4th Annual NIGMS P41 QE-Map Symposium/ Workshop September 10-12, 2024

MICHIGAN STATE UNIVERSITY
Interdisciplinary Sciences and Technology Building
766 Service Road, East Lansing MI, 48824

Workshop Agenda

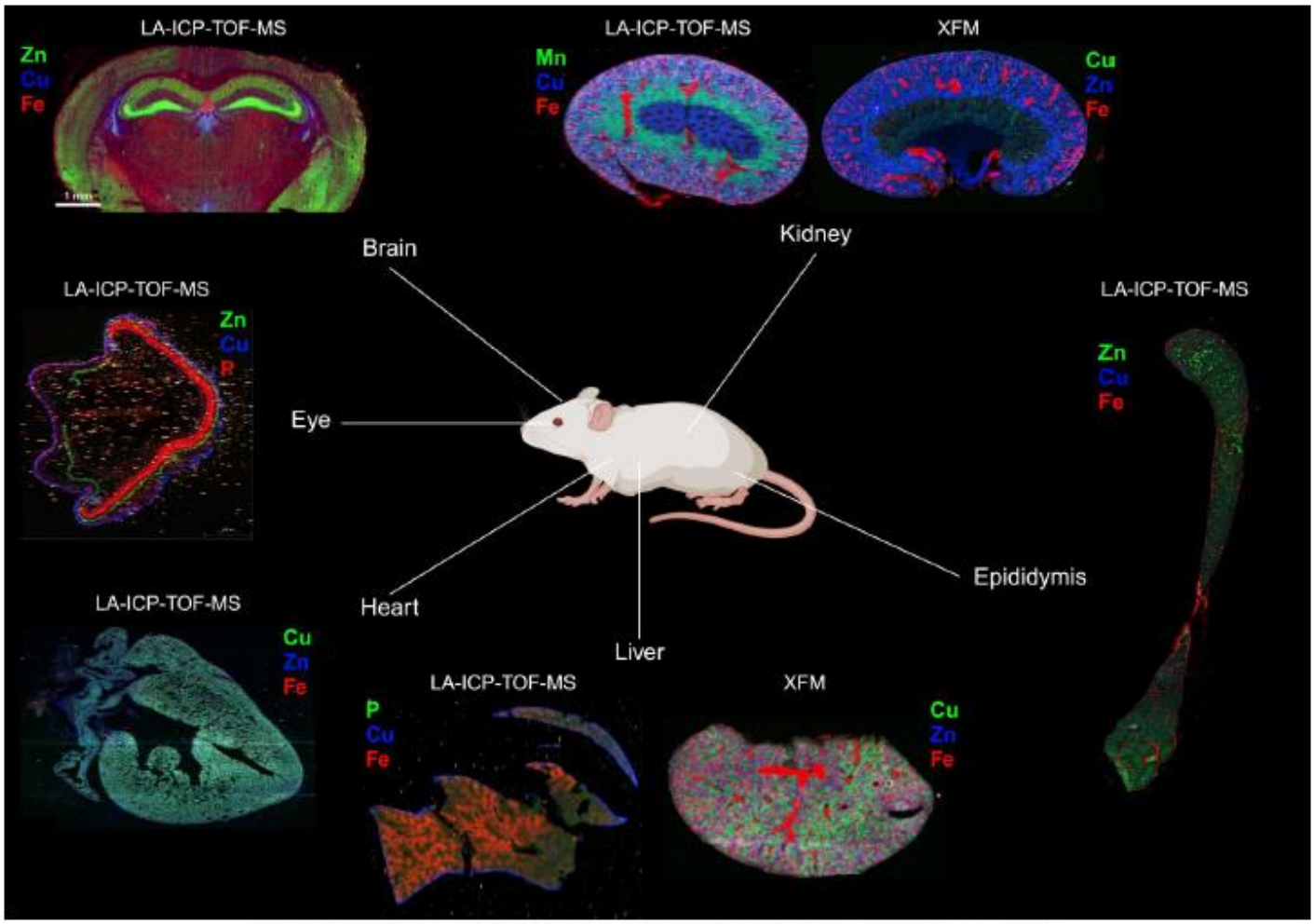
- Day 1: EAC meeting, half day of symposium talks
- Day 2: half day of symposium talks, half day of workshop
- Day 3: full day of workshop

Please fill out the Microsoft Teams Poll:

https://forms.office.com/r/yZ2PdTEvxN

QBEAM
QUANTITATIVE BIO ELEMENT ANALYSIS AND MAPPING CENTER

QE MAP



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Welcome

Dear Colleagues,

It is a great pleasure to welcome you to Michigan State University and the 4th annual (3rd in-person) NIGMS P41 QE-Map Symposium and Workshop in East Lansing, Michigan.

As we gather here, we are bringing together members of the NIGMS P41GM135018 grant as well as other members of the bioelement imaging and analysis community. Over the next few days, we will discuss the National Research Resource Center for Quantitative Mapping in the Life Sciences (QE-Map) and how technology research and development (TR&D) projects facilitate research among the driving biological projects (DBP) and beyond. We will hear about progress in laser ablation inductively coupled plasma time-of-flight mass spectrometry (LA-ICP-TOF-MS, TR&D 1), synchrotron-based X-ray fluorescence microscopy (XFM, TR&D 2), and photoacoustic microscopy (PAM, TR&D 3) and how we can answer fundamental biological questions using the aforementioned technologies.

We will also have a workshop on days 2 and 3 to expose students, postdoctoral researchers, and faculty to the cutting-edge instrumentation that we are developing in this resource. We encourage open dialogue and discussions throughout the event and hope you will all actively participate.

We are highly grateful for the support and generosity of our sponsors and have set up lunchtime partner talks where we will hear directly from the instrument manufacturers about development of new technologies and implementation of their current ones.

On behalf of the NIGMS P41 QE-Map Executive Advisory Committee, we wish you a warm welcome to East Lansing and Michigan State University and look forward to an engaging symposium and workshop.

Thomas V. O'Halloran
Principal Investigator P41 National Research Resource (QE-Map)

P41 Members
Technology Research and Development (TR&D) Leads

TR&D 1, PI: **Thomas V. O'Halloran**, *Michigan State University*

TR&D 2: **Chris Jacobsen**, *Northwestern University/Argonne National Laboratory*

TR&D 3: **Cheng Sun**, *Northwestern University*

Driving Biological Projects (DBP)

Yevgenia Kozorovitskiy, *Northwestern University*

Svetlana Lutsenko, *Johns Hopkins University*

Somshuvra Mukhopadhyay, *University of Texas-Austin*

Valeria Culotta, *Johns Hopkins University*

Eric Skaar, *Vanderbilt University*

Christoph Fahrni, *Georgia Institute of Technology*

Carole LaBonne, *Northwestern University*

Hossein Ardehali, *Northwestern university*

Malek El Muayed, *Northwestern University*

Donald McClain, *Wake Forest University*

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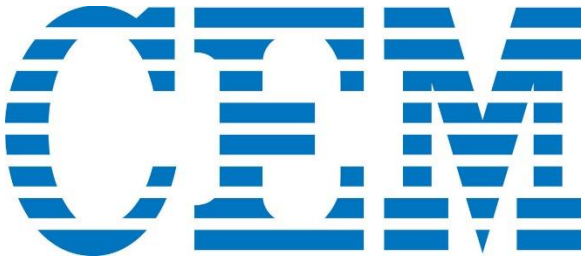

