



IIT UPDATE

INSTITUTE FOR INTEGRATIVE TOXICOLOGY



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In Memory of Lawrence J. Fischer (September 2, 1937 - August 7, 2018)



Lawrence Joseph Fischer began his career at Michigan State University in 1985 as the Director for the Institute of Environmental Toxicology (IET). He received his bachelors and masters degrees in Pharmacy from the University of Chicago and a Ph.D. in Pharmaceutical Chemistry from the University of California in San Francisco. After receiving his Ph.D., Dr. Fischer undertook postdoctoral training at St. Mary's Hospital in London. In 1966 he was recruited by Merck & Company, in Norristown, Pennsylvania. In 1968 Dr. Fischer accepted a faculty position at the University of Iowa Department of Pharmacology.

During his nineteen-year tenure and under his leadership, toxicology research and graduate training at Michigan State became, and continues to be, recognized nationally and internationally for excellence. As Director of the IET he brought together investigators with diverse scientific backgrounds to establish coordinated research teams focused on various aspects of environmental toxicology. These research teams, led by Dr. Fischer, successfully competed for what is presently the longest standing program project grant at Michigan State, which is currently in its thirtieth consecutive year of funding by the Superfund Research Program. Dr. Fischer

was also instrumental in shaping toxicology undergraduate, graduate, post-graduate and professional student training in toxicology. In addition to teaching, he served as the Director of the Graduate Training Program in Environmental Toxicology. In this capacity, he successfully competed for what continues to be the longest standing National Institutes of Health Training Grant at Michigan State, for which he served as the Principal Investigator for fifteen years. In addition, Dr. Fischer trained numerous doctoral and postdoctoral students in his own laboratory many of whom presently hold important positions in government and industry. He has also served on many scientific advisor committees throughout his career including the Governor's Michigan Environmental Science Board, the Michigan Air Toxics Policy Committee, the US EPA Science Advisory Board on Mercury, the Science Advisory Group on Electromagnetic Fields and Childhood Leukemia Study for the National Cancer Institute, and the National Academy of Science Committee on Drinking Water Contaminants. His legacy at Michigan State will be that he helped to coordinate toxicology related activities of an appreciating faculty. He will be remembered for his open and relaxed demeanor, which was a hallmark of his effectiveness in building campus-wide relationships.

Dr. Lawrence Fischer is survived by his wife Betsy and their three daughters Julie, Pamela and Karen. ☘

MSU Superfund Program Helps Develop MI Safe Fish App with the State of Michigan



The Research Translation Core of the MSU Superfund Program continues to work diligently with the Michigan Department of Health and Human Services (MDHHS) to develop an app based off the MI Eat Safe Fish Guide available

on the State of Michigan website. The MDHHS test filets of fish taken from Michigan's lakes and rivers to find the average amount of chemical contaminants in the fish species located there. They use this information to make recommendations on monthly fish consumption in their Eat Safe Fish Guide. The collaboration between MDHHS and the MSU Superfund Program will bring

this information to more consumers in a user-friendly mobile app, available for download this fall.

The MI Safe Fish app has eight categories:

- » **MI Serving** – Tool to help you determine the serving size of fish in relation to your body weight.
- » **Eat 8** – A visual guide to help you choose fish low in mercury from restaurants and grocery stores.
- » **Three Cs** – A visual guide to the three Cs of fish consumption – choose, clean and cook.
- » **Fish ID** – Upload a photo of your catch and the app will compare and identify your fish. Or browse the thirty Michigan fish in the gallery to make your own comparisons.
- » **Chemical Risks** – Learn more about each of the chemicals identified in the Eat Safe Fish Guide.
- » **Eat Safe Fish Guide** – Download the

Eat Safe Fish Guide for the region of Michigan you are fishing.

- » **FAQs** – Get the answers to the most commonly asked questions about the Eat Safe Fish Guide.
- » **About** – Learn about the app collaborators.

