Autumn 2024

CTTSS
CLINICAL AND TRANSLATIONAL TOXICOLOGY SPECIALTY SECTION

The Newsletter of the
Clinical and Translational Toxicology Specialty Section

News & features

Outgoing President's Message

by Hartmut Jaeschke

Dear Colleagues and Members of CTTSS,

As my term as President of our Specialty Section ends, I would like to thank you for the opportunity to serve in this capacity. It was an honor and a privilege to work with the dedicated members of our leadership team and I have full confidence that my successor, Dr. Deidre Dalmas Wilk, will carry on the torch successfully guiding this Specialty Section in the coming year.

Ongoing challenges of the Section are membership and finances, which are interrelated problems. We have started to address these issues in new ways by organizing a mentoring session at the Annual Meeting and by an educational webinar "Exploring Careers in Translational Toxicology: The Life of a Clinical and Translational Toxicologist" expertly organized by our Graduate Student Representative, Joanna Woo. We hope that these educational events will help inform more SOT Members of the value of our Specialty Section and the expertise of our members. In addition, I want to encourage everyone in CTTSS to actively recruit new members and potentially consider a donation (no donation is too small) to ensure the vitality and long-term growth of clinical and translational toxicology at SOT. Thank you again for the honor to serve as CTTSS President. I look forward to continuing to support you as Past President.

Best wishes,
Hartmut Jaeschke, PhD, ATS
CTTSS President (2023-2024)

Incoming President's Message

By Deidre Dalmas Wilk, MS, PhD
CTTTSS President (2024-2025)

Dear Fellow CTTSS Members,
As incoming President (term 2024-2025), I would like to thank my predecessor, Hartmut Jaeschke, for leading us through this past successful year. Also, a big thank you to the outgoing officers (highlighted in the newsletter) and Emma for all the hard work in getting the newsletter out. Everyone's valuable insights over the past year were critical to CTTSS making an impact. I also wanted to welcome the newly elected officers noted in the newsletter and on the CTTSS home page. I look forward to serving as the President this year.

We had a great turnout at the CTTSS Luncheon in Salt Lake City at the SOT Annual Meeting. It was so great to see everyone. As Hartmut mentioned, CTTSS Officers and other volunteers are busy working to reinvigorate CTTSS, and we are producing new and exciting opportunities to join various committees to help develop events and foster more engagement. These new committees will offer opportunities to have leadership roles that will report back to the CTTSS Officers and enable individuals to attend our Executive Council meetings. Some of these committees have already started (e.g., SOT Session Proposal Review Committee, Mentor-Match Committee) and many thanks to those who got involved early and have helped get these committees off the ground in 2024. Some additional committees that we will be starting and, therefore, asking for volunteers soon include a Program Committee, Officer Nomination Committee, Award Review Committee, and Communication Committee. Please be on the look-out for an announcement to join as we need everyone to participate to make CTTSS a continued success. We are also soliciting ideas on any events or additional committees, symposiums, or webinars you feel would help promote the CTTSS. Please reach out with your thoughts/ ideas.

This year, we will also be looking for volunteers to run for Officer roles that will open for the 2025-2026 term: Councilor, VP-Elect, and Graduate Student Representative. **If you would like to nominate someone or self-nominate, please let myself (deidre.a.dalmas@outlook.com) or one of the other current officers know ASAP.**

Finally, our Section is nothing without its members, and I would encourage you to convince other colleagues to join the Section and help us to grow the field of clinical and translational toxicology. **We would also like to thank Acetaminophen Toxicity Diagnostics for their incredibly generous donation to the Specialty Section. Best wishes to you all and have a great fall.**

Deidre Dalmas
President CTTSS (2024-2025)

Deidre Dalmas
2024-2025 CTTSS President

CTTSS Receives Generous Donation

CTTSS would like to acknowledge the generous donation of ATD Acetaminophen Toxicology Diagnostics, LLC.

ATD is a CLIA and CAP Certified Laboratory for Acetaminophen Adduct Testing. Find out more about their services by visiting their website.

Support our Section's initiatives yourself!

