

# IIT UPDATE

INSTITUTE FOR INTEGRATIVE TOXICOLOGY



## in this issue....

MSU SRP Center .....	1
Favor Fellowship .....	3
Achievements .....	3
SRP Center Projects .....	4
SRP Center Cores .....	5
CRIS Science Day 2022 .....	6
Seminar Series Fall .....	7
EITS Graduate .....	7

## Institute for Integrative Toxicology Successfully Competes for NIEHS Superfund Research Center

A multidisciplinary team of researchers at MSU has received a five-year, \$10.5 million Superfund Research Program Center (SRP) grant from the National Institute of Environmental Health Sciences to conduct innovative and collaborative biomedical and remediation technology research.

In 2000, the US EPA identified high-levels of dioxin-like compound contamination in the Tittabawassee River and adjacent floodplain near its confluence with the Saginaw River in the state of Michigan. Based on the potential for human health and environmental impact of this contamination, a highly innovative MSU SRP Center research team will investigate dioxin-like compounds in this area. The goal of the team is to develop innovative solutions for reducing these toxins and better understand the health risks they cause.

The chemicals in the halogenated aromatic hydrocarbon (HAH) family are persistent environmental contaminants that accumulate in the food chain. The chemicals of greatest concern to human and environmental health bind with high affinity to a protein called the aryl hydrocarbon receptor (AhR) and are often described as “dioxin-like.” These chemicals, which include polychlorinated dibenzo-p-dioxins, dibenzofurans, biphenyls and polycyclic aromatic hydrocarbons, are environmentally

persistent, fat soluble contaminants that accumulate in the food chain leading to human and wildlife exposure. Although dioxin-like compounds have been studied widely, there does not yet exist a precise understanding of the relationship between alterations in specific biochemical processes and particular toxic responses observed in animals or humans. There is also limited understanding of how dioxin-like compounds interact with components of soil, which may act as a type of filter and help to limit their effects on living organisms. In addition, knowledge of the enzymes present in microorganisms within the environment capable of degrading dioxin-like compounds is currently limited.

Based on these crucial data gaps, three complementary and highly integrated biomedical research projects are the basis of the newly funded MSU SRP Center grant with the objective of linking biochemical processes induced by dioxin-like compounds to specific toxic responses produced in the liver, thyroid and the immune system. In addition, two environmental science and engineering projects will work to advance existing knowledge on dioxin-like compound bioavailability when adhered to soil components and to characterize environmental microbial organ-

...continued on page 2

# IIT Superfund Research Center cont.

...continued from page 1

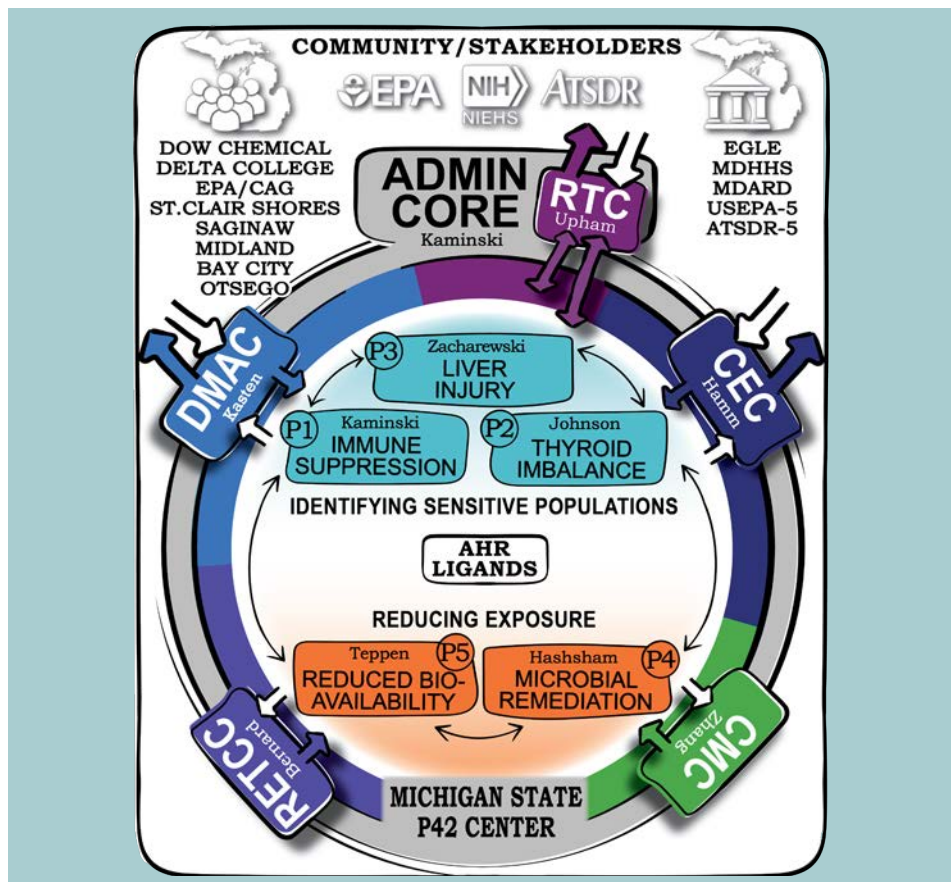
isms capable of degrading dioxin-like compounds, including the specific enzymes involved. “The MSU SRP Center provides a unique opportunity for cross disciplinary approaches and collaborations,” commented Principal Investigator Dr. Norbert Kaminski, “which is critical when addressing complex scientific problems.”

