Newsletter:
Fall 2016

Drug Discovery Toxicology Specialty Section (DDTSS)

President's Message

DDTSS President Ray Kemper

It is my very great pleasure and privilege to be President of the DDTSS for the 2016-2017 term. I have the good fortune to follow in the footsteps of a series of exceptional leaders in Discovery toxicology, most recently Past President Dan Kemp, who have grown the DDTSS into the outstanding organization it is today. DDTSS had a very strong year in 2015-2016. The current membership stands at 367 members, down slightly from 379 in 2015. In the previous year, DDTSS presented 2 webinars on topics of interest to drug discovery toxicologists: *"Advanced cell systems for toxicological profiling: 3D models, microtissues and microphysiologcal systems"*, presented by Matt Wagoner from AstraZeneca and "*Use of different physico-chemical properties, DMPK, and* in vitro *toxicity parameters for assessing risk of hepatotoxicity*", given by Will Proctor from Genentech. DDTSS was also quite active at the 2016 SOT Annual Meeting in New Orleans, holding a student/postdoctoral fellow luncheon, hosting the Specialty Section reception, which included a lively panel discussion led by Pete Newham (VP-Elect, AstraZeneca) entitled "*Can micro-physiological systems provide a more predictive tool for safety testing?"* and of course awarding the Emil Pfitzer travel award for outstanding student/postdoctoral posters (see page 5 for this year's winners).

These successes provide a strong foundation upon which to build on in the coming year, but also set a very high bar for us to live up to. In 2016-2017, DDTSS will continue the impactful webinar series started in 2014, with 2-3 such presentations planned for the coming term. Planned topics include "**Safety assessment in a world of expanding immuno-oncology approaches & modalities**" (Dec 7th – mark your calendar!) and "**The therapeutic use of Precise Genome Editing (PGE), safety assessment will be key to its success**" (Date - TBD, See special guest contribution by Mick Fellows on page 3).

A primary focus for DDTSS in 2016-2017 will be increasing student and postdoctoral engagement in Discovery Toxicology and DDTSS. In order for the sub-discipline of Discovery Toxicology to thrive and remain vibrant, we need to ensure a steady flow of new talent into the field. In the coming year, DDTSS will implement a variety of approaches to stimulate student and postdoctoral interest in Discovery toxicology, including targeted recruitment at the Annual Meeting in Baltimore, University Outreach visits and an informational webinar discussing the various aspects and potential career paths in Drug Discovery Toxicology. I would like to take this opportunity to call on the DTSS membership to provide additional thoughts on how we can increase engagement of young scientists in our discipline. Send us your ideas!

I look forward to seeing you all at the 56th Annual Society of Toxicology Meeting in Baltimore MD!

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Announcements

New Specialty Section – Computational Toxicology

A new ***Computational Toxicology Specialty Section*** is being proposed for 2017. Computational techniques are part of our stock-in-trade as drug discovery scientists and this specialty section should be of interest to many DDTSS members. This Specialty Section is distinct from the Biological Modeling Specialty Section, and has the following objectives:

1. To serve as the focal point for interaction of members of the Society of Toxicology interested in Computational Toxicology.
2. To enhance the understanding and acceptance of computational toxicology within the Society of Toxicology and in the public domain.
3. To foster the evolution of scientifically relevant approaches to and interpretation of toxicological aspects unique to Computational Toxicology.
4. To develop, propose, and conduct a variety of cutting-edge programs and educational activities that emphasize the latest developments and issues in Computational Toxicology.
5. To act as a resource to the Society in the area of Computational Toxicology.

