

Newsletter: 2019

Drug Discovery Toxicology Specialty Section (DDTSS)

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Welcome to the Drug Discovery Toxicology Specialty Section newsletter!

As the drug discovery community grows, we have many opportunities to interact and engage across multiple disciplines since the founding of the section in 2005. We are constantly seeking to bring the community together, and more specifically, to highlight issues and resolutions, as well as new technologies. For example, we have held two consecutive competitions for the "Paper of the Year awards; we are currently soliciting submissions for the third in Anaheim. The winning lead author was Hasane Ratni, and co-author Stefan Kustermann presented their work to an audience of DDTSS members at our 2019 annual reception in Baltimore, MD ([Page 4](#)). We also continue to sponsor webinars that highlight exciting new areas of research, and are constantly looking for new suggestions, so please reach out with suggestions or if you wish to present!



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 Baltimore, we hosted our student/post-doctoral fellow mentoring luncheon ([Page 5](#)) in addition to acknowledging outstanding student/post-doc posters ([Page 6](#)) by presenting Emil Pfitzer 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. We have also hosted 2 webinars, one on "Lead Optimization Drug Safety Strategies for Small Molecule" and one on "In Vitro Platforms to Predict CNS Toxicity". We are looking for ideas to continue outreach to our students and post-doctoral members.

As we move through 2020 we also plan to host more DDTSS sponsored webinars. The first will focus on nonclinical strategies for gene therapy. We are still planning others for later in 2020 based on feedback from the recent survey, so there is always a chance for members to get involved in sharing their experiences with the larger community!

Personally, I've been involved in the DDTSS leadership committee since 2016; I'm so proud to be a part of this community. I'm amazed at the amount of time and energy devoted to furthering the drug discovery field within this group. I encourage you all to continue your involvement with the section, in any way you can, and provide feedback on any ideas you may have or ways we can continue to grow and improve.

Looking forward to seeing you at the SOT annual meeting in Anaheim, CA in March 2020!



It is no secret that social media has somehow caught up with traditional media. That is why, DDTSS now in on LinkedIn to provide one place that scientists, scholars, and researchers privilege for their communication.

Follow the DDTSS LinkedIn page and invite your peers to join. You can now connect with peers and the general public, share ideas, discuss and communicate research. This is a fantastic way to increase your discoverability.

How to gain from this essential social platform?

Whether you're an author, editor, reviewer, or early career researcher, boost your knowledge and help your work reach a wider audience with your involvement.

Get the activity going: Pose questions or respond to queries from other members in groups to position yourself as a thought leader in your respective field.

Open opportunities for collaboration: Simply want to get your voice heard by a wider audience, use this LinkedIn as a channel to reach out to people with whom it's unlikely you'd get face time.

Start a conversation: Introduce your research and ideas to this LinkedIn network, you are personally helping evolve the production and dissemination of scientific knowledge as we know it.

Join DDTSS linkedIn page: <https://www.linkedin.com/company/30646653>

Winner – Stefan Kustermann
Discovery of Risdiplam, a
Selective Survival of Motor
Neuron-2 (SMN2) Gene Splicing
Modifier for the Treatment of
Spinal Muscular Atrophy (SMA)
J. Med. Chem., 2018, 6501-6517

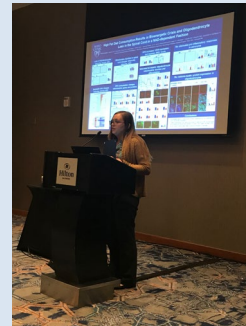
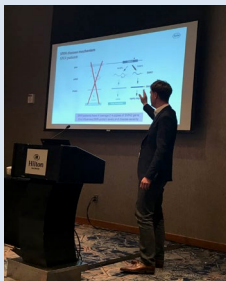
Stefan started off describing the significance of “survival of motor neuron” (SMN) and the requirement of SMN for survival of spinal motor neurons. Reduced SMN protein is responsible for SMA disease, in which loss of SMN results in loss of motor neurons and progressive muscle atrophy. The hypothesis of treating the disease is to modify SMN2 splicing to increase SMN2 protein and slow or halt disease progression.

Publications have shown that small molecule SMN2 splice modifiers were feasible and in a transgenic mouse model of the disease could affect disease progression and increase longevity. The team, lead by Roche and in collaboration with the SMA Foundation and PTC Therapeutics, discovered risdiplam, an oral, systemically distributed investigational small molecule for the development of SMA. They demonstrated that risdiplam increased *SMN2* mRNA and SMN protein levels in fibroblasts. Additionally, risdiplam treatment increased lifespan and body weight in a transgenic mouse model of SMA. The specificity of splice modification was one potential safety concern for risdiplam, therefore they generated data demonstrating specificity of risdiplam for *SMN2*-preRNA. Stefan described the journey to discover risdiplam, and the lead optimization strategies the team undertook, including lowering basicity, enhancing potency, and reducing/eliminating metabolites with potential off-target effects. He further discussed the findings that risdiplam distributed to key tissues and organs that could be affected in SMA; further, they demonstrated that concentrations could be achieved in key target organs such as brain and muscle. Lastly, they showed that SMN in the periphery could be used as a surrogate or biomarker. Much of this work contributing to the discovery of risdiplam has been published or will be published in future. For reference please see: J. Med. Chem. 2018, in press; Nature Com. 2017; J. Med. Chem. 2017, 60, 4444; J. Med. Chem. 2016, 59, 6086; Hum. Mol. Gen. 2016, 25, 1885; Hum. Mol. Gen. 2016, 25, 964; PLoS ONE 2015, 10 (10); Science, 2014, 345, 68.