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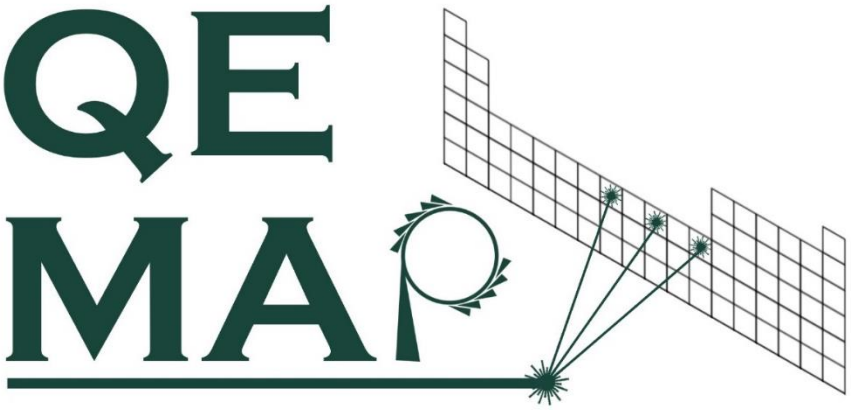
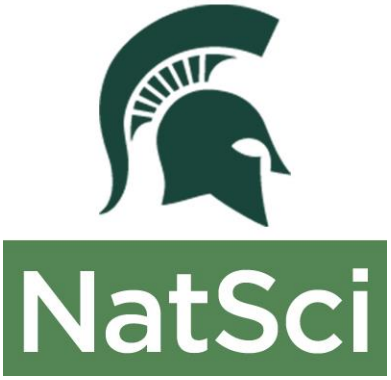

QE
MAP


NatSci

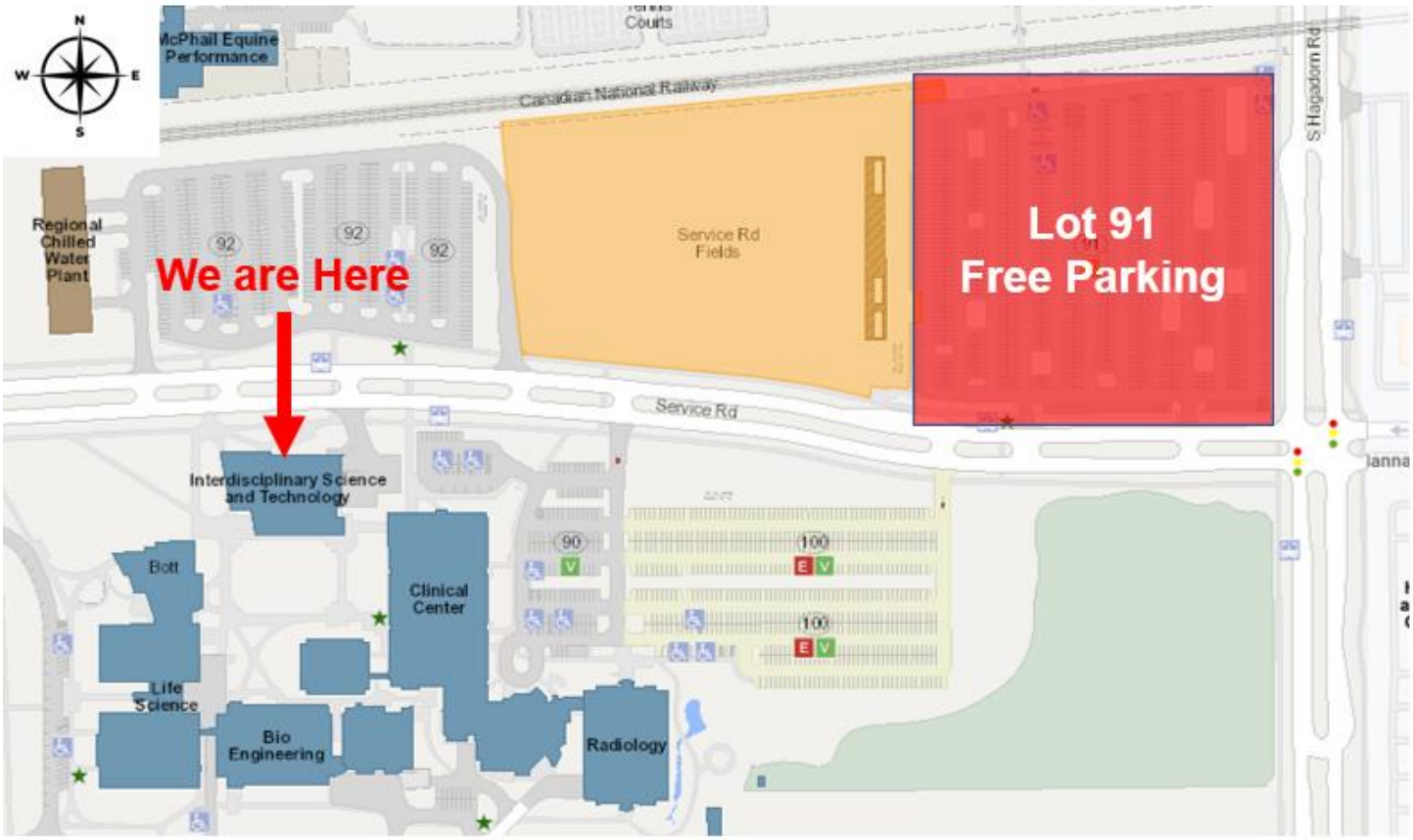
Conference Venue

The venue for the 2024 QE-Map Symposium/Workshop is Michigan State University and the Interdisciplinary Science and Technology Building (ISTB). ISTB was built in 2019 to provide state-of-the-art laboratories for diverse research groups including engineering, biology, computer science, and chemistry.

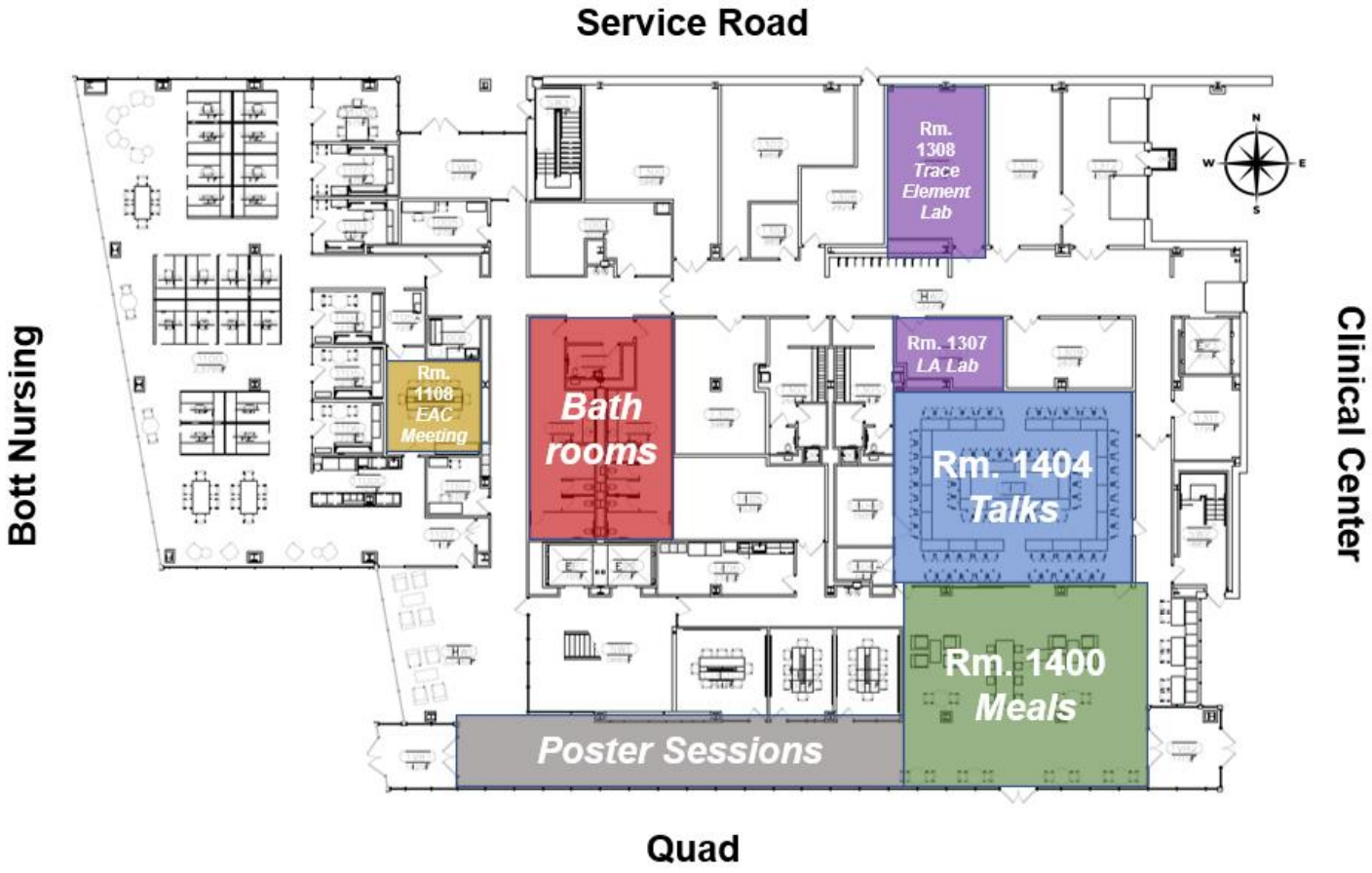
Venue Address: 766 Service Road, East Lansing, MI 48824

