

Spring 2018 Newsletter

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Message from the President



This has been an exciting year for CTTSS with many accomplishments. First and foremost, we conducted a survey to better understand your interests. In addition, Phillip Wages, our Postdoctoral Rep., organized and hosted a webinar on 2/14/18 on “Research Beyond Basic Science: Pursuing Topics in Clinical and Translational Toxicology.” (If you have ideas on future webinars, please contact your CTTSS leaders. These bring recognition to our SS.)

At the 2018 SOT Annual Meeting, Horst Thiermann, a previous CTTSS President, and Sally Bradberry, our incoming Vice President-Elect, organized a Symposium titled: “Clinical and Translational Toxicology: From Theory to Therapy” that was held on Tuesday, March 13. They both spoke along with Jiri Aubrecht (CTTSS Past President), John-Michael Sauer (incoming President) and myself. We had approximately 180 attendees at the symposium! If you have an idea for symposium topics for the 2019 SOT Annual Meeting, please contact your CTTSS leaders for support before you submit the idea to SOT.

Allister Vale (a founding member and Past President of CTTSS) spoke at our business meeting/reception on poisoning (see below). Luckily it was not related to food poisoning, so everyone enjoyed the appetizers.

Science continues to move forward and progress continues to be made on topics of interest to CTTSS including microphysiological systems (aka human on a chip), stem cells (used as an assay and as a human/veterinary therapeutic), understanding how the microbiome affects drug efficacy/safety and protects us from diseases, etc. This is an exciting time to be a scientist.

It has been an honor to be your President and I encourage you to put your name forward for CTTSS office during the next election period.

Donna L. Mendrick, PhD

How and Why Laundry Pods are Toxic?

Allister Vale (School of Biosciences, University of Birmingham, UK) spoke on the toxicity of laundry pods during the CTTSS reception that was held during the SOT Annual Meeting in San Antonio. For those of you who were unable to attend this entertaining and informative talk, below is a summary.



The American Association of Poison Control Centers (AAPCC) has highlighted the increase among teenagers in the number of exposures to liquid laundry detergent packets (liquid laundry detergent capsules in Europe), commonly known as laundry pods. According to AAPCC, in 2016 and 2017, US poison control centers handled 39 and 53 cases of intentional exposures, respectively, among 13-19 year olds. That number has increased to 196 among the same age group in the first two months of 2018.

The cleaning products industry launched liquid laundry detergent packets in Europe in 2001 and these products were first marketed in the US in 2011. Currently, ≥ 1 billion are sold annually in the UK and ≥ 4 billion in the US. Detergent packets consist of concentrated liquid laundry detergent (24-45 mL in the US) in a water soluble polyvinyl alcohol membrane. The packets are mechanically strong when dry but on contact with moisture (e.g. from saliva, a moist hand or water) they can release their contents prematurely. Laundry packets contain anionic detergents ($\leq 10\%$ in US), non-ionic detergents ($\leq 75\%$ in US), propylene glycol (8-20%) and ethanol (2-5%). All packets now contain denatonium benzoate, a bittering agent. The liquid usually has a neutral pH, but the contents of some packets can have a pH of 9.

Professor Vale described 4,268 exposures to laundry detergent packets reported to the UK National Poisons Information Service.¹⁻³ Exposure to these packets occurred as a result of ingestion *alone* (81%), eye contact *alone* (8%) and skin contact *alone* (1%); multiple routes of exposure were involved in 10% of cases. The severity of the ensuing features was graded: 37% were asymptomatic, 60% had mild features (Poisoning Severity Score [PSS] 1), 2% were moderately poisoned (PSS 2) and 17 were severely poisoned of whom one adult died. In those ingesting the contents of a packet, vomiting occurred in 47%, coughing in 4%, CNS depression in 3% (due to non-ionic surfactants⁴) and stridor in 1%. Eye contact was involved in 14% of cases, principally causing conjunctivitis and corneal ulceration, which occurs primarily due to the surfactants in the packet.⁵⁻⁷ Skin exposure was involved in 7% of cases and most commonly resulted in rash and irritation.

