Michigan Pioneer Fellows Symposium 2024

MICHIGAN PIONEER
FELLOWS PROGRAM

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MICHIGAN PIONEER FELLOWS PROGRAM

Michigan Pioneer Fellows **Symposium Keynote**

Dec 11, 2024
3:30–4:30 p.m.
BSRB Kahn Auditorium

KEYNOTE SPEAKER

CATHERINE DRENNAN, PH.D.

Professor of Biology and Chemistry, MIT;
Investigator and Professor,
Howard Hughes Medical Institute

1:00 p.m. **Welcome and Introductions**

1:05 p.m. **Senior Pioneer Fellow Talks**
Dominik Awad, Ph.D. (2022)
Ashley Calder, Ph.D. (2022)
Jutta Diessl, Ph.D. (2022)
Luis Ortiz-Rodríguez, Ph.D. (2022)
Jason Witek, Ph.D. (2022)
Amanda Erwin, Ph.D. (2021)
Mike McFadden, Ph.D. (2021)

3:30 p.m. **Catherine Drennan, Ph.D., Keynote Address**
"Capturing One-Carbon Chemistry, One-Structural Snapshot at a Time"

4:30 p.m. **Poster Session**

5:30 p.m. **Concluding Remarks and Reception**

The Program

OVERVIEW

The Medical School and its Endowment for the Basic Sciences, the Life Sciences Institute, the College of Pharmacy and the College of Literature, Science, and the Arts, at the University of Michigan (participating units) have partnered to offer the Michigan Pioneer Fellows program, a highly competitive postdoctoral fellowship program to enhance the research program of the entire life and biomedical sciences enterprise at Michigan.

The Michigan Pioneer Fellows program provides financial and mentoring support to highly motivated and accomplished post-doctoral fellows bound for research-intensive careers. The program offers competitive salary and financial resources, and provides mentorship focused on nurturing and launching innovative scientists into groundbreaking careers.

HISTORY

In 2023, the Michigan Life Sciences Fellows program (MLSF) and the Michigan Postdoctoral Pioneer program (MP3) combined to form the Michigan Pioneer Fellows program. These two programs merged to provide maximum professional growth, mentorship and collaborative opportunities to participants. Combined, these two programs offer postdoctoral fellows unique opportunities to interact and grow with a cohort of peers, while receiving both the independence to pursue their scientific projects and the necessary support to develop as scientific leaders. The idea for the Michigan Life Sciences Fellows program effort was initiated by the LSI Scientific Advisory Board and Leadership Council under the leadership of Roger Cone, Ph.D., Mary Sue Coleman Director of the Life Sciences Institute and Vice Provost for the Biosciences Initiative. Yukiko Yamashita, Ph.D., served as the first director of the MLSF program. The Michigan Postdoctoral Pioneer program effort was initiated by Pierre Coulombe, Ph.D., Department Chair of Cell & Developmental Biology with support from the Endowment for Basic Sciences in the Medical School.

About the directors

"Fostering the potential of postdoctoral fellows is not just about guiding their research; it's about empowering their journey towards innovation and leadership. Through this mentorship program, I am committed to cultivating their capabilities, inspiring excellence, and shaping the next generation of pioneering minds." – ***Carole Parent, Ph.D.***

Director, Michigan Pioneer Fellows Program
Research Professor, U-M Life Sciences Institute
Raymond and Lynne Ruddon Professor of Cancer Biology and Pharmacology, U-M Medical School
Professor of Cell and Developmental Biology, U-M Medical School

Dr. Parent joined the University of Michigan after serving as senior investigator and deputy director of the Center for Cancer Research at the National Cancer Institute. Dr. Parent's research interest focus on understanding how neutrophils detect and respond to external chemotactic signals and, in particular, how the spatial and temporal relay of chemotactic signals between cells impact single and group cell migration in the context of inflammation. She is a Fellow of the American Society for Cell Biology and a Fellow of American Association for the Advancement of Science. She was inducted in the Johns Hopkins University Society of Scholars, received the Arthur S. Flemming Award as well as NIH Merit Awards.

About the directors

"I am dedicated to mentoring the next generation of scientists, fostering their skills, resilience, and curiosity to advance their careers and grow as scientists." – ***Yatrik Shah, Ph.D.***

Co-Director, Michigan Pioneer Fellows Program
Horace W. Davenport Collegiate Professor of Physiology, U-M Medical School
Professor of Molecular & Integrative Physiology and Internal Medicine, U-M Medical School

Dr. Shah did his undergrad at Bowling Green State University and obtained his Ph.D. at the Medical College of Ohio in 2005. He did a postdoctoral fellowship at the NCI in the laboratory of Dr. Frank Gonzalez. In 2010 he began as an Assistant Professor in the Department of Molecular & Integrative Physiology with a joint appointment in the Department of Internal Medicine, Division of Gastroenterology. He is currently Horace W. Davenport Collegiate Professor of Physiology and Rogel Cancer Center Scholar. His primary research focuses on the role of iron/oxygen coordination in altering cellular metabolism in cancers and chronic inflammatory disorders.

About the directors

"I am excited to interact with these bright and passionate early career scientists." – ***Wenjing Wang, Ph.D.***

Co-Director, Michigan Pioneer Fellows Program
Research Assistant Professor, U-M Life Sciences Institute
William R. Roush Assistant Professor, Department of Chemistry,
U-M College of Literature, Science, and the Arts

Dr. Wang is a research assistant professor at the LSI and the William R. Roush Assistant Professor of Chemistry in the College of Literature, Science, and the Arts. Her lab uses cutting-edge protein engineering methods to design novel molecular tools with widespread utilities across cell biology and neuroscience. She is a recipient of the NIH Director's New Innovator Award, the Camille Dreyfus Teacher-Scholar Award, the NSF CAREER Award and an Alfred P. Sloan Research Fellowship.

Administration

Behind every great board of directors there is a great suite of administrators.

Traci Carulli

Administrative Project Coordinator,
U-M Life Sciences Institute

Jacqueline Popma, Ph.D.