Parking

Parking is free in Lot 91 for the summer! It's on the corner of Service Road and South Hagadorn Road and is a short 2-3 block walk from Lot 91 to the ISTB building.



Floor Plan



Internet Access

MSU guests and visitors can connect to MSUNet Guest Wireless without needing an MSU NetID or register their devices.

Guest users without an MSU NetID can join the Wi-Fi network (SSID) MSUnet Guest or MSUnet Guest 3.0 under your device's wireless connection options. You'll also need to agree to abide by the MSU Acceptable Use Policy for Information Technology Resources.

Food

Tuesday September 10, 2024 (Morton's Fine Catering, ISTB Atrium Rm. 1400)

Lunch: 11:30 am-1:00 pm

Meat option: Rosemary chicken thighs w/ roasted garlic, lemon, and rosemary

Vegetarian option: Caprese mostaccioli w/ fresh mozzarella baked in penne pasta with marinara, torn basil leaves

Sides: Roasted red potatoes, seasonal vegetable medley, artisan breadbasket

Dessert: Brownie bites

Coffee: 3:00-3:30 pm

Coffee and Tea with cookies from the MSU Bakery

Dinner: 6:00-8:00 pm

Meat Option: Wild Mushroom Roasted Pork Loin w/ a mushroom demi-glace

Vegetarian option: Ratatouille (vegan, gf) French Provencal stewed vegetables such as eggplant, zucchini, peppers, squash, with white beans in an herbed tomato sauce

Sides: Wild rice pilaf, Garden salad (Champagne Vinaigrette, baby greens and romaine, cucumber, carrot, radish, tomatoes, & dressing), Artisan breadbasket

*Dessert***:** Lemon Bars

Wednesday September 11, 2024 (Morton's Fine Catering, ISTB Atrium Rm. 1400)

Breakfast: 8:30-9:30 am

Meat option: Sausage or Bacon Breakfast Burritos with fluffy scrambled eggs, black beans, and cheese rolled in a flour tortilla

Vegetarian option: Cheese Breakfast Burritos with fluffy scrambled eggs, black beans, and cheese rolled in a flour tortilla

Sides: Salsa, hot sauce, sour cream, fresh fruit display

Coffee: 10:30-11:00 am

Coffee, tea, and snacks

Lunch: 12:00-1:00 pm

Meat Option: Sweet Lemon Chicken Thighs with garlic, cinnamon, thyme, dates, and lemon sauce

Vegetarian option: Artichoke Pasta w/ kalamata olives, capers, sun-dried tomatoes, red onion, peppers, garlic and olive oil

Sides: Roasted potatoes, artisan breadbasket, Michigan Salad (champagne vinaigrette spring mix, dried cherries, candied pecans, & gorgonzola)

*Dessert***:** Cookie Assortment

Coffee: 2:30-3:00 pm

Coffee and Tea with cookies from the MSU Bakery

Dinner: *Meat option:* Meat Lasagna w/ ground beef with ricotta and marinara

Vegetarian option: Roasted Vegetable Lasagna w/ peppers, eggplant, tomatoes, mushrooms and zucchini with mozzarella and ricotta, house marinara

Sides: Artisan breadbasket, Caesar salad (Caesar dressing, romaine, parmesan, & croutons)

Dessert: Brownie Bites

Thursday September 12, 2024 (Morton's Fine Catering, ISTB Atrium Rm. 1400)

Breakfast: 8:00-9:00 am

Meat option: Ham or Sausage breakfast sandwiches on a warm croissant

Vegetarian option: Egg and cheese breakfast sandwiches on a warm croissant

Sides: Fresh fruit display

Coffee: 10:30-11:00 am

Coffee, tea, and snacks

Lunch: 12:00-1:00 pm

Meat Option: Homestyle Meat Loaf topped w/ tomato sauce

Vegetarian Option: Roasted Root Vegetable Paella w/ roasted parsnips, potatoes, carrots, fennel, and asparagus tips with Spanish inspired flavors of saffron, herbs, and tomato in arborio rice

Sides: Whipped potatoes (w/ butter, cream, and roasted garlic), artisan breadbasket, Mediterranean Garden Salad (Italian dressing, mixed greens, tomatoes, cucumbers, garbanzo beans, kalamata olives, bell peppers, feta)

Dessert: Cookie assortment

Coffee: 2:30-3:00 pm

Coffee and Tea with assorted cookies from the MSU Bakery

Agenda

DAY 1 - SEPTEMBER 10, 2024

Start	End	Speaker	Affiliation	Session/Title	Page
8:00 AM	9:00 AM				
9:00 AM	9:30 AM				
9:30 AM	10:00 AM				
10:00 AM	10:30 AM	EAC MEETING: ISTB 1108			
10:30 AM	11:00 AM				
11:00 AM	11:30 AM				
11:30 AM	12:00 PM	Lunch/Registration/Partner Seminar: **ISTB 1st Floor Lobby Rm. 1400**			**15**
12:00 PM	1:00 PM				
Center Overview Session (All talks in ISTB Room 1404)					
1:00 PM	1:30 PM	Thomas O'Halloran	Michigan State University	*QE-Map Center Overview*	**19**
1:30 PM	2:00 PM	Keith MacRenaris	Michigan State University	***TR&D 1:*** *LA-ICP-MS and High Throughput Elemental Histology*	**20**
2:00 PM	2:30 PM	Chris Jacobsen	Northwestern University	***TR&D 2:*** *X-ray fluorescence: The Advanced Photon Source, Beamline 8-BM, and Correcting for Self-Absorption*	**21**
2:30 PM	3:00 PM	Cheng Sun	Northwestern University	***TR&D 3:*** *Photoacoustic Microsopy for In Vivo and Whole Tissue Imaging*	**22**
3:00 PM	3:30 PM	Break/Recap - Cookes from MSU Bakers Location: **ISTB 1st Floor Lobby Rm. 1400**			
Symposium Session 1 (All Talks in ISTB Rm. 1404)					
3:30 PM	4:00 PM	Hossein Ardehali	Northwestern University	*DBP D: Novel Mechanisms of Iron Sensing*	**24**
4:00 PM	4:30 PM	Adelita Mendoza	University of Colorado Boulder	*DBP D: A Lysosomal Expansion Compartment Mediates the Zinc Dyshomeostasis Response in C. Elegans*	**25**
4:30 PM	5:00 PM	Roger Guillory II	Medical College of Wisconsin	*Biocomaptibility of Bioabsorbable Metals*	**26**
5:00 PM	6:00 PM	Poster Session Location: **ISTB 1st Floor Lobby**			
6:00 PM	8:00 PM	Dinner Location: **ISTB 1st Floor Lobby Rm. 1400**			

