May 2020

Northern California

Past President's Message

Dear NorCal SOT Regional Chapter Members,

It was truly my pleasure to serve as the President of the Northern California Regional Chapter of the Society of Toxicology. A warm welcome to our new members and newly elected board members for 2020–2021! I would like to personally welcome our new and returning board members Andrea Kim (President), Chris Frantz (VP), Mingyi Trimble (VP Elect), Donna Lee (Councilor), Vanessa Clark (Councilor), Ray Zhang (Treasurer), Hemant Chavan (Secretary), Alexandra Colón-Rodriguez (Postdoctoral Representative), and Bianca Yaghoobi (Student Representative). I would like to sincerely thank outgoing members Will Proctor (Councilor), and particularly our Past President Kathryn Page, who has spent many years serving on the chapter's board. I am deeply sorry that we did not get a chance to thank our outgoing board members at the NorCal SOT reception in March; we will be sure to do so at our next meeting, whenever that will be! I want to express my gratitude for their continued service to this Board and maintaining continuity to provide support for all the events throughout the year. The Board spends many hours throughout the year, and with that dedication we will continue to provide support to students/postdocs, as well as to current and new members to network and participate in fantastic events!

It has been an interesting and evolving year already, and we are adjusting to the changing environment, particularly as it relates to groups getting together. The NorCal SOT Regional Chapter continues to provide a variety of opportunities for the membership. The chapter is the 2^{nd} largest in SOT, with over 500 members! We were unable to hold the NorCal Reception at the Annual SOT Meeting in Anaheim, and unable to hold the Spring Symposium as planned (despite the great efforts of our Organizers Chris, with help from Donna and Will!). We hope to plan something in the Fall, so stay tuned! Please reach out to board members with any ideas, or topics you would like to see.

We continue to provide strong student outreach with our K-12 Education Outreach Events, as well as various mentoring opportunities for undergraduate, graduate, and postdoctoral students. Our Past Presidents Doris Zane and Toufan Parman have done a fantastic job on promoting K-12 Education Outreach; we look forward to volunteers on continuing the tradition when schools are back in session. Keep a look out for upcoming K-12 Education Outreach events this year. In the meantime, please do not hesitate to reach out

Officers

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Student Representative
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K-12 Committee
Dinah Misner

Newsletter Editor & Website Liaison
Hemant Chavan

to any member if you would like to start or need help with a local K-12 event in your area. Additionally, please check out upcoming mentoring and professional development events brought to us by Alexandra and Bianca this fall, assuming we are back in business!

The NorCal SOT Board is extremely grateful for the significant support of our Sponsors. Without their support we would not be able to continue with our outreach and scientific programs. If you are interested in becoming a Sponsor, please contact Ray Zhang to learn more about how your Sponsorship can contribute to the growth and success of the chapter.

On a personal note, I have been a member of NorCal SOT for many years and have met so many people through the organization that I now call friends and mentors. One of the things that has always stuck with me was how involved the leadership was in the chapter, their dedication to involving and engaging students and postdocs, and connecting people in Northern California through meetings and events. My favorite memories are from all the fun receptions we hold at the national SOT Annual Meeting every year, and constantly meeting new people there—I'm sad we weren't able to join together this March, but look forward to March 2021!

In closing, I encourage you all to continue your involvement with the chapter's program, in any way you can and provide feedback on any ideas you may have or ways we can continue to grow and improve. We look forward to your continued participation and support in 2020-2021.

Best wishes,

Dinah Misner, PhD, DABT, DSP
Past President, Norther California SOT Regional Chapter

A Review of the 2019 Fall NorCal SOT Symposium

On October 24, 2019, NorCal SOT hosted the 2019 Fall Symposium at South San Francisco Conference Center in South San Francisco, CA. The title of the symposium was "The Hematopoietic System: Therapeutics, Toxic Responses, and Strategies for 21st Century". The NorCal SOT President, Dr. Dinah Misner, along with the Board of Directors greeted over 100 registered attendees from regional business, government, and academia. Our featured speakers and their topics were as follows:

