Newsletter: Winter 2024

Drug Discovery Toxicology Specialty Section (DDTSS)

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2024–2025 Officers

See you in Orlando in 2025!

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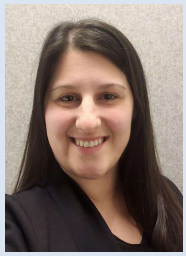

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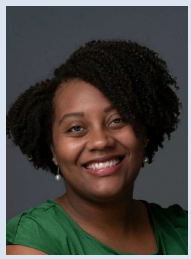


Graduate Student Representative
Zakiyah Henry
zakiyah.henry@nih.gov

See you in Orlando in 2025!

President's Message

Satoko Kiyota

In April of 2019, the 12th century Parisian landmark, Notre Dame Cathedral, was ruined by devastating fire, smoke and water damage. While French President Emmanuel Macron vowed to complete restoration within 5 years, experts said that it could take decades to complete the project. In 2024, reopening to the public is set for December (note that work will continue on the grounds around the cathedral until 2028). I have no expertise in this project; still, it is clear to me that human-machine collaboration was essential to achieve this ambitious and bold timeline.

So, where are we now with human-machine collaboration in Drug Discovery Toxicology? There are great examples where computational approaches have increased efficiency in discovery processes (e.g., hERG, phospholipidosis, mutagenicity predictions for small molecule development). However, there are still tremendous opportunities to transform our approaches to improve and accelerate the drug development pipeline. In my opinion, ***the most pressing need is to reduce the Time to Insight - e.g., Target Safety Assessment, hypothesis generation for mechanistic investigation, Omics data analysis, and use of New Approach Methodologies (NAMs).*** Such approaches can accelerate Early Drug Discovery through the selection of a safer target with a more appropriate modality for target indications, and by leveraging data from more relevant systems in risk assessment in a more meaningful way.

Computational Toxicology has a tremendous role to build the future of Toxicology. Does this mean that all Discovery Toxicologists should be savvy in Computational Science? The answer should be "No" - it is impossible to be an expert at everything!

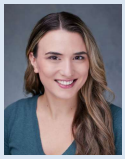
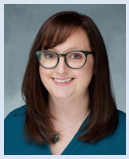
Similar to any other projects, the road to success is paved with collaboration - our ability to communicate a clear path, key priorities, and primary objectives with Computational Scientists is required more than ever. Also, each of us should get familiarized with computational thinking and advantages and limitations of machines.

In any situation, ***a well-trained toxicologist with good judgement will always be invaluable to risk assessment and the health of their respective institution*** (highly recommend reading the President's Message by Jon Maher in DDTSS Newsletter 2023). Continuing education and training and experience through actual drug development projects are the best and possibly only way to develop and polish good judgement.

Finally, in this year's DDTSS Newsletter, we have a special issue, which provides an expert opinion on antibody drug conjugate (ADC) development. An additional special edition focuses are on career and professional development for graduate students. We sincerely appreciate the authors for their contribution!

I hope to see you all in Orlando for the SOT Annual Meeting! ***Please make sure to join us for the in-person reception at the Hyatt Regency Orlando on Tuesday, March 18*** - it is the best way to explore new and cool ideas and expand your network!

Special Edition 1:
Platform Approach for the Development of ADCs


Sarah Carratt, Haley Neff-LaFord, Christina de Zafra
Drug Safety Research & Development, Pfizer

Antibody-drug conjugates (ADCs) have been studied as treatments for cancer for nearly 3 decades. Since the first US FDA approval of an ADC (gemtuzumab ozogamicin) in 2000, 12 additional molecules have been marketed and hundreds are in various stages of development in oncology as well as non-oncology indications.

ADCs are designed to reduce systemic toxicity by delivering potent payloads (drug) via a tumor target-specific antibody. The targeting antibody is connected to the payload by a linker, with the linker-payload portion of the ADC often being kept constant while the antibody portion is varied to enable targeting to different molecular markers of disease.

When assessing the toxicity of ADCs, test article-related changes can largely be categorized as antigen-dependent and antigen-independent. Antigen-dependent findings are test article-related changes in tissues expressing the target antigen and/or changes that were more pronounced with targeted ADCs than with the payload alone. Antigen-independent findings occur with, and are driven by, the linker-payload. ADC toxicity is primarily attributable to the payload portion of the molecule (e.g., Saber and Leighton, 2015; Nguyen et al., 2023; Neff-LaFord and Carratt et al., 2024).

