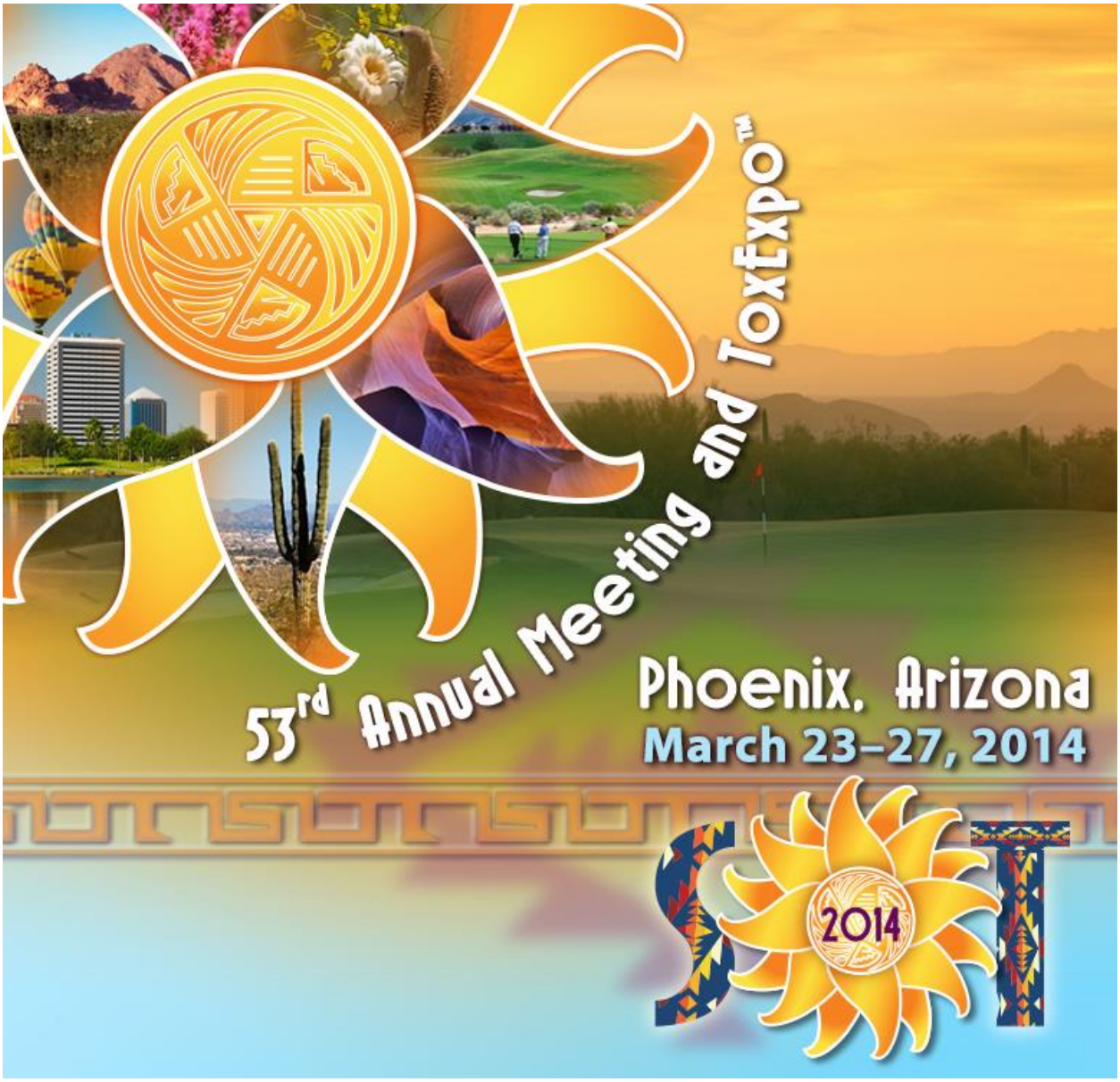
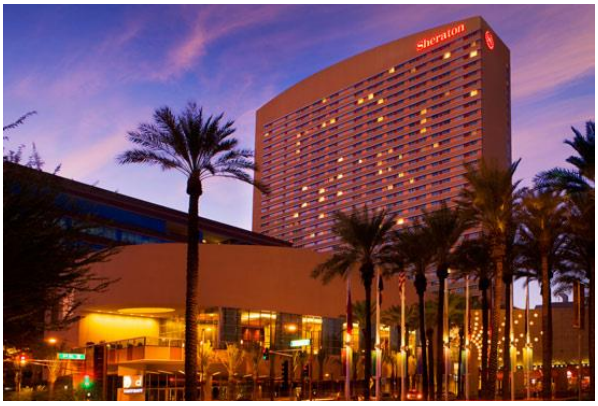
Clinical and Translational Toxicology
Specialty Section