- **Toxicology or Exaggerated Pharmacology: The MOA of the IMiD Drugs:** *Brian Cathers (Plenary Speaker), PhD, Global Blood Therapeutics*
- **FDA Guidance on Nonclinical Development of Pharmaceuticals for Severely Debilitating or Life-Threatening Hematologic Disorders***: John Leighton, PhD (Remote Speaker), Office of Hematology and Oncology Products, US Food and Drug Administration*
- **De-Risking Hematopoietic Toxicity – The Need for More Complex In Vitro Tools:** *Aaron Fullerton, PhD, Genentech*
- **The Hematologic Toxicity of Anilide Herbicides and Its Use in Characterizing the Human Health Risk of Propanil:** *Peter Lohstroh, PhD, Department of Pesticide Regulation, California Environmental Protection Agency*
- **Cholinesterase Inhibition by Pesticides and Determinants of Intra- and Inter-Individual Variability:** *Heather Bolstad, PhD, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency*
- **Mechanisms and Investigations into Hematotoxicity:** *Nancy Everds, DVM, DACVP, Seattle Genetics*
- **SB-525, a Novel Gene Therapy for Treatment of Hemophilia A:** *Kathleen Meyer, MPH, PhD, DABT, Sangamo Therapeutics*

The meeting was a great success, with high attendance and excellent comments post meeting.

Above all, we would like to recognize and thank our Sponsors for making this event a success:

Silver Sponsors for NorCal SOT Fall Symposium 2019

- Battelle

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Bronze Sponsors for NorCal SOT Fall Symposium 2019

- Altasciences, Inotiv (previously BASi/Seventh Wave Laboratories), BioReliance Millipore Sigma, Calvert Laboratories, Charles River Laboratories, Covance, Emulate, Eurofins, Experimur, ITR Laboratories, Lovelace Biomedical, Novabiosis (previously Promethera Biosciences), Sinclair Research Center, SNBL, Stemonix, Theravance Biopharma, WuXi AppTec

Friend Sponsors for NorCal SOT Fall Symposium 2019

- Frontage Laboratories, Genentech, InSphero, SRI International

Welcome to New NorCal SOT Members as of May 2020

Greetings,

On behalf of the members of the Northern California Regional Chapter, it is our pleasure to welcome the new members of the Society of Toxicology and the Northern California Regional Chapter. As a Regional Chapter member, you will discover many opportunities for communicating, collaborating, and connecting with your fellow members at the regional and national level. You can find more information on the Northern California SOT website including information on meetings, newsletters, awards, governance, educational outreach, and more. We welcome you again to the Society of Toxicology and invite you to become an active participant in the Northern California Regional Chapter.

Sincerely,
Your Northern California SOT Executive Committee

First Name	Last Name	Affiliation
Elizabeth	Mutter-Rottmayer	University of North Carolina
Lindsey	Garnick	Cardno ChemRisk
Gulzar	Ahmad	Info Tox International Inc
Lennart	Anger	Genentech, Inc.
Maria	Arolfo	SRI International
Amy	Oldendorp	Genentech, Inc.
Yi-Hua	Tsai	University of California, Davis
Wilson	Rumbeiha	University of California, Davis
Matthew	Hayes	Genentech Inc.
Lisa	Truong	University of California, Los Angeles
Lisa	Liang	Cardno ChemRisk
Vivek	Lawana	American Preclinical Services, LLC
Andrew	Lickteig	Charles River Laboratories
Fjodor	Melnikov	Genentech, Inc.
Kari	Neier	University of Michigan
Peter	Andrew	University of California, Davis
Nakul	Ruparel	Apple Inc.
Huanhuan	Jiang	University of California, Riverside
Allison	Ehrlich	Oregon State University
Kitae	Kim	Seoul National University
Sakha	Jamadar	Texas Southern University
Priya	Upadhyay	University of California Davis
Gwendolyn	Osborne	Office of Environmental Health Hazard Assessment
Veneese	Brown	University of California, Davis
Nicole	McNabb	University of California, Davis
Bonnie Ransom	Stern	BR Stern and Associates LLC
Lowei	Lin	University of California, Davis
Anna	Kalashnikova	Department of Pesticide Regulation

Welcome to New NorCal SOT officers

VP – Elect: *Mingyi W. Trimble, ScD, DABT*
Mingyi has over 15 years of preclinical R&D experience supporting regulatory drug development for a wide range of therapeutic products and indications. She is currently a Senior Technical Director in Toxicology for WuXi AppTec Laboratory Testing Division. Mingyi is a Diplomate of the American Board of Toxicology since 2005. She received her Doctor of Science degree in Toxicology and a MS in Regulatory Toxicology and Risk Assessment from Tulane University in New Orleans.