CTTSS Reception and Awards

The CTTSS awards reception featured a new mentoring session at the beginning of the event, which allowed trainees to engage with translational clinical and toxicology experts from academia, government, and industry. The mentoring session was followed by awards for outgoing officers. Harmut Jaeschke received a plaque honoring him as outgoing President (bottom, left). Kai Kehe was awarded for his services as Past President, followed by John Benitez (Councilor) and Jephte Akakpo (Postdoctoral Representative). Kenneth McMartin received a career achievement award (bottom, right) for substantial scientific contributions to the translation of theories at the bench to treatments at the bedside over the course of his career. Trainee awards are on the following page.

Trainee Award Winners

1st - Diego Paine-Cabrera

The role of Connective Tissue Growth Factor (CTGF) in liver regeneration after acetaminophen overdose

3rd - Kevin Schichlein

Aerosolized Vitamin D Attenuates Ozone-Induced Inflammation and Immune Dysfunction

2nd - Luiz Paulo de Aguiar Marciano

Risk Assessment of Exposure to Triazole Fungicides by Human Biomonitoring & Mechanistic Data

Hon. Mention - Christine Kim

Dual Activation of Melatonin Receptors and NRF2 Signaling to Prevent Vancomycin-induced Nephrotoxicity

Hon. Mention - Shari Yarde

Regulation of Hox and ParaHox Genes by Epalrestat in Mouse Liver

Hon. Mention - Tingying Xie

Melatonin metabolite 6-hydroxymelatonin sulfate disposition in human livers and kidneys

Translating Toxic Mechanisms into Antedotal Treatments

by Kenneth McMartin, PhD, FAACT, Department of Pharmacology, Toxicology & Neuroscience, Louisiana State University Health Sciences Center – Shreveport

Kenneth McMartin was the recipient of the 2024 CTTSS career achievement award. To help celebrate this achievement, we asked him to share a summary of his work.

Academic scientists often conduct mechanistic work with antidotes but are infrequently involved in further drug development. This article presents the development of 4-methylpyrazole (4MP; fomepizole) as an antidote for methanol and ethylene glycol (EG) poisonings. Methanol is readily available in windshield washer fluids and other automotive products, while EG is the major constituent of automotive antifreeze. Poisonings are relatively uncommon (about 5000 exposures in the US annually) but can be fatal or produce sequelae if treatment is delayed. Mechanistic research established that neither toxicant was poisonous but had to be metabolized to toxic metabolites. The initial metabolic step of both is oxidation via alcohol dehydrogenase (ADH) to formaldehyde and glycolaldehyde respectively. Further metabolism produces formic acid, the proximate toxicant for methanol, and glycolic acid and oxalic acid (with formation of calcium oxalate crystals), which produce the toxicity of EG poisoning.

4MP was first synthesized in 1960 by AB Astra. Their goal for developing pyrazole derivatives was to treat the organ toxicities of alcoholism, assuming that inhibition of ADH diminishes ethanol's adverse metabolic effects. Their studies showed that 4MP was a potent competitive inhibitor of ADH, it inhibited ethanol elimination in humans, it was nontoxic in rodents and it suppressed ethanol's metabolic effects in animals and humans. Soon thereafter, the laboratory of Thomas Tephly showed that formate was responsible for the acidosis and the ocular toxicity produced by methanol. This group showed for the first time that 4MP potently blocked the accumulation of formate and could reverse and prevent the toxicity of methanol. As such, 4MP was shown experimentally to be a potential antidote for methanol poisoning. About this same time, efficacy of 4MP versus EG toxicity was shown by the veterinary toxicology group of Mary Thrall. Their studies showed that ethanol and 4MP were equally effective at reversing the acidosis produced by EG, but that 4MP did not increase the CNS depression unlike ethanol.

Article Continued...

Translation of 4MP as a marketed therapeutic was stimulated by the Orphan Product Act, which provided funding of academic researchers to conduct initial clinical studies, with hopes of attracting liaisons with drug companies to promote the development of the orphan products towards approval. Between 1986 and 1990, five Phase 1 studies of 4MP were conducted by a research group at LSU Health Sciences Center – Shreveport. These double blind, randomized trials, involving 65 healthy male volunteer subjects, included an ascending, single-dose study, an ascending, multiple-oral dose study, an ADH inhibitory study with ethanol, an IV/oral dose kinetic study and an IV study of ethanol-4MP interactions. These studies showed that 4MP was well tolerated with minimal adverse effects after either oral or IV doses in the range of 5 – 20 mg/kg every 12 h; the studies also confirmed that such doses of 4MP were effective at inhibiting ethanol metabolism as a surrogate for ADH activity. The Phase 1 studies also revealed interesting metabolic and kinetic information about 4MP.For example, 4MP elimination in humans at doses in the therapeutic range (10 – 20 mg/kg) was by nonlinear, Michaelis-Menten kinetics, with "zero order" rates about 5-10 µmol/L/h. Elimination of 4MP was mostly via metabolism to 4-carboxypyrazole (4CP), whose excretion in the urine accounted for > 50% of the dose. The multiple dose study in humans, in which doses were administered every 12 h for 96 h, provided evidence that 4MP appeared to induce its own elimination. In these studies, 4MP plasma levels could not be maintained at a steady state unless the dose was increased at 48 h. Auto-induction was further suggested by the increasing rate of elimination over time from 0 – 12 up to 72 – 84 h periods. This latter information is the basis for the recommended dosing schedule in use today, where the maintenance dose is recommended to be increased at 60 h.