2018 Drug Discovery Toxicology Paper of
the Year Award

Marie Lemper (Secretary) presented the award



Highlights of the DDTSS reception

At our annual DDTSS reception, which was attended by approximately seventy scientists, awards for paper of the year, and student and post-doc poster awards were handed out. Presentations of the paper of the year and post-doc winner were made. Please just us again in Anaheim!!!



DDTSS student/post-doctoral fellow mentoring luncheon

The DDTSS hosted another successful mentoring event over lunch during the 2019 SOT Annual Meeting in Baltimore, attended by mentees and DDTSS mentors with a wide range of backgrounds, expertise, and experience levels. The informal setting allowed an interactive roundtable discussion between participants, where the main topics discussed ranged from types of industry roles for toxicologists (e.g. discovery and preclinical safety, clinical trials, regulatory, business etc.), range of qualifications and skills for each type of position, strategic approaches to career and talent development and rewarding aspects of working as a toxicologist in industry. We will host a mentoring lunch again at the 2020 SOT annual meeting in Anaheim, don't miss the opportunity to join us!

From the Attendees...

"The DDTSS mentoring lunch was an excellent opportunity to engage with individuals at varying levels in their career working in different sectors across the globe! The panel discussion permitted for an open dialogue between students and mentees and provided me with a better understanding of less traditional opportunities beyond graduate school!"

Brianna Rivera
3rd year doctoral candidate at
Oregon State University

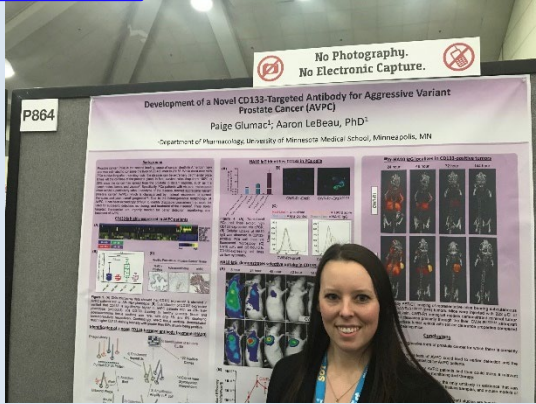
"I really enjoyed the DDTSS Mentoring Lunch event in Baltimore. It was great to hear from discovery toxicology and safety assessment experts from various companies, and their career paths prior to their current roles. This experience has definitely encouraged my interest in drug discovery tox!"

Yvonne Chang
5th year doctoral candidate at
Oregon State University

"I found it really useful to be able to network in a less formal setting that did not require me to "stalk" people at SOT in order to ask these types of questions. In grad school, no one explains the details of different career options or what extra skill sets you may need to focus on. It was certainly helpful to interact with everyone, and it's helpful to know that the mentors were open to being contacted with future questions."

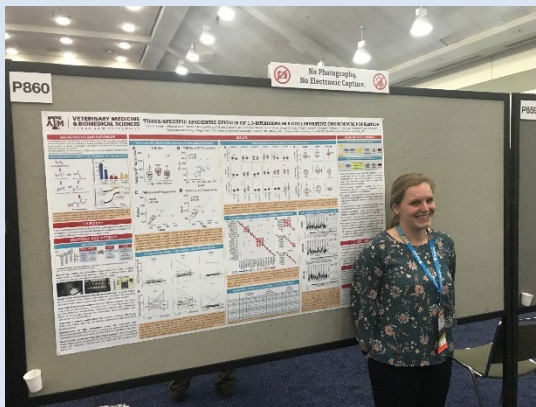
Monica Langley, postdoctoral research
fellow at Mayo Clinic

Graduate student Winners



1st Place: Paige Glumac, Department of Pharmacology, University of Minnesota Medical School, Minneapolis, MN.