These research projects will be supported by five cores. The Computational Modeling Core will develop dynamic computational models of biological responses induced by AhR ligands. An Administrative Core will support research, training, community engagement, data management, and information and technology transfer. Within the Administrative Core, a research translation group will share research findings with target audiences in government, industry and academia. A Community Engagement Core will communicate with community stakeholders through engagement with county and city health officials in three new Michigan communities that continue to experience dioxin exposure. A Data Management and Analysis Core will provide the technology, expertise, infrastructure and training necessary to curate datasets, metadata, processing and analyses needed to properly manage and share high quality reproducible data. Lastly, a Research Experience and Training Coordination Core (RETCC) will ensure cross-disciplinary training to pre- and postdoctoral trainees.

The MSU SRP Center research team includes 25 investigators from Michigan State University (20), Emory University (1), Purdue University (1), Rutgers University (2) and the Michigan Department of Health and Human Services (1). The grant is administered by the Institute for Integrative Toxicology (IIT) at MSU.

Results from MSU SRP Center studies will be integrated using data science approaches to develop predictive computational models of adverse effects in support of risk assessment efforts.

To learn more about each of the MSU SRP Center projects and cores, please see pages 4 and 5. 📖



## MSU Superfund Research Center - The Details

The **overall objective** of the MSU SRP Center is to elucidate mechanistic, quantitative and computational interactions of AhR agonists with biotic and abiotic processes.

The **major research thrusts** will provide new mechanistic information regarding:

- » the diversity and physiogenomic responses of (chloro)dioxin degrading microbial populations indigenous to soils, sediments and groundwater;
- » the geochemical parameters governing adsorption, bioavailability and long-term fate of AhR ligands through interactions

with components in soils and sediment, namely char-like black carbon geosorbents;

- » and the elucidation and computational modeling of specific biochemical pathway interactions with the ligand-activated AhR which cause adverse responses in the liver, thyroid and immune system, specifically in B cells.

A **major goal** of the MSU SRP Center is to develop new innovative tools that identify sensitive human subpopulations and reduce exposure through effective remediation of contaminated Superfund sites. This will be achieved by:

- » identifying and sequencing genes encoding novel (chloro) dioxin-metabolizing enzymes in microbial organisms;
- » computationally modeling biological responses in mammalian systems;
- » and defining the physico/chemical properties of soil components that affect PCDD/F bioavailability, biodistribution, and microbial biotransformation.

Collectively, these three goals will provide valuable information regarding the human risk associated with environmental contamination by AhR agonists.

# Favor Selected for 2022 Gina M. Finzi Memorial Student Summer Fellowship Program



EITS graduate student, Olivia Favor, was selected as one of six recipients to receive the prestigious 2022 Gina M. Finzi Memorial Student Summer Fellowship from the Lupus Foundation of

America. The fellowship program was developed to cultivate an interest in lupus research among young scientists. Recipients of the fellowship have spent their summer conducting research in areas that are critical to moving the lupus research field forward and are mentored by an established lupus investigator throughout the duration of their research. The results of research by the awardees will contribute to new

therapies, prevention strategies and educational interventions to better understand, detect and treat people with lupus. Since its founding, the Gina M. Finzi Memorial Student Summer Fellowship Program has supported the work of nearly 200 young investigators throughout North America.

Favor is mentored by IIT-affiliated faculty member, Dr. James Pestka, and was awarded for her project, “Soluble Epoxide Hydrolase Inhibition: A Novel Approach for Suppressing Environmentally-Triggered Lupus.”