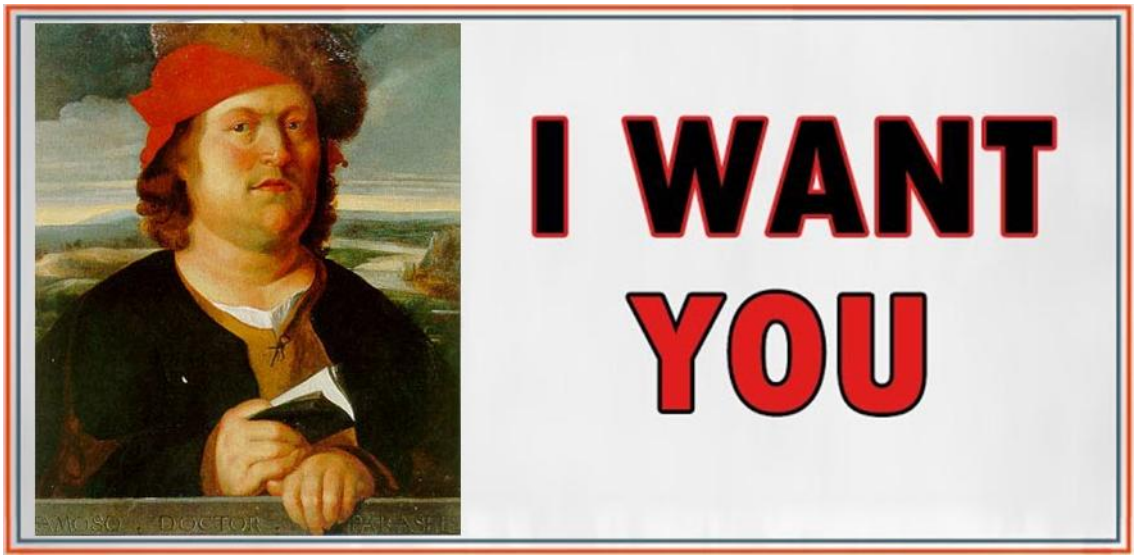
If you are interested in becoming a member of this new specialty section, please contact Lisa Beilke: Lisa D. Beilke (lisa@toxsolutionsinc.com).

Awareness in Regulatory Toxicology working group

How do toxicology graduate students and postdoctoral scholars equip themselves for careers in regulatory toxicology?

This is an important question both for those seeking jobs and for those who are hiring. Many students and postdoctoral scholars are not familiar with opportunities that exist in the field of regulatory toxicology or how they could enhance their skills in this field of toxicology. The Awareness in Regulatory Toxicology (ART) Work Group, a group within the SOT Graduate Education Subcommittee, was recently formed to raise awareness and encourage knowledge about the field of regulatory toxicology among trainees. The ART Work Group is composed of a diverse group of volunteers who bring experience from academia, government and industry. One of the first tasks for the ART Work Group is to compile a list of resources that students and postdoctoral scholars can access to seek more information about regulatory toxicology and training opportunities within the field. The ART Work Group will be sharing the list of resources with trainees during the SOT 2017 meeting. If you would like to learn more about the goals and activities of the ART Work Group, or if you have resources to share, please contact Angela Lynch alynch@toxplusconsulting.com or Betty Eidemiller at bettye@toxicology.org.

Emil A. Pfitzer Travel Award



…To submit your outstanding research in the 2017 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 Baltimore. 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 no later than January 30, 2017. Abstracts should be submitted to Jonathan Phillips (jonathan_phillips@vrtx.com).

Special Guest Contribution

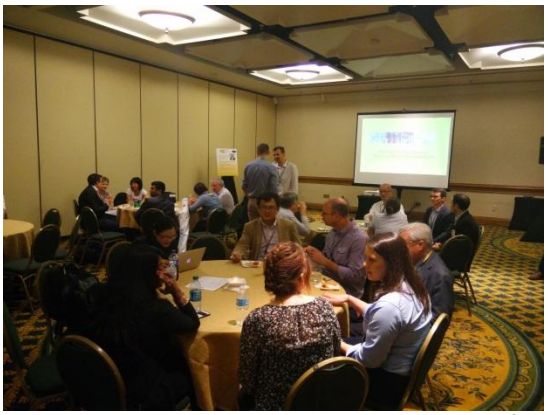
The therapeutic use of Precise Genome Editing (PGE), safety assessment will be key to its success –Contributed by Mick Fellows, Principal Scientist, AstraZeneca

Gene therapy has been around for decades and whilst there have been some recent successes, e.g. the approval of Glybera, it has perhaps not reached its full potential. This has at least in part been because of safety concerns seen during the first clinical trials. The emergence of technologies for precise genome editing (PGE) and in particular the therapeutic use of CRISPR/Cas9 has the potential to revolutionize gene therapy, with hitherto 'undruggable' targets becoming accessible to correction at the genetic level. However, just as the challenges encountered in some trials for gene therapy has hindered its progression, there is an urgent need to ensure the correct pre-clinical safety assessment is made before widespread use of PGE in man. Of course *ex vivo* gene editing is already in the clinic with Sangamo leading the use of zinc finger technologies to edit CCR5 in HIV patient derived T-cells. This therapy has reached Phase II clinical trials. Furthermore, Juno and Sichuan University are leading the race to treat cancer patients with CRISPR/Cas 9 modified T-cells, with lung cancer patients being recruited at the time of writing for the Chinese trial.