DAY 2 - SEPTEMBER 11, 2024

Start	End	Speaker	Affiliation	Session/Title	Page
8:30 AM	9:30 AM		Breakfast/Check In Location: **ISTB 1st Floor Lobby Rm. 1400**		
			Symposium Session 2 (All Talks in ISTB Rm. 1404)		
9:30 AM	10:00 AM	Soo Hyun Ahn	Michigan State University	*Elucidating iron regulation and distribution pattern using LA-ICP-TOF-MS and other experimental approaches in autoimmune-mediated epididymitis*	**28**
10:00 AM	10:30 AM	Joanna Melia	Johns Hopkins University	*Beyond iron: Systemic and organ-level metal homeostasis in inflammation and infection*	**29**
10:30 AM	11:00 AM		Coffee Break/Recap Location: **ISTB 1st Floor Lobby Rm. 1400**		
			Student/Post Doctoral Session (All Talks in ISTB Rm. 1404)		
11:00 AM	11:20 AM	Alex Yaw	Michigan State University	*From Late Pregnancy to Parturition: Mapping Magnesium and Zinc in the Pregnant Mouse*	**31**
11:20 AM	11:40 AM	Aidan Reynolds	Michigan State University	*MALDI-TOF Imaging Reveals Spatial Dysregulation of Lipids in Epididymides of Autoimmune Regulator Deficient Male Mice*	**32**
11:40 AM	12:00 PM	Matthew Schnizlein	Michigan State University	*Cardiolipin synthases in Bacteroides fragilis play integral roles in lipid synthesis and intracellular ion homeostasis*	**33**
12:20 PM	1:20 PM		Lunch/Partner Talks Location: **ISTB 1st Floor Rm. 1404**		**15,16**
			Workshop Day 1		
1:20 PM	1:30 PM	Keith MacRenaris	Michigan State University	***Workshop Overview***	
1:30 PM	2:00 PM				
				Workshop Session #1	
2:00 PM	2:30 PM				
2:30 PM	3:00 PM		Coffee Break/Recap Location: **ISTB 1st Floor Lobby Rm. 1400**		
3:00 PM	3:30 PM				
				Workshop Session #2	
3:30 PM	4:00 PM				
4:30 PM	5:30 PM		Poster Session Location: **ISTB 1st Floor Lobby**		
6:00 PM	8:00 PM		Dinner Location: **ISTB 1st Floor Lobby Rm. 1400**		

DAY 3 - SEPTEMBER 12, 2024

Start	End	Speaker	Affiliation	Session/Title	Page
8:00 AM	9:00 AM		Breakfast/Check In Location: **ISTB 1st Floor Lobby Rm. 1400**		
			Workshop Day 2		
9:00 AM	9:30 AM	Shubhrajit Roy (Svetlana Lutsenko)	Johns Hopkins University	*The Distinct Roles of Copper Transporters in Brain Development and Function*	**34**
9:30 AM	10:00 AM				
				Workshop Session #3	
10:00 AM	10:30 AM				
10:30 AM	11:00 AM		Coffee Break/Recap Location: **ISTB 1st Floor Lobby Rm. 1400**		
11:00 AM	11:30 AM				
		Andrew Crawford	Michigan State University	***Data Analysis Workshop #1***	
11:30 AM	12:00 PM				
12:00 PM	1:30 PM		Lunch Location: **ISTB 1st Floor Rm. 1404**		
1:30 PM	2:00 PM				
		Keith MacRenaris	Michigan State University	***Data Analysis Workshop #2***	
2:00 PM	2:30 PM				
2:30 PM	3:00 PM		Break/Recap Location: **ISTB 1st Floor Lobby Rm. 1400**		
3:00 PM	3:30 PM				
		Soo Hyun Ahn	Michigan State University	***Data Analysis Workshop #3***	
3:30 PM	4:00 PM				
4:00 PM	4:30 PM		End of QE-Map P41 Workshop Location: **ISTB 1st Floor Lobby**		

Lunch Seminars and Visits

Day 1 – Tuesday August 22nd, 2022 (ISTB Rm. 1404)

12:20 – 12:50

Elemental Scientific Lasers discussion about bioimaging and LIBS

Derrick Quarles (Derrick.Quarles@icpms.com) Sr. Scientist and Product Manager

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Day 2 – Wednesday August 23rd, 2022 (ISTB Rm. 1404)

12:20 – 12:40

Factors that Affect Performance of Laser Ablation (LA)-ICP-MS

Abe Gutierrez (abe.gutierrez@agilent.com) ICP-MS Product Specialist

Abstract: Most LA-ICP-MS applications generate short lived signals and in some applications like elemental mapping the signal varies throughout the analysis. These types of measurements require an ICP-MS that can operate with fast scan speeds to collect multielement data with good time resolution. While speed is very important, signal strength is also critical when dealing with short acquisition times since shorter integration times give fewer counts for each mass and greater variability in the measurement of the background signal, which means higher detection limits,

During this presentation we will discuss how high signal to noise of ICP-M+QQQ enables accurate measurement of trace level analytes when using short acquisition times to characterize short-lived LA signals. We will be also discussing other life sciences applications that see benefits from the use of MSMS technology.

12:40 – 1:00

CEM discussion about sample preparation and microwave digestion of biological samples

Melissa Dean (Melissa.Dean@cem.com) and Macy Harris (Macy.Harris@cem.com)

1:00 – 1:20 pm

icpTOF for Laser Ablation Mapping and the Analysis of Single Cells

Martin Tanner (m.tanner@tofwerk.com) Product Manager icpTOF

Abstract: With its high-speed mass spectral acquisition and simultaneous analysis of all isotopes, the icpTOF is the ideal ICP-MS detector for multi-element mapping using laser ablation or for the analysis of single cells.

Crucial for successful analysis of any type are good data quality and reproducibility. Good data quality requires robust plasma conditions and a linear detection system. Reproducibility is improved by working with routines and standard operation procedures. The TOFpilot software of icpTOF instruments provides the workflows and autotuning functionalities to get the same results independent from the day of analysis or the user in front of the instrument.

The icpTOF hardware and linear detection system will be introduced and how robust plasma conditions can be controlled and monitored for reliable sample data [1]. TOFpilot autotuning functions for liquid analysis as well as for laser ablation will be shown and how they can be used to optimize instrument performance and to make sure to get a high day to day reproducibility.

[1] Günther, Detlef, and Bodo Hattendorf. "Solid sample analysis using laser ablation inductively coupled plasma mass spectrometry." TrAC Trends in Analytical Chemistry 24.3 (2005): 255-265.

Workshops at-a-glance

Workshop #1 – Gelatin standards and tissue preparation, cryosectioning, slide mounting, and storage.

Location – ISTB 3202 Histology Laboratory

Workshop Leader – Niharika Sinha, PhD

Workshop #2 – Microwave digestion (CEM MARS6) and ICP-OES (Agilent 5800) of various sample types.

Location – ISTB 1308 Trace Element Analysis Laboratory

Workshop Leader(s) – Bongjin Hong, PhD

Workshop #4 – ICP-QQQ-MS (Agilent 8900) of various sample types.

Location – ISTB 1404 Seminar Room

Workshop Leader – Aaron Sue, PhD

Workshop #3 – Slide scanning (Zeiss Axioscan 7) and LA-ICP-TOF-MS (Tofwerk S2 ICP-TOF-MS w/ an ESL Bioimage 266 laser ablation system) of gelatin standards and mouse tissues.

Location – ISTB 1307 Bioelement Mapping Laboratory

Workshop Leader – Keith MacRenaris, PhD and Soo Hyun Ahn, PhD

Data Analysis Workshop – Thursday September 12, 2024

Data Analysis Workshop #1 – LA-ICP-TOF-MS data analysis including new software tools for peak fitting (AutoSpec and InSpec), drift correction, and image overlays.

Location – ISTB 1404 Seminar Room

Workshop Leader(s) – Andrew Crawford, PhD

Data Analysis Workshop #2 – Image analysis and standardization using Iolite software.

Location – ISTB 1404 Seminar Room

Workshop Leaders – Soo Hyun Ahn, PhD and Niharika Sinha, PhD

Talk Abstracts

All presentations and abstracts will be posted on the QE-Map website at https://qemap.ehi.msu.edu/qe-map-workshop-2024 following the workshop.

