Newsletter: Fall 2017

Drug Discovery Toxicology Specialty Section (DDTSS)

INSIDE THE ISSUE……

Officers

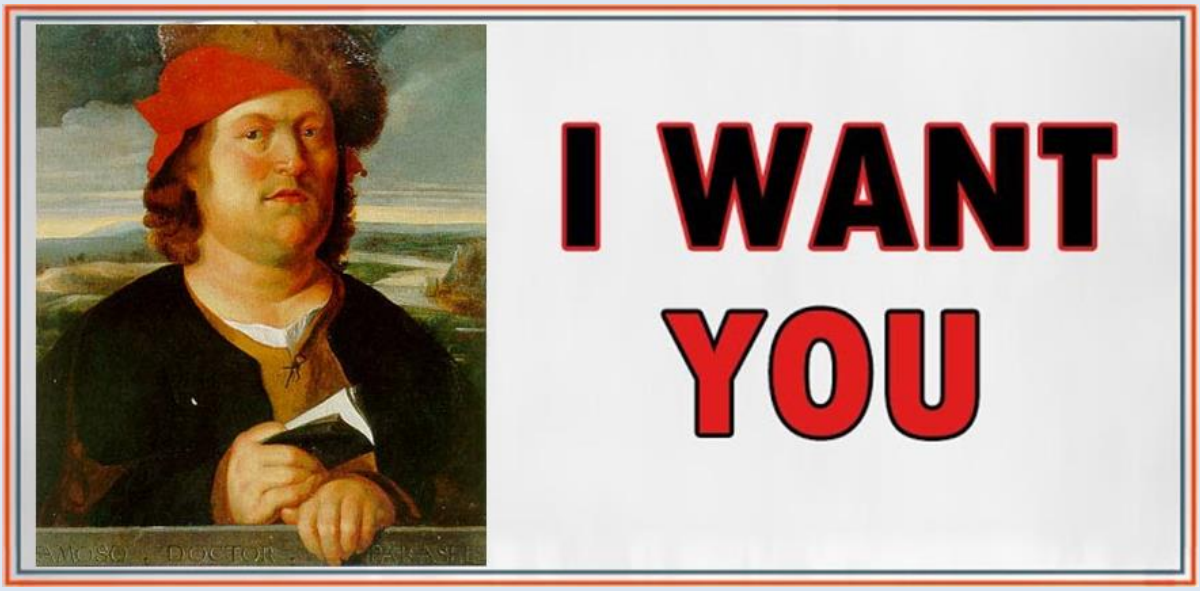
President's Message

DDTSS President Pete Newham

Welcome to the Drug Discovery Toxicology Specialty Section Newsletter, Fall 2017!
Since joining the Executive Committee in 2015 it has been a terrific pleasure to work with the previous presidents and contribute to the wide-ranging activities that our section gets involved in. It has also been great to work with the talented committee members in developing ideas and making them happen; which all helps maintain our group as a vibrant member of the SOT community.

In the last year or so we in DDTSS we have been considering what it means to be active in drug discovery toxicology today. We have continued our Webinar series with an *immune oncology* special feature with several speakers. Thanks to CRL for their sponsorship of our series. We of course held our annual reception at the 2017 SOT Annual Meeting in Baltimore and also hosted our student/postdoctoral fellow luncheon. During the reception we acknowledged our outstanding student/postdoc posters (see page 4-5 for this year's awardees) by presenting Emil Pfitzer travel awards; a special mention to two-time recipient Priyanka Trivedi! The DDTSS reception also continued the theme of drug toxicology diversity with one of our panel discussions to debate the skills required by discovery toxicologists in the evolving pharmaceutical/biotech landscape. Distinguished panellists included Yvonne Will (Pfizer), Scott Henry (Ionis Pharma) and Kathila Rajapaksa (Genentech). The session was moderated by DDTSS then Vice President Pete Newham and Vice President-Elect Howard Mellor. You can read more about this later in the newsletter, but to explore this topic further, we also have a special contribution article from Dinah Misner on "Diverse Techniques and Innovation Required in Drug Discovery Toxicologist".

Finally we have a number of plans for 2017/18. We will continue our webinar series, but also focus on highlighting great investigatory drug toxicology science via our new *'Paper of The Year Competition'* (see page **2**) and our continuing education (sponsored 2018 SOT Annual Meeting session: Lead Optimization Of Therapeutic Small Molecules: From Drug Target To Clinical Candidate Selection, Strategies And Decision Making). Finally we are planning on a seeking 'SOT Contemporary Concepts in Toxicology' support for a specific DDTSS symposium in 2018. With that in mind I'd like to seek your input via our Survey Monkey poll for areas you'd like us to consider for the symposium.
Looking forward to seeing you at the 57th Annual Society of Toxicology Meeting in San Antonio, TX!



