MORGRIDGE INSTITUTE FOR RESEARCH • FALL 2024

FEARLESS SCIENCE

REGENERATION RULES: Planaria power new insights in biology

SUPERFLY: *Drosophila* help rewrite the book on diet, fertility and obesity

How to mend a broken heart (through regenerative medicine)

An engineering perspective on reducing preterm birth

FEARLESS SCIENCE MAGAZINE

A publication of the Morgridge Institute for Research in Madison, Wis.

Morgridge is an independent biomedical research organization closely affiliated with the University of Wisconsin–Madison. The institute is structured to help scientists push into new frontiers of biology to advance human health. Learn more at **www.morgridge.org**

EDITOR IN CHIEF

Brian Mattmiller, chief communications and engagement officer

ASSOCIATE EDITORS

Mariel Mohns, science writer and social media manager

Alicia Williams, science editor

DESIGN

Huston Design, Madison

Matt Stefely, graphic designer (Morgridge Institute)

LEAD PHOTOGRAPHY

David Nevala Photography, Madison

CONTRIBUTORS

Dennis Chaptman, freelance writer, Chaptman Connect

Lydia Larsen, freelance science writer

Steven Gottlieb, consultant, Gottlieb Group Communications

Karen Lowry Miller, writer, Gottlieb Group Communications

Michael Penn, freelance writer and director of communications, Global Health Institute, Duke University

Cassandra Willyard, freelance science writer and current president, National Association of Science Writers

ABOUT THE COVER

Morgridge Research Fellow Melanie Issigonis examines a dish filled with dozens of adult planaria, a flatworm capable of completely regenerating itself from the tiniest body fragment.

Planaria are a powerhouse model for studying regenerative biology — and at Morgridge, they may point to a way to prevent a global health scourge.

Curiosity + Courage = Fearless Science

Welcome to the inaugural publication of Fearless Science.

At the Morgridge Institute, we believe in fearless science. This means we follow interesting and important questions, wherever they may lead. Some may call this risky; we say it's what scientists are supposed to do.

Curiosity drives us. In fact, it is the ultimate engine that drives science.

The important advances come about because somebody wants to know how something works — and is allowed to do so. **Keith Yamamoto**, past president of the American Association for the Advancement of Science, recently spoke at Morgridge and noted that 95% of drugs approved by the FDA from 2010 to 2015 were discovered through curiosity-driven research.

This requires patience. The median time from first discovery to approval of the treatments cited by Yamamoto was 32 years. But the payoff is tremendous. Since 1975, for example, the mortality rate from heart disease has improved by 60% or 1 million lives saved per year.

Curiosity-driven science is by its nature unpredictable. There is a tendency to try and increase efficiency by asking scientists to identify intermediate goals in their research. But we are trying to discover what isn't known. How can we get from point A to point B more efficiently if we don't know what point B is?

This is why our first issue of the magazine explores some of the fascinating curiosity-driven questions being explored at the Morgridge Institute. We profile the work of **Phil Newmark**, **Daniela Drummond-Barbosa** and **Kenneth Poss** and the fundamental questions of regenerative biology they seek to answer.

We also invite guest scientists who exhibit this philosophy in their careers to share their curiosity-driven approach to basic research.

Eric Wright of the University of Pittsburgh studies bacteria to understand why some antibiotics can avoid resistance. **Celina Juliano** of UC Davis studies hydras to understand how to harness stem cells. And **David Mangelsdorf** of UT Southwestern studies nuclear receptors to understand how to counter diseases such as alcoholism.

> **"Some may call this risky; we say it's what scientists are supposed to do."**
>
> BRAD SCHWARTZ

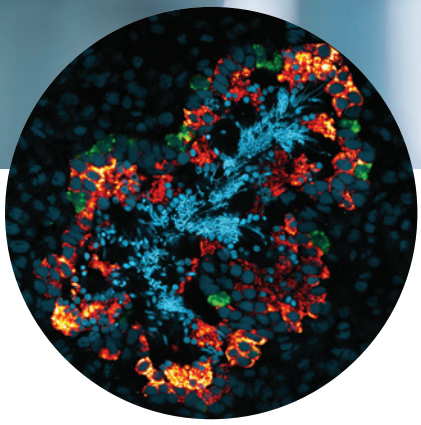
Curiosity-driven research also requires courage. We recognize the challenge when there is so much pressure to measure accomplishments with shorter-term metrics such as grant dollars attained and papers published.

We are charting our own path. People expect us to focus on discovering truths, and we are determined to live up to this. And we have the courage to do this, because we know that's what society wants.

We hope you enjoy this deeper look into curiosity-driven science at Morgridge.

BRAD SCHWARTZ, CEO

FEARLESS SCIENCE



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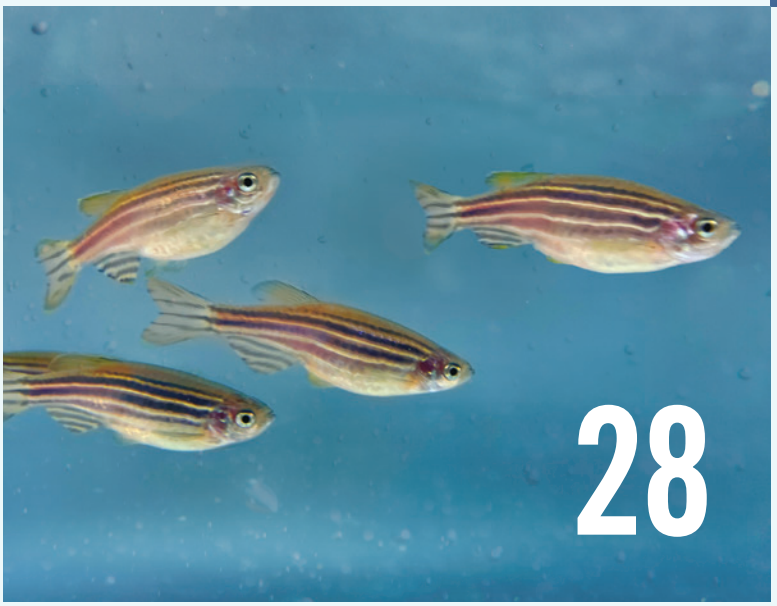


Little fish, big splash

Kenneth Poss, Morgridge’s newest investigator, studies how zebrafish can restore what is irreparable in humans — including damaged heart tissue

LIZ HAYNES

Big questions on the brain

Liz Haynes grew up near a national forest, which sparked her interest in science and the natural world. She would catch anoles, lizards with the ability to jettison their tails and then regrow them, which sparked questions about development and regeneration — the basis of her research today.

"All kids are basically little scientists asking endless questions about their world, and I just never grew out of it."

At this point in her career, that big question centers around microglia in the brain — long-lived immune cells that can be decades old. Microglia become dysfunctional as they age, and may play a key role in Alzheimer's disease and dementia. Better understanding of the pathways involved in this process can lead to new ways to predict and prevent cognitive decline.

A former postdoctoral researcher in the Morgridge Fab Lab, Haynes is now establishing her own lab in the department of Cell and Regenerative Biology at the UW–Madison School of Medicine and Public Health. She credits great scientific mentors as pillars of support throughout her journey — something she hopes to pay forward to the students she mentors.

ANDRÉS TIBABUZO

How to paralyze a parasitic worm

While most people fear snakes and their venomous bite, Andrés Tibabuzo has always looked at them with wonder. Could something that causes so much harm be used instead to do something beneficial? This is the question that led him toward an early interest in biochemistry.

The overarching theme that drives Tibabuzo is that idea to translate research at the bench into something that can be used in a real-world context.

"I see my career as a way to collect more tools in my toolbox to be able to tackle any kind of question."

As a Morgridge Postdoctoral Fellow in the Newmark Lab, he studies the flatworm *Schistosoma mansoni*, a parasite that causes schistosomiasis, a major and neglected tropical disease. Tibabuzo is using his learned lab techniques in biochemistry and molecular biology to study a paralyzing compound that prevents the parasite from infecting a mammalian host.

This compound is produced by rotifers, microscopic organisms that live on the shells of snails that act as an intermediate host in the schistosome life cycle. While the rotifers produce this compound that is harmful to the schistosome, ultimately it could be useful for developing a drug or treatment to prevent the parasitic worm from causing disease in humans.

GINA GALLEGO-LOPEZ

Linking parasites to cancer through advanced imaging

A native of Colombia, Gina Gallego-Lopez grew up in an area where tropical diseases are prevalent. Her mother was a lab technician, and she would visit the lab where bacteriologists would show her microorganisms under the microscope. That early curiosity evolved into a research career.

As an assistant scientist in the Skala Lab, Gallego-Lopez uses optical metabolic imaging and molecular biology methods to study the metabolism of parasites such as *Toxoplasma* and *Cryptosporidium*.

