational tool. Please bring a hearty appetite also – we always seem to have a plethora of food at the reception. As one of the newer specialty sections within SOT, it is reassuring to know that we have maintained an active and growing membership - thank you so much for renewing your membership this year. If for some reason (like being truly snowbound in Boston) you still need to renew your SOT membership, please remember to “tick the box” for CTTSS.

Because we are looking for innovative ventures that our specialty section can undertake,

I encourage you to interact with the officers at our reception to tell us what you would like for this section to do for you. What activities would you like us to undertake? We have considered presenting a CTTSS-relevant webinar or webinar series – I encourage you to send us some ideas of topics. Another activity that we welcome your ideas would be to offer a theme for a CTTSS- sponsored CCT (Contemporary Concepts in Toxicology) meeting. These tend to be one or two-day meetings on a focused topic, so are ideal for a small group like ours to sponsor. Importantly, SOT provides seed money to help in the planning and will share the profits with us. Lastly consider putting together a symposium for the annual meeting – this is one of the major purposes of specialty sections after all. Just remember that the final submission deadline for next year will be April 30, 2015 – but our own deadline is April 17th in order to give our Program Committee time to critique the proposals so that revisions can be made by the final deadline of April 30. Please contact Horst Thiermann or Jiri Aubrecht who will be in charge of this committee this year.

I have one last request (oh, that doesn't sound good, does it) – please consider making a tax deductible donation to CTTSS (through SOT). CTTSS does not have an endowment fund, but our policy has been that any money donated to the section will be used strictly for awards. Right now our travel awards are helpful, but are only \$300 per award. It would be nice to increase the amount, but we need more money in the “awards account” to do that. Be sure to indicate when you send money to SOT, that you want it dedicated to CTTSS and for their awards.

Thank you for your attention – looking forward to seeing you in San Diego.

*Ken McMartin, Ph.D.
President*



Shreveport, LA, Blizzard of '15

The
**CTTSS Reception and
Business Meeting**

will be held on

**Wednesday, March 25th
2015**

6:00 to 7:30 pm

at the

**San Diego Convention Center
Room 31A**

6:00 – 6:30

Appetizers and Refreshments

6:30 – 6:50

Richard S. Paules, Ph.D.

6:50 – 7:30

**Business Meeting and CTTSS
Award Ceremony**

We hope to see you at the reception!

This will be a great opportunity to make new acquaintances, renew old ones, and network with colleagues old and new. A short business meeting will be held to report on the Specialty Section's activities in the last year, to present an award and to discuss plans for future activities.



2014 CTTSS Executive Council

Business Meeting and Award

1. Welcome and introduction:
Kenneth McMartin, President
2. **Awards**
Career Achievement Award
In recognition of his distinguished contributions to clinical and translational toxicology
Richard S. Paules, Ph.D.
Graduate Student Travel Award
Blessy George
Postdoctoral Fellows Travel Award
Mira Pavkovic PhD
3. To thank the CTTSS Executive Committee 2014-2015.
4. Report from the Secretary-Treasurer: *Tao Wang*
5. Reports from the following Committees:
Program Committee: *Horst Thiermann*
Nominations Committee: *Horst Thiermann*
Awards Committee: *Kenneth McMartin*
Membership: *Rick Wang*
Newsletter/Website Committee: *Tao Wang*
6. New members of the Executive Committee were elected by ballot and will serve from 1 May 2015. The new committee will consist of:
President: *Horst Thiermann*
Vice President: *Jiri Aubrecht*
Vice President-Elect: *Donna Mendrick*
Secretary-Treasurer: *Tao Wang*
Three Councilors: *Charles Lindamood III, Kenneth McMartin and Sally Bradberry*
Postdoctoral Representative (postdoctoral fellow/researcher; fellow in clinical/medical toxicology): *Mitch McGill*
Student Representative (medical student; graduate student; medical resident): *Corie Robinson*
7. Survey the membership of the Specialty Section in regard to their overall experience as members of SOT and their specific aspirations and expectations for this Specialty Section.
8. Propose Symposia, Workshops and Continuing Education programs for the 2016 annual meeting.
9. Review the Report of the the Specialty Section Collaboration and Communication Group: *Kenneth McMartin*
10. Old and new business, Adjournment

Identifying Biological Patterns for Understanding Adverse Effects for Clinical and Regulatory Use – Transcriptomics and Beyond CTTSS reception featured speaker

Richard S. Paules, Ph.D., is the Acting Chief of the Biomolecular Screening Branch (BSB) in the Division of the National Toxicology Program at the National Institute of Environmental Health Sciences, NIH. He also holds adjunct faculty appointments as Professor in the Department of Pathology and Laboratory Medicine and Member in the Lineberger Comprehensive Cancer Center at the University of North Carolina at Chapel Hill.

