IIT UPDATE

Spring 2016

INSTITUTE FOR INTEGRATIVE TOXICOLOGY

in this issue....

Above: Past and future MSU SOT Presidents gathered at the annual IIT Alumni and Friends Reception at the 55th Annual Society of Toxicology Meeting. Pictured from top left clockwise, IIT Director Dr. Norbert Kaminski, Dr. Jerry Hook, Dr. James Bus, Dr. Ken Wallace, Dr. Patricia Ganey, and Dr. Jay Goodman.

IIT AFFILIATES SUCCESSFUL AT 55TH SOT MEETING IN LOUISIANA

Students and faculty of the MSU Institute for Integrative Toxicology were highly honored at this year's 55th annual Society of Toxicology (SOT) meeting in New Orleans, Louisiana with numerous abstracts presented and many special honors awarded.

The SOT annual meeting is the largest toxicology meeting and exhibition in the world, attracting more than 7,000 scientists from industry, academia and government from various countries around the globe. This year's meeting was held March 13 -17, 2016.

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IIT AFFILIATES SUCCESSFUL AT SOT cont.

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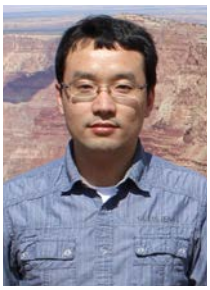
The following students in the MSU-IIT's Environmental and Integrative Toxicological Science (EITS) training program received awards or honors:

Nikita Joshi, training with Dr. James Luyendyk, received the Graduate Student Leadership Committee Outstanding Leadership Award for her work as a Regional Chapter student representative of the Michigan Chapter of the SOT. Joshi also received the 3rd place Carl C. Smith Graduate Student Award from the Mechanisms Specialty Section for her abstract, "*Fibrinogen Inhibits Biliary Hyperplasia and Fibrosis in Mice by Modulating IFNg-driven Macrophage Activation*."

Natalia Kovalova, training with Dr. Norbert Kaminski, received the 3rd place Best Student Presentation from the Immunotoxicology Specialty Section for her abstract, "*Role of Aryl Hydrocarbon Receptor (AHR) Polymorphisms in TCDD-Mediated Biological Activity in the Human B Cell*."



Jinpeng Li, training with Dr. Norbert Kaminski, received the American Association of Chinese in Toxicology and Charles River Best Abstract Award, 2nd place, as well as the 3rd place Best Student Presentation from the Immunotoxicology Specialty Section, for his abstract, "*2,3,7,8-Tetrachlorodibenzo- p -dioxin (TCDD)-Mediated Alterations of EBF1 in Impaired Early Human B Cell Development*."

Ashley Maiuri, 2015 EITS graduate who trained with Dr. Robert Roth, received a 3rd place award from the In-Vitro and Alternatives Specialty Section for her thesis, "*Drug-Cytokine Cytotoxic Interaction to Indiosyncratic Drug-Induced Liver Injury.*"

Rance Nault, training with Dr. Timothy Zacharewski, won the 1st place Graduate Student Research Award from the Molecular and Systems Biology Specialty Section, as well as the 1st place Carl C. Smith Graduate Student Award from the Mechanisms Specialty Section for his abstract, "*Pyruvate Kinase Isoform Switching and Hepatic Metabolic Reprogramming by the Environmental Contaminant 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)*." Rance also received a Graduate Student Travel Award from the SOT. **Dr. Zacharewski** received the Graduate Student Mentor Award from the MSBSS.

Alexandra Turley, training with Dr. Cheryl Rockwell, received the 1st place student presentation award from the Immunotoxicology Specialty Section for her abstract, "*Nrf2 Promotes Th2 Differentiation in Murine and Human CD4 T Cells*."

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Left: Dr. Anna Kopec and Rance Nault were both award recipients from the Molecular and Systems Biology Specialty Section.

Bottom: Nikita Joshi receiving the Outstanding Leadership Award.

Top Left: Current EITS students- Joe Zagorski and Kelly Fader, along with research technician Jenna Bursley.

Top Right: Dr. Weimin Chen, past EITS graduate with current EITS student Jiajun (Brian) Zhou.