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

We are pleased to announce that for the first time this year we will be awarding a prize for the drug discovery toxicology 'Paper of the Year'. The awardee will receive a plaque of recognition and a financial award at the 2018 SOT Drug Discovery reception. There will also be an opportunity for this work to 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, 2017. Papers for consideration can be submitted at any time before the January 12th 2018 deadline to Marie Lemper Marie.Lemper@ucb.com. Please feel free to encourage students and/or postdocs and to reach out to colleagues to make them aware of this new and exciting opportunity to share their work.

…and to submit your outstanding research in the 2018 DDTSS Student and Postdoctoral Fellow Poster Competition and Emil A. Pfitzer 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 6 student abstracts and the top 6 postdoc abstracts will be invited to present their posters for judging at the SOT meeting in San Antonio. First, second, and third place awardees 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 January 30th 2018.

Special Guest Contribution

Diverse Techniques and Innovation Required in Drug Discovery Toxicologist: What Skills are Required to be Successful? Dinah Misner, JnJ

Understanding biology of the target you are working on:

From *in vitro* to *in vivo*; need to understand potency and efficacy data generated on project, to put into context with any safety data you generate.

Need to research literature around biological pathways of target to be able to understand potential on-target effects you might see *in vivo*, or related pathways associated with target engagement (and depending on target, little or much may be known).

Nature of target(s) you work on can be broad, depending on where you are working; may have to switch hats between very diverse indications and associated biology/pharmacology.

Building strategies to assess molecules at your target, from early lead ID through to clinical candidate selection

Need to work closely with project team (in particular the clinical team) to understand what your target product profile will look like (e.g. what is the target population, what is acceptable for the indication).

Need to be nimble and flexible, as emerging data impact screening strategy; the phase the project in may also impact the paradigm.

Many different in vitro assays are used in drug discovery paradigm

In general, need broad knowledge of available platforms, pros and cons for each, and where to use each appropriately; down to how much material is required for each study and where the assays can be run and at what cost, as those be limiting factors.

Secondary pharmacology/off-target screening requires knowledge of differences between binding assays and functional assays; if you have a hit, what do you do with the data, what might potential downstream consequences be—your team will ask!

Cardiovascular screening assays very diverse, often specialized; likely need to understand how assays can be used to predict potential effects *in vivo.*

Genetox screening assays are often critical and positive results could be show-stopper; must identify if there isn't a concern, or more studies are required; there are many different endpoints from an assay, how do you pick the right assay at the right time to minimize finding out no-go data just prior to clinical candidate selection; also have to work with chemists to get material of appropriate purity and quantity.

Cytotoxicity assessments across different cell types (e.g. hematopoietic, hepatocytes, neurons, cell lines) may be very project-specific, and each cell type may have different endpoints or are of varying concern to your project team; you will likely have to put results into context for your team, and if there are particular endpoints that are more concerning for your project (and this will likely vary from project to project).

Need to work with colleagues in DMPK and chemistry understanding how physiochemical properties and SAR might drive any effects you see across these assays and which are most critical.

Technology ever-evolving, so also need to stay on top of latest developments, across many different domains.

Special Guest Contribution (continued)

Diverse Techniques and Innovation Required in Drug Discovery Toxicologist: What Skills are Required to be Successful?

***In vivo* studies are critical in late LO and selecting your final clinical development**

Designing appropriate *in vivo* studies with material you have available, where you will need to collaborate with DMPK colleagues to select doses, chemists on material requirements, and *in vivo* lab or CRO on which endpoints to collect.

You may be asked to be creative because material is limited but data is required; for early studies, particularly rodents, samples are limited so you need to use all knowledge above to pick right endpoints (biomarkers, other endpoints, which tissues, etc.).

Biggest challenge you may face is putting together all the *in vitro* and *in vivo* data you have generated and how the data translates, what it means to the project moving forward; often working closely with project team to put data into context and generate safety margins or multiples over efficacious doses, to determine whether the molecule has a chance of moving forward.

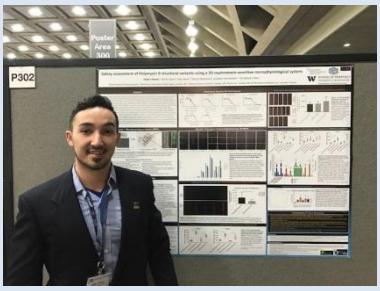
Unanticipated findings often happen during these *in vivo* studies; need to interpret the data, potentially design studies to understand mechanism, and revisit your screening paradigm to see if you can identify liability earlier.

A critical skill is to be collaborative and work closely with your project team, each of whom has specific areas of expertise; it is critical to not work in isolation, and utilize knowledge within team. Additionally, you may not be an expert at everything across the field in drug discovery toxicology, but need to be able to identify individuals who can help, whether within your organization, consultants, CROs, etc.

