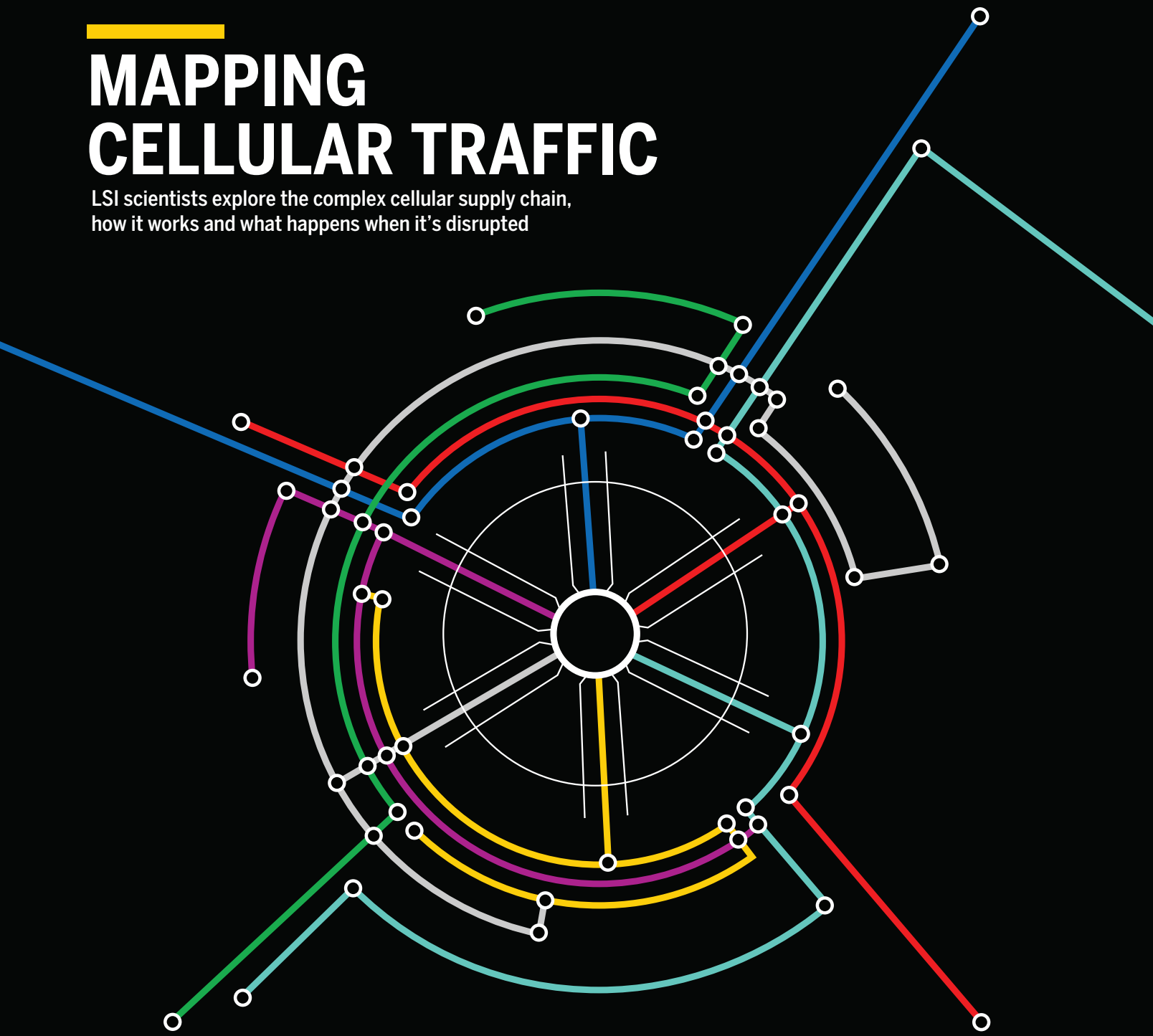
LIFE SCIENCES INSTITUTE
UNIVERSITY OF MICHIGAN
SPRING 2022

MAPPING CELLULAR TRAFFIC

LSI scientists explore the complex cellular supply chain, how it works and what happens when it's disrupted



BREATHING SCIENCE INTO ART

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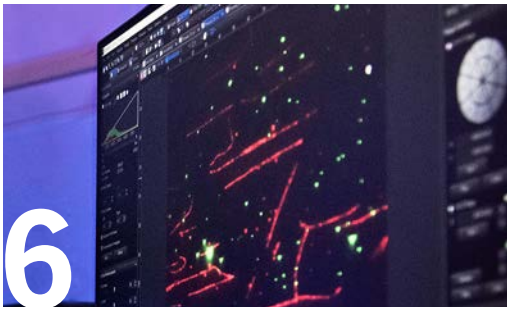

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ON THE COVER: Abstract depiction of the cell's transport pathways. Design by LSI Multimedia Specialist Rajani Arora.

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From the **Director**

As I enter my second five-year term directing the Life Sciences Institute at the University of Michigan, I have been thinking a lot about roadmaps: charting where we are as an institute now, which routes we should pursue next and how we can forge new paths as a national leader in collaborative discovery science. In particular, how can our unique strengths in structural and chemical biology, novel educational programing and cutting-edge discovery tools transport the institute to new frontiers of scientific innovation?

Throughout the pages of this magazine, you will see these themes and questions play out not just at a programmatic level, but in the microscopic context of cells, and even through the visual design, based on representations of prototypical subway maps.

The feature article, "Mapping Cellular Traffic," describes our researchers' efforts to chart the molecular highways and transport systems that deliver cellular cargo to the right place at the right time — and to understand how disruptions to this supply chain affect human health. Many of these efforts capitalize on our state-of-the-art cryo-electron microscopy tools, revealing atomic-level structures that will have profound impacts on our understanding of how these transporters and their cargo function. And in the "Perspectives" interview, faculty member Carole Parent describes how her lab investigates transport at the whole-cell level, mapping out how neutrophils travel to sites of inflammation and to tumors.

To continue expanding our impact at the university, nationally and internationally, we will follow what has been one of our cardinal directions since the LSI's inception: cross-disciplinary collaboration. In "Breathing Science into Art," you will see this pillar of the LSI ethos in practice here on campus, broadening collaborations beyond scientific fields and into the arts.

Our map to success cannot be complete without providing clear routes that connect today's students to their futures in science. Over the next five years,

Leisa Thompson Photography

we will strive to expand the training programs we have developed, with support from generous donors, for researchers from the high school level through postdoctoral training. In the article "STEM Connector," you will learn about one such program, which has enabled over 100 undergraduates from across the state to spend a summer at the LSI exploring hands-on discovery research with our faculty.

While the future roadmap of our journey will certainly involve curves and speedbumps, I am thrilled to be helping steer the path forward over the next five years. I invite you to follow our progress by signing up for our quarterly e-newsletters and by continuing to learn about our progress on Twitter, @UMLifeSciences.

Sincerely,

Roger D. Cone

Roger D. Cone, Ph.D.
Mary Sue Coleman Director, Life Sciences Institute

Advances

LSI opens new windows into the cell

The structural biology program at the University of Michigan Life Sciences Institute is transforming how biologists can see and learn from the molecular machines at work within cells, with new support from the Arnold and Mabel Beckman Foundation.

The $1.5 million award supports the expansion of a cutting-edge technique called cryo-electron tomography (cryo-ET) at U-M. Rather than revealing cellular components that have been purified and isolated out of cells, as other structural biology approaches do, cryo-ET shows complex molecular machines within the cellular environment.

The technique requires not only expertise in a quickly evolving field but also access to highly advanced microscopes and other technologies to capture the 3D structures. The Sample Preparation for Cellular Cryo-ET Award offers funding for both.

"This award will allow us to support our early-career faculty with the most state-of-the-art technology, which is essential for their career development," says LSI faculty member Melanie Ohi, Ph.D., the program's principal investigator. "But a big part of this work will also be broadening access across the university, to build a vibrant community of researchers in various fields who can use this technique to answer important biological questions."

"One hundred years ago, the devastating Spanish flu pandemic and a world at war gave birth to the physician-scientist. Today, COVID-19 and the war against science call for a reforging of our profession. We must ask ourselves: How strong is our commitment to supporting the successor generation and to ensuring a critical supply chain of physician-scientists that is agile and sustainable?"

—**Vivian Cheung, M.D.,** and co-authors argue for actions to support new generations of physician-scientists. "Translating science to medicine: The case for physician-scientists," *Science Translational Medicine* (Feb/2022)

Rajani Arora, LSI

Mapp lab
Journal of the American Chemical Society
Jun/2021

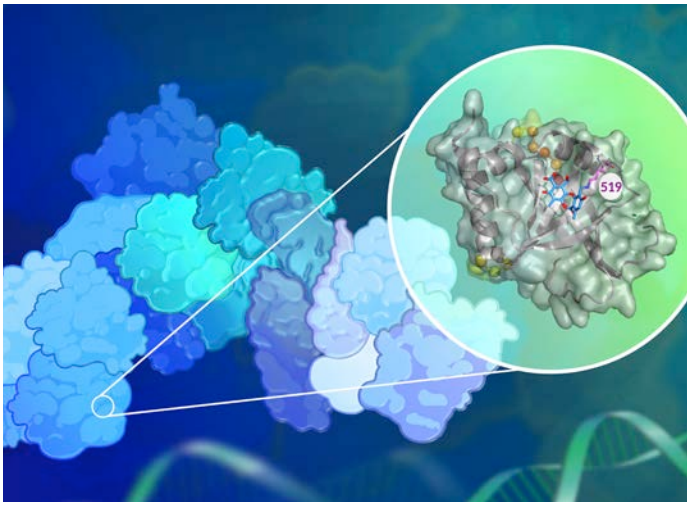
Targeting 'undgruggable' proteins, with help from nature

A team of researchers led by Anna Mapp, Ph.D., has developed a new approach to block the activity of Med25, a so-called undruggable protein, in human-derived breast cancer cells.

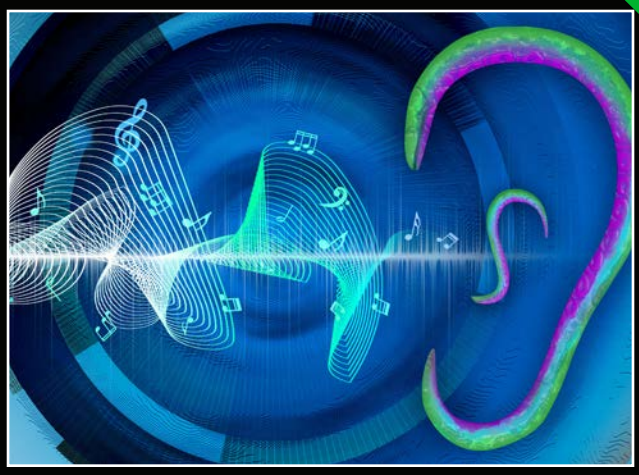
Med25 is a type of protein called a transcriptional coactivator. Errors in transcriptional coactivators' activity give rise to a host of human disorders, from cancer to diabetes, making them a desirable target for new therapeutics.