Technology transfer for antidotes is not easy because interest from major pharmaceutical companies is minimal. Although the newly named "fomepizole" received official Orphan Product Designation, initial efforts at enticing development were ignored. Luckily, investors with pharmaceutical experience (Mericon Investment Group) saw its promise and licensed it to Orphan Medical, Inc.

Article Continued...

Orphan Medical had a business plan of concentrating development on orphan drugs, so was aggressively pursuing this type of product. Orphan Medical sponsored the first clinical studies of efficacy in the US using a complex multi-center trial, which was needed to enroll enough patients from these rare poisonings to obtain the data for an NDA submission. These trials required a group of 20 clinical toxicologists associated with poison centers directed by Jeff Brent. This trial also designated a common analytical center (LSUHSC-S) for measuring the levels of fomepizole and of the toxic alcohols and their metabolites. There were two arms to the trial, one for EG and another for methanol, which allowed for separate assessment of efficacy. The open label trials had a defined dosing schedule, employed specific criteria for use of hemodialysis, and assessed acid-base status, renal (or visual) function, and kinetics of fomepizole and EG/methanol metabolism at predetermined intervals. Both arms of the clinical trials showed the efficacy of fomepizole against both poisonings.

Fomepizole was approved by the US FDA for marketing for treatment of EG poisoning in 1997 and was first sold as Antizol® by Orphan Medical for this use in 1998. Approval for the methanol indication did not occur until 2000. Physicians soon learned of its clinical superiority over ethanol, so that fomepizole rapidly became the standard of care. These clinical benefits include maintaining therapeutic blood levels better than ethanol, having fewer adverse effects, and being less labor intensive. By 2002, fomepizole was being used in over 50% of treatable cases in the US and today probably accounts for over 90%. Ironically for a drug that was marketed as an orphan product, it has been so useful that generic versions have been approved by the US FDA and they now control the market.

Development by individual investigators of antidotes for use in clinical toxicology, even as orphan products, is not easy. Among the problems are the need for a suitable source of the chemical (Good Manufacturing Practice-certified), a difficulty in attracting seed money, necessity for recruiting centers for the multi-center trials, and the need for lots of time and patience (30 years from discovery of fomepizole activity until it reached the market). Advancement of fomepizole for the treatment of methanol and EG poisoning only became possible through mechanistic research that showed the key role of metabolites. Beyond strong mechanistic research, other aspects that helped fomepizole reach the market was its unquestionable preclinical efficacy, the therapeutic need, and just luck (such as the Orphan Product act, timing of scientific collaborations, and development of innovative drug companies).

Special thanks to Ken McMartin for this essay.

2024-2025 CTTSS Awards

Don't forget to spread the word about the CTTSS awards. **Please note that deadlines have changed!** Check out the descriptions on the following pages for awards criteria.

Graduate Student Research Award

Deadline: December 2, 2024
Instructions: On the "Awards" section of the CTTSS website, hit the "Apply" button

Current PhD students attending the SOT Annual Meeting and submitting an abstract for presentation at the SOT Annual Meeting in 2025 are encouraged to apply. The award recognizes outstanding research in the area of translational and clinical toxicology.

Multiple award(s) may be given depending on the number of applicants which will be at the discretion of the CTTSS Awards Committee. Recipient(s) will be announced at the CTTSS business meeting at the SOT Annual Meeting. The first-place winner will receive an award certificate (or plaque) and a cash award. All other winners will receive an award certificate (or plaque).