Drs. Brad Upham, James Cole and Syed Hashsham from the MSU Superfund Program worked alongside Michelle Bruneau and Tom Mata from the State of Michigan Fish Advisory Program to bring the MI Safe Fish app to life. Collin Nicaise, Umama Fakher, and Maggie Williams from the MSU Superfund Program also contributed to the development of this app. The MSU Superfund Research Translation Core is proud to be involved in this project and hopes to work with other SRP centers in the future to develop this type of app for their own regions across the country. 🌟

IIT Affiliated Faculty Contribute to *Casarett & Doull's Toxicology: The Basic Science of Poisons*

In November, McGraw-Hill Education will release the ninth edition of toxicology's gold-standard text, *Casarett & Doull's Toxicology: The Basic Science of Poisons*, with several IIT affiliated faculty members featured as contributing authors to chapters. The world renowned toxicology text book is completely updated to reflect the latest breakthroughs and discoveries with more than one-third of the chapters authored by scientists who

write the chapter on "Toxic Responses of the Liver." "This was the textbook that catalyzed my passion for the field as an undergraduate. It is a true honor to contribute to this chapter, with the intent of developing the next generation of toxicologists," commented Luyendyk. This was their first time authoring the chapter and they rewrote it to include the most up-to-date principles and discoveries. Roth commented, "Leading the

Dr. Michael Holsapple, Dr. Courtney Sulentic, and Dr. Helen Haggerty. This edition of the text was the third time Kaminski has worked on the book; he also co-authored "Toxic Responses of the Immune System," for the seventh and eighth editions of the text. "Each time, it has been quite an honor to be asked to author a chapter as this is the most widely used toxicology textbook in the world," said Kaminski.

“ This was the textbook that catalyzed my passion for the field as an undergraduate. It is a true honor to contribute to this chapter, with the intent of developing the next generation of toxicologists. ”

- J. Luyendyk

have not made previous contributions to the book. The textbook covers a thorough overview of modern toxicology, including the key principles, concepts, mechanisms, chemical-specific toxicity, and modes of thought fundamental to the discipline of toxicology.

IIT affiliated faculty members, **Dr. Robert Roth** and **Dr. James Luyendyk**, worked with Dr. Hartmut Jaeschke to

charge in writing the chapter on hepatotoxicity for the new edition was a task I welcomed. It was a pleasure working with the co-authors, and thanks to the folks at MSU who kindly reviewed the drafts for this chapter.”

IIT Director, **Dr. Norbert Kaminski**, also co-authored a chapter on "Toxic Responses of the Immune System," along with colleagues, Dr. Barbara Kaplan,

The process to write a chapter is extremely extensive. Once invited to write a chapter by editor, Kurt Klaassen, authors begin work a couple of years ahead of the scheduled publication date. Kaminski, Roth and Luyendyk began their work in 2016, provided a final draft in the summer of 2017 and revised galley proofs this past summer of 2018. The ninth edition will be released on November 23, 2018. 🌟

Andrechek's Breast Cancer Research Could Expand Lung Cancer Therapies

New research by [Dr. Eran Andrechek](#) into a genetic mutation's role in breast cancer could open new treatment options for an even more deadly disease, lung cancer. Andrechek is an IIT-affiliated faculty member and Associate Professor in the Department of Physiology.

"We sequenced the whole genome of tumor samples and found a driving mutation that has previously not been recognized as important," said Andrechek. "This mutation, once we validate and confirm it with ongoing work in our laboratory, has clear potential to identify lung cancer patients who should be receiving therapy that's already approved by the FDA."

Andrechek presented his research, "Modeling Cancer in Mice: Integration of Bioinformatics and Therapy," to MSU's Board of Trustees on Friday, June 22, 2018.

Using lab mice and computational analysis of sequenced genes, he and his colleagues learned that a mutation present—but apparently not consequential—in breast cancer turns out to inhibit growth of certain human lung cancer tumors. About 5 percent of lung cancer cases carry this mutation, he said.



That works out to approximately 11,000 people in the United States alone who could gain precious time from the most vicious of major cancers. "It's not a cure yet," he cautioned. "It's extending life span and essentially buying time."

Breast cancer is the most common among women, as prostate cancer is among men. But with improved screening for those cancers, at least in the developed world, lung cancer kills more people than breast, prostate and colon cancer combined, according to the American Cancer Society. Overall, one in

15 men and one in 17 women will develop it in their lifetimes, with smokers at higher risk.

Andrechek's initial research was funded by the National Institutes of Health and Worldwide Cancer Research. A conversation with Vice President for Research and Graduate Studies Steven Hsu led to MSU funding further gene sequencing work, with later support from the Midland, Michigan-based Elsa U. Pardee Foundation.