The BSB develops and carries out programs in medium and high throughput screening of environmental substances for rapid detection of biological activities of significance to toxicology. The BSB administers the NTP high-throughput screening (HTS) program initiative to implement its vision for toxicology in the 21st century. This NTP vision places an increased emphasis on the use of alternative assays for targeting the key pathways, molecular events, or processes linked to disease or injury, and attempts to incorporate them into a research and testing framework. In support of this program, BSB members represent the NTP in the Toxicology in the 21st Century (Tox21) Partnership between members of the NTP, US EPA, US FDA and the National Center for Advancing Translations Science (NCATS) at NIH.



The research interests of Dr. Paules include integrating conventional studies of environmental exposures and toxicity with global "omics" approaches, or *toxicogenomics*. These studies are designed to relate alterations in global gene expression to adverse events as defined by conventional parameters of toxicity and pathology. The goal of these toxicogenomic studies is to provide insight into mechanisms of injury and disease as well as to establish signatures of adverse effects to develop putative biomarkers of exposure or adverse effects. The group also develops new approaches that can be used to understand genetic and epigenetic differences in susceptibility to toxicity and disease. Using the tools of toxicology, bioinformatics and comparative genetic analysis, the identification of human orthologs of causally related animal genes will aid the extrapolation between animal models and human toxicity and disease related to environmental, occupational, and/or medicinal exposures.

Dr. Paules received his Ph.D. from the Department of Pathology at UNC-CH and then received postdoctoral training with George F. Vande Woude at the National Cancer Institute, NIH before joining NIEHS in 1990. He has authored over 95 peer-reviewed articles in leading biomedical journals, as well as over 18 book chapters and invited publications. Since joining the NIEHS, he has been recognized with several awards, including four NIH Merit Awards and an NIH Director's Award, as well as the Society of Toxicology's *Leading Edge in Basic Science Award* at the 2010 SOT Annual Meeting.

2015 CTTSS Travel Award Recipients

Congratulations to the winners!

The CTTSS is pleased to announce the winners of the section's awards for this year, both intended to help defray some expenses for travel of a student and a postdoctoral fellow to present their research at the SOT annual meeting in San Diego in March. Both awardees will receive a recognition plaque and more importantly a check for \$300 at our Section reception at the annual meeting. We hope that you are able to attend the reception to warmly greet our winners. As an aside, this was a great year for these awards because of a heavy competition in both categories, making the job of the Awards Committee most difficult. We have provided the presentation information for our two winners below – we hope that you have time to visit our winners at their posters and to congratulate them.

Blessy George, the winner of the Student Travel award, is enrolled at Rutgers University in the Joint Graduate Program in Toxicology under the mentorship of Dr. Lauren Aleksunes.

The title of her abstract is "*Urinary KIM-1 Detection of Subclinical Nephrotoxicity in Oncology Patients Treated with Cisplatin*". Her abstract and poster numbers are 1219 and 650, respectively.



Her presentation date and time is March 24, 2015 from 9:00 AM to 12:30 PM.

Mira Pavkovic, Ph.D., the winner of the Postdoc Travel award, is working in the Laboratory of Systems Pharmacology at Harvard Medical School under the mentorship of Dr. Vishal S. Vaidya.

The title of her abstract is "*Early Detection of Kidney Toxicity in Humans using Urinary microRNA-21, -200c and -423*". Her abstract and poster numbers are 2297 and 561, respectively.



Her presentation date and time is March 25, 2015 from 1:00 PM to 4:30 PM.