Graduate Student & Postdoc Coordinator,
Department of Cell & Developmental Biology,
U-M Medical School

Traci and Jacqueline manage the annual recruitment process for new fellows, schedule monthly fellow meetings and program offerings, organize the annual symposium, serve as liaisons with fellows home departments, track fellows milestones and accomplishments, update the website and respond to program inquiries.

Current Fellows

2023

In a project that spans the Medical School's Department of Microbiology and Immunology and the Life Sciences Institute, **Christophe-Sebastien Arnold, Ph.D.**, will use metabolomics, high-content imaging and machine learning to understand parasite-host interactions under nutritional stress. Arnold received a Ph.D. in virology, immunology and microbiology from the Université Grenoble-Alpes, France, before coming to U-M. Mentors: Vern Carruthers & Carole Parent.

Working in the Medical School's Department of Neurology, **Merci Best, Ph.D.**, aims to uncover how specific genetic mutations can damage the architecture of the central nervous system and thus promote neurodegeneration. Best received a Ph.D. in pharmacology at the University of Virginia School of Medicine.
Mentor: Henry Paulson, M.D., Ph.D.

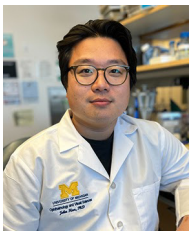
Maurinne Bonnet, Ph.D., completed her graduate studies in medicinal chemistry at the Institut de Chimie de Nice, France. Now, in the College of Pharmacy's Department of Medicinal Chemistry, she plans to develop new approaches to RNA-targeted drug discovery. Mentor: Amanda Garner, Ph.D.

In the Life Sciences Institute, **Brian Curtis, Ph.D.**, will apply protein engineering to overcome a bottleneck that hinders scientists' ability to efficiently develop biologically important natural product analogues. Curtis comes to the LSI from Cornell University, where he received a Ph.D. in chemistry and chemical biology.
Mentor: David Sherman, Ph.D.

Fabio Andrés Gómez-Cano, Ph.D., received a Ph.D. in biochemistry and molecular biology from Michigan State University. He joined the College of Literature, Science, and the Arts Department of Molecular, Cellular, and Developmental Biology, where he intends to unravel the intricate mechanisms through which living organisms respond to stress by studying the co-evolution of cis-regulatory regions and environmental stress.
Mentor: Alexandre Marand, Ph.D.

Current Fellows

2023

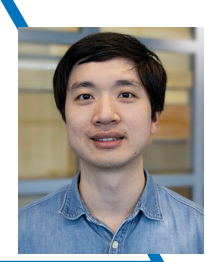


In the Medical School's Department of Ophthalmology and Visual Sciences, **John Han, Ph.D.**, will explore the role of lipid droplets and mitochondrial metabolism in lipoprotein particle formation and secretion in age-related macular degeneration. Han received his Ph.D. in cell biology and regenerative medicine from Thomas Jefferson University in Philadelphia.
Mentor: Jason Miller, M.D., Ph.D.

Working across the College of Literature, Science, and the Arts departments of Biophysics and Ecology and Evolutionary Biology, and the Medical School's Department of Internal Medicine, **Jacob Moran, Ph.D.**, will investigate how bacterial communities coordinate across different length and time scales to resist antibiotic treatments. Moran comes to U-M from Washington University in St. Louis, where he received a Ph.D. in physics. Mentors: Luis Zaman, Ph.D. and Robert Woods, M.D., Ph.D.

In the Medical School's Department of Pathology, **Siva Kumar Natarajan, Ph.D.**, will build on his graduate work by exploring how the crosstalk between tumor cells and immune cells contributes to aggressive forms of brain cancer. Natarajan received his Ph.D. in molecular and cellular pathology from U-M, where he identified metabolic vulnerabilities in pediatric brain cancers to develop new therapies.
Mentors: Sriram Venneti, M.D., Ph.D. and Costas Lyssiotis, Ph.D.

Morgan Pimm, Ph.D., has joined the Medical School's Department of Cell and Developmental Biology, where she will study how one class of cytoskeletal filaments, known as microtubules, are regulated to promote directed cell migration, which is essential for tissue formation, immune responses and wound healing. Pimm received a Ph.D. in biochemistry and molecular biology from the State University of New York Upstate Medical University. Mentors: Kristen Verhey, Ph.D. and Ryoma Ohi, Ph.D.



In the Life Sciences Institute, **Jingcheng Wang, Ph.D.**, is characterizing protein receptors that facilitate the movement of specific proteins (cargos) along the secretory pathway to the surface or outside of the cells, with a particular interest in the mechanisms that enable receptors to recognize their corresponding cargos. Before coming to U-M, Wang completed his graduate studies at the University of Texas Southwestern Medical Center.
Mentor: David Ginsburg, M.D.

Current Fellows

2023

In the Medical School's Department of Molecular and Integrative Physiology, **Kristina Weaver, Ph.D.**, plans to establish new animal models to study how environmental changes, such as touch, can reprogram neural states in the brain and impact aging. Weaver received her Ph.D. in molecular and integrative physiology from U-M.
Mentors: Scott Pletcher, Ph.D. and Megan Killian, Ph.D.

In the Medical School's Department of Microbiology and Immunology, **Guolei Zhao, Ph.D.**, is investigating the mechanisms that drive skin colonization in *Candida auris*, which can cause life-threatening infections. Prior to joining U-M, Zhao received her Ph.D. in biological sciences from the State University of New York-Buffalo.
Mentor: Teresa O'Meara, Ph.D.

2022

In the Medical School's Department of Molecular and Integrative Physiology, **Dominik Awad, Ph.D.**, studies the role of microbiome-derived metabolites and their impact on the pancreatic tumor microenvironment. He received his MSc in Microbiology from the University of Graz, Austria, studying ribosome biogenesis in yeast. Prior to joining the University of Michigan for his postdoctoral studies, Awad earned a Ph.D. from the University of Texas MD Anderson Cancer Center, where his research focused on prostate cancer lipid metabolism. Mentors: Costas Lyssiotis, Ph.D. and Donnele Daley, M.D.