Highlights of the 2017 DDTSS Reception

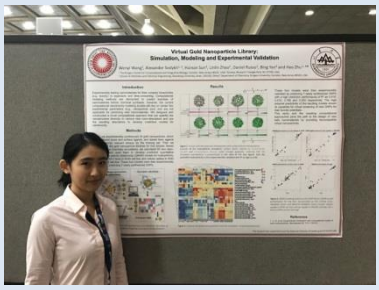
On the evening of Monday 13th March at the SOT Annual Meeting in Baltimore we held our annual DDTSS reception, which was attended by approximately fifty scientists. After some refreshments, the meeting was opened with a welcome and introduction from DDTSS President Ray Kemper. Pete Newham, DDTSS Vice President then awarded the prizes to the recipients of our graduate and postdoctoral poster competition, which was judged by a panel of DDTSS officers earlier in the day. The finalist's posters were displayed at the reception and the poster competition outcome is summarized in the following section.

Annual Meeting Poster Awards: Graduate Student Recipients

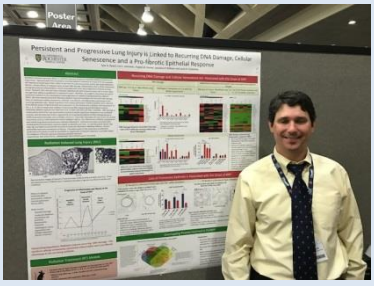


1st Place: Elijah Weber, Department of Pharmaceutics, University of Washington, Seattle , WA

Elijah's winning poster was entitled '*Safety assessment of Polymyxin B structural variants using a 3D nephrotoxin-sensitive microphysiological system '*. Here, a 3D renal microphysiological test system exhibited Polymyxin-induced cell-associated injury, biomarker release and transcriptional changes. Next-generation analogues exhibited an improved *in vitro* safety profile.

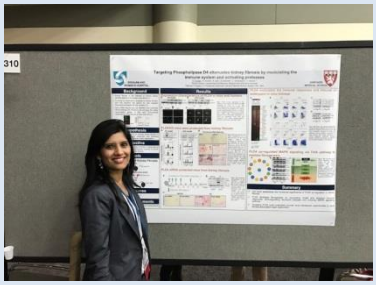


2nd Place: Wenyi Wang, The Rutgers Center for Computational & Integrative Biology, Camden, NJ Wenyi's poster was entitled *'Virtual gold nanoparticle library: simulation, modelling & experimental validation'*. In this study a novel computational approach was developed to quantify nanostructure diversity via various new nano-descriptors, enabling *in silico* prediction of nanotoxicity.

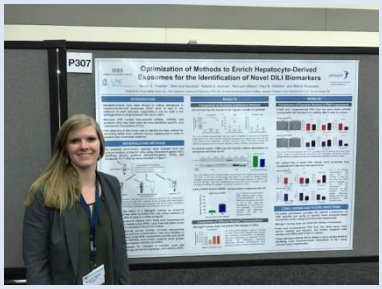


3rd Place: Tyler Beach, University of Rochester Medical Center, Rochester, NY
In his poster entitled *'Persistent & progressive lung injury is linked to DNA damage, cellular senescence & a pro-fibrotic epithelial response'*, Tyler demonstrated that following radiation exposure, ROS production & activity, as well as stimulation or suppression of immune responses, are possible targets for mitigation of fibrosis.

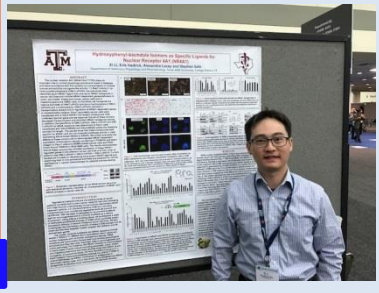
Postdoctoral Recipients



1st Place: Priyanka Trivedi, Harvard Medical School, Brigham & Women's Hospital, Boston, MA
Priyanka's winning poster was entitled *'Targeting phospholipase D4 attenuates kidney fibrosis by modulating the immune system & activating proteases'.* Here the regulation of immune responses, MAPK signalling and neutrophil elastase by PLD4 was demonstrated, highlighting PLD4 as an attractive drug target for treating fibrotic diseases.



2nd Place: Sarah Thacker, Institute for Drug Safety Sciences, UNC Eshelman School of Pharmacy, Chapel Hill, NC In Sarah's poster entitled *'Optimization of methods to enrich hepatocyte-derived exosomes for the identification of novel DILI biomarkers'* she described how utilization of fresh human hepatocytes combined with ultracentrifugation-based exosome enrichment is the optimal approach to isolate exosomes for novel DILI biomarker discovery.