Lupus is a chronic autoimmune disease with no cure that causes skin rash, joint pain, inflammation, and kidney damage. Continual exposure to air pollutants in the environment, such as silica dust, are known to exacerbate lupus symptoms in genetically susceptible individuals. To improve quality of life, patients with lupus often use steroids, but their long-term usage can have side

effects like heart disease, diabetes, and bone loss. A novel class of drugs that inhibit an enzyme called soluble epoxide hydrolase (sEH) is a new promising steroid-sparing strategy that promotes production of pro-resolving fatty acid metabolites in tissues to counter inflammation. The goal of Favor’s project is to determine whether inhibiting sEH will prevent early-onset silica-triggered inflammation and autoimmunity in lupus-prone mice. Lupus-prone mice will be given either control diet or experimental diet containing an sEH inhibitor, intranasally exposed to one dose of silica, then sacrificed one week or four weeks after silica exposure. Positive results from this study could be a first step leading to clinical development of sEH inhibitors as safe, inexpensive steroid-sparing drugs that improve longevity and quality of life in lupus patients.



## Student and Faculty Achievements

- » **Jonathan Diedrich**, postdoctoral fellow in the laboratory of Dr. Jamie Bernard, received the IMS Young Investigator Award for Exemplary Abstract from the 19<sup>th</sup> International Myeloma Society Annual Meeting. The meeting took place in Los Angeles, California, August 25-27, 2022. His abstract was, “*The Role of Bone Marrow Adipocyte-Modulated Aryl Hydrocarbon Receptor Activity in Multiple Myeloma Cellular Growth and Survival.*”
- » **Sophia Kaska**, EITS alumnus, was named an Early Career Representative on the Federation of American Societies for Experimental Biology (FASEB) Board. Kaska is a manager of science initiatives and outreach at Research!America.
- » **Ebenazar Okoyeocha**, (pictured at right) EITS student training with Dr. Neera Tewari-Singh, received a travel award for his

presentation in the 15<sup>th</sup> Annual CounterACT Network Research Symposium in New Orleans, Louisiana, in June 2022. The symposium was organized by the National Institute of Environmental Health Sciences, the National Institute of Allergy and Infectious Diseases and the National Institute of Health Office of the

Director. Okoyeocha spoke on, “*The Role of Nrf2 Pathway in Chloropicrin Induced Ocular Toxicity in Human Corneal Epithelial Cells and Mice.*”

- » **Brad Upham**, IIT-affiliated faculty member, received the Distinguished Service Award from the 2022 National Meeting of the Society of In Vitro Biology. Two of Upham’s undergraduate students also received awards recently. Anna Heath received a first place presentation award at the 2022 University Undergraduate Research and Arts Forum. Jamie Liebold received a first place presentation award at the 2022 Great Lakes Pediatrics Research Forum.



## MSU Superfund Research Center Projects

### Project 1: Dioxin-like Compounds Suppress IgM Responses by Targeting CD5<sup>+</sup> (Innate-like) B Cells, which can Serve as a Biomarker of Susceptibility to Environmental AHR Ligands

Norbert Kaminski, Project Leader

Lance Blevins, Co-Investigator

Dioxin-like halogenated aromatic hydrocarbons (DLC) are ubiquitous environmental contaminants that suppress antibody responses. A population of white blood cells, termed CD5<sup>+</sup> B cells, is exquisitely sensitive to suppression by DLC and accounts for impairment of

antibody responses. This project uses human white blood cells to elucidate the mechanism by which DLC suppress antibody responses in CD5<sup>+</sup> B cells and also proposes to use the percentage of circulating CD5<sup>+</sup> B cells as an indicator of human sensitivity to immune suppression by DLC.

### Project 2: Coupling Bioengineered and Computational Models of Thyroid Homeostasis to Support Human PCDD/F Risk-Assessment

Brian Johnson, Project Leader

Thyroid hormones regulate cellular energy metabolism throughout the body and chemical disruption of this function in humans causes neurological, hearing, and vision dysfunction in children, as well as metabolic disorders and cancer in adults. Due to the complex nature of the thyroid system, the way many Superfund chemicals disrupt thyroid function is unclear.

This project proposes to bioengineer thyroid and liver microtissues and use them along with computational modeling to understand how these chemicals cause toxicity, test chemicals and their mixtures for their ability to disrupt thyroid signaling, and translate the findings to determine how chemical exposures might affect human populations.