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Travel Award Winner

CTTSS Postdoctoral Fellow Travel Award

Dushani Palliyaguru, Ph.D.

Department of Pharmacology and Chemical Biology,
University of Pittsburgh

Presentation: Repurposing an Occupational Exposure Biomarker as a Biomarker of Cruciferous Vegetable Intake in Clinical Trials



“I'm very grateful to the CTTSS for the Postdoctoral Travel Award this year which allowed me to travel to the annual SOT meeting to present my research. It was a pleasure meeting fellow investigators working in clinical and translational toxicology and I hope to build upon this professional experience in the years to come as I advance in my career as a scientist.”

-Dr Palliyaguru

The Translational Nature of Clinical Toxicology

John-Michael Sauer

A statement on the field of Clinical Toxicology adapted from the opening statement at the Clinical and Translational Toxicology: From Theory to Therapy scientific session (see page 2).

Clinical toxicology is the discipline within toxicology concerned with the toxic effect of agents, (including drugs and devices) whose intent is to treat, ameliorate, modify, or prevent disease states. Clinical toxicology also includes the study of agents used with non-therapeutic intent—for example, alcohol and drugs of misuse and chemical byproducts of industrial development including environmental contaminants. Clinical toxicologists are typically medically qualified graduates who have specialized knowledge of the adverse effects of drugs and other chemicals in humans. They also have specific training in how to treat patients who have been exposed to a toxic substance.

Translational research has a variety of definitions but is commonly considered to be research that translates new information or knowledge created in one area to another area or application. There are two general categories of translational research: basic to clinical and clinical to population. Much like translational research, translational toxicology strives to translate observations in nonclinical models (*in silico*, *in vitro* and *in vivo*) into an assessment of risk and potential safety issues in humans. Assessment of human safety risk can also be back translated to define mechanisms in nonclinical models.



Mechanistic *in vitro* safety tools can increase our ability to predict true human safety issues during drug development and help investigators avoid wrongly associating preclinical safety issues with human risk. It is likely that mechanistic *in vitro* assays will never completely supplant the need for whole animal testing, but instead these assays will allow for better translation of preclinical findings.

The Translational Nature of Clinical Toxicology

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Two approaches to human biology based *in vitro* safety tools are organ-based tools such as organ on a chip (complex cultures) and pathway-based tools that are organ agnostic but can predict outcomes across multiple organs. However, the data from these *in vitro* tools must be put into perspective, likely utilizing computational approaches, and combined with other information such as systems toxicology.

Systems toxicology is the study of the effects of toxicants on molecular/cellular networks, as defined in systems biology. Systems toxicology also encompasses those related processes and pathways that contribute to toxicant exposure (i.e., fate, absorption, distribution, metabolism) and toxicant effects beyond the cell (i.e., whole organisms and populations). Accordingly, systems toxicology involves the integration of all aspects of toxicology into a coherent explanation or prediction of toxicity. The strength of a systems approach to understanding toxicology resides in the amount and integrity of the data used to model systems-level toxicity. However, the predictive accuracy of these approaches is highly dependent upon the quality of information used to develop such tools.

In conclusion, application of improved translational safety strategies will take years to complete and will require a progressive approach to implementation. Health authorities will continue play a dual role as both supporting innovation and ensuring scientific quality. Academic research needs to support translational safety objectives by providing practical approaches that can be implemented in drug development. Industry scientists need to embrace a more mechanistic approach to safety assessment and develop a better understanding of the basic biology that drives species differences in drug induced toxicity. Most importantly, improvements in translational safety will require a deeper and continued collaboration between Ph.D. and M.D. scientists.