In the Medical School's Department of Internal Medicine, **Ashley Calder, Ph.D.**, studies the signaling mechanisms driving biliary injury and repair. She received her undergraduate education at Utah Valley University, where she earned her B.S. in Biotechnology. Calder completed her graduate training in Biomedical Sciences at the University of Central Florida, where her research investigated the mechanisms of chemosensory signaling in the oral cavity.
Mentors: Linda Samuelson, Ph.D. and Nataliya Razumilava, M.D.

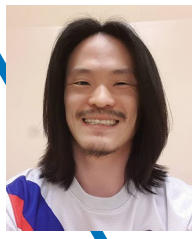
Current Fellows

2022

From sugars and lipids to metals and gases, **Jutta Diessl, Ph.D.**, studies cellular biology at the intersection of molecular biology and bioinorganic chemistry. During her graduate studies, Diessl investigated glucolipotoxicity in yeast (M.Sc., University of Graz, Austria) and dysregulated calcium and manganese homeostasis in yeast and flies (Ph.D., Stockholm University, Sweden). In the U-M Medical School's Department of Biological Chemistry, Diessl now elucidates the crosstalk of hydrogen sulfide and copper metabolism and its impact on mitochondrial bioenergetics and metabolism in mammalian cell culture and mice. Mentor: Ruma Banerjee, Ph.D.

In the College of Literature, Science, and the Arts Department of Chemistry, **Luis Ortiz-Rodríguez, Ph.D.**, is developing next-generation single-molecule microscopy methods for measuring subcellular interactions in living microbial cells. Ortiz-Rodríguez comes from Luquillo, Puerto Rico and graduated with his B.S. in biology from University of Puerto Rico-Humacao Campus. He earned a Ph.D. in physical chemistry at Case Western Reserve University in Cleveland, Ohio, where he scrutinized the excited state dynamics and electronic relaxation pathways of thionated heavy-atom-free photosensitizers for photodynamic therapy applications. Mentor: Julie Biteen, Ph.D.

In the Life Sciences Institute, **Mónica Rivas Morales, Ph.D.**, focuses on the development and application of allosteric modulators of dynamic proteins in transcription. After earning her B.S. in Chemistry from the University of Central Florida, Rivas completed her graduate studies in Chemistry at the University of Texas at Dallas, developing methods for robust and rapid alkyl radical generation, and their application to 18F-incorporation for the synthesis of positron emission tomography agents. Mentor: Anna Mapp, Ph.D.



In the Medical School's Department of Radiology, **Jason Witek, Ph.D.**, is working on the design and development of novel opioid PET radioligands that are agonist/antagonist pairs. After graduating with his B.S. in Chemistry from U-M, he earned a M.Sc. in Chemistry focusing on alkaloid natural product total synthesis at Penn State University. Witek continued his graduate studies at Yonsei University, earning a Ph.D. in Pharmaceutical Sciences focusing on medicinal chemistry and organic synthesis of drug-like molecules. Mentors: John Traynor, Ph.D. and Peter Scott, Ph.D.

Current Fellows

2021

Amanda Erwin, Ph.D. is implementing a multimodal imaging pipeline to investigate TDP43 pathology in ALS and FTD. During her Ph.D. at the University of Michigan, Erwin studied the structure and function of an *H. pylori* virulence factor and developed new methodology for protein structure determination with cryo-electron microscopy. At the Life Sciences Institute, Erwin is focused on determining the structures of disease-associated fibrils in the context of ALS/FTD and characterizing the cellular responses to TDP-43 aggregation within cultured human neurons. Erwin's research aims to elucidate molecular mechanisms underlying neurodegenerative diseases to find potential therapeutic targets.
Mentors: Shyamal Mosalaganti, Ph.D. and Sami Barmada, M.D., Ph.D.

Mike McFadden, Ph.D., has a long-standing interest in the molecular biology of host-pathogen interactions. He received a B.S. in Genomics and Molecular Genetics from Michigan State University, where he studied tripartite interactions between disease vector mosquitoes, pathogens they transmit, and the endosymbiotic bacterium Wolbachia. He then studied post-transcriptional regulation of antiviral gene expression and virus-host interactions at Duke University for his Ph.D. work. In the Medical School's Department of Microbiology and Immunology, McFadden studies how macrophage cell stress responses elicited by *Candida albicans* infection influence antifungal innate immunity. Mentors: Teresa O'Meara, Ph.D. and Mary O'Riordan, Ph.D.

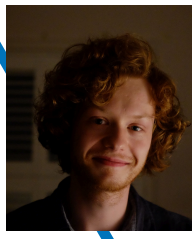
Congratulations, 2024 cohort!

2024

In the U-M Department of Biomedical Engineering, **Emmanouil Agrafiotis, Ph.D.**, plans to identify shared signaling pathways driving myofibroblast activation and cardiac fibrosis post-myocardial infarction using inducible cardiomyocyte apoptosis in human and mouse models, exploring heterocellular communication and fibrotic responses through genetic switches, marker analysis, and single-cell transcriptomics. Agrafiotis received his Ph.D. in biomedical engineering from the Graz University of Technology, Austria. Mentor: Brendon Baker, Ph.D.

In the Medical School's Department of Human Genetics, **Ritvija Agrawal, Ph.D.**, will investigate the unique mechanisms through which protamine proteins influence sperm chromatin structure and early embryonic development, thereby enhancing our understanding of the biological basis of various types of infertility and embryonic failure. Agrawal received her Ph.D. in molecular, cellular and developmental biology from U-M. Mentor: Sue Hammoud, Ph.D.

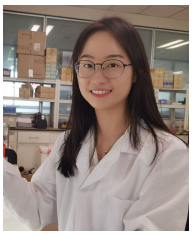
In the Medical School's Department of Molecular and Integrative Physiology, **Prarthana Dalal, M.D., Ph.D.**, will explore how hypoxic stress alters endothelial cell metabolic crosstalk with cancer cells and immune cells in the tumor microenvironment. Dalal completed her M.D./Ph.D. training at Northwestern University, focusing on vascular biology, specifically leukocyte transendothelial migration. Mentor: Yatrik Shah, Ph.D.



