LIFE SCIENCES INSTITUTE
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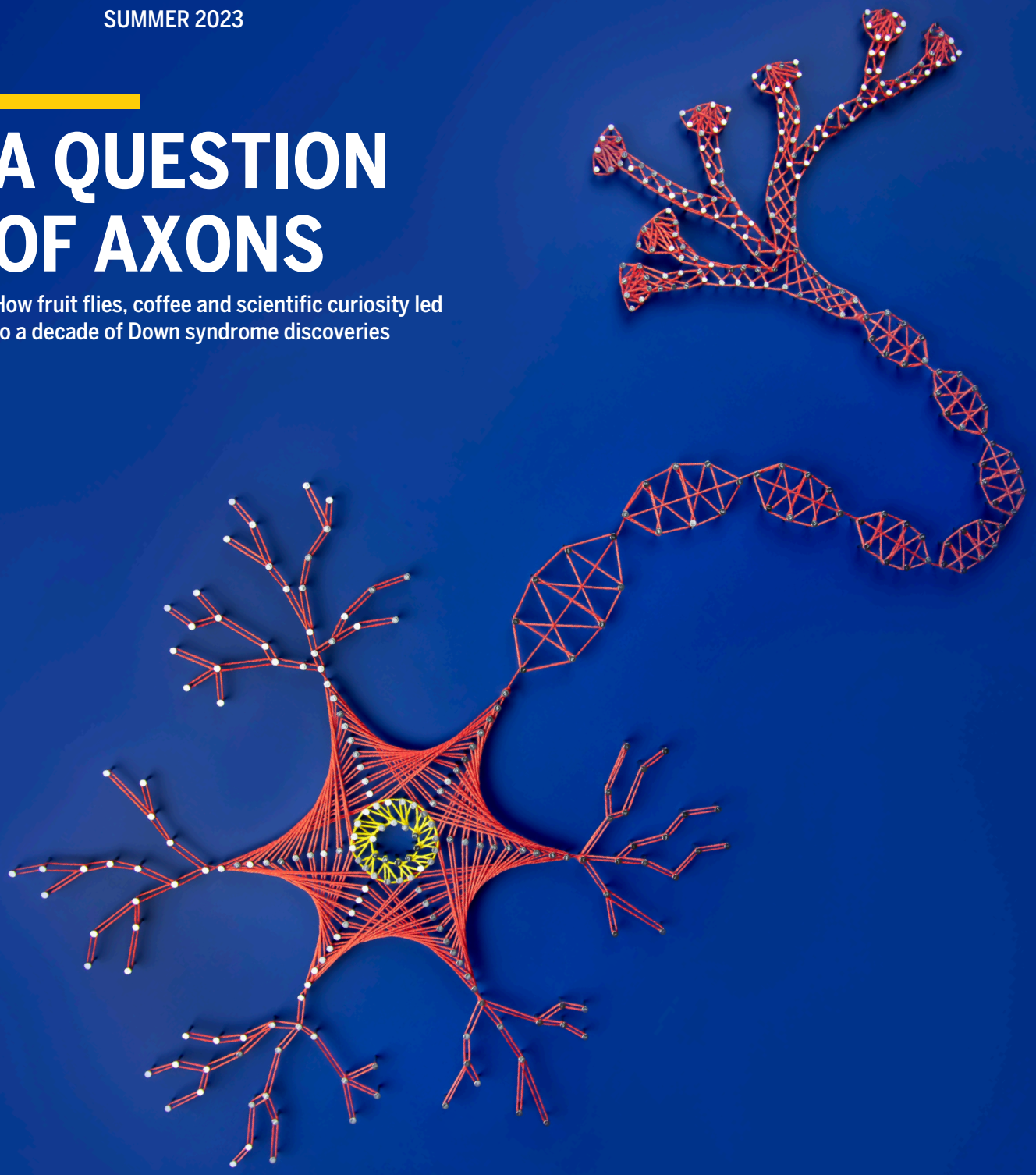
A QUESTION OF AXONS

How fruit flies, coffee and scientific curiosity led to a decade of Down syndrome discoveries



COURAGE TO COLLABORATE

What happens when academia and industry team up to tackle anorexia nervosa

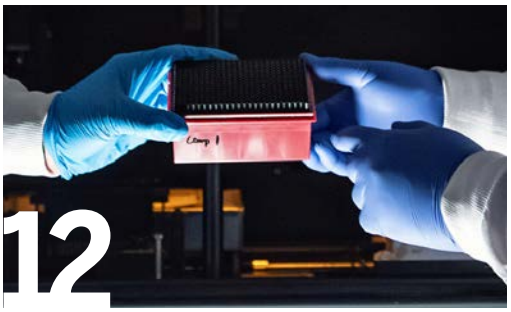
CAREER CONNECTOME

LSI trainees are mapping pathways to diverse careers

FAMILY AND FATE OF A NEURON

Tracing cells' pasts and predicting their progeny

Contents



Features

06 **A QUESTION OF AXONS**

How fruit flies, coffee and scientific curiosity led to a decade of Down syndrome discoveries

12 **COURAGE TO COLLABORATE**

What happens when academia and industry team up to tackle anorexia nervosa

16 **CAREER CONNECTOME**

LSI trainees are mapping pathways to diverse careers

Departments

01 **FROM THE DIRECTOR**

02 **NEWS & UPDATES**

20 **PERSPECTIVES**

24 **INSIDE THE LSI**

30 **ALUM PROFILE**

32 **YEAR IN PHOTOS**

ON THE COVER: String art representation of a neuron. String art throughout the magazine is original work created by Rajani Arora.

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From the Director

Here at the LSI, we strive to understand and build many different types of networks — from probing the complex neuronal connections that form a nervous system, to fostering collaborations that bridge the life sciences disciplines, to helping our trainees forge new connections to their futures in science. This issue of the *LSI Magazine* highlights the breadth of these various connections, through both the topics of articles and the artwork.

The feature article "A Question of Axons" describes how a basic science question about the molecular basis for neural networking connected Bing Ye's lab to investigations into the cellular mechanisms underlying Down syndrome pathophysiology.

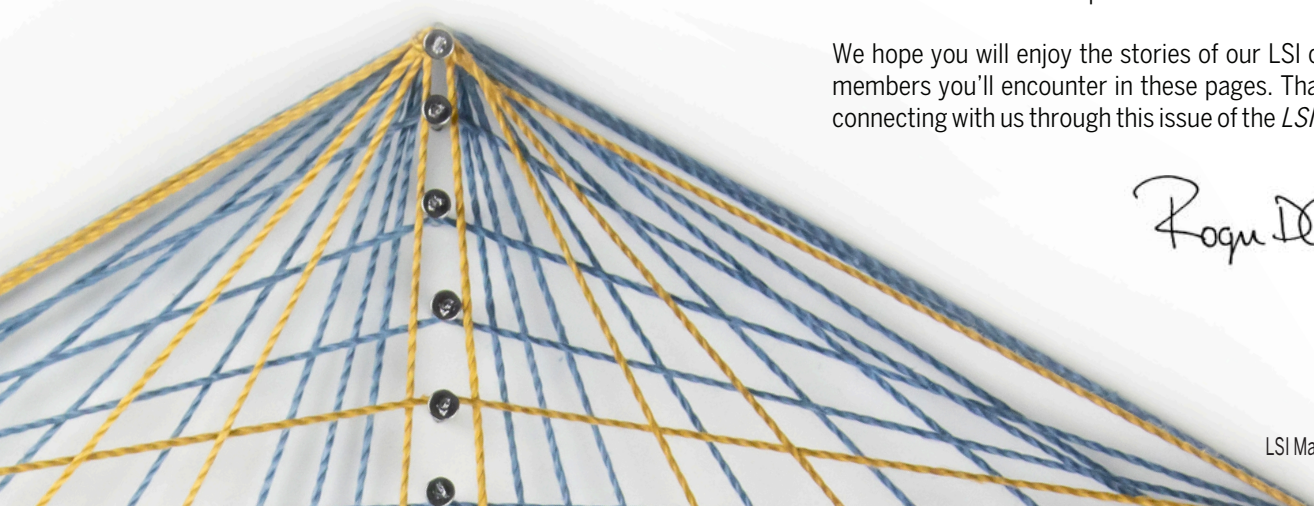
In "Courage to Collaborate," you will learn how connections to industry have provided new opportunities for discovery in my laboratory, while "Career Connectome" approaches the topic of network connections from a career standpoint. You will see examples of the many ways that LSI trainees are developing their professional networks, utilizing resources that U-M and the LSI provide to open a variety of career paths.

This issue also introduces the work of one of our newest LSI faculty members, Tzumin Lee, an HHMI investigator and the Peter D. Meister Professor of the Life Sciences, who recently joined the University of Michigan from HHMI's Janelia Research Campus. At the LSI, Lee is advancing understanding of brain development by mapping how the complex network of hundreds of thousands of neurons arise from only a few stem cells to form a functioning nervous system. As Lee describes in the "Perspectives" article, the cutting-edge tools he has developed for neural lineage mapping are applicable to other species, and he is already working to extend his discoveries to the vertebrate, and then the mammalian brain.

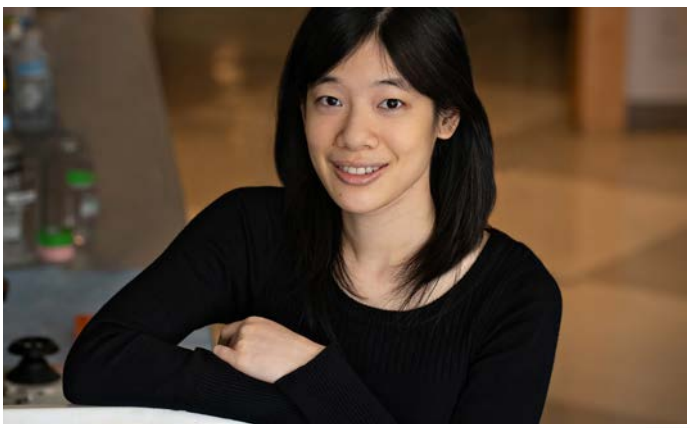
This theme of networks continues in the string art throughout this issue, which was created by LSI Multimedia Designer Rajani Arora. The intricacies found within these string images mirror the complexities of the interwoven nervous system, and even of the social networks that play such a critical role in our professional lives.

We hope you will enjoy the stories of our LSI community members you'll encounter in these pages. Thank you for connecting with us through this issue of the *LSI Magazine*!

Roger D. Cone



Advances



New faculty broaden LSI's campus reach and relationships

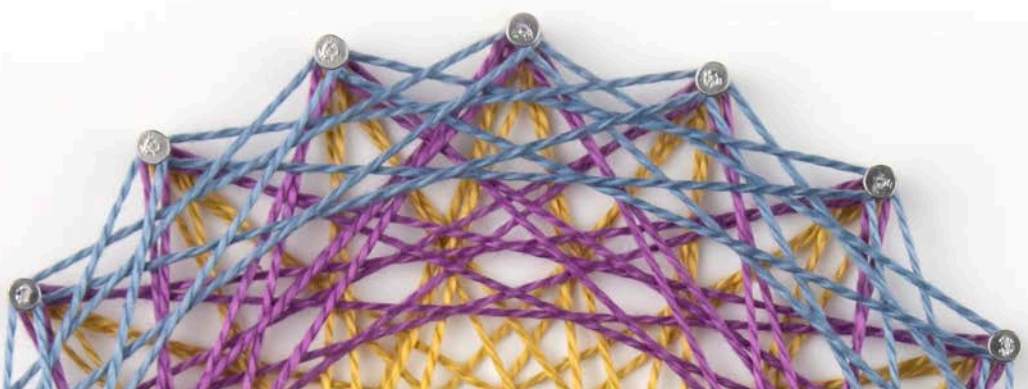
In the 2022-2023 academic year, the University of Michigan Life Sciences Institute added three junior faculty members who are advancing the institute's research portfolio and strengthening its connections across campus.

Two of these appointments for the first time expanded the institute's footprint outside the walls of Mary Sue Coleman Hall, with faculty members who maintain labs in their academic departments while participating as full members of the LSI. And with the third, the LSI established its first joint appointment with the College of Engineering.

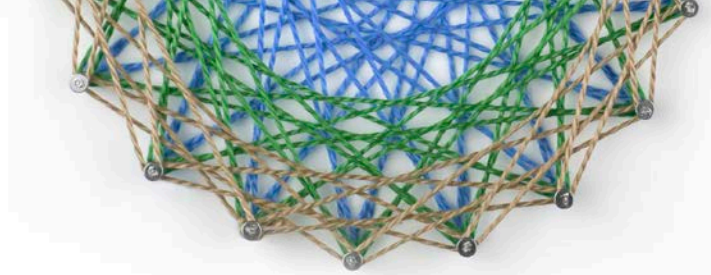
As an assistant research professor at the LSI and an assistant professor of biological chemistry in the Medical School, Jay Brito Querido uses advanced cryo-electron microscopy and biochemistry to study how the process of translating messenger RNA into proteins is initiated within cells. His lab operates out of the Medical Sciences Research Building, while also utilizing the LSI's cryo-EM facility.

Chelsey Spriggs holds appointments as an assistant research professor at the LSI and an assistant professor of cell & developmental biology at the Medical School. The Spriggs lab, located in the Biomedical Science Research Building, investigates how viruses interact with their hosts to cause infection, as well as the relationships between viruses and cancer.

Biomedical engineer Connie Wu joined U-M as a research assistant professor at the LSI and an assistant professor of biomedical engineering in the College of Engineering. Her two-pronged research program at the LSI aims to develop both diagnostic and drug-delivery tools, with a long-term goal of improving detection and treatment of human diseases such as cancer.