P41 QE-Map Overview: Advancements in Elemental Imaging and Analysis

Thomas V. O'Halloran[1,2,3] (ohallor8@msu.edu)

[1]Department of Microbiology, Genetics, and Immunology (MGI), and Chemistry, Michigan State University, East Lansing, MI, USA.
[2]Elemental Health Institute, Michigan State University, East Lansing, MI, USA
[3]Quantitative Bio Element Analysis and Mapping (QBEAM) Center, Michigan State University, East Lansing, MI, USA

The National Resource for Quantitative Elemental Mapping for the Life Sciences (QE-Map) is developing novel analytical and imaging technologies that enable biomedical research teams to image changes in metal localization in a quantitative manner across length scales from the cellular level to tissue, and whole animal. QE-Map integrates multiple technologies to create transformative approaches to answer compelling biological questions about the functions of metals and other essential elements in health and disease.

The BTRR is composed of three Technology Research and Development Projects (TRDs), and 4 thematic areas for Driving Biomedical Research Projects (DBPs). The three TRD projects were identified based on complementary potentials to (a) enable accurate analysis of inorganic elements across length scales; (b) achieve sensitivity sufficient to allow single cell analysis; (c) accurately determine metal localization; and (d) measure dynamics of intracellular and extracellular metals in response to fluctuations in response to physiologic signals. We are addressing current limitations of laser ablation inductively coupled plasma mass spectrometry (LA-ICP-MS) and scanning x-ray fluorescence microscopy (SXFM) in a wide variety of tissue samples as well as developing photoacoustic methods (PAM) and probes to enable studies at the tissue level and, eventually, in living mammalian models. We are developing workflows and software that allow co-registration of images and standardization of quantitative data that will maximize the impact of these technologies and accelerate their application to a broad range of biomedical research questions.

TR&D 1: LA-ICP-MS and High Throughput Elemental Histology

Keith MacRenaris[1,2,3] (macrenar@msu.edu)

[1]Department of Microbiology, Genetics, and Immunology (MGI) Michigan State University, East Lansing, MI, USA.
[2]Quantitative Bio Element Analysis and Mapping (QBEAM) Center, Michigan State University, East Lansing, MI, USA
[3]Elemental Health Institute, Michigan State University, East Lansing, MI, USA

Cells must accumulate several metals, such as zinc and iron, to millimolar levels to survive. Fluctuations in the metal content can control processes as varied as the mammalian cell cycle, pathogen infection, and neurological function. The critical regulatory role of metals is emphasized by the observation that one-third of all protein-encoding genes in the human genome encode metal-dependent proteins. To gain a complete picture of the role metals play in systems biology, multiple imaging modalities are being deployed including, laser ablation inductively coupled plasma time-of-flight mass spectrometry (LA-ICP-TOF-MS; *TR&D 1*), synchrotron-based X-ray fluorescence microscopy (XFM; *TR&D 2*), and photo-acoustic imaging (*TR&D 3*). To unleash the full potential of elemental imaging using multi-modal approaches we must be able to image the same sample using different platforms. This will allow us to corroborate findings between the different imaging modalities while offering true pixel-by-pixel overlays which will provide fully quantitative elemental maps in a multitude of tissues and cell types. In this talk I will discuss, in detail, substrate selection and their effects on sample preparation and analysis across all TR&D imaging modalities.

TR&D 2: X-ray fluorescence at Argonne: Before and After the Upgrade of the Advanced Photon Source

Chris Jacobsen[1,2,3] (c-jacobsen@northwestern.edu)

[1]Department of Physics and Astronomy, Northwestern University, Evanston, IL, USA
[2]Advanced Photon Source, Argonne National Laboratory, Lemont, IL, USA
[3]Chemistry of Life Processes Institute, Northwestern University, Evanston, IL, USA

Scanning fluorescence x-ray microscopy is available at several beamlines at the Advanced Photon Source at Argonne. Some experimental setups have used zone plate optics for 50-200 nm spatial resolution (including one that can work with frozen hydrated specimens), while others have used mirror optics to obtain 3-30 micrometer resolution. The endstation 8-BM has been used heavily by our resource for scanning larger tissue samples, with upgrades in detectors and optics tested before the April 17 shutdown for upgrading the APS. A brief summary of recent results will be provided, along with a discussion of capabilities one might expect after the APS Upgrade is completed in 2024.

TR&D 3: Photoacoustic Microscope for In Vivo and Whole Tissue Imaging

Cheng Sun[1] (c-sun@northwestern.edu)

[1]*Department of Mechanical Engineering, Northwestern University, Evanston, IL, USA*

Functional photoacoustic microscopy (PAM) has been studied extensively for its unique capability in noninvasive label-free imaging of biological samples in 3D. PAM Photoacoustic generation employs a ns-pulse laser to illuminate light-absorbing materials. The transient thermo-expansion and the following rapid thermal relaxation by the light-absorbing material upon the absorption of the laser energy led to a temporally confined photoacoustic wave, which is proportional to the tissue absorption. Thanks to reduced acoustic attenuation in tissue, PAM nearly doubles the penetration depth of confocal microscopy using the same wavelength. However, the commonly used sizeable and opaque piezoelectric ultrasonic detectors featuring limited ultrasound detection bandwidth often impose a serious constraint. To this end, optical-based ultrasonic detection techniques may offer a more desirable solution. Because light oscillates more than five orders of magnitude faster than ultrasonic waves, optical-based detection methods can potentially allow more sensitive ultrasonic detection over a much wider frequency band. We have thus developed a coverslip-style optically transparent ultrasound detector based on a polymeric optical micro-ring resonator (MRR). We have demonstrated an optically transparent ultrasound detector with the total thickness of 250 um. It enables highly sensitive ultrasound detection over a wide receiving angle with a bandwidth from DC to 140 MHz, which corresponds to a photoacoustic saturation limit of 287 cm−1, at an estimated noise-equivalent pressure (NEP) of 6.8 Pa. We also established a theoretical framework to provide general design guideline for optical-based ultrasound detectors. The optimal design was further validated experimentally for its key sensing characteristics including sensitivity, bandwidth, angular dependence, and functional imaging capabilities including lateral/axial resolution and saturation limit. We have further demonstrated the functional integration of PAM with the optical microscope and endoscope, by making use of the transparent MRR detectors. In a recent study, we have successfully integrated the MRR to the inner surface of cranial window, which enables the experimental demonstration of long-term in vivo intravital cortical photoacoustic microscopy of live rodents over a 28-day period.

NOTES

DBP D: Novel Mechanisms of Iron Sensing

Hossein Ardehali[1] (h-ardehali@northwestern.edu)

[1]Thomas D. Spies Professor of Cardiac Metabolism, Professor of Medicine (Cardiology) and Pharmacology – Northwestern University, Feinberg School of Medicine, Chicago, IL, USA

In my presentation, I will talk about novel mechanisms of iron sensing. All living cells require a minimal iron threshold to sustain anabolic metabolism. However, the mechanisms by which cells sense iron to regulate anabolic processes are unclear. Here, we report a universal eukaryotic pathway for iron sensing in which molecular iron is required to sustain active histone demethylation and maintain the expression of critical components of the pro-anabolic mTORC1 pathway. Specifically, we identify the iron-binding histone-demethylase KDM3B as an intrinsic iron sensor that regulates mTORC1 activity by demethylating $H3K9me^2$ at enhancers of a high-affinity leucine transporter and *RAPTOR*. By directly suppressing leucine availability and RAPTOR levels, iron deficiency (ID) supersedes other nutrient inputs into mTORC1. This process occurs *in vivo* and is not an indirect effect by canonical iron-utilizing pathways. These data demonstrate a novel mechanism of eukaryotic iron sensing through dynamic chromatin remodeling and repression of mTORC1 mediated anabolism. Due to ancestral eukaryotes sharing homologues of KDMs and mTORC1 core components, this pathway likely predated the emergence of the other kingdom-specific nutrient sensors for mTORC1.