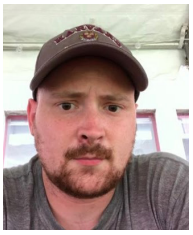
In the College of Literature, Science, and the Arts Department of Physics, **Daniel Duffy, Ph.D.**, will research the mechanisms by which leaves develop their distinctive shapes during growth. Duffy received his Ph.D. in engineering from the University of Cambridge. Mentor: Suraj Shankar, Ph.D.

Congratulations, 2024 cohort!

2024



In the Medical School's Department of Microbiology and Immunology, **Jiawen Fu, Ph.D.**, will investigate how *Toxoplasma gondii* delivers its effector proteins to host cells and plans to identify novel parasite proteins that mediate effector protein trafficking. Fu received her Ph.D. from the Harbin Veterinary Research Institute, Chinese Academy of Agricultural Sciences. Mentor: Yifan Wang, D.V.M., Ph.D.



In the Medical School's Department of Biological Chemistry, **Duncan Kountz, Ph.D.**, works on metalloenzymes from anaerobic microbes that play key roles in the carbon cycle and climate. Kountz received his Ph.D. in chemical biology from Harvard University. Mentor: Stephen Ragsdale, Ph.D.

In the College of Literature, Science, and the Arts Department of Psychology, **Arpit Kumar Pradhan, Ph.D.**, is working to understand the neural mechanisms underlying sound salience processing during sleep using electrophysiological and optical recordings. Pradhan received his Ph.D. in systemic neuroscience from Ludwig Maximilian University of Munich, Germany. Mentor: Ada Eban-Rothschild, Ph.D.

In the Life Sciences Institute, **Christabel Tan, Ph.D.**, is working to track and reprogram the epigenomes of closely related neuronal lineages in the fly brain to reveal the detailed genetic and epigenetic mechanisms of neural diversification. Tan received her Ph.D. in cell biology at Duke University. Mentor: Tzumin Lee, M.D., Ph.D.

Congratulations, 2024 cohort!

2024

In the Medical School's Department of Internal Medicine Division of Hospital Medicine, **Hitarthi Vyas, Ph.D.**, is focusing on creating the most comprehensive functional map of the Low-Density Lipoprotein Receptor (LDLR) locus using high-throughput CRISPR screens. Additionally, she seeks to develop a synthetic enhancer to improve LDLR activity with the ultimate goal of advancing therapeutic options for treating atherogenic cardiovascular disorders. Vyas received her Ph.D. from Maharaja Sayajirao University of Baroda, where she investigated circadian-regulated microRNAs and their role in the onset and progression of atherosclerosis. Mentor: Brian Emmer, M.D., Ph.D.

In the Medical School's Department of Psychiatry, **Hasini Weerathunge, Ph.D.**, is investigating the application of non-invasive neurostimulation techniques to improve the effectiveness of current behavioral approaches to stuttering treatment. Weerathunge received her Ph.D. in biomedical engineering from Boston University, where her work centered on utilizing auditory and somatosensory motor perturbations of voice and speech to develop neurocomputational models of speech motor control to better understand motor speech disorders. Mentor: Soo-Eun Chang, Ph.D.

Alumni

Faran Baroz (MLSF '18) | AI/ML Data Scientist, T2S Solutions

Joshua MacCready (MLSF '18) | Research Associate, Michigan State University

Brittany Morgan (MLSF '18) | Assistant Professor, University of Notre Dame

Aaron Morris (MLSF '18) | Assistant Professor, University of Michigan

Jennifer Yeung (MLSF '18) | Research Fellow, Cincinnati Children's Hospital Medical Center

Krista Armbruster (MLSF ' 18) | Research Lab Specialist, University of Michigan

Jacob Berv (MLSF '19) | Schmidt AI in Science Fellow, University of Michigan

Laura Kirby (MLSF '19) | Bioinformatics Scientist, Bio-Rad Laboratories

Yilai Li (MLSF '19) | Research Scientist, ByteDance

Mohammad Siddiq (MLSF '19) | Research Lab Specialist, University of Michigan

Kyoung Jo (MP3 '19) | Research Scientist, Nationwide Children's Hospital

Zeribe Nwosu (MP3 '19) | Assistant Professor, Cornell University

Michael Kalyuzhny (MLSF '20) | Principal Investigator, Hebrew University of Jerusalem

Einar Olafsson (MLSF '20) | Research Fellow, University of Michigan

Pilar Rivero-Rios (MLSF '20) | Research Investigator, University of Michigan

Catherine Scull (MLSF '20) | Scientist, Servier Pharmaceuticals

Carolyn Walsh (MLSF '20) | Assoc. Director of Medical Information, AstraZeneca

Mingmin Zhang (MLSF '20) | Postdoctoral Scholar, UCLA

Alex Knights (MP3 '20) | Assistant Professor, Washington University in St. Louis

David Hanna (MP3 '20) | Research Fellow, University of Michigan

Samantha Hodges (MP3 ' 20) | Senior Medical Writer, AbbVie

Helen Rich (MP3 '21) | Scientist, Cerberus Therapeutics

Pioneer Talk

Dominik Awad, Ph.D.
2022 cohort
Mentors: Costas Lyssiotis, Ph.D. and Donnele Daley, M.D.
Michigan Medicine, Department of Molecular and Integrative Physiology
awaddo@umich.edu

Mycobiome-derived metabolites impact the pancreatic tumor microenvironment

Recent studies demonstrated that the development of pancreatic ductal adenocarcinoma (PDA) is also accompanied by an influx of bacteria and fungi into the pancreas, which can contribute to tumor growth and interfere with chemotherapeutic response. While most studies focus on bacteria derived-metabolites, little is known about the impact of intratumoral or circulating fungal-derived metabolites on pancreatic cancer. We found that fungal depletion in syngeneic orthotopic murine PDA models results in a significant decrease in tumor burden, which can be reversed via the repopulation of the gut using clinical isolated fungi. Our metabolomic analysis found that fungal depleted mice demonstrated an increase in tryptophan in the gut and tumor, as well as a decrease in tryptophan-derived metabolites such as indoles and kynurenic acid. Clinical isolated fungi from pancreatic cancer patients produced several key indoles and kynurenic acid when grown in tumor defined media conditions. Since these metabolites are known to impact PDA growth and chemotherapy efficacy, we then tested the impact of fungal produced metabolites on various immune cells. We observed a significant decrease in T-cell proliferation upon their exposure to fungal-derived metabolites. In addition, we found that fungal condition media can polarize macrophages via aryl hydrocarbon receptor signaling, a known mediator of the immunosuppressive pancreatic tumor microenvironment. Together, our results provide important insights into how fungi, in addition to bacteria, contribute to pancreatic cancer progression and therapy resistance by reprogramming the tumor microenvironment.