Bottom: Past and present Zacharewski lab members: Rance Nault, Anna Kopec, Lyle Burgoon, Ed Dere, Agnes Karmaus, and Kelly Fader.

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Postdoctoral student, **Dr. Anna Kopec**, from the lab of Dr. James Luyendyk, won the 1st place Postdoctoral Fellow Research Award from the Molecular and Systems Biology Specialty Section for her abstract, "*RNA Sequencing Reveals Induction of Mmp12 by Fibrin(ogen) Engagement of Leukocyte αMβ2 Integrin as Critical for Liver Repair After Acetaminophen Overdose in Mice*." Correspondingly, **Dr. Luyendyk** received the Postdoctoral Fellow Mentor Award from MSBSS.

Jessica Ray, who worked in the lab of Dr. James Luyendyk and recently graduated with her B.S. in Animal Science from MSU, received the SOT Undergraduate Intern Travel Award for her abstract, "*Epigenetic Alterations in Response to the Inhalation of Different Sized Multi-Walled Carbon Nanotubes*." This research was completed during the Summer Undergraduate Research Program at the Center for Environmental Health Sciences at the University of Montana in 2015.

Lizbeth Perez-Castro, undergraduate student from the University of Puerto Rico at Cayey and summer research program participant in the lab of Dr. William Atchison, won the Perry J. Gehring Diversity Student Travel Award and the Pfizer SOT Undergraduate Student Travel Award for her abstract, "*Mitochondrial Membrane Potential Changes in Response to Methylmercury-Induced Toxicity in Motor Neuron-Like Cells, NSC34 Cells: The Role of Dimethyl Fumarate in Neuronal Protection*."

The SOT Inhalation and Respiratory Specialty Section awarded Dr. Kazuyoshi Kumagai and his co-authors, Ryan Lewandowski, **Daven Jackson-Humbles**, **Ning Li**, Steven Van Dyken, **James Wagner** and **Jack Harkema** with the Paper of the Year Award for the publication, "*Ozone-induced Nasal Type 2 Immunity in Mice is Dependent on Innate Lymphoid Cells*," which was published in the American Journal of Respiratory Cell and Molecular Biology. Dr. Kumagai, a MSU visiting toxicologic pathologist from Tokyo, Japan, worked in the laboratory of Dr. Harkema for two years (2014-2016).

Dr. James Luyendyk, affiliated faculty member in the Department of Pathobiology and Diagnostic Investigation, received the Mentoring Award from the Women in Toxicology Special Interest Group. The Women in Toxicology Mentoring Award is used to reward and encourage individuals who, by their outstanding roles as mentors, have made important contributions to women in the field of toxicology. This award recognizes an individual (male or female) in academia, government, industry, or a related field who has been a major influence in the mentoring of women scientists entering the field of toxicology and/or whose leadership and service have provided career development opportunities for women toxicologists or encouraged women to achieve their professional goals.

Dr. James Wagner, affiliated faculty member in the Department of Pathobiology and Diagnostic Investigation, will be the Host/Mentor for the Inhalation and Respiratory SS Donald E. Gardner Inhalation Toxicology Education Award, which was awarded to Katherine Zychowski postdoctoral fellow from the University of New Mexico. She will be working in Dr. Wagner's lab in the summer of 2016.

ROCKWELL SELECTED AS ONE OF FIVE TO RECEIVE NIEHS ONES AWARD

Cheryl Rockwell, Assistant Professor in Pharmacology and Toxicology and IIT-affiliated faculty member, has been selected as one of five exceptional early-career scientists to receive a grant as part of the Outstanding New Environmental Scientist (ONES) Program. The National Institute of Environmental Health Sciences (NIEHS) created the ONES award to support researchers, in the formative stages of their careers, who conduct cutting-edge research to study how the environment influences human health.

"The ONES awardees are a talented group of scientists with tremendous potential," said Gwen Collman, Ph.D., NIEHS Division of Extramural Research and Training director. "We hope that receiving this grant at a pivotal time will propel them into successful careers in environmental health research."

As a junior investigator, this award is vital for expanding and maintaining Rockwell's research program. Specifically, this award will allow her to pursue her investigation into how the food additive, tBHQ, modulates T cell differentiation as well as the downstream effects on allergy and the role of the transcription factor Nrf2 in this process. Her lab's preliminary data suggests that activation of Nrf2 by tBHQ promotes the differentiation of CD4 T cells into Th2 cells, an allergy-like phenotype, and this ultimately exacerbates downstream immune response to allergen. The main purpose of this research project is to determine the mechanism for these effects.

