Newsletter: Summer 2018

Drug Discovery Toxicology Specialty Section (DDTSS)

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Officers

President's Message

DDTSS President Howard Mellor

Welcome to the Drug Discovery Toxicology Specialty Section newsletter, Summer 2018!

Over the last few years, we've been aiming to highlight science and innovation in drug discovery toxicology and to provide opportunities for our membership to engage with this to an even greater extent. For example, at the end of 2017 we successfully held our first *Drug Discovery Toxicology Paper of The Year* competition. The winning lead author, Matt Peters (Drug Safety and Metabolism, IMED Biotech Unit, AstraZeneca), presented his work to an audience of DDTSS members at our 2018 annual reception in San Antonio, TX **(Page 4)**. Also of note, Dinah Misner (VP, DDTSS) and Dolo Diaz led a highly successful CE course at the 2018 SOT Annual Meeting entitled *Lead Optimization Of Therapeutic Small Molecules: From Drug Target To Clinical Candidate Selection, Strategies And Decision Making.*

Another key area of continuing focus for us is the mentoring and development of the next generation of discovery toxicologists. At the Annual Meeting in San Antonio, we hosted our student/postdoctoral scholar mentoring luncheon **(Page 5)** in addition to acknowledging outstanding student/postdoc posters **(Page 6)** by presenting Emil Pfitzer Endowment Travel Awards. The mentoring luncheon is an increasingly popular event and several of the DDTSS leadership committee were in attendance to answer questions and provide guidance about discovery toxicology careers in the pharmaceutical industry. In this regard, you may also recall that at our 2017 meeting reception we held a panel discussion focused on discovery toxicology skills required in the evolving pharmaceutical landscape. As we move through 2018 we also plan to host more DDTSS sponsored webinars. The first will focus on lead optimization toxicology strategies, as an extension of the successful CE course. The second will focus on strategies for identifying and addressing neurotoxicity. Personally, I've really enjoyed being involved in the DDTSS leadership committee over the last few years, contributing to our various initiatives and helping to develop ideas for new ones. It's really great to collaborate with such a diverse group of talented people, to learn from them and to support toxicology students and postdocs. I'd really encourage those of you with a passion for discovery toxicology to get involved with the section, to help shape the DDTSS and to lead it into the future!

Looking forward to seeing you at the SOT Annual Meeting in Baltimore, MD in March 2019!

Special Guest Contribution

Report on "Lead Optimization and Candidate Identification Strategies and Practices" course for FDA PharmTox Reviewers organized by IQ DruSafe and BioSafe Leadership Groups by Zoe Zhong (DDTSS Vice President-Elect)

The IQ DruSafe and BioSafe Leadership Groups have jointly organized a 2-day training course for the FDA PharmTox Reviewers on "Lead Optimization and Candidate Identification Strategies and Practices." The training took place on May 21-22, 2018 at the FDA White Oak campus. The objective was to provide a comprehensive and diverse overview of the strategic approaches, screening and model platforms currently used by the pharmaceutical industry to inform decision-making for drug candidate (small molecule and biotherapeutics) lead optimization and identification. The premise is that robust and thoughtful early safety involvement would reduce attrition in later phases of drug development.

Toxicology representatives from 14 biopharmaceutical companies (Abbvie, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, Roche, Sanofi, UCB) gave presentations on a range of topics important in safety assessment in the Drug Discovery space. For small molecules, the topics included target safety assessment, secondary pharmacology, cardiovascular toxicity, hepatotoxicity, genetic toxicity, and traditional and non-traditional animal models including genetically modified animals. For biologics, additional topics included the screening and optimization of mAbs/proteins and antibody drug conjugates for safety, pharmacology, PK, physico-chemical properties, off-targets and immunogenicity. The presenters did a fabulous job and the training was very well-received by US FDA with extremely positive feedback. There was good attendance from US FDA with over 100 attendees, and FDA participants were very engaged. This training course highlighted the strategies and approaches used by discovery toxicologists that impact the optimization and selection of clinical molecules. It's great to see the increased interest and awareness by regulators of the significant work by industry that shapes the clinical molecules that they get to review in the regulatory filing.

