DDTSS Newsletter: Winter 2025

SOT Drug Discovery Toxicology Specialty Section

2025–2026 Officers

See you in San Diego in 2026!

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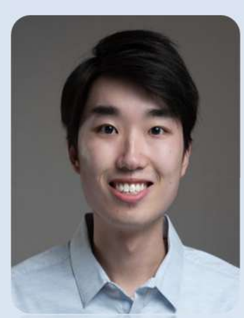

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Welcome to Join DDTSS

President's Message
Wendy Hu

As I thought about what to write for this newsletter, it occurred to me that quite a few of my friends who recently switched jobs had all asked me a similar question: small vs large companies, which is better to work for as a toxicologist. This year marks my third year at a mid-size biotech company heading the toxicology function. Prior to that, I have been working as a toxicologist and group leader at a global mega-size pharmaceutical company for 15 years. Back when I just started, I had worked in both large pharma and startup biotech with less than 30 people. I would share my perspective drawn from personal experiences. In a large pharmaceutical company, a drug discovery toxicologist is typically part of a highly compartmentalized organization with deep resources and specialized expertise. Toxicology studies are typically conducted in house with less hands-on involvement. In contrast, a toxicologist at a small biotech company typically wears multiple hats, covering a broad range of responsibilities and working more closely with other functions and external CROs. Neither path is inherently better, the right choice depends on your personality, professional aspiration and stage of your career. Large pharma could be right for you if you excel in a structured work environment and would like to develop deep expertise in specialized areas. Small biotech would be perfect for you if you want to be more hands-on and would like to cover toxicology disciplines from A to Z. Especially, working for start-up biotech companies would require you to excel in fast-paced and nimble environment, and not shy away in a high-risk, high-reward situation. Throughout my career, I enjoyed the whole spectrum of companies I had worked at and have built invaluable network and friendship along the way. Future generation of toxicologists may not even observe such distinctions as artificial intelligence and globalization starting to revolutionize how we work.

AI is unlikely to replace toxicologist, but it will fundamentally transform the role. AI could act as a "copilot", automating routine tasks, summarizing literatures, mining historical data and harmonizing reporting process. Machine learning tools and NAMs models can build databases of chemical structures, ADME properties, *in vitro* data and historical results to predict toxicity at earlier stage while reducing animal testing. This would allow toxicologists to focus more on complex, high-value work. Human intervention would still be needed to curate the training data that will feed into models, to eliminate bias in data interpretation and especially for strategic decision making. Good judgement, critical thinking and problem-solving skills are still critical for toxicologists to be successful in conducting risk assessment. Multidisciplinary collaboration and integration of information is going to be more important than ever.

In this Newsletter, you can find our special edition focusing on the current scientific trends – how AI and machine learning could have potentially transformative impact on drug discovery toxicology and the career corner featuring an early career discovery toxicologist and her professional development and career journey. We sincerely appreciate the authors for their contribution!

I hope to see you all in **San Diego for the 2026 SOT Annual Meeting!** Please mark your calendars and make sure to join us for the in-person **DDTSS reception and mentoring events** - it is the best way to explore new ideas and expand your network!

Machine Learning for Toxicity Prediction

Srijit Seal (University of Cambridge) and Deidre Dalmas (Independent)

The manuscript is available in *Chemical Research in Toxicology* as "Machine Learning for Toxicity Prediction Using Chemical Structures: Pillars for Success in the Real World" (DOI: 10.1021/acs.chemrestox.5c00033)

In a recent landmark collaboration among 30 scientists from 15 pharmaceutical companies, government agencies, and academic institutions, AI innovators outlined the essential pillars for using machine learning (ML) to predict chemical toxicity. A major cause of attrition in drug development is safety, and existing preclinical systems continue to show limited nonclinical to clinical translation and concordance with human outcomes. The review proposes a five-pillar framework for reliable, actionable toxicity modeling. It draws from the expertise of scientists from companies including Novartis, Eli Lilly & Company, Merck Inc., AstraZeneca, Bayer Crop Science, Pfizer, GSK, Recursion, Novo Nordisk, Sanofi, Relay Therapeutics, and others, as well as government experts from the National Institute of Environmental Health Sciences (NIEHS) and thought leaders from academia, including Cambridge and the Broad Institute of MIT and Harvard.