Whilst the safety assessment of *ex vivo* gene editing is not trivial, improved and unbiased next generation sequencing for off target analysis in the edited cells and the use of validated methodologies to ensure modified cells do not have an inherent toxic or tumorigenic risk has meant regulatory authorities can be satisfied with pre-clinical safety. Or at least be satisfied that PGE is not in itself increasing the already known toxicity associated with T-cell therapies. However, the real challenge is to provide sufficient pre-clinical safety data to demonstrate that PGE is safe to use systemically, thus vastly increasing the number of potential disease targets.

The systemic use of PGE inevitably poses the tricky question of just how precise is precise genome editing? A great quote from George Church (one of the CRISPR/Cas9 pioneers) suggested that 'in the best case scenario' CRISPR-Cas9 is capable of less than 1 error in 300 trillion base pairs, given that the human genome is only 3 billion base pairs, that equates to one off-target hit per 100,000 cells. To add an even greater perspective to this it should be realized that each human cell is subjected to around 20,000 endogenous DNA lesions per day. If this could be definitively proven in man, CRISPR/Cas9 off-target editing could be considered to be the biological equivalent to the active ingredient in a homeopathic remedy! Unfortunately, the simple answer is we do not currently know whether PGE is really that exact. Whilst new and more precise sequencing technologies are available, it is still a real challenge to be able to sequence down to the level required for complete reassurance that PGE cannot have an adverse effect when systemically dosed. In essence the very precision makes detection difficult, but cognizance does still need to be taken that any off-target edit in an oncogene or tumor suppressor gene could have serious consequences. The additional challenge with preclinical assessment of PGE is of course that animal models will inevitably have different potential off-target DNA sequences than man. Then there is the additional consideration of human SNP's if PGE is to be used in a wide patient population. This may all sound a little pessimistic, but in reality the way forward will be to ensure the safety concerns of PGE are worked through now before issues are seen in the clinic. Fortunately regulators are willing to take a pragmatic approach to the use of new therapies that will make real contributions to the treatment of life threatening conditions. Furthermore, the really good news is some of the brightest preclinical and clinical research scientists are working on new methodologies and safety testing paradigms to ensure the therapeutic use of PGE will be a success.

Highlights of the 2016 DDTSS Reception



At the annual reception, the specialty section awarded six promising young scientists a share of the annual Emil A. Pfitzer prize.

2016 SOT Meeting Poster Awards

Graduate Student Winners

1st Place: Bahrat Bushan

Bahrat's first place poster was titled "Dual Role of Epidermal Growth Factor Receptor (EGFR) Signaling in Acetaminophen induced Liver Injury and Regeneration." In this work, he identifies a novel role of EGFR both in development of APAP injury and in stimulation of subsequent compensatory liver regeneration after APAP overdose.

2nd Place: Rosa Chan

Rosa's poster was titled "BDDCS Classification Does Not Support BSEP Inhibition As Being DILI Causative." She discovered that there is physicochemical differentiation between drugs with high and low risk for adverse drug reactions. For example, anti-epileptics drugs that cause drug hypersensitivity reactions have distinct features of being extensively metabolized, highly permeable, poorly soluble while nonreactive compounds were not extensively metabolized, poorly permeable, and highly soluble.

3rd Place: Monica Langley

Monica's poster was titled "Prokineticin 2 Plays a Role in Altered Neurogenesis and Non-Motor Deficits in PD Models." In this poster, she presents novel findings suggesting that the development of non-motor symptoms in MitoPark mice coincides with impaired adult neurogenesis, and that PK2 may play a compensatory role in regulating neurogenesis by promoting proliferation and differentiation of neural stem cells.

