



IIT UPDATE

INSTITUTE FOR INTEGRATIVE TOXICOLOGY

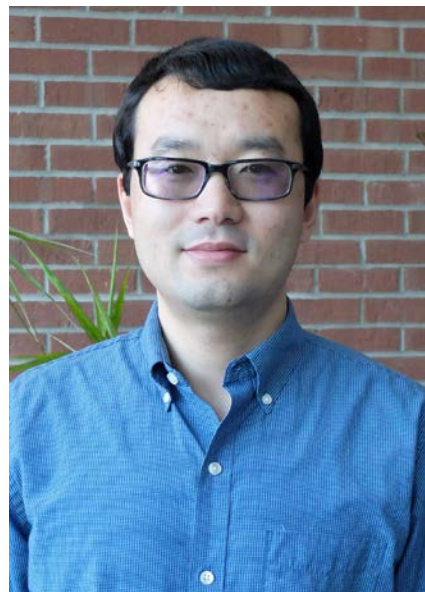


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EITS Alumnus Jinpeng Li Joins CRIS and IIT Faculty

Dr. Jinpeng Li, EITS alumnus, joins the Center for Research on Ingredient Safety as an assistant professor and the IIT as an affiliated faculty member. Li is a cellular and molecular toxicologist interested in better understanding and promoting the safe use of chemicals to protect as well as enhance public health. A major focus of his research is the development and application of physiologically relevant new approaches and methodologies to predict the potential toxicity of chemicals. He has established and published an in vitro human B lymphopoiesis model to investigate the effects of dioxin on human B cell development and the underlying molecular mechanisms. Li has also established a 3D spheroid culture system using human hepatocytes to predict hepatotoxicity, as well as a neurotoxicity assessment model using human iPSC-derived neurons and the microelectrode array technology. At the Center for Research on Ingredient Safety, one of his current research focuses is to characterize the effect of cannabidiol on immune responses, es-



pecially in the context of inflammation, using human leukocytes.

Li completed his postdoctoral training with the Toxicology and Environmental Research and Consulting team at the Dow Chemical Company, where he worked to advance predictive toxicology by developing new approaches and methodologies, including a state-of-the-art 3D spheroid liver cell culture system to predict hepatotoxicity and an integrated testing strategy for assessing

developmental neurotoxicity.

Li received his Ph.D. in Genetics and Environmental Toxicology from Michigan State University in 2017 and was mentored by Dr. Norbert Kaminski in the EITS program. His dissertation research project involved establishing an innovative model to assess the effects of chemicals on the development of the human immune system and investigating the underlying molecular mechanisms.

Both CRIS and the IIT are pleased to welcome Dr. Li back to MSU! 🍷

A.J. Robison and Team Find Gender Distinct Circuit for Depression



IIT-affiliated faculty member, **A.J. Robison**, along with a team of scientists, has found a gender-distinct circuit for depression that activates during stress and is controlled by testosterone.

Robison is an associate professor in the Department of Physiology.

Depression affects women nearly twice as much as men, but unraveling the brain's blueprint that regulates this behavior, let alone identifying specific molecular differences between sexes, has proven difficult.

Robison and his team, however, have found and flipped a switch in the brain, revealing a single circuit in mice that activates during stress and is controlled by testosterone. The results, published in *Biological Psychiatry*, focus on the activity between neurons in the ventral hippocampus, which become active under stress and emotion, and their activation of nucleus accumbens neurons, critical players in reward and motivation.

"What makes these findings stand out is not only identifying this new circuit," said Robison, lead author of the study, "but also observing and confirming how it drives different behaviors in males and females."

"Oddly enough, many circuit-specific animal model studies involving depression-related behaviors don't include female subjects. This gap exists

despite sex differences in several depression-related brain regions, including the hippocampus," Robison added.

To help close this void, Robison and his team focused on this hippocampus-accumbens circuit and saw that the activity in male brains during stress was significantly lower than in females, and this required testosterone. When they removed testosterone, however, the male mice began expressing depression-like behaviors.

Conversely, the team observed increased circuit activity in female brains, but when testosterone was introduced, the neurons quieted, and the female mice became resistant to the depression-like behaviors.

"Even with our best antidepressants, such as Prozac, we don't know exactly how they work," Robison said. "This is the first time we've found a circuit that drives this sexually different behavior; other scientists can now

explore how this could translate to identifying new therapeutic targets in humans."