This paper provides a practical guide to using AI in decision-making, outlining strategies on how to select the right data and models and validate them as well as the application to real-world scenarios such as compound deselection or risk assessment. The overall purpose of the article was to examine what machine learning has delivered in toxicity prediction and how the approaches can be made technically sound and relevant to real-world drug discovery.

Various leaders across the field drove this work with their practical experience across industry and academia. While we were excited and enthusiastic about artificial intelligence in safety assessment, we still repeatedly observed that models performing well in past datasets (retrospective benchmarks) frequently fail for novel molecules (in prospective conditions). In this perspective, we drove the discussion away from technical claims and towards standards for training machine learning models that can be implemented (and validated) in real programs.

Many toxicity labels used in machine learning models are proxies for complex biological processes. For example, ion channel inhibition is often used as a surrogate for cardiac risk; however, the mechanistic link is not universal and is context-dependent. In this review, we argue that model performance should be interpreted in light of biological distance from the clinical phenotype of interest, rather than being treated as purely statistical exercises. Further, commonly used public and proprietary datasets often do not account for experimental variability, and when state-of-the-art model performance is reported in most publications, this does not account for models performing better than the very experimental assay it is trained on. In many standard assays, replicate measurements diverge by several-fold, and a nontrivial fraction of repeated experiments produce contradictory classifications. Such noise imposes a ceiling on achievable predictive accuracy, regardless of algorithm choice.

A major focus is on using chemical structures to predict toxicity. Chemical structures most often need to be encoded in some representation form for machine learning models. We detailed workflows for chemical structure standardization, including salt stripping, tautomer normalization, treatment of stereochemistry, and management of protonation states, to ensure compounds are encoded consistently to improve the models.

In our analysis of molecular representations, we compared hand-crafted descriptors and learned representations in practical settings. Structural keys, which contain information on the presence or absence of particular substructures, are known to offer interpretability, but they were designed for library searching and not modelling. Circular fingerprints, which encode structures based on neighborhoods, provide strong baseline performance across many classification tasks, but suffer in areas where similar compounds can exhibit very different properties (known as activity cliffs). Physicochemical descriptors like logP, polar surface area, etc, are often comparable to more complex representations for certain endpoints, particularly when datasets were small. Graph-based neural networks have shown promise in large, diverse datasets, but they have been unstable in low-data regimes. We emphasize that representation choice is an experimental variable that should be tuned rather than assumed.

Once the dataset and representation of chemistry are chosen, the next step is selecting a suitable model, which is a problem of aligning data and algorithmic assumptions. In the review, we discussed the limitations of linear models, ensemble methods, kernel approaches, and deep architectures in the context of toxicity. We analyzed the distinction between local and global models. Most deployed systems function effectively only within restricted regions of chemical space defined by their training data. We argued that attempting to enforce global generalization without sufficient data diversity leads to false confidence and poor predictions. We addressed the impact of class imbalance, hidden confounders, and evolving chemical series on model stability over time.

Further, we provide concrete examples of how randomly selecting a part of the data for testing a model can lead to overly optimistic metrics. Time-split validation and project-based splits are more realistic alternatives. We discussed uncertainty quantification, including conformal prediction and Bayesian approaches, as mechanisms to surface the confidence limits of individual predictions. Knowing when a model is likely to fail is often more valuable than marginal gains in average accuracy.