Pioneer Talk

Ashley Calder, Ph.D.
2022 cohort
Mentors: Mentors: Linda Samuelson, Ph.D. and Nataliya Razumilava, M.D.
Michigan Medicine, Department of Internal Medicine
ascalder@umich.edu

WNT signaling regulates the extrahepatic bile duct proliferative response to acute biliary obstruction

Patients with chronic biliary diseases (cholangiopathies) represent ~8% of liver transplants in the U.S., and 10% of patients with cholangiopathies will develop biliary cancer. Acute obstructive injury increases the risk of cholangiopathy development and is a recurrent condition in cholangiopathies. Quiescent cholangiocytes that line the biliary tree proliferate in response to obstructive injury. Understanding the mechanisms that underlie the cholangiocyte response to biliary obstruction are relevant to both reparative mechanisms and maladaptive responses. WNT signaling is implicated in cell fate determination, proliferation, and disease progression in GI organs, including the liver; however, its role in cholangiocyte biology is not as well understood. Using bile duct ligation (BDL) as a model of acute biliary obstruction, we demonstrate a cholangiocyte proliferative response 24-hours post-BDL. Bulk RNA-seq of the extrahepatic bile duct (EHBD) in mice confirm these findings with proliferation markers and cell cycle genes being among the most highly induced after obstruction. Transcriptomic analysis of WNT signaling identified an increase in WNT ligand, Wnt7b, and several WNT target genes following BDL. Further, in vivo inhibition of WNT ligand secretion attenuated obstruction-induced cholangiocyte proliferation. Single-cell RNA-seq analysis identified cholangiocytes as a major source of WNT ligands in the EHBD. Lastly, the inhibition of WNT signaling in biliary organoids showed cholangiocyte-derived WNT ligands induce organoid growth through β-catenin dependent signaling. These data indicate that WNT signaling contributes to the acute biliary injury response in the EHBD. Targeting WNT signaling may provide a tool to regulate biliary proliferation either to promote regeneration or oppose carcinogenesis.

Pioneer Talk

Jutta Diessl, Ph.D.
2022 cohort
Mentor: Ruma Banerjee, Ph.D.
Michigan Medicine, Department of Biological Chemistry
jdiessl@umich.edu

Sulfide stress induces copper accumulation

Hydrogen sulfide (H_2S) is a substrate and an inhibitor of the electron transport chain and a product of both mammalian and microbial metabolism. In mammals, the mitochondrial enzyme, sulfide quinone oxidoreductase (SQOR) couples sulfide oxidation to the electron transport chain, supports ATP synthesis, and helps maintain low steady-state levels (<100 nM) of sulfide in cells. However, gut microbial metabolism routinely exposes colonocytes to high sulfide concentrations (0.2-2.4 mM), which inhibit complex IV-driven respiration, potentially slowing down sulfide detoxification. This raises the question whether alternative sulfide detoxification strategies exist. Here, we discovered that sulfide exposure perturbs metal homeostasis and leads to an up to ~10-fold copper (Cu) accumulation across human cell lines. X-ray fluorescence microscopy analysis revealed that Cu is diffusely distributed in puncta in colon-derived HT-29 cells cultured with low, chronic H_2S exposure. In a mouse model for SQOR deficiency in intestinal epithelial cells, colon Cu is 2-fold higher and is concentrated at the apical side of the crypts. Notably, the inhibitory effects of H_2S exposure on respiration and cell proliferation are reversible. In the current working model, exogenous H_2S downregulates metallothionein, which mobilizes Cu for rapid sulfide sequestration and subsequently promotes Cu dependent sulfide sequestration in intracellular vesicles. Whether Cu and sulfide are present as complexes or salts is not known. Intracellular sulfide also leaches Cu from MT-CO2, destabilizing this complex IV subunit, resulting in sustained complex IV inhibition and metabolic reprogramming. Collectively, these data point to a previously unknown mechanism for sulfide sequestration in response to H_2S stress.

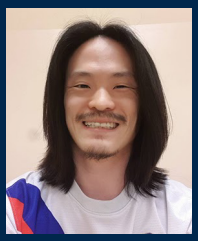
Pioneer Talk

Luis Ortiz-Rodríguez, Ph.D.
2022 cohort
Mentor: Julie Biteen, Ph.D.
College of Literature, Science, and the Arts, Department of Chemistry
lortz@umich.edu

Biomolecular Condensation Enables Material State Changes that Dynamically Regulate RNA Metabolism

Recently, biomolecular condensates have emerged as a broadly utilized mechanism for organizing biochemical pathways within cells, and this organizational paradigm is particularly important within bacteria because these organisms generally lack membrane-bound organelles. Bacterial ribonucleoprotein bodies (BR-bodies) are dynamic biomolecular condensates that play a pivotal role in bacterial RNA metabolism. In this talk, I will demonstrate how BR-bodies orchestrate mRNA decay and storage based on a multidisciplinary approach that combines single-molecule fluorescence microscopy, bulk imaging techniques, biochemical assays, and rigorous quantitative analyses. During exponential growth, BR-bodies act as fluid-like condensates that enhance mRNA decay. This function pivots under stress conditions, during which BR-bodies transition into more solid-like states, becoming reservoirs that store mRNA. This shift is characterized by slowed internal dynamics, increased molecular density, and prolonged residence time of ribonuclease E. Our investigations also show that ATP levels and translation rates drive these changes, suggesting that mRNA accumulation of ribosome-free mRNA is a key factor driving these material state transitions. Moreover, I will demonstrate that, upon nutrient replenishment, stationary-phase BR-bodies disassemble, releasing stored mRNAs for rapid translation and demonstrating that BR-body function is governed by a reversible mechanism for resource management. These findings reveal adaptive strategies by which bacteria regulate RNA metabolism through condensate-mediated control of mRNA decay and storage.