2 sponsored symposia will be held Tuesday March 24th :

Local and Systemic Toxicity from Cobalt and Chromium-Containing Hip Prostheses is scheduled for **Tuesday, March 24, 2015** from **9:00 am to 11:45 am**.

Over 500,000 patients in the United States have received a metal-on-metal hip prosthesis. Movement of loosened components in a failing prosthesis and friction between bearing surfaces can result in increased local and systemic metal concentrations, principally of cobalt and chromium. The generation of large numbers of nanoparticles of 25–50 nm diameter is of toxicological importance due to the ability of these particles to enter cells and cause tissue damage. Metallic debris affects bone health through direct effects on bone cells and through indirect inflammatory signalling. These effects vary with the metal, its concentration, physical form and valency. Cobalt and chromium localize at nuclear and perinuclear sites in osteoblasts, suggesting uptake through cell membrane transporters and is modulated by P2 receptor blockade. Metallic debris induces a range of cellular responses by direct cytotoxicity mediated through activation of redox reactions or the substitution of other bivalent cations in biological pathways, and through cytokine induction that is potentiated by direct and indirect activation of inflammasome signalling. Clinical studies have demonstrated that cobalt causes cardiovascular, visual, auditory and thyroid dysfunction; malnourished heavy drinkers, for example, develop cardiomyopathy.

It has been shown that under conditions of protein deficiency, causing depletion of cobalt-chelating amino acids, cobalt inactivates lipoate, a co-factor for pyruvate dehydrogenase, thus inhibiting the Krebs cycle. Cobalt also produces depletion of retinal ganglion cells, axonal swelling and myelin thinning of the optic nerve, and a reduction of hair cells of the Organ of Corti.

Cobalt administration is associated with goiter and hypothyroidism. These effects appear to be due to the inhibition of tyrosine iodinase and the subsequent decrease in thyroidal iodine uptake and incorporation of iodine into thyroid hormones. Eighteen patients with systemic toxicity in association with a metal-containing hip have been reported. The reported systemic features fell into three main categories: neuro-ocular toxicity (14 patients) peripheral neuropathy (six cases), sensori-neural hearing loss (seven), cognitive decline (five), ocular toxicity (six), cardiotoxicity (11 patients) and thyroid toxicity (nine patients).

Currently, there is no evidence that chelation with any antidote will exert a beneficial therapeutic impact on clinical outcome in patients with health problems associated with cobalt containing hip prostheses.

Hip prostheses: what toxicologists need to know *Allister Vale MD*

Adverse local tissue responses to metal *Mark Wilkinson MD*

Mechanisms of cardiovascular, neurological, and thyroid effects of cobalt toxicity

Jeffrey Brent MD PhD

Systemic toxicity following insertion of a cobalt and chromium-containing prosthesis: A critical review of published cases

Sally Bradberry MD

Is there a role for chelating agents in the management of adverse health effects in patients with cobalt and chromium containing hip prostheses?

Michael J. Kosnett MD MPH

New Developments in the Management of Nerve Agent Poisoning, is scheduled for **Tuesday, March 24, 2015, from 1:30 pm to 4:15 pm**

Nerve agents have been employed by Iraq and Syria and were released by terrorists in Japan on 11 occasions in 1994–5. These releases indicate that countries must be prepared to treat civilian as well as military casualties. This requires an understanding of the mechanisms of toxicity of these agents, the factors that influence their clinical impact and knowledge of potential treatments. Much research is underway to improve the current treatment regimens, which include an anticholinergic drug (e.g. atropine) to antagonize the effects of excess acetylcholine (ACh) at muscarinic effector sites, the use of an oxime to reactivate nerve agent-inhibited acetylcholinesterase (AChE) and an anticonvulsant benzodiazepine to prevent or stop nerve agent-induced seizures. A series of novel phenoxyalkyl pyridinium oximes that show efficacy in the brain have been tested and found to reduce brain AChE inhibition and attenuate seizures.

The in service (military) medical countermeasure provision is based on carbamate pre-treatment; such an approach is not possible in the case of a civilian population who are also not likely to be wearing personal protective equipment (PPE). The concept of employing physostigmine, hyoscine and HI-6 in a single autoinjector in the absence of any form of pretreatment may reduce incapacitation significantly. In addition, the potential of human recombinant butyrylcholinesterase alone, and in combination with standard therapy, as a post-exposure treatment and the use of antinicotinic drugs to reduce the effects of accumulated ACh could offer additional benefits.