This protein's dynamic, unstable structure allows it to bind to DNA and other proteins to adjust which genes are active in a cell at any given time. But without a stable structure to work with, scientists have struggled to develop chemicals that can block the protein's activity.

Researchers in Mapp's lab discovered that a chemical compound produced naturally by lichens can block the activity of Med25 by binding to a secondary site on the protein — a strategy that may be useful in targeting other challenging proteins, Mapp says.



Illustrations: Rajani Arora, LSI



These worms take the 'ear' out of 'hear'

Xu lab
Neuron
Sep/2021

LSI researchers discovered that a species of roundworm that is widely used in biological research can sense and respond to sound, despite having no ear-like organs.

The team's findings, which appeared in the journal *Neuron*, are the final piece to a sensory puzzle, revealing the full picture of how *Caenorhabditis elegans* use all five major senses to respond to their environment.

The roundworms sense airborne sound waves through their skin. But rather than feeling the vibrations through the sense of touch, they sense these tones by acting as a sort of whole-body cochlea, the spiraled, fluid-filled cavity in the inner ear of vertebrates.

The research raises the possibility that other earless animals with a soft body like the *C. elegans* might also be able to sense sound.

The team now hopes to uncover new insights into the genetic mechanisms and neurobiology that drive these sensations across species.

"This opens a whole new field for studying auditory sensation, and mechanosensation as a whole," says study senior author Shawn Xu, Ph.D.

Cone lab
Nature
Nov/2021

Brain monitors energy status to influence maturation

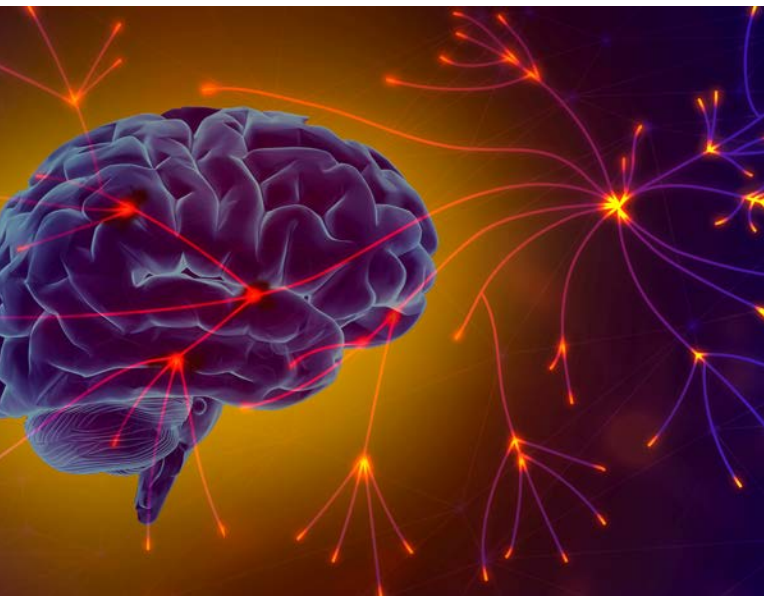
Scientists have shown for the first time how the melanocortin 3 receptor (MC3R) in the brain uses information about the body's energy balance to regulate growth rate and the onset of puberty in children.

Roger Cone, Ph.D., and colleagues discovered the MC3R gene in mice more than 20 years ago and demonstrated that animals lacking this protein exhibit reduced linear growth, reduced lean mass and increased obesity.

These latest findings, which appeared in *Nature*, show strikingly similar characteristics in humans, as well as one new effect: a delay in the onset of puberty.

For this latest study, the Cone lab and collaborators at the Vanderbilt School of Medicine were able to verify this finding in mouse models. They now propose that MC3R plays a role in communicating nutritional deprivation to the reproductive axis.

"It took 20 years for researchers to find the first patient with MC3R deficiency, because these loss-of-function alleles are exceedingly rare," Cone explains. "Importantly, we now know the mouse model recapitulates human physiology."

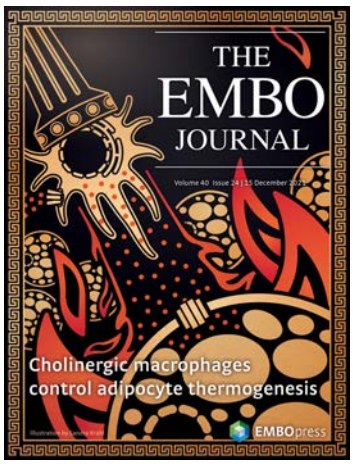


Wu lab
The EMBO Journal
Nov/2021

Immune cells turn up the heat on fat

Immune cells can produce a chemical typically found in the brain to promote fat-burning in mice, according to a new study led by LSI scientists.

The research, featured on the cover of the *EMBO Journal*, offers hints about how this immune cell–fat cell interaction might be harnessed to improve human health.



Thermogenic fat, or beige fat, can convert chemical energy into heat rather than storing it as fat. Since its discovery, scientists have sought ways to activate this fat tissue in humans to treat metabolic disorders such as diabetes.

Scientists from the lab of Jun Wu, Ph.D., have identified a signaling pathway in mice that activates thermogenic fat through an organic chemical called acetylcholine. This chemical is most often found in the nervous system, where it sends signals between neurons. Wu and colleagues have now demonstrated that some immune cells also secrete acetylcholine to regulate heat-burning fat tissue.

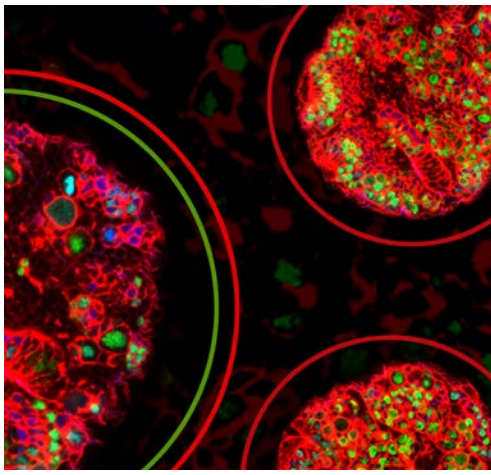
"There are already several drugs approved for humans that target acetylcholine signaling between neurons to treat neurodegenerative diseases," Wu says. "One could envision that a similar approach could eventually be applied to the signaling between immune cells and fat cells."

Illustration: Rajani Arora, LSI

Lee lab
Nature Communications
Dec/2021

Reverse specialization

A collaboration between scientists at the LSI and the University of Wisconsin-Madison shed light on the mechanisms that allow adult stem cells to pause, and even reverse, their development into other cell types.



Studying neuronal stem cells in the common model organism *Drosophila melanogaster* (fruit flies), the scientists identified a protein that can access stem-related genes that have been closed off in the genome, and open the genes back up for activation. An excess of this protein can impede brain development and result in too many neuronal stem cells, resembling a tumor.

This research from the lab of Cheng-Yu Lee, Ph.D., and colleagues offers new understandings of how errors in cellular reprogramming can lead to cancer, and the findings could lead to new strategies for regenerating cells or tissue to restore function.

Cone lab
Nature Metabolism
Jan/2022

Dialing up leptin sensitivity

LSI researchers have found a way to improve leptin sensitivity and reduce obesity in mice by blocking the activity of one enzyme inside fat cells.

The hormone leptin helps regulate the balance between food intake and energy expenditure. But efforts to use leptin as a treatment for obesity have been unsuccessful. That's because as obesity increases, the brain stops sensing and responding to the hormone. This is known as "leptin resistance."

For this study, researchers gave mice a compound to block an enzyme called histone deacetylase 6 (HDAC6). Within a few weeks, body weight decreased by almost 25% for obese mice, and overall metabolic health improved. Lean mice treated with the same compound did not lose body mass, nor did obese mice that were genetically unable to produce leptin. In both cases, however, HDAC6 inhibition increased sensitivity to leptin administration.

"Obviously the most important questions are: Is HDAC6 inhibition going to have the same effect in humans, and is it going to be safe?" says Işin Çakir, Ph.D., the study's lead author. "And a lot more research is needed before we will have the answers."

Power and potential in nature's proteins

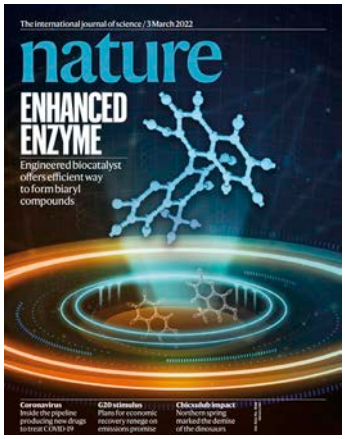
LSI researchers developed an efficient, greener method for building a molecule that sits at the core of many indispensable medicines and materials.

Narayan lab
Nature
Mar/2022

Rather than using the traditional process involving harmful chemicals, this method relies on biocatalysts — proteins found in nature that accelerate chemical reactions inside cells. Such proteins typically have evolved to conduct only one type of reaction, and conduct it very well.

"The challenge is to coax them into performing the reactions that we want to do, not just the ones they've evolved to do," says Alison Narayan, Ph.D., the study's senior author.

Researchers from Narayan's lab have now done just that with a protein produced in yeast. Through protein engineering methods, they created a version of the enzyme that could produce their desired molecule at rates higher than traditional chemistry methods.



The findings, featured on the cover of *Nature*, demonstrate the potential power of engineered enzymes for cleaner chemistry in pharmaceutical and industrial manufacturing.

Illustration and cover: Rajani Arora, LSI

Mapping Cellular Traffic

LSI scientists explore the complex cellular supply chain, how it works and what happens when it's disrupted

By Emily Kagey

Not long ago, the global supply chain wasn't a common topic at most dinner tables. But in early 2020, toilet paper disappeared from store shelves. Then it was baker's yeast.

And before long, a ship lodged in an Egyptian canal was causing a garden gnome shortage in the United Kingdom, while leaving Lebanese olive oil that was destined for Los Angeles stranded in Malaysia.

It was easier to take the supply chain for granted before converging challenges forced us to consider the complex, delicately balanced system that delivers goods and materials to the right place at the right time.