Award Receipient – Matt Peters (Drug Safety and Metabolism, IMED Biotech Unit, AstraZeneca) & colleagues

Deconvoluting Kinase Inhibitor Induced Cardiotoxicity

***Toxicological Sciences*, 2017, 1–14**

2017 Drug Discovery Toxicology Paper of the Year Award

Marie Lemper (Secretary) presented the award

In his presentation, Matt described how many drugs designed to inhibit kinases are limited by cardiotoxicity-related label warnings or prescribing restrictions. While this liability is widely recognized, designing safer kinase inhibitors (KIs) requires knowledge of the causative kinase(s). Previous efforts to identify the causative kinases have been hampered by the underlying complexity, particularly around kinase promiscuity of the inhibitors at therapeutically relevant concentrations. Matt described how sixty-five KIs with known kinome-scale polypharmacology profiles were assessed for effects on cardiomyocyte (CM) beating.

Changes in human iPSC-CM beat rate and amplitude were measured using label-free cellular impedance, and correlations between beat effects and kinase inhibition profiles were mined by computation analysis to identify associated kinases. Thirty kinases met criteria of having (1) pharmacological inhibition correlated with CM beat changes, (2) expression in both human-induced pluripotent stem cell-derived cardiomyocytes and adult heart tissue, and (3) effects on CM beating following single gene knockdown.

A subset of these 30 kinases were selected for mechanistic follow up. Examples of kinases regulating processes including calcium flux (RPS6KA3, IKBKE) and action potential duration (MAP4K2) were identified. This led to the creation of a simple model to predict functional cardiotoxicity whereby inactivity at three sentinel kinases (RPS6KB1, FAK, STK35) showed exceptional accuracy *in vitro* and translated to clinical KI safety data. This approach has the potential for significant utility in drug discovery, where identifying causative kinases and introducing a predictive model could influence medicinal chemical design. Further, discovering kinases previously unrecognized as influencing cardiovascular biology should stimulate investigation of underappreciated signaling pathways.

Puzzling through the evening….

At our annual DDTSS reception, which was attended by approximately seventy scientists, the team had a great time solving riddles. And it was fun to see everyone working together and imparting their creativity and interpretations.

DDTSS Student/Postdoctoral Scholar Mentoring Luncheon

"It was a great opportunity for me to network with professionals from the industry. Being in academia, I did not have deep knowledge about the working environment in the industry. The session had mentors from different industries who provided the necessary guidance and comprehensive details of the hiring process such as resume selection, phone interview, on-site interview etc. The guidance certainly helped me to portray my potentials to the maximum during my future job search and to understand the work culture and job recruitment process in different industries. The food provided during the luncheon was good. Finally, I would recommend this mentoring luncheon to all students and early-career scientists who are actively looking for an industrial career path at both entry and experienced level."

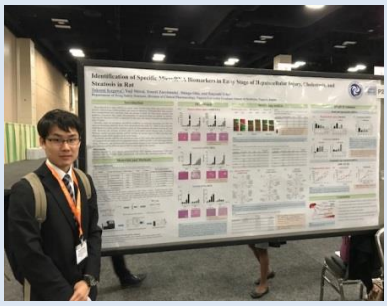
Navatha Alugubelly
Graduate student
Mississippi State University

"Getting the perspective of leadership in an informal setting was extremely valuable. I could ask questions to someone outside my usual team. So, being able to talk with someone who went through similar path, helped me improve my own work and career goals."

Pankajini Mallick
Postdoctoral fellow
PBPK modeling
ScitoVation

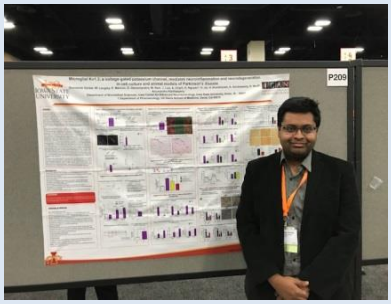
Annual Meeting Poster Awards

Graduate Student Awardees



1st Place: Takumi Kagawa, Department of Drug Safety Sciences, Nagoya University, Japan

Takumi's winning poster was entitled '*Identification of specific microRNA biomarkers in early stage hepatocellular injury, cholestasis and steatosis in rat*'. Here, time-dependent changes in plasma mRNA profiles were identified that were associated with specific liver pathologies & changed earlier than traditional DILI biomarkers.