Robison's group used chemogenetic tools to manipulate specific circuit activity in the mouse brain in this study. Such tools may inform the development of "genetic medicine" for the treatment of human diseases in the future.

Additional MSU scientists who contributed to this research include: Elizabeth Williams, Claire Manning, Andrew Eagle, Ashlyn Swift-Gallant (now at Memorial University of Newfoundland), Natalia Duque-Wilckens, Sadhana Chinnusamy, Adam Moeser, Cynthia Jordan and IIT-affiliated faculty member, **Gina Leininger**.

This research was funded in part by the National Institute of Mental Health, the National Institute of Neurological Disorders and Stroke, the National Institute on Drug Abuse and the Avielle Foundation. 📌



EITS Research Evening Celebrates Student Research

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 Wednesday, December 4, 2019 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:



Tyler Firkus, training in the lab of Dr. Cheryl Murphy, spoke on, "*The Sublethal Effects of Sea Lamprey Parasitism on Lake Trout Reproduction and Growth.*" Firkus is a doctoral student in the De-

partment of Fisheries and Wildlife and has focused his graduate research on assessing the influence of stressors on fish reproductive physiology, immune function, and growth. He is also interested in assessing how perturbations at the molecular, organ, and individual level have consequences for populations as well as the interface between chemical and non-chemical stressors.

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Neera Tewari-Singh Receives \$1.423 Million U01 Grant from the National Institutes of Health



IIT-affiliated faculty member, **Neera Tewari-Singh**, was recently awarded a \$1.423 million U01 grant from the National Institutes of Health - Countermeasures Against Chemical

Threats Program (CounterACT) and National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) for her project, “*Targeted Therapeutic Approaches to Counteract Toxicity from Phosgene Oxime Skin Exposure.*” This three year grant is an extension of her ongoing studies under the previously awarded R21 grant, “*Phosgene oxime cutaneous toxicity and mechanisms to identify therapeutic targets.*” Dr. Tewari-Singh is an assistant professor in the Department of Pharmacology and Toxicology.

Tewari-Singh’s project is a part of the comprehensive research CounterACT program, a trans-agency initiative launched by the Department of Health and Human services after the 9/11 attacks to improve the nation’s emergency preparedness by engaging academia in countermeasures research for a more rapid and effective medical response

during a civilian chemical emergency. The research under the NIH-CounterACT program is highly significant because technological advances and increasing industrialization pose an enhanced risk of occupational and/or accidental human exposure to chemical agents in addition to their potential international use in terrorism.

Phosgene oxime (dichloroform oxime, CX), classified as a vesicating agent, is a potent urticant or nettle chemical weapon which was first synthesized in 1929 and stored during World War II. In March of 2019, the FBI found large quantities of CX in a home in Lawton, Oklahoma, which could have been used on the civilian population. Compared to other vesicating agents like sulfur mustard (mustard gas), CX causes bewilderingly rapid effects on the skin, eye and mucus membranes including instant pain and prompt penetration. Even though it is considered the most harmful vesicant with real warfare and terrorist threat potential that can be used for rapid incapacitation and death, very little is known regarding the toxic effects of CX following its cutaneous exposure and its mechanism of action is unknown. Based on the results obtained from current studies under Tewari-Singh’s R21 grant, the goal of this breakthrough U01 award is to investigate if mast cells are key players and molecular targets in CX tox-

icity. Dr. Tewari-Singh’s research focus is to investigate whether blocking these targets using mouse toxicity models, will assist to mitigate CX-induced skin morbidity and mortality resulting from its cutaneous exposure. In addition, Tewari-Singh anticipates identifying a therapeutic strategy that can target mast cell activation and release of histamine to mitigate CX-induced skin injury including urticaria and mortality from CX cutaneous exposure.

“This grant is extremely important for the ongoing study on CX in my lab and my career in the field of chemical medical defense research,” commented Tewari-Singh. “It is a great honor to receive this U01-CounterACT award since very few people are awarded these U01 grants and we are one of the only labs conducting research on CX. Outcomes from this study will provide the first major insights into CX-induced toxicity and related mechanisms following its cutaneous exposure. The overall impact of the ongoing research is very promising with the goal of further optimizing any targeted therapeutic agent/s identified under the current NIH-CounterACT U01 funding, which can be further optimized for treatment to enhance the nation’s medical response capabilities for rapid medical intervention during any potential civilian chemical emergencies due to vesicating/nettle agents exposure.”