DBP D: A lysosomal expansion compartment mediates the zinc dyshomeostasis response in *C. elegans*

Adelita D. Mendoza*,[1,2] (adelitadmendoza@wustl.edu), Nicholas Dietrich*, Chieh-Hsiang Tan, Daniel Herrera, Jennysue Kasiah, Zachary Payne, Daniel L. Schneider, Kerry Kornfeld[1]

[1]*Department of Developmental Biology – Washington University School of Medicine, St. Louis, MO, USA*
[2]*Incoming Assistant Professor of Biochemistry – University of Colorado Boulder, Boulder, CO, USA*

Zinc is a transition metal that is essential for many cellular processes and serves in a structural role across all enzyme classes and is part of 10% of the predicted proteome. The Kornfeld lab has uncovered high and low zinc metabolic pathways in *C. elegans* that are involved in sensing perturbations in cytosolic zinc levels and responding to try to correct perturbations in zinc metabolism. Zinc dyshomeostasis leads to multiple human pathologies.

Intestinal lysosomes are a site of zinc trafficking. Lysosomes contain ZIPT-2.3 and CDF-2, which mobilize zinc across the membrane in a reciprocally regulated manner. To determine how zinc is mobilized across the membranes, we performed genetic and biochemical assays to show that ZIPT-2.3 mobilizes zinc into the cytoplasm, and that the *zipt-2.3* gene is necessary for this function in zinc deficient conditions. Using super-resolution microscopy, we discovered that lysosomes alter their morphology in response to available cytosolic zinc. Using line scans, we defined specific sub-compartments and membrane boundaries in three zinc conditions. Lysosomes contain two main compartments: the acidified compartment and the expansion compartment. ZIPT-2.3 and CDF-2 populate membranes that surround the acidified compartment, and CDF-2 is localized to the expansion compartment. The acidified compartment is comprised of the LysoTracker region, and the zinc region.

The expansion compartment is highly dynamic and deviates greatly in size. Our model predicts that in zinc deficient conditions, ZIPT-2.3 expression increases and CDF-2 expression decreases, promoting the net flow of zinc into the cytosol. In zinc excess conditions, CDF-2 expression increases, and ZIPT-2.3 expression decreases, facilitating net flow into the gut granule. The expansion compartment expands in zinc excess conditions but shrinks in zinc deficient and zinc replete conditions. Based on these observations, we predict that lysosomes remain the same size, while the expansion compartment grows and shrinks to accommodate zinc. To test this prediction, we performed preliminary time course super resolution microscopy in excess zinc. Preliminary data shows that in excess zinc, lysosomes widely vary in size, and their “nascent” form contains all components as the “mature” form, suggesting that lysosomes are equipped early to manage zinc dyshomeostasis. Bilobe formation is not restricted to zinc. Animals incubated in copper for 16 hrs. also form bilobes in high concentrations

Based on our work with *C. elegans*, we have demonstrated that lysosomes are a critical site of zinc trafficking and metabolism by utilizing zinc transporters and by altering morphology to compensate for perturbations in zinc levels. We reasoned that these mechanisms are conserved, and to test this hypothesis we performed transfections in HEK293 cells in collaboration with the Diwan lab. Preliminary data shows that human ZIP2 localizes to human lysosomes, and ZIP2 localizes changes from a spherical distribution to a crescent distribution. The observation that ZNT2 is localized is the first step in answering the question if zinc is also reciprocally regulated in humans and how dysfunction in zinc trafficking affects human health.

Vascular Biocompatibility of Bioabsorbable Metals

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To minimize post-surgical complications, newly engineered stents must support healthy reendothelialization, prevent or avoid excessive inflammation, and avoid smooth muscle cell hyperplasia response during the lifetime of the stent. The next generation biomaterials to fill this niche are bioabsorbable metals, which include metal alloys comprised of magnesium (Mg), zinc (Zn), iron (Fe), and molybdenum (Mo). Maintaining vascular biocompatibility is critical during the functional bioabsorption process and is contingent on many factors such as implant location, metal alloy chosen, absorption timeframe, and the corrosion products that are generated. This talk will cover the topic of vascular biocompatibility for a range of bioabsorbable materials, and relate factors such as material microstructure, implant location/ manufacturing differences, and eluted products (measured via LA-ICP-TOF-MS) to the performance of vascular implants.

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DBP C: Elucidating iron regulation and distribution pattern using LA-ICP-TOF-MS and other experimental approaches in autoimmune-mediated epididymitis

Soo Hyun Ahn[1] (ahnsooh1@cvm.msu.edu), Keith W. MacRenaris[2,3], Aaron Sue[2,3], Katrina Halgren[4], Margaret G. Petroff[1,2,5], and Thomas V. O'Halloran[2,3]

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Iron is a naturally abundant element found ubiquitously in biological systems. Mainly found as a component of hemoglobin in red blood cells, inadequate recycling and homeostatic regulation of the amount of iron result in undesirable pathologies including hemochromatosis of the liver and idiopathic pulmonary fibrosis. Here, we use a mouse model deficient in autoimmune regulator, which develops epididymal fibrosis, to understand the distribution and cellular localization of iron in the presence and absence of fibrosis using LA-ICP-TOF-MS. Further, we use RNAscope to measure the mRNA transcript expression of ferroportin 1 and divalent metal transporter 1, two transporters of iron, to understand not only the localization of these transporters in the epididymis but also to reveal how the distribution and concentration of these transporters are modified by fibrosis. Together, we introduce a new model of chronic, pathogenic fibrosis, and the results of this research will contribute to our lack of understanding of how iron deposition promote fibrogenesis in tissues such as the liver and the lung.

DBPD B: Beyond iron: Systemic and organ-level metal homeostasis in inflammation and infection

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Nutritional immunity governs host-pathogen interactions taking advantage of the shared need for metals between the host and the invading organism. The quintessential example of nutritional immunity is iron sequestration and hypoferremia in the setting of infection or inflammation. Through innate immune response molecules like calprotectin, sequestration of iron, and other metals including zinc and manganese, are essential to local tissue response. This talk will focus on an emerging appreciation of the dynamics of systemic manganese homeostasis in response to infection and inflammation, as well as the utilization of advanced imaging techniques like LA-ICPMS to visualize changes in tissue levels of key transition metals in response to infection using the model pathogen Candida albicans. Together, these observations begin to uncover shifts in the levels and distribution of metals in tissues that may participate in novel dimensions of nutritional immunity.

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DBP C: From Late Pregnancy to Parturition: Mapping Magnesium and Zinc in the Pregnant Mouse

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From the timed luteinizing hormone surge that triggers ovulation to the circadian (24h) timing of labor onset, circadian processes play an essential role in the establishment and maintenance of a healthy pregnancy. In humans and mice, normal pregnancy is hallmarked by alterations to locomotor activity patterns, including the timing of sleep/wake cycles. What drives these changes remains largely unknown. Essential trace elements (TE), such as manganese (Mn) and zinc (Zn), have been implicated in the regulation of circadian rhythms, sleep quality, and pregnancy outcomes. However, it remains unclear if TE modulate neuronal and muscle function in pregnancy, potentially contributing to the changes in activity patterns and uterine function during this period. One brain area through which TE can influence sleep-wake and activity patterns is the suprachiasmatic nucleus (SCN). The SCN, often called the body's "master clock", guides the timing of circadian processes, including sleep/wake cycles, locomotor activity, and peripheral tissue function via timed hormone release. We recently found that the mouse SCN exhibits changes in neuropeptide expression during late gestation. This, coupled with mid-gestation circadian shifts in activity patterns, suggests that the circadian system exhibits changes at key timepoints throughout pregnancy. To understand if TE are present within the SCN during pregnancy, we used laser ablation time-of-flight mass spectrometry (LA-ICP-TOF-MS). Our preliminary data suggest that Mn, but not Zn, is enriched in the non-pregnant mouse SCN, but is reduced during late gestation. As the timing of parturition is circadian, we used ICP-MS to determine if TE change in maternal serum or the myometrium of the uterus between late gestation and labor. Although no differences in Mn or Zn were detected in maternal serum, Zn, but not Mn, decreased in the myometrium during the transition from late pregnancy to labor, a time-point where the myometrium becomes highly contractile. These results identify tissue-specific changes in TE during pregnancy and highlight the need to further investigate TE within tissues and their potential contributions to circadian rhythms and tissue function during pregnancy.