Andrechek's research is under review for scientific journal publication. His laboratory group, meanwhile, awaits a decision on new grant funding. That would go toward better describing and then manipulating the mutation's effect on the protein that regulates cancer tumor growth, before any human clinical trials can begin. He's also working with another MSU laboratory to secure grant funding to apply the findings once again to breast cancer research.

A version of this article originally appeared on MSUToday.

Wierenga Wins 1st Place New Investigator Award

[Kathryn Wierenga](#), EITS trainee with [Dr. James Pestka](#), recently attended the 13th Congress of the International Society for the Study of Fatty Acids and Lipids (ISSFAL) in Las Vegas, Nevada, on a New Investigator Award. Wierenga presented an oral presentation, "Percent n-3 in highly unsaturated fatty acids (HUFAs) is a predictor of disease outcomes in an environmental toxicant-triggered lupus mouse model." She received first place for this presentation out of more than 50 competing research presentations.

Wierenga earned her bachelor's degree in Chemistry in 2016 from Hillsdale College and is now working on her Ph.D. in Biochemistry and Molecular Biology with a dual major in Environmental Toxicology. Wierenga has always been interested in health and nutrition, particularly the molecular mechanisms behind how our bodies function and the ways our environment can alter those functions. She found the perfect niche for her interests in Dr. James

Pestka's laboratory, where they used a lupus-prone mouse model to show that dietary docosahexaenoic acid (DHA) can protect against autoimmunity induced by inhalation of crystalline silica (cSiO₂), a known environmental trigger of human autoimmune disease. Wierenga's project focuses on the molecular mechanisms behind the protective actions of DHA on the innate immune system. Since joining the lab last May, she assisted in establishing two in vitro models for alveolar macrophages, which she now uses to study how DHA impacts early steps of inflammation in macrophages upon exposure to cSiO₂. She is also involved in in vivo studies, where she utilizes GC and LC/MS/MS to correlate



Kathryn Wierenga receives her award at Haofbrauhaus in Las Vegas from Dr. Richard Bazinet, University of Toronto, ISSFAL President, and Dr. Arthur Spector from the National Institute of Alcohol Abuse and Alcoholism.

the fatty acid composition and lipid metabolite profile of tissues to disease severity in the laboratory's mouse model. 🍷

Gulbransen and Team Discovers Early Source of Irritable Bowl Syndrome

MSU Foundation Associate Professor and IIT-affiliated faculty member, **Dr. Brian Gulbransen** and a team of MSU researchers have identified an early cause of intestinal inflammation, one of the first stages of inflammatory bowel disease and irritable bowel syndrome, which afflicts around 11 percent of the world's population.

The research, "*The cholinergic activation of enteric glia is a physiological mechanism that contributes to the regulation of gastrointestinal motility*," published in the *American Journal of Physiology* in June of 2018, points to communication between sensory neurons in the gut and a class of non-neuronal cells - enteric glia - as the culprits for the early intestinal inflammation.

"The gut has its own brain and that has more neurons in the intestines than in the spinal cord. Within your intestines lies a 'second brain' called the enteric nervous system," said Gulbransen. "The enteric nervous system is an exceedingly complex network of neural circuits that programs a diverse array of gut patterns and is responsible for controlling most gastrointestinal functions."

Accompanying the neurons in this second brain are enteric glia, which are responsible for regulating inflammation. The disruption of neural circuits in the gut by inflammation is considered an important factor in the development of irritable bowel syndrome and in-



flammatory bowel disease.

The research team pinpointed that before the first hints of intestinal pain or rumblings, specific molecular changes spark the discomfort. Tachykinins, peptides that are keys to pain transmission and intestinal contractions, drive enteric neuroinflammation.

The gut's major source of tachykinins are enteric neurons. Tachykinins drive neuroinflammation in the gut through a "multicellular cascade" of enteric neurons, bead-like TRPV1-positive nerve fibers and enteric glia.

Gulbransen's team revealed that glial cells, once thought to be supporting cells, are active signaling cells involved in much of the cross-talk that happens in the gut. The key is isolating a single voice rather than stifling the entire cacophony, Gulbransen said.

"Post inflammation, there are still many angry glial cells. Because they've amped up their signaling, they make you, and your gut, more sensitive," Gulbransen said. "We hope we can turn them back to happy glia, reduce the sensitivity and return gut function to normal."