Finally, we discuss the practical challenges of deploying models. Toxicity is inherently dose-dependent, and structure-based predictions alone cannot be interpreted independently of pharmacokinetics, bioavailability and the like. We discussed ways of coupling toxicity models to exposure prediction systems and highlighted the risk of binary decision thresholds that ignore gradations of biological response. We reviewed species-specific expression differences, divergent metabolic pathways, and immune-mediated effects that limit direct extrapolation. The emergence of new approach methodologies, including human-derived organoids and microphysiological systems, was acknowledged for both their promise and their current technical constraints. In our opinion, machine learning is positioned as a tool for integrating heterogeneous signals and augmenting experiments rather than as a replacement for biological experimentation. We need to overcome several organizational challenges to make the best impact with machine learning for toxicity prediction, such as fragmentation of data across organizations, inconsistent annotation standards, and reluctance to share negative results, all of which limit progress.

Overall, we aimed to establish a set of working principles and clarify the upper bounds of current methods, define realistic expectations, and provide technical vocabulary that allows experimental and computational teams to communicate more precisely.

Special Edition - Career Corner:
Career Journey of a Drug Discovery Toxicologist

Leslie Valencia, PhD
Senior Scientist, Translational Safety,
Genentech Inc

I completed my PhD in Developmental Biology at Stanford University in Dr. Alistair Boettiger's lab, where I developed a super-resolution microscopy approach to study RNA and DNA dynamics, chromatin structure, and gene expression at the single-cell level in *Drosophila* embryos. This work combined advanced imaging with quantitative analysis to address fundamental questions about gene regulation. At the same time, I found myself asking how discoveries at the bench could ultimately benefit patients. That question motivated me to explore career paths where I could contribute more directly to translating science into medicines.

In addition to my research, I was actively involved in SACNAS (the Society for Advancement of Chicanos/Hispanics & Native Americans in Science) at Stanford, where I served as a founder and president of the Stanford chapter. In this role, I organized panels and career talks with employees from local biotech companies (e.g., Gilead, 23andMe, etc.), which gave me my first exposure to industry and ultimately led me to learn about Genentech. Through these experiences and the professional connections I made, I discovered Genentech's brand-new Drug Development Training Program (DDTP), a three-year rotational program for early-career PhDs providing hands-on training across preclinical and clinical development. As part of DDTP's first cohort, I joined the Translational Safety department and began my training in the Investigative Toxicology (iTox) group, where I examined drug-induced nephrotoxicity using *in vitro* 2D and 3D models, leveraging cytotoxicity and biomarker assays, immunostaining, and live imaging to compare effects across species and models. This experience gave me foundational exposure to preclinical safety evaluation and the tools used to investigate potential toxicity mechanisms.

After completing my time in iTox, I transitioned into project toxicology, initially working under the mentorship of experienced project toxicologists. I had the opportunity to shadow ongoing programs and take on backup molecules, which allowed me to gain hands-on experience in evaluating potential safety risks and understanding the broader drug development context. This structured mentorship prepared me to fully take on my current role as a project toxicologist, where I am responsible for assessing the safety of both oncology and non-oncology programs, ensuring that drug candidates are carefully evaluated before entering clinical trials. The program not only gave me the technical foundation I needed but also reinforced the importance of collaboration and teamwork in making safer drugs for patients. For those interested in industry careers, I encourage you to seek out training opportunities, mentorship, and professional networks—they can open doors to paths you might not have known existed.

Previous DDTSS Officers:

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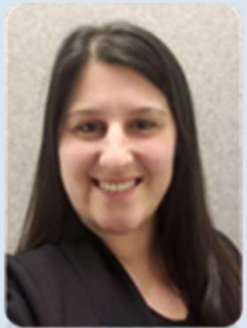
Jon Maher