While these parasitic infections pose little harm to healthy individuals, they can result in severe consequences for immunocompromised people.

Her research is centered on the way these parasites infect host cells and fundamentally change the host cell metabolism. This work may also offer clues as to why immunocompromised people are more susceptible to disease.

She is particularly interested in how some Cryptosporidium infections are an associated risk factor for colorectal cancer, but this link is still poorly understood.

"I want to understand how it's possible that these parasites can induce metabolic changes in the host to be able to induce cancer with time."

Optical metabolic imaging is just one new tool that Gallego-Lopez has adopted to pursue her goal of landing an academic position to start her own lab. She is eagerly learning new methodologies like gene expression analysis to help identify genetic targets involved in these metabolic pathways. Ultimately, these data could inform better drug development and treatment.

KIM HUGGLER

Creative solutions in cell culture

Cells grown in cell culture thrive in media enriched with the right combination of nutrients and metabolites. Kim Huggler thrives in a scientific environment powered by creativity and collaboration.

As a graduate research assistant in the Cantor Lab, Huggler studies how environmental factors affect cancer metabolism.

Many cell culture models use culture media that don't reflect conditions in the human body. Cantor and his team designed a cell culture medium that closely models average human plasma.

Huggler hopes their work can reveal new or unforeseen aspects of biology to improve the development of cancer treatments.

While scientists are armed with technology and tools, Huggler notes that those machines and techniques have limitations. She believes that creation and innovation are the fuel of scientific discovery, and that they should always be pushing existing technology in new ways.

"The questions people are asking in science aren't easy. If they were easy, they'd be answered. Hard questions mean that you have to come up with creative solutions."

Huggler hopes to use her experience and doctorate to pursue a career in clinical chemistry — using the techniques she's learned to analyze patient samples and assist in the diagnosis of disease to make an impact on patient care.

KAYVAN SAMIMI

Building better imaging tools to prevent preterm birth

Kayvan Samimi describes himself as an electrical engineer by training and a scientist by accident. As an assistant scientist in the Skala lab, he uses his penchant for tinkering and building to develop new scientific tools and methods in biomedical imaging.

"I never stopped tinkering. In fact, I have made a career of it."

During his time as a Morgridge Postdoctoral Fellow, he used his education in medical physics to pivot from ultrasound-based imaging to optical techniques for cellular imaging. He embarked on a multi-year project to investigate biomechanical risk factors of preterm birth.

Fetal membranes are too thin to be clearly detected by ultrasound, so Samimi developed an imaging method using optical coherence tomography to observe fetal membrane tissues and analyze structural integrity.

This generated a robust dataset that is now used to develop and improve new tools and methods through collaboration with partnering hospitals. The ultimate goal is to combine this data with other related pregnancy studies to develop an early warning system that doctors can use to assess preterm birth risk.

Samimi continues tinkering and tool-building to scale down the lasers and optical instruments used in real-time fluorescence imaging. The result is an accessible, low-cost yet high-performing instrument comparable to larger, more expensive microscopes. The goal is to democratize fluorescence imaging technology.

KATHERINE OVERMYER

Serving up cutting-edge multiomics

Katherine Overmyer recognizes the power of scientific mentorship and the passing of knowledge to strengthen the scientific community.

As the associate director of the Lab for Biomolecular Mass Spectrometry in the Joshua Coon Lab, she manages students in the lab and oversees collaborations with other scientists at institutions outside the lab.

These collaborative projects are diverse and come with unique challenges, but Overmyer enjoys the challenge of finding the right strategy to tackle different problems. The Coon Lab uses metabolomics and proteomics to understand the interplay between metabolites and proteins.

Overmyer specializes in mass spectrometry methods and data analysis, and hopes to see science move toward a more integrated approach to viewing multiple levels of biology under different contexts — called a multiomic approach.

"We're pushing the cutting edge of what's possible, and that's really where we want to be."

One challenging but rewarding project came during the early months of the COVID-19 pandemic, where collaborators studied plasma biomolecules in samples from COVID-19 patients. Another project utilized a sophisticated analysis pipeline that opens the door to using the oral microbiome as an indicator of other health issues.

Overmyer says the lab is always seeking new collaborative projects that push the boundaries of its technology, improve its methods and unlock important new findings. The ultimate reward in her eyes is being part of those bigger efforts to improve human health.

AMANI GILLETTE

From engineering to entrepreneurship

When Amani Gillette landed an apprenticeship in a medical microbiology lab in high school, it opened her eyes to what science looks like outside the context of a classroom. The act of not knowing — and asking why — permeated all of the work in the lab.

"Being a scientist isn't just about being smart, it's more important to be curious and stubborn in the search for answers."

Her curiosity led her to the field of biomedical engineering. As a postdoctoral researcher in the Skala Lab, Gillette uses fluorescence lifetime imaging to learn more about cancer growth and treatment.

Her work has culminated in her greatest experiment yet: entrepreneurship.

Gillette founded SeLight, LLC where she is working to commercialize a label-free microscope system that could revolutionize cell manufacturing. The device can sort and screen T cell samples in real time to predict which cells are most fit for CAR T cell therapy, a promising cancer treatment.

Gillette envisions a low-cost, user-friendly system that can be implemented in all hospitals. Her dream outcome is that SeLight would be used to help identify which patients are most likely to benefit from cellular therapies.

The business world operates very differently from that of science, but Gillette jumped into it with the curiosity of a scientist and determination to find answers. The big question that drives her: How can we help people with this work?

PETER DUCOS

Targeting molecular machines with cryo-EM

Peter Ducos made a military career of viewing the world from high above the earth, and a research career of examining the tiny particles of life up close.

Fascinated with how small molecular machines could cause dramatic effects in the human body, Ducos specifically sought out graduate programs that employed cryo-electron microscopy (cryo-EM) — a groundbreaking technique that reveals the exquisite detail of biological molecules at a near-atomic resolution.

He landed in the Tim Grant Lab, where he collaborates with different researchers across campus trying to answer complex and varied biological questions.

When he served as a U.S. Army soldier and instructor pilot of remotely-operated aircraft, Ducos operated a control panel not so different from the one he uses to control the technology involved in single-particle cryo-EM.

Ducos regularly leans on his military experiences to work with others in a mission-oriented way — sharing expertise and support for each other to produce solutions to big problems.

"I would like to push the limits of cryo-EM to answer questions we cannot currently ask."

‘Listen to what the flies tell us’

BY LYDIA LARSEN

Drosophila have something to say about climate, diet and survival

Lining a wall in the Daniela Drummond-Barbosa Lab sits a row of unassuming, windowless incubators — the homes of vials and vials of fruit flies, all kept at a specific temperature and humidity. Some are genetically modified, some are on special diets, some are destined for dissection under a microscope.

Within these flies as well as every animal, small populations of stem cells help maintain the numerous tissues that all connect to make up a complete organism. For these stem cells to function correctly, they need to respond to the changes in diet, metabolism and physiology that affect the whole body.

Odette Herrand, research specialist in the Drummond-Barbosa Lab, studies how a yeast diet impacts fly fertility.

“People ask, ‘How’s that going to cure this or that? But they forget that everything comes down to some basic knowledge that somebody got just by being curious about how things work.”

DANIELA DRUMMOND-BARBOSA —
MORGRIDGE INVESTIGATOR AND PROFESSOR
AT THE UW–MADISON DEPARTMENT OF GENETICS

To understand this complex process, Drummond-Barbosa — Morgridge investigator and professor at the UW–Madison Department of Genetics — finds that fruit flies are a great place to start. *Drosophila melanogaster* is a powerful model system that Drummond-Barbosa uses to answer big questions about the how environmental factors affect the production of reproductive cells, processes known as oogenesis in females and spermatogenesis in males.

With a focus on fundamental research, the Drummond-Barbosa Lab adopts a curiosity-driven approach to its work. By asking interesting questions about fundamental biology, Drummond-Barbosa can advance understanding of these systems. Down the road, other scientists could rely on that past discovery or approach to solve an important problem.

Drummond-Barbosa believes that all researchers benefit from understanding the history of science, where basic research regularly served as the foundation for a transformative application. The CRISPR/Cas9 genome editing method that has revolutionized genetic research, for example, stemmed from fundamental discoveries about repetitive sequences in *E. coli* DNA made in the late 1980s.

Graduate student Emily Wessel says the curiosity-driven approach drew her to the Drummond-Barbosa Lab. Her project investigates the steps of stem cell lineage differentiation in *Drosophila* and the role of sugars and fats in that process.

“If we get a cool result that maybe doesn’t match our hypothesis, we get excited and follow it,” Wessel says. “We listen to what the flies tell us. If it wasn’t what we were thinking, we’re not bummed. It’s interesting.”

Making an impact requires both basic and applied science. Drummond-Barbosa sees a movement toward universities and funding agencies placing more emphasis on applied science. If that trend continues, she fears paradigm-shifting findings may dwindle.