Because ADC toxicity is largely driven by the linker-payload, it has been proposed that a "platform" approach could be used in the development of future ADCs. This means that studies with non-binding ADCs and/or the small molecule payload alone could be used to establish/characterize the toxicity for all ADCs sharing that same linker-payload, reducing the need for repeated toxicology studies with each ADC iteration within a platform (e.g., ADCs with different targeting antibodies).

A recent publication by Neff-LaFord and Carratt et al. on vedotin ADCs supports the use of a "platform" approach, recommending leveraging common payload toxicology studies and non-binding ADC evaluations to significantly reduce the number of animals needed to assess the safety of each ADC. This paper synthesizes two decades of preclinical safety data for 14 vedotin (vc-MMAE) ADCs to show that most nonclinical toxicities were antigen-independent, common across all ADCs, and included hematologic, lymphoid, and reproductive toxicity related to the pharmacology of the payload, MMAE. The authors found that tissue expression of the targeted antigen of an ADC rarely correlated with dose limiting toxicities (DLT); with only 2 of the 14 ADCs having antigen-dependent skin DLTs. Further, studies longer than one month in duration detected the same or fewer toxicities than one-month studies and had no additional findings that affected human risk assessment.

The timeline from target discovery to first-in-human trials is long, even for platforms and drug classes with well-established toxicity profiles. Additionally, the preclinical studies required by regulatory agencies have extensive costs in terms of animal use, time, and money. The platform approach detailed in the Neff-LaFord and Carratt et al. paper is likely not unique to ADC therapeutics. The comprehensive dataset provided sets a foundation of principles that should be considered for ADCs with linker-payloads other than vedotin. Further, other classes of molecules, such as CD3 bispecific antibodies and CRISPR/Cas9 therapies, may be able to leverage a comparable strategy to streamline toxicology programs and accelerate the pace of drug development, thereby achieving a reduction in animal use and delivering medicines to patients more quickly.

Special Edition 2:
Journey of a Graduate Student

Zakiyah Henry, PhD

Past - PhD Candidate in Toxicology at Rutgers University

Current - Postdoctoral Fellow at NIEHS

Hello! My name is Zakiyah Henry and I have served as the Graduate Student Representative for the Drug Discovery in Toxicology Specialty Section (DDTSS) for approximately one year and a half! This has truly been a rewarding experience to network and engage various individuals at different stages in industry while being the voice for graduate students. By the author descriptor, you will notice that I am no longer a graduate student as I recently received my PhD in Toxicology from Rutgers University in New Jersey (August 2024). I am now a Postdoctoral Fellow in the Division of Translational Toxicology (DTT) - Systems Tox Branch at the National Institute of Environmental Health Sciences (NIEHS). Although no longer a graduate student, I still have much insight to share with prospective graduate students. Let me start by sharing a bit about my journey!

I am a proud alum of the illustrious Winston-Salem State University, a historically black university (HBCU) in North Carolina where I majored in biology and obtained minors in chemistry and physics. WSSU is a relatively small liberal arts school that although did not offer a wide array of science majors, the training I received as a student and trainee was phenomenal! Like many other HBCUs, the environment at WSSU was family-oriented with a central focus on student success. WSSU gave me a solid foundation to build upon and I would not be the scholar or trainee that I am if it had not been for the amazing mentorship and guidance received during my time there. While at WSSU, I was engaged in two different NIH-NIGMS funded training programs, the RISE and MARC U*STAR programs. Through these programs, I received laboratory experience with my undergraduate PI, attended conferences, participated in various workshops, and completed internships at various universities.

One of these internships occurred at Rutgers University. My experience at Rutgers changed my life. The Summer Undergraduate Research Fellowship (SURF) program provided me additional exposure to the field of Toxicology as I only had one prior experience at a different internship at Clemson University. During my summer at Rutgers, I was able to fully submerge myself in Toxicology research while also learning more about the graduate program through talking to the students, staff, and faculty. I found the Joint Graduate Program in Toxicology (JGPT) to be a supportive and nurturing program, that challenged and thoroughly prepared every student matriculating through, to go out and be successful in whatever field they chose. This experience finalized my decision to not only pursue a PhD but to pursue one in the field of Toxicology.