DBP C: MALDI-TOF Imaging Reveals Spatial Dysregulation of Lipids in Epididymides of Autoimmune Regulator Deficient Male Mice

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Autoimmune regulator (*Aire*) is a transcription factor expressed in the thymus and is essential for establishing central immune tolerance. Humans with *AIRE* mutations suffer from autoimmune polyglandular syndrome type 1 (APS-1), with males commonly experiencing testicular insufficiency and infertility. Infertility in *Aire*-deficient mice has previously been reported to be associated with epididymal inflammation characterized by fibrosis and dysregulation of endogenous metal homeostasis. The epididymis is responsible not only for storage and transport of spermatozoa; it is also responsible for sperm maturation and confers fertilization capacity. This maturation process involves significant molecular remodeling of sperm, with each region of the epididymis contributing to different stages of sperm development. To better understand the infertility associated with *Aire*-deficiency, molecular profiling must be done to assess how the loss of *Aire* impacts the sperm maturation process. Traditional approaches for molecular profiling have relied on epididymis tissue extractions or isolation of sperm from epididymal regions; however, these approaches result in the loss of precise *in situ* localization of molecules. This loss of spatial information requires the usage of alternative techniques which can adequately map molecules natively distributed throughout the epididymis. Herein we performed *in situ* lipidomic investigations into the epididymis of *Aire*-deficient male mice using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry imaging (MALDI-TOF MSI) to discern the correlation between male infertility and alterations in lipid content in the luminal, epithelial and interstitial spaces of the epididymis. Through MALDI-TOF MSI, we show that the luminal environment becomes enriched with phosphatidylcholines, sphingolipids, and seminolipid in wildtype epididymides as sperm traverse the corpus and cauda whereas *Aire*-deficient epididymides show a reduction of several essential lipid species including seminolipid, triglycerides, and free fatty acids. *Aire*-deficient epididymides also experienced depletion of plasma membrane lipid species in epithelia throughout the corpus and cauda. These results emphasize the sensitivity of epididymis to immune system dysregulation caused by *Aire*-deficiency and demonstrates that the loss of *Aire* dysregulates epididymal lipid profiles in the male reproductive tract.

DBP B: Homologous, functionally non-redundant cardiolipin synthases in *Bacteroides fragilis* play integral roles in lipid synthesis and intracellular ion homeostasis

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As an opportunistic pathogen in the human gut, *Bacteroides fragilis* must adapt to bile acids, which modulate bacterial growth in part by membrane disruption. Cardiolipins, a membrane lipid, help reduce membrane permeability. While cardiolipin synthases are well-characterized in *E. coli*, there is little known about these enzymes in the *Bacteroides*, particularly their role in minimizing membrane leakiness. Through a combination of barcoded transposon- and RNA sequencing, we identified genes for two cardiolipin synthases important for *B. fragilis*' stress response to the microbially-modified bile acid deoxycholate. We made clean gene deletions (Δ*clsA*, Δ*clsB*, and Δ*clsA*Δ*clsB*) and characterized their impact on *B. fragilis* growth under deoxycholate, osmotic, ionophore stress and quantified intracellular elements levels through ICP-MS and membrane lipid composition through LC-MS/MS. Using *in vitro* growth curves, *B. fragilis cls* knockout strains each had decreased fitness under deoxycholate and Na^+ stress. The ionophores resulted in decreased fitness of the Δ*clsB* strain, but increased fitness in Δ*clsA*. *cls* knockout strains also had lower intracellular K^+ than WT. ClsA and ClsB are also responsible for synthesizing different sets of cardiolipins with unique levels of acyl chain length and unsaturation. Further work will characterize how the lipid products of each enzyme mediates the observed fitness benefits. We will also explore how these cardiolipin synthases compare functionally to those in *E. coli* through heterologous expression. These findings suggest the importance of these widely conserved enzymes in *Bacteroides* fitness in the gut and will inform future efforts to treat *B. fragilis* infections.

DBP A: The Distinct Roles of Copper Transporters in Brain Development and Function

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Copper (Cu) plays a crucial role in the normal development and functioning of mammalian brain. Cu-misbalance is associated with neurodegenerative disorders: Wilson Disease, Menkes Disease, and Fatal Congenital Copper Transport Defect. In a healthy brain, Cu is enriched around the ventricles and in the locus coeruleus (LC). The LC contains neurons that express Dopamine β hydroxylase (DBH); an enzyme essential for the conversion of dopamine (DA) to Norepinephrine (NA/NE). Two homologous Cu-transporting P-type ATPases, Atp7a and Atp7b, and a high affinity Cu transporter Ctr1 maintain Cu homeostasis in tissues, including LC. Atp7a facilitates Cu entry into the brain and the metalation of Cu-dependent enzymes such as DBH. The role of Atp7b in brain development is unclear. We found that inactivating Atp7b in mice causes significant reduction in Cu levels in the developing brain (at 4 weeks), the loss of cilia and an abnormal arrangement of microtubules in choroid plexus epithelial cells (ChPl). Furthermore, Atp7b inactivation is associated with down-regulation of Atp7a in locus coeruleus (LC) and catecholamine imbalance, despite normal expression of DBH. To better understand the regulation of DBH by Atp7a and Atp7b, we inactivated these two transporters individually in DBH-expressing cells in mice. Atp7aΔDBH mice shows abnormal metabolic changes and a significant loss of DBH positive neurons in LC. We also found significant decrease of Cu in LC region of Atp7bΔDBH mice when compared to the age-matched controls. These findings illustrate distinct functions and of Atp7a and Atp7b in mammalian brain development, highlighting the need for careful management of Cu levels during treatment.

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Posters

All presentations and abstracts will be posted on the QE-Map website at https://qemap.ehi.msu.edu/qe-map-workshop-2023 following the workshop

Poster Title: **Elucidating the Metalloproteome by LC-ICP-MS**

Authors: *Abigail Hagwood, Buyun Liu, Arielle Nabatilan, Jiyao Yu, M. Thomas Morgan, and C.J. Fahrni*

Affiliation: Georgia Institute of Technology

Poster Title: **Interplay of Aging on Polyunsaturated Fatty Acid Oxidative Metabolism and Ferroptosis in Neurodegeneration in *C. elegans***

Authors: *Jennifer Hinman, Morteza Sarparast, Elham Pourmand, Jamie Alan, Kin Sing Stephen Lee*

Affiliation: Michigan State University

Poster Title: **Using a Bending Magnet Beamline for Large-Area Metal Mapping in Biological Materials**