Finally, a beta-cyclodextrin with an attached oxime function may offer an alternative approach by enhancing detoxification of nerve agents.

Nerve agents: an introduction to nomenclature, mechanisms of action, clinical features, overview of current treatment and past releases

Allister Vale MD

Therapeutic problems of central effects of nerve agents

John H McDonough PhD

The development of novel centrally effective oxime reactivators for organophosphate-inhibited acetylcholinesterase

Janice E Chambers PhD

Translation of experimental findings into recommendations for the treatment of nerve agent poisoning

Horst Thiermann MD

New approaches in the therapy of nerve agent poisoning

Paul Rice OBE MD

Please make time to attend these cutting-edge Symposia and encourage others to do so!

Meet the new officers!

Colonel (MC) Prof. Dr. Horst Thiermann, the incoming President

Colonel (MC) Prof. Dr. Horst Thiermann is head of the Bundeswehr Institute of Pharmacology and Toxicology, the German national centre of competence for medical defence against chemical warfare agents. This institute is the only institution in Germany allowed to use chemical warfare agents for medical research. The main focus is directed on medical prophylaxis, diagnosis and therapy of nerve- and blistering agent poisoning. The research programme ranges from molecular (cholinesterases) and receptor level (nicotinic, muscarinic receptors) cellular signal pathways, work on complex organ models (e.g. phrenic-diaphragm preparations, complex cell culture models) to animal experiments. The final level consists in collaboration with clinical toxicological units in order to correlate newest clinical findings with scientific results from laboratory work. Here, the extremely few cases with sulphur mustard or nerve agent poisoning and especially the in South East Asia frequently occurring poisonings with organophosphorus pesticides, resulting in several hundred thousands of deaths each year, meet the special interest of Colonel (MC) Prof. Dr. Thiermann.



The ongoing collaboration with clinical toxicologists clearly elucidated that especially in this area, distinct strategies are necessary for translation of results from basic research into development of new therapeutic protocols, new antidotes as well as in clinical practice and clinical assessments. On the other hand, clinical observations and results from randomised clinical trials can frequently not be transferred directly and uncritically to a specific intracellular pathway or distinct receptor interaction that have been revealed with genetically modified organisms. Thorough considerations of species dependent differences and comprehensive translations of results from basic research into clinical practice and vice-versa appear to be the appropriate approach to solve toxicological problems.

After studying medicine at the University of Regensburg and Technical University Munich, Bavaria, Germany, Colonel (MC) Prof. Dr. Thiermann worked at the Bundeswehr Hospital Munich in the departments of anesthesiology and surgery. In 1989, he joined the Bundeswehr Institute of Pharmacology and Toxicology, Munich. His training as Pharmacologist and Toxicologist included a stay at Walther-Straub-Institute of Pharmacology and Toxicology, Ludwig Maximilians-University Munich. He completed his specialisation as Clinical Pharmacologist after a two-year stay at MDS PharmaServices, Höhenkirchen-Siegertsbrunn, Germany. Horst Thiermann received his PhD from the Technical University of Munich, Germany and was appointed adjunct professor at the same university.

In PubMed he is listed as author/co-author of 160 publications. He is Vice-Chairman of the Committee for the Assessment of Intoxications of the Federal Institute for Risk Assessment (BfR), member of the Board and scientific committee of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) and German representative in a medical NATO-Group. As member of the Society of Toxicology (SOT), he was elected Vice-president of the Clinical and Translational Toxicology Speciality Section (CTTSS).

Meet the new officers!

Dr. Donna L. Mendrick is our new Vice President elect



Dr. Mendrick is the Associate Director of Regulatory Activities at the National Center for Toxicological Research (NCTR). Prior to this, she was the

Director of the Division of Systems Biology at NCTR. She is the FDA's *ad hoc* member of the Advisory Committee to the National Institutes of Environmental Sciences. Dr. Mendrick's FDA committee assignments include the Senior Science Council, Tox21, and ICCVAM. She has many years of experience in the fields of histology, immunology, pathology, pharmacogenomics, pharmacology, toxicology and toxicogenomics employing small molecule drugs, recombinant therapeutic proteins and monoclonal antibodies.