SOT Meeting Highlights

The CTTSS endorsed eight sessions of the 2018 SOT Annual Meeting Program, including the following as the primary endorser:

- Changes to the Common Rule Regulations and Implications for Human Research
- Unlocking the ‘Omics Archive: Enabling Toxicogenomic/Proteomic Investigation from Archival Samples
- Clinical and Translational Toxicology: From Theory to Therapy

Clinical and Translational Toxicology: From Theory to Therapy

The Clinical and Translational Toxicology: From Theory to Therapy symposium session was well attended and spurred great discussion amongst the speakers and attendees. A few key points from the symposium are highlighted below.

Restoration of nerve agent induced paralysis of human respiratory muscles *in vivo*- how to translate results from *in vitro* to the clinic?

Horst Thiermann

The use of the nerve agent sarin in Syria with nearly 1500 fatalities points to the urgent need for more efficient therapeutic strategies. Because there are hardly any patients with this type of poisoning in everyday life, randomized controlled clinical studies or other types of clinical research is nearly impossible. Therefore, extrapolation from experimental poisoning or clinical poisoning with related compounds can be used as a basis for rational extrapolation.

Glutamate Dehydrogenase in Diagnosis of Liver Injury: A Biomarker Journey from Enabling Clinical Trials to Improving Medical Care

Jiri Aubrecht

It is well known that ALT increases can be transient, and elevations can be due to liver and/or muscle damage. Thus, a new liver biomarker strategy is needed to identify liver injury in clinical practice especially in patients with muscle disease. GLDH, is an example of a sensitive and specific biomarker of liver injury. Studies have demonstrated that GLDH blood levels are not affected by acute muscle damage in humans with Duchenne muscular dystrophy and that GLDH can detect onset of liver injury in subjects with muscle disease. In addition, GLDH has been qualified for use in an IND supporting specific muscular dystrophy trials and is under review as a Drug Development Tool at CDER and EMA. It has obtained an "in vitro diagnostic" designation in the US.



From Bedside to Bench – What only our patients can teach us.

Sally Bradberry

The widespread abuse of synthetic cannabinoids presents a major challenge to clinical toxicologists caring for patients at the front line of medical practice. The number of compounds within this class of drugs is ever increasing as new analogues are developed, giving rise to drugs of varying activity with unpredictable clinical effects. Therefore, clinical toxicologists are faced with treating patients poisoned with agents for which there is limited understanding of mechanisms of toxicity, metabolism, and dose response data. Patients may present with extremely challenging neuropsychiatric manifestations in addition to cardiac, metabolic, and renal complications. Without analytical confirmation of synthetic cannabinoid use in a clinically meaningful time, other medical/psychiatric diagnoses have to be considered with the potential need for expensive and/or invasive investigations. Thus, a close working relationship between clinical toxicologists and analytical colleagues facilitates real time identification of synthetic cannabinoid use. This will reduce the need for unnecessary costly invasive investigations. Continuing collaboration is necessary to adapt to the rapidly changing profile of drugs encountered in clinical practice.

Clinical and Translational Toxicology: From Theory to Therapy

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Importance of Translation from *In Vitro* Testing to Approved Products and Treatments

Donna L. Mendrick

Many scientists believe the use of human cells *in vitro* will allow for better translation of preclinical findings to the clinic; while also accepting as true that the regulatory agencies, including the FDA, are resistant to the new approaches. *In vitro* approaches allow the manipulation of the environment and the assessment of damage to individual cells. However, the cells do not always exhibit a differentiated phenotype and lack both immune and circulatory systems, making it challenging for *in vitro* cells to replace animal testing. It is important to keep these issues in mind in order to better determine what human cells *in vitro* can achieve.

New Officers

The results are in from our election that ended in February and we are happy to work with our new officers as they fill their positions in May of 2018.

Vice President-Elect: Sally Bradberry
Secretary/Treasurer: William Mattes
Junior Councilor: Tracy Chen

As we welcome the new members to the leadership of the CTTSS, we also thank those that will be transitioning off.

Jiri Aubrecht
Haiyan Tong
John G. Benitez



2017-2018 Officers

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