EITS Research Evening cont.

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Sean Nguyen, training in the lab of Dr. Margaret Petroff, spoke on, “*Placental Extracellular Vesicles in Murine Pregnancy.*” Nguyen is a doctoral student in the Cell and Molecular Biology Program and

has focused his graduate research on placental extracellular vesicles (pEVs) and their function during pregnancy. He is specifically interested in the cellular targets of pEVs in vivo as well as understanding the mechanisms by which they localize to maternal tissues in pregnancy.



Di Zhang, training in the lab of Dr. Karen Liby, spoke on, “*Identification of an Unfavorable Immune Signature in Advanced Lung Tumors from Nrf2-Deficient Mice.*” Zhang is a doctoral student in the Department of

Pharmacology and Toxicology and has focused her graduate research on investigating the role of the Nrf2 pathway in cancer. Inhibition of the Nrf2-Keap1 pathway has become an attractive target for lung cancer treatment, since mutations in the NFE2L2 gene (encodes Nrf2), which are associated with chemoresistance and poor survival, have been found

in lung cancer patients. However, there are no specific and potent Nrf2 inhibitors currently available. Zhang has identified a novel Nrf2 pathway inhibitor through a high throughput drug screen. She is currently working on further validating this novel compound and investigating how it inhibits the Nrf2 pathway.

To those who attended, thank you for joining us for this special evening of celebration, camaraderie, and learning!

Laura McCabe Named MSU Foundation Professor



IIT-affiliated faculty member, **Laura McCabe**, was recently named a MSU Foundation Professor, a designation given to outstanding faculty who demonstrate excellence in re-

search and teaching while enhancing the prominence of the institution. McCabe and three other professors joined the ranks of 36 fellow colleagues who have

been named Foundation Professors in MSU history.

McCabe, professor in the Departments of Physiology and Radiology, has long been engaged in exploring the mechanisms regulating bone cell differentiation and bone formation, and in developing new strategies for the prevention and treatment of osteoporosis.

McCabe's research has generated an expansive body of work, with critical contributions to more than 90 peer-reviewed articles and numerous book chapters. Many scientific symposia have benefited from her organizational leadership, and she has been a frequent

adviser on a wide range of grant review boards and committees both here and abroad.

She holds several patents, with additional patents pending, related to the treatment of osteoporosis. Her internationally recognized research program has been continuously funded for nearly 20 years through external federal agencies, including the National Institutes of Health, National Science Foundation and the U.S. Department of Defense, as well as private foundations.

McCabe was recognized during a special investiture event on September 26, 2019. 🌟

Pacyga Selected for Environmental Health Scholars Retreat at Brown University



EITS graduate student, **Diana Pacyga**, was selected as one of 15 trainees from across the country to participate in the prestigious Environmental Health Scholars Retreat held at Brown University. The retreat gives pre- and postdoctoral trainees an opportunity to present children's environmental health research in a supportive environment to leading researchers and each other. The two-and-a-half day program is designed to enhance career development for

the trainees chosen through networking, career development workshops and keynote lectures from leaders in the field. The

highlights of the retreat are the presentations of ongoing fellow research with feedback from experienced environmental health scientists in a collaborative and collegial setting. The retreat is organized and sponsored by the Academic Pediatrics Association, the Mount Sinai P30 Core Center, the Mount Sinai NICHD-funded T32, the Mount Sinai CTSA Program, and the Brown University School of Public Health.

Pacyga is mentored by IIT-affiliated faculty member, Dr. Rita Strakovsky, and will be presenting on, "*Sex-Specific Associations Between Gestational Di(2-ethylhexyl) Phthalate Exposure and Maternal Steroid Hormones - Modification by Maternal Adiposity.*" 🌟

Zhang Receives NCI Predoctoral to Postdoctoral Fellow Transition Award (F99/K00)



EITS graduate student, **Di Zhang**, is the recipient of a National Cancer Institute Predoctoral to Postdoctoral Fellow Transition Award (F99/K00) for her proposal, "*Targeting the Nrf2 Pathway in Cancer.*" The award supports outstanding Ph.D. and other research doctoral candidates while they complete their dissertation research training (F99 phase) and transition in a timely manner to mentored, cancer-focused postdoctoral career development research positions (K00

phase). Zhang's F99 phase began in September and she will most likely begin to transition to the K00 phase in spring 2020 in a postdoctoral position where she can receive further

training in cancer immunology and immunotherapy.