Leisa Thompson Photography



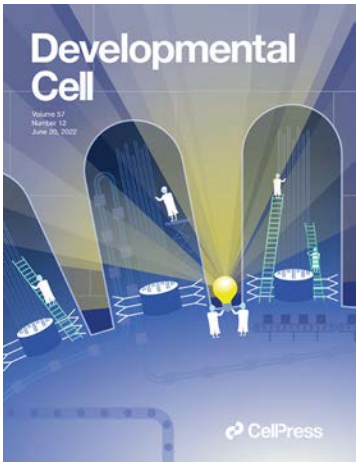
S. Xu lab
Developmental Cell
May/2022

Roundworms shed light on vision loss

While trying to determine how tiny roundworms called *C. elegans* can sense light without any eye-like organs, LSI scientists uncovered new evidence for how a rare human genetic disorder leads to vision loss.

The disorder, Bardet-Biedl syndrome (BBS), arises when a protein complex called the BBSome malfunctions. Because the BBSome regulates the form and function of cilia, the hair-like structures on the surface of cells, BBS has been classified as a disease of the cilia.

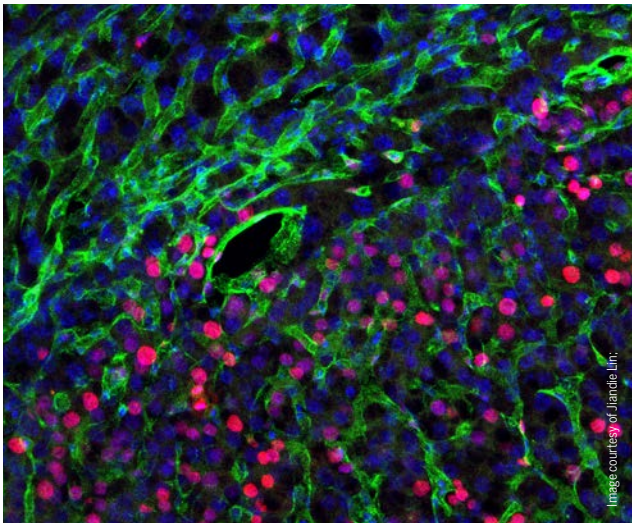
But the disorder's wide spectrum of symptoms — the most common of which is vision loss, as well as obesity, extra fingers or toes and kidney malfunction — has led to hypotheses that the cause of the syndrome may not lie solely within the cilia.



Research from Shawn Xu's lab has confirmed this hypothesis, at least in one common model organism. His lab demonstrated that the BBSome operates outside cilia to support sight.

They found that mutations in the BBSome, even in organisms that lack cilia, caused worms to stop sensing light. And, like the progressive vision loss that BBS patients experience, the worms with BBSome mutations progressively lost the ability to sense light as they aged.

"We are not disputing that BBS is tied to defects in the cilia. We are just offering direct evidence that the BBSome can also function outside of cilia, and it has a role there related to light sensation," Xu explains. "Perhaps this can broaden the view of how to develop treatments for BBS."



Lin lab
Cell Metabolism
Aug/2022

Microenvironmental conservation

The liver contains dozens of different cell types working in concert to maintain the organ's health. New research from Jiandie Lin's lab at the LSI has revealed how disruptions to this cellular harmony increase the risk for hepatocellular carcinoma (HCC), the most common form of liver cancer.

Lin and his team use mice as a model to study the molecular and cellular changes that occur in the relatively benign condition called fatty liver disease and how these changes induce progression of this disease to nonalcoholic steatohepatitis (NASH) and even cancer.

Their research found that changes in two types of immune cells in the liver, T cells and macrophages, appear to create a microenvironment where cancer can thrive.

The team also found that a hormone called NRG4, which is secreted by fat cells, can reprogram that microenvironment to suppress HCC. Mice lacking NRG4 developed more severe NASH and more liver tumors than mice with normal levels of NRG4, and boosting this hormone in mice curbed the cancer's progression.

The findings offer a proof-of-concept for developing therapies against liver cancer.

All illustrations by Rajani Arora, unless otherwise noted

Sherman lab
Journal of the American Chemical Society
Oct/2022

Nature's chemical tools, improved

A team from the LSI's Sherman lab and the University of Utah is using data science to improve the power of nature's chemistry.

Living organisms use biocatalysts to manufacture natural products, the chemical compounds they need for survival. These enzymes have each evolved to perform the necessary chemical reaction with extreme specificity, introducing new atomic groups to a starting material, or substrate, to churn out the desired product.

Biocatalysts have the potential to initiate powerful chemical reactions in the lab, as well; but to reach their full potential, they need to perform new jobs with new substrates, without sacrificing their well-evolved efficiency.

Using data from previous reactivity experiments, along with genetic and structural biology data, David Sherman and colleagues developed a statistical model that explains why biocatalysts perform well or poorly with various substrates, and predicts which tweaks to the enzymes could improve their performance.

The team believes this new strategy will have wide applications in the field of biocatalysis, helping to develop more efficient and effective biocatalysts that can perform important chemical reactions in a less toxic, less expensive manner than synthetic chemistry.

Wang and Li labs
Nature Methods
Dec/2022

Peptide power switch

A collaboration between two LSI labs has produced a new research tool for manipulating when and where cellular functions are activated.

The tool works by controlling the activity of peptides, short chains of amino acids and the building blocks of cellular proteins.

Existing peptide tools lack the necessary flexibility to work with a variety of peptides across different tissues. Some require light activation, for example, and work only in transparent tissues.

Researchers in the labs of Wenjing Wang and Peng Li teamed up to overcome these challenges, creating a tool that can "switch on" a peptide using a chemical instead of light — and can be adapted to activate a range of peptides. Tests with four different types of functioning peptides, in both cell culture and in two different organs in mouse models, found their new tool to be effective in all cases.

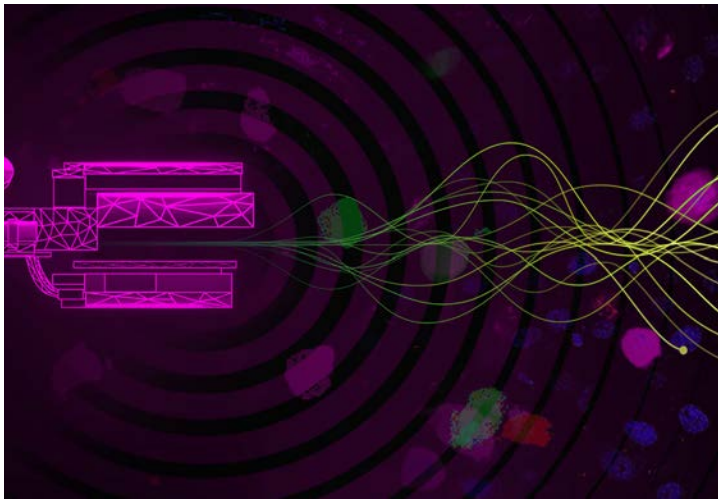
The ability to activate peptides on demand has several potential future applications, the team says, such as changing cellular function or even developing safer therapeutics.

... roughly 75% of approved antibiotics are derived from natural products. There are thousands of microorganisms in the ocean left to explore as potential sources of drug candidates, not to mention all the ones on land. In the search for new drugs to combat antibiotic resistance, natural products may still be the way to go.

—**Ashootosh Tripathi,** Director of the Natural Product Discovery Core and Associate Research Scientist, Life Sciences Institute; Research Assistant Professor, College of Pharmacy, in *The Conversation,* July 2022

Li lab
Current Biology
Feb/2023

Low O_2? Sigh.



Researchers from Peng Li's lab have uncovered the neural circuit in mice that activates sighing in response to low oxygen levels, or hypoxia, to increase oxygen in the blood.

Li's lab investigates how neural pathways produce various forms of breathing and sighing, and how disruptions in these pathways lead to diseases. The team previously identified a neural circuit that produces emotional sighs in mice under stress conditions.

These latest findings revealed that when oxygen levels dip too low, the body's oxygen monitoring sends signals to activate the same neurons that control emotional sighs.
In response, sighs increased at a greater rate, and lasted longer, than changes in regular breathing rates.

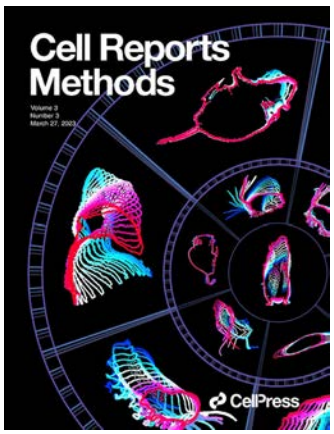
"We now have a map showing how the peripheral oxygen sensor in the body connects to the breathing control center to regulate hypoxia-induced sighing," Li says. "We are beginning to really see how different types of inputs all converge onto the same site in the brain stem to regulate the same behavior — sighing — in response to very different conditions."

Artificial intelligence, authentic analysis

Ye lab
Cell Reports Methods
Feb/2023

Scientists in Bing Ye's lab have developed a software tool to help researchers more efficiently analyze animal behaviors, using the power of artificial intelligence.

The open-source software, LabGym, is designed to "think" more like a human would to identify, categorize and count defined animal behaviors in various species. By combining information from video data and pattern images — still images that show movement by merging outlines of the animal's position at different time points — LabGym applies more flexible cognition than other existing programs to accurately recognize behavior types.



The new program is also user-friendly for biologists who may not have expertise in coding, Ye says.

"It's written for biologists, so they can adapt it to the species and the behavior they want to study without needing any programming skills or high-powered computing."

Alternative route to memory lane

Weisman lab
Journal of Cell Biology
May/2023

Neurons send signals to each other using cell-to-cell connections called synapses. To process these signals, the neuron on the receiving end of the message needs to have the right types and number of receptor proteins on its surface.

Scientists previously mapped one pathway that these receptor proteins travel to get from the center of the cell up to the surface when needed. But researchers from Lois Weisman's lab have now discovered a second cellular pathway that shuttles these proteins to the neuron's surface to maintain healthy synaptic function.

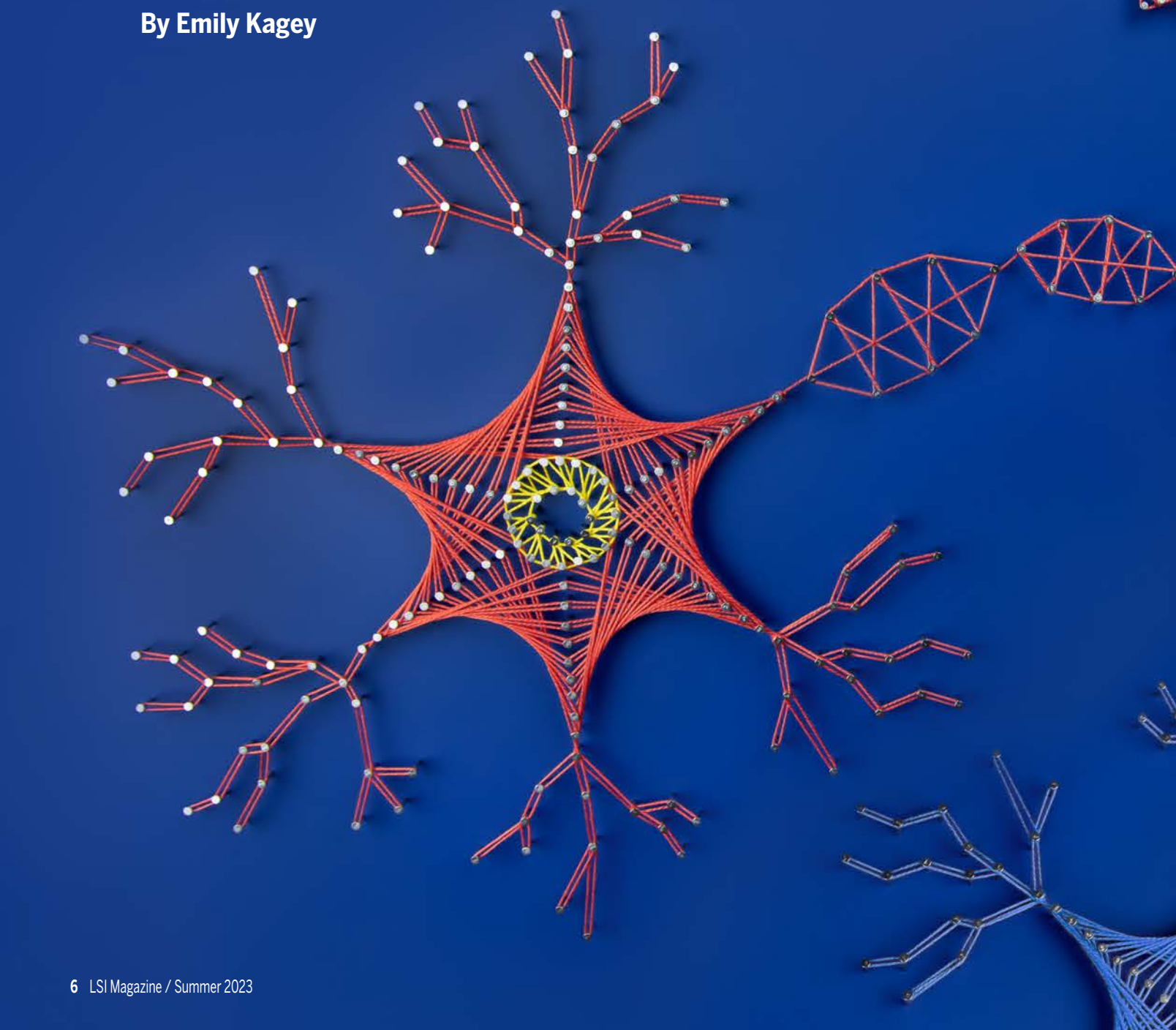
Furthermore, the team found that the proteins are recruited to synaptic sites along this pathway particularly during the type of cell-to-cell activity involved in a model of long-term memory formation.