The same is true at the microscopic level of cells.

"I think in general, people take cellular cargo trafficking for granted," says Michael Cianfrocco, a biochemist and faculty member at the University of Michigan Life Sciences Institute. "It's kind of like, 'These things move — so what?' But we don't actually have a lot of principles to explain what triggers this movement."

Cianfrocco's lab is one of several research groups at the LSI that are investigating the cellular supply chain, mapping how cargo gets transported within our cells and how snarls in that system lead to disease.

Somaye Badieyan, Ph.D. (left) and Michael Cianfrocco, Ph.D. (right), use single-molecule fluorescence microscopy to look at viruses trafficking on microtubules.

Similar to the organs that keep our bodies running, our cells contain specialized subunits called organelles that perform the fundamental functions that drive life. Mitochondria, for example, turn glucose into chemical energy to fuel these activities. The lysosome breaks down cellular components that are no longer needed and recycles the building blocks to generate new materials.

But how do mitochondria move to the sites that need fuel? How do unneeded cellular components get to the lysosome? And when a cell divides, how do the organelles themselves distribute correctly to the new cells? Through the intricate, tightly controlled system — superhighways, side streets, specialized transporters — that is the cellular supply chain.

Within this transport system, the Cianfrocco lab is particularly focused on the delivery trucks: motor proteins called kinesin, dynein and myosin. Cruising along the cell's transportation routes, they carry essential cargo toward the center of the cell (in the case of dynein) or export cargo to destinations around the cell (kinesin and myosin).

"If you think about a neuron that extends the full length of your leg, motor proteins carry sensory information from the outer perimeter back to the central nervous system," explains Cianfrocco, who is also an assistant professor of biological chemistry at the U-M Medical School.

Without the delivery trucks, proteins and other molecules would have to rely on diffusion to move from one end of the cell to another. And while diffusion is technically possible (after all, the cytoplasm that surrounds everything within the cell is fluid), the process would take long enough to bring the cellular functions to a halt.

Cianfrocco compares it to a tennis ball in JELL-O. The tennis ball is not likely to move on its own, but something could drag the ball fairly easily. For cellular transport, that something is motor proteins.

"We can see this in the way the rabies virus hijacks this system to infect a host," he explains. "The virus hitches a ride on motor proteins to get to the spine or brain, before any symptoms set in. So the time between infection and the onset of symptoms depends on how far the infection site is from the spine or the brain, or how far the virus has to travel. If the virus was left to diffuse on its own, it would take thousands of years to see any symptoms."

Recently, Cianfrocco and his colleagues have turned their attention to deciphering how these delivery trucks

Leisa Thompson Photography

stop — because, as he notes, "you can't load the truck if it never stops moving."

Employing cryo-electron microscopy (cryo-EM), a process that uses electron beams to reveal the 3D structures of molecules flash-frozen in vitreous ice, his lab recently discovered how one protein acts as a parking boot on kinesins. The aptly named kinesin-binding protein latches on to one of the kinesin's two feet. Once the protein attaches, the kinesin can no longer contact or move along its path.

"Because they are involved in virtually every cellular operation, kinesins must be carefully controlled," Cianfrocco says. This kinesin-binding protein, for example, is just one of the methods cells use to inhibit kinesin movement. Yet when this protein is mutated, it alone can cause a rare but serious autosomal disorder called Goldberg-Shprintzen syndrome.

Figuring out how these molecular delivery trucks pause for loading is just the beginning of what Cianfrocco hopes to map out when it comes to intracellular transport. He's also working out how that truck secures its cargo and starts moving again.

"In my lab we spend a lot of time watching these proteins walk and trying to figure out: How does that happen? How does the cargo tell the motor protein to move it?" Cianfrocco says.

To answer that, he has turned to myosin and a bit of baker's yeast.

Ever since she made a fortuitous discovery as a postdoctoral researcher, Lois Weisman has been fascinated by cellular transportation. Studying yeast, she noticed that when a new cell was budding on the mother cell, the lysosome started to dance around before projecting a small portion of itself into the budding daughter cell.

"This was before people had a good way of looking at cells with live imaging. It was just serendipitous that I was able to find this," recalls Weisman, a faculty member at the LSI and professor of cell and developmental biology at the Medical School. "And it raised all of these questions about how this occurs: How do you get that kind of movement in a cell?"

In her own lab, Weisman continues to explore the twisted paths that those questions have opened — including the path traversed by the myosin type V motor protein.

In mammals, type V myosins deliver cargo involved in processes ranging from skin pigmentation to brain and gut function. Minor mutations in one of these proteins cause Griscelli syndrome, which results in neurological defects and unusually light hair and skin color.

Weisman's lab investigates myosin V's counterpart in yeast to disentangle the processes that allow this motor protein to load and deliver its vital cargo.

The lab has published several papers explaining how myosin releases its cargo at the right destination. Now, through a collaboration with the Cianfrocco lab, the researchers are studying the other end of that journey: how the cargo gets loaded onto myosin in the first place.

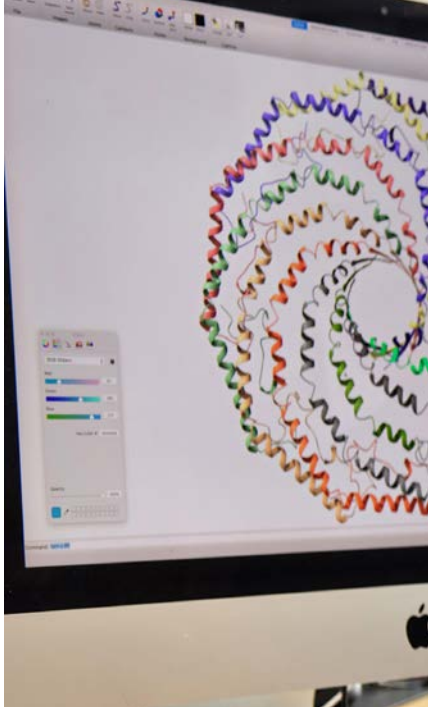
Splitting her time between the Weisman and Cianfrocco labs, graduate student Lily Hahn is using live-cell imaging and cryo-EM to understand how an adapter protein hitches cargo onto myosin for delivery.

"These are very foundational cellular events that we might take for granted," Hahn says. "But when cells divide, whether they are cancer cells or budding yeast, they have to make sure the right amount of each organelle gets transported to the new cells. And to understand how that happens, or how it goes wrong in disease, we need to understand the fundamental mechanisms."

While teasing apart the genetic drivers of these mechanisms, Weisman and her colleagues stumbled upon another serendipitous discovery: a pathway that they are learning affects not only how cargo moves within cells, but also how cells themselves move.

"When I see something new, I just think, 'I wonder how it works,' and I want to study it," Weisman says.

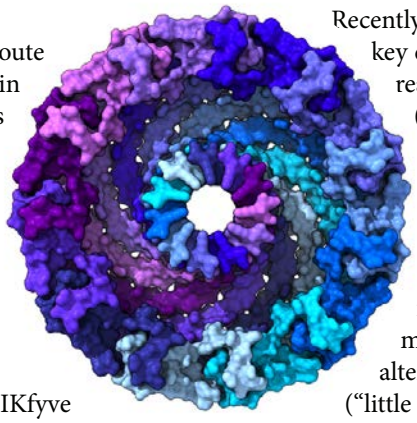
In this case, "it" is an enzyme that makes a critical, but very low-abundance, signal inside cells — so low that Weisman's lab is still one of the only research groups in the world that can measure it at all. The enzyme and its signal have recently attracted greater attention as a potential drug target to treat neurodegenerative diseases, cancers and even COVID-19.



From left: Huseyin Karaburk; Lois Weisman, Ph.D.; and Lily Hahn

The enzyme, called PIKfyve, helps keep the cellular recycling system in balance at the lysosome. But researchers in Weisman's lab recently discovered that PIKfyve also plays an unexpected role in the pathway that transports sensors to the cell surface. In particular, it recycles sensors called integrins, which help control cell migration.

This latest study also opened a new route to understanding PIKfyve's role in neurodegeneration. Minor mutations in this sensor recycling pathway have been tied to various neurological diseases. Weisman's lab is now investigating whether the enzyme's role close to the cell surface could be necessary for proper communication between nerve cells.



"We know that completely blocking PIKfyve in animal models is lethal," Weisman says. "But if we can tease apart its various roles, we could perhaps begin to design therapeutics that target specific pathways that PIKfyve regulates."

While Weisman and Cianfrocco are deciphering how proteins move within cells, and even how some of these movements allow the entire cell to migrate, their colleague Melanie Ohi is focused on what happens when these proteins run into their confining barrier: the plasma membrane.

"How do cells deal with the barrier of a membrane? Because it is an actual barrier, and the cell needs to have ways to alter or overcome it," says Ohi, a faculty member at the LSI and a professor of cell and developmental biology at the Medical School. "They need to form channels that allow things to pass into and out of the cell, but they also need to be able to rearrange the architecture of that membrane."

Recently, her lab revealed the 3D structure of a key engineer involved in that architectural rearrangement: the caveolin-1 protein (or Cav1 for short).

The cell membrane is not a rigid wall just holding in the contents of the cell. This dynamic surface constantly remodels to support normal cell functions, growth and even cellular migration. One of the major ways cells alter this membrane is through caveolae ("little caves") that fold the membrane in on itself. These tiny indentations offer one entryway into the cell, but they can also be released when the cell surface is under tension, allowing the membrane to expand without snapping apart.

The Cav1 protein attaches to the inside of the cell membrane, laying the foundation for the caves. The protein was discovered more than 30 years ago, and research has shown that mutations in this critical cave-builder lead to cardiovascular and muscular disorders in humans. But without a clear picture of what the protein looks like, scientists have not been able to precisely map how it works, or where its disease-causing vulnerabilities lie.

Leisa Thompson Photography; Cav1 structure: Jason Porta, LSI

Melanie Ohi, Ph.D., discusses the Cav1 structure with Jason Porta, Ph.D., a postdoctoral fellow in her lab and lead author of a study in *Science Advances* that revealed the 3D structure.

"People are really interested in this protein because it's one of the major ways that cells are regulating signaling at the plasma membrane, and there are many mutations that create disease," says Ohi, whose lab has been studying Cav1 since 2015. "But it's just a really challenging protein to work with."

Earlier this year, Ohi and her colleagues had a major breakthrough, with the help of some *Escherichia coli*. Caveolin proteins are naturally found only in multi-celled animals (including humans). But the Ohi lab used genetically modified *E. coli* bacteria as Cav1 factories.