Zhang is mentored by IIT-affiliated faculty member, Dr. Karen Liby, in the Department of Pharmacology and Toxicology. Currently, Zhang is working on investigating the role of the Nrf2 pathway in cancer. Inhibition of the Nrf2-Keap1 pathway has become an attractive target for lung cancer treatment, since mutations in NFE2L2 gene (encodes Nrf2), which are associated with chemoresistance and poor survival, have been found in lung cancer patients. However, there are no specific and potent Nrf2 inhibitors currently available. Zhang has identified a novel Nrf2 inhibitor through a high throughput drug screen. She is still working on further validating this novel compound and investigating how it inhibits the Nrf2 pathway. 🌟

Albers Receives Clifford Humphrys Fellowship for Preservation of Water Quality in the Great Lakes



EITS graduate student, **Janice Albers**, was selected as one of five recipients of the 2019 Clifford Humphrys Fellowship for Preservation of Water Quality in the Great Lakes. The Clifford Humphrys Fellowship for Preservation of Water Quality in the Great Lakes benefits students enrolled in any graduate program at MSU studying or doing research on water quality, especially as it relates to the Great Lakes and Lake Michigan in particular. The Fellowship is

intended to encourage students who have demonstrated the capacity to achieve educational and professional goals, the motivation to achieve these goals, and the initiative to seek opportunities to further their progress.

Albers is mentored by IIT-affiliated faculty member, Dr. Cheryl Murphy, in the Department of Fisheries and Wildlife. The focus of Albers' dissertation is to explore the sublethal levels of polychlorinated biphenyl 126 (PCB126) and methyl mercury (MeHg) impacts on an economically important Lake Michigan fish species, the Yellow Perch (YP) by constructing a fish larvae neurobehavior Adverse Outcome Pathway (AOP) model. Specifically, her study will focus on multiple subleth-

al water pollutant exposure levels that alter the expression of genes at the molecular level which will be identified and quantified. Gene expression alterations can impair motor and sensory functions, thus altering larval swimming and feeding behavior, which will be assessed using laboratory-based behavioral assays. The resulting pollution dose response behavioral relationships will be input parameters for simulated fish larvae as they swim around, forage for food and avoid predators in computer generated simulations; where each individual virtual larva is monitored as it grows and whether it starves, gets eaten, or lives through the summer.

Albers' dissertation project will advance aquatic conservation science by applying the new theoretical framework of AOPs to a long existing problem of neurotoxic pollutants in the Great Lakes. By focusing on the process of biological contamination and individual and population level impacts, she will be able to not only make the hierarchical connections between MeHg/PCB126 sublethal pollution and YP population declines but also apply this process to other neurotoxicants that impact numerous fish species in the same way. The results from this work will be used by managers and society to better understand how water pollution impacts Great Lakes fisheries and how these impacts can be managed through risk assessment, restriction or mitigation, resulting in the restoration of Great Lakes water quality and fisheries. ♡

Spring 2020 Lineup for IIT Seminar Series

The IIT is thrilled to host four prestigious speakers this spring to conclude the 2019/2020 IIT Seminar Series. The first speaker to kick off the 2020 lineup will be Dr. Bernard Goldstein.



January 14: Bernard Goldstein

Professor Emeritus and Dean Emeritus, University of Pittsburgh Graduate School of Public Health

Dr. Goldstein will speak on, "Challenges to Science: Changes to EPA's Advisory Processes and the EU's Use of the Precautionary Principle to Ban Agricultural Imports," on January 14, 2020, at 11:00 a.m. in 162 Food Safety and Toxicology Building.

Dr. Felicia Wu will host this seminar.

Dr. Goldstein's Lecture Synopsis:

The processes by which science is employed in policy-making are under attack in both the US and the EU. I will describe two seemingly disparate examples, both at the behest of major industries. The current US government is altering EPA advisory processes for the benefit of fossil fuel industries, and the EU has deliberately misused the precautionary principle to pro-

tect its agricultural industry. In both cases public support is achieved by approaches that denigrate science and scientists.