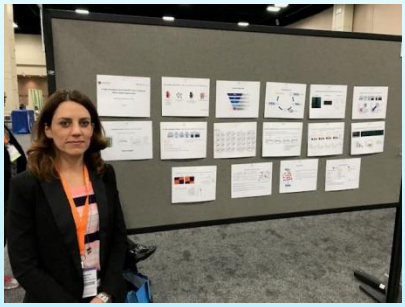
2nd Place: Souvarish Sarkar, Iowa Center for Advanced Neurotoxicology, Iowa State University, Ames, IA, USA

Souvarish's poster was entitled *'Microglial Kv1.3, a voltage – gated potassium channel, mediates neuroinflammation & neurodegeneration in cell culture & animal models of Parkinson's disease'*. He showed that Kv1.3 is highly induced in animal models of PD & post-mortem brains. Kv1.3 inhibitors exhibit anti-inflammatory effects *in vitro* & *in vivo.*

3rd Place: Kyle Saitta, Rutgers Robert Wood Johnson Medical School, Piscataway, NJ, USA

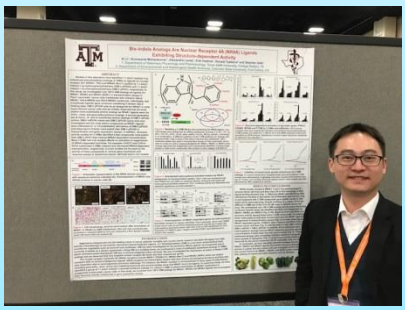
In his poster entitled *'The Metabotropic Glutamate Receptor Agonist 2-chloro-5-hydroxyphenylglycine (CHPG) Increases BDNF & Myelin Proteins after Cuprizone-Induced Demyelination'*, Kyle showed that mGluR Group I agonists such as CHPG could be used to increase BDNF & myelin proteins & potentially treat demyelinating diseases.

Postdoctoral Awardees



1st Place: Maria Beatriz Monteiro, Harvard Medical School, Boston, MA, USA

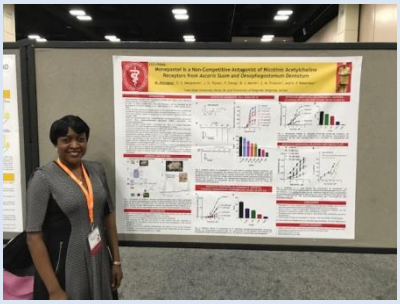
Maria's winning poster was entitled '*A high-throughput screen identifies novel targets for kidney tubular regeneration'*. Here, potential first-in-class compounds were identified that stimulate kidney epithelial cell regeneration following acute kidney injury *in vitro*.



2nd Place: Xi Li, Department of Veterinary Physiology & Pharmacology, Texas A&M University, College Station, TX, USA

In his poster entitled '*Bis-indole Analogs Are Nuclear Receptor 4A (NR4A) Ligands Exhibiting Structure-dependent Activity'*, Xi described how these ligands exhibit structure-dependent activity in cancer, non-cancer cells & xenograft models. The current focus is on the design & evaluation of NRA4A1-3 active ligands in cancer & other diseases.

Postdoctoral Awardee



3rd Place: Melanie Abongwa, Iowa State University, Ames, IA

Melanie's poster was entitled *'Monepantel is a Non-Competitive Antagonist of Nicotinic Acetylcholine Receptors from Ascaris Suum and Oesophagostomum Dentatum'. Using* two-electrode voltage-clamp electrophysiology, Melanie showed that the mode of action of monepantel is more complex than previously described.

DDTSS is pleased to announce our upcoming fall webinar

"Lead Optimization Drug Safety Strategies for Small Molecules."