With a healthy supply of purified proteins from *E. coli*, the researchers turned to cryo-EM to uncover the 3D structure of the full protein. The recently published structure differs markedly from some of the prevailing models and theories about Cav1's shape, and thus its mode of function and malfunction, Ohi says.

"It is kind of a classic example of why we do structure analysis," she explains. "Now that we have a full structure, we can begin to make informed mutations to study the functions in disease. It just opens a whole new avenue for understanding how this protein works."

The Ohi lab employs bacteria as more than just protein manufacturers. The lab also studies how these organisms build their own machines to transport infectious agents across the cell membrane into their hosts.

One of these bacterial species, *Helicobacter pylori*, is a leading cause of stomach ulcers and the strongest known risk factor for stomach cancer. It spreads infection by forming protein machines that inject a harmful protein directly into the host's gastric cells.

"And once it gets inside, this protein messes up all the transportation systems in the cell," Ohi says.

Her lab is investigating the structures of these machines across several bacterial species, in hopes of identifying weaknesses that could be exploited to halt the delivery of infectious material.

"Whether you're looking across cells or within the cell itself, so much depends on these complicated, overlapping transport systems," Ohi says. "The more we can understand about the fundamental biology that drives cellular transport, the better we can predict and capitalize on its roles in health and disease."

"The more we can understand about the fundamental biology that drives cellular transport, the better we can predict and capitalize on its roles in health and disease.

Breathing

Science Into Art

Can the science of breath improve artistic performance?

By Emily Kagey

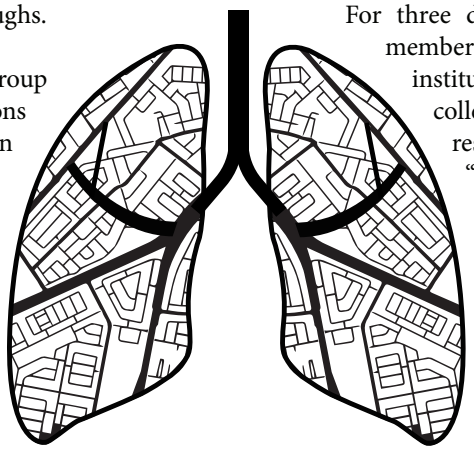
A neuroscientist, a physician, a harpsichordist, an engineer and an artist walk into a ballroom.

But instead of a punchline, what emerges from this grouping is a proposal to improve human performance using the one thing that connects their divergent research interests: **breath**.

Leisa Thompson Photography

From left: Peng Li, Ph.D.; Sophia Brueckner, M.F.A.; and Joseph Gascho, D.M.A.

Peng Li explores breathing at the cellular level. In his lab at the University of Michigan Life Sciences Institute, the neuroscientist teases apart the circuits in the brain that induce different forms of breath, such as emotional sighs, automatic sighs and even coughs.



More specifically, Li's research group monitors how individual neurons fire within a mouse's brain when the animal is placed in various scenarios (e.g., stress-inducing, cough-inducing), and then maps out how distinct neuronal paths merge, converge and intersect to alter normal breathing patterns.

So what does that have to do with playing the harpsichord?

"Compared to some other musicians, like singers or wind instrument players, breath is not directly connected to our sound," says Joe Gascho, a professional harpsichordist and associate professor of music at U-M. "But we know that good breathing is one of the most helpful ways to improve our playing."

Gascho and Li are two members of a five-person interdisciplinary team that hopes to determine how breathing patterns can influence human performance in activities that may not seem directly related to breath, through the 2Inspire project.

Culturing creativity

2Inspire is one of five projects that emerged from the first Biosciences Initiative Ideas Lab at the University of Michigan.

Based on the National Science Foundation's model, the U-M event convened faculty from both within and outside of traditional life sciences fields to consider a central scientific challenge. The goal was to stimulate creative research projects that capitalize on the full breadth of expertise across the university.

"One of the great things about Michigan is that we're a very large institution that has experts in basically anything you might want to study," says Daniel Forger, a member of the Biosciences Initiative Coordinating Committee who organized the inaugural Ideas Lab. "So I think this is an area where Michigan can clearly be a leader. How many other institutions have such strength across so many different fields?"

For three days in October 2019, 25 faculty members from 14 U-M schools, colleges and institutes gathered to determine how their collective expertise could incubate new research ideas related to the theme "Predicting Human Performance."

"One of the central ideas that came up was to understand the relationship between the quality of breathing and the quality of performance," recalls Sophia Brueckner, an assistant professor of art and design and the primary investigator on the 2Inspire project. "And that's how our team came together — we're all interested in breathing but coming from totally different disciplines."

Another kind of artistic inspiration

The 2Inspire project draws its name from two meanings of *inspire*: to draw in breath, and to create in someone the urge to do or feel something.

"First we have to understand the quality of breath — we have to be able to measure it and communicate quality of breath to a performer," Brueckner explains. "Then the next stage is to understand if that information can actually inspire better performance. Does it improve the way they play, the emotion of how they play, the artistry, the expression?"

To answer these questions, the multidisciplinary team is developing new technologies both to monitor breathing and to feed breath-related data back to performers in real time.

The most common systems for monitoring breath are either not suitable for use outside of a laboratory setting or cannot accommodate the movement and posture changes of performing musicians.

Drawing on the expertise of biomedical engineer James Ashton-Miller, the team has devised a new system of wearable sensors that overcomes these challenges.

The sensors are incorporated into a discrete vest that can measure a variety of breathing parameters while musicians perform. During the first phase of the project, the team is using this system to collect and analyze baseline data from keyboardists at a variety of skill levels.

The project's second phase relies on a biofeedback system devised by Brueckner, who specializes in designing wearables that communicate with people through the sense of touch (temperature change or gentle vibrations, for example). This system will deliver information to performers, in ways that don't distract from their playing, about when and how they need to modify their breathing for optimal performance. In this phase, the team hopes to determine whether real-time feedback of breathing patterns can improve musical performance, and whether an expert's breathing pattern can be used to guide a beginner.

"What we really want to do is find a way in real time to show the players the data of what's happening with their lungs while they are performing, and therefore allow them to adapt to that," Gascho explains. "And then we would simultaneously record that data, so a student could observe 'this is how my teacher, or a fellow student, or an expert is breathing during this piece, so that's something I want to emulate.'"

With his expertise in the neurological underpinnings of breath, Li is helping the team define the precise parameters they will need to measure to determine the quality of breath. And in a more conceptual sense, he and fellow scientist Muneesh Tewari bring an understanding of what is needed to design and document a reproducible scientific study, along with Tewari's expertise in leading human subject studies.

"It's been really enlightening to see how we each raise different questions about the same topics," Li observes. "We have found that we really synergize well, because our different areas of expertise allow us to view things completely differently and educate each other on our own research or experiences."

As the professional musician and self-described "guinea pig" for the project, Gascho is the first expert whose breath will be monitored to determine how breathing correlates with exceptional performance. Eventually, his students also will provide breathing data and use feedback data to measure the causal effect of breathing on performance quality.

2Inspire: Optimizing breathing for exceptional musical performance

The 2Inspire project aims to answer:

- What physiological features of breathing are associated with, and might predict, exceptional musical performance?
- Can we improve performance by changing how the performer breathes?
- Can representations of how expert performers breathe transfer knowledge to beginning and advanced students to help them learn more quickly and effectively?
- How can this research be applied to other types of performance?

The project will draw on the expertise of **five investigators** representing **nine schools, colleges and institutes** across the university.

Professor James Ashton-Miller, Ph.D.,
biomedical engineer

College of Engineering; School of Kinesiology; Medical School

Associate Professor Sophia Brueckner, M.F.A.,
human-computer interaction designer

Penny W. Stamps School of Art & Design; School of Information; College of Literature, Science, and the Arts

Associate Professor Joseph Gascho, D.M.A.,
keyboard performer

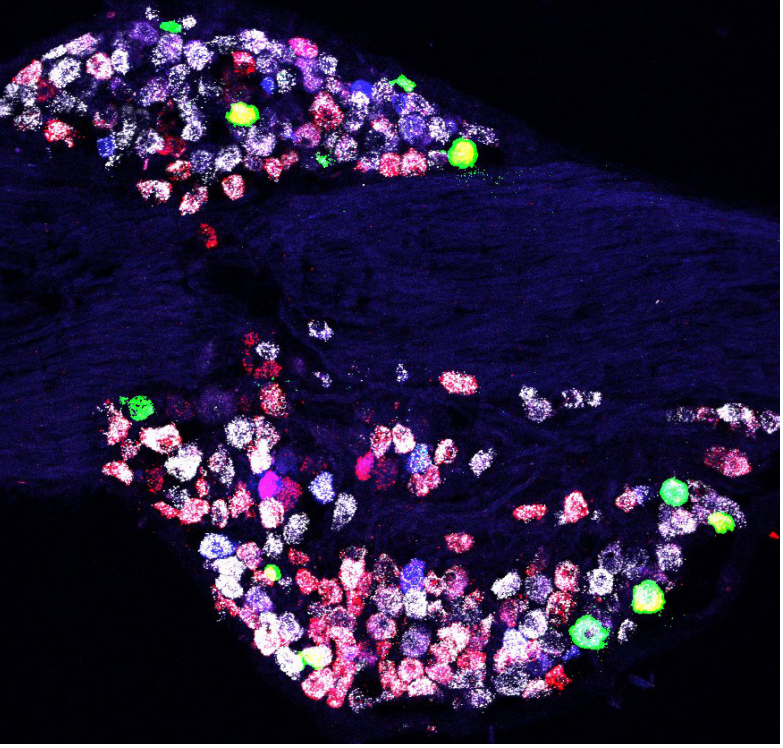
School of Music, Theatre & Dance

Assistant Professor Peng Li, Ph.D.,
neuroscientist

Life Sciences Institute; School of Dentistry; Medical School

Professor Muneesh Tewari, M.D., Ph.D.,
physician-scientist and oncologist

Medical School; College of Engineering



Sensory neurons in a mouse vagal ganglion connect different visceral organs, including the airways, to the brain.

The project is initially focusing on breathing and performance quality in harpsichordists, precisely (though perhaps counterintuitively) because their instrument does not require breath to operate. The team argues that such performers are likely to have a wider range of breathing characteristics, and thus can offer more data points for correlating breathing quality with performance quality.

> **We're really hoping to lay a foundation for how we can use this same approach to enhance performance in a lot of other domains.**

"But ultimately, we're really hoping to lay a foundation for how we can use this same approach to enhance performance in a lot of other domains," Tewari says.

He has already begun envisioning how this type of effort could translate to helping patients manage intense cancer treatments. For example, can the breathing patterns of a patient who handled a particular cancer treatment well be used to help other patients persevere through difficult treatments?