The following speakers will be on campus in February, April and May:

- » **Mark Harris**, Managing Principal Scientist and Cofounder, ToxStrategies, will speak on **February 11**. This seminar will be co-sponsored by the MSU BEST Program and Dr. Timothy Zacharewski will host this seminar.
- » **Teresa WM Fan**, Professor, Edith D. Gardner Chair in Cancer Research, Toxicology and Cancer Biology, University of Kentucky, will speak on, "Mapping human tumor metabolism in vivo and in preclinical models using Stable Isotope - Resolved Metabolomics (SIRM)," on **April 14** at 11:00 a.m. in 162 Food Safety and Toxicology Building. This seminar will be co-sponsored by the Department of Biochemistry and Molecular Biology and Dr. Timothy Zacharewski will host this seminar.
- » **Donna Zhang**, Professor, Department of Pharmacology and Toxicology, University of Arizona, will speak on **May 12**. Dr. Cheryl Rockwell will host this seminar.

If you are interested in meeting with any of the speakers while they are on campus, please contact Kasey Baldwin, kbaldwin@msu.edu. We hope you can join us for one or all of these exciting seminar opportunities! ♡

Goodman Named AAAS Fellow



Jay Goodman, professor of pharmacology and toxicology and IIT-affiliated faculty member, was recently awarded the distinction of Fellow by the American Association for the Advancement of Science (AAAS) along with five other distinguished MSU faculty members. These individuals were selected for this honor because of their efforts toward advancing science applications that are deemed scientifically or socially distinguished. AAAS Fellow's lifetime honor comes

with an expectation that recipients maintain the highest standards of professional ethics and scientific integrity.

Dr. Goodman was chosen for this honor for his distinguished contributions to toxicology, particularly research on the key role epigenetic alterations play in carcinogenesis, and efforts to advance science-based safety assessment of chemicals.

AAAS is the world's largest general scientific society and publisher of the journal *Science*, as well as *Science Translational Medicine*, *Science Signaling* — a digital, open-access journal — *Science Advances*, *Science Immunology* and *Science Robotics*.

The tradition of AAAS Fellows began in 1874. Currently, members can be considered for the rank of fellow if nominated by the steering group of their respective sections, by three fellows, or by the Association's chief executive officer.

Each steering group then reviews the nominations of individuals within its respective section and forwards a final list to the AAAS Council. The AAAS Council votes on the final aggregate list.

New fellows will be presented with an official certificate and a gold and blue rosette pin — representing science and engineering, respectively — on Saturday, Feb. 15, at the AAAS Fellows Forum during the 2020 AAAS Annual Meeting in Seattle, WA. 📍

Karen Liby Selected for Mi-Kickstart & Mi-TRAC Awards



IIT-affiliated faculty member, **Karen Liby**, was recently selected for a Mi-Kickstart award from the University of Michigan MTRAC for Life Sciences Innovation Hub for her project, “*Novel Nrf2 Inhibitors*.” She also received a Mi-TRAC award in 2019 for her project, “*Novel Reginoids for Oncology*.” Liby is an associate professor in the Department of Pharmacology and Toxicology.

Mi-TRAC and Mi-Kickstart awards

are part of the University of Michigan MTRAC for Life Sciences Innovation Hub, a statewide program that supports translational research projects in life sciences with high commercial potential. Mi-Kickstart early-stage funding awards are given quarterly and offer funding in the \$25k-\$50k range. Mi-TRAC mid-stage funding awards are given once a year in January and offer funding in the \$100k-\$250k range.

Liby will work with Dr. Aaron Odom on the Mi-Kickstart award, “*Novel Nrf2 Inhibitors*.” Liby will work with Dr. Edmund Ellsworth on the Mi-TRAC award, “*Novel Reginoids for Oncology*.” Congratulations to Dr. Liby on these two fantastic awards!



Faculty Accomplishments and Awards



IIT-affiliated faculty member, **Jay Goodman**, was awarded Honorary Membership in the Federation of European Toxicologists and European Societies of Toxicology (EUROTOX). He is the first non-European to receive this award.