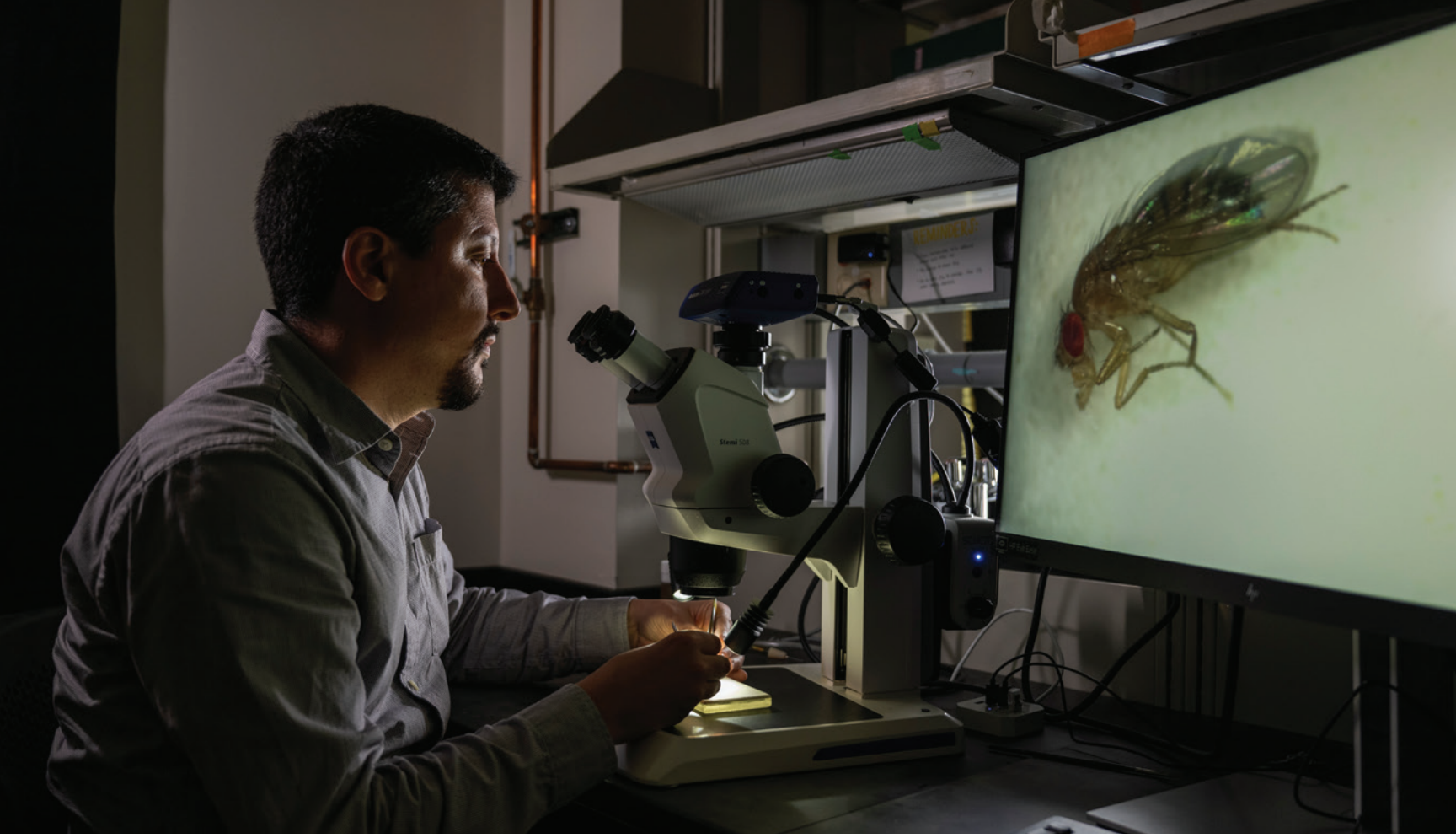
“People ask, ‘How’s that going to cure this or that?’” Drummond-Barbosa says. “But they forget that everything comes down to some basic knowledge that somebody got just by being curious about how things work.”

When Drummond-Barbosa moved her lab from Johns Hopkins University to UW–Madison in 2022, they discovered a haven in the Morgridge Institute. Ana Caroline Gandara, an assistant scientist in the lab, finds that here she shares a common language with other researchers, making collaborations easier.

“I think the Morgridge Institute is a really rare example where the leadership really believes in fundamental science,” Drummond-Barbosa says.

Sugar, Obesity and Fertility

Drummond-Barbosa fell in love with *Drosophila* in graduate school. Her doctoral work was in a virology lab, but she was exposed to cutting-edge developmental biology research using *Drosophila*



Rodrigo Dutra Nunes says Drosophila research can take scientists in a multitude of directions. "We are not shy of the hard pathways."

as a model system. Coming from Brazil, she struggled to understand the professors during lectures and spent a lot of time puzzling over new papers.

"That was really great because I had to read so much that it started really clicking," Drummond-Barbosa says. "I was amazed at the power of a mutagenesis screen . . . and figuring out how the mutants fell into a certain pattern."

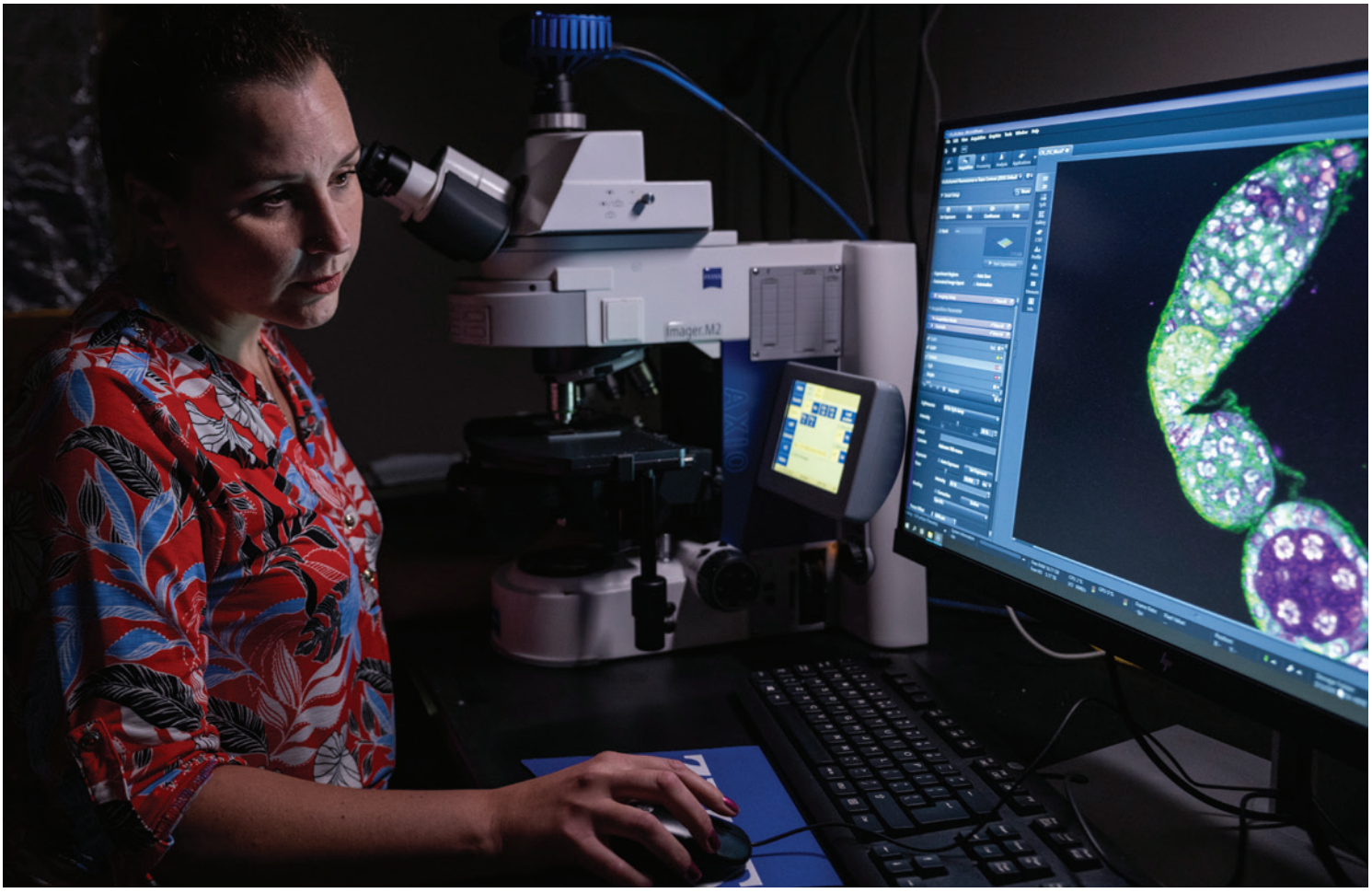
Using *Drosophila* as a model system allows researchers to tease apart different variables that would be difficult with other organisms. Researchers know that a high-sugar diet leads to obesity in humans and mice, for example, which can then lead to fertility issues. But Rodrigo Dutra Nunes, a scientist in the lab, uses *Drosophila* to better understand the precise relationship between obesity, diet and infertility.f"[With *Drosophila*], there are so many tools and there's so much you can do with the short generation time," Drummond-Barbosa said. "You're not restricted by how many flies you can analyze so the power of your analysis and your confidence in your results is really huge."