Submission Requirements

1. An abstract must be submitted for the upcoming SOT Annual Meeting with the graduate student as the presenting author. A late breaking abstract is acceptable. Provide a copy of the abstract and SOT Submission ID number.
2. A letter of recommendation must be included from the mentor or nominator outlining the student's role in the research and the relevance to clinical and translational toxicology. If the graduate student is a CTTSS member, no additional documents are required. If neither the graduate student nor the mentor is a CTTSS member, a letter of recommendation from a CTTSS member is required.
3. A graduate student can receive the award more than once if the research is novel, non-overlapping, and the abstract being presented does not include research referenced in a prior award application. A description of how the research is different should be described in the recommendation letter provided by the mentor/nominator.

The awardee will be selected based on submitted materials by the CTTSS Awards Committee and CTTSS Executive Council.

Deadline for Submission: December 2, 2024 (11:59 pm EST).
Questions? Contact Anup Ramachandran (aramachandran@kumc.edu), CTTSS Councilor.

Postdoctoral Scholars Research Award

Deadline: December 2, 2024
Instructions: On the "Awards" section of the CTTSS website, hit the "Apply" button

Current postdoctoral scholars attending the SOT Annual Meeting and who have submitted an abstract for presentation are encouraged to apply for the Clinical and Translational Toxicology Specialty Section (CTTSS) Postdoctoral Scholar Research Award.

The 1st place awardee will receive a monetary prize and a recognition certificate. Depending on the number of applicants, additional awards may be offered at the discretion of the CTTSS Awards Committee.

Submission Requirements

1. A copy of the abstract submitted for the upcoming SOT Annual Meeting with the postdoctoral fellow as the presenting author.
2. A letter of recommendation must be received from a mentor or appropriate nominator.
3. If the postdoctoral scholar is a CTTSS member, no additional documents are required. If neither the postdoc nor the mentor is a CTTSS member, a letter of recommendation from a CTTSS member is required. This letter should outline the postdoc's role in the research and the relevance to translational / clinical toxicology.
4. A postdoctoral scholar/researcher can only win the CTTSS Postdoctoral Scholars Research Award once for the same piece of research. A CTTSS Postdoctoral Scholars Research Award can be won more than once if the research is novel, non-overlapping, and abstract being presented does not include research referenced in a prior award application. A description of how the research is different should be described in the recommendation letter provided by the mentor/nominator.

The awardee will be selected based on submitted materials by the CTTSS Awards Committee and CTTSS Executive Council.

Deadline for Submission: December 2, 2024 (11:59 pm EST).
Questions? Contact Anup Ramachandran (aramachandran@kumc.edu), (CTTSS Councilor).

Clinical and Translational Toxicology Specialty Section Career Achievement Award

Deadline: November 1, 2024
Instructions: On the "Awards" section of the CTTSS website, hit the "Apply" button

The Clinical and Translational Toxicology Specialty Section (CTTSS) would like to recognize an individual who over the course of their career has provided substantial scientific and/or service contribution to the field of translational and clinical toxicology. The nominee must be a member, or retired member of CTTSS who has made significant scientific and/or service contributions over a sustained period of time (>15 years) that have had major impact on the field.

Applicants for this award may be self-nominated or nominated by a colleague.

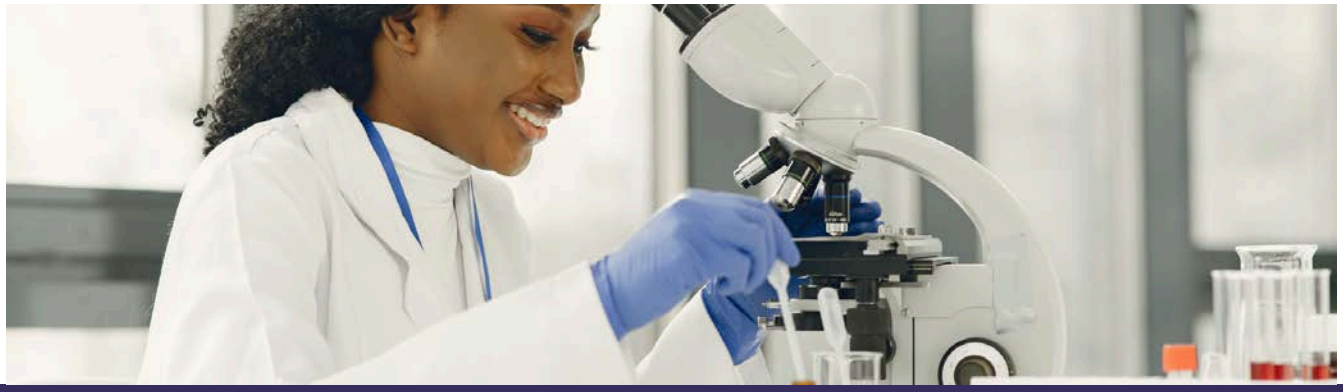
Submission requirements are:

1. A short (nor more than 1-page) summary of key contributions the individual has made to the area of translation toxicology, service to SOT, and/or mentoring in the area of translational toxicology, etc.
2. A letter of recommendation must be received from the nominator. If self-nominated, a summary of qualifications for the award is required along with a letter of support from a current full CTTSS member.
3. A current CV of the nominee must be included.

The Awardee will be selected based on review of nominations of candidates by the CTTSS Awards Committee and CTTSS Executive Council. The awardee will be contacted in advance of the SOT Annual Meeting and recognized by presentation of an award certificate (or plaque) at the CTTSS reception or a designated business meeting typically at the SOT Annual Meeting and would be expected to be in attendance to receive the award. In addition, the awardee will be asked to give a brief speech about their experiences.

Nomination materials must be submitted no later than November 1, 2024 (11:59 PM US EST). The awardee will be notified by the end of November.
Questions? Contact Anup Ramachandran (aramachandran@kumc.edu), (CTTSS Councilor).

Current CTTSS members are encouraged to nominate a colleague for the Clinical and Translational Toxicology Specialty Section Career Achievement Award.



Events/Programs of Interest

Workshops on Increasing Research and Poison Centre Capabilities

G Hotel Gurney, Penang, Malaysia 11th & 12th Nov 2024

Scholarships include:

- attendance at APAMT; 11th –14th Nov 2024
- US$1000 towards travel & accommodation
- Poison Centre workshop (11th Nov)
- Research Training symposium (12th Nov)

Asia Pacific Association of Medical Toxicology
www.apamt.org

Research Training:

- increase research capabilities
- improve scholarly output
- expand networks
- develop collaborations

WP4

THE UNIVERSITY of EDINBURGH

Poison Centre Training:

- interactive cases
- use of TOXBASE
- use of patient information database
- use of poison centre data

WP5

TOXBASE.org

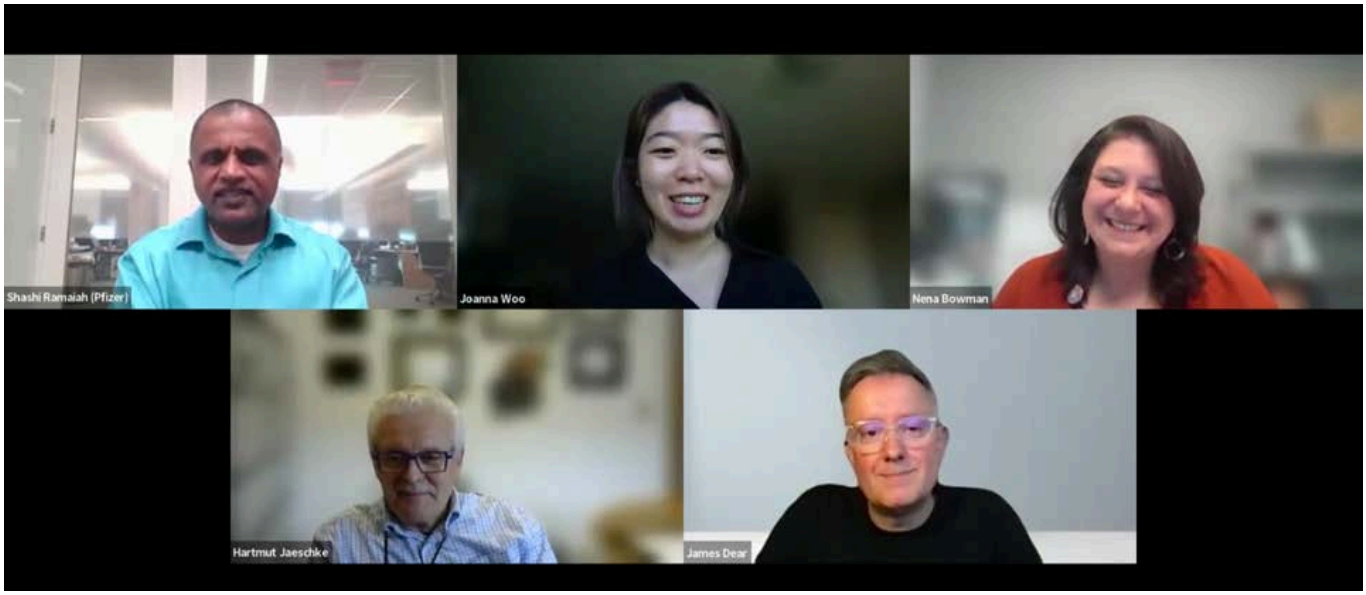
To **APPLY** for a scholarship contact: annie.watt@nhs.scot