Postdoctoral Winners

1st Place: Dr. Priyanka Trivedi, Harvard Medical School, Brigham & Women's Hospital, Boston, MA

Dr. Trivedi's first place poster was titled "Mechanistic role of phospholipase D4 in regulating kidney fibrosis." Her research showed that PLD4$^{-/-}$ mice have reduced expression of the *serpina1d* gene at baseline, which encodes the alpha-1 antitrypsin (AAT). Sustained activation of proteases due to absence of AAT in PLD4$^{-/-}$ mice led to an efficient degradation of collagen rescuing these mice from scar tissue formation in the kidney, suggesting PLD4 has the potential to be a novel therapeutic strategy for kidney fibrosis.

2nd Place: Dr. Sridhar Jaligama, University of Tennessee Health Science Center, Le Bonheur Children's Foundation Research Institute, Memphis, TN

Dr. Jaligama's poster was titled "Regulatory T cells and IL10 Suppress Pulmonary Host Defense during Early-Life Exposure to Radical Containing Ultrafine Particulate Matter." He describes how particulate matter induced regulatory T cells and their effector cytokine, IL 10, to suppress adaptive T cell responses. These factors lead to increased influenza severity in infected neonatal mice, suggesting a mechanistic role for particulate matter contributing to more severe bouts of flu.

3rd Place, Dr. Hemant Chavan, University of Kansas Medical Center, Kansas City, KS

Dr. Chavan's poster was titled "Mitochondrial function links non-linear dose response of arsenite to growth and survival in human and mouse primary hepatocytes." His work suggests a nonlinear dose-response characteristic of arsenite in primary hepatocytes with low-dose arsenite, promoting a transient increases in mitochondrial function that act as transducers of arsenite induced hormesis.

Following announcement of the award winners, a provocative panel discussion on where, when and how microphysiological systems, otherwise known as organs-on-a-chip, was presented and discussed.

Panel discussion: Can microphysiological systems provide a more predictive tool for efficacy and safety testing?

Pete Newham gave a short presentation on the promise of microphysiological systems in drug discovery and safety assessment.