Councilor: *Vanessa M. Clark, BS, ALAT, PMP*
Vanessa has been in the Safety Assessment group at Genentech since 2014, currently as a Scientific Manager and Study Monitor overseeing operations for CRO-outsourced nonclinical studies. In this role, she is responsible for ensuring comprehensive Sponsor oversight of regulated toxicology studies and collaborates cross-functionally on study design, execution and reporting. Within Genentech/Roche, she serves as the operational lead on a number of Immunology- and Pediatrics-focused advisory and expert working groups. Vanessa has over 15 years of experience in biotech, with previous Project Manager and Research Associate roles. Outside of work, she volunteers for Gene Academy, providing weekly STEM mentoring to 3rd -5th graders from local public schools. She has been a member of SOT since 2018. Vanessa is excited to join the NorCal SOT board as a Councilor.

Postdoc/Student Corner

Congratulations to Our 2020 Award Winners!!!

First Place Award Winner:

Peter Andrew, UC Davis
Pharmacological inhibition of mTOR activation by rapamycin attenuates neuroinflammation and spontaneous recurrent seizures in a rat model of acute organophosphate (OP) intoxication (Advisor: Dr. Pam Lein)

Second Place Award Winner:

Jonas Carlsbeek, UC Davis
The role of nicotinic receptors in seizure activity and death triggered by acute organophosphate intoxication in a mouse model (Advisor: Dr. Pam Lein)

Honorable Mentions:

Iemaan Rana, UC Berkeley
Formaldehyde and brain disorders: A meta-analysis and bioinformatics approach (Advisor: Dr Luoping Zhang)

Bianca Yaghoobi, UC Davis
RyR-active polychlorinated biphenyls (PCBs) cause neurobehavioral deficits in larval zebrafish (Advisor: Dr. Pam Lein)

Nicole McNabb, UC Davis
Multigenerational Impacts of Dietary Exposure to the Flame Retardant, BDE-99, in the Atlantic Killifish (*Fundulus heteroclitus)* (Advisor: Dr. Andrew Whitehead)

NorCal SOT Awardee Highlight!

I am Peter Andrew, a second-year PhD student in the laboratory of Pamela Lein at UC Davis interested in the development of therapeutic strategies for the prevention and treatment of drug-resistant epilepsy. In the Lein Lab, we study the long-term neurological consequences of organophosphate (OP) intoxication and identify approaches to mitigate these adverse outcomes. OPs are a class of compounds that are widely used around the world as pesticides, however, some have also been weaponized as nerve agents. Globally, accidental and intentional poisonings with OPs result in significant morbidity and mortality. Moreover, recent high-profile poisonings, including the use of OP nerve agents in the Syrian War and the assassination of Kim Jong-nam, point to the continued relevance of research on OP neurotoxicity.

OPs inhibit the enzyme acetylcholinesterase, a critical regulator of cholinergic neurotransmission throughout the body. This inhibition results in accumulation of acetylcholine at central and peripheral synapses, and excessive cholinergic neurotransmission. Acute intoxication with OPs elicits seizures and parasympathetic symptoms, which can be fatal without prompt therapeutic intervention. Current therapeutic countermeasures significantly improve survival following acute OP intoxication. However, clinical and preclinical data demonstrate that survivors develop chronic neurologic sequelae, such as cognitive and behavioral deficits and electrographic abnormalities, regardless of treatment. Most notably, current therapeutic countermeasures do not adequately protect against the development of spontaneous recurrent seizures (SRS) following acute OP intoxication. Thus, there remains an urgent need to develop more effective therapeutic regimens for the mitigation of chronic neurological effects of acute OP intoxication.

While numerous pathological mechanisms have been targeted to attenuate long-term consequences of acute OP intoxication, most interventions yield modest improvements. Emerging data, however, suggest that neuroinflammatory processes contribute to chronic neurotoxic effects of acute OP intoxication, including SRS. Acute OP intoxication produces robust and persistent neuroinflammation that correlates both spatially and temporally with the development of other neuropathological outcomes. Additionally, anti-inflammatories show some therapeutic efficacy in attenuating long-term outcomes of acute OP intoxication. These connections suggest that neuroinflammation could contribute to pathogenic processes following acute OP intoxication.