"I would say more people than ever are aware of how technology can make you more stressed or tense, or of the harmful effects of technology," Brueckner adds. "Well, if we know technology can shape our behavior and the way we feel, what if we actually harness those forces to do good things, like help people with resiliency through their breathing?"

Back to the brain

For his part, Li is excited about how this research might be applied back in his lab at the LSI. In a bit of a reversal from the typical flow of scientific research, he plans to apply what the team learns from humans to the study of neurology in mice.

Li's research has focused primarily on how the brain changes breathing patterns — how signals between different groups of neurons can generate distinct forms of breath.

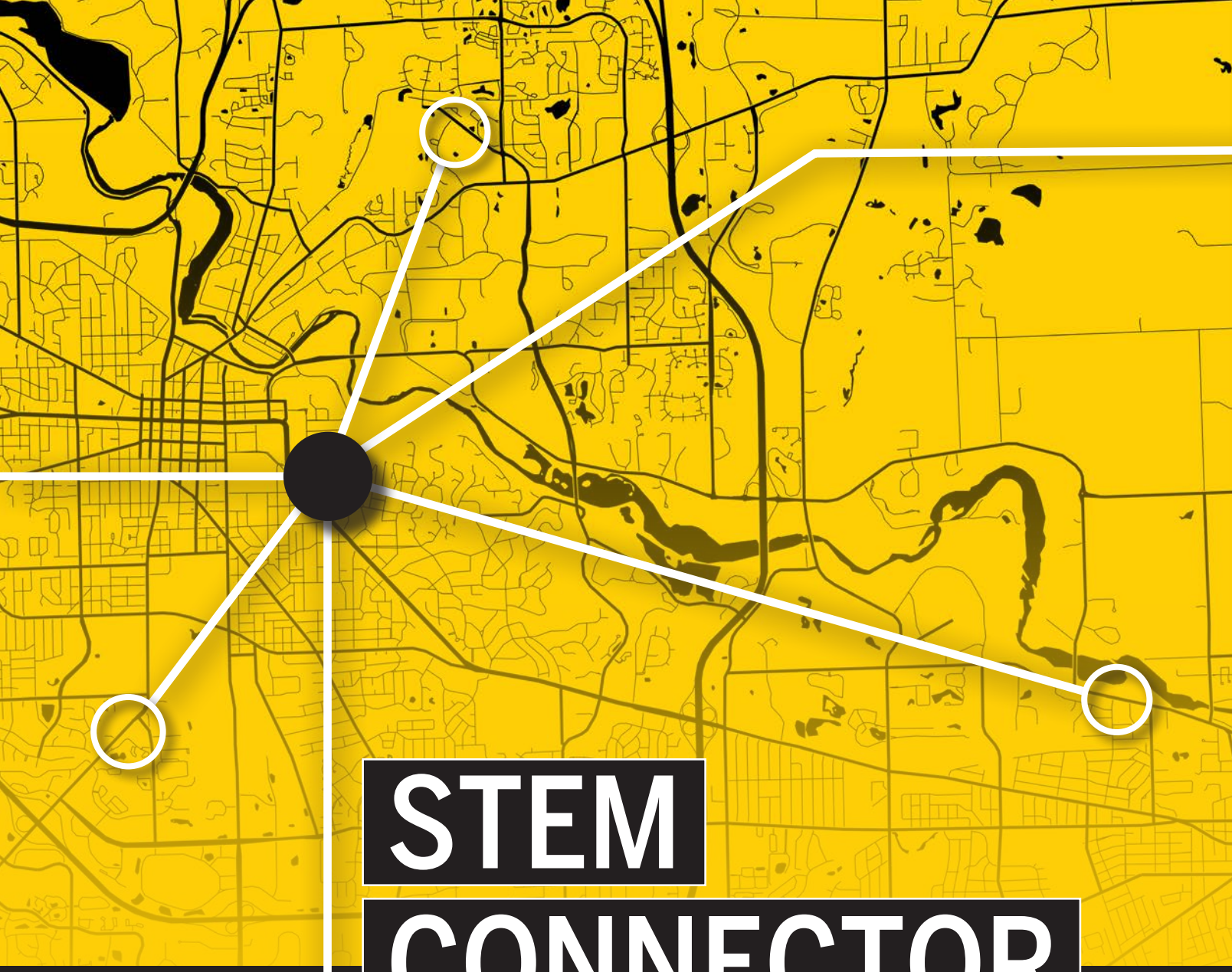
But he is also interested in how breathing patterns can change the brain. Some studies in humans have shown that certain breathing patterns correlate with certain emotional or mental states. Li wants to explore how information about breathing pattern gets back to the brain and alters its state.

"Is there a neuronal component involved here? Is the full brain receiving certain inputs from your internal organs, or from the breathing control centers, to change the activity or state of the brain?" he asks. "That's the type of thing we can investigate in animal models, but not in humans — really figuring out the cellular and molecular mechanisms at play."

Since, as Li puts it, "we can't just ask animals to voluntarily breathe in a certain way," he envisions synchronization between his work with humans for 2Inspire and his future lab work. The knowledge gained from 2Insipre could inform new experiments in animal models, which can then offer new insights into the biological mechanisms taking place in humans.

"There's a lot of really interesting science that can happen at the convergence of all these disciplines, when you get people who aren't usually talking to each other to start talking," Forger says. "This project is a perfect example."

Image courtesy of Lusi Zhang, Li lab, LSI



STEM CONNECTOR

A summer fellowship at the LSI prepares Michigan undergrads for the next leg of their STEM journey

By Sarah Kearns

Jacquelyn Roberts knows firsthand the power of authentic research opportunities for young scientists.

"It only takes a single experience to start building your research career," says the University of Michigan graduate student.

As a researcher in Melanie Ohi's lab at the U-M Life Sciences Institute, Roberts currently uses cutting-edge microscopy techniques to explore the 3D structures of cellular protein machines. But her introduction to the LSI came three years ago, while she was an undergraduate student at Eastern Michigan University, through the LSI's Perrigo Undergraduate Summer Fellowship.

The LSI launched the Perrigo fellowship program in 2004 with a gift from the Michigan-based Perrigo Company, then headquartered in Allegan. From the outset, the program's goal has been "to encourage highly talented undergraduates from throughout Michigan to pursue careers in the life sciences." Students enrolled in any Michigan college or university can apply, so long as they're interested in biochemistry, cell biology, pharmacology or related fields.

When the program began, Michigan was experiencing some of the worst "brain drain" — the outflow of young, highly educated or skilled professionals to other states — in the nation. And while the landscape has changed for the Michigan labor force in general, attrition in STEM fields in particular remains a national challenge.

The Perrigo program plays a small but important role in retaining Michigan-based students in STEM programs. By offering hands-on experiences to undergraduate students from around the state — often from primarily undergraduate institutions with smaller research infrastructures — the program provides opportunities for students to conduct scientific research, while learning to see themselves as capable of persevering in a STEM career.

"Throughout the 10 weeks, students are immersed in the lab activities and are treated as regular lab members," explains LSI faculty member Bing Ye, director of the Perrigo program. "It gives a sense of belonging and instills interest in their lab work."

Accepted fellows come to the Ann Arbor campus for the summer to work full-time in a laboratory that matches their interests, and they are assigned a mentor within the lab whom they work with throughout their project. When not at the bench, the fellows participate in science communication workshops, seminar talks, mentor lunches and other activities that build their network outside the lab. In addition to extensive training, students receive a stipend and housing support.

"The state of Michigan has been short of talent in scientific research and development, so creating an opportunity for students across our state to experience the actual work with U of M's outstanding faculty has been an exceptional investment in our future," says Mike Jandernoa, former CEO and chairman of Perrigo

Ty Hergenreder

Company, who was instrumental in the formation of the Perrigo fellowship program.

Building enthusiasm at the bench

To inspire interest in bench research, the Perrigo program emphasizes providing each student with a unique and individualized project of their own.

"We were never just doing 'busy-work,'" recalls Ty Hergenreder, who worked in Ye's lab as a member of the 2018 cohort of Perrigo fellows. "We were fully thrown into a project, and we basically had free rein with our mentors guiding us."

Hergenreder had conducted field-based botany research as an undergrad at Hope College, but he was hoping to switch to neuroscience. He applied to multiple summer research opportunities across the state; when he was accepted into the Perrigo program, he immediately turned down all other offers so he could pursue the opportunity to work in Ye's neuroscience lab at the LSI.

The Ye lab uses fruit flies as a model organism to study neuronal development processes and disorders. For his summer project, Hergenreder injected fruit flies with different compounds to determine which could cross the blood-brain barrier and investigated the chemicals involved in Down syndrome.

Compared to his previous undergrad research work, Hergenreder appreciated the depth of understanding that full-time lab work could provide. Both his direct mentor and Ye took the time to share not only the techniques but also the motivation behind the research project and the experimental setup.

> **That's the coolest thing about research: We get to see something that no one else has seen before.**

This hands-on neuroscience experience further encouraged Hergenreder to switch fields from botany and continue down a more medical track. After graduating from Hope College, he returned to Ye's lab to work as a technician while he applies to medical school. He says his experience with the Perrigo program solidified his enthusiasm for conducting research and his interest in applying that enthusiasm to patient care.

"That's the coolest thing about research: We get to see something that no one else has seen before," Hergenreder says. "I'm getting results and information that will hopefully help people in the future and will help us understand more about the scientific problem that we are studying."

Leisa Thompson Photography

Jacquelyn Roberts

Finding the right fit in STEM

When she applied for the Perrigo program, Jacquelyn Roberts already had some research experience, and even some interactions with the U-M research infrastructure, under her belt. As an undergraduate researcher at Eastern Michigan University in Ypsilanti, she sometimes had to drive her samples to neighboring Ann Arbor for DNA sequencing analysis at U-M.

Roberts came to work in Ohi's lab as a Perrigo fellow in 2019, using the state-of-the-art cryo-electron microscopy facility at the LSI to characterize part of the protein machinery that the bacteria *Helicobacter pylori* use to spread infection.

Perrigo fellows work alongside graduate students and postdoctoral fellows, so they have opportunities to build connections and networks with their peers. For Roberts, those connections introduced her to the experiences of graduate students and made her feel like graduate school was a valid option for her.

"Spending my summer here made me feel like graduate school would be a good fit for me … and all the support from the lab cemented my desire to go into STEM," Roberts says. "The combination of having the time along with financial and departmental support really made me feel free to focus on research without having to worry about other things."

Spending my summer here made me feel like graduate school would be a good fit for me … and all the support from the lab cemented my desire to go into STEM.