"From a neuroscience perspective, we have now identified a new player involved in learning and memory formation," says Pilar Rivero-Rios, a postdoctoral researcher in the Weisman lab and lead author of the study.

A Question of Axons

How fruit flies, coffee and scientific curiosity led to a decade of Down syndrome discoveries

By Emily Kagey



On a summer afternoon in 2012, Bing Ye and Jung Hwan Kim decided to take a walk and get some coffee.

"We needed to get out of the lab," Kim recalls. "We were trying to understand what our results really meant, and we thought, 'Let's just go get some downtime and talk about it.' "

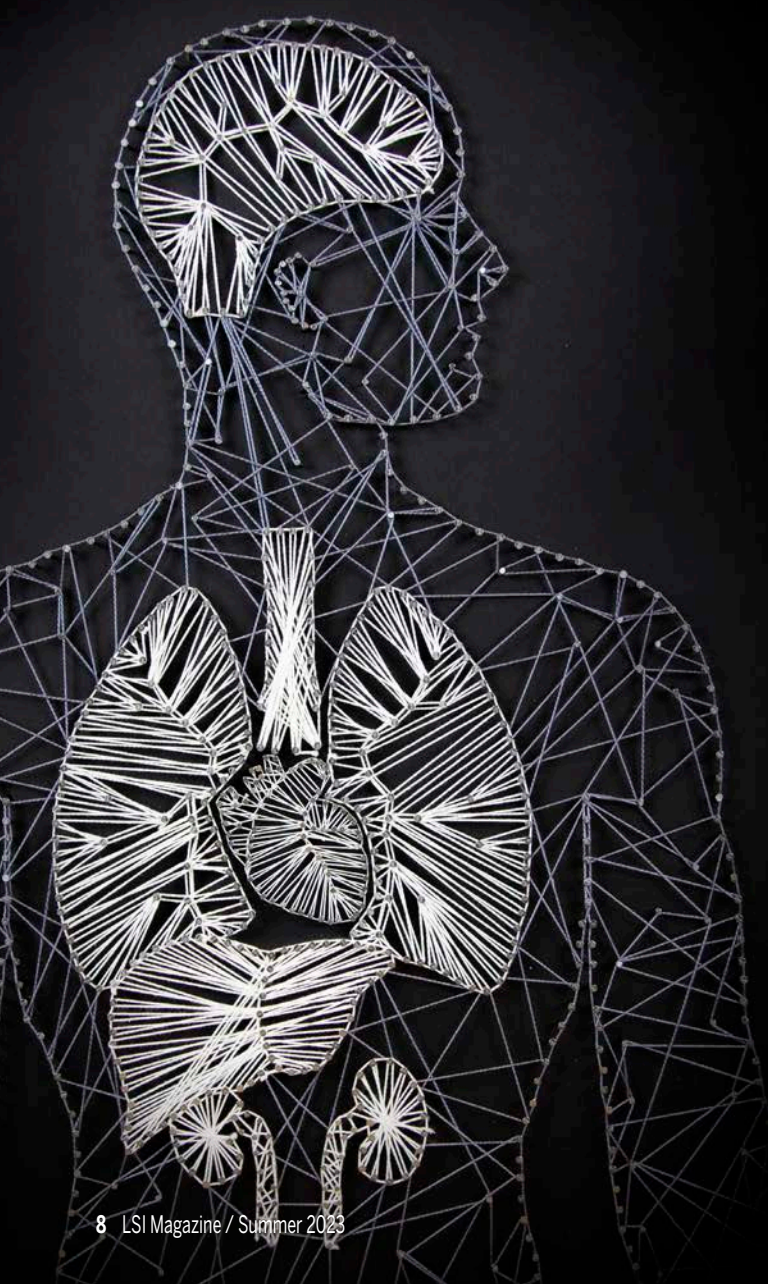
Kim was the first postdoctoral researcher Ye hired when he opened his new lab as an assistant professor at the University of Michigan Life Sciences Institute less than four years earlier. While building his research program, Ye was working with Kim to investigate how genetic mutations impact neuron development in fruit flies.

"So we were just walking and drinking coffee. And during that, I don't know, maybe 30 minutes, we got our idea," says Kim, who is now an assistant professor of biology at the University of Nevada, Reno.

The researchers ran with that idea — and over the past decade, it has led them from discovery science to disease models, from flies to mice and back again, while unearthing new understandings of human neurological disorders and particularly Down syndrome.

Down syndrome is a human genetic condition resulting from an extra full or partial copy of chromosome 21, also known as trisomy 21. Approximately **1 in 700** people are born with Down syndrome, making it the most common human chromosomal disorder.

Symptoms and their severity vary across individuals with Down syndrome. In addition to experiencing mild to moderate intellectual and developmental disabilities, they are at increased risk for developing other conditions such as congenital heart disease, gastrointestinal defects, blood disorders, vision problems and hearing loss.



‘A fundamental discovery question’

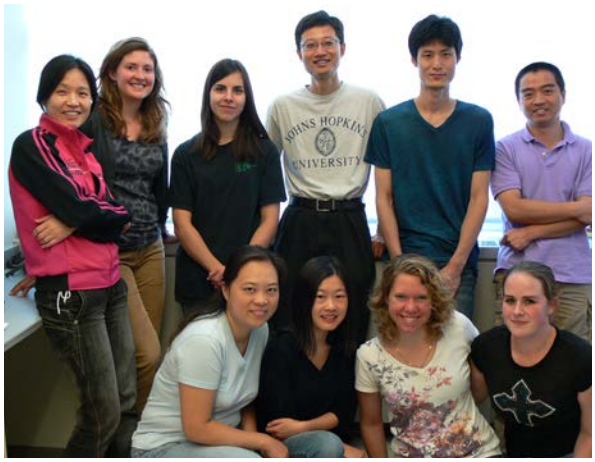
“I didn’t actually plan to study Down syndrome,” Ye says. It is spring 2023, and his lab is about to publish its seventh paper related to this chromosomal disorder. “But when we saw those effects of DSCAM, I started to realize how much was still unknown about the molecular and cellular mechanisms underlying the condition.”

DSCAM — or Down syndrome cell adhesion molecule — is the cellular protein he and Kim were studying when they went out for that coffee in 2012. At the time, there was no evidence that the molecule was involved in any of the characteristics of Down syndrome (its name was derived simply from the fact that the *DSCAM* gene that encodes the protein lies on chromosome 21 and is found in trisomy 21).

There was evidence, however, that mutations to *DSCAM* affected one particular aspect of neuronal development, and that’s what drew Ye to study it.

“It really started as a fundamental discovery question: If we mutate this gene, what happens in the various parts of neurons?” explains Ye, now a research professor at the LSI and professor of cell and developmental biology at the U-M Medical School.

Every neuron has three main parts: the cell center (or soma), where the nucleus resides; dendrites, which branch out from the soma to gather signals from other neurons; and axons, which extend out to send signals to other neurons through connections called synapses.



The Ye lab, 2011. Bing Ye and Jung Hwan Kim are fourth and fifth from the left, respectively, in the back row. Photo courtesy of Bing Ye.

Postdoctoral researcher Ruonan Li in the Ye lab.

Genetic mutations that affect dendrites do not necessarily have the same effect on axons, and vice versa. That phenomenon was what Ye set out to study when he opened his lab in late 2008.

A lack of DSCAM was known to affect dendrites in *Drosophila*, or common fruit flies, which the Ye lab uses as a model organism. Because of their well-mapped nervous system and genetic similarities to humans, they can reveal important insights about the molecular and cellular mechanisms at play in many human disorders.

> *And then we over-expressed this DSCAM, and we suddenly observed something very striking in the axons.*

"We were looking at a bunch of different mutants to see if there was anything different between dendrites and axons, because they are in fact so different," Kim recalls. "We were just testing here and there. And then we over-expressed this DSCAM, and we suddenly observed something very striking in the axons."

What the researchers saw were axons that could not stop growing. Axons typically go through a period of rapid expansion during early brain development. But in the DSCAM mutants they kept growing well past the developmental checkpoint when they should have stopped.

This was the finding that Ye and Kim were discussing when they went to get coffee. They came up with an idea to directly compare levels of DSCAM proteins in neurons with the amount of axonal growth. When Kim mapped the data, he found a complete correlation: the more DSCAM protein present, the more the axons grew.

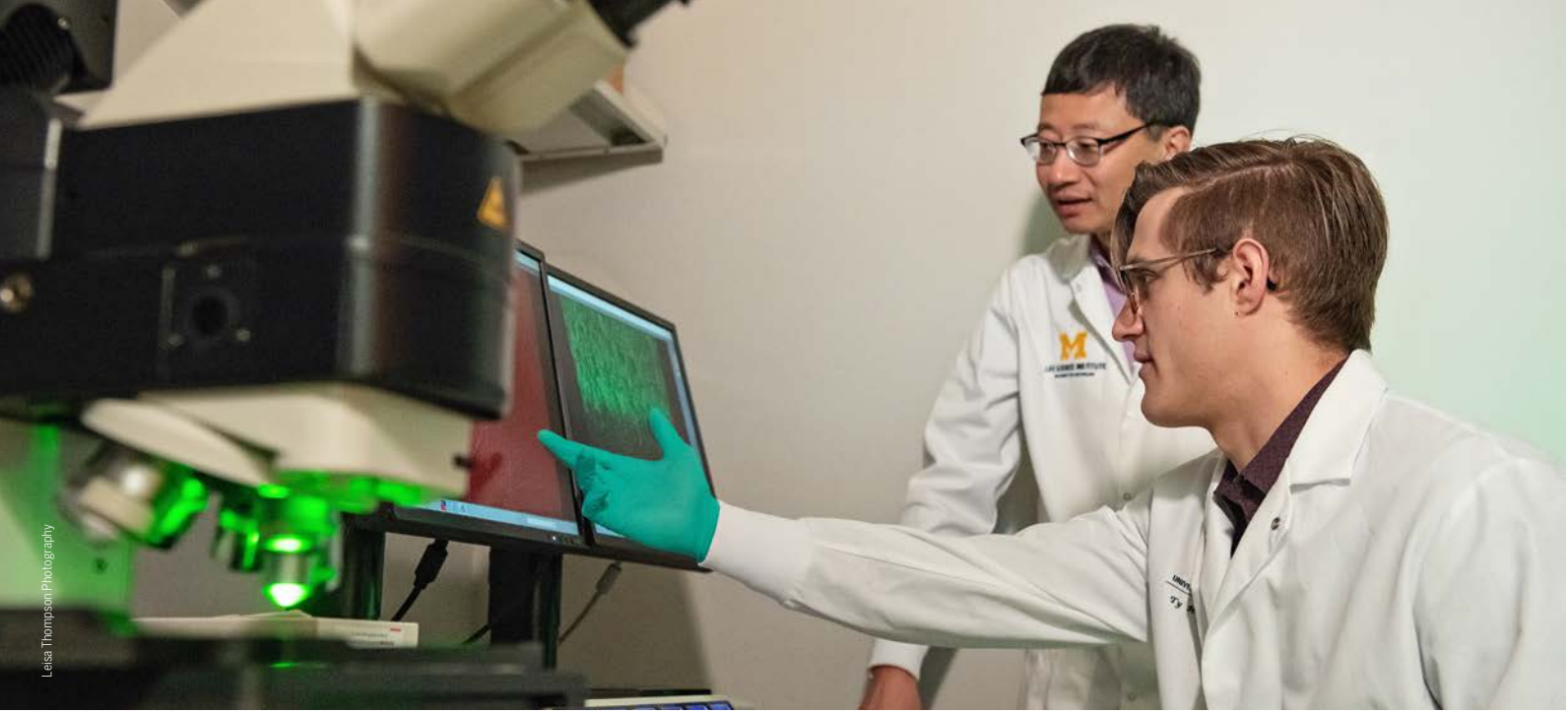
"Even at the time, we were not actually sure how this could be related to Down syndrome," Kim says. "But with an additional copy, such as is found in Down syndrome, there is the opportunity to express more of those gene products. And we had shown that changing the level of this product had a dramatic effect on neurons."

Ye's curiosity was piqued: DSCAM levels are known to be elevated in patients with Down syndrome and other neurological disorders (including autism spectrum disorder, fragile X syndrome and some types of epilepsy). But could DSCAM be contributing to the disorders by causing axon overgrowth?

To answer that question, he needed to enlist a more complex organism.

From correlation to causation

Ye had been a *Drosophila* researcher from his time as a postdoctoral fellow through the establishment and



Leisa Thompson Photography

Bing Ye and Ty Hergenreder, a research technician in the Ye lab, view confocal microscopy data.

growth of his own lab. But the DSCAM findings in flies gave Ye the motivation he needed to approach his question in a mammalian system and the necessary clues about where to start.

"Flies are an excellent model for discovering disease mechanisms, but a fly is not just a tiny human with two wings," he says. "They give us a great starting point. But to translate those mechanisms into information that's more applicable to humans, we need an intermediary step."

In 2015, he began the arduous work of creating a mouse model that could shed light on how DSCAM drives axon overgrowth in mammals, and whether it could be involved in Down syndrome and other neurological conditions.