Pioneer Talk



Jason Witek, Ph.D.
2022 cohort
Mentors: John Traynor, Ph.D. and Peter Scott, Ph.D.
Michigan Medicine, Department of Radiology
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Synthesis, Evaluation and Radiolabeling of a Mu Opioid Antagonist

Opioid receptors (mu, delta, kappa and nociceptin/orphanin FQ peptide) play a key role in the mechanism of action of both synthetic and natural analgesics. Since the 1970s, PET imaging of opioid receptors has provided a useful tool to understand the role of opioid receptors in addiction as well as in other psychiatric and neurological disorders. Currently, the radioligand of choice for studies related to the mu opioid receptor is agonist [11C]carfentanil. [11C]Carfentanil is useful in its current role but presents safety issues because of its potency. The development of a selective mu opioid receptor antagonist would address safety issues and allow for studies using agonist/antagonist radioligand pairs. Working to address this unmet need, an array of fentanyl derivatives has been synthesized and evaluated in vitro. One compound (3FN) with the best properties was selected for fluorine-18 radiolabeling. Full automation of [18F]3FN has been successfully carried out and has been evaluated in vivo in non-human primates.

Pioneer Talk

Amanda Erwin, Ph.D.
2021 cohort
Mentors: Shyamal Mosalaganti, Ph.D. and Sami Barmada, M.D., Ph.D.
Life Sciences Institute, Department of Cell and Developmental Biology
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Visualizing TDP43 Pathology with Cryo-Electron Tomography

In amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD), the RNA-binding protein TDP43 is excluded from the nucleus and abnormally accumulates in the cytoplasm. Although this is a hallmark of ALS and FTLD, the mechanisms underpinning the origin and ultrastructure of these cytosolic deposits remain elusive. Emerging evidence suggests that abnormal RNA homeostasis may play a critical role in TDP43 mislocalization, triggering RNA misprocessing and neuronal degeneration.

In my research, I have demonstrated that the introduction of small monovalent oligonucleotides effectively reproduces pathological TDP43 mislocalization and aggregation in induced pluripotent stem cell-derived neurons (iNeurons). Utilizing a state-of-the-art, multimodal in situ cryo-correlative light and electron microscopy (cryo-CLEM) pipeline, my work investigates the impact of RNA on TDP43 localization and aggregation within a near-native cellular environment. My findings reveal that mislocalized TDP43 forms ordered fibrils within lysosomes and autophagosomes in both iNeurons and from patient-derived tissues, providing unprecedented high-resolution visualizations of TDP43 aggregates in situ.

Through this work, I establish a robust cellular model that enables the exploration of initial pathogenic events in ALS, FTLD, and other TDP43-proteinopathies. This model not only enhances our understanding of disease mechanisms but also opens avenues for future therapeutic interventions targeting TDP43 pathology.

Pioneer Talk

Mike McFadden, Ph.D.
2021 cohort
Mentors: Teresa O'Meara, Ph.D. and Mary O'Riordan, Ph.D.
Michigan Medicine, Department of Microbiology and Immunology
mcfaddmj@umich.edu

IRE1α promotes phagosomal calcium flux to enhance macrophage fungicidal activity

The mammalian ER stress sensor IRE1α is a crucial regulator of cellular homeostasis and also serves broad roles in regulating responses to infection, including innate immunity and microbicidal activity. While the IRE1α-XBP1S axis is known to regulate host responses to infection, XBP1S-independent and homeostatic functions of IRE1 α are not well understood. Further, the roles of IRE1α during fungal infection are only beginning to emerge. We report that the fungal pathogen, Candida albicans, activates macrophage IRE1α through C-type lectin receptor signaling and independently of protein misfolding, suggesting that pathogens can trigger IRE1α activation through non-canonical mechanisms. Functionally, IRE1α enhances macrophage fungicidal activity in vitro and in vivo by promoting phagosome maturation, which is crucial to contain rapidly growing C. albicans hyphae. This novel role for IRE1α in phagosome regulation occurs through the ability of IRE1α to promote early phagosomal calcium flux after phagocytosis of C. albicans, which is required for phagolysosomal fusion. Interestingly, in macrophages lacking IRE1α endoribonuclease activity, defective phagosomal calcium flux correlates with fewer contact sites between the ER and early endosomes at resting state, suggesting a homeostatic role for IRE1α in promoting these membrane contact sites. Together, these data provide mechanistic insight for the non-canonical activation of IRE1α during infection and reveal a novel role for IRE1α in supporting organelle contact sites between the ER and endosomes/phagosomes at resting state. Our data suggest this function of IRE1α provides a safeguard against infection by rapidly growing microbes through coordination of phagosome maturation and microbicidal activity.

MICHIGAN PIONEER FELLOWS PROGRAM

Michigan Pioneer Fellows **Symposium Keynote**

Dec 11, 2024
3:30–4:30 p.m.
BSRB Kahn Auditorium

KEYNOTE SPEAKER

CATHERINE DRENNAN, PH.D.