By the time Roberts arrived back at U-M as a graduate student, she had already secured a Graduate Research Fellowship from the National Science Foundation. Her application was based on the work she completed during the Perrigo fellowship, which she is now expanding as a second-year graduate student in the Ohi lab.

"It really shows the impact that experiences like this can have," Ohi says. "In this case, Perrigo not only helped a student get a prestigious fellowship, but it helped U-M snag a very talented young scientist."

'A community I could rely on'

More than 15 years in, the Perrigo program continues to seek new ways to break down barriers that might prevent aspiring scientists in Michigan from remaining in STEM fields. Toward that goal, the LSI has recently partnered with the ReBUILDetroit program at the University of Detroit Mercy.

ReBUILDetroit is one of 10 programs funded through the National Institutes of Health's Building Infrastructure Leading to Diversity (BUILD) Initiative.

Leisa Thompson Photography

Amber Abram

At Detroit Mercy, the program recruits students from NIH-designated underrepresented populations who are interested in research, and provides them with the intensive training and support they need to prepare for success in graduate school and STEM-based careers.

"No matter your background, in order to pursue a career in research you have to see yourself there and feel like you belong," explains Jacob Kagey, a biology professor at Detroit Mercy and the director of student training for ReBUILDetroit.

To facilitate this sense of belonging, the program requires first-year students to join a research lab either at Wayne State University or Detroit Mercy. In subsequent years, the students are encouraged to apply to research programs or fellowships at other universities, to get a diverse range of lab experiences.

Amber Abram was looking forward to just that type of new experience when she was notified in early 2020 that she would be one of the first Perrigo students accepted from the ReBUILDetroit program. She felt it was a perfect opportunity to explore genetics — she had taken an advanced genetics course and "loved it so much I barely had to study for any of the exams," she remembers. She was placed in David Ginsburg's lab and she hoped to learn especially from Ginsburg, himself a medical doctor turned researcher, as she sought to marry clinical work with research.

But, just like almost everything else in spring 2020, her plans changed when COVID-19 restrictions forced the program to pivot to a fully online format for the summer. Because Abram planned to become a genetic counselor and not a research scientist, she used the summer to build her network and become familiar with the opportunities and connections on campus.

The 2020 fellows were invited back to complete an in-person fellowship in summer 2021, and Abram was finally able to conduct research in the Ginsburg lab. By then, she had already applied and been accepted into U-M's genetic counseling program, but nevertheless wanted to capitalize on the opportunity to further strengthen her research experience and community.

Although she had worked in a lab at a smaller university and attended several scientific conferences, Abram still anticipated feeling a bit like a small fish in a big pond.

"But Dr. Ginsburg and the lab made it a mission to speak to me and made me feel included in the overall lab experience," Abram recalls. "It made the transition from a smaller university to a larger one a lot easier. I had a point person and a community I could rely on."

The research experience helped Abram with her genetic counseling coursework. The insight she gained into the types of questions genetics researchers ask has informed her thinking about the clinical work she'll be doing.

"The lab environments are instrumental in nurturing this kind of interest," Ye says of the Perrigo program. "Even though 10 weeks is very short, the learning experience could become lifelong." ↙

Leisa Thompson Photography

Perspectives

MIXED SIGNALS

Decoding the trafficking signals that drive neutrophils, for better or worse

Cell migration is essential for development and survival, from the cells of an embryo arranging into tissues and organs, to adult immune cells converging on the site of an infection. But our cells don't just move randomly. They need signals to tell them when and where to go. And when a tumor gets a hold of these signals, it can use them to recruit immune cells to its team.

Carole Parent, Ph.D., a faculty member at the University of Michigan Life Sciences Institute, explains how her lab investigates the signals that drive immune cells' migration to infected sites and tumors — and how her approach may translate to new avenues for disease treatment.

Leisa Thompson Photography

Q: What is chemotaxis?

A: Chemotaxis is the ability of cells to respond to and move toward chemical cues. The process is fundamental in many physiological responses, including development, wound healing and inflammation. When you have a cut on your skin, for example, immune cells are recruited to that area to initiate inflammatory responses, eliminate the bacteria and prevent infection. To find these sites, the immune cells follow chemical signals that are secreted from bacteria and neighboring cells. This process of sensing and migrating toward these signals is chemotaxis.

My lab investigates the mechanisms that regulate chemotaxis by studying the process in immune cells called neutrophils, breast cancer cell lines, *Dictyostelium discoideum* and mouse models. This combination of simple and complex model systems allows us to dissect the molecular mechanisms of migration under various conditions.

Q: You recently published a study examining how neutrophils, which normally fight disease, might be involved in the progression of triple-negative breast cancer. What did you find?

A: Coming back to the immune response I just mentioned, neutrophils are key in this response, acting as the first line of defense against pathogens. Interestingly, aside from these established immune defense functions, neutrophils are emerging as one of the key immune cell types that influence cancer progression. Tumors are actually quite heterogeneous. In addition to the cancer cells, many normal cells get recruited to the tumor by chemical cues that are released within the tumor environment.

Given our interest in chemotactic responses, we wanted to answer two main questions in this study: Do breast cancer cells have the innate ability to recruit neutrophils? And if so, do all types of breast cancer cells do this? We found that highly aggressive triple-negative breast cancer cells are actually more effective at recruiting neutrophils than less invasive hormone receptor-positive breast cancer cell lines. The cancer cells secrete the same chemical signals that normally recruit neutrophils, but they also use another signal called TGF-β, which has been shown to promote the generation of "pro-tumor" neutrophils.

In this case, it appears the recruitment of these immune cells to the tumor is actually harmful to patients. Once they get there, the neutrophils activate responses that create an environment where the cancer cells mutate and grow more, and more effectively migrate to reach distant sites. But the role of neutrophils in the context of tumor progression is still a young field compared to other types of immune cells that have been shown to infiltrate tumors. There's a lot to be discovered.

The role of neutrophils in the context of tumor progression is still a young field compared to other types of immune cells that have been shown to infiltrate tumors. There's a lot to be discovered.

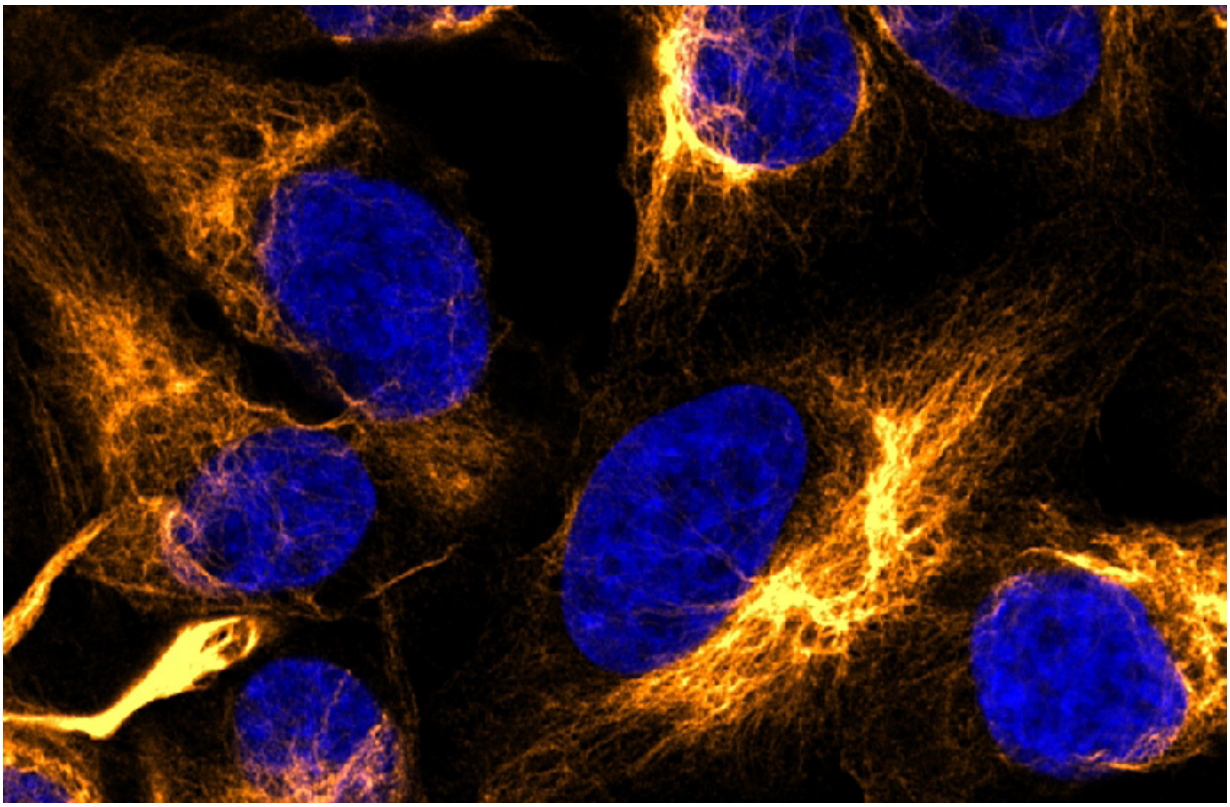
Q: It sounds like in studying the mechanisms of how the neutrophils get to the tumor, you're also uncovering more about how the breast cancer cells themselves interact with the neutrophils.

That's right, and also about how the two cell types form a sort of cross-talk with each other. On one side, the breast cells are secreting components that are going to affect the neutrophils. But once they get there, the neutrophils also alter the properties of breast cancer cells. We want to better understand how all these things work together at a basic biological level.

Q: How do the various model systems you use come together to drive these types of discoveries?

A: We use what I would call a reductionist approach. To avoid the complexity of the tumor microenvironment, for instance, we use a simpler system where we can focus on identifying cancer cell-intrinsic effects on neutrophil function. This allows us to form hypotheses that we can test in more complex model organisms. Indeed, in more complex systems, like a mouse, it becomes difficult to tease apart the very fundamental mechanisms because so many things are changing at the same time.

Another example of this approach is our research into how neutrophils reach sites of inflammation. We began



Immunofluorescence image of breast cancer cells.

with isolated neutrophils, where we could control the immune cell environment. We identified a small lipid mediator that is essential for recruiting of neutrophils to these sites, and then we used mouse models to confirm that the lipid mediator is also required in animal systems. But to identify the mechanisms that regulate the release of the lipid mediator, we had to go back to working with the neutrophils. This led us to uncover potential therapeutic avenues for treating chronic inflammatory disease, where the presence of neutrophils becomes harmful.