"It is a tremendous honor to have been selected for this prestigious award," said Rockwell. "I am personally acquainted with a number of previous ONES awardees and am thus well aware of the notable accomplishments of the alumni of this program. I cannot describe how thrilled and grateful I am to be considered among the ranks of the ONES investigators."

LI AWARDED USDA GRANT TO STUDY FRESH PRODUCE, FOOD SAFETY

Hui Li, Associate Professor in Plant, Soil and Microbial Sciences and IIT-affiliated faculty member, has been awarded a $475,000 grant from the U.S. Department of Agriculture to study human exposure to the harmful chemicals present in fresh produce.

Addressing a primary aspect of food safety, Li's research will focus on produce absorption of pharmaceutical and personal care products, commonly known as chemicals of emerging concern, or CECs. Consumption of these chemicals may lead to increased antibiotic resistance and other health issues.

A better understanding of how vegetables absorb CECs from soil and water will help the scientific community in its efforts to reduce these chemical risks.

"The human health consequences of chronic exposure to an undefined mixture of pharmaceuticals designed to be bioactive at low concentrations are largely unknown, but potentially of enormous significance," Li said.

Li will use new, state-of-the-art equipment to analyze various CEC levels and determine how soil management and irrigation practices can decrease absorption of these substances.

The three-year project is made possible by the USDA's Agriculture and Food Research Initiative. It will extend through October 2018 in collaboration with fellow IIT-affiliated faculty Stephen Boyd and Wei Zhang, as well as Ray Hammerschmidt, all from the Department of Plant, Soil and Microbial Sciences at MSU.

RESEARCH EVENING 2016 A SUCCESS

The Institute for Integrative Toxicology's Annual Research Evening showcased trainees in the Environmental and Integrative Toxicological Sciences Graduate Training program and their accomplishments. This year's event took place on November 23, 2015 in the Lincoln Room at the MSU Kellogg Center. The event included dinner, student posters and platform presentations. Three EITS graduate students presented the platform presentations.

Nikita Joshi, working in the lab of Dr. James Luyendyk, spoke on, "Fibrin Deposition Following Bile Duct Injury Limits Fibrosis Through an αMβ2-Dependent Mechanism." Joshi has focused her graduate research on identifying mechanisms whereby the coagulation protein fibrin(ogen) inhibits liver injury and fibrosis in experimental xenobiotic-induced liver fibrosis.

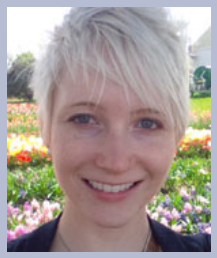
Natalia Kovalova, working in the lab of Dr. Norbert Kaminski, spoke on, "Role of Aryl Hydrocarbon Receptor (AHR) Polymorphisms on TCDD-Mediated Biological Activity in Human B Cells." Kovalova has focused her graduate research on identifying molecular mechanisms of TCDD-induced suppression of IgM secretion by human B cells and the effect of aryl hydrocarbon receptor (AhR) single nucleotide polymorphisms (SMPs) on B cell sensitivity to TCDD-mediated suppression of B cell effector function within the human population.

Rance Nault, working in the lab of Dr. Timothy Zacharewski, spoke on, "Disruption of Hepatic Metabolism by Repeated TCDD Exposure in Mice." Nault has focused his graduate research on examining the role of the aryl hydrocarbon receptor (AhR) in the development of fatty liver disease. To do this he leverages 'omics' and systems biology approaches which allows him to examine large datasets in their biological context, and gain some insight on mechanisms.

Next year's Annual Research Evening will take place on November 30, 2016 at the MSU Kellogg Center.

ACHIEVEMENTS BY IIT STUDENTS

Isola Brown, EITS student in the lab of Dr. Brian Gulbransen, was awarded the 2016 Takeda Research Award from the Gastrointestinal & Liver Physiology (GI&L) Section of the American Physiological Society. She will be presenting a 10 minute talk at the GI&L Trainee poster symposium at the Experimental Biology meeting in San Diego, California the first week of April on her abstract, "*Regulation of the Antioxidant Glutathione by Enteric Glia During Inflammation*."



