Midwest Regional Chapter
Society of Toxicology

Fall 2019 Newsletter

The MRC-SOT
Proudly Presents the Annual Fall Meeting:

Application of Toxicology Research in Human Health Protection

October 25, 2019
University of Wisconsin-Madison Pyle Center
Madison, WI

Sponsored by:
SOT Faculty United for Toxicology Undergraduate Recruitment and Education (FUTURE) Committee
Regional Chapter Undergraduate Activity Funding
And
AbbVie, Inc.

President's Message

Hello MRC-SOT members,

The Midwest Regional Chapter is proud to present the 2019 Fall meeting and career outreach event. The meeting will take place on Friday, October 25th from 12:00 pm to 4:00 pm at the Pyle Center, University of Wisconsin-Madison. The topic will focus on research efforts to protect human health.

Prior to the meeting, students and postdocs will also have the opportunity to gain first-hand knowledge of the drug discovery and development process by attending a tour at Exact Sciences at 9 am to 11:30 am on Oct 25th. The event will be open to 30 students and postdocs on a first-come-first-serve basis. The meeting will feature a panel discussion with representatives in industry and academia who work in the area of toxicology and human health. This is an excellent opportunity for students and trainees to learn about employment opportunities in toxicology.

The detailed meeting information, including registration, directions, and scientific program can be found in the newsletter. Many thanks to our President-Elect/Program Chair Chuck Mattis and Dr. Kira Light (Exact Sciences) for their efforts in coordinating the fall meeting and the career outreach event.

On behalf of the executive committee, I would like to thank you for the continued support of our regional chapter.

Thanks again,
Chad Vezina

Want to know more about the Midwest Regional Chapter?

Regional Chapter newsletters, information pertaining to membership, MRC-SOT awards, and nomination/application forms may be viewed or printed from our website:
http://www.toxicology.org/groups/rc/midwest/index.asp

MRC/SOT Fall Meeting Registration Information

The meeting will take place on Friday, October 25th from 12:00 pm to 4:00 pm at the Pyle Center, University of Wisconsin-Madison. Additional details (including location and full program) are included further in the newsletter. Contact Chad Vezina (chad.vezina@wisc.edu) with questions.

Online registration is available at the SOT website (link provided below). If not an SOT member, at the first login screen, there is an option to "click here" to create a new account. Upon the creation of a new account, the registrant can select the meeting from the "Events" drop down box and register for the meeting.

Click here for Online Registration

Exact Sciences Tour Registration
Students and postdocs can register for the Exact Sciences tour when they register for the Fall Meeting above. The tour of the Exact Sciences Facility will be held from 9 to 11:30 am on October 25, and is open to 30 students and postdocs on a first-come-first-served basis. A UW-Madison Fleet Vehicle will provide transportation from Union South to Exact Sciences and retuning to the Pyle Center. Additional details on location of the tour are included on page 5 of the newsletter.

Registration Cost
Midwest Regional Chapter of the Society of Toxicology Members: $50
Non-members: $75
Graduate Students: $10
Undergraduates: $0