Q: In addition to investigating multiple model organisms, you've also collaborated with researchers across fairly divergent life sciences fields. What led you to develop this transdisciplinary approach, and what impact has it had on your discoveries?

A: For me, a multidisciplinary approach is key to my research program. Before I came to U-M, I was at the National Cancer Institute, where I helped establish a collaborative environment between cancer biologists and physicists. That experience exposed me to people who think differently than me and helped me think outside of my box even more. It led me to go much deeper into questions in ways that I really hadn't thought about before.

The LSI was a perfect next step for me, because the institute houses investigators from different fields, working together and helping each other grow scientifically. And that's really where I want to be: in places where I can interact with people who think differently and can help me think of new ways to explore fundamental scientific questions.

Q: What is next for your lab at the LSI?

A: Every day provides a new "next" or new opportunity for discovery. We are often faced with unexpected results that open new questions to explore. Right now, I'm looking forward to expanding our work with animal models through collaborations, so we can continue to apply our basic science knowledge to systems that are more relevant for translational research. ↙

Interview by Emily Kagey

Image courtesy of Shuvasree SenGupta, Ph.D., Parent lab, LSI


Structural Biology
Metabolism & Obesity
Cell Biology
Genetics
Neuroscience & Neurological Disease
Chemical Biology & Chemistry

Cancer Biology

INSIDE THE LSI

LSI Faculty

Vivian Cheung, M.D.

Research Professor

Frederick G.L. Huetwell Professor of Pediatric Research, Professor of Pediatrics and Human Genetics, **Medical School**

Research areas: RNA biology, genetics, neurodegeneration

LSI MED

Michael Cianfrocco, Ph.D.

Research Assistant Professor

Assistant Professor of Biological Chemistry, **Medical School**

Research areas: cryo-electron microscopy, single molecule methods, biochemistry, intracellular transport

LSI MED

Roger D. Cone, Ph.D.

Mary Sue Coleman Director
Research Professor

Vice Provost and Director, **U-M Biosciences Initiative**; Professor of Molecular and Integrative Physiology, **Medical School**; Professor of Molecular, Cellular, and Developmental Biology, **College of Literature, Science, and the Arts**

Research areas: neurobiology of obesity, energy homeostasis, cachexia, anorexia nervosa

LSI LSA MED

David Ginsburg, M.D.

Research Professor

James V. Neel Distinguished University Professor of Internal Medicine and Human Genetics, Warner-Lambert/Parke-Davis Professor of Medicine, Professor of Pediatrics, **Medical School**; Howard Hughes Medical Institute Investigator

Research areas: hematology, blood clotting, genetics, intracellular transport

LSI MED HHMI

Ken Inoki, M.D., Ph.D.

Research Associate Professor

Roger C. Wiggins Collegiate Professor of the Life Sciences; Associate Professor of Internal Medicine and Molecular and Integrative Physiology, **Medical School**

Research areas: nutrient sensing, mTOR/AMPK signaling, diabetic complications, cancer

LSI MED

Daniel J. Klionsky, Ph.D.

Research Professor

Alexander G. Ruthven Professor of Life Sciences; Professor of Molecular, Cellular, and Developmental Biology, **College of Literature, Science, and the Arts**

Research areas: autophagy, cell biology

LSI LSA

Cheng-Yu Lee, Ph.D.

Research Associate Professor

Robert H. Bartlett Collegiate Professor of the Life Sciences; Associate Professor of Internal Medicine and Cell and Developmental Biology, **Medical School**

Research areas: stem cells, neurological disease

LSI MED

Peng Li, Ph.D.

Research Assistant Professor

Assistant Professor of Biologic and Materials Sciences, **Dental School**; Assistant Professor of Molecular and Integrative Physiology, **Medical School**

Research areas: molecular neuroscience, breathing and sighing

LSI DENT MED

Tools and Model Systems

Cell culture | Computational biology | Cryo-EM/ET | *Drosophila* | Mice | Yeast | Zebrafish

Leisa Thompson Photography

LSI Faculty

Jiandie Lin, Ph.D.
Research Professor

Bradley M. Patten Collegiate Professor in the Life Sciences; Professor of Cell and Developmental Biology, **Medical School**

Research areas: obesity-associated metabolic disease, signaling and gene transcription, metabolic tissue development

LSI MED

Anna Mapp, Ph.D.
Research Professor

Associate Dean for Academic Programs and Initiatives, **Horace H. Rackham School of Graduate Studies**; Edwin Vedejs Collegiate Professor of Chemistry, **College of Literature, Science, and the Arts**

Research areas: synthetic organic chemistry, chemical biology, molecular biology

LSI LSA

Rowena Matthews, Ph.D.
Research Professor Emerita

G. Robert Greenberg Distinguished University Professor Emerita of Biological Chemistry, **Medical School**; Professor Emerita of Chemistry and Research Professor Emerita of Biophysics, **College of Literature, Science, and the Arts**

Research areas: vitamin-derived cofactors in the catalysis of complex chemical reactions

LSI LSA MED

Shyamal Mosalaganti, Ph.D.
Research Assistant Professor

Assistant Professor of Cell and Developmental Biology, **Medical School**

Research areas: cryo-electron tomography, cryo-electron microscopy, organelles

LSI MED

Alison Narayan, Ph.D.
Research Associate Professor

Mary Sue Coleman Collegiate Professor in the Life Sciences; Associate Professor of Chemistry, **College of Literature, Science, and the Arts**

Research areas: biocatalysis, complex molecule synthesis, natural products

LSI LSA

Melanie Ohi, Ph.D.
Research Professor

Rowena G. Matthews Collegiate Professor in the Life Sciences; Professor of Cell and Developmental Biology, **Medical School**

Research areas: cryo-electron microscopy, biochemistry, genetics, bacterial pathogenesis

LSI MED

Carole Parent, Ph.D.
Research Professor

Raymond and Lynne Ruddon Collegiate Professor of Cancer Biology and Pharmacology, Professor of Cell and Developmental Biology, **Medical School**

Research areas: cancer biology, cell biology, pharmacology, chemotactic signaling

LSI MED

David H. Sherman, Ph.D.
Research Professor

Hans W. Vahlteich Professor of Medicinal Chemistry, **College of Pharmacy**; Professor of Microbiology and Immunology, **Medical School**; Professor of Chemistry, **College of Literature, Science, and the Arts**

Research areas: natural product biosynthesis, synthetic organic chemistry, marine microorganisms, drug discovery

LSI LSA MED PHARM

Tools and Model Systems

Cell culture · Cryo-EM/ET · Mice · Natural products · Yeast

Leisa Thompson Photography

LSI Faculty

Janet L. Smith, Ph.D.

Associate Director
Research Professor

Martha L. Ludwig Distinguished University Professor of Biological Chemistry, **Medical School**; Margaret J. Hunter Collegiate Professor in the Life Sciences; Professor of Biophysics, **College of Literature, Science, and the Arts**; Director, Center for Structural Biology

Research areas: structural biology of viral and antiviral proteins and enzymes of natural product biosynthesis

LSI LSA MED

Wenjing Wang, Ph.D.

Research Assistant Professor

Assistant Professor of Chemistry, **College of Literature, Science, and the Arts**

Research areas: chemical biology, protein engineering, neuroscience, optogenetics, nanobody design

LSI LSA

Lois Weisman, Ph.D.

Research Professor

Sarah Winans Newman Collegiate Professor in the Life Sciences; Professor of Cell and Developmental Biology, **Medical School**

Research areas: organelle inheritance, phosphoinositide signaling, cancer, neuroscience

LSI MED

Stephen J. Weiss, M.D.

Research Professor

E. Gifford and Love Barnett Upjohn Professor of Internal Medicine and Oncology, **Medical School**

Research areas: cancer, metastasis, stem cell functions, angiogenesis, inflammation

LSI MED

Jun Wu, Ph.D.

Research Associate Professor

Associate Professor of Internal Medicine and Molecular and Integrative Physiology, **Medical School**

Research areas: "beige" thermogenic fat cells, metalbolism, alcoholic liver disease, nonalcoholic steatohepatitis

LSI MED

X.Z. Shawn Xu, Ph.D.

Research Professor

Bernard W. Agranoff Collegiate Professor in the Life Sciences; Professor of Molecular and Integrative Physiology, **Medical School**

Research areas: sensory transduction, synaptic mechanisms underlying behavior and addiction, aging and longevity

LSI MED

Zhaohui Xu, Ph.D.

Director, Undergraduate Training
Research Associate Professor

Associate Professor of Biological Chemistry, **Medical School**; Interim Director, Program in Chemical Biology

Research areas: structural biology, protein folding, molecular chaperones

LSI MED

Bing Ye, Ph.D.

Research Associate Dean
Research Professor

Burton L. Baker Collegiate Professor of the Life Sciences; Professor of Cell and Developmental Biology, **Medical School**

Research areas: neuronal development, neurodevelopmental diseases

LSI MED

Tools and Model Systems

C. elegans · Cell culture · *Drosophila* · Mice · X-ray crystallography · Yeast

Leisa Thompson Photography

LSI Honors & Awards

Alison Narayan

Arthur C. Cope Scholars Award

Melanie Ohi

Elected Fellow of the American Association for the Advancement of Science

Janet L. Smith

Mildred Cohn Award in Biological Chemistry

Named the Martha L. Ludwig Distinguished University Professor of Biological Chemistry

Bing Ye

Elected Fellow of the American Association for the Advancement of Science

PROMOTION

Jun Wu

Research Associate Professor, LSI

Associate Professor of Internal Medicine and Molecular and Integrative Physiology, Medical School

Alum Profile

Xu Liu wants to make better cancer treatments by harnessing autophagy

By Staci Vernick

As a senior scientist in oncology research and development at AstraZeneca, Xu Liu strives to make cancer drugs safer and more tolerable. But this patient-focused work has its roots in the fundamental science of a cellular process that sparked his curiosity more than a decade ago.

One day in 2010, while studying as an undergraduate at Wuhan University in China, Liu found himself engrossed in an article in *Scientific American*. The topic was autophagy, a metabolic process somewhat akin to an intracellular recycling station. Little did the young biology major realize at the time, the article's author would eventually help launch Liu's career as a scientist.

Autophagy — from the Greek words auto- ("self") and phagein ("to eat") — degrades and recycles cellular components to protect cells from stress, starvation and infection. Liu read about how disruptions to this process can lead to diseases such as neurodegeneration and diabetes, whereas cancer cells can co-opt autophagy to resist treatment and promote recurrence.

Now, that's interesting, he thought. What if there is a way to safely modulate autophagy activity for therapeutic purposes?