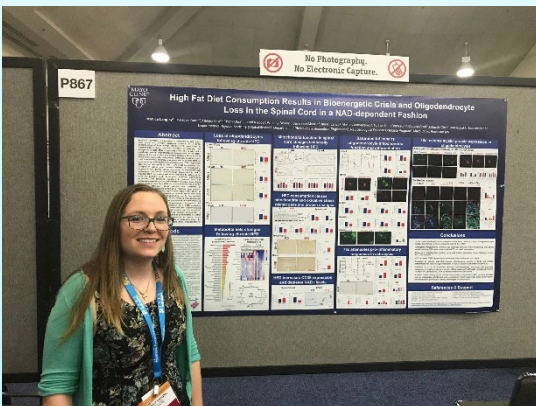
Paige's winning poster was entitled '*Development of a Novel CD133-Targeted Antibody for More Selective Monitoring and Treatment of Aggressive Variant Prostate Cancer*'.



2nd Place: Lauren Lewis, Texas A&M University, College Station, TX.

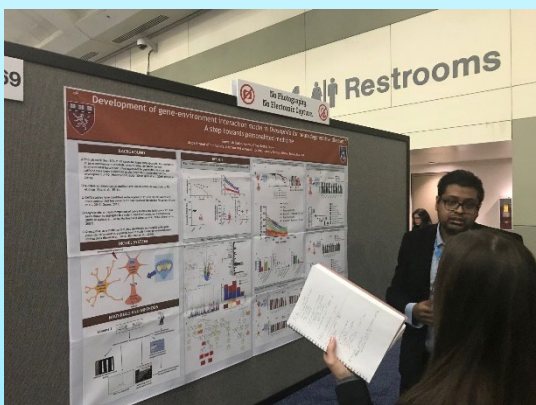
Lauren's poster was entitled '*Tissue-specific epigenetic effects of 1,3-butadiene in a Collaborative Cross mouse population*'. He showed that Kv1.3 is highly induced in animal models of PD & post-mortem brains. Kv1.3 inhibitors exhibit anti-inflammatory effects *in vitro* & *in vivo*.

Postdoctoral Winners



1st Place: Monica Langley, Mayo Clinic, Rochester, MN.

Monica's winning poster was entitled '*High Fat Diet Consumption Results in Bioenergetic Crisis and Oligodendrocyte Loss in the Spinal Cord in a NAD-dependent Fashion*'.



2nd Place: Souvarish Sarkar, Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Sarkar's poster was entitled '*Development of gene-environment interaction model in *Drosophila* for neurodegenerative disease: A step towards personalized medicine*'.



W•E•B•I•N•A•R

DDTSS is pleased to announce
our upcoming winter webinar
“**Nonclinical Safety Strategies
for Gene Therapy.**”

Organized by Marie Lemper, PharmD,
PhD, DABT, ERT, UCB Belgium and Zoe
Zhong, PhD DABT, Genentech

Tuesday Feb 25th
11-12 am
Eastern Daylight Time
(New York, GMT-05:00)

The panelists are Drs. **Timothy Maclachlan**, Executive Director, PCS TA Head, New Indications Discovery Unit, Novartis and **Kelly Flagella**, Executive Director, Toxicology, Ultragenix. The intended audience is scientists across all career stages interested in deepening their knowledge of gene therapy and drug discovery.

Stay Tuned—More to Come!!!

**CTSS
Webinar**
(Computational
Toxicology
Specialty
Section)

“**US FDA Experience in the Regulatory Application
of (Q)SAR Modeling**”

Organized by Catrin Hasselgren, PhD, Genetech,
and David Szabo, PhD, DABT, PPG Industries

Wednesday, February 5th
11-12 am

Eastern Daylight Time (New York, GMT-05:00)

The panelist is Naomi Kruhlak, FDA, CDER. For more information, please contact Catrin Hasselgren (hasselgren.catrin@gene.com).



.....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 this 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 2020 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, 2019. Papers for consideration can be submitted at any time before the **Friday February 7th 2020 deadline** to Dinah Misner (dmisner@aligos.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 for...

The 2020 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 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 Dinah Misner (dmisner@aligos.com) no later than **Friday 7th February 2020**.



DDTSS student/post-doctoral fellow mentoring luncheon SOT 2020 Anaheim

We will be holding another mentoring luncheon for students and post-docs at the 2020 SOT meeting in Anaheim on Tuesday, March 17th. 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 2020 Anaheim Workshops/Symposium sponsored by DDTSS

- *“Using Human Genetics to Aid Safety Assessment of Therapeutics”*
- *“In Vitro Microphysiological Systems: Developing Tools to Evaluate Immunotoxicity of Drug Candidates”*
- *“Chemical Probes in Toxicology: From Defining Exposures to Identifying Novel Toxicity and Druggable Targets”*
- *“Organ to Silicon Chip: Emerging In Vitro and In Silico Tools for Evaluation of Cardiotoxicity”*
- *“Express Yourself (or Not...): The Nonclinical Safety of Oligonucleotide Therapeutics”*
- *“Applications of Innovative Analytical Platforms to Improve De-Risking Therapeutic Compounds and Related Efficacy/Safety Biomarker Selections”*

List of Past Presidents

Howard Mellor	2018
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 Anaheim in 2020!
DDTSS reception Tuesday March 17th