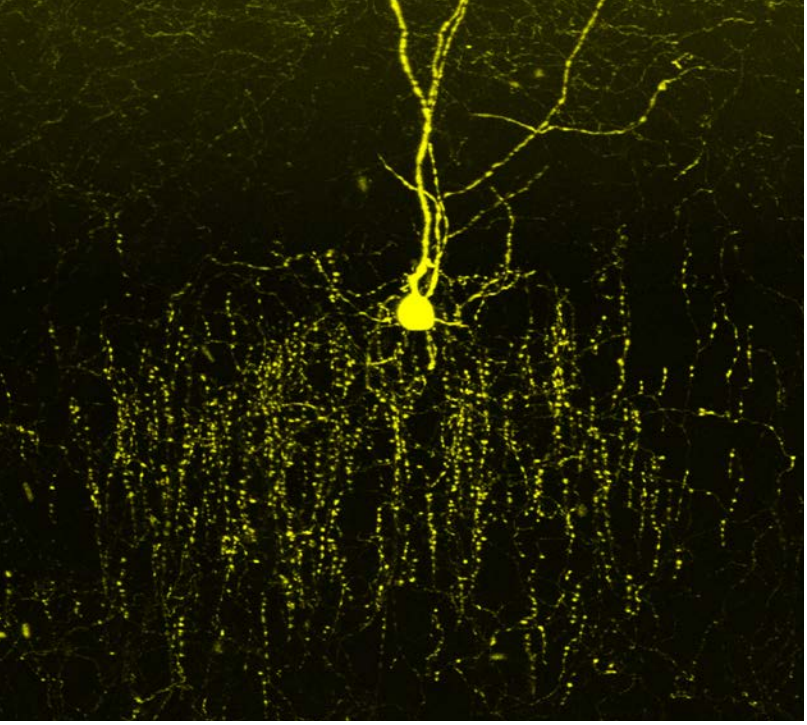
When they analyzed the neurons of mice that had three copies of *DSCAM*, they found the same axonal overgrowth they observed in flies. But they also saw something new that explained how the axons were impairing neuronal function.

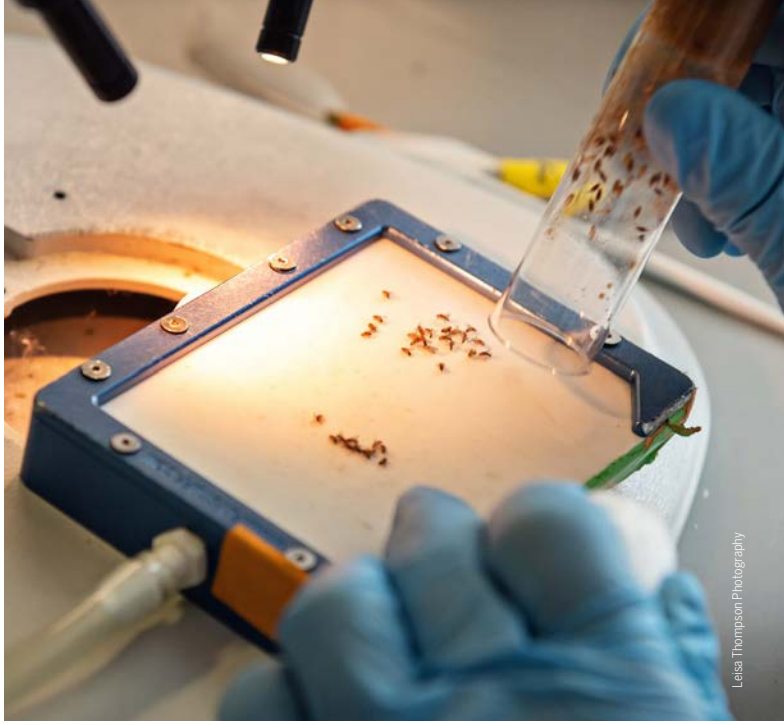
In mice, the overgrowth was taking place specifically on inhibitory neurons in the cerebral cortex — neurons that suppress activity in other neurons.

"When these neurons have increased synapses with another neuron, they actually have a dampening or quieting effect," Ye says. "And we found not only increased axon growth, but also increased synapses with other neurons in the part of the brain that controls things like cognition and behavior."

The team discovered that restoring DSCAM to normal levels reversed this effect. In mice that had only two copies of the *DSCAM* gene, but three copies of the other genes that are equivalent to human chromosome 21 genes, axon growth was normal.

> *Without the clear evidence we already had from* Drosophila, *we wouldn't have known to test DSCAM effects in mice.*





Left: A chandelier neuron with overgrown axons. Right: *Drosophila melanogaster* under the microscope.

This extensive project demonstrates the power of model organisms to provide new insights into human disease, Ye says: A basic science question tested in flies led to the discovery of the underlying genetic cause behind one characteristic of Down syndrome.

"Without the clear evidence we already had from *Drosophila*, we wouldn't have known to test DSCAM effects in mice, and we wouldn't have known to look at the axons. The fly work is what pointed us in the right direction," he says.

It's a model the Ye lab plans to replicate with more Down syndrome-related genes.

A 200-gene puzzle

When scientists know or even suspect which gene leads to a single-gene disease in humans, they can turn to animal models to identify the exact cellular mechanisms that the gene affects to uncover potential targets for treatment.

"But approaches that are useful for studying single-gene diseases are not applicable to Down syndrome," Ye explains. "There are over 200 functional genes on chromosome 21, and there is a long list of medical conditions associated with the syndrome. Our major challenge is figuring out which genes on chromosome 21 cause which medical conditions."

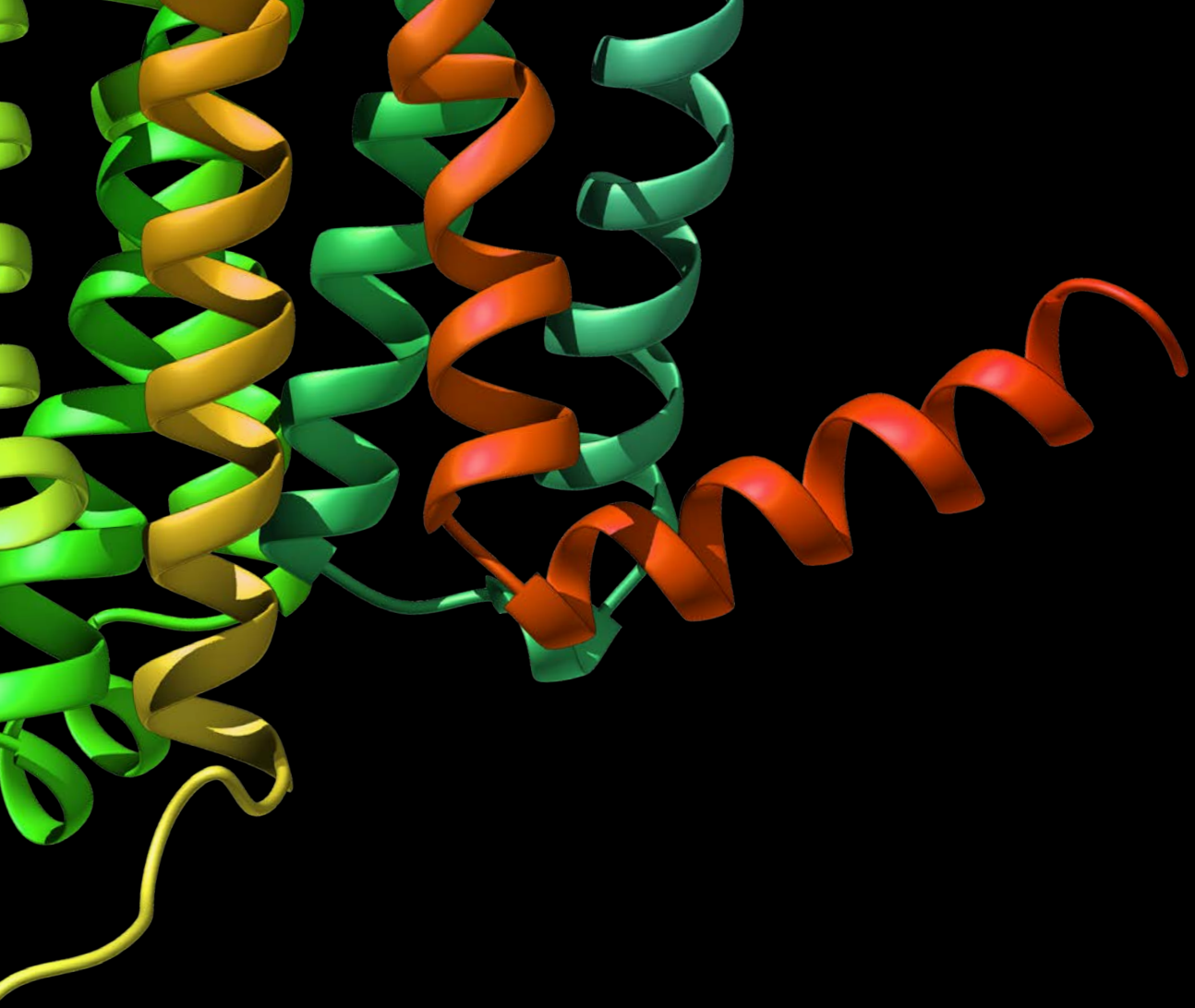
In 2018, while still pursing the DSCAM research in mice, Ye returned to flies to tackle this challenge. With an award from the LSI's Klatskin-Sutker Discovery Fund, he is assembling a legion of genetically modified fruit flies to begin matching individual genes to specific characteristics of Down syndrome. This philanthropic fund was established by a gift from the Klatskin and Sutker families to encourage this type of creative, early-stage research that has potential to have a positive impact on human health.

Our major challenge is figuring out which genes on chromosome 21 cause which medical conditions.

Because fruit flies have a very short life span, multiple generations can be created within a matter of weeks. And their well-mapped genome allows researchers to study the roles of specific genes, which leads to a better understanding of how those genes function in humans.

Starting with 60 genes expressed in the nervous system (Ye's area of expertise), the Ye lab has created 60 different genetic lines of fruit flies — each over-expressing one gene found on chromosome 21. He has already uncovered one gene that interacts with DSCAM to cause changes in *Drosophila* neurons.

Ye hopes this project will point to more potential genetic culprits driving the various symptoms associated with Down syndrome in humans.



COURAGE TO COLLABORATE

What happens when academia and industry team up to tackle anorexia nervosa

By Emily Kagey

"I had a lot of time on my hands, so I started digging into the science."

It was 2018, and Dan Housman had taken a leave of absence from his job as a managing director in Deloitte's health care and life science consulting practice to support his daughter as she underwent in-patient treatment for anorexia nervosa. During all the downtime at the hospital and outpatient facilities, he decided to learn as much as he could about the disease.

Housman was frustrated by the lack of any FDA-approved drugs for a deadly illness affecting so many children like his daughter. With a background in molecular biology, he was determined to figure out whether some genetic glitch could be driving the illness at a cellular level.

"I was convinced, and I continue to be convinced, that you're not going to develop anorexia nervosa without some biological difference driving this extreme condition. And that difference should be something we can address with new medicines, not just psychological treatments," he says.

He pored over scientific papers and researched his family's own genetic history. Eventually, he narrowed in on a potential candidate that could be involved in the disease: a cellular protein called the melanocortin 4 receptor (or MC4R).

"I made a list of everyone who researched MC4R and had found ways to chemically turn it off or on in the lab," Housman recalls. "And, of course, Roger was right up there at the top of the list."

Roger Cone has been studying melanocortin receptors since the early 1990s, when he and his colleagues published the first cloning of the melanocortin receptor genes.

"We found the first two receptors, which were known to regulate pigmentation and adrenal steroid production. When more receptor genes were discovered by my lab and others, nobody even knew what they were," recalls Cone, now the Mary Sue Coleman Director of the University of Michigan Life Sciences Institute. "Then, when I found out MC3R and MC4R were expressed in neurons, I became fascinated with figuring out why these proteins that we thought were involved in pigmentation and hormonal regulation would be so active in the brain."

Research over the past three decades, including many studies led by Cone, has revealed that the melanocortin family plays central roles in metabolism and energy balance. Cone's team helped define how MC4R regulates the body's energy balance by controlling how much energy is stored as fat. When body weight dips too low, MC4R is suppressed to stimulate appetite and restore weight. Mutations in the gene that encodes MC4R lead to early-onset obesity, a genetic condition that affects up to one in 300 people.

This role in energy balance is what grabbed Housman's attention. Multiple members of his family, including two who have anorexia nervosa, carry a genetic abnormality that he thought might be over-activating MC4R. Stimulating this protein can result in lower food intake — one drug already exists to treat a type of syndromic obesity by increasing MC4R's activity. Housman wondered if another drug could be developed to do the opposite: dampen MC4R and stimulate appetite in patients with anorexia nervosa.

"I emailed Roger about the possibility of developing a drug to act against MC4R, and I think the timing was just fortuitous," Housman says. "He wrote back and said he wasn't sure that antagonizing MC4R would work, but he had some very new findings that looked even more promising."

Those findings were related to another melanocortin receptor, MC3R. The Cone lab had cloned MC3R, and even deleted it out of the mouse genome to characterize it, but then largely ignored it for two decades.

"We had defined this protein more than 20 years ago, but we could never really understand what it actually did," Cone says. "It seemed to have all these conflicting effects on body mass and appetite in our animal models. Mutations in the MC3R could cause the animals to gain too much weight in some instances and lose too much weight in others."

Around the time that Housman was reaching out to MC4R researchers, Cone's lab unraveled the mystery: MC3R was responsible for defining how far out of

Leisa Thompson Photography

It's resulted in a lot of really compelling science that I would have been unable to do just in my own lab.

balance the energy state could get before MC4R kicked in to affect appetite.

As a negative regulator of MC4R neurons, MC3R suppresses MC4R to increase appetite and food consumption. Basically, it does naturally what Housman hoped a drug could do.

But that's not all it was doing.

"We also found that it's active in other brain regions, where it's involved in anxiety and fear. Boosting MC3R can boost appetite while also reducing those competing motivational states," Cone explains. "Those results seemed ideal for addressing anorexia nervosa, where there is not only this lack of eating but also anxiety and fear around eating and gaining weight."

"I flew out to Ann Arbor with a couple of advisors, and we met with Roger, and I said, 'Let's do it,'" Housman recalls. "Let's form a company around this and see if we can get a drug to market."

Working with U-M's Innovation Partnerships, which supports university researchers to increase the impact of their work, the team formed Courage Therapeutics.