Professor of Biology and Chemistry, MIT;
Investigator and Professor,
Howard Hughes Medical Institute

Capturing One-Carbon Chemistry, One-Structural Snapshot at a Time

Ni-Fe-S-cluster containing carbon monoxide dehydrogenase (CODH) and acetyl-CoA synthase (ACS) play major roles in the global carbon cycle through the consumption of CO and CO_2 gases, the production of acetate, and the breakdown of acetate for methane generation. In this presentation, I will describe my lab's journey to understand the structural basis of one-carbon chemistry at Ni-Fe-S clusters. Our work shows that to perform the biological equivalent of the water-gas shift reaction ($CO + H_2O <=> CO_2 + H_2$) and of the Monsanto process ("syn gas" to acetic acid), CODH/ACS enzymes use internal gas channels and employ dramatic conformational rearrangements. Our goal is to capture structural snapshots of CODH/ACS enzymes in order to visualize how nature produces and consumes greenhouse gases CO_2 and methane using organometallic chemistry.

About the Speaker

Cathy L. Drennan is the John and Dorothy Wilson Professor of Biochemistry at the Massachusetts Institute of Technology, and a Professor and Investigator with the Howard Hughes Medical Institute. During her AB in chemistry from Vassar College, she worked with Professor Miriam Rossi and discovered her passion for X-ray crystallography and for vitamin B_{12}. But she did not head straight to graduate school, instead teaching high school in West Branch, Iowa, for three years. By day, she taught chemistry, biology, and physics and by night, she staged high school plays, such as *The Importance of Being Earnest*. Realizing that teaching science and scientific research go hand in hand, Cathy enrolled in a PhD program at the University of Michigan to more fully experience the world of research. Carrying out her graduate studies in biological chemistry with the late Professor Martha L. Ludwig, Cathy used X-ray crystallography to show for the first time how vitamin B_{12} binds to a protein.

Following postdoctoral studies with Professor Douglas C. Rees at Caltech, Cathy joined the faculty of the Massachusetts Institute of Technology. Her laboratory seeks to understand how nature harnesses and re-directs the reactivity of enzyme metallocenters to perform challenging reactions. By combining X-ray crystallography and electron microscopy with other biophysical methods, the Drennan laboratory's goal is to "visualize" molecular processes by obtaining snapshots of enzymes in action. Some of the proteins studied are newly characterized, and others have eluded structural characterization due to issues of oxygen sensitivity, conformational flexibility, protein heterogeneity, or structural complexity. The Drennan laboratory has specialized in tackling and solving these more challenging problems in structural biology. In total, Drennan is an author on ~190 publications, over 200 Protein Data Bank submissions, and has given over 200 invited talks. Her research has been featured in the iBIOLOGY online seminar series Metalloproteins in Action.

For twenty of her twenty-five years at MIT, Drennan has taught the large introductory science classes, known as the science General Institute Requirements or GIRs. For fourteen years, she taught 350-person-plus introductory chemistry class 5.111, which is available online on the MIT OCW site and for the past six years, she taught the 250-500-person introductory biology class 7.012. In 2006, Drennan was selected as a "Million Dollar Professor" by the Howard Hughes Medical Institute, allowing her to run an education research group (separate from her biochemistry research group) for eight years. As part of her education program, she co-authored a teacher training guide, *What Every Teacher and Mentor Should Know: A Guide to Identifying and Reducing Stereotype Threat to Maximize Student Performance* and ran workshops based on this material all over the country and produced an online version. She also created classroom material that showcases

About the Speaker

the importance of chemical principles to solving real world problems and diversity among chemists. Drennan has also spoken in national forums about being dyslexic, including on CBS Sunday Morning and PBS's RoadTrip Nation. Her goal as an educator is to engender an appreciation for the disciplines of chemistry and biology and to convey that scientists are a diverse group of people. In her own research group, Drennan has trained a total of eighty-eight undergraduate students, forty graduate students, and twenty-two postdocs.

Cathy has been recognized with both teaching and research awards, including MIT's Baker Award for Excellence in Undergraduate Teaching, MIT's Edgerton Faculty Achievement Award, a Sloan Fellowship, an ASBMB-Schering-Plough Research Institute Scientific Achievement Award, a Presidential Early Career Award for Scientists and Engineers, a Searle Scholar Award, the Dorothy Crowfoot Hodgkin Award from the Protein Society and the Rose Award from the ASBMB. She is an AAAS Fellow, an ASBMB Fellow, an ACA Fellow, a MacVicar Faculty Fellow, and a member of the American Academy of Arts and Sciences and the National Academy of Sciences. Cathy resides with her husband, Boston University Professor Sean J. Elliott, daughter Sammy, labradoodle Casey, and cat Lacie in Newton, Massachusetts.

Posters

1. Emmanouil Agrafiotis
Engineering and Medical School, Biomedical Engineering

Deciphering Cardiomyocyte-Fibroblast Paracrine Interactions in Homeostasis and Cardiac Fibrosis Using a Compartmentalized Biomimetic Model

2. Ritvija Agrawal
Michigan Medicine, Human Genetics

"Understanding the functional consequences of rapid evolution of protamine protein sequences"

3. Sydney Alibeckoff
Michigan Medicine, Biological Chemistry

"Redox shifts in the cysteine proteome in response to sulfide"

4. Christophe-Sebastien Arnold
Michigan Medicine, Microbiology & Immunology

"Defining how Toxoplasma modulates host ER stress to support its growth".

5. Subhash Arya
Life Sciences Institute

"Exosomal cPLA2α Promotes Nuclear Mechanotransduction during Neutrophil Chemotaxis "

6. Merci Best
Michigan Medicine, Neurology

"From Organoids to Autopsies: Unraveling the Mysteries of Frontotemporal Dementia (FTD) and Progressive Supranuclear Palsy (PSP)"

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Posters

7. Maurinne Bonnet
Pharmacy, Medicinal Chemistry

"Development of a Direct-to-Biology approach to target miRNA biogenesis"

8. Sam Collie
Michigan Medicine, Cellular and Molecular Biology

"Nuclear Envelope Budding and Nuclear Pore Complexes in Activated Neutrophils"

9. Brian Curtis
Life Sciences Institute

"Investigating the biocatalytic flexibility of the pikromycin polyketide synthase: Substrate scope, bottlenecks, and engineering efforts"

10. Prarthana Dalal
Michigan Medicine, Physiology/Hematology & Oncology

"Targeting Cholesterol Biosynthesis Potentiates the Effect of HIF-2α Inhibition in Colorectal Carcinoma"