On-line registration open: Now
On-line registration close: October 11, 2019

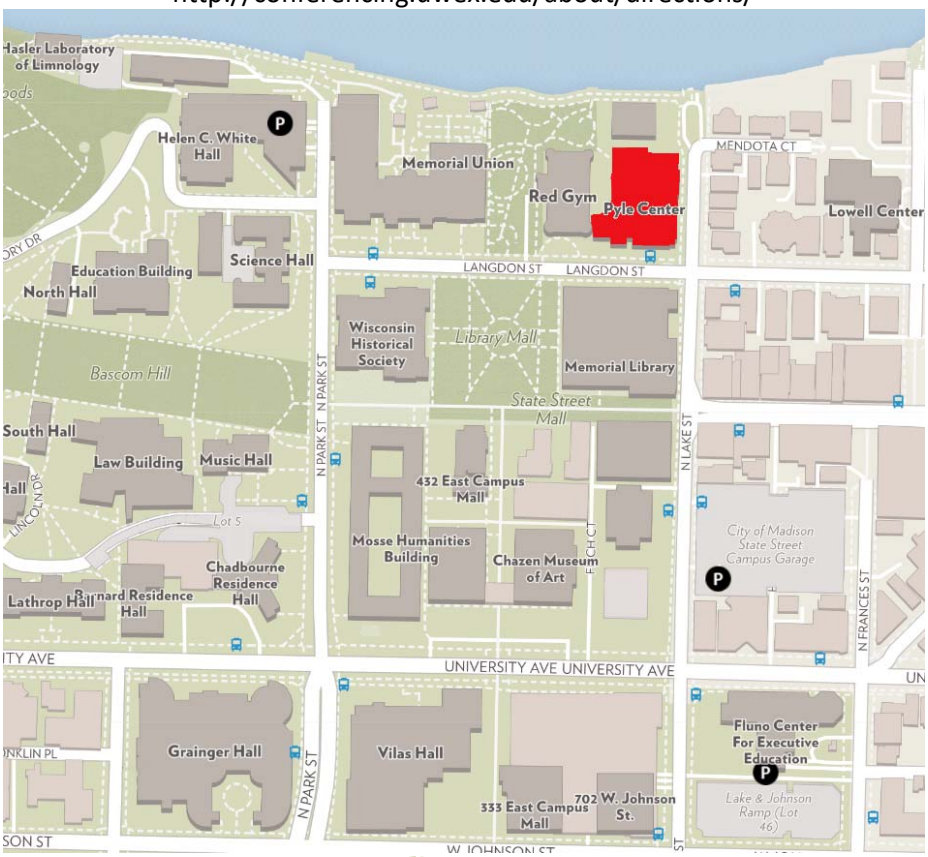
Cancellation Policy
Registrations are transferable but no refunds will be granted after October 11, 2019. We reserve the right to cancel or to change speakers if necessary. In the event of meeting cancellation, all registrants will receive a full refund. We are not responsible for travel expenses in the event of a cancellation or date change.

Meeting Location

University of Wisconsin-Madison Pyle Center, 702 Langdon St, Madison, WI 53706
Phone: (608) 262-1122
http://conferencing.uwex.edu/about/pyle-center/

Map of Meeting Location (The Pyle Center is in Red)

http://conferencing.uwex.edu/about/directions/



Parking

Lot 6 – Helen C. White Garage ($14/day/vehicle)
600 N Park St, Madison, WI 53706

Lot 83 – Fluno Garage ($12/day/vehicle)
601 University Ave, Madison, WI 53715

City of Madison State Street Garage ($1.50/hr/vehicle)
430 N. Frances St. (Frances St. side) Madison, WI

For parking inquiries, please contact the Pyle Center front desk at 608-262-1122.

Exact Sciences Tour

Limited to 30 applicants, first come, first serve

145 E. Badger Rd., Madison, WI 535713

Phone (for questions before day of tour): Ms. Kira Light, 608-535-8882

Phone (for questions day of tour): Ms. Hannah Winkel, 920-277-6454

Tour Meeting Location and Instructions

There are a limited number of parking spots. Security will have name tags and confidentiality forms in the main entrance. **Please check in at 8:45 am and the tour will begin promptly at 9am. The tour will conclude at 11:30 am.**

MRC-SOT Fall Meeting

October 25, 2019

"Application of Toxicology Research in Human Health Protection"

Career Outreach Event at Exact Sciences (RSVP Required)
9:15 – 11:30 am

Registration & Luncheon
12:00 – 1:00 pm

Welcome and Introductions
Chad Vezina, President, University of Wisconsin-Madison
Chuck Mattis, AbbVie, President-Elect
1:00 – 1:15 pm

Presentations

Rob Lipinski, PhD
University of Wisconsin Madison
Defining environmental influences in complex human birth defects
1:15 - 1:35 pm

Michael McCoy, M.S., CIH, CSP
Stantec Consulting Services, Inc.
Occupational Toxicology and Industrial Hygiene: Synergistic Disciplines for Improving Worker Health
1:45 - 2:30 pm

Refreshment Break
2:30– 2:45 pm

Mohan Rao, PhD
AbbVie, Inc.
Computational Approaches to Preclinical Projections
2:45 – 3:30 pm

Panel Discussion – Employment Opportunities in Toxicology and Human Health
3:30 – 4:00 pm

Concluding Remarks
Charles Mattis, President-Elect
AbbVie, Inc.