PRE-MEETING 2014 Newsletter



Don’t forget to register for the upcoming SOT meeting in Phoenix!

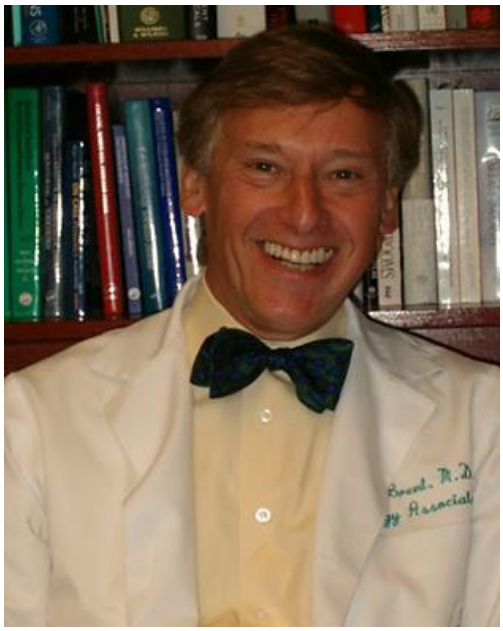
The CTTSS Reception and Business Meeting will be held on Tuesday, March 25th 2014 from 6:00 to 7:30 pm at the Sheraton Hotel Downtown Phoenix



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.

6:00–6:30PM Appetizers and refreshments
6:30–6:50 PM Professor Jeffrey Brent MD PhD FAACT FACMT

Translational Antidote Research: a Bedside to Bench Tale



Jeffrey Brent obtained a BA in chemistry, a masters degree in molecular biology and completed his PhD in biochemistry at Mount Sinai School of Medicine. He earned his MD from State University of New York at Buffalo's School of Medicine. Dr Brent holds the title of Distinguished Clinical Professor of Medicine, University of Colorado School of Medicine and Colorado School of Public Health.

He is a former President of the American Academy of Clinical Toxicology (AACT), a former member of the Board of Directors of the American College of Medical Toxicology (ACMT), a recipient of the Louis Roche award from the European Association of Poisons Centres and Clinical Toxicologists, the Career Achievement Award from the AACT, and the Ellenhorn Award from the ACMT.

6:50–7:30 PM Business Meeting and CTTSS Award Ceremony

Please RSVP to John Benitez if you plan to attend the Reception and Business Meeting: john.benitez@Vanderbilt.Edu

Agenda for Business Meeting

1. Welcome and introduction
   Allister Vale, President
2. **Awards**
   Career Achievement Award

   In recognition of his distinguished contributions to clinical and translational toxicology

   Jeffrey Brent

   Graduate Student Travel Award
   Corie Robinson

   Postdoctoral Fellows Travel Award
   Mitchell McGill
3. To thank the CTTSS Executive Committee 2013-2014
4. Report from the Secretary-Treasurer
5. Reports from the following Committees:

   Program Committee: *Ken McMartin*

   Nominations Committee: *Allister Vale*

   Awards Committee: *Allister Vale*

   Membership: *Rick Wang*

   Newsletter/Website Committee: *John Benitez*
6. The new Executive Committee was elected by ballot and will serve from 1 May 2014 and will consist of:

   President: *Ken McMartin*

   Vice President: *Horst Thiermann*

   Vice President-Elect: *Jiri Aubrecht*

   Secretary-Treasurer: *Tao Wang*

   Three Councilors: *Charles Lindamood III, Allister Vale and Richard Wang*

   Postdoctoral Representative (postdoctoral fellow/researcher; fellow in clinical/medical toxicology): *Tracie Baker*

   Student Representative (medical student; graduate student; medical resident): *Michelle Carroll Turpin*
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 new Specialty Section.
8. Propose Symposia, Workshops and Continuing Education programs for the 2015 annual meeting.