Previous work in the lab established a connection between the fat cells and oogenesis. So initially, Dutra Nunes thought they were embarking on a relatively simple paper regarding the effects of obesity on fertility in female flies. They started by feeding the flies either a normal diet or a high-sugar diet, which caused obesity and reduced fertility. But then they introduced another group of flies and knocked down two different anti-obesity genes in their fat cells. These flies became just as fat as those with the high-sugar diet — but their fertility remained normal. Surprisingly, obesity alone wasn't causing the fertility issues in the flies.

What started as a quick paper became a much more intensive, but also more interesting project.

"My creativity can drive me, and I think that's great," Dutra Nunes says. "We are not shy of the hard pathways. We went down that path, and it took much longer than we expected to show the whole story and use multiple methods to show obesity is not affecting fertility."

In the flies fed a high-sugar diet, Dutra Nunes identified two stages of oogenesis where there were higher rates of death in the developing germ cells as well as low hatching rates. Interestingly, when given extra water, those flies remain obese, but their glucose levels decreased and their fertility issues were largely resolved. Taken together, the results indicate that in obese flies insulin signaling is above the required threshold for oogenesis to occur properly.



▲ Ana Caroline Gandara investigates how climate change could pose existential threats to cold-blooded species like *Drosophila*.

"Instead of just showing that obesity is not a factor in infertility and moving to another project, which would be easier, we continue to investigate because the biology is interesting," Dutra Nunes says.

Temperature and Fertility

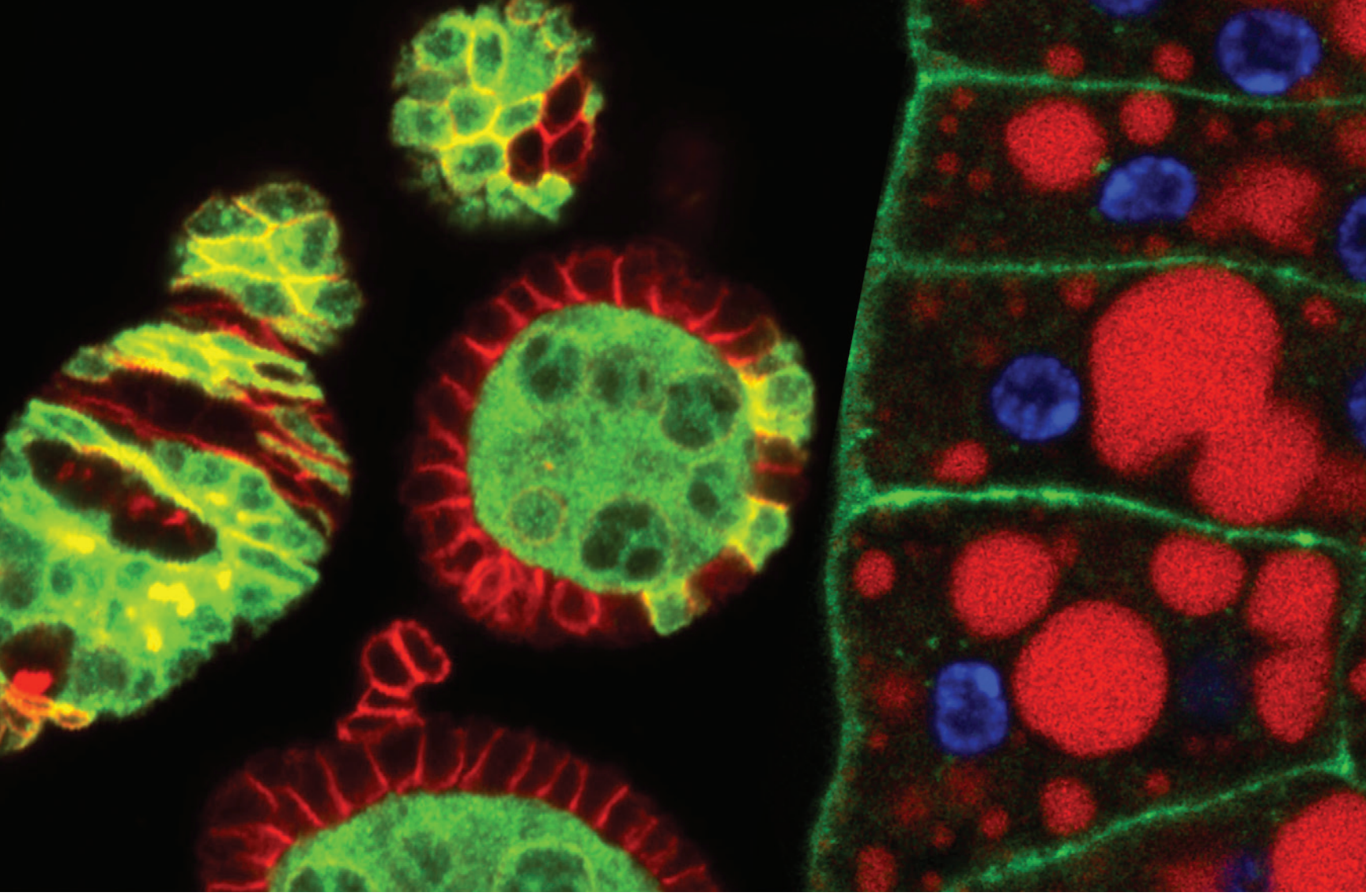
Drummond-Barbosa had long studied the effects of diet on *Drosophila* by the time Gandara arrived in her lab. But diet is far from the only environmental factor insects face, and understanding insects' responses to temperature has become more important with climate change.

"All animals are having to adjust to loss of habitat, and with the loss of habitat or micro-habitats, it becomes harder to deal with the higher temperatures," Drummond-Barbosa says. "So, it's a double whammy because insects are cold-blooded and they really rely on being able to find micro-habitats to control their temperature."

Continuing the focus on *Drosophila oogenesis*, Gandara published her first paper with the lab on the effects of colder or warmer, suboptimal temperatures on female fertility. She raised the flies under normal temperatures, but after they reached adulthood, they were split into warm, normal and cold groups. The temperature changes the flies underwent were minimal by our standards, but they had drastic negative effects on *Drosophila oogenesis*, especially at higher temperatures.

Gandara's next paper investigated the effects of cold and warm temperatures on *Drosophila* male fertility. Many studies have investigated the effects of warm temperatures on male insect fertility, but none have explored their effects on the different steps in spermatogenesis in detail. The warmer temperatures led to a considerable reduction in the quality and amount of sperm. Gandara's results also indicate that while spermatogenesis proceeds relatively normally at the beginning of the process, the damage seems to occur at the later stages of differentiation.

As the lab's first publications on temperature research, these papers set out to simply describe the effects of suboptimal temperatures — temperatures whose lethality over time is felt through their impact on fertility. The lab will build on the initial discoveries.



▲ Microscopy of germline cells with different features highlighted in fluorescence.

Looking Ahead

Gandara is now comparing *Drosophila* ovaries at different temperatures using an "omics" approach, which involves analyzing many subsets of biological molecules to better understand cell function. She's analyzing datasets of RNA, proteins, phosphorylated proteins and lipids. Within this massive amount of data, she's searching for pathways that control the fly ovary's response to temperature increases or decreases. This data will help her find a place to begin investigating the mechanisms whose effects she observed in her past research.

Both Gandara and Dutra Nunes are collaborating with research computing experts at Morgridge who can help them better organize and analyze parts of their respective data. Dutra Nunes is working with Anthony Gitter, a Morgridge investigator and UW–Madison associate professor of biostatistics, on his own omics data. And Gandara is collaborating with Ben Anderson, a postdoc in the Joshua Coon Lab. For Gandara, the shared interests, resources and culture at Morgridge are a welcome change from the lab's previous university department, as it was shifting its focus to more applied science.