### Project 3: The Role of HMGCR in Modulating TCDD-induced, AHR-mediated NAFLD

John LaPres, Co-Project Leader  
Timothy Zacharewski, Co-Project Leader  
Rance Nault, Co-Investigator

The aryl hydrocarbon receptor (AhR) is a sensor protein for environmental pollutants such as 2,3,7,8-tetrachlorodibenzo-p-dioxin and related compounds. These chemicals have been linked to adverse outcomes, including non-alcoholic fatty liver disease (NAFLD) and this project will investigate

the link between AhR activation and changes in cholesterol homeostasis in TCDD elicited hepatotoxicity and the progression of NAFLD. Given that ~20 million Americans suffer from NAFLD, investigating the link between AhR activation and the progression of NAFLD is of national importance.

### Project 4: Design Principles and Field-Deployable Models for Economical Remediation of Dioxin-Contaminated Sites

Syed Hashsham, Project Leader  
Allison Cupples, Co-Investigator

Donna Fennell, Co-investigator  
Gerben Zylstra, Co-Investigator

Some anaerobic bacteria are capable of breathing dioxins. This project aims to leverage this capability to develop integrated methods for economical clean-

up of dioxin-contaminated sites. Key advancements include reduction in time to clean-up and toxicity, development of biomarkers indicative of the rates, and establishment of decision-making tools.

### Project 5: Bioavailability as a Central Concept in Determining Remediation Goals and Strategies for PCDD/F-Contaminated Superfund Sites

Brian Teppen, Project Leader  
Stephen Boyd, Co-Investigator  
Cliff Johnston, Co-Investigator  
Hui Li, Co-Investigator

This project directly addresses NIEHS Superfund Mandate #4 for the development of "basic biological, chemical, and physical methods to reduce the amount and toxicity of hazardous substances." Project 5 will help US EPA understand whether activated carbon (AC) is an effective soil/sediment amendment to sequester PCDD/Fs in forms that eliminate their mammalian bioavailability

and toxicity, and thus protect human and ecosystem health. Project 5 will test a cause-and-effect relationship for the rates at which AC can reduce or eliminate mammalian bioavailability by measuring a multi-year time series for a) the rates at which AC amendments accumulate PCDD/Fs; and b) the mammalian bioavailabilities of PCDD/Fs from these same soils.

# MSU Superfund Research Center Cores

## Administrative Core

Norbert Kaminski, *Core Leader*  
Brad Upham, *Co-Investigator*

The Administrative Core provides support for the research, training, community engagement, data management and information and technology transfer in this Center Program. The Administrative Core will take leadership for regular communication with Center

investigators and NIEHS for exchange of information, prepare progress reports, fiscal responsibility, technology transfer and communication with stakeholders in government, academia and industry regarding the research program.

## Data Management and Analysis Core

Eric Kasten, *Core Leader*  
Jonathan Babbage, *Co-Investigator*  
Sudin Bhattacharya, *Co-Investigator*  
Rance Nault, *Co-Investigator*

The Data Management and Analysis Core (DMAC) will support effective data management and data science-based analysis through the implementation of a comprehensive data management and analysis plan. This will involve: 1) facilitating coordination between projects and cores to foster data science approaches for identifying new associations within disparate data that lead

to the formation of new hypotheses, 2) enabling data sharing between MSU SRC projects and cores, as well as external stakeholders, and interoperability with external repositories, 3) implementing data quality assurance and quality control procedures and processes, and 4) providing center-wide training regarding data management and analysis principles.

## Community Engagement Core

Joseph Hamm, *Core Leader*  
James Dearing, *Co-Investigator*  
Kristin Ward, *Co-Investigator*  
Adam Zwickle, *Co-Investigator*

The Community Engagement Core proposes to expand our existing close collaboration with the Michigan Department of Health and Human Services through a novel set of engagement activities that will listen to three Michigan communities affected by dioxins, empower them to make informed prevention decisions through health education interventions, and evaluate the impacts of those engagements. We will innovate on our previous work by

leveraging the state of the science on trust, risk, and community engagement to optimally position the engagements to build trusting relationships between the Department and Michigan communities. We also propose to disseminate what we learn to our wider Center and the entire Superfund Research Program to better position them to build trust with the various individuals and groups impacted by their work.