IIT-affiliated faculty member, **John Goudreau**, has been named the new director of the Clinical and Translational Sciences Institute at MSU. Goudreau has an outstanding background in basic, translational and clinical research.



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New CRIS Research on Food Grade Titanium Dioxide Shows No Evidence of Adverse Outcomes

New research on the ingredient titanium dioxide (E 171) from the Center for Research on Ingredient Safety shows no evidence of adverse health outcomes.

Safety concerns surrounding food-grade titanium dioxide, termed E 171, were raised by findings recently reported by Bettini and coworkers (2017) claiming that oral administration of this ingredient to rats produced lesions in the colon (aberrant crypt foci), and change to the immune system. The study conducted by a team of French government scientists was reviewed by European Food Safety Authority (EFSA), the European Union regulatory agency counterpart to the U.S. Food and Drug Administration, and they determined that the Bettini study had serious methodological flaws. These flaws included administration of E 171 in drinking water despite E 171 being insoluble in water and not present in any liquid food products.

To disperse E 171 in water Bettini and coworkers sonicated E 171 raising questions that the material may have been altered by the sonication procedure.

Concerns were also raised that critical controls were omitted in the Bettini study, there was an absence of a statistically significant increase in aberrant crypt foci, and there was a lack of a sufficient number of experimental doses to adequately establish whether E 171 was, in fact, responsible for any of the effects Bettini and coworkers claimed were due to E 171 administration.

To further address the Bettini study, Michigan State University (MSU) investigators at the Center for Research on Ingredient Safety in collaboration with the University of Nebraska Medical Center (UNMC), conducted additional studies correcting for the methodological flaws in the Bettini report. Here E 171 was administered for 7- and 100-days to rats in the diet using multiple doses, which were less than, similar to, and greater than those used by Bettini.

In addition, appropriate experimental controls were included and perhaps most importantly, the study was conducted in a blinded manner such that the investigative team did not know which tissues came from which experimental

animals until the analysis of all biological samples was completed to eliminate the possibility of experimental bias.

In this most recent study reported in the journal *Food and Chemical Toxicology*, MSU and UNMC scientists were unable to demonstrate any adverse effects due to E 171 including aberrant crypt foci or changes in immune parameters reported by Bettini. Moreover, the National Toxicology Program within the National Institute of Environment Health Sciences in the U.S. also conducted a 2-year study in rats that showed no adverse effects by titanium dioxide placed in the diet at doses approximately 10-fold higher than the highest dose used by MSU and UNMC researchers.

The French government has announced plans for a ban on food products containing E 171 beginning January 2020, which at this time is not supported by other EU countries.

Read the full study, “*Evaluation of immunologic and intestinal effects in rats administered an E 171-containing diet, a food grade titanium dioxide (TiO₂)*,” in the academic journal, *Food and Chemical Toxicology*. 🌐

EITS Student Accomplishments and Awards



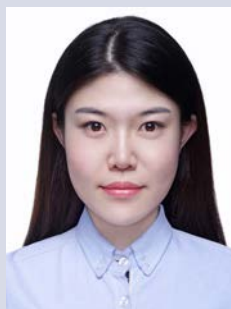
EITS graduate student, **Olivia Favor**, was appointed to the Integrative Pharmacological Sciences T32 Training Program. Favor is mentored by Dr. Kin Sing Lee and will receive two years of stipend and tuition support.



EITS graduate student, **Bradley Ryva**, gave a platform presentation on, “*Associations of Bisphenol Exposure with Nausea and Vomiting Symptoms in Pregnancy*,” at the Michigan Regional Chapter of the Society of Toxicology Annual Fall Meeting in Ann Arbor, MI on October 18. Ryva is mentored by Dr. Rita Strakovsky.



EITS graduate student, **Jeremy Gingrich**, received the Best Poster Award at the Annual Research Day of the Reproductive and Developmental Sciences Program. Gingrich is mentored by Dr. Almudena Veiga-Lopez.



EITS graduate student, **Wenjie Qi**, gave a platform presentation on, “*A Combination of DNA Sequence and Epigenetic Modifications Accurately Predicts Genome-wide Aryl Hydrocarbon Receptor Binding Sites*,” at the Michigan Regional Chapter of the Society of Toxicology Annual Fall Meeting on October 18. Qi is mentored by Dr. Sudin Bhattacharya.



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