Nearly two million Americans develop anorexia nervosa at some point in their lifetime. It has the highest mortality rate of any psychiatric illness. While the National Institutes of Health invests about $273 million a year in research on schizophrenia, for example — a psychiatric illness with a similar prevalence to anorexia and half the mortality rate — it spends about 5% as much on anorexia.

Moreover, recent research has found that it is, in fact, not just a psychological condition but also a genetic one. And there is no approved pharmaceutical treatment.

Above: Cone lab members Luis Diaz Gimenez and Savannah Williams are developing compounds to interact with the melanocortin system.

Innovation Partnerships, a unit of the Office of the Vice President for Research, helps connect U-M researchers with the private sector through corporate-sponsored research collaborations, licensing discussions and startup company formation.

In the 2022 fiscal year, Innovation Partnerships supported the creation of:

16
New startups

94
New corporate-sponsored research agreements

278
License agreements

409
U.S. patent applications

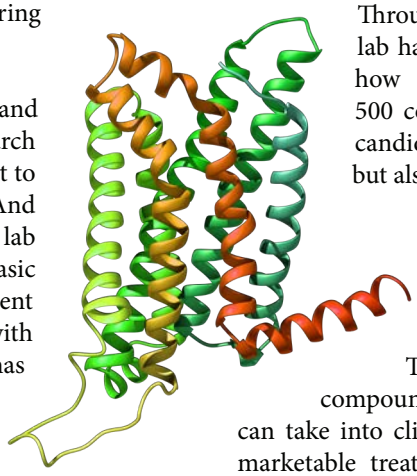
> *These types of partnerships can help connect the research to the application and can ultimately lead to better science.*

"It's an area that really needs more attention," Cone says.

The Courage Therapeutics team hopes to meet this need by merging the expertise and resources available within academia and industry.

As an industry-academia collaboration, the team can explore paths to discovery that would not be open to either group separately. For example, the startup qualifies for Small Business Technology Transfer funding from the NIH. This program supports early-stage small businesses working in partnership with nonprofit research institutions to bring scientific innovations to the market.

Through an agreement between U-M and Courage, the company sponsors research in the Cone lab and then has the right to license the outputs of that research. And with support from Courage, the Cone lab can create tools that advance both basic discovery science and the development of novel compounds that interact with the melanocortin system. Courage has already received three NIH grants that provide support to the Cone laboratory.



"There's a strong crosstalk between the basic science helping to advance drug discovery, and the drugs that are discovered helping to advance our basic science program," Cone says. "It's resulted in a lot of really compelling science that I would have been unable to do just in my own lab."

"It's a great example not just for a startup, but for an active, successful collaboration between industry and academia," adds Stefan Koehler, the director of therapeutics licensing for Innovation Partnerships, who manages U-M's relationship with Courage.

The company also can partner with leading scientists outside the university to bring in expertise that complements the work being done in the Cone lab. That's how Tomi Sawyer became involved in the project.

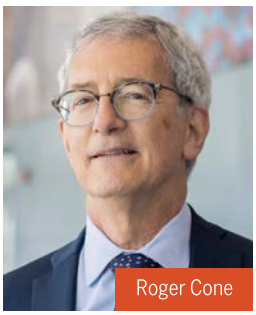
Sawyer specializes in developing peptide drugs — short chains of amino acids designed to trigger reactions that synthetic small molecules can't address and that larger proteins perhaps can't reach. His 40-plus-year career as a peptide drug hunter has spanned pharmaceutical companies such as Parke-Davis, Pfizer and Merck, as well as the biotech industry. He is credited with multiple drugs that have advanced in the clinic and to the market, including one melanocortin peptide.

Through Courage, Sawyer and the Cone lab have been able to combine their know-how to design and test approximately 500 compounds so far to identify the best candidates for treating not only anorexia, but also obesity.

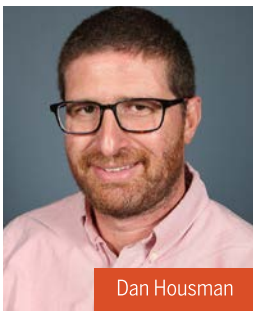
"The partnership between Courage and U-M has really become an engine for drug discovery," Sawyer says.

The group's goal is to develop lead compounds that they or a strategic partner can take into clinical trials, and eventually provide a marketable treatment for patients. Their work with MC4R-focused treatments for obesity has already produced compounds resulting in significant interest from potential industry partners. Work on MC3R has led to the first highly specific drug-like peptide agonist which is currently in the preclinical testing stage for disorders such as anorexia nervosa.

"There is a lot of synergy that can come from this kind of collaboration," adds Housman. "We conduct research to better understand how things work. At some point, that research also could have real-world applications. These types of partnerships can help connect the research to the application and can ultimately lead to better science. We intend to use the science to make a new medicine against a deadly disease that continues to impact my family and so many other people we care about." ◉



Roger Cone



Dan Housman

Above: Structure of the melanocortin 3 receptor, courtesy of Luis Diaz Gimenez.

Cone portrait, Leisa Thompson Photography

CAREER CONNECTOME

LSI trainees are mapping pathways to diverse careers

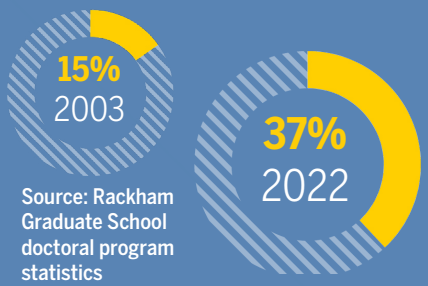
By Fatima Javed

Ivan Misner believes networking is "more about 'farming' than it is about 'hunting.'"

"It's about cultivating relationships," says the founder of Business Network International, one of the largest referral organizations in the world.

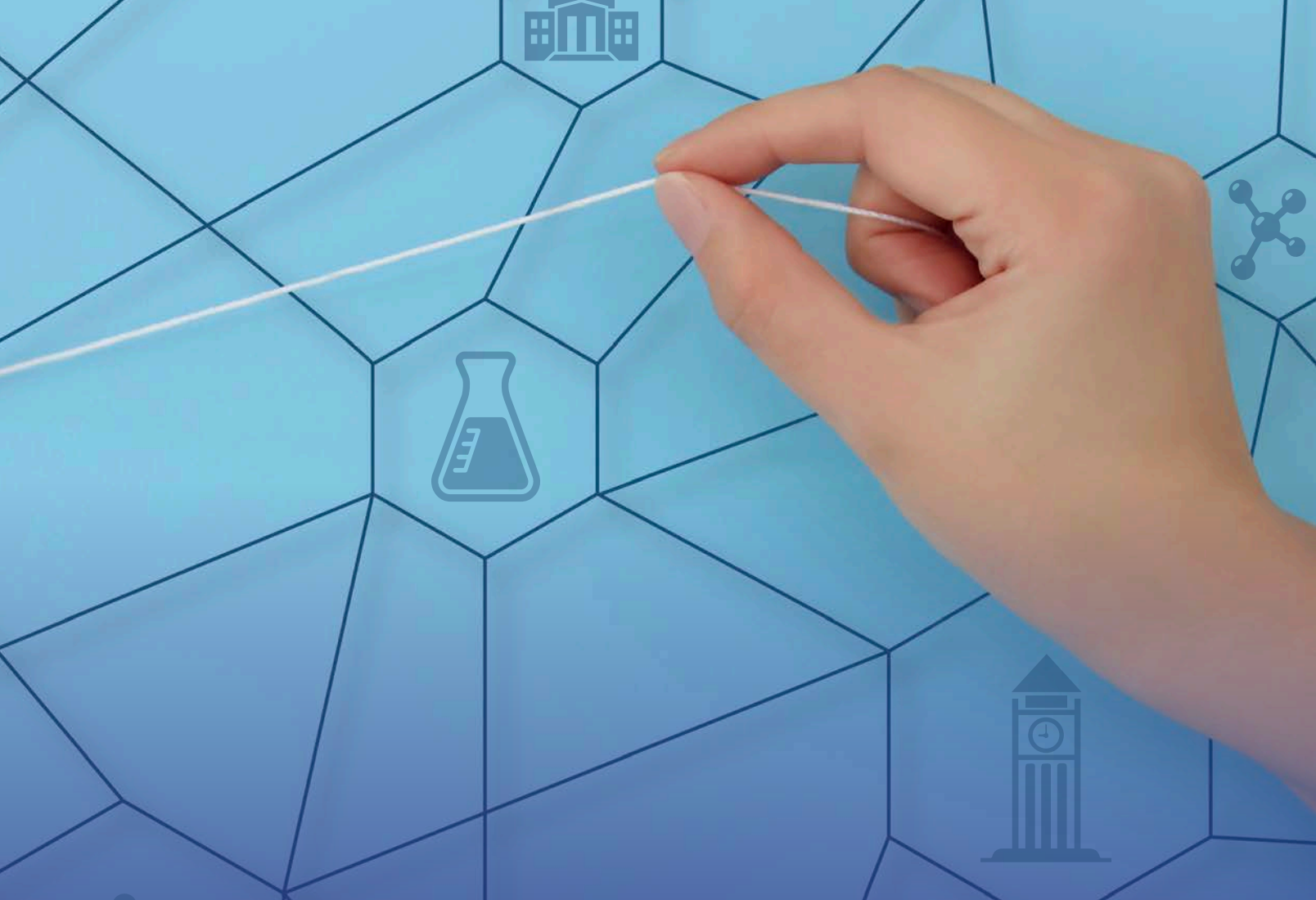
The knowledge and skills that graduate students gain while earning a Ph.D. are transferable to careers in variety of fields: from traditional academic institutions to biotech startups, patent law to science communication. And as more graduates pursue careers outside of academic tracks, the ability to find, foster and "farm" relationships can open opportunities that students may not have even known existed when they entered their graduate programs.

U-M biological and health sciences doctorate recipients entering non-academic professions:



Source: Rackham Graduate School doctoral program statistics

At the U-M Life Sciences Institute, graduate students and postdoctoral researchers are not waiting until they enter the "real world" to sow the seeds for professional networks that can connect them to their futures. Using programs offered at the LSI and U-M — and in some cases, even developing new programs — they are cultivating the connections today that can foster their scientific careers tomorrow.



A consulting call

As a graduate student in Janet Smith's lab at the LSI, Tyler McCullough studies polyketide synthases — enzymes found in bacteria, fungi and plants that can be modified to form the base of antibiotics, anticancer drugs and pesticides.

Although he has been passionate about biochemistry since college, McCullough realized early in his Ph.D. experience that he felt drawn more to the business side of science rather than a career at the bench.

Knowing he did not plan to pursue the academic path, McCullough began his career exploration early, completing a graduate certificate in innovation and entrepreneurship while continuing his Ph.D. studies.

After dabbling in intellectual property and medical science liaison as career options, McCullough became involved with miLEAD as a pro-bono scientific consultant. This nonprofit organization provides U-M graduate students and postdoctoral fellows with practical experience working with the business community.

McCullough's work with miLEAD exposed him to a variety of companies, but he says one project in particular helped him realize: "You know what? I really love doing this."

A client came to McCullough with an antiviral and asked him which virus they should prioritize in medical trials. While working with a medical-focused client to evaluate major viruses and existing therapeutics, Tyler says he found his calling in scientific consulting.

Of course, there was still the matter of transforming this passion into a career.

As he approached the end of his Ph.D. program, McCullough turned to the professional network he had developed as a graduate student to help him bridge the gap between "career interest" and "career." Talking with his vast network of colleagues at miLEAD, as well as members of the LSI's Leadership Council, helped him prepare for and acquire a position as a consultant at Clarion Life Sciences Consulting in Boston.

Knowing first-hand how exposure to new professional opportunities can shape a career, McCullough has also helped create more of these opportunities within the LSI. He worked with the LSI Development team to organize a new series of career talks for graduate students and postdocs. These events facilitate networking between trainees and the biomedical industry leaders, venture capitalists and government officials who advise and support the LSI as members of the Leadership Council.

"I think the LSI, and the university in general, has a really good ecosystem of programs to help people explore career opportunities," McCullough says. "I want to help others benefit from these opportunities as much as I have."

Lab prep

While some LSI trainees, like McCullough, are building their connections to industry, others are capitalizing on U-M resources to bolster their network within academia in preparation for launching their own labs.

Maribel Okiye, a graduate student conducting research in the LSI's Sherman lab and Natural Products Discovery Core, hopes to become a tenure-track professor with a lab that works at the intersection of genomics, transcriptomics and metabolomics.

In addition to the support and connections she is gaining from her mentors, David Sherman and Ashootosh Tripathi, Okiye also participates in the Research University Alliance (RUA). This National Science Foundation-funded partnership among nine universities offers professional development, mentoring and networking opportunities with the goal of increasing diversity in the future professoriate. After participating in an RUA conference in 2021, Okiye stayed on as the RUA student coordinator at U-M.

"I realized that there aren't many students who know about the RUA," she says. "I wanted to help others, specifically at U-M, know about some of the great opportunities that RUA provides."

One of those opportunities is the Research Exchange program that Okiye recently completed. This program allows graduate students and postdoctoral fellows to visit any of the nine participating universities for several weeks to learn a new technique, find mentors, start a new collaboration or learn about potential postdoctoral opportunities.

"I want to help others benefit from these opportunities as much as I have."

While visiting a lab at Harvard University that she was interested in pursuing for a postdoctoral position, Okiye says she gained valuable insight into what she wants from her next career step.

"Prior to that, I really didn't know what to look for in a postdoc," she recalls. "But when I left, I felt I knew what I really need not only from my lab but also from the university itself and the people that I interact with. I need someone that will help me set myself up well to apply for academic positions later."

Like McCullough, Okiye is still fostering more networking opportunities for her peers at the LSI while wrapping up her thesis work. Working with the

Left: Tyler McCullough.

Letsa Thompson Photography

"Anything you explore, you will learn something in the process. Nothing is a waste of time."