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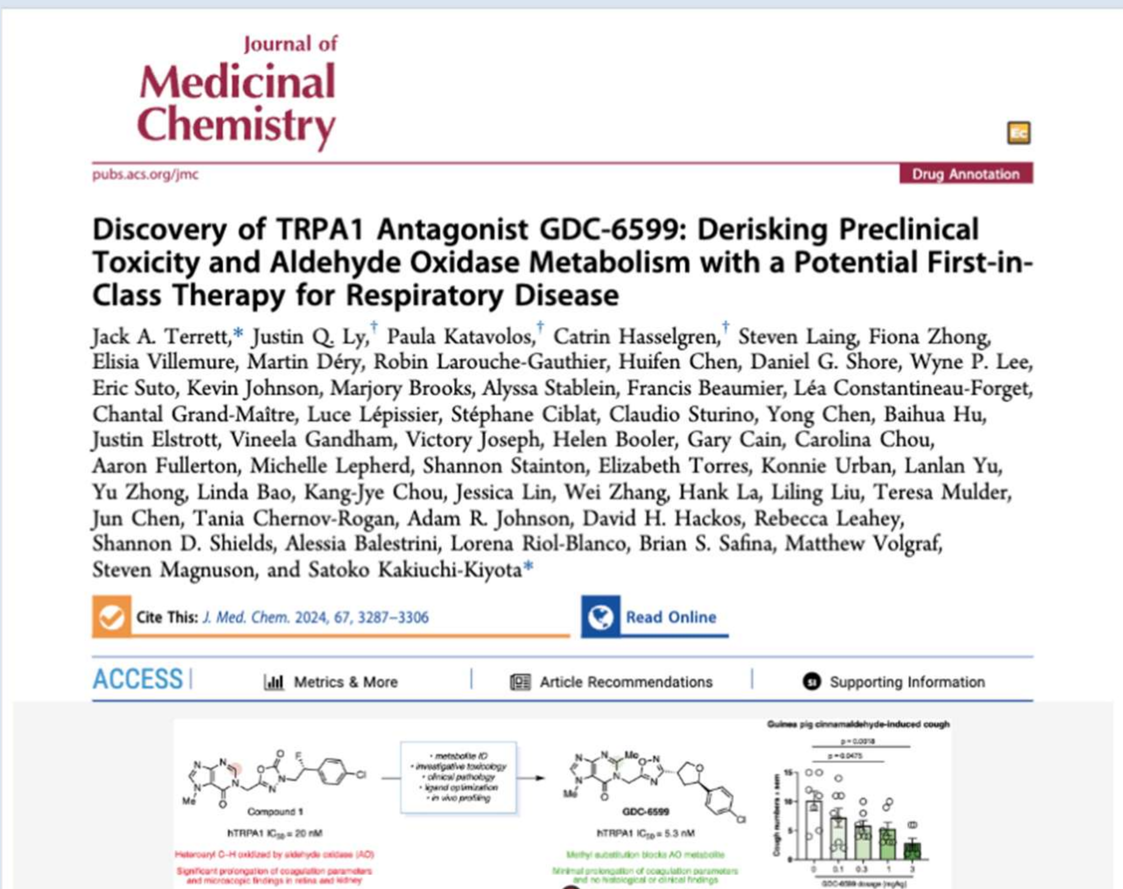
Postdoc Rep
Cody Robarts

Graduate Student Rep
Zakiyah Henry

2024 Drug Discovery Toxicology Paper of the Year Award

Satoko Kiyota accepted the award during the DDTSS reception at the 2025 SOT annual meeting.



Journal of Medicinal Chemistry

pubs.acs.org/jmc

Drug Annotation

Discovery of TRPA1 Antagonist GDC-6599: Derisking Preclinical Toxicity and Aldehyde Oxidase Metabolism with a Potential First-in-Class Therapy for Respiratory Disease

Jack A. Terrett,* Justin Q. Ly,† Paula Katavolos,† Catrin Hasselgren,† Steven Laing, Fiona Zhong, Elisia Villemure, Martin Déry, Robin Larouche-Gauthier, Huifen Chen, Daniel G. Shore, Wyne P. Lee, Eric Suto, Kevin Johnson, Marjory Brooks, Alyssa Stablein, Francis Beaumier, Léa Constantineau-Forget, Chantal Grand-Maître, Luce Lépissier, Stéphane Ciblat, Claudio Sturino, Yong Chen, Baihua Hu, Justin Elstrott, Vineela Gandham, Victory Joseph, Helen Booler, Gary Cain, Carolina Chou, Aaron Fullerton, Michelle Lepherd, Shannon Stainton, Elizabeth Torres, Konnie Urban, Lanlan Yu, Yu Zhong, Linda Bao, Kang-Jye Chou, Jessica Lin, Wei Zhang, Hank La, Liling Liu, Teresa Mulder, Jun Chen, Tania Chernov-Rogan, Adam R. Johnson, David H. Hackos, Rebecca Leahey, Shannon D. Shields, Alessia Balestrini, Lorena Riol-Blanco, Brian S. Safina, Matthew Volgraf, Steven Magnuson, and Satoko Kakiuchi-Kiyota*