The mammalian target of rapamycin complex 1 (mTORC1) has been identified as a critical mediator of inflammatory responses and epileptogenic processes, suggesting the possibility that mTORC1 signaling is involved in OP-associated outcomes. Thus, we are investigating the role of mTORC1 in adverse neurological sequelae, particularly SRS, following acute OP intoxication. We have previously developed and characterized a model of acute diisopropylfluorophosphate (DFP) intoxication (see Siso et al., 2017, Guignet et al., 2020) to evaluate these processes. Prior to my involvement in this project, Dr. Michelle Guignet identified that daily administration of the mTORC1 inhibitor rapamycin (6mg/kg, i.p.) reduced metrics of microglial activation following DFP intoxication. Rapamycin suppresses microgliosis, expression of phagocytic markers, and morphological shifts characteristic of microglial activation at 7 days post exposure (DPE) (Fig.1a-c). Additionally, pilot data suggested an attenuation of DFP-induced SRS in animals treated with rapamycin. Collectively, these results identified the therapeutic potential of mTORC1 inhibition following OP intoxication to improve neuroinflammatory and electrographic sequelae.

To further characterize the role of mTORC1 in the context of OPs, I mapped the temporal profile of mTORC1 activation following acute DFP intoxication. A number of studies indicate that mTORC1 activity is upregulated following chemical-induced seizures; however, this relationship had not been evaluated in OP models. Using western blot analyses of the phosphorylation state of the mTORC1 downstream effector, ribosomal protein S6, I confirmed that hippocampal mTORC1 activity is upregulated within hours of DFP intoxication before returning to baseline by 3DPE. We then demonstrated that a single dose of rapamycin (6mg/kg, i.p.) administered at 40 minutes post DFP intoxication, inhibits DFP-induced upregulation of mTORC1 activity at 1DPE. Moreover, a single dose of rapamycin continued to suppress mTORC1 activity below baseline at 7DPE, suggesting a lasting impact of rapamycin on mTORC1 signaling following DFP intoxication. These data point to the therapeutic potential of a single dose of rapamycin to improve neuroinflammatory metrics and attenuate SRS following acute DFP intoxication.

We then sought to determine whether pharmacological inhibition of mTORC1 with rapamycin in conjunction with standard of care attenuates neuroinflammation and SRS to a greater extent than standard of care alone following acute DFP intoxication. Animals were instrumented to allow for continuous EEG and video recordings for 28DPE to assess the development and severity of SRS (Fig. 1d). Animals that did not receive any therapeutic interventions developed severe SRS following DFP intoxication. Alternatively, the animal that received standard of care still developed SRS, however, the frequency of seizures was reduced. Furthermore, the animal that received rapamycin in conjunction with standard of care did not develop SRS within 28DPE. While preliminary, these data are highly encouraging and suggest that rapamycin provides a degree of protection against the development of SRS following acute DFP intoxication.

Unfortunately, most research at UC Davis has been suspended due to the current COVID-19 public health crisis. Thus, I am planning the next directions of this research. First, I aim to continue evaluating the therapeutic efficacy of rapamycin to attenuate neuroinflammation and the development of SRS. Additionally, I hope to characterize the cell-type specific pattern of mTORC1 activation following acute DFP intoxication.

While these studies remain preliminary, our results suggest that targeting inflammatory processes following acute DFP intoxication is a promising strategy for mitigating the development of chronic adverse outcomes, including SRS. Such data will contribute greatly to our understanding of the role of inflammatory processes triggered by acute OP intoxication and inform further therapeutic development for mitigating persistent neurologic sequelae.