## Research Experience and Training Coordination Core

Jamie Bernard, *Core Leader*  
Jay Goodman, *Co-Investigator*  
Brian Teppen, *Co-investigator*

The Research Experience and Training and Coordination Core (RETCC) will be the innovative and coordinating hub that facilitates the Michigan State University Superfund Research Center's aim to provide multi-method, interdisciplinary training to predoctoral and postdoctoral students through research

collaborations across biomedical and non-biomedical research projects as well as the Community Engagement Core, Data Management and Analysis Core and the Administrative Core's Research Translation functions.

## Computational Modeling Core

Qiang Zhang, *Core Leader*  
Sudin Bhattacharya, *Co-Investigator*  
Rance Nault, *Co-Investigator*

By supporting multiple biomedical and environmental engineering projects, the Computational Modeling Core develops a suite of innovative computational tools to help improve our understanding of the

toxicological effects of dioxin on immunity, thyroid hormone homeostasis and lipid metabolism, and support health risk assessment of dioxin exposure.

# CRIS Science Day 2022 - Developmental Immunology & Immunotoxicology

The 2022 Center for Research on Ingredient Safety Science Day held on October 12, 2022, focused on developmental immunology and immunotoxicology as well as on the effects of nanoplastics on human health. Three sessions were held:

## Session One: Developmental Immunology and Immunotoxicology

\*Co-hosted by the Alternatives to *in vivo* Developmental Immunotoxicity Testing Working Group

- » **Fenna C.M. Sillé, Ph.D.**, Johns Hopkins Bloomberg School of Public Health  
*A Path Forward: Current and Future Perspectives on Developmental Immunotoxicity Testing*
- » **Eliver Ghosn, Ph.D.**, Emory University School of Medicine  
*Prenatal Immunity Represents a Functionally Distinct Hematopoietic Lineage*
- » **Juan Carlos Zúñiga-Pflücker, Ph.D.**, University of Toronto  
*From Stem Cells to T Cells, Applications and Implications*
- » **Isha Khan, Ph.D. Candidate**, Michigan State University  
*Characterization of an In Vitro Model of Human Hematopoiesis to Study the Role of Aryl Hydrocarbon Receptor Signaling in Human Hematopoietic Differentiation*

## Session Two: Effects of Nano- and Microplastics on Human Health

- » **Robert Ellis-Hutchings, Ph.D.**, Dow Chemical  
*Microplastics and Human Health - What Do We Know and What Are We Missing?*
- » **Christie Sayes, Ph.D.**, Baylor University  
*Progress and Challenges in Developing Nano- and Microplastic Particle Reference Materials for Environmental Health Effects Testing*
- » **Baoshan Xing, Ph.D.**, University of Massachusetts Amherst  
*Microplastics Reduce Lipid Digestion in Simulated Human Gastrointestinal System*

## Session Three: Science Communication Panel Discussion

Discussion Topic: Building Trust in Scientific Information in an Era of “Fake News”

This session looked at changing public perceptions about science and scientific information. Panelists included:

- » **Helena Bottemiller Evich**, Founder and Editor-in-Chief of FoodFix.co, *Evich is an award-winning reporter who previously led food coverage at Politico, launched Food Fix to be the go-to source*

*for food policy news and analysis, for insiders and consumers alike*

- » **Elisabeth Anderson**, Director of Science Communication, CRIS, *Anderson focuses on demystifying dense subjects using a human-based storytelling approach that meets individuals where they are, not where experts assume they should be. She specializes in digital media and digital tools.*

With moderator:

- » **Roger Lowe**, Principal, RKL Communications Strategies, *Lowe is a senior communications and public affairs leader with more than 40 years of experience at a leading trade association, one of America’s most recognized non-profit brands, top public affairs agencies and as a newspaper reporter. His multi-faceted experience enables him to effectively position initiatives, manage high-risk crises and enhance and protect an organization’s reputation.*

For more information on the Center for Research on Ingredient Safety, please visit: <https://cris.msu.edu>. ☘

## Recent CRIS Blog Topics

The Center for Research on Ingredient Safety continues to use their expert knowledge to research, fact check, and supply the global community with the latest science-based information about the ingredients in food, beverages and other consumer products. Here are some of CRIS’s most recent blog post topics:

- » Special Edition - Homemade Infant Formula
- » How to Series - Removing Pesticide Residue
- » What’s the Risk? Food Packaging
- » What’s the Risk? Talc-Based Cosmetic Products
- » Trending - Organic Foods
- » Trending - Mycotoxins
- » What’s the Risk? Zinc Oxide
- » How to Series - Interpret a Study: Background
- » How to Series - Interpret a Study
- » What’s the Risk? Titanium Dioxide
- » Trending - Anti-nutrients
- » Trending - Laundry Detergent Enzymes

Read more on all of these topics at: <https://www.canr.msu.edu/cris/news-views/>

## Save the Date!

The **IIT Research Evening** is back this year! We are excited to once again celebrate our EITS trainees and their accomplishments at our annual event.