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Graduate Student and Postdoctoral Researcher Abstract Awards

Graduate Student

First place	Sierra Wilson	*Diploid Hepatocytes Resist Acetaminophen-induced Acute Liver Injury*
Second place	Tong Wang	*Integrating transporter data and machine learning approaches to predict drug transport across the placental barrier*
Third place	Christine Kim	*Selective Receptor Modulation During Melatonin Renoprotection Against Vancomycin Toxicity*

Postdoctoral Researcher

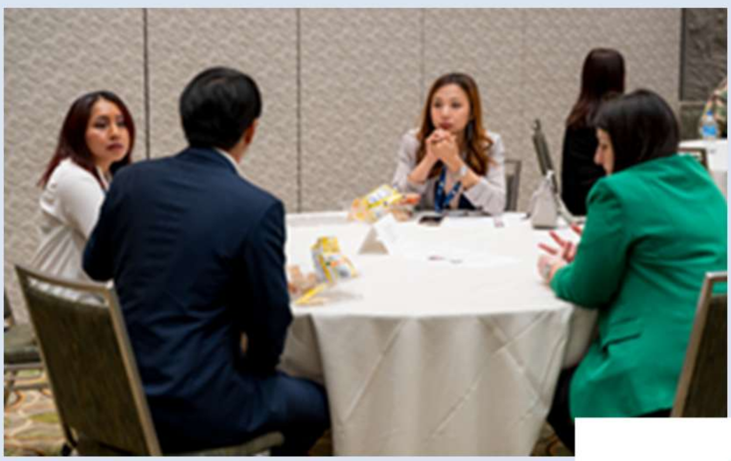
First place	Xuelian Jia	*Application of Machine Learning and Mechanistic Modeling to Predict Intravenous Pharmacokinetic Profiles in Humans*
Second place	Siddhi Jain	*Hepatocyte-Specific MET Ablation Exacerbates Liver Injury and Impedes Regeneration in Acetaminophen-Induced Hepatotoxicity Model*
Third place	Chander Negi	*Comparative Analysis of Species-Specific Hepatocyte Function and Drug Effects in a Liver Microphysiological System PhysioMimix LC12 and 96- Well Plates*

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!**

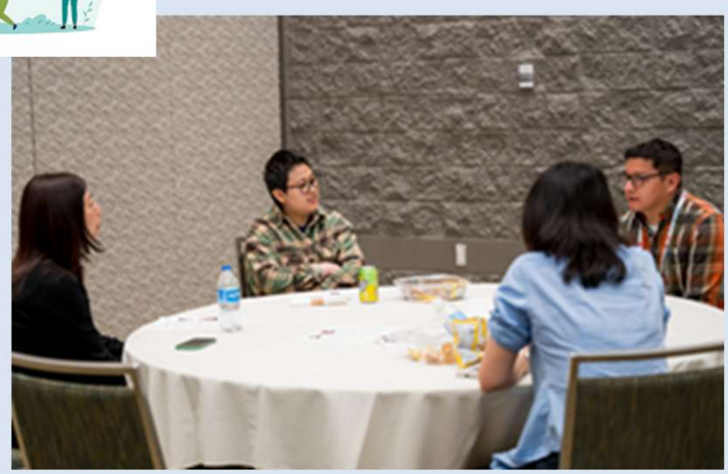
Thank you for attending the DDTSS Mentoring Event at the 2025 SOT Annual Meeting!