11. Nupur Das
Michigan Medicine, Molecular and Integrative Physiology

"The role of intestinal ferritinophagy in iron-related disorders"

12. Andrea Paola De La Lama Flores
Michigan Medicine, Cell and Developmental Biology

"Advanced Optical Clearing Methods for Whole Mouse Organs Embedded in Improved Hydrogel "

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Posters

13. Carli DeJulius
Michigan Medicine, Orthopaedic Surgery

"Sustained Biomaterial-mediated Inhibition of R-spondin 2 to Target Pathological Wnt Signaling in Post-Traumatic Osteoarthritis"

14. Daniel Duffy
LSA, Physics

"Shape-programmed shells"

15. Easton Farrell
Engineering and Medical School, Biomedical Engineering

"PIEZO1 promotes synovial fibrosis and inflammation"

16. Jiawen Fu
Michigan Medicine, Microbiology & Immunology

"MYR complex-mediated dense granule protein (GRA) export in *Toxoplasma gondii*"

17. Adrienne Giannone
Michigan Medicine, Orthopaedic Surgery

"Investigating the role of Sox5 in synovial fibroblast function during homeostasis and post-traumatic osteoarthritis"

18. Fabio Gómez Cano
LSA, Molecular, Cellular, and Developmental Biology

"Defining the regulatory grammar of the stress-responses in maize"

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Posters

19. John Han
Michigan Medicine, Ophthalmology

"The Role of Lipid Droplets in RPE Lipid Handling"

20. Olivia Harlow
Michigan Medicine, Microbiology & Immunology

"Pneumolysin influences the tissue-resident adaptive immune landscape of the murine lung"

21. Gabriel Jimenez-Pagan
Michigan Medicine, Cellular and Molecular Biology

"Breaking Stereotypes: Investigating the Role of Cell Cycle Regulators in the Mitochondria-Dependent Macrophage Response to Infection"

22. Duncan Kountz
Michigan Medicine, Biological Chemistry

"Evidence for succinate production by an electron-bifurcating fumarate reductase in the mammalian gut"

23. Abhiram Kunamneni
Life Sciences Institute

"Elucidating role of HUWE1 in mTORC1 pathway in mice hepatocytes"

24. Lindsey Lammlin
Michigan Medicine, Orthopaedic Surgery/Molecular and Integrative Physiology

"A novel role for CXCL16 in synovial inflammation and joint nociception"

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Posters

25. Ling-Yu Liu
Dentistry, Biologic and Materials Sciences & Prosthodontics

"Decoding reflexive and pain outputs from acute orofacial stimulation"

26. Sahiti Marella
Michigan Medicine, Dermatology

"Single-cell atlas of healthy human skin reveals body site-specific cellular diversity, pathway enrichment, and intercellular communication networks."

27. Behrokh (Bianca) Marzbanabbasabadi
Michigan Medicine, Molecular & Integrated Physiology

"Sex differences in calcitonin receptor (CalcR) neurons of the ventral premammillary nucleus: potential role in neuroendocrine regulation"

28. Jacob Moran ⬢
LSA, Biophysics

"The spread of antibiotic resistance in multi-colony networks"

29. Siva Kumar Natarajan ⬢
Michigan Medicine, Pathology

"Assessing the role of hypoxia-induced metabolites in ERG fusion-driven prostate cancers"

30. Hannah Navarrete
Michigan Medicine, Microbiology & Immunology

"Inflammatory biogenesis and macrophage function: Defining features and consequences"

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Posters

31. Ritam Neupane
Michigan Medicine, Biochemistry

"Translation of human papillomavirus E6 protein from mRNAs with extremely short 5′-UTRs"

32. Morgan Pimm
Michigan Medicine, Cell and Developmental Biology

"Regulation of the microtubule lattice by end-binding proteins"

33. Arpit Kumar Pradhan
LSA, Psychology

"Understanding the neural mechanisms underlying sound salience processing during sleep"

34. Shangyi Qian
Life Sciences Institute

"Understanding eicosanoid biogenesis pathways in alveolar macrophages"

35. Joanna Rew
Michigan Medicine, Dermatology

"Targeting VGLL3-TEAD interaction to treat lupus"

36. Ryan Singer
LSA, Chemical Biology

"Engineering genetically encoded tools for the activation of endogenous melanocortin-4 receptor"

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Posters

37. Debatrayee Sinha
Life Sciences Institute and Michigan Medicine

"Characterization of the role of vimentin intermediate filaments in regulating neutrophil activity during the innate immune response"

38. Christabel Tan
Life Sciences Institute

"How do epigenomic mechanisms guide neuronal diversification?"

39. Helen Tran
Engineering and Medical School, Biomedical Engineering

"A Cellular Proximity Atlas of Post-Traumatic OA Synovium by Single-cell Spatial Transcriptomics"

40. Nathalie Tsimhoni
Michigan Medicine, Ophthalmology

"Extracellular Lactate Regulates RPE Glucose Transport"

41. Hitarthi Vyas
Michigan Medicine, Internal Medicine

"Functionally defining the noncoding landscape of the Low-Density Lipoprotein Receptor locus. "

42. Jingcheng Wang
Life Sciences Institute

"Deep mutational scanning analysis to define recognition motifs for the cargo receptors, LMAN1 and SURF4"

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Posters

43. Kristy Weaver
Michigan Medicine, Molecular and Integrative Physiology

"Somatosensory modulation of aging and behavior"

44. Hasini Weerathunge
Michigan Medicine, Internal Medicine

"Differences in White Matter Fiber Density and Fiber-bundle Cross-section in Children who Stutter compared to Controls: a Fixel-based Analysis"

45. Guolei Zhao
Michigan Medicine, Microbiology & Immunology

"*Candida auris* skin colonization is mediated by Als4112 and interactions with host extracellular matrix proteins"

46. Liang Zhao
Michigan Medicine, Molecular and Integrative Physiology

"tRNA Methyltransferase ALKBH8 promotes ferroptosis defense in colorectal cancer"

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See you next year!