Brittany Winner, EITS student in the lab of Dr. John Goudreau, was given a travel award from the Society for Neuroscience to attend and present at the Forum for European Neuroscience Societies in Copenhagen, Denmark in July 2016. She will present on, "*Promotion of Autophagy by UCH-L1 in Parkin Deficient Mice*."

Sophia Kaska, EITS student in the lab of Dr. Michelle Mazei-Robison, was recently awarded a PhRMA Foundation graduate fellowship. Kaska's project is focused on investigating the molecular mechanisms that contribute to susceptibility to stress and stress-induced opiate reward in the ventral tegmenta area in order to better understand the co-morbidity of depression and opiate addiction. Identifying the neuroadaptations that occur in depression and addiction may help identify novel molecular targets for therapeutic intervention.

Juliette Brown, EITS student in the lab of Dr. Gina Leinninger, was awarded a Ruth L. Kirschstein Predoctoral Individual National Research Service Award (NIH F31) for her abstract, "*Role of Neurotensin Neurons in Coordinating Adaptive Energy Balance*."

IIT WELCOMES THREE NEW AFFILIATED FACULTY

This winter the MSU-IIT added three new affiliated faculty members Dr. Sudin Bhattacharya, Dr. Ned Jackson, and Dr. Wei Zhang. These faculty join the IIT as research collaborators as well as contributors to the Environmental and Integrative Toxicological Sciences Graduate Training Program.

Sudin Bhattacharya
Assistant Professor, Institute for Integrative Toxicology

Dr. Bhattacharya received his B.M.E. in Mechanical Engineering from Jadavpur University in 1997, his M.S.M.E. in Mechanical Engineering from University of Kentucky in 1999, and his Ph.D. in Mechanical Engineering from the University of Michigan in 2006.

Dr. Bhattacharya is broadly interested in several areas of computational toxicology. A major focus of his work is the application of computational methods to study the signaling and transcriptional regulatory networks that underlie the determination of cell fate, and the perturbation of these networks by environmental pollutants like dioxin. Specifically, he is interested in integrating diverse genomic data sets to map and model transcriptional regulatory networks and their environmental perturbation in the immune system and the liver. He is also interested in the extraction of predictive features from genomic data sets to model the toxic potential of chemical agents and pharmaceuticals, and spatial multi-scale modeling of tissue-level phenomena like toxicant-induced liver injury. He relies primarily on mathematical and statistical modeling as a research tool, and works in close collaboration with experimental scientists.

Wei Zhang
Assistant Professor, Department of Plant, Soil and Microbial Sciences, Environmental Science and Policy Program

Dr. Zhang received his B.S. in Environmental Chemistry from Nanjing University in 2000, his M.S. in Biosystems Engineering from Oklahoma State University in 2006, and his Ph.D. in Environmental Engineering from Cornell University in 2010.

Dr. Zhang is broadly interested in the quality and sustainability of soil and water resources, with emphasis on the movement of water, solutes (e.g., nutrients, agrochemicals, and environmental toxins), and fine particles such as microorganisms, abiotic colloids, and engineered nanoparticles in natural and engineered systems, particularly in unsaturated soils. His current research focuses on the fate and transport of emerging contaminants in the soil-water-biota continuum within the framework of "one health". The overarching goal of his research is to promote human and environmental health by understanding fundamental transport processes and developing sustainable agricultural practices. Recently, his laboratory is studying the fate and transport of three major emerging contaminants: (1) veterinary pharmaceuticals and hormones, (2) engineered nanoparticles, and (3) emerging microbial plant pathogens. Other broader research themes are environmental and soil physics and hydrology, environmental nanotechnology, and colloidal and interfacial science.

James E. "Ned" Jackson
Professor, Chemistry

Dr. Jackson received his A.B. in Chemistry from Harvard University in 1977, his Ph.D. in Chemistry from Princeton University in 1986, and was a postdoctoral fellow at Ohio State University from 1986-1988.