SOT MARCH 16–20 ORLANDO

Thank you for attending the DDTSS reception at the 2025 SOT Annual Meeting!

SOT MARCH 16–20 ORLANDO

Call for Participation in the Paper of the Year and Graduate Student and Postdoc Abstract Awards

DDTSS Paper of the Year Award

Contact: Email Connie Kai Wu.
Description:
The Paper of the Year Award was created to highlight a scientific achievement in the field of Discovery Toxicology. The recipient will receive a plaque of recognition and a financial award ($1,000) at the SOT DDTSS reception. There will also be an opportunity for this work to be presented at a Webinar.

The applicant must be one of the authors and the paper must be accepted or published within 2025. At least one of authors must be a member of DDTSS. If none of the authors are members of DDTSS, please contact us.

DDTSS Postdoctoral and Graduate Student Abstract Competition - Annual Meeting

Contact Email Siddhi Jain and Tony Hu.
Description:
Applicants must have an abstract accepted by SOT for the 2026 Annual Meeting. The graduate student competition is open to all current graduate students. For the postdoctoral award, the applicants much have completed a PhD program. Applicants should submit their abstract as well as a cover letter to provide additional context and explain the relevance of the work to drug discovery toxicology. To participate in the abstract competition, membership in SOT and/or DDTSS is encouraged but not necessary. For each competition (graduate student competition and postdoctoral competition) first ($1,000), second ($400) and third ($150) place prizes will be presented at the DDTSS reception during the 2026 SOT Annual Meeting. This award is made possible by the Emil Pfitzer Drug Discovery Toxicology Endowment Fund.

APPLY NOW

SOT MARCH 22-25 SAN DIEGO

Exciting Events by DDTSS at the 2026 SOT Annual Meeting!

Sessions endorsed by DDTSS

Session Type	Session Title
Workshop	Toward AI-Enabled Digital Biomarkers: Improving the Predictivity of Toxicology in the 21st Century
Roundtable	Mice with a Mission: Optimal Use of Humanized Transgenic Mice as an “FDA Innovative Platform”
Continuing Education	Lost in Translation? Navigating Species Selection for Immunotoxicological Assessment in Preclinical Studies

Mentoring Event

We will be holding a ***Mentoring Event for Students and Postdoctoral Fellows*** at the 2026 SOT Annual Meeting in San Diego on March 23, 2026. Members of the DDTSS leadership will be available to discuss careers in pharmaceutical drug discovery toxicology and to answer any questions.

DDTSS Reception

You are cordially invited to our ***DDTSS reception*** at the Marriott Marquis San Diego Marina ***on Wednesday, March 25, 2026*** during the SOT Annual Meeting in San Diego. This will be a great networking event. We hope to see you there!

SOT MARCH 22-25 SAN DIEGO

DDTSS Sponsored Webinars Series

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

DDTSS Webinars	
11/11/2025	DDTSS Webinar: **2025 Drug Discovery Paper of The Year and DDTSS Award Winners Presentations**
1/30/2026	*Joint WIT and DDTSS Webinar—Protein Degrader series part I* **Nonclinical Safety Assessment of Targeted Protein Degraders: An Industry Perspective**
2/6/2026	*Joint WIT and DDTSS Webinar—Protein Degrader series part II* **Current Practices and Considerations for Preclinical Safety Assessment of Targeted Protein Degraders**

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)
- Treasurer/Secretary (2-year commitment)

Thank you for nominations! Election results will be announced at the DDTSS reception during the 2026 SOT Meeting!

APPLY NOW

To do list for SOT 2026 Meeting:

1. **Apply for a DDTSS award! 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:** See page 11!
   - **DDTSS Mentoring event:** More info to come!

Thanks for the generous contribution to support DDTSS:

The Emil A Pfitzer Drug Discovery Endowment Fund

The McKeeman Early Career Award in Mechanistic Toxicology

scan to donate

SOT MARCH 22-25 SAN DIEGO