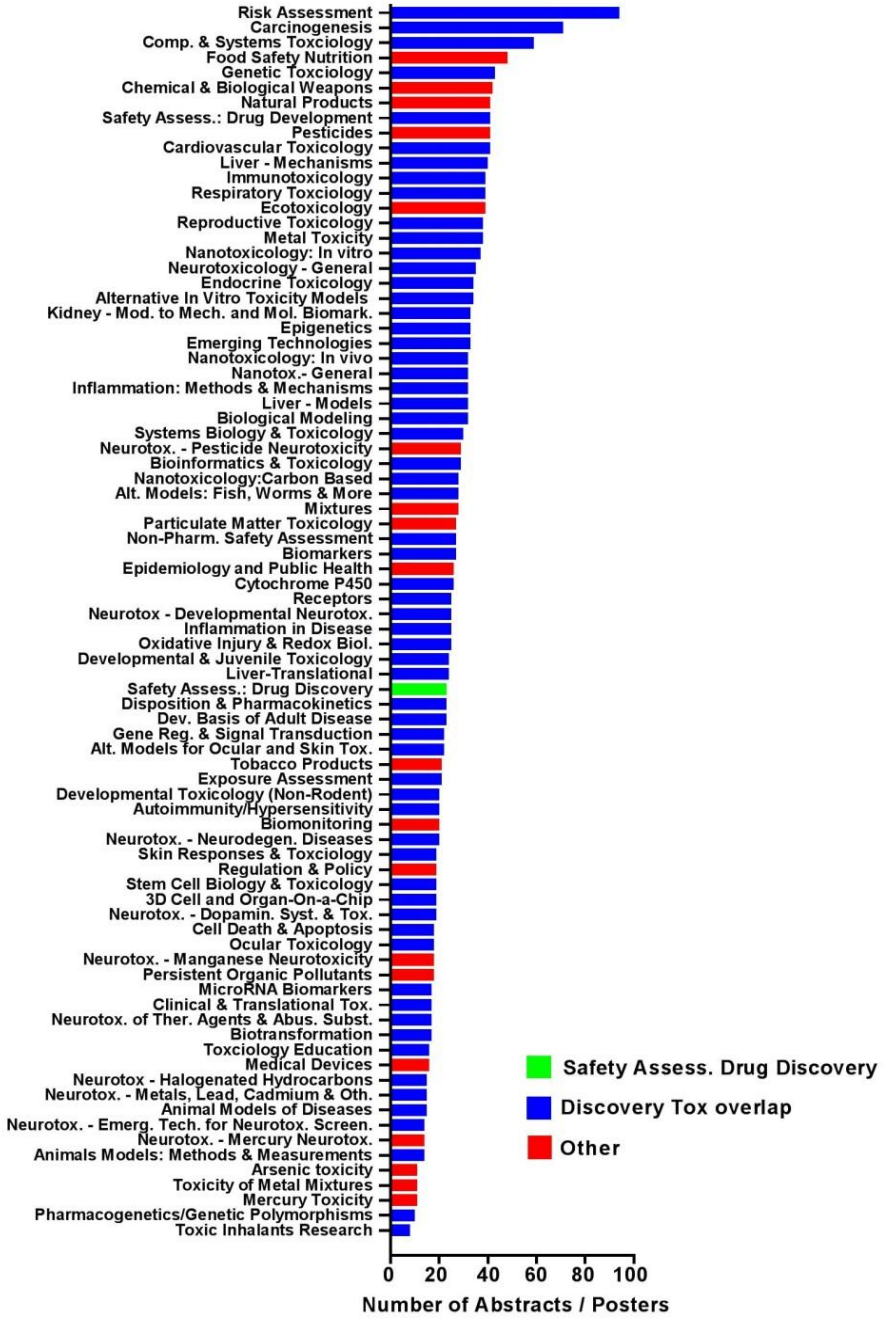
What are microphysiological systems? "3-dimensional cell models" or tissue organoids based on primary or appropriately differentiated stem cells are showing much promise in more accurately capturing cell and tissue phenotype when compared to more traditional monolayer culture systems. However the inclusion of physiological strain (e.g. stretching) and fluid flow dynamics have been also been demonstrated to regulate cell phenotype stability in culture, adding an additional dimension to model fidelity. Finally, advances in materials technology are permitting prototypic connected model organ systems or so called microphysiological "body-on-a-chip" systems to be developed. Together these innovations offer opportunities to better understand the behavior of cell function in health and disease and improve new medicines evaluation by transforming translational research to become more relevant to the clinic and less reliant on traditional animal model-based studies of efficacy and safety.

In medicines research a key goal is to understand the relationship, or tipping point, between benefit and adverse effect in the same (human model) system. In order to achieve this, humanized microphysiological systems that capture both healthy and disease states could become of critical importance.

Pete Newham, acknowledged Dr. Lorna Ewart for material used in the microphysiological systems presentation and posed the reception with three questions to explore: Can MPS systems revolutionize toxicology? What are the priority issues to address? How can they be addressed? Kenneth Brower (Qualyst), and J. Lowery Curley, AxoSim Technologies facilitated the debate of these questions and reception participants engaged in active discussion on the critical evidence required to assess the utility of microphysiological systems. There was a real desire in the room to develop greater understanding of the science of microphysiological systems, but also the real world issues of applying this science in the toxicological arena. It was agreed that microphysiological system-focused SOT2017 symposium proposals would be developed and sponsored by the DDTSS. It is gratifying to report that microphysiological systems symposia are featured in the 2017 SOT program.

(Left to right) Drs. Peter Newham, AstraZeneca, Kenneth Brower (Qualyst), and J. Lowery Curley, AxoSim Technologies, provide their perspectives on use of microphysiological systems in a dialog with the DDTSS.

2016 SOT Annual Meeting Poster Review



2016 SOT Annual Meeting Poster Review contd.

A diverse range of excellent posters were expertly presented at the Annual Meeting again this year. It is encouraging the see so many in areas which are applicable to, and have overlap with, discovery toxicology (see blue bars above). An area of future focus for the DDTSS will be to increase the number and breadth of poster contributions to the 'Safety Assessment Drug Discovery' poster session (green bar above; 22 posters). Increased sharing of applied discovery toxicology examples is a great way of enhancing our collective knowledge and developing our field in general.

List of Past Presidents

Dan Kemp	**2015**
Andrew Olharski	**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 2017!