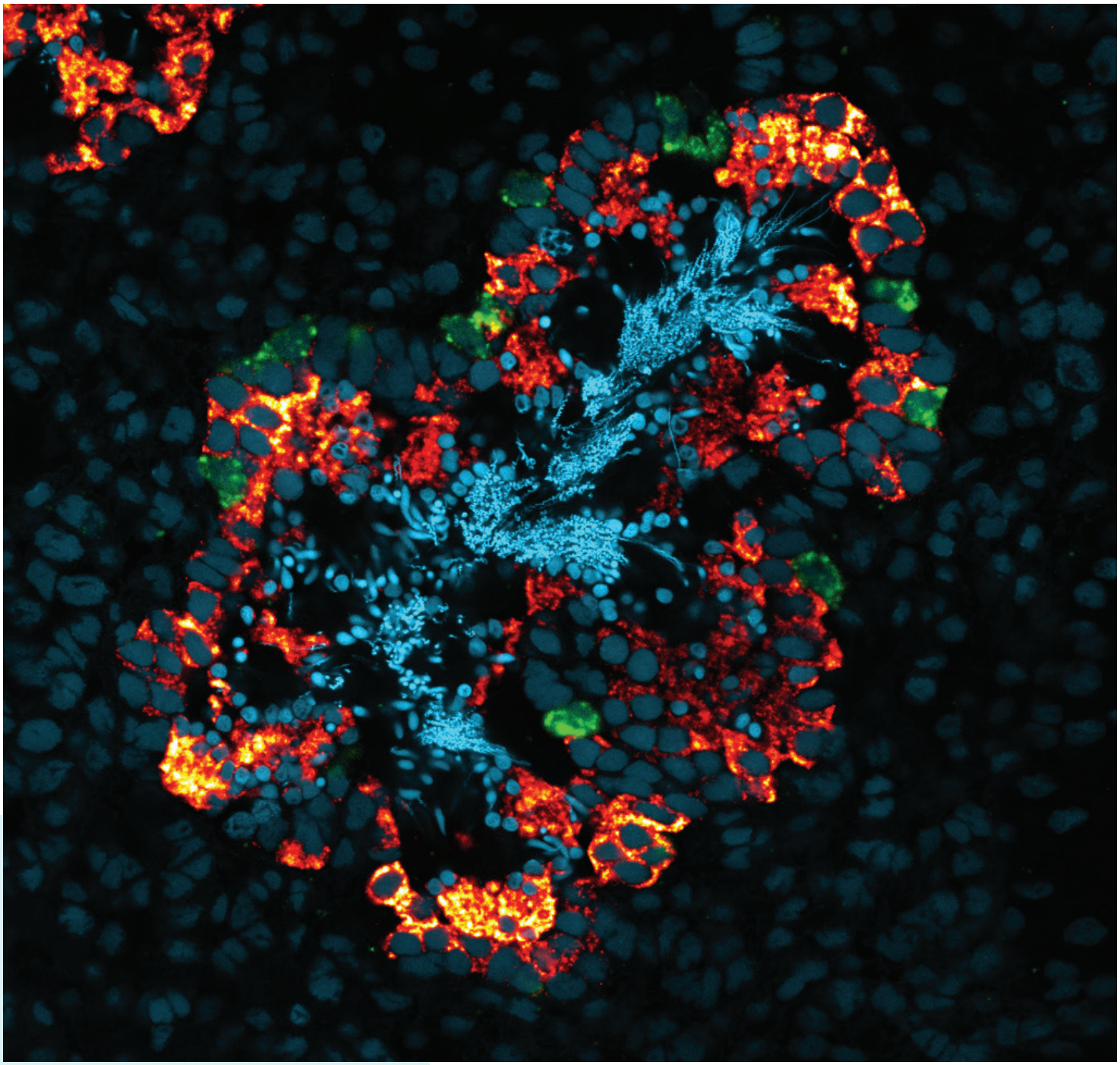
"We have more chances to collaborate, more chances to find useful information for us," Gandara says. "We can offer collaborations and even bring the right expertise to help people. It's much easier to help and be helped."

Dutra Nunes believes that a high-sugar diet has a systemic effect on the flies — that is, his findings are likely not the result of one gene that he can manipulate. To further investigate the effects of diet on *Drosophila* fertility, Dutra Nunes is turning to omics to better understand changes in proteins, phosphorylated proteins, and metabolites from different tissues under normal and high sugar conditions.

"With that we will have a process that will be really curiosity-driven," Dutra Nunes says. "After the results come out, we'll have too many directions to possibly follow. And that's a good problem."

SCIENCE IS BEAUTIFUL

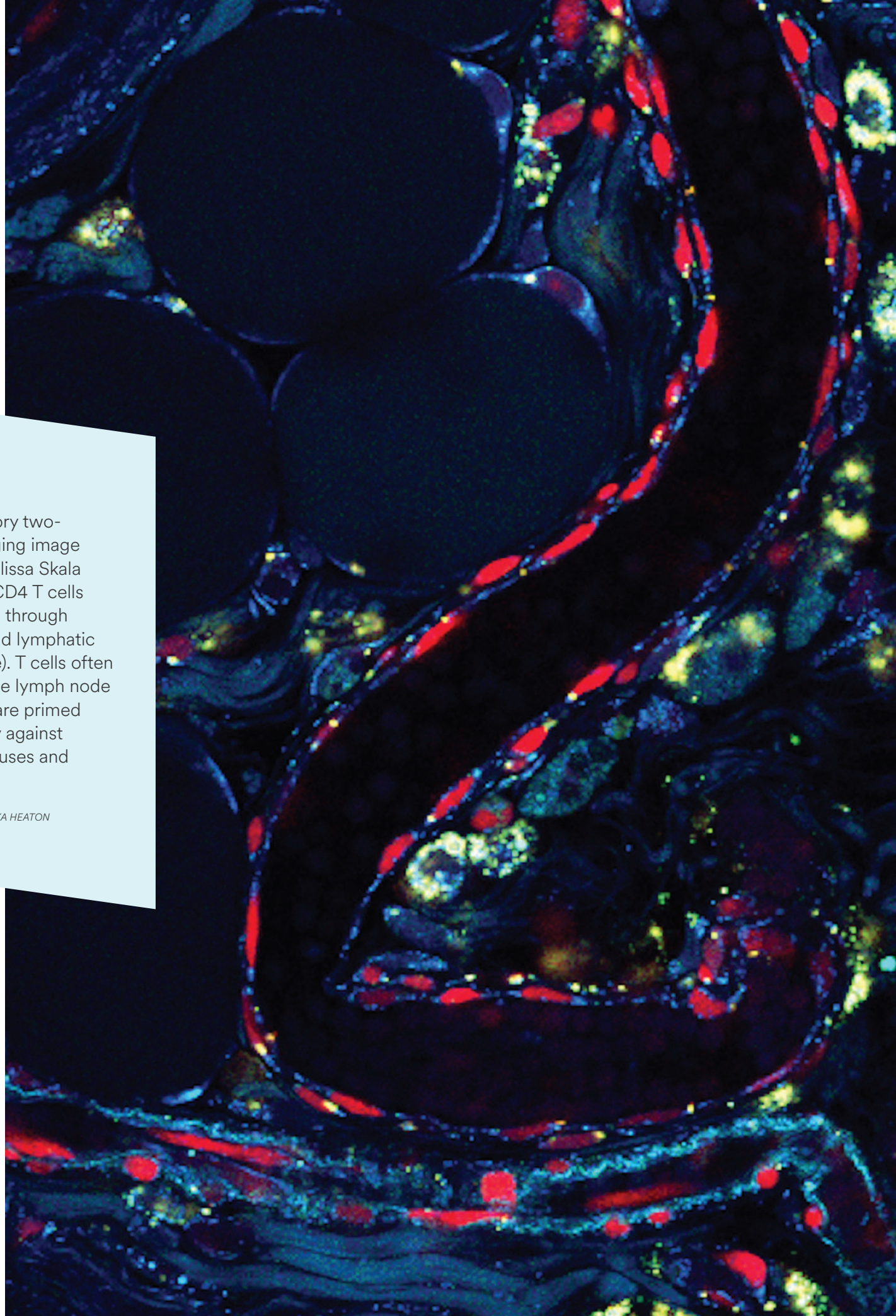
MICROSCOPY FROM THE LENS OF MORGRIDGE SCIENTISTS



1

The Newmark/Issigonis Lab discovered that monoamines — similar to neurotransmitters in the brain — are involved in a signaling pathway within somatic gonadal cells that regulate germ cell development. Testes in the planarian *Schmidtea mediterranea* contain an outer layer of spermatogonial cells at the periphery (green), and more differentiated cell types (yellow, red and cyan) toward the center.