I can honestly say that, life as a graduate student was great! Sure there were challenges along the way, but overall, I enjoyed my time at Rutgers. The Rutgers Association of Toxicology Students (RATS), the toxicology graduate student organization of the JGPT, played a huge role in my enjoyment of graduate life. I believe community is vital for survival and the RATS helped to foster a supportive, fun, and loving community for all graduate students within the JGPT and for those in other programs. Communities like these are ones I encourage upcoming graduate students to find, foster, and/or create. I am originally from NC, so finding a “home away from home” in NJ, made maneuvering graduate school that much better. I also encourage prospective graduate students to not be afraid to leave home and pursue their higher education in a different geographical location. There are unique, diverse training opportunities that await you outside of your comfort zone, and you can expand….

your network. In fact, networking is how I acquired my postdoc over six months before I finished my PhD. You never know how the connections made in graduate school will assist you in the future.

I conclude this article by leaving you with "10 Pieces of Advice for Prospective and Current Graduate Students":

1) **Complete at least 1 internship in undergrad.** Internships not only provide useful research experience that you can add to your CV when applying for graduate school, but also allow you to explore a potential graduate program of interest

2) **When interviewing for graduate programs, remember that you are interviewing them just as much as they are interviewing you.** Find your match! Spend approximately five years in a program that you will thrive in and be happy.

3) **Utilize campus resources.** If you are a student from a diverse and underrepresented population, find out if the university has organizations and support systems in place to help you succeed.

4) **Be open!** Have your areas of interest, but still be open to learn and try different things as you may discover a new interest

5) **Mentorship > Research.** In my opinion, it is easier to find great research over great mentorship. Who you select as your PI that will guide you in your dissertation work, will influence your overall graduate life experience. Don't rush your decision - it is a big commitment!

6) **Talk to the students of the laboratory you are interested in joining.** They can speak directly to the lab environment and mentoring style.

7) **Network!!!** Everyone says this because it is TRUE! Talk to people at your institution, at other schools, visiting speakers, other attendees at conferences, etc.. Don't worry if you're not sure how to network, you will learn! Networking alongside a friend is helpful for those that are timid.

8) **Get involved!** Join local, regional, and national societies to get involved as a graduate student. Also, get involved in your program and university. If there is something that you want to see change, work to make it happen! "Be the change you want to see!" Advocate for yourself AND others.

9) **Foster community outside of school.** The friends and connections you make in the confines of graduate school are critical to your overall success, but connections made in your local community are just as important. You are not just a graduate student machine that should spend all of your time in the lab. Take a moment to smell the flowers and enjoy this stage of life you are in. Many say there is no such thing as "work-life balance". You may not PERFECTLY balance work and life, but you can make an effort to step away from the bench from time to time and do the things you enjoy!

10) **Give yourself grace!** Graduate school is not easy, and it is not meant to be. Work hard and do your best - that's all that anyone can ask for. Lean on your family and friends for support, mental health services, etc. Take care of yourself :)

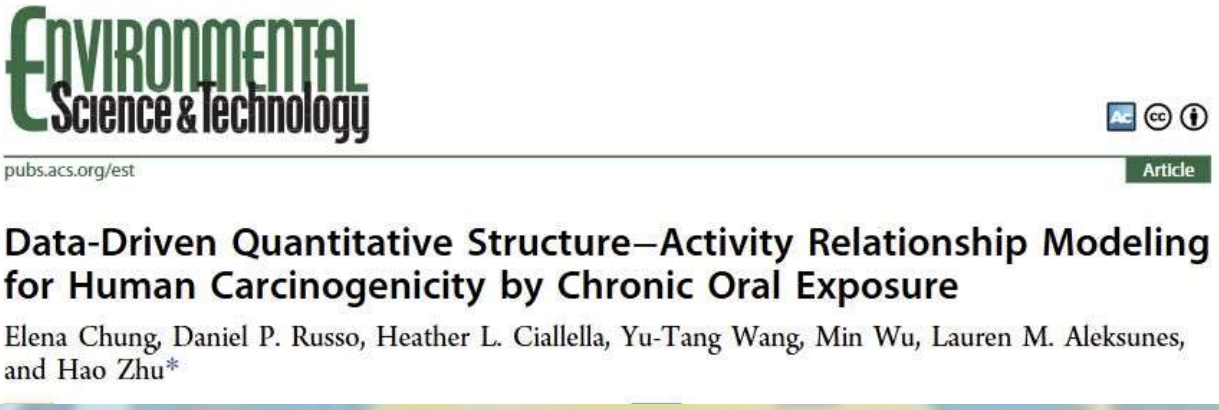
Previous DDTSS Officers:

Past President
Brandon Jeffy

Councilor
Lauren Lewis

2023 Drug Discovery Toxicology Paper of the Year Award

E Chung, DP Russo, HL Ciallella, YT Wang, M Wu, LM Aleksunes, H Zhu. Data-driven quantitative structure-activity relationship modeling for human carcinogenicity by chronic oral exposure**.** Environ Science & Tech. 2023 Apr. 7 (16), 6573-6588.



ENVIRONMENTAL Science & Technology

pubs.acs.org/est Article

Data-Driven Quantitative Structure–Activity Relationship Modeling for Human Carcinogenicity by Chronic Oral Exposure

Elena Chung, Daniel P. Russo, Heather L. Ciallella, Yu-Tang Wang, Min Wu, Lauren M. Aleksunes, and Hao Zhu*

Elena Chung, PhD student presented this work during our DDTSS-sponsored webinar on Sept 19th, 2024, and accepted this award at the 2024 DDTSS reception at the SOT Annual Meeting in Salt Lake City, UT. ***See pages 8 and 9 for some great photos of our reception!***

Congratulations!

DDTSS SOT Annual Meeting Abstract Awards (March 2024)

Graduate student

1st Place: Veronia Basaly, Department of Pharmacology and Toxicology, Rutgers University, Piscataway, NJ, USA

"Phosphorylation Mutation of Pregnane X Receptor (PXR) at Ser347 Alters Bile Acid Metabolism during MASH Development in Mice"

2nd Place: Pablo Reina-Gonzalez, Department of Environmental Medicine, University of Rochester Medical Center, NY, USA

"Multiomic analysis identifies peroxisomal biogenesis regulates neuronal toxicity in Manganese-induced models of Parkinsonism"

Postdoctoral Researcher

1st Place: Rosiane (Borba) de Aguiar, Universidade de São Paulo, Ribeirão Preto, Brazil

"Can planarians become a complementary alternative for behavioral studies in Ecotoxicology?"

2nd Place: Alessio Gamba, University of Liege, Liege, Belgium

"New approach to study chemicals toxicities in the kidney based on the physiological map and ontologies"

3rd Place: Taylor Carter, Department of Pathology, Microbiology, and Immunology, University of South Carolina School of Medicine, Columbia, South Carolina, USA

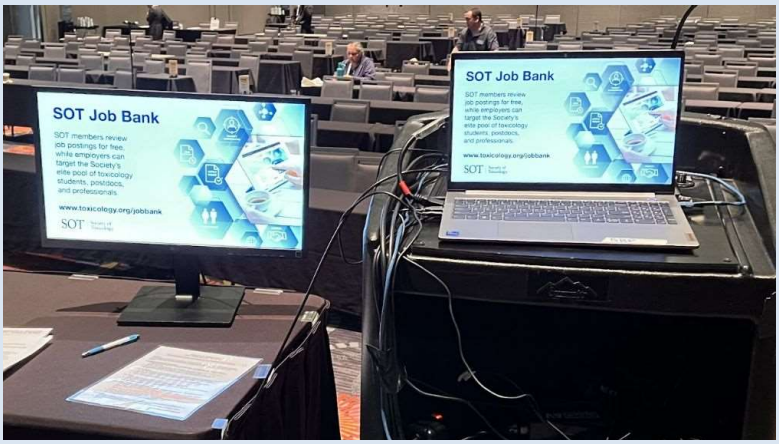
"Delta-9-Tetrahydrocannabinol attenuates macrophage differentiation through downregulation of intra-cellular Reactive Oxygen Species"

We encourage all Graduate Students and Postdoctoral Researchers with abstracts relevant to Drug Discovery Toxicology to apply for our upcoming poster awards!
See page 10 for more info!

Thank you for attending the CE course and DDTSS reception at the 2024 SOT Annual Meeting!