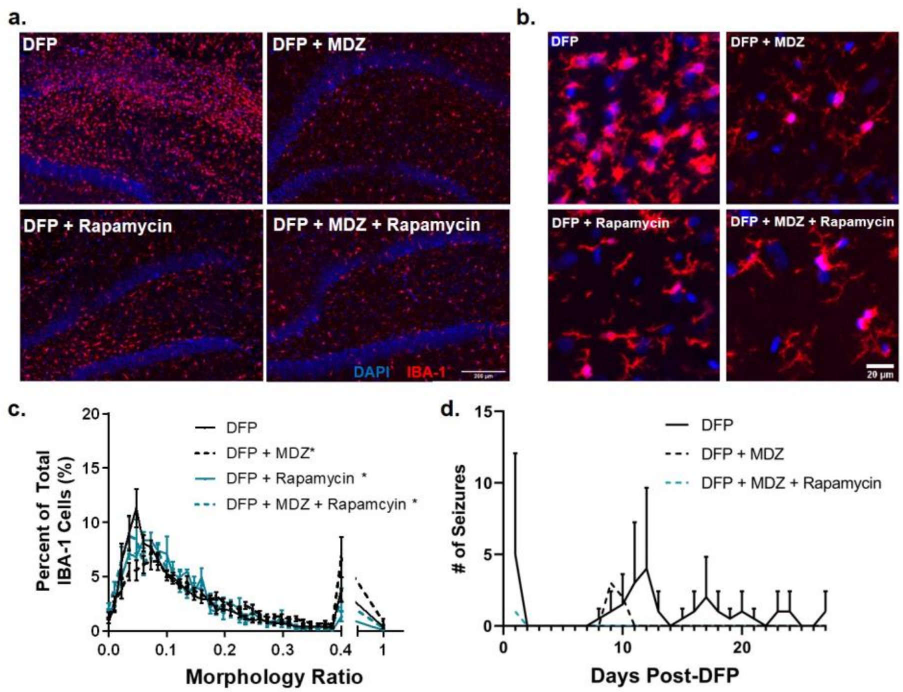

Figure 1. Rapamycin significantly reduces microglial activation and SRS following acute DFP intoxication. a. Representative photomicrographs of IBA-1 (red) immunolabeling and DAPI (blue) staining in the dentate gyrus of the hippocampus at 7 days post exposure (DPE). MDZ = midazolam; Scale bar = 200 µm. **b.** Higher magnification images of panel a showing morphologies of microglia in the dentate gyrus. Scale bar = 20 µm. **c.** Effect of rapamycin on the morphology of IBA-1 immunopositive cells shown as the distribution of cells exhibiting a specific morphology ratio in the dentate gyrus of the hippocampus. A morphology ratio of 0.0 corresponds to fully amoeboid cells (activated microglia) and a ratio of 1.0 corresponds to fully ramified "resting" microglia. Data are binned in 0.015 units, and presented as the mean value ± SE for all animals in each treatment group (n = DFP: 14; DFP + MDZ: 14; DFP + Rapamycin: 5; DFP + MDZ + Rapamycin: 5). *Significantly different from DFP at $p<0.05$ as determined by Friedman test with Dunn's multiple comparisons. **d.** Effect of a single dose of rapamycin on SRS within 28DPE presented as the mean number of seizures per day ± SD (n = DFP: 2; DFP + MDZ = 1; DFP + MDZ + Rapamycin = 1).

Upcoming Events

NorCal SOT Webinar Series 2020

Computational and *In Silico* Approaches in Toxicology:
Real World Case Studies

	July 30th at 12 pm (PT)
12:00 pm-12:10 pm	**Chapter announcements, acknowledgements, and membership survey results** *Dinah Misner (Past-President), Andrea Kim (President), Christopher Frantz (Vice President)*
12:10 pm-12:35 pm	**Computational Toxicology methods for Prediction of Preclinical Safety Endpoints** *Lennart T. Anger, PhD, ERT, Genentech*
12:35 pm-1:00 pm	**Small Molecule Lead Optimization to Increase Selectivity and Minimize Off-Target Effects** *Yu (Zoe) Zhong, PhD, DABT, Genentech*
	More webinars are planned for late summer and fall **Stay tuned and stay healthy**

NorCal SOT Spring Meeting - Canceled

As you are all aware we unfortunately had to cancel the Spring NorCal SOT Symposium due to the COVID-19 pandemic. In the meantime we are working on webinar series to substitute, and the first one is scheduled for July 30. We will send future event emails, so watch you email for announcements.

NorCal SOT Mentoring Event Postponed

We regret to inform you that our bi-annual Mentoring Event during this spring has been postponed. We made this difficult decision due to the ongoing COVID-19 pandemic. We hope to hold our future Mentoring Event (possibly virtual event) during this upcoming fall, as we know this is a valuable opportunity for students and postdocs to connect and learn from leaders in academia, government, and industry sectors. Please keep an eye out for future meeting announcements to either participate as a mentee or volunteer as a mentor.

SOT Virtual Meeting Program

Throughout the next few months, SOT will be presenting Scientific Sessions and Continuing Education courses originally planned for presentation in Anaheim as live webinars.

Virtual Meeting Schedule

More than 600 ePosters are available for viewing through the online version of the app, as well as the Online Planner and SOT Event App. SOT also has developed a 2020 ePoster Index, allowing you to view the ePosters by Poster Session