9. Review the Report of the the Specialty Section Collaboration and Communication Group: *Ken McMartin*
10. Contemporary Concepts in Toxicology Meetings

New Executive Committee members from 1 May 2014

Vice President-Elect

Dr Jiri Aubrecht PharmD PhD

Dr. Aubrecht is a Senior Director at Pfizer, Worldwide Research and Development in Groton, CT, where he leads the Safety Biomarker Laboratories. He received his doctorate in clinical pharmacy (PharmD) from Charles University, Prague Czech Republic in 1987 and doctorate in philosophy (PhD) from Czechoslovak Academy of Sciences in Prague, Czech Republic in 1992.

Dr. Aubrecht was a postdoctoral fellow at Harvard School of Public Health in Boston, MA from 1993-1997. Dr. Aubrecht has extensive experience in biotech and pharmaceutical industry, authored over 50 peer-review publications in leading biomedical journals, as well as five book chapters.

In addition, he has one issued patent and several patent applications that are currently pending. His research interests are in development and evaluation of translational biomarkers with emphasis on qualification of novel biomarkers for risk assessment.

Dr. Aubrecht is a member of the Advisory Committee of the Predictive Safety Testing Consortium (PSTC) and has served as a chair of the Technical Committee on Application of Genomics to Mechanism-Based Risk Assessment at the ILSI Health and Environmental Science Institute. He was also a member of the scientific advisory board of the EU project CarcinoGenomics.

Dr. Aubrecht has been a member of the SOT since 1999 and has organized/chaired three symposia including 2014 SOT symposium titled "Clinical Evaluation of Emerging Biomarkers of Drug-Induced Liver Injury".

Secretary-Treasurer

Dr Tao Wang MD PhD DABT

Dr. Wang is Associate Director and Senior Investigator in the Preclinical Safety Department at Novartis Pharmaceuticals. Dr. Wang leads safety evaluation for drug development projects, and provides expert opinions regarding risk assessment in support of clinical trials.

She has been an active member of SOT for over 17 years, and has served in a number of elected and appointed positions, including the Membership Committee (current co-chair), the Continuing Education Committee, and the Global Strategy Task Force. Dr. Wang has also served on the executive boards of several regional chapter and Special Interest Groups (Northern California regional chapter- Secretary, Vice President, and President, Women in Toxicology-Councilor, and current Vice President, and American Association of Chinese in Toxicology-Councilor). Dr. Wang joined the Clinical and Translational Toxicology Specialty Section (CTTSS) in its inaugural year. As a relatively new subgroup of the Society of Toxicology, CTTSS has enormous potential for growth. For example, in the drug development field, identifying potential toxicities of drug candidates is no longer the only task for the industrial toxicologists. Increasingly, their efforts are also being spent on developing strategies to mitigate toxicity in preclinical models, with the goal of bringing the drug candidates to patients more safely.

I will devote my energy to support CTTSS's missions in the following areas:

- Assisting in recruitment efforts to bolster new membership, and just as importantly maintaining the interest of current members by multiple mechanisms, such as promoting clinical and translational toxicology-related scientific programs and releasing timely and interesting newsletters.
- Assisting in fund raising to provide solid financial support to promote CTTSS growth and related scientific/membership networking events

I will approach these tasks with the same energy and dedication that I have brought to all of my previous leadership roles, and I will work closely with other CTTSS officers and members to promote the core mission of CTTSS.

CTTSS Travel Awards

The 2014 CTTSS **Graduate Student Travel Award** was awarded to **Corie Robinson.**

C.N. Robinson, G.M. Landry, C.L. Dunning, K.E. McMartin. Department of Pharmacology, Toxicology and Neuroscience, Louisiana State University Health Sciences Center, Shreveport, LA

Are succinate and diglycolic acid taken up into human kidney proximal tubule cells by the same sodium dicarboxylate transporters?