CE course 2024 (PM 09): Bridge over Adverse Waters: Integrating Pathology Findings into the Interpretation of Toxicology Studies

Thank you for attending the CE course and DDTSS reception at the 2024 SOT Annual Meeting!



SOT SALT LAKE CITY MARCH 10–14

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

Our Annual Science Competition! – 2025 Drug Discovery Toxicology Paper of the Year Award!

We are pleased to announce that for the seventh 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 2025 SOT Drug Discovery reception. There will also be an opportunity for this work to be presented at the reception. The application is open to all DDTSS members. You must be senior or first author and the paper must have been accepted or published in 2024. Papers for consideration can be submitted at any time before the **December 15th, 2024 deadline** via SOT Apply. Please feel free to encourage students and/or postdocs and to reach out to colleagues and make them aware of this exciting opportunity to share their work! For questions, please contact Cody Robarts and Wendy Hu.

…and to submit your outstanding research for…

The 2025 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. 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. Use SOT Apply to submit your abstract by **December 29th, 2024**. For questions, please contact Brita Kilburg-Basnyat or Laura Armstrong.

SOT MARCH 16-20 ORLANDO

DDTSS Activities at the 2025 SOT meeting

Sessions endorsed by DDTSS

Workshop		
3/18/2025	4:30-6:30	Advancements in **Microphysiological Systems** for Toxicity Assessment: Bridging the Gap between *In Vitro* and *In Vivo* Models
3/19/2025	1:30-4:15	**Vaccine Toxicology** in the Post-COVID Era
Symposium		
3/17/2025	1:45-4:30	Leveraging **AI and Genomics in Gene and Cell Therapies** for Advancing Personalized Medicine Approaches in Safety Assessments

Mentoring Event

We will be holding a ***Mentoring Event for Students and Postdoctoral Fellows*** at the 2025 SOT Annual Meeting in Orlando. Keep an eye out for an email with details! Members of the DDTSS leadership will be available to discuss careers in pharmaceutical drug discovery toxicology and to answer any questions. Students and postdoctoral fellows wishing to attend can contact Satoko Kiyota (kiyota.satoko@gene.com).

DDTSS Reception

Please join us for our ***DDTSS reception*** at the Hyatt Regency Orlando ***on Tuesday, March 18*** at the 2025 SOT Annual Meeting in Orlando. We hope to see you there!

DDTSS Sponsored Webinar Series

Registration for upcoming webinar(s), materials, and recordings for past webinars can be found on the DDTSS website

DDTSS 2024 Webinars	
12/5/2024	*Joint DDTSS, CTSS and British Toxicology Society Webinar*—**Don't Miss the Mark! How Secondary Pharmacology Can Affect Pharmaceutical Drug Development**
10/18/2024	*Joint WIT and DDTSS Webinar*—**Nonclinical Safety Studies for Investigational New Drug and New Drug Application Filing for Small Molecules Part 1: Overview and Safety Pharmacology**
9/19/2024	*DDTSS Webinar*—**2023 Drug Discovery Paper of The Year: "Data-Driven Quantitative Structure-Activity Relationship Modeling for Human Carcinogenicity by Chronic Oral Exposure"**
2/8/2024	*Joint CTSS and DDTSS Webinar*—**Advancing Toxicology in Drug Discovery using Generative Adversarial Networks**

Engage Undergraduates in the Pursuit of Toxicology Career!

Access ToxScholar Outreach: https://www.toxicology.org/awards/gf/toxscholar.asp

DDTSS leadership positions in this coming year's election:

- Vice President-Elect (4-year commitment)
- Councilor (2-year commitment)
- Postdoctoral Rep (2-year commitment)
- Graduate Student Rep (2-year commitment)

Thank you for nominations! Election results will be announced at the DDTSS reception of 2025 SOT Meeting!

To do list for SOT 2025 Meeting:

1. **Apply for awards! Find the information here**
   - Paper of the Year Award
   - Graduate Student / Postdoctoral Abstract Awards
2. **Make sure to attend:**
   - **Sessions endorsed by DDTSS**
   - **DDTSS Reception:** More info to come!
   - **DDTSS Mentoring event:** More info to come!

2024 generous contribution to support DDTSS:

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Thank you!

List of Past Presidents

Jon Maher	2023
Brandon Jeffy	2022
Marie Lemper	2021
Zoe Zhong	2020
Dinah Misner	2019
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 Orlando!