One of those single voices - the key to intestinal happiness - is NK2R, a receptor that's a critical mechanism in driving neuron-to-glia signaling. The team is just starting to understand the genes involved and inventorying what's being activated and what's not. But NK2R is proving promising.

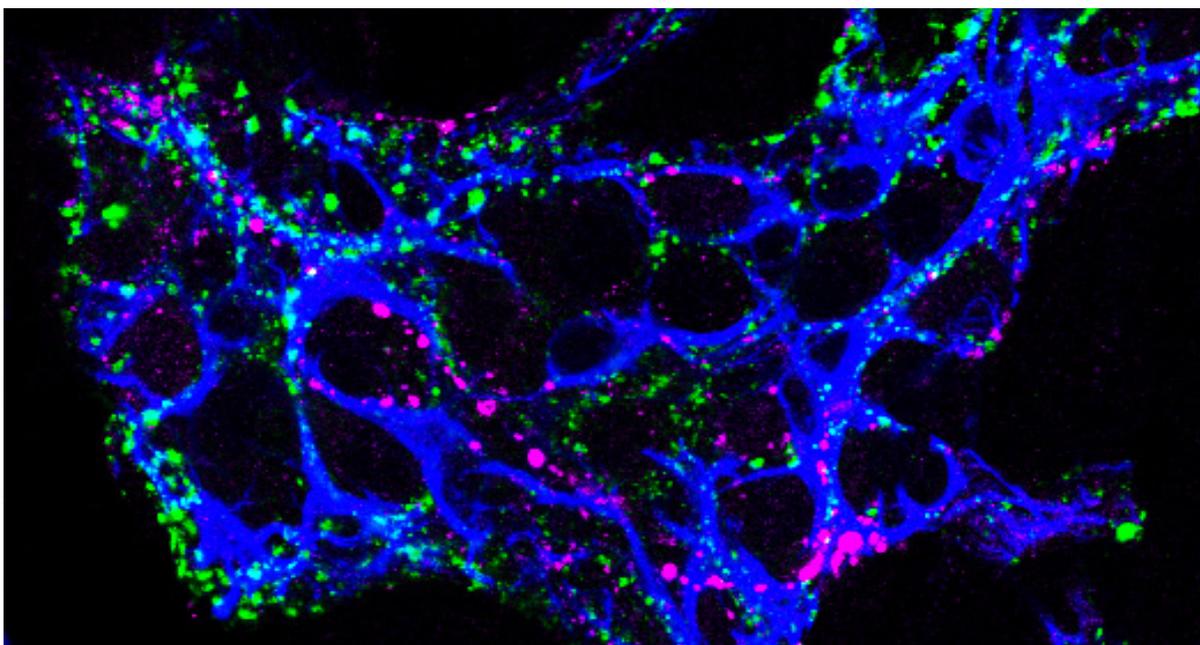
"By blocking the receptor with GR 159897, which is a known NK2 receptor antagonist drug, it disconnected the signaling between neurons and glia," he said. "It proved to be quite effective in accelerating recovery from inflammation."

This foundation could lead to more targets that could be treated with drugs that would reset the sensitivity of these neurons.

MSU scientists, including Ninotchka Delvalle, Christine Dharshika, Wilmarie Morales-Soto, David Fried and Lukas Gaudette, all contributed to this study.

This research was funded by the National Institutes of Health and the Crohn's and Colitis Foundation of America. 🐾

A version of this article originally appeared on MSUToday.



Left: NK2R (green) and enteric glial (blue) are keys to achieving "intestinal happiness."

CRIS Hires Director of Science Communication

The Center for Research on Ingredient Safety (CRIS) is pleased to introduce Elisabeth Anderson, Director of Science Communication. CRIS is an academic, science-based center within the Institute for Integrative Toxicology, that serves as a leading source for information on the safe use of chemical ingredients in consumer packaged goods including foods, beverages, cosmetics and household consumer products.

Elisabeth has extensive experience in communications, specializing in digital media and tools. In her most recent position, she served as the Communications Manager for Michigan State University Information Technology. In this role, Elisabeth was responsible for developing and managing communication strategies for MSU IT, writing and editing content for the MSU Community, implementing digital media campaigns and curating content for monthly newsletters.