Diglycolic acid (DGA) is now considered to be the primary toxic metabolite of diethylene glycol (DEG), leading to the acute kidney injury from DEG overdose. DGA is a four- carbon dicarboxylic acid, with structural similarity to the TCA cycle intermediate, succinate. We hypothesize that DGA and succinate are taken up by the same sodium dicarboxylate transporter (NaDC) located in the proximal tubule cells of the kidney. This study compared the intracellular uptake of DGA and succinate, via apical (NaDC-1) and basolateral (NaDC-3) transporters. Human kidney proximal tubule cells were cultured until confluent, then subcultured onto membrane inserts in 24 well plates, that allow for distinct apical and basolateral uptake. Using ^{14}C-substrates, uptake was measured at increasing time points and concentrations for both succinate and DGA, along with measurements of sodium dependence of the NaDC transporters. Cellular uptake of succinate from both the apical and basolateral membrane demonstrated sodium dependence, suggesting mediation via NaDCs, with somewhat higher uptake by the apical NaDC-1. Uptake of DGA was not sodium dependent from the apical direction and was not saturable, suggesting a transporter-independent mechanism.

Basolateral uptake of DGA was sodium-dependent and was saturable with a K_m of about 16 mmol/L. The magnitude of DGA uptake at non-toxic concentrations was greater from the basolateral side than the apical. These results suggest that DGA and succinate transport have differing characteristics in human kidney cells.

The 2014 CTTSS **Postdoctoral Fellows Travel Award** was awarded to **Mitchell McGill**.

Mitchell R. McGill, William M. Lee, Hartmut Jaeschke. Department of Pharmacology, Toxicology, and Therapeutics, University of Kansas Medical Center, Kansas City, KS, USA; Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center, Dallas, TX, USA

Serum biomarkers of mitochondrial damage in survivors and non-survivors of acetaminophen-induced acute liver failure: implications for the mechanism of hepatotoxicity in humans

Acetaminophen (APAP) overdose is a major problem. Although most patients survive, the volume of cases makes it the most common cause of acute liver failure (ALF) and ALF-related deaths in the US. We are only beginning to translate the mechanisms of hepatotoxicity from rodents to humans. Our group recently reported evidence of mitochondrial dysfunction in APAP overdose patients using biomarkers of mitochondrial damage (mitochondrial DNA [mtDNA], glutamate dehydrogenase [GDH], and nuclear DNA [nDNA] fragments). In this study, we wanted to determine if these markers correlate with death or survival.

We measured mtDNA by qPCR, GDH activity by kinetic assay, and nDNA fragments by ELISA in serum from APAP-induced ALF patients who did (n = 35) and did not (n = 34) survive. All three parameters were elevated at or near the time of peak ALT in patients with APAP-induced liver injury. Unlike ALT, peak levels of both GDH and nDNA fragments were higher in serum from non-survivors than survivors (1,083±177 vs. 513±74 U/L and 259±2 vs. 209±4 % of control, respectively). GDH and nDNA fragments also exhibited weak but significant correlations with ALT, prothrombin time, and with each other. Importantly, receiver operating characteristic (ROC) curve analysis revealed that higher peak levels of both GDH and nDNA fragments better associated with non-survival (AUC=0.68 and 0.65 for GDH and nDNA, respectively; $p<0.03$) than ALT (AUC=0.60, $p=0.11$). Limited data suggest similar results for mtDNA. Conclusions: Biomarkers of mitochondrial damage are higher in non- survivors with APAP-induced ALF. This indicates that patients with more mitochondrial damage are less likely to survive. Mitochondrial biomarkers could be useful as part of a panel for patient prognosis. (NIDDK U-01 DK58369 to the Acute Liver Failure Study Group)

Contact the Officers

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2014 Meetings of interest

http://www.toxicology.org/ai/meet/cct futureToxII.asp

March 28-30, 2014, ACMT, Phoenix
http://www.acmt.net/2014_Annual_Sciientific_Meeting.html

May 27-30 May, EAPCCT, Bruxelles
http://www.eapcct.org/publicfile.php?folder=congress&file=Brussels_Brochure.pdf

September 20-22, 2014 ACMT, Medical Toxicology Board Review Course, Salt Lake City UT
http://www.acmt.net/2014_Board_Review_Course.html

October 17-21, 2014 North American Congress of Clinical Toxicology, New Orleans, LA
http://www.clintox.org/index.cfm

Remember to renew your SOT AND YOUR CTTSS membership NOW!

You can do so online at: http://www.toxicology.org/ms/renew.asp