Image courtesy of Xu Liu

Chance meetings and a choice mentorship

With his bachelor's degree from one of the most prestigious biology programs in China in hand, Liu set out to pursue this path of inquiry. As he explored options for graduate studies in the United States, the University of Michigan — with its world-renowned biomedical research programs, expert faculty and large international community — rose to the top of his list.

"I thought I would get a unique experience exposed to different cultures, making friends with people from all over the world while working with world-class scientists," Liu explains.

As chance would have it, the graduate admissions advisory committee member who interviewed Liu was Daniel Klionsky, a faculty member at the U-M Life Sciences Institute and the author of the *Scientific American* article that had captured Liu's interest. Klionsky recommended Liu for admission to the Molecular, Cellular, and Developmental Biology Ph.D. program and ultimately offered Liu a position in his lab at the LSI.

In the Klionsky lab, where he was known for his kind and generous personality and collaborative nature, Liu studied the molecular mechanisms that drive autophagy and its regulation under different stress conditions. Among Liu's stand-out scientific contributions, Klionsky says, is the first study to show that a naturally occurring mutation in the key autophagy gene ATG5 is associated with ataxia, a neurodevelopmental disease.

"Xu was a fantastic student and postdoc — technically skilled, but also willing to try and develop new experimental approaches, at which he was usually successful," Klionsky recalls. "In fact, Xu worked out the procedure for RNA immunoprecipitation, which has become an important technique in my lab. He played a critical role in developing my lab's interest in post-transcriptional regulation of autophagy."

Autophagy applied, from organoids to oncology

While he enjoyed studying the basic science of autophagy and his projects at the LSI, Liu says he was eager to see this work applied more directly to human physiology and disease. After completing his Ph.D. and early postdoctoral work at U-M, he joined the lab of Matthew Waldor at Harvard Medical School.

As a postdoctoral researcher, Liu investigated the role of autophagy in infection and the mechanisms by which disease-causing pathogens infect cells lining the gastrointestinal tract. He developed small intestine and colon organoids (three-dimensional cell cultures that more closely resemble human tissue) to better understand the signaling pathways that regulate pathogen infection.

My hope is to continue to grow as a scientist and apply my expertise to help develop better therapeutics for patients with unmet medical needs.

Throughout his graduate and postdoctoral work, Liu vacillated between whether to pursue an academic research career or one in the biomedical industry. He recalls many talks with Klionsky, who helped him navigate his options.

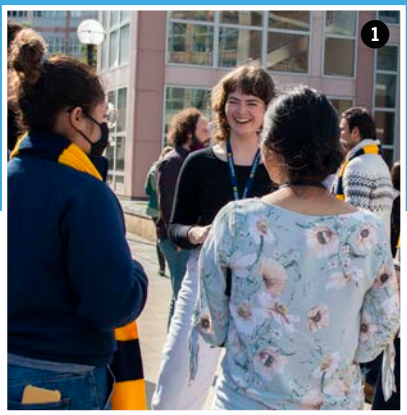
"I am so grateful for having Dan as my mentor," Liu says. "I got state-of-the-art training from one of the pioneers in the autophagy field and enjoyed the freedom to explore projects, with Dan always available to discuss and provide insightful suggestions. He is not just a great scientist who tries to help students become independent biologists, but he really cares about his students' career development."

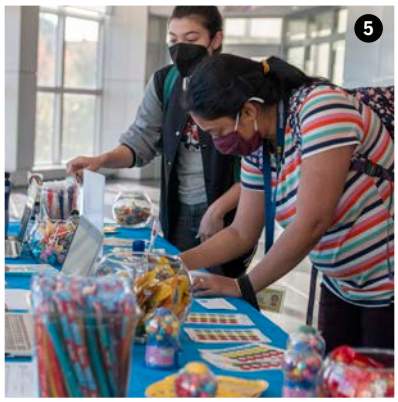
Determined to pursue research that more directly applies to human health, Liu turned to the biomedical industry for his next step and joined AstraZeneca in 2020.

Now, he leverages his knowledge of the fundamental biology of autophagy and infection to develop better cancer drugs. He supports the oncology therapeutic pipeline by assessing and predicting drug-induced gastrointestinal toxicity.

"My hope is to continue to grow as a scientist and apply my expertise to help develop better therapeutics for patients with unmet medical needs," Liu says. "In recent years autophagy has attracted much attention in the pharmaceutical industry. My ultimate goal is to harness autophagy to treat human disease."

Year in Photos





1 LSI community members gather for a welcome-back event to connect in person and learn about the LSI's Learning Spaces for Diversity, Equity and Inclusion.

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3 At "Plant the Seed" Day, LSI community members planted seeds symbolizing commitment to growing a more inclusive LSI.

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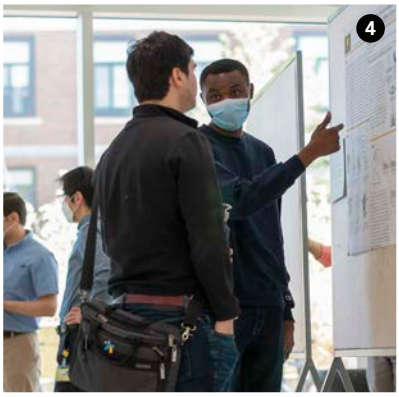
5 Participants in an International Pronouns Day celebration discussed the importance of recognizing and using individuals' correct pronouns.

6 Tyler Brant (left) and Amanda Erwin, Ph.D. (right), use the LSI's newest cryo-confocal microscope to peer into cells.

7 *New York Times* reporter Matt Richtel delivers the 2022 LSI SciComm Speaker Series lecture.

Rajani Arora, LSI



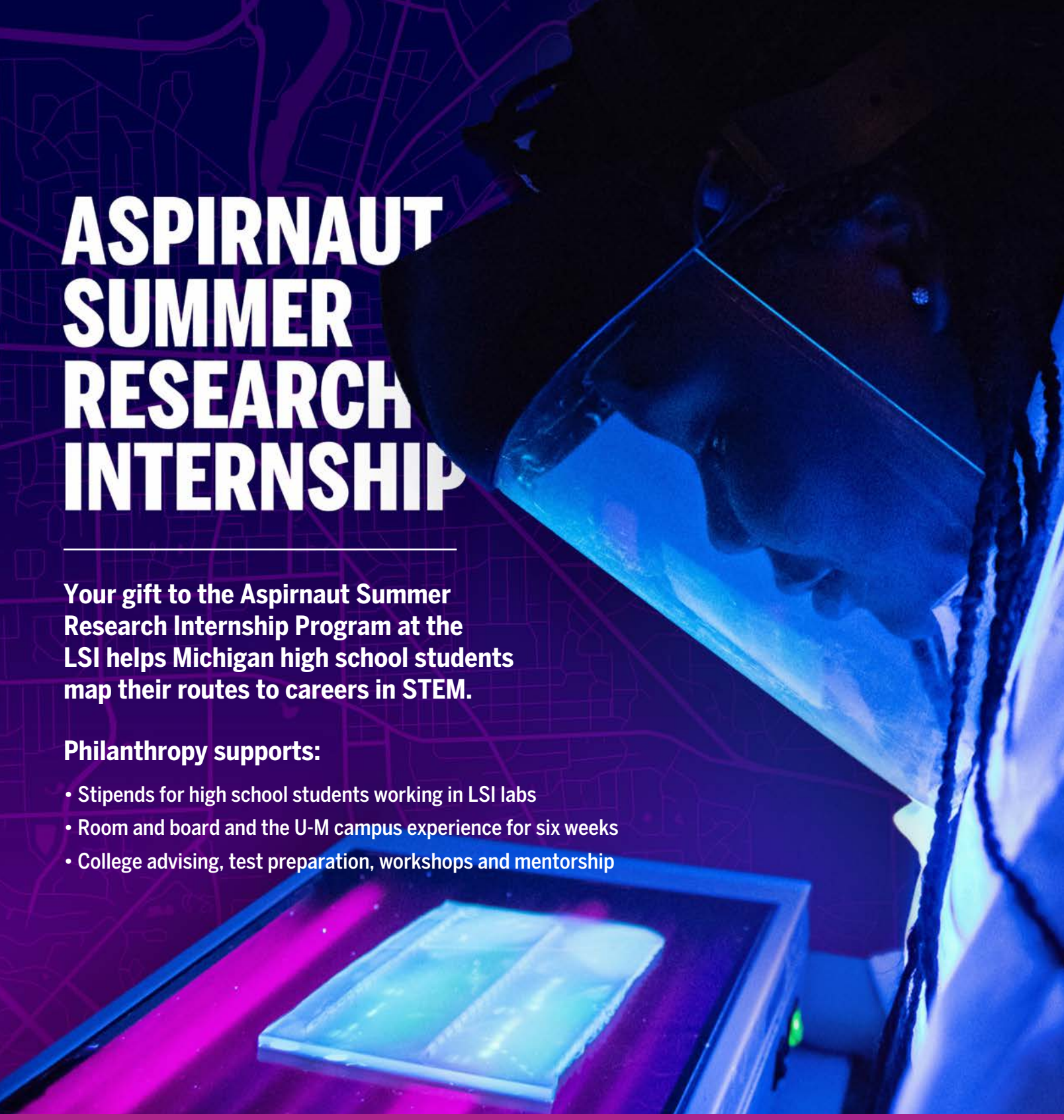
1 University leaders
2 celebrate the renaming of the building that houses the LSI as Mary Sue Coleman Hall with the unveiling of a new plaque for the building.

3 During the 2021 remote Aspirnaut Summer Research Internship program, high school students (including Mercedes Morin, pictured) collected local sediment samples at home for analysis in the LSI's Natural Products Discovery Core.

4 U-M scientists present their virology research during the Saltiel Life Sciences Symposium poster session.

5 The 2022 Saltiel Life Sciences
6 Symposium explored viral evolution and viral-host interactions. (Left: Symposium planning committee and speakers with U-M President Mary Sue Coleman; right: Harmit Malik, Ph.D., presents at the symposium.)

Photos 1 and 2: Austin Thomason, Michigan Photography; Photo 3: Courtesy of Mercedes Morin; Photos 4–6: Rajani Arora, LSI



Your gift to the Aspirnaut Summer Research Internship Program at the LSI helps Michigan high school students map their routes to careers in STEM.

Philanthropy supports:

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BACK COVER: Malignant migration. Researchers in the Weiss lab use human tumor cells and three-dimensional collagen hydrogels to model and investigate how malignant cancers invade surrounding connective tissues. Chains of cancer cells (blue nuclei) are seen migrating away from the center of the tumor by cutting their way through the tissue, leaving degraded collagen (green) in their wake as they invade. (Image courtesy of Adam Olson.)

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