Defining environmental influences in complex human birth defects

Rob Lipinski, PhD
Associate Professor
Associate Director, Molecular and Environmental Toxicology Graduate Program
Department of Comparative Biosciences
University of Wisconsin-Madison
Madison, WI

Abstract

Most birth defects are caused by complex gene-environment interactions. While research focus is often placed on genetics, identification of environmental influences provides a more direct path to developing prevention strategies. Determining culpable environmental influences in etiologically complex human outcomes, however, remains a major barrier to this goal. We are pursuing a mechanism-driven approach to investigating environmental influences in holoprosencephaly (HPE), a rare human birth defect of the forebrain and face. Our investigations are focused on the pesticide synergist piperonyl butoxide (PBO) because this widely used environmental chemical was recently discovered to inhibit Sonic hedgehog (Shh) signaling, a pathway critical for face and brain morphogenesis. We first used mouse teratogenicity assays targeting the critical period of Shh signaling to demonstrate that acute PBO exposure can cause the characteristic brain and face malformations of human holoprosencephaly. Using mice that model the most common human HPE mutations, we then found that these normally silent genetic factors exacerbate the teratogenic impact of PBO exposure. To investigate the potential contribution of PBO exposure to human holoprospencephaly, we have teamed with collaborators at the NIH to develop a questionnaire-based retrospective case-control study to estimate household, occupational, and environmental pesticide exposure in the world's largest HPE patient cohort. Early results suggest an increased risk for HPE with report of maternal exposure during pregnancy to select pesticides including personal insect repellants and insecticides applied to pets. Using a mechanism driven-approach and integrating mouse teratogenicity and human epidemiological examinations, these studies have identified a specific pesticide compound as a potential risk factor for a rare and complex human birth defect.

Biosketch

Dr. Lipinski is an Associate Professor of Comparative Biosciences and Associate Director of the Molecular and Environmental Toxicology Graduate Program at the University of Wisconsin. After receiving his Ph.D. in Molecular and Environmental Toxicology from the University of Wisconsin in 2008, he conducted postdoctoral studies in embryology and teratology at the University of North Carolina at Chapel Hill. Leveraging his multidisciplinary training in developmental biology and toxicology, Dr. Lipinski's research focuses on understanding etiologically complex human birth defects, particularly those affecting the face and brain. To resolve complex gene-environment interactions, his group integrates clinically relevant mouse models with tractable in vitro approaches, and collaborates extensively with molecular geneticists working in human populations. The ultimate goal of Dr. Lipinski's research is to develop prevention strategies based upon identification of at-risk populations and culpable and avoidable environmental influences.

Occupational Toxicology and Industrial Hygiene: Synergistic Disciplines for Improving Worker Health

Michael McCoy, M.S., CIH, CSP
Senior Industrial Hygienist and Toxicologist
Stantec Consulting Services, Inc.
Mequon, Wisconsin

Abstract

Occupational toxicology is the application of the principles and methodology of toxicology toward understanding and managing chemical, biological, radiological and physical hazards in the workplace. Industrial hygiene is the art and science of anticipation, recognition, evaluation and control of workplace hazards. These scientific disciplines have significant overlap in both their definitions and scope of practice, and when utilized together, they can help prevent, evaluate and ultimately improve worker health. Mr. McCoy will share some interesting consulting projects to demonstrate how occupational toxicology and industrial hygiene can be used simultaneously to evaluate worker exposure, both in the present and historically. From these exposures he will help the audience understand and evaluate health effects from these exposures. He will also share his experiences with toxic tort and other litigation associated with occupational exposures to dusts, metals, fibers and volatile organics.

Biosketch

Mr. McCoy is an industrial hygiene, occupational health and toxicologist with specific strengths in occupational exposure reconstruction, historical exposure evaluation and complex industrial hygiene evaluations. Michael has conducted applied research in clinical and diagnostic laboratory medicine, and medical pharmacology and toxicology. From 1995 to 1998 he worked as a clinical scientist in several medical laboratories performing analysis for therapeutic and illicit drugs, and other clinical laboratory testing. In addition, Michael has six years of business management experience in a Fortune 500 firm prior to joining GZA GeoEnvironmental, Inc. (GZA) in 2007. Michael served as a consulting industrial hygienist and toxicologist with GZA until December 2017. From January 2018 through May 2018, Michael worked as industrial hygienist and safety manager for Alcami Corporation, a global contract pharmaceutical manufacturing firm. His role involved complex industrial hygiene and safety management at Alcami's Germantown, Wisconsin active pharmaceutical ingredient (API) manufacturing operations. He also owned and operated McCoy Industrial Hygiene, LLC and provided industrial hygiene and toxicology services. As a Senior Industrial Hygienist and Toxicologist at Stantec Consulting Services, Inc. (Stantec), Mr. McCoy trains and mentors Stantec's industrial hygienists and safety specialists in the United States and Canada. He primarily provides industrial hygiene and toxicology consulting services to Stantec's global clients and is a member of Stantec's Global Health, Safety, Security and Environment (HSSE) team. Mr. McCoy has a M.S. from the Medical College of Wisconsin in Pharmacology and Toxicology and a B.S. from Marquette University in Medical Laboratory Technology and is a Certified Industrial Hygienist (CIH) and Certified Safety Professional (CSP).