Authors: *Ben Roter, Qiaoling Jin, Andrew Crawford, and Chris Jacobsen*

Affiliation: Northwestern University, Argonne National Laboratory

Quantitative Bio Element Analysis and Mapping (QBEAM) Center

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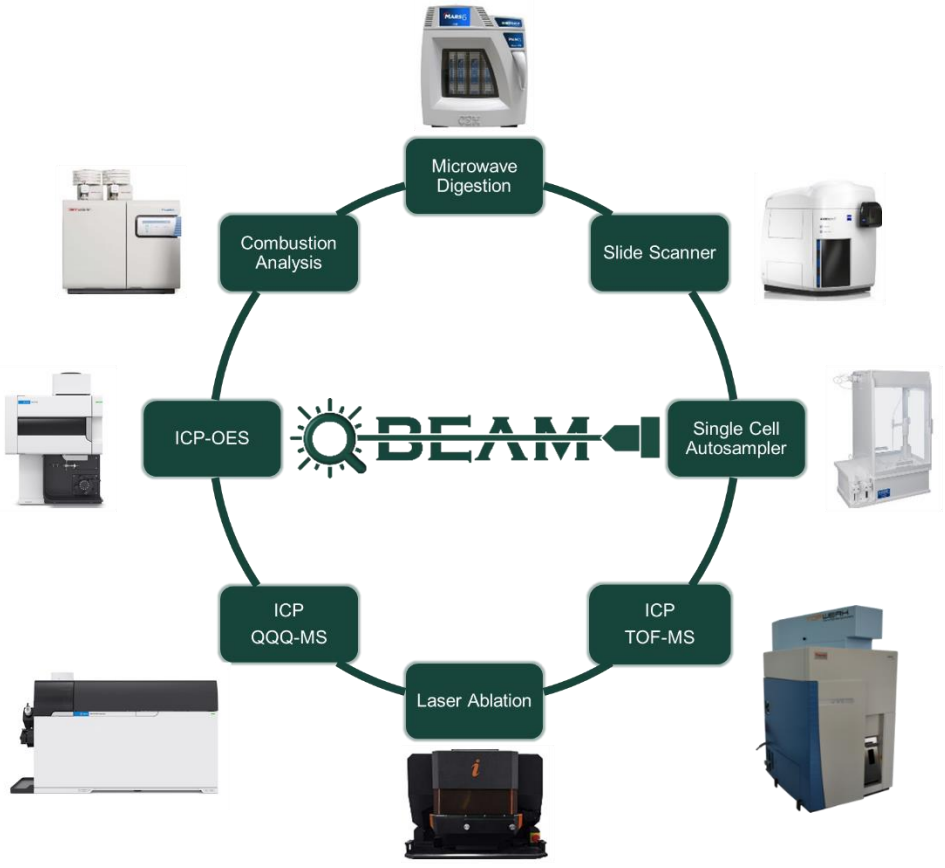
The Quantitative Bio Element Analysis and Mapping (QBEAM) center was founded by Professor Thomas V. O'Halloran at MSU in January of 2021 as an interdisciplinary center within the elemental Health Institute (EHI) focused on elemental mapping and analysis. QBEAM's mission is examining elemental quotas in biology from single cells to whole organisms and how the interplay between metals and systems biology can be harnessed to develop therapeutics, elucidate the mechanisms of disease, and further our understanding of the ecological and environmental consequences of metal exposure.

The center has developed a suite of high-resolution instruments capable of quantitatively imaging biologically essential elements in individual cells. QBEAM's instrumentation has enabled teams of physical, life, and material scientists to begin analyzing metal quotas at scales ranging from the subcellular level to entire ecosystems shaping global biogeochemical cycles. This work is expected to yield a fundamental understanding of the co-evolution of microbial and eukaryotic life within a broad range of challenging chemical environments.

Complementing QBIC's research mission is its role as a shared resource facility serving investigators within the Northwestern scientific community and beyond. In this capacity, the Center provides researchers with access to state-of-the-art imaging and quantification instrumentation while supporting its use with an expert technical staff that offers a range of services, including instrument training, sample preparation and analysis, experiment design, and grant proposal assistance.



Mapping of Elemental Content in Semisoft Biological Samples

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Cells have several strategies for mobilizing elements in response to intrinsic and extrinsic stimuli, which may alter the elemental distribution within a cell, tissues, organs, and even whole organisms. Identifying these fluxes in elements can indicate possible impacts on biological processes, or how disturbances in biological processes can affect how an organism meets elemental quota. Significant advances in technology and methodology have given an unprecedented view of elements in both spatial resolution and sensitivity for a variety of human and mice tissues. As biological studies using elemental mapping techniques become more prevalent in understanding the interface between metals and biology, new challenges will arise as a result of employing other model systems besides mammals. Although nonhuman mammalian model systems are generally considered the most representative of human biology, understanding the metal content of evolutionarily distant organisms is useful for uncovering elemental biology that is applicable beyond the scope of just that species. Samples that have cell walls or chitinous or collagenous exoskeletons may alter not only sample preparation, but also microscopic or spectroscopic behaviors. This necessitates developing methodologies for mapping elements in biological samples that may have variable physical properties.

We utilized two model organisms, *Caenorhabditis elegans* and *Arabidopsis thaliana*, to investigate preparation and mapping techniques that will allow for optimal structure preservation and highest resolution mapping. Both systems are fast growing, isogenic, genetically tractable, have a low cost of maintenance, and have shared biology with distantly related species. *C. elegans* are small enough to be mapped in their entirety, providing a view of the elemental content of an intact system, while we investigated *A. thaliana* pistils due to the large size of the whole *Arabidopsis* flower. Both samples were mapped using a laser ablation inductively coupled plasma time-of-flight mass spectrometer (LA-ICP-TOF-MS). We found that flash freezing nematodes in a uniform layer of optimal cutting temperature (OCT) compound was sufficient to preserve nematode structure and allowed for complete ablation. *Arabidopsis* provided a greater challenge due to the impermeability of the cell wall to OCT as well as pistil thickness. Despite suboptimal sectioning conditions, we were still able to visualize accumulation of specific elements in specific structures of the pistil. Although sample preparation optimization is not complete, we uncovered interesting elemental signatures in these model systems, particularly the manganese distribution in both nematodes and thale cress pistils. Given the sparse data on manganese biology in nematodes and manganese reproductive biology in thale cress, these data demonstrate the value of examining elemental distributions, and how samples can require specific preparation techniques.

Machine Learning to Guide Selection of Single E. coli Cells in X-ray Fluorescence Microscopy

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The microscopy research at the Bionanoprobe (beamline 9-ID of Advanced Photon Source) of Argonne National Laboratory focuses on applying synchrotron X-ray fluorescence (XRF) techniques to obtain trace elemental mappings of cryogenic biological samples to gain insights about their role in critical biological activities. The elemental mappings and the morphological aspects of the biological samples, in this instance, the bacterium Escherichia coli (E. coli), also serve as label-free biological fingerprints to identify live and dead cells. The key limitations of achieving good identification performance are the extraction of cells from raw XRF measurement via binary conversion, definition of features, noise floor and proportion of differently treated cells in the measurement. Automating the cell extraction from raw XRF measurements across different types of chemical treatment and the implementation of machine learning models to distinguish cells from the background and their differing treatments will be described. Principal components are calculated from domain knowledge specific features and clustered to distinguish healthy and poisoned E. coli cells from the background without manual annotation.

Effect of Iron Deficient Diet on Metal Homeostasis of Mouse Tissues, and Inorganic Signatures of Heart Failure Mouse Models

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Iron is a critical element for cellular function, but because disorders of iron homeostasis are common and often result in serious diseases, an iron level in a body is tightly regulated. Iron deficiency (ID) is the most prevalent nutritional disorder in the world, affecting over a quarter of the world's population. Usually, ID is diagnosed by examining blood iron and protein contents. To understand how the ID disturbs metal homeostasis in a body which leads to relevant diseases, however, its effect should be scrutinized at a tissue and cell level. Previous animal studies reported that ID could change the homeostasis of various metals in tissues and its effect vary depending on tissue types, but these results are often conflicting each other, probably due to limitation in detection accuracy and sensitivity of their measurement methods. In addition to the animal studies, recent clinical studies also showed a big controversy in iron therapy in in patients with cardiac diseases. While intravenous (IV) iron therapy provides symptomatic benefit to patients with heart failure, chelation therapy also improves outcome in patients with cardiovascular disease. Thus, given the significant controversy in the field and widespread use of IV iron in patients with heart failure, it is critical to perform a comprehensive analysis of the cardiovascular system in ID conditions. With the aid of an inductively coupled plasma mass spectrometry (ICP-MS), X-ray fluorescence microscopy (XFM), and laser ablation-inductively coupled plasma-time-of-flight mass spectrometry (LA-ICP-TOF-MS), I have been studying the effect of ID diet on metal homeostasis of various mouse tissues and determining the levels of iron and other essential metals in normal heart and in heart failure at baseline and with systemic ID. In this presentation, the relevant research results will be demonstrated.