Top: Maribel Okiye. Bottom: Shuvasree SenGupta.

LSI's managing director, she is helping to develop a curriculum vitae profile platform for LSI trainees and to facilitate connections between trainees and members of the LSI Scientific Advisory Board, a committee of leading scientists from academia and industry.

Lessons in leadership

In addition to helping students build networks through resources like the Leadership Council and Scientific Advisory Board, the LSI also supports trainees to build connections in their specific scientific fields by participating in scientific conferences and seminars.

Through the donor-funded David and Michelle Kroin Family Scholarship Fund, for example, trainees can receive financial support to cover registration and travel expenses for one conference each year.

Shuvasree SenGupta, a research investigator in Carole Parent's lab at the LSI, found this networking method highly motivating and productive. She became involved in the Society for Leukocyte Biology (SLB) as a graduate student and then co-chaired the Members in Transition and Training Committee section of the SLB. She was involved in screening abstracts as well as recruiting for and organizing the SLB school at the group's annual conference. This daylong session offers historical perspectives of the conference theme and training sessions on various scientific techniques.

Through her conference activities, SenGupta gained experience in taking on a leadership role and building her own network to bring professional development opportunities to the next generation of scientists. But she also learned something valuable about herself: that her interests and leadership skills are much more suited to benchwork than event organization. Even so, she says she found value in the experience, gaining new skills and refining her career goals.

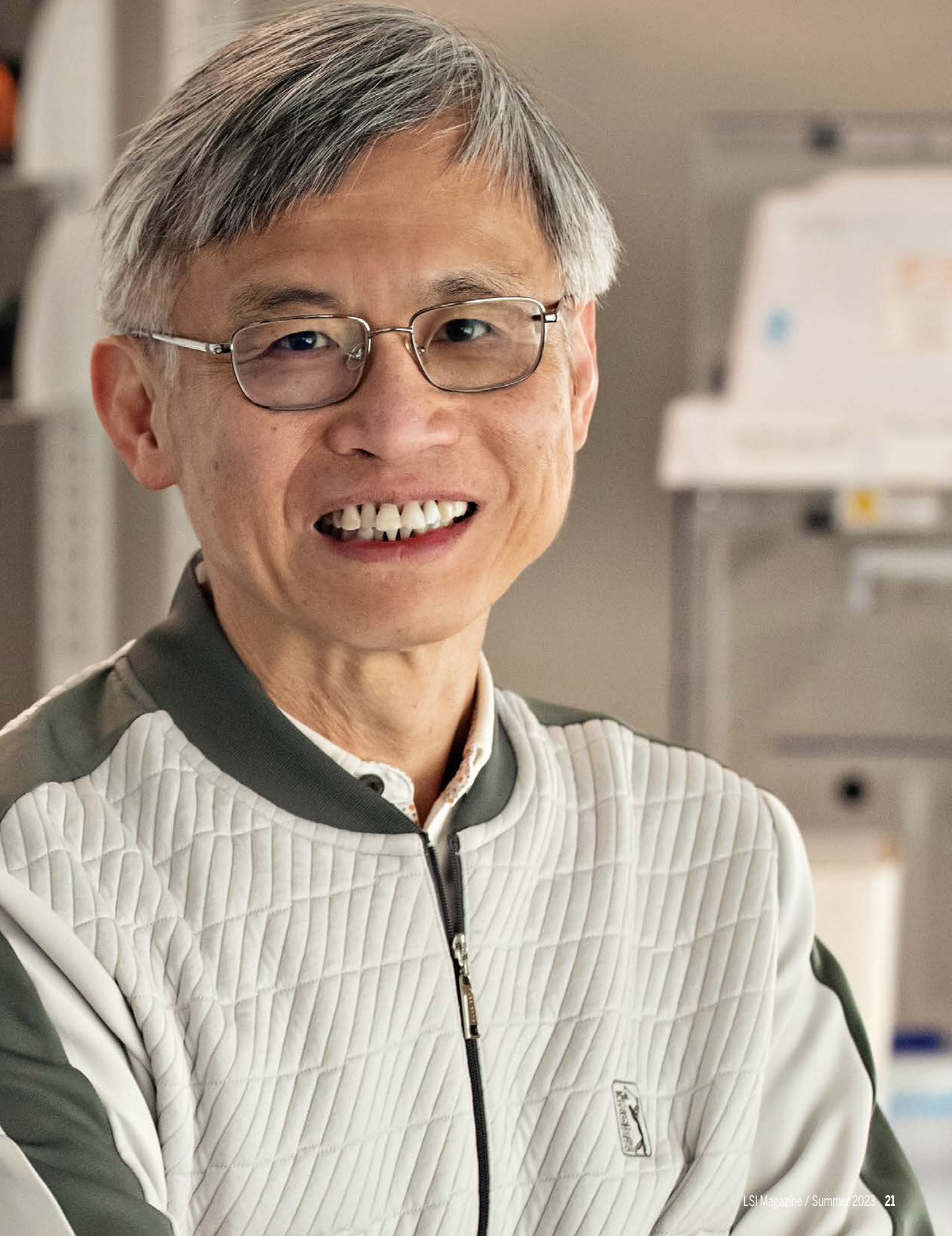
"Anything you explore, you will learn something in the process," she says. "Nothing is a waste of time."

family and Fate of a Neuron

Every cell has a past: ancestors whose genes and adaptations are passed down over many generations to shape the cell's identity, its activity as part of a larger organism, even its ability to survive. Tzumin Lee knows that uncovering this past is essential for understanding not just how the cell came to be, but what more it could become.

Lee explains how his lab at the University of Michigan Life Sciences Institute is developing tools to trace cells' ancestral pasts and predict their progeny — with the goal of revealing the processes that turn a single stem cell into complex tissue and how those processes might be harnessed to regenerate damaged cells and tissues.

Leisa Thompson Photography



Q: How did you get started in this line of investigation, looking at cell lineage and cell fate?

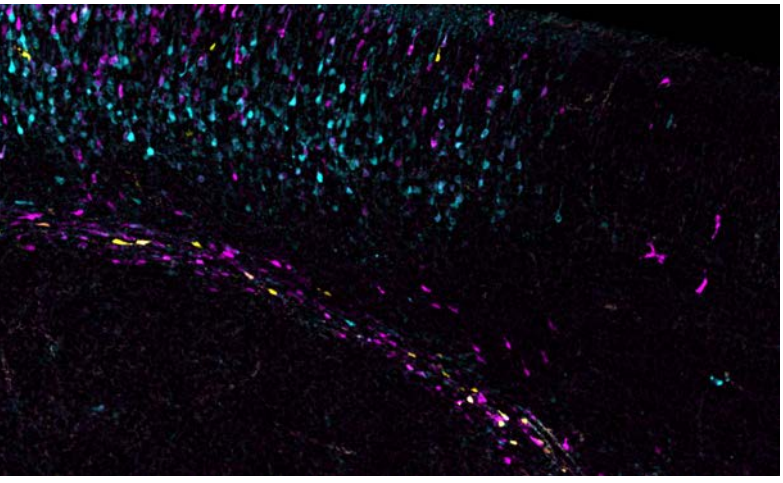
A: I am curious about developmental biology. Initially, I wanted to understand how the genome can encode a complex tissue. Every cell in an organism contains the same genome, the same code, and yet that code results in an enormous variety of cell types. The most complex tissue in the body is the brain, so I started out with the question: How can the genome create a complex organ like the brain?

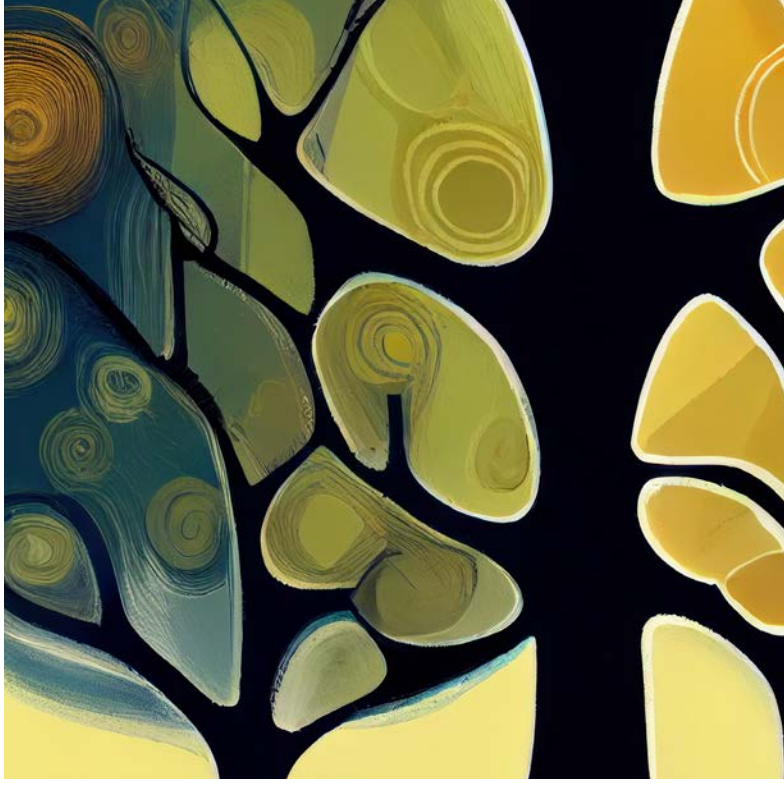
I began to answer this question using *Drosophila* [common fruit flies], because their development is much more trackable. Because the genome is passed on through cell lineage, we started with tracking cell lineage. Through this work, we came to understand a lot about how the fly brain developed, and we started to uncover some of the molecular mechanisms that drive brain development in flies.

But in that process, I also discovered that cell lineage is much more important than I had thought. I realized that without knowing the cell lineage, I wouldn't be able to figure out the detailed mechanisms of development.

Q: When you say you found cell lineage to be more important than you expected, why do you think that is the case?

A: When I started out, even I didn't believe cell lineage controlled everything. I thought it would just set a foundation, and then many subsequent events would refine the cell type. But that turns out to be not true. Cell lineage dictates cell fate. It is the blueprint for the development of an entire organism, including the brain.





In the complex nervous system, every neuron has a unique form and function. It is striking to see how every neuron knows what it should do based on its origin — both the neuronal stem cell it originated from as well as its birth order.

One neuronal stem cell can produce multiple neurons in a long sequence. There are 100 neuronal stem cells in *Drosophila*, for example, and each one divides roughly 80 to 120 times. Every *Drosophila* neuron knows what it should do in the complex brain based on which neuronal stem cell it arose from and then also whether it was the first neuron produced, the second or the hundredth.

Tracking the cell lineage back to its origins allows us to see the cellular processes that enable 100 cells to develop into an entire nervous system. If you don't resolve the lineage of each cell, you won't be able to appreciate such stereotyped patterns of neurogenesis and cannot figure out how one genome creates this vast diversity of cells in complex tissues.

Q: In addition to this backward tracing — finding where each neuron originates — your lab also looks forward to predict what stem cells will become, right?

A: That's right. In flies, we started with the retrospective approach because we had tools that we could use for that. But now, with technologies like single-cell RNA sequencing and CRISPR gene editing, we can also look prospectively, from a stem cell to its progeny. Now we

Visualization of mouse cortical neurogenesis, revealing neurons created at different developmental stages (cyan, magenta, yellow). Image courtesy of Tzumin Lee and Isabel Espinosa-Medina.

> *Cell lineage dictates cell fate. It is the blueprint for the development of an entire organism, including the brain.*

are tracking both retrospectively and prospectively in both flies and vertebrates. Ultimately, we plan to connect the cell lineage information and the developmental trajectory to map the true cell lineage in both directions and reveal the gene dynamics directly. This is particularly crucial for the tracking of many more neuronal lineages in vertebrate brains.

Q: How have technological developments and new tools allowed your research program to tackle cell lineage in both directions?

A: One major development that allowed our approach to evolve is single-cell genomics. We can now sequence the output of the genome at the single-cell level. Every cell in an organism has the same genome, but the genome's output is different across different cells. We can profile those outputs now, which we couldn't do when I started.

That advancement, along with the CRISPR gene-editing technology, has allowed my lab to build more powerful tools for lineage tracing. During my postdoctoral research, I developed a tool that allowed us to discover the functions of genes and trace the lineages of neurons by random clonal labeling. Then, while I was at the HHMI's Janelia Research Campus, we were able to incorporate CRISPR into tools for targeting and labeling specific lineage branches. This allows us to target specific neural progenitors based on multi-gene expression patterns and then track the lineages with the serially derived neurons labeled in distinct colors based on birth order. We can now map neuronal lineages with fine temporal resolution, both prospectively and retrospectively.