Prior to her employment at MSU, Elisabeth held a variety of positions in the communications field. She spent three years at Ohio State University as the Digital Communications Specialist for the Office of Academic Affairs. There she served as the brand ambassador

for the Office of Academic Affairs and developed branding guidelines, as well as leadership skills, for the Discovery Themes initiative. Among her many responsibilities, she developed and implemented digital and traditional media strategies, overhauled and streamlined the Office of Academic Affairs website and developed digital media platforms.

Elisabeth also served as a Social Media and Website Specialist for the State of Michigan, where she was responsible for creating and updating digital media platforms to bring attention to specific projects. At the State of Michigan, she worked with the American Recovery & Reinvestment Act, using social platforms to raise public awareness.

CRIS welcomes Elisabeth and looks forward to adding her experience and skillsets to the CRIS team. ♡



Bernard Laboratory Wins 2018 Jean P. Schultz Biomedical Research Endowment Award

The Bernard laboratory is the recipient of the 2018 Jean P. Schultz Biomedical Research Endowment Award. This endowment was created by Bob Schultz, an MSU graduate, in memory of his

wife who died of cancer in 1988. IIT affiliated faculty member, **Dr. Jamie Bernard**, as well as EITS student, **Vanessa Benham**, presented their research on June 27, 2018 to four generations of the

Schultz family and the entire Bernard laboratory attended a luncheon alongside Dean Norman Beauchamp Jr. and Dean Walter Esselman at the Arcadia Bluffs Gold Club.

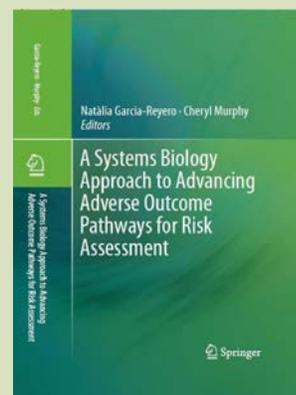
Faculty and Student Recent Accomplishments



IIT-affiliated faculty member, **Dr. Cheryl Murphy**, co-edited, *A Systems Biology Approach to Advancing Adverse Outcome Pathways for Risk Assessment*, with Natàlia Garcia-Reyero Vinas. Released in 2018, the book focuses on The Adverse Outcome Path-

way, an analytical construct that describes a sequential chain of causally linked events at

different levels of biological organization that lead to an adverse health or ecotoxicological effect. While past efforts have focused on toxicological pathway-based vision for human and ecological health assessment relying on in vitro systems and predictive models, The Adverse Outcome Pathway framework provides a simplified and structured way to organize toxicological information. Within the book, a systems biology approach supplies the tools to infer, link, and quantify the molecular initiating events and the key events and key event relationships leading to adverse outcomes.



Loan Cao, EITS doctoral student, training with Dr. Leslie Bourquin in Food Science and Human Nutrition, recently won first place in the 3-Minute Thesis Competition at the International Association for Food Protection (IAFP) annual meeting in Salt Lake City, Utah. Loan's presentation, "*Relationship of arsenic and lead concentrations in soil and that in fruits and leaves of apple trees at selected orchards in Michigan*," was on a portion of her dissertation research.

Loan's research interests focus on the assessment and management of food safety hazards in fruit juices, particularly screening for contamination by different heavy metals in apple juice. Her current research investigates the relationship between the historical usage of lead arsenate at orchard sites, persisting lead and arsenic concentrations in the soil, and the amount of the two elements in plant tissues, fruit and juice.



Dr. Jack Harkema won the 2018 Outstanding Mentor Award from the Society of Toxicologic Pathology at their annual Symposium in Indianapolis,

Indiana on June 20, 2018.

Dr. Harkema's undergraduate research assistant, **Amy Freeland**, received the 2018 University Undergraduate Research and Arts Forum Grand Prize Award in the Science, Technology, Engineering and Mathematics division for her project, "*Docosahexaenoic Acid Consumption Blocks Silica-Triggered Autoimmune Responses in the Kidneys and Lungs of Lupus-Prone Mice*."