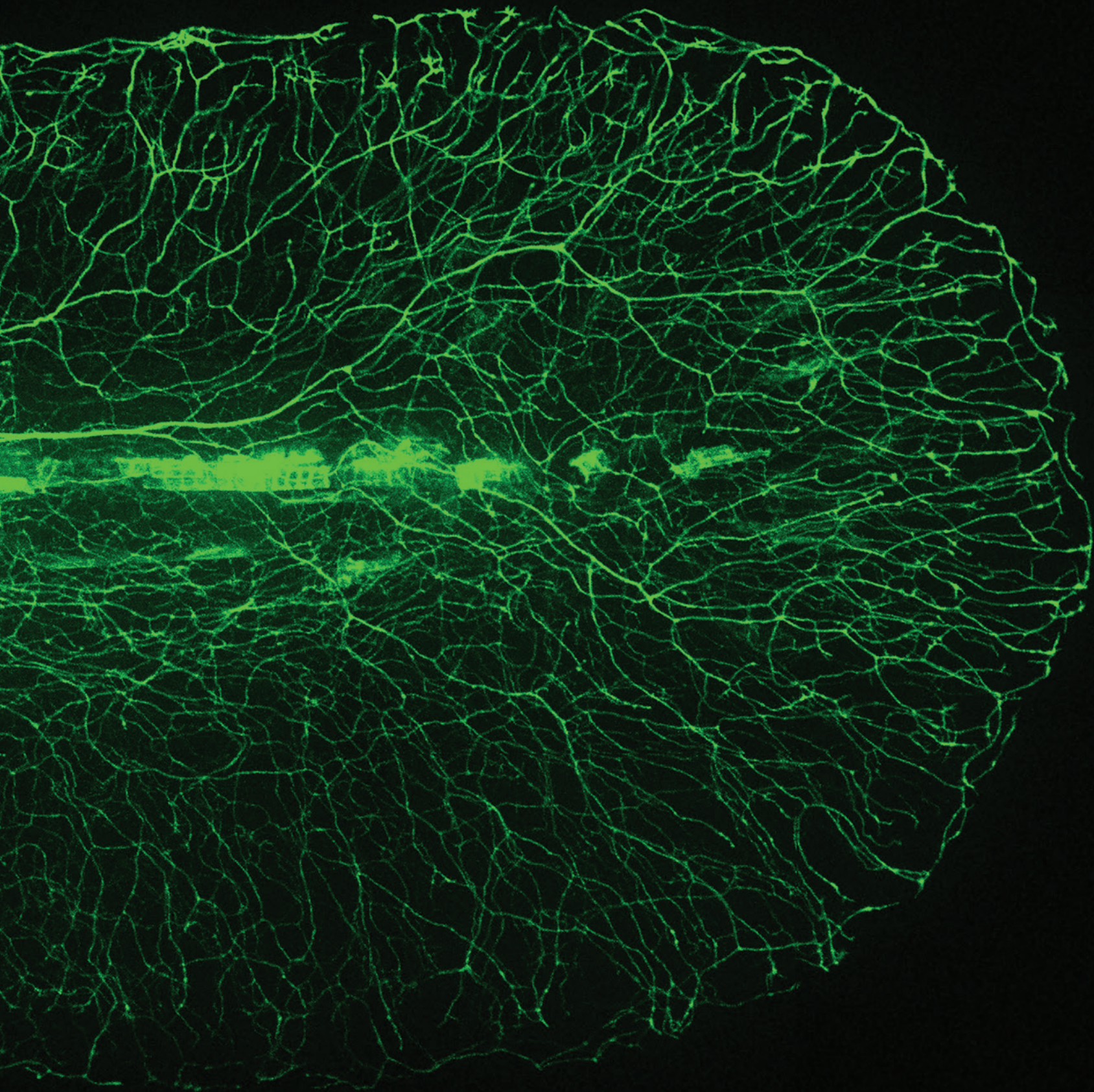
PHOTO CREDIT: MELANIE ISSIGONIS

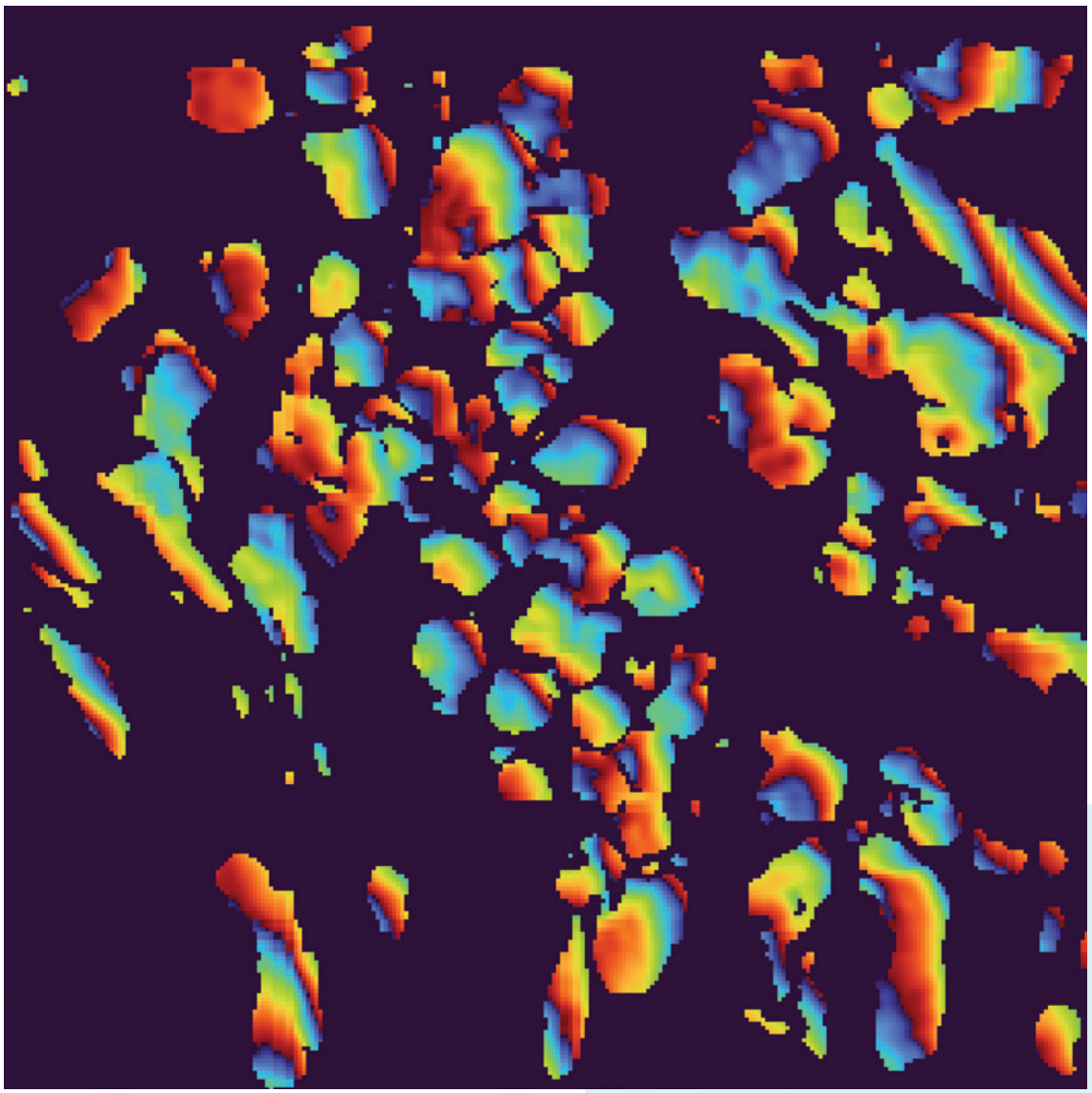


2

An exploratory two-photon imaging image from the Melissa Skala Lab shows CD4 T cells (red) moving through the blood and lymphatic vessels (blue). T cells often localize at the lymph node where they are primed for immunity against infection, viruses and cancer.