Dr. Mendrick is past President of the National Capital Area Chapter of the Society of Toxicology and currently is the Chair of the Current Concepts in Toxicology (CCT) committee, a member of the Scientific Liaison Council (SLC) and on the planning committee for the Future Tox III CCT meeting.

Meet the new officers!

Dr. Sally Bradberry, BSC, MD, MRCP, FAACT, is our new Councillor



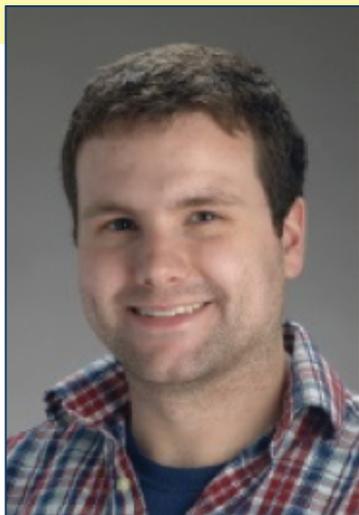
Dr. Bradberry is the Deputy Director of the National Poisons Information Service (Birmingham Unit) and the West Midlands Poisons Unit, City Hospital, Birmingham, UK.

She also holds an appointment as Senior Lecturer in Toxicology in the University of Birmingham, UK. She has served on the Board and/or Scientific Committee of the European Association of Poisons Centres and Clinical Toxicologists since 2002 and was awarded the Fellowship of the American Academy of Clinical Toxicologists in 2010. Her main research interests are in the toxicity of metals and pesticides and the management of human poisoning due to these chemicals.

She has advised the UK Health and Safety Executive on human pesticide toxicity since 1999. She was on the Senior Editorial Board of Clinical Toxicology for eight years (2004-2012) and continues to review for this and other journals.

Meet the new officers!

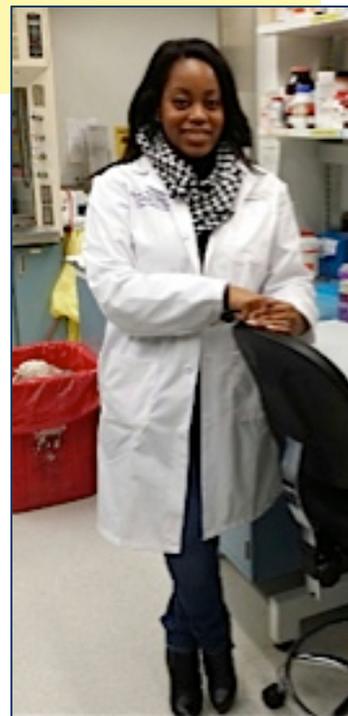
Dr. Mitchell R. McGill, Ph.D., is our new Postdoctoral Representative



Dr. McGill earned his Ph.D. in Toxicology at the University of Kansas Medical Center (KUMC) in 2013. The focus of his dissertation research was translation of the mechanisms of acetaminophen hepatotoxicity from rodent models to humans using mechanistic serum biomarkers. After graduating, he continued this work at KUMC as a postdoctoral fellow, but will move to Washington University in St. Louis as a fellow in Clinical Chemistry in July 2015. He has been a member of SOT since 2009 and of the Clinical and Translational SS since 2014. He has previously served as the Graduate Student Representative for the Central States regional chapter of SOT (2012-2013) and as a member of the SOT Graduate Student Leadership Committee (2012-2013).

Meet the new officers!

Corie Robinson is our new Student Representative



Corie received her BS in chemistry from Xavier University of Louisiana in 2012 and is currently working on her PhD at LSU Health Sciences Center-Shreveport in the department of Pharmacology, Toxicology and Neuroscience. Her research involves mechanistic studies on agents of clinical poisoning concern. She received the Regulatory Science Award at the South Central Chapter Society of Toxicology Meeting in 2013. She received the Clinical and Translational Specialty Section Graduate Student Travel Award to attend the Annual Society of Toxicology Meeting in 2014 and has been a member of SOT for over a year.



Clinical and Translational Toxicology
Specialty Section

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