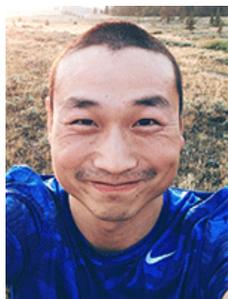
Research conducted by IIT-affiliated faculty member **Dr. Ilce Medina-Meza**, and funded by a 2017 CRIS research grant, was recently published in the journal, *Food and Chemical Toxicology*. Dr. Medina-Meza's paper, titled "*The Role of Cholesterol Oxidation Products in Food Toxicity*," was also featured in International Life Sciences Institute (ILSI) June 2018 Food Safety Briefs. The paper summarizes results from the CRIS funded grant

entitled, "*Assessment of exposure and risk associated with cholesterol oxidation product in food using dietary intake modeling*."



Vanessa Benham, EITS student training with Dr. Jamie Bernard, received 1st runner up for her oral presentation, "*Mechanisms and chemoprevention of adiposity-associated breast cancer*," at the 2018 Pharmacology Colloquium.

Recent EITS Graduates



Pengchao Hao
Chemistry
Mentor, Ned Jackson

Dr. Pengchao Hao received his Ph.D. after completing the dual major program in Chemistry and Environmental Toxicology. His dissertation was, “*Electrocatalytic Hydrogenation of Monomeric, Dimeric and Polymeric Lignin Model Compounds with Raney Nickel: Chemistry, Mechanistic, and Product Toxicity Studies.*”

Hao now works as a Senior Testing Engineer for SGS Life Science Services in Shanghai, China. His work involves conducting extractables and leachables studies on drug packaging systems.

Hao hopes to make major contributions to the structure elucidation of trace organic impurities in final drug products and lead teams to push the boundaries of unknowns.



Alexandra Turley
Pharmacology and Toxicology
Mentor, Cheryl Rockwell

Dr. Alexandra Turley received her Ph.D. after completing the dual major program in Pharmacology and Toxicology and Environmental Toxicology. Her dissertation was, “*The Role of Nrf2 in the Activation of Primary CD4 T Cells from Mice and Humans.*”

Turley continued in the lab of Cheryl Rock-

well as a postdoctoral researcher and is currently interviewing. She hopes to work as a toxicologist in government or industry.



Joseph Henriquez
Pharmacology and Toxicology
Mentor, Norbert Kaminski

Dr. Joseph Henriquez received his Ph.D. after completing the dual major program in Pharmacology and Toxicology and Environmental Toxicology. His dissertation was, “*Δ9-Tetrahydrocannabinol-mediated Suppression of the Interferon- α (IFN α) response by Plasmacytoid Dendritic Cells (pDC) and IFN α -mediated*

Activation of T Cells in Healthy and Human Immunodeficiency Virus (HIV) Infected Donors.”

Henriquez is currently interviewing for positions across the country.

UPCOMING EVENTS FALL 2018

IIT Seminar Series

The IIT Seminar Series returns again this fall with four fantastic speakers planned on the following dates:

- » **Friday, September 14** - Dr. Tomás Guilarte, Florida International University, will speak on, “*TSPO: A biomarker of neuroinflammation and brain injury looking for a function.*”
- » **Friday, October 12** - Dr. Edward Calabrese, University of Massachusetts Amherst, will speak on, “*What is the Future of Cancer Risk Assessment? Is LNT Dead? Is Hormesis Ready for Prime Time?*”
- » **Friday, November 16** - Dr. Lance Blevins, postdoctoral fellow with Dr. Norbert Kaminski, will speak on, “*Identification and Characterization of a Sensitive Immunologic Target of TCDD: CD5⁺ Innate-like B cells.*”
- » **Wednesday, December 5** - Dr. Sabrina Spencer, University of Colorado-Boulder, will speak on, “*Single-cell dynamics of the proliferation-quiescence decision.*”

All seminars will be held in room 162 of the Food Safety and Toxicology Building on the campus of MSU at noon.

CRIS Science Day

The Center for Research on Ingredient Safety will host a Science Day, **November 14, 2018**, during their 2018 Annual Meeting held at MSU. Science Day will feature 7 speakers across a variety of topics and is open to the public. Check cris.msu.edu this fall for more information.

EITS Research Evening

The Institute for Integrative Toxicology will host our annual Research Evening to showcase trainees in the Environmental and Integrative Toxicological Sciences Training Program and their accomplishments on **Thursday, December 6, 2018**, 5:15 to 8:00 p.m., in the Lincoln Room of the MSU Kellogg Center. The event will include dinner, student presentations and a poster session.

EITS Fall Mixer

An EITS Fall Mixer is in the works - a date will be announced soon!



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