The Research Evening will be held Wednesday, **November 30, 2022**, 5:15 to 8:00 p.m. in the Lincoln Room at the MSU Kellogg Center. The evening will

include a poster session, dinner and student presentations. Please RSVP to Kasey Baldwin, [kbaldwin@msu.edu](mailto:kbaldwin@msu.edu) by November 22.

## IIT Seminar Series Fall 2022

The IIT is excited to host the IIT Seminar Series this fall once again with three fantastic seminars.

The IIT hosted **Dr. Lance Blevins** Assistant Professor, Institute for Integrative Toxicology, MSU, on September 20. He spoke on, “AHR Activation Suppresses Human CD5<sup>+</sup> Innate-like B Cell IgM Secretion Via Enhancement of CD9<sup>+</sup> B Regulatory Cell Function.”

In October, the IIT is pleased to host **Dr. Katherine Hanson**, Associate Director, PPD, Thermo Fisher Scientific on Tuesday, October 18. She spoke on, “Academia to Pharmaceutical Industry, My Pathway.”

The final seminar of the fall will feature **Dr. Justin Colacino**, Associate Professor, Department of Environmental Health Sciences and Department

of Nutritional Sciences, University of Michigan on Tuesday, November 15. He will speak on, “Chemical Exposures, Dys-regulated Stem Cell Biology, and Breast Cancer Disparities.”



**Dr. Lance Blevins**  
September 20

“AHR Activation Suppresses Human CD5<sup>+</sup> Innate-like B Cell IgM Secretion Via Enhancement of CD9<sup>+</sup> B Regulatory Cell Function”



**Dr. Katherine Hanson**  
October 18

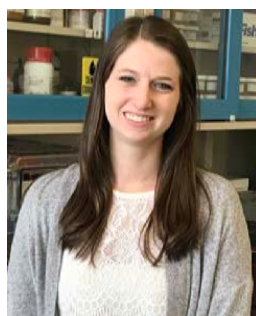
“Academia to Pharmaceutical Industry, My Pathway”



**Dr. Justin Colacino**  
November 15

“Chemical Exposures, Dys-regulated Stem Cell Biology, and Breast Cancer Disparities”

## Recent EITS Graduates



**Dawn Kuszynski**  
Pharmacology and Toxicology  
Mentor, Adam Lauver

Dr. Dawn Kuszynski received her Ph.D. after completing the dual major program in Pharmacology and Toxicology and Environmental Toxicology. Her dissertation was, “The Vascular Effects of Clopidogrel.”

Kuszynski is now the head of *in vivo* research at Therapeutic Systems Research Laboratories (TSRL), Inc. TSRL is a preclinical drug accelerator that helps drugs developed at universities get to the clinical trial phase. Kuszynski is a junior PI being trained in the writing of SBIR grants. Her current work focuses on drugs to treat infections, but she will be expanding into thrombosis in the future.

## IIT Welcomes New EITS Students

The IIT is pleased to welcome the following students who have joined the EITS program in the past several months:

- » **Saamera Awali**, training with Dr. Cheryl Rockwell
- » **Ankita Bhattacharya**, training with Dr. Courtney Carignan
- » **Jennifer Hinman**, training with Dr. Kin Sing Lee
- » **Patricia Hsu**, training with Dr. Felicia Wu
- » **Maria Kloboves**, training with Dr. Rita Strakovsky
- » **Ebenazar Okoyeicha**, training with Dr. Neera Tewari-Singh
- » **Christine Wei**, training with Dr. James Luyendyk
- » **Nat Yawson**, training with Dr. Jamie Bernard
- » **Xu Zhiliang**, training with Dr. Hui Li



### The IIT on Facebook

Did you know the IIT has a Facebook account? Keep up to date with seminar announcements, upcoming events and news links right from our page. When you visit, make sure to click “Like” so you don’t miss out on important IIT news!

[facebook.com/instituteforintegrativetoxicology](https://facebook.com/instituteforintegrativetoxicology)



# Institute for INTEGRATIVE TOXICOLOGY

Michigan State University  
1129 Farm Lane  
Food Safety and Toxicology, Rm 165  
East Lansing, MI 48824

517.353.6469  
tox@msu.edu