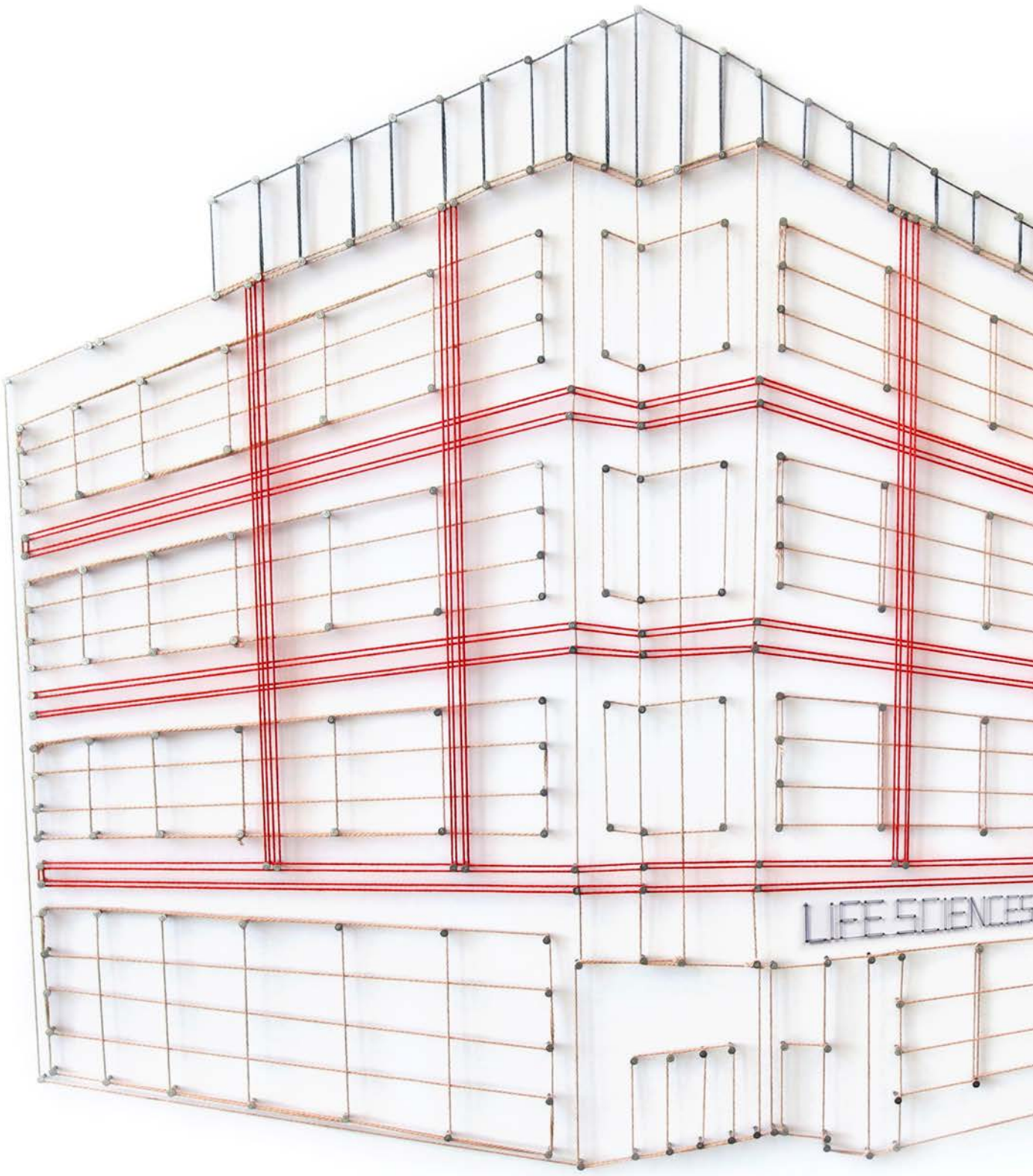
Q: What's next for your lab at the University of Michigan?

A: At the LSI, we're building new facilities to combine cell lineage, single-cell genomics and the CRISPR technology. My vision is to track and tailor genome output along cell lineage to unravel how the genome guides brain development. Comparing this developmental process across species would inform us how to steer brain development. So our research extends from fly to fish and mouse and, finally, hopefully, to a human brain organoid.

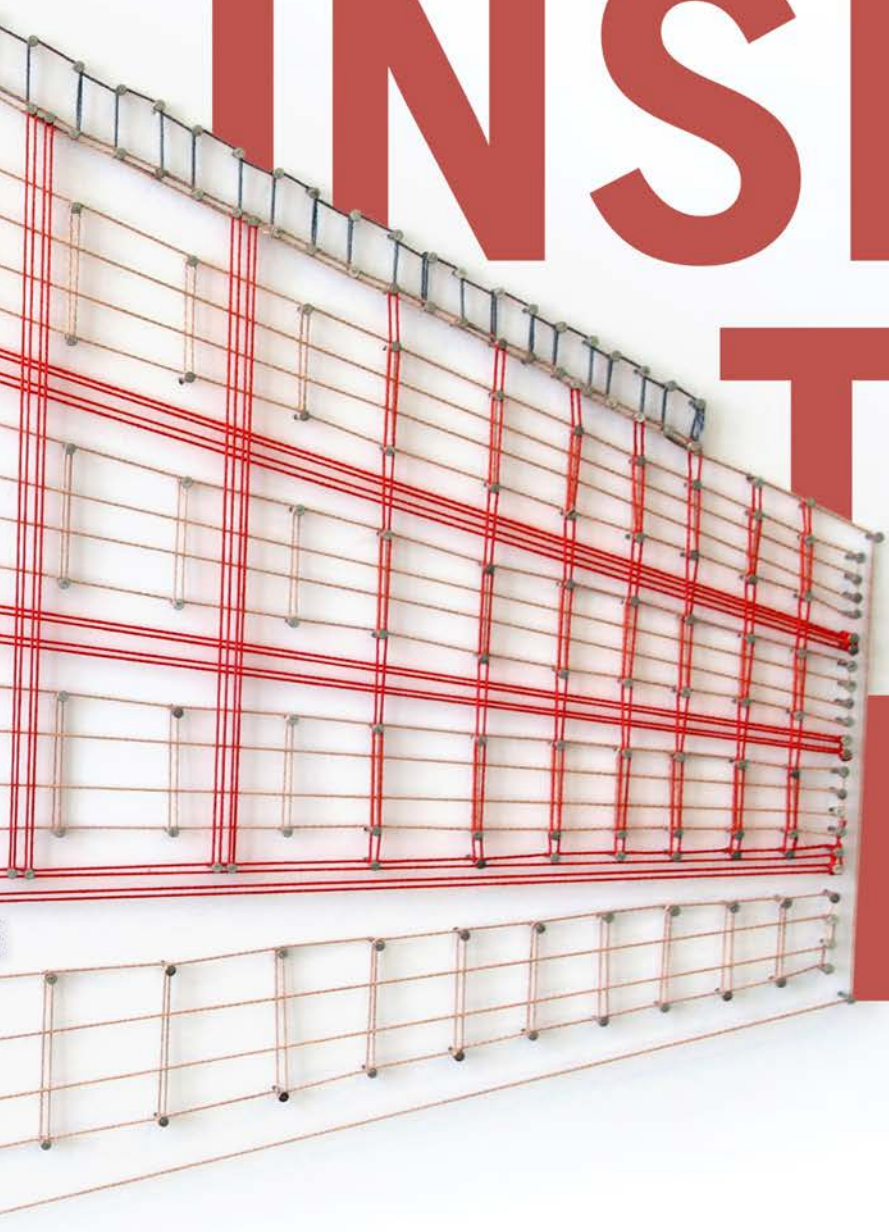
Given that this ambition is far beyond what a single lab can possibly achieve, I'm excited to be at the University of Michigan. With the medical school located so close to the academic campus, and the LSI connecting them, I hope to team up with many labs to push the science forward together. We aim to enable new biomedical research for many to follow. We can then keep working on new things and moving on to the next challenge.

Tzumin Lee is the Peter D. Meister Professor of the Life Sciences; Professor of Molecular, Cellular, and Developmental Biology in the College of Literature, Science, and the Arts; and a Howard Hughes Medical Institute Investigator. Interview by Emily Kagey. Interview has been edited for clarity and length.

Cary Peterson, Adobe Stock


LIFE SCIENCES

INSIDE THE LSI



LSI Faculty

Jay Brito Querido, Ph.D.
Research Assistant Professor

Assistant Professor of Biological Chemistry, **Medical School;** Faculty Scholar, Center for RNA Biomedicine

Research areas: cryo-electron microscopy, mRNA translation, RNA helicases, biochemistry

LSI MED

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

Tools and Model Systems

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

Leisa Thompson Photography

LSI Faculty

Tzumin Lee, M.D., Ph.D.
Research Professor

Peter D. Meister Professor of the Life Sciences; Professor of Molecular, Cellular, and Developmental Biology, **College of Literature, Science, and the Arts**; Howard Hughes Medical Institute Investigator

Research areas: cell lineage, brain development, neural stem cell fate, neural regeneration, single-cell genomics

LSI | LSA | HHMI

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

Jiandie Lin, Ph.D.
Research Professor

Bradley M. Patten Collegiate Professor of 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;** Assistant Professor of Biophysics, **College of Literature, Science, and the Arts**

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

LSI | LSA | MED

Alison Narayan, Ph.D.
Research Associate Professor

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

Research areas: biocatalysis, complex molecule synthesis, natural products

LSI | LSA

Melanie Ohi, Ph.D.
Research Professor

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

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

LSI | MED

Tools and Model Systems

Cryo-EM/ET | *Drosophila* | Mice | Natural products | Yeast | Zebrafish

Leisa Thompson Photography

LSI Faculty

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

Janet L. Smith, Ph.D.

Associate Director
Research Professor

Martha L. Ludwig Distinguished University Professor of Biological Chemistry, **Medical School**; Rita Willis Professor of 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

Chelsey Spriggs, Ph.D.

Research Assistant Professor

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

Research areas: viral-host interactions, oncolytic and oncogenic viruses, cell biology

LSI | MED

Wenjing Wang, Ph.D.

Research Assistant Professor

William R. Roush 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 of 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

Connie Wu, Ph.D.

Research Assistant Professor

Assistant Professor, Biomedical Engineering, **College of Engineering**; Assistant Professor of Pharmaceutical Sciences, **College of Pharmacy**

Research areas: biomolecular engineering, single-molecule detection, RNA therapeutics, clinical diagnostics

LSI | ENG | PHARM

Tools and Model Systems

Cell culture | Mice | Natural products | X-ray crystallography | Yeast

Leisa Thompson Photography

LSI Faculty

Jun Wu, Ph.D.
Research Associate Professor

Jessica Schwartz Collegiate Professor of the Life Sciences; Associate Professor of Molecular and Integrative Physiology and Internal Medicine, **Medical School**

Research areas: "beige" thermogenic fat cells, metabolism, 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.
Research Associate Professor

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

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

Leisa Thompson Photography

Honors & Awards

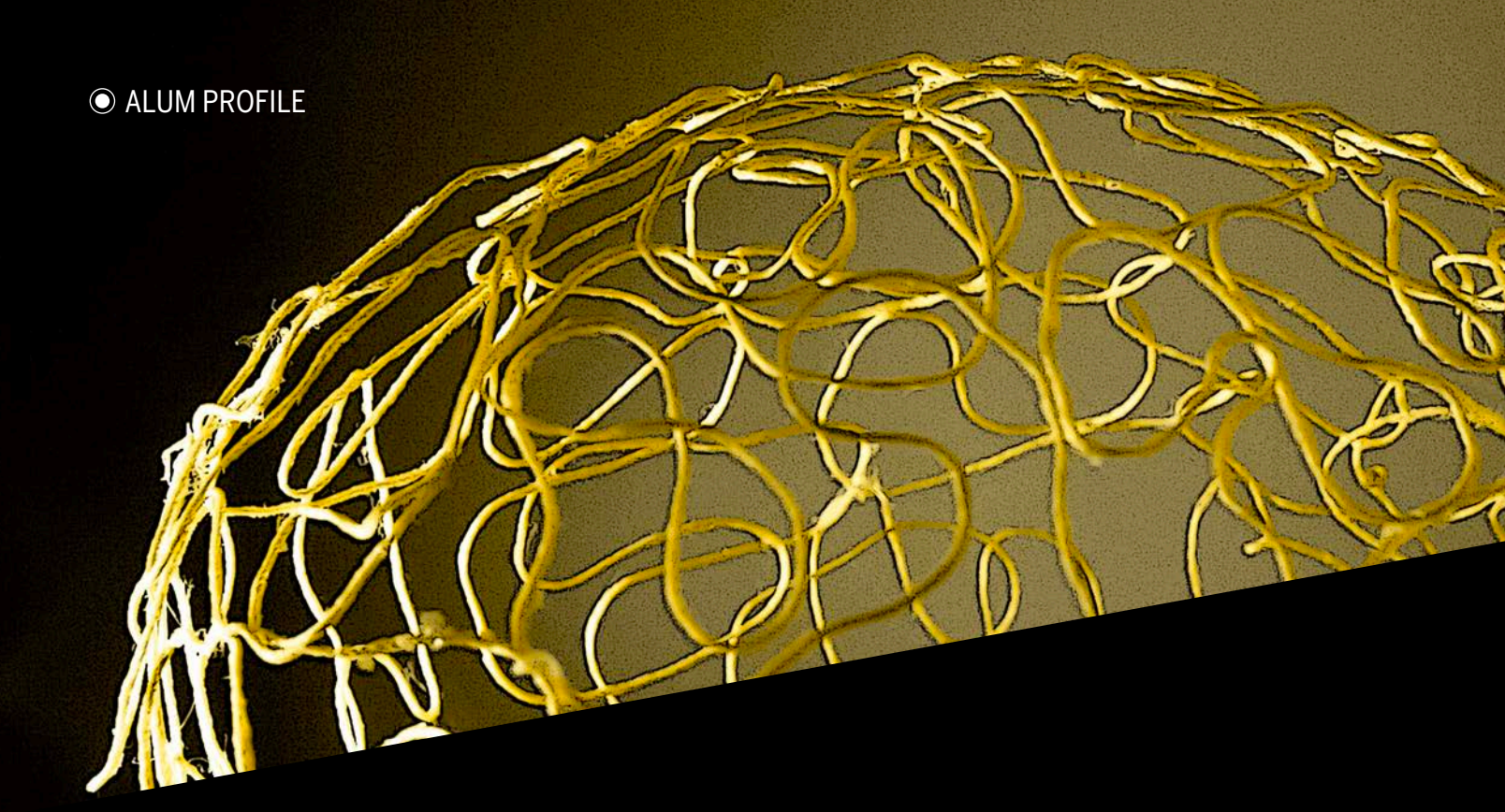
Roger Cone
Received the Rolf Luft Award from the Karolinska Institute

Tzumin Lee
Named the Peter D. Meister Professor of the Life Sciences

Shyamal Mosalaganti
Received the NIH Director's New Innovator Award

Janet Smith
Named the Rita Willis Professor of the Life Sciences

Wenjing Wang
Received the NIH Director's New Innovator Award; Named a Camille Dreyfus Teacher-Scholar



MAKING CONNECTIONS FROM STEM CELLS TO BRAIN DEVELOPMENT

By Staci Vernick

U-M alumna works to understand how bioelectrical activity in neural circuits influences brain development — knowledge that could lead to new treatments for developmental disabilities and cancer

When she was a child, Beverly Piggott (Ph.D., '12) dreamed of being a physician. As she watched her mother, a four-time lymphoma survivor, go through various treatments, Piggott witnessed first-hand how scientific advances — such as the evolution from chemotherapies to immunotherapies — can save lives.