Dr. Jackson is excited to join the illustrious ranks of IIT members. Jackson group efforts bring mechanistic organic chemistry to problems of "greening" energy and chemicals production and pharmaceutical synthesis. Based on fossil-free (solar, wind, nuclear) electric power, electrocatalytic conversions of organic compounds are under study to bypass reagent-based chemistry and the resulting byproduct/waste streams. For instance, a recent finding is an electroactivated method that replaces classical halocarbon alkylating agents with simple alcohols to alkylate amines, a step widely practiced in drug manufacture. The large-scale goal is to open the door to replacement of fossil (petroleum) with bio-derived feedstocks in our energy and chemical technologies and industries. This work has grown out of long term collaborations with chemical engineers Dennis Miller and Chris Saffron, and analytical chemist Greg Swain at MSU.

A second direction is the discovery and tuning of novel hydrogen bonding modes. Recent fundamental insights into links between aromaticity and hydrogen bonding have implications for understanding and design of organocatalysis and pharmaceutical ligand binding, as well as natural molecular recognition processes such as DNA associations. Related work has led to materials for detoxification of mercury-contaminated waters.

Tools commonly used in the group include kinetics, isotope labeling, and stereochemical studies to map out the detailed atomic motions involves in these and other molecular processes, informed by high level quantum chemical simulations to probe energetics and dynamics.

RECENT EITS GRADUATES

Heidi Hannon
Pharmacology and Toxicology
Mentor, William Atchison

Hannon will defend her dissertation, "Assessing the Role of the Transient Receptor Potential Ankyrin 1 Channel in Methylmercury-Induced Neurotoxicity," on May 4, 2016 and earn her Ph.D. degree in Pharmacology and Toxicology and Environmental Toxicology.

Hannon will then be a postdoctoral associate at Indiana University-Purdue University, Indianapolis (IUPUI) Stark Neurosciences Research Institute in the laboratory of Dr. Armin Blesch. Her research will focus on mechanisms of pain associated with spinal cord injury.

In the next five years, Hannon hopes to continue an active research career in the pharmaceutical industry.

Erica Clark
Food Science and Human Nutrition
Mentor, James Pestka

Clark defended her dissertation, "Impact of Sex and Age on Deoxynivalenol (DON)-Induced Anorexia Using a Murine Model," on August 20, 2015 and earned her Ph.D. degree in Food Science and Human Nutrition and Environmental Toxicology.

Clark is currently applying for industry and postdoctoral positions in a variety of locations. In five years she hopes to be a project manager at a consulting company.

UPCOMING EVENTS SPRING 2016

IIT Seminar Series

The Institute for Integrative Toxicology is excited to once again host a seminar series this year that will feature experts and students in the field of toxicology.

- EITS student Denis Male will speak on, "The Potential Association Between Alflatoxin B_1 Exposure and Severity of Malaria Among Children," on Tuesday, April 26, 2016, at 12 noon in 162 Food Safety and Toxicology Building.
- Dr. Jamie Bernard, Assistant Professor, Pharmacology and Toxicology, MSU, will speak on, "Environmental Impacts on Adipose Tissue: Implications for Inflammation and Tumor Growth," on Tuesday, May 3, 2016 at 12 noon in 162 Food Safety and Toxicology Building.

Introduction to Physiologically Based Pharmacokinetic (PBPK) Modeling Short Course

PHM 980, Section 301, 1 credit
May 18-20, 2016 (two full days and one half day)

Location: Food Safety and Toxicology Building, Rm 162
Instructors: Sudin Bhattacharya, Michigan State University, Rory B. Connolly, US EPA, Qiang Zhang, Emory University

This short course will cover the principles of physiologically based pharmacokinetic (PBPK) modeling and introduce the application of this technique in chemical health risk assessment and drug development. Upon completion of this course, you will be able to:

- Understand the fundamental concepts underlying PBPK modeling
- Describe the absorption, distribution, metabolism, and elimination of chemicals using mass balance differential equations
- Build PBPK models to simulate tissue dosimetry using Berkeley Madonna®
- Appreciate the application of PBPK models in human health risk/safety assessment and drug development

The course comprises lectures and hands-on computer simulation exercises. Students will be required to bring a PC (not Mac) laptop computer each day to the class to run simulation exercises.

All course participants should register at http://commerce.CASHNet.com/msu_3813.

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