Computational Approaches to Preclinical Projections

Mohan Rao, PhD
Computational Toxicologist
Investigative Toxicology and Pathology
AbbVie, Inc.

Abstract

Most small molecule drugs interact with unintended, often unknown, biological targets and these off-target interactions may lead to both preclinical and clinical toxic events. Undesired off-target interactions are often not detected using current drug discovery assays, such as experimental poly-pharmacological screens. Thus, improvement in the early identification of off-target interactions represents an opportunity to reduce safety-related attrition rates during preclinical and clinical development. In order to better identify potential off-target interactions that could be linked to predictable safety issues, a novel computational approach to predict safety-relevant interactions currently not covered was designed and evaluated. These analyses, termed Off-Target Safety Assessment (OTSA), cover more than 7,000 targets (~35% of the proteome) and > 246,704 preclinical and clinical alerts. The approach described herein exploits a highly curated training set of > 1 million compounds (tracking > 20 million compound-structure activity relationship/SAR data points) with known in vitro activities derived from patents, journals, and publicly available databases. This computational process was used to predict both the primary and secondary pharmacological activities for a selection of 857 diverse small molecule drugs for which extensive secondary pharmacology data are readily available (456 discontinued and 401 FDA approved). The computed physicochemical properties such as clogP (i.e. lipophilicity), molecular weight (MW), pKa and logS (i.e. solubility) were found to be statistically different between the approved and discontinued drugs. The OTSA process predicted a total of 7990 interactions for these 857 molecules. Of these, 3923 and 4067 possible high-scoring interactions were predicted for the discontinued and approved drugs, respectively, translating to an average of 9.3 interactions per drug. The OTSA process correctly identified the known pharmacological targets for > 70% of these drugs, but also predicted a significant number of off-targets that may provide additional insight into observed in vivo effects. About 51.5% (2025) and 22% (900) of these predicted high-scoring interactions have not previously been reported for the discontinued and approved drugs, respectively, and these may have a potential for repurposing efforts. Moreover, for both drug categories, higher promiscuity was observed for compounds with a MW range of 300 to 500, TPSA of ~200, and clogP ≥7. This computation also revealed significantly lower promiscuity (i.e. number of confirmed off-targets) for compounds with MW > 700 and MW < 200 for both categories. In addition, 15 internal small molecules with known off-target interactions were evaluated. For these compounds, the OTSA framework not only captured about 56.8% of in vitro confirmed off-target interactions, but also identified the right pharmacological targets for 14 compounds as one of the top scoring targets. In conclusion, the OTSA process demonstrates good predictive performance characteristics and represents an additional tool with utility during the lead optimization stage of the drug discovery process. Additionally, the computed physiochemical properties such as clogP (i.e. lipophilicity), molecular weight, pKa and logS (i.e. solubility) were found to be statistically different between the approved and discontinued drugs, but the internal compounds were close to the approved drugs space in most part.

Biosketch

Mohan Rao obtained his doctoral degree in Computational Biology from the Indian Institute of Science, Bangalore, India. He then advanced his scientific training at the Molecular Biology department, The Scripps Research Institute, La Jolla, CA, USA. During this tenure, he developed novel computational methods to solve the x-ray structure and atomic contacts of enzymes and receptors involved in the blood clotting cascade. Using cutting edge computational technologies, he also explored molecular contacts that lead to abnormal clotting and inflammation.

Mohan joined TransTech Pharma, NC, USA, as a senior research scientist, progressively advancing in that system and became the Director of the computational drug discovery group. In TransTech Pharma, he made significant contributions in inventing towards developing novel drug candidates for diseases of the central nervous system, inflammation, cancer, diabetes and thrombosis. In particular, he developed a protein-protein interaction models for the RAGE complex. This computer model played a significant role in the discovery of novel orally bioavailable drug molecules to treat Alzheimer's disease, and one of these compounds is currently in a Phase III clinical trial.

He joined the Preclinical Safety department at AbbVie, Inc. in 2015 as a Computational Toxicologist. His role in PCS is to develop and use a multi-omics analysis framework (Genomics, Proteomics, Metabolomics and interactomics) together with bio/cheminformatics and AI/ML tools to predict potential on/off-targets/biomarkers and its associated preclinical and clinical outcomes. Mohan presented his research findings at various professional scientific meetings and has published several peer-reviewed manuscripts and more than 25 US patents.

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