It was as a graduate student at the University of Michigan that Piggott began to connect this passion for physiology with her blossoming interest in neurobiology.

Under the mentorship of Shawn Xu at the U-M Life Sciences Institute, she explored how the nervous system generates behavior by studying the neural circuitry in millimeter-long roundworms called *C. elegans*.

"In Shawn's lab, I came to appreciate the beautiful architecture of the brain and how the nervous system creates brains in a very defined way," recalls Piggott, who is now an assistant professor of neuroscience at the University of Montana. "I became interested in understanding how the brain is built and how electrical activity influences development."

Neurons cause excitable tissue, like muscle, to contract using electrical activity that is regulated by proteins called ion channels. But researchers are also finding that this bioelectricity plays an essential role in non-excitable tissues such as stem cells, the progenitors that differentiate, proliferate and eventually develop into a worm, a sunflower, a human being — or sometimes a brain tumor.

Changing the channel

To better understand how and why these channels work in stem cells, Piggott headed west in 2012 to pursue a postdoctoral fellowship in the lab of pioneering neuroscientist and ion channel expert Yuh-Nung Jan at the University of California, San Francisco. There, she began studying the role of ion channels in the developing brain, both in a normal context and in cancer.

Trading worms for *Drosophila melanogaster* — the common fruit fly — she investigated proteins called voltage-gated sodium channels in neural stem cells. She found that removing or mutating these ion channels stunted normal brain development. Moreover, by manipulating the channels in brain tumor models, she was able to shrink the tumors; it appeared they use these sodium channels to grow.

"Looking at these channels in a developmental context in cancer is important because ion channels are incredibly druggable," Piggott says. "If we can understand what these proteins do in proliferation, potentially we could use different drugs to manipulate their activity. You could potentially have new therapies for developmental disorders, regeneration and cancer."

Flying in Big Sky Country

In 2020, at the height of the COVID-19 pandemic, Piggott accepted a tenure-track faculty position at the University of Montana. She packed up her fruit flies and drove to Big Sky Country to start her own lab.

Assistant Professor Beverly Piggott studies *Drosophila* (top) while mentoring students (bottom) in her lab at the University of Montana.

Being able to continue pursuing research where I can carve out a new idea that could potentially help someone someday, that's a real inspiration to me.

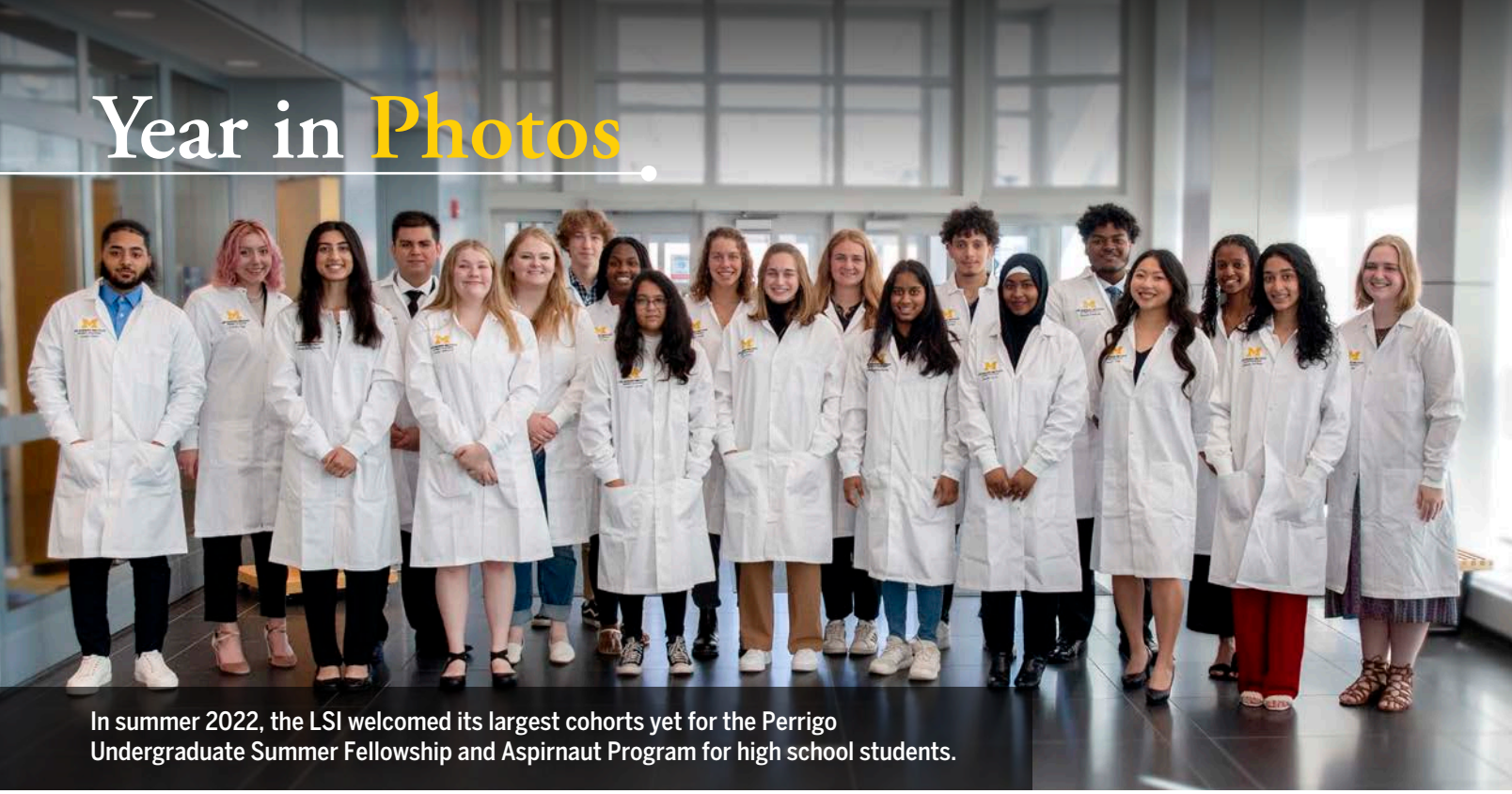
"Beverly is an incredible young scientist with a great trajectory. She sets high goals and works really hard toward them," says Xu, the Bernard W. Agranoff Collegiate Professor in the Life Sciences and professor of molecular and integrative physiology at the U-M Medical School. "She is passionate about science and loves what she has been doing. I still miss the days while she was at the LSI. I am very proud of her."

Following in Xu's footsteps, today Piggott mentors students of her own. The six-member Piggott Lab explores the function of ion channels in normal brain development and in cancer using *Drosophila*.

"I learned how to be a scientist in Shawn's lab. He taught me how to ask interesting, novel questions," Piggott says. "And now, being able to continue pursuing research where I can carve out a new idea that could potentially help someone someday, that's a real inspiration to me because I've seen it in my own life."

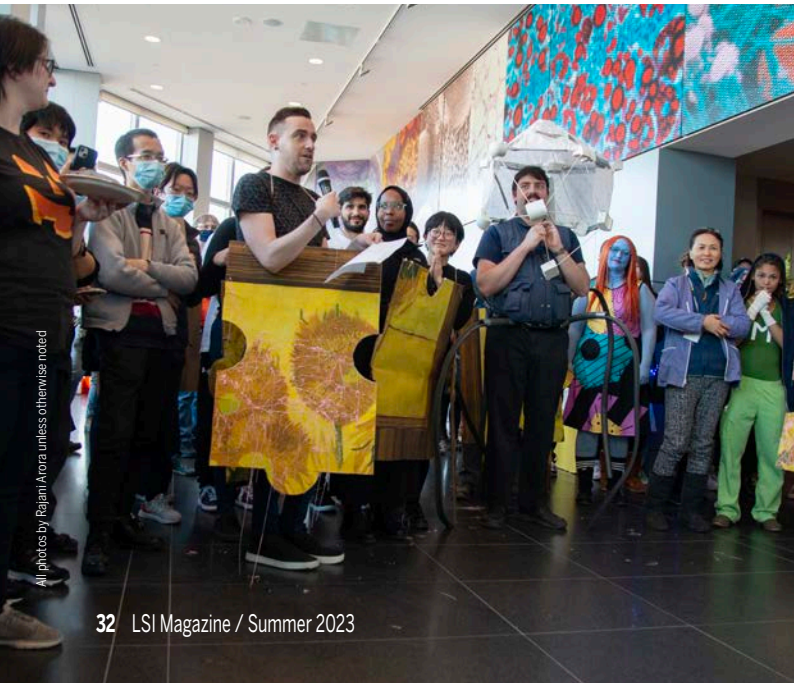
Images courtesy of Beverly Piggott

Year in Photos



In summer 2022, the LSI welcomed its largest cohorts yet for the Perrigo Undergraduate Summer Fellowship and Aspirnaut Program for high school students.

The Center for Structural Biology introduced U-M researchers to its new on-site X-ray crystallography facility.



All photos by Rajani Arora unless otherwise noted

LSI community members enjoyed opportunities to celebrate together at events like the fall welcome back event (above), Lunar New Year Celebration and annual Halloween costume contest and celebration (left).

Liz Neeley and Ed Yong delivered this year's LSI SciComm Series lecture, discussing the art and science of sense-making in a time of crisis.

Eric Bronson, Michigan Photography

Eric Bronson, Michigan Photography

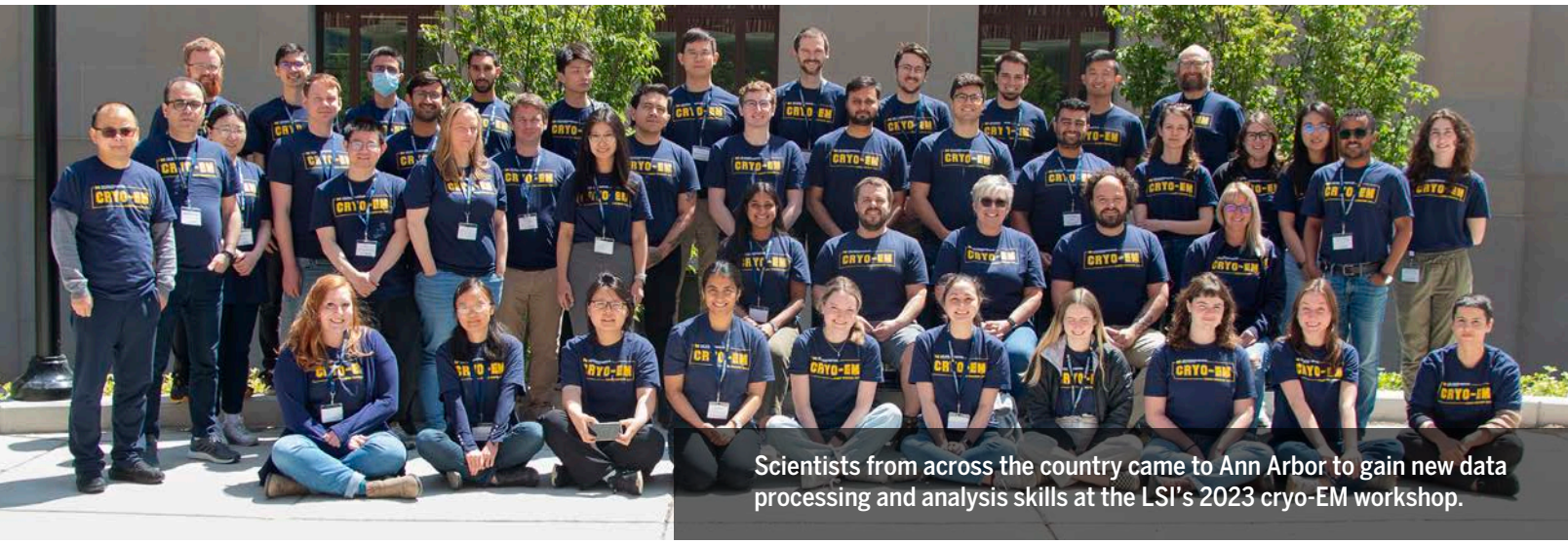
LSI faculty and trainees helped welcome President Santa J. Ono to campus with a tour of Mary Sue Coleman Hall.

Jose Juarez, Michigan Photography

The LSI celebrated the naming of Janet Smith as the Rita Willis Professor of the Life Sciences, representing the first appointment to an endowed professorship at the institute.

The 2023 Saltiel Life Sciences Symposium explored what aging research in a wide variety of model organisms is teaching us about the human aging process and age-related disease.

Graduate students attended science talks, workshops and networking events at the Program in Chemical Biology spring retreat.



Scientists from across the country came to Ann Arbor to gain new data processing and analysis skills at the LSI's 2023 cryo-EM workshop.

Graduates of the Program in Chemical Biology's master's degree program celebrated during Commencement weekend.

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BACK COVER: Large projections form connections between neurons, allowing them to transmit signals to other neurons. Researchers in the Weisman lab are mapping the pathways that transport cellular proteins to these cell-to-cell connections to maintain a functioning neural network. Image courtesy of Pilar Rivero-Rios.

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