PHOTO CREDIT: ALEXA HEATON





3

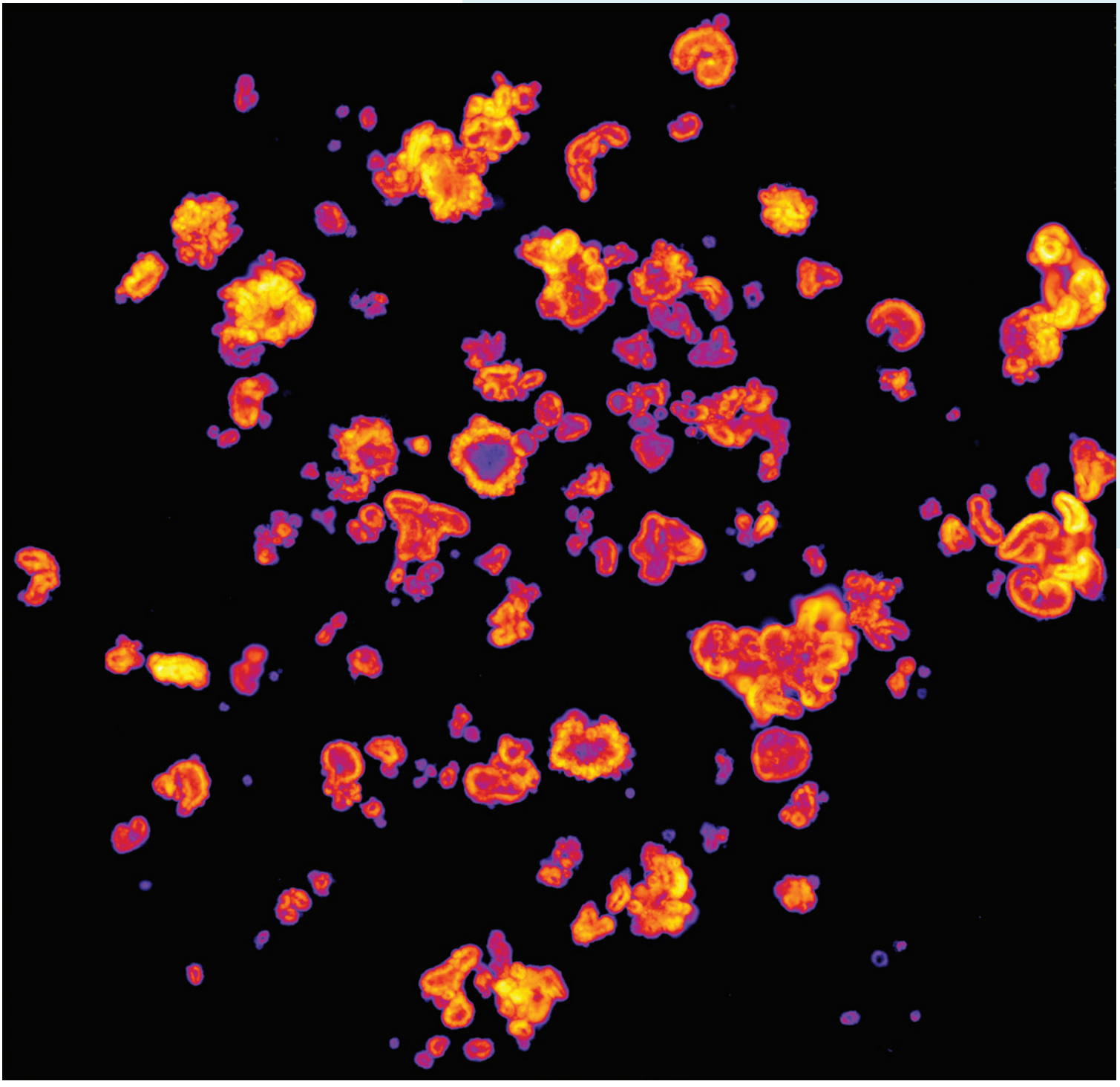
Green fluorescent protein (GFP) highlights the neural network in the tail fin of a live zebrafish. Zebrafish are an ideal model organism for biomedical research due to their genetic similarity with humans, transparent embryos to observe the development of internal structures and regenerative abilities. The Morgridge Fab Lab collaborates with researchers across many fields to solve biomedical problems through imaging, as well as prototyping and fabrication of novel research tools.

PHOTO CREDIT: PUI-YING LAM/KEVIN ELICEIRI

4

Osteoblasts in developing bone appear as a psychedelic rainbow in an image using third harmonic generation (THG). Recent work in the Randy Bartels Lab demonstrates the use of THG holographic microscopy — where the frequency of laser light is tripled when it interacts with materials — to collect full phase information in addition to measurements of light intensity. This technique opens up the possibility to solve problems with new applications in biomedical imaging and material science.

PHOTO CREDIT: RANDY BARTELS



5

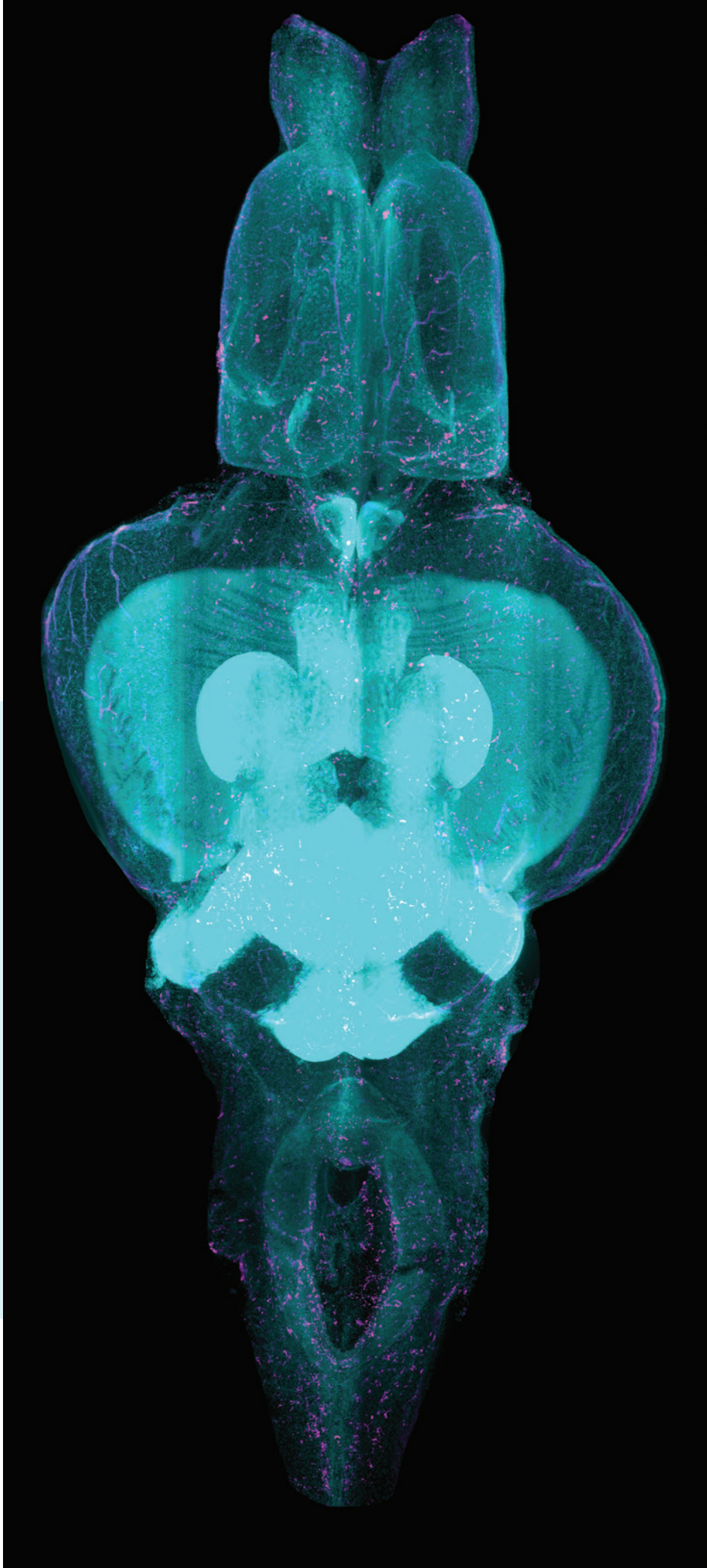
The Melissa Skala Lab uses optical metabolic imaging, a non-destructive and non-invasive method, to observe metabolic activity. These round clusters are patient-derived cancer organoids, used to study metabolic changes in response to drug treatment. The fluorescence intensity from low to high energy (purple to yellow gradient) is captured from metabolites that are naturally fluorescent.

PHOTO CREDIT: AMANI GILLETTE

6

A microscopic image of a zebrafish brain gives an inside look to observe changes in microglia, the brain's innate immune cells, to better understand their role in aging and neurodegenerative disease such as Alzheimer's disease.

PHOTO CREDIT: LIZ HAYNES



The infinite worm

BY CASSANDRA WILLYARD

Scientists Melanie Issigonis (left) and Katherine Browder peer into an aquarium teeming with planaria, tiny freshwater worms capable of regenerating whole organisms from small fractions of their bodies.

Scooped from a fountain in Spain, a colony of planarians help scientists unravel the rules of regeneration

In a Petri dish filled with water, about ten juvenile planaria float. The tiny flatworms are decidedly underwhelming. Their tiny gray forms morph from stationary circular blobs to gliding oval blobs depending on how active they are. They're not particularly hardy either. "They're like the consistency of wet tissue paper," says Katherine Browder, a graduate student who manages operations in the lab run by Phil Newmark and Melanie Issigonis.

Even their mating is understated. In a humming room in the basement, Browder scans one of the many tanks teeming with planarians. This one contains adults, the largest about the length of a macaroni noodle. She is hoping to catch a pair in the act. "Oh, there they are," she exclaims. "They're just high fiving each other from the back."

But the drab appearance of these worms belies what's inside: a treasure trove of amazing biological capabilities. They can regenerate their tails, but also their heads. They can repopulate their germ cells. Some can switch from asexual reproduction to sexual reproduction, or vice versa. The list of fascinating oddities goes on and on and on.