Applications close: 31st July 2024 **Scholarship offers: 31st August 2024**

Please also consider submitting an abstract via www.apamt2024.usm.my/submission/online-submission

CTTSS Webinar Series:

Careers in Translational Toxicology



This past May, CTTSS hosted a webinar on careers in clinical and translational toxicology, designed to connect current trainees and early career scientists interested in this dynamic field. The webinar highlighted emerging roles that integrate translational components into toxicology research and development.

We had the privilege of hosting the following experts on our panel:

- **Dr. Hartmut Jaescke from the University of Kansas Medical Center**
- **Dr. James Dear from the University of Edinburgh**
- **Dr. Nena Bowman from the Tennessee Department of Health**
- **Dr. Shashi Ramaiah from Pfizer**

Our panelists shared insights into their roles, current projects, and the evolving landscape of clinical and translational toxicology. They highlighted the critical need to understand clinical applications when translating research to human health. The discussion also underscored the importance of multidisciplinary collaboration and teamwork in addressing complex research questions in this dynamic field.

Special thanks to the CTTSS Graduate Student Represenative, **Joanna Woo,** for organizing this event.

To learn more about the role of clinical and translational toxicologists, you can watch the webinar recording in the CTTSS Events section!

Past Presidents of CTTSS attend the 60th Birthday of the EAPCCT in Munich

Past CTTSS presidents from left to right: Alister Vale, Sally Bradberry, Kenneth McMartin, Horst Thiermann

The 60th birthday of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) was celebrated at the annual congress held in May in Munich, Germany. **In attendance were 4 Past Presidents of the CTTSS (photo above) of the Society of Toxicology!** Almost 400 participants from 49 nations participated including representation from the World Health Organization (WHO), American Academy of Clinical Toxicology, American College of Medical Toxicology, Asia Pacific Association of Medical Toxicology, and the Middle East and North Africa Clinical Toxicology Association.

One of the symposiums attended by past CTTSS presidents focused on lung toxicology in which basic science met clinical practice and highlighted the importance of appropriate translation of experimental findings in clinical routine. The issue emphasized the importance of the link between CTTSS and EAPCCT.

The next congress of the EAPCCT will take place in Glasgow, Scotland (27-30 May, 2025). See the EAPCCT website for more information.

Photo and update provided by: Prof. Dr. Horst Thiermann, Col retired (Past President of CTTSS and EAPCCT) and Prof. Dr. Paul Dargan (current President EAPCCT).

Undergraduate Educator Network (UEN) Community available on ToXchange

Help recruit the next generation of toxicologists!

On behalf of the SOT Education and Experiential Opportunities Committee, we would like to invite you to be part of an amazing community called the Undergraduate Educator Network (UEN). The UEN is an SOT community for those interested and/or currently engaged in undergraduate education; it is open to any SOT member and includes a ToXchange community, semi-annual newsletters, curricular materials, and webinars to support undergraduate teaching. It is also a great place to learn more about SOT resources available to faculty teaching/mentoring undergraduate students and resources available for undergraduate students to get more involved in SOT.

If you or any SOT members might be interested in joining, log into ToXchange, go to "Communities" in the navigation bar, and select "Open Groups"; "Undergraduate Educator Network" will display, and then you can click the "Join" button. You can also join the UEN through the SOT Undergraduate Educators page.

Graduate students and postdocs that might be interested in careers in academia are welcome and encouraged to join!

Don't forget: Awards for undergraduates are available. The deadline is October 15, 2024.

SOT Undergraduate Research Award **Undergraduate Diversity Student Travel Award**