3rd Place: Xi Li, Department of Veterinary Physiology & Pharmacology, Texas A&M University, College Station, Texas
In his poster entitled *'Hydroxyphenyl-bisindole isomers as specific ligands for nuclear receptor 4A1 (NR4A1)*, Xi evaluated a number of different DIM-CpPhOH analogs in transactivation assays and in the regulation of NR4A1-dependent genes. The novel analogs exhibited greater antagonist potency than the published analog DIM-CpPhOH.

Panel Discussion – Discovery Toxicologist Skills & Capabilities

The session started with Scott describing how for many modalities, early safety evaluation can be incorporated into pharmacology studies, where a collaborative mind-set and strong communication skills are key attributes. He also highlighted the need for a rigorous scientific approach and therefore the importance of a toxicologist 'asking tough questions'. Yvonne raised a point about the diversity of the approaches applied during early safety assessment, from evaluating physical-chemical property space to conducting specific assays to identify specific mechanistic concerns (e.g. mitotox).

Yvonne then spoke about a series of key discovery toxicology competencies including being scientifically curious, being competent to understand and establish technical models, being 'data capable' – ability to manipulate, analyse and integrate complex datasets and being a strong communicator and partner to the other drug discovery functions e.g DMPK. Kathila, who was providing a perspective from the large-molecule space, highlighted the need for the toxicologist to develop an in depth understanding the target biology. She also raised the importance of toxicologists adopting a translational perspective, appreciating and understanding potential risks to the target population and establishing a good relationship with clinicians.

When asked about the evolving nature of discovery toxicology as a discipline, the panel agreed that drug discovery innovation moves at pace and toxicologists must maintain and develop the skills to be at the forefront of this. Scott highlighted both the need and challenge for toxicologists to 'stay at the cutting edge', for example by continuously exploring and developing new models that can take toxicological assessment forward. Yvonne highlighted how high-throughput approaches and our ability to generate large datasets quickly have transformed drug discovery toxicology from a more practical science into a more analytical one. Kathila expanded on this point to propose that, despite our now extensive access to information and technology, there remains a need to focus on the key project safety questions and to understand the best approach to answer each question.

In summary, multi-modality drug discovery is evolving at a fast pace and discovery toxicology is a key component of this. Modern discovery toxicologists need to be dynamic, continuous learners who balance deep scientific and data processing expertise with a range of inter-personal skills that enable them to gain the most from the multi-disciplinary environment they operate in.

Contemporary Concepts in Toxicology

DDTSS Past President Yvonne Will introduced Contemporary Concepts in Toxicology (CCT) meetings to the group. These are SOT sponsored state-of-the-art meetings and webinars that provide an opportunity to increase the scientific impact of toxicology through. For further information follow the link http://www.toxicology.org/CCT. The DDTSS will aim to organise a CCT meeting in 2018.

DTSS Plans and Outreach

To increase exchange with our members/students/postdocs we have decided to create a Survey Monkey Poll to help prioritize ideas for forthcoming DDTSS events. In the next year or so we would like to organize a science symposium under the banner of the Contemporary Concepts in Toxicology initiative and would really like to hear what topics you would be interested in. These topics could also be selected for seminars, workshops, CE courses, reception discussion items, newsletter topics and more. The seminars and workshops organized last year were a huge success and we would like to continue to create even more opportunities in that area.

At the same time, we would like to introduce a MENTORING program. The idea would be to give our members the opportunity to connect with a mentor in Drug Discovery, which can be a tremendous asset. By introducing this mentoring program we would like to gauge what our mentees would specifically search for in a mentor meaning: discussions about work-life balance, job hunt, career development and other area's of interest. Again, we will use the Doodle Poll format to gather input.
We want to hear from YOU, give our members a bigger VOICE. So be sure to fill in the Survey monkey Poll and participate to the discussion.

Survey Monkey: https://www.surveymonkey.com/r/3D6BNJ8

2018 SOT San Antonio CE Session Sponsored by DDTSS

Lead Optimization Of Therapeutic Small Molecules: From Drug Target To Clinical Candidate Selection, Strategies And Decision Making

SOT 2018 San Antonio Workshop and Platform Sessions Sponsored by DDTSS

Cardiovascular Adverse Effects are Still Causing Late Attrition of Novel Therapeutics: Developing Solutions to Detect and Avoid Cardiovascular Toxicity in the Clinic (Workshop)

Mitochondria: Critical Targets in Pharmaceutical and Environmental Toxicity (Workshop)

Revising Biology: Using Genomic and Epigenomic Editing to Gain Novel Insight into the Molecular Mechanisms of Toxic Exposure Effects and Susceptibility (Platform)

List of Past Presidents

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 San Antonio in 2018!

DTTS reception Tuesday March 13th