Organized by Jennifer Cohen, PhD, DABT, Takeda California Inc, and Marie Lemper, PharmD, PhD, DABT, UCB Belgium

Oct 29 from 8-9 am Pacific

The panelists are **Drs Zoe Zhong, PhD, DABT** (Associate Director, Head of Small Molecule Discovery Toxicology at Genentech) and **Mark Fielden, PhD, DABT** (Scientific Director, Comparative Biology and Safety Sciences at Amgen). The intended audience is scientists across all career stages interested in deepening their knowledge of drug discovery.

RSESS Webinar
(Regulatory & Safety Evaluation Specialty Section)

"Assessment of Adversity and NOAEL in Toxicology Studies to Support Regulatory Decision

Wednesday, October 10, 2018 12:00 pm Eastern Daylight Time (New York, GMT-04:00)

The purpose of this webinar is to present suggested best practices for making consistent interpretations of test article-related effects as "adverse" and assigning no-observed-adverse-effect level (NOAEL) in nonclinical toxicity studies that could support regulatory submissions and interpretation. The term, adverse, indicates harm to the test species, while non-adverse indicates lack of harm. The interpretation of findings in toxicity studies as either adverse or non-adverse and the subsequent determination of the NOAEL (the highest dose with no adverse effects observed within the study) have been used to communicate the relevance of animal toxicity data for predicting potential human outcomes. The webinar will discuss the recommended best practices for toxicology study interpretation of adversity and determination of NOAEL. Case studies will be presented as examples.

…..to submit your ground-breaking drug discovery toxicology publications for…

Our Annual Science Competition! – Drug Discovery Toxicology Paper of the Year Award!

We are pleased to announce that for the second year running we will be awarding a prize for the drug discovery toxicology 'Paper of the Year.' The winner will receive a plaque of recognition and a financial award at the 2019 SOT Drug Discovery reception. There will also be an opportunity for this work to be presented at the reception. Application is open to all DDTSS members. You must be senior or first author and the paper must be accepted or published between January 1-December 31, 2018. Papers for consideration can be submitted at any time before the **Friday January 11th 2019 deadline** to Marie Lemper Marie.Lemper@ucb.com. Please feel free to encourage students and/or postdocs to reach out to colleagues and to make them aware of this new and exciting opportunity to share their work.

…and to submit your outstanding research for…

The 2019 DDTSS Student and Postdoctoral Scholar Poster Competition and Emil A. Pfitzer Endowment Fund Travel Award!

Abstracts should describe original research with high relevance for the field of drug discovery and investigative toxicology. All abstracts will be evaluated for scientific merit and relevance and authors of the top 5 student abstracts and the top 5 postdoc abstracts will be invited to present their posters for judging at the SOT meeting in San Antonio. First, second and third place winners will be announced at the DDTSS reception and cash prizes will be awarded from the Emil A. Pfitzer Endowment fund for winning entries. Abstracts should be submitted to Marie Lemper (Marie.Lemper@ucb.com) no later than **Friday 1st February 2019**.

DDTSS Student/Postdoctoral Scholar Mentoring Luncheon SOT 2019 Baltimore

We will be holding another mentoring luncheon for students and postdocs at the 2019 SOT Annual Meeting in Baltimore **(date and time TBD)**. Members of the DDTSS leadership committee will be available to discuss careers in pharmaceutical drug discovery toxicology and to answer any questions. Anyone wishing to attend, please contact Marie Lemper Marie.Lemper@ucb.com. Marie will collate numbers and provide an e-ticket.

SOT 2019 Baltimore Workshop Sponsored by DDTSS

Pharmaceutical investigative toxicology: case studies in optimizing drug discovery and guiding human risk assessment.

List of Past Presidents

Peter Newham	**2017**
Ray Kemper	**2016**
Dan Kemp	**2015**
Andrew Olaharski	**2014**
Yvonne Will	**2013**
John Wisler	**2012**
Craig Thomas	**2011**
Cindy Ashfari	**2010**
John Davis	**2009**
Kyle Kolaja	**2008**
Drew Badger	**2004-2007**

See you in Baltimore in 2019!

DDTSS Reception Wednesday March 13th

58TH ANNUAL MEETING
& ToxExpo · MARCH 10–14, 2019