It was this long list of unique capabilities that drew Phil Newmark to the flatworms when he was in graduate school in the early 1990s. He spent the next two decades working tirelessly to push planarian research into the age of molecular biology, overcoming failed experiments, colony collapses, and the skepticism of many of his colleagues. The plan worked. When Newmark began, just a handful of labs studied planarians (and none in the U.S.). Today, there are dozens. "It's become a pretty popular model for trying to understand stem cell-based regeneration," he says.

Now Newmark, part of the regenerative biology research focus at the Morgridge Institute for Research, uses these tools he helped develop to study what first interested him: planarian stem cells and their amazing ability to regenerate.

But his planarian research has also opened a new avenue of exploration into parasitic flatworms, which share many similarities with their benign, free-swimming cousins. A better understanding of how parasitic flatworms infect their hosts and reproduce inside could help them develop new strategies to control the parasites.

Warming to worms

Newmark first became interested in planarians as a graduate student at the University of Colorado. At the time, he was studying fruit flies. But he was also a member of the developmental biology journal club, which had a rule that each member had to present a paper outside of their area of research. Newmark stumbled across a paper on planarian regeneration. A team of researchers from Barcelona had taken planarians, irradiated them to eliminate their ability to regenerate, and then transplanted stem cells, called neoblasts, from healthy planarians to restore their regenerative capabilities. But here is what blew Newmark's mind: They demonstrated that they could introduce neoblasts from a planarian that reproduces sexually into a planarian that reproduces asexually and convert it to sexual reproduction. "I thought that was probably one of the coolest things I've ever seen," he says.

He presented the paper and then dove into the literature. One paper led to another and Newmark became more and more fascinated by planarian biology and the possibility of applying new molecular biology techniques to studying these worms. "I can totally see studying this for the rest of my life," he remembers thinking.

At the time there were no planarian labs in North America. So Newmark joined the lab of Jaume Baguñà at the University of Barcelona to study them. When he returned to the U.S., he packed the worms in thermoses and brought them with him to Alejandro Sánchez Alvarado's lab at the Carnegie Institution for Science in Baltimore, Md. There, he painstakingly built up a colony. When that colony collapsed because of a mishap with a water filter, he and Sánchez Alvarado flew to Barcelona, collected more from the fountain where he had found the original planarians, and flew them back to Baltimore again.

Together, Newmark and Sánchez Alvarado developed the tools they needed to study planarian biology. "Back then it was not even an emerging model," Newmark says. "We were just getting everything going." Today, he is using those tools to investigate some of the most perplexing questions related to planarian biology.

Fateful decision

Melanie Issigonis, who joined the lab in 2011 when Newmark was still at the University of Illinois in Urbana-Champaign, has been focused on a single overarching question: how do cells decide whether to become reproductive cells or the building blocks for the rest of the body? "It's just really cool fundamental biology," she says.

All species that reproduce sexually have essentially two main cell types. Germ cells give rise to sperm and eggs. Somatic cells form everything else. This process typically happens during embryogenesis, but in planarians, it also happens during regeneration. "If you chop the head right above where any of the reproductive tissues are, you get these little head fragments that don't have any germ cells at all," Issigonis says. But over time the worm will regenerate everything, including germ cells. "It will have all of its reproductive organs again," she says. "So we know that it's going from having only somatic tissues to being able to regenerate de novo germ cells." That's a rare capability in the animal kingdom.

But how the new cells decide whether to become somatic cells or germ cells is still mostly a mystery. "That's a big fate choice," Issigonis says.

Planarians have a number of other reproduction-related quirks as well. The worms are hermaphrodites, so each organism contains both eggs and sperm. In addition, they lay unusual eggs. Most eggs have a yolk on the inside, but planarians have specialized organs that produce yolks on the outside of their eggs.

The team recently reported that the worms' yolk cells and germ cells share a gene that seems to play a key role in the function of both. When they knocked down expression of the gene, germ cells lost their ability to make sperm and eggs and yolk cell production plummeted. As a result, the planarians couldn't reproduce.

Issigonis is still unraveling the secrets of planarian reproduction, but it's clear that what she finds will have implications beyond planarians. For example, all animals specify which cells will become germ cells. "That's a fundamental thing that every

▲ Phil Newmark became the first scientist to establish a planaria research colony in the United States. Today, there are dozens of labs studying their stem cell-based regenerative traits.

animal does," Newmark says. "It's relevant to how animals make germ cells across evolution."

A Lucky Fluke

As Newmark and his colleagues began sequencing planarian genes, they found many that were shared with the worms' parasitic cousins, the blood flukes. Blood flukes, or schistosomes, are a massive public health issue, affecting more than 200 million people worldwide. "We get infected by this thing that swims out of the snail," Newmark says. They burrow through the skin within minutes, and then enter the bloodstream, causing, in some case, massive damage.

In 2009, one of Newmark's postdoctoral fellows, Jim Collins, started characterizing some of the chemical messengers in the brain that are in involved in reproduction. One of these molecules, called neuropeptides, seemed to regulate the maturation of the reproductive system. When the team blocked expression of that gene, called *npy8*, in adult planarians, the worms' reproductive systems regressed to a juvenile state. "Jim had identified this peptide hormone that basically, when you knocked it down, made a

> ***I just thought, I can totally see studying planaria for the rest of my life.***
>
> ***— Phil Newmark***

This caught Newmark's attention. Could he and his colleagues identify this chemical and leverage it to prevent schistosomiasis?

flatworm reproductive system go away," Newmark says.

Collins realized the implications right away. Blood flukes are flatworms too. He found the same neuropeptide gene in the schistosome genome. If he could inhibit that neuropeptide, he might be able to stop the flukes from producing eggs and prevent the worst effects of blood fluke infection. "He came into my office and said, I think we should look at schistosomes," Newmark recalls.

Newmark always hoped that a parasitologist would see his lab's work, notice the similarities between planarians and parasitic flatworms, and then reach out to collaborate. But that never happened. So in 2009, he and Collins went to visit the main resource center for schistosomes in Rockville, Md. to learn how to culture the animals and maintain their wildly complex lifecycle. Schistosomes need freshwater snails as hosts in order to produce millions of cercariae, tiny fork-tailed creatures that swim in the water until they find a mammal to serve as a host.

While the pair visited the lab, then-director Fred Lewis cautioned them to make sure that the water used to house the infected snails was free of rotifers, tiny organisms that sometimes live on the snails' shells. He and his colleagues had discovered in the 1980s that rotifers can release a chemical into the water the paralyzes the infectious larvae.

This caught Newark's attention. Could he and his colleagues identify this chemical and leverage it to prevent schistosomiasis?

Stopping schistosomiasis

Cercariae, the free-swimming form of schistosomes, aren't visible to the naked eye, but under the microscope they thrash wildly. "Their one goal in life is to seek out a host," says Ian Donovan, a research specialist in Newmark's lab. "They have about 24 hours of energy reserves before they perish." The thrashing serves two purposes. It propels them through the water in search of a host, but it also helps them wiggle their way through the skin once they find a suitable mammal. "So in the lab, that would be a mouse. In real life, it could be a human walking through, say, a rice paddy that might be flooded," Donovan says.

In the 1980s, Lewis and his collaborator Peg Stirewalt noticed that rotifers produced a factor that paralyzed cercariae. But the pair ran out of funding before they could uncover the identity of the mysterious substance. Lewis shared his unpublished observations with Newmark and his colleagues, and once he had established schistosomes in the lab, the team picked up the quest.

Newmark grew rotifers and confirmed what Lewis and Stirewalt had observed: the rotifers were producing something that stopped the wiggling. They then collaborated with chemist Jonathan Sweedler's lab at University of Illinois Urbana-Champaign to isolate the compound. They named it schistosome paralysis factor or SPF for short. "It's a pretty odd-looking molecule for something that's secreted by an animal. The closest known analogs are actually in bacteria and plants and fungi," Donovan says.

The team also showed that SPF could prevent infection in mice. "We'd like to come up with ways to prevent an infection in the first place," Newmark says.

The next step will require a bit more work though. In order to make SPF a useful preventative, they need to have enough of it to run tests. But so far, no one has had any luck synthesizing the compound. "We actually have a company that's still working on it. They've been working on it for years," Newmark says. "We're their best customer," Issigonis adds.

In the lab, Donovan is focused on uncovering how the rotifers make the compound. If he could identify the enzymes responsible, the team might be able to engineer yeast or bacteria to produce it.

In the meantime, there are enough questions about flatworm biology to keep the lab busy for decades. But Newmark finds the many questions exciting rather than daunting. Now he and his colleagues have cutting-edge tools to answer them. "Back when the only tool was a razor blade, you do this experiment, and you throw your hands up in the air," he says. But now his team can dive deep into planarian biology and investigate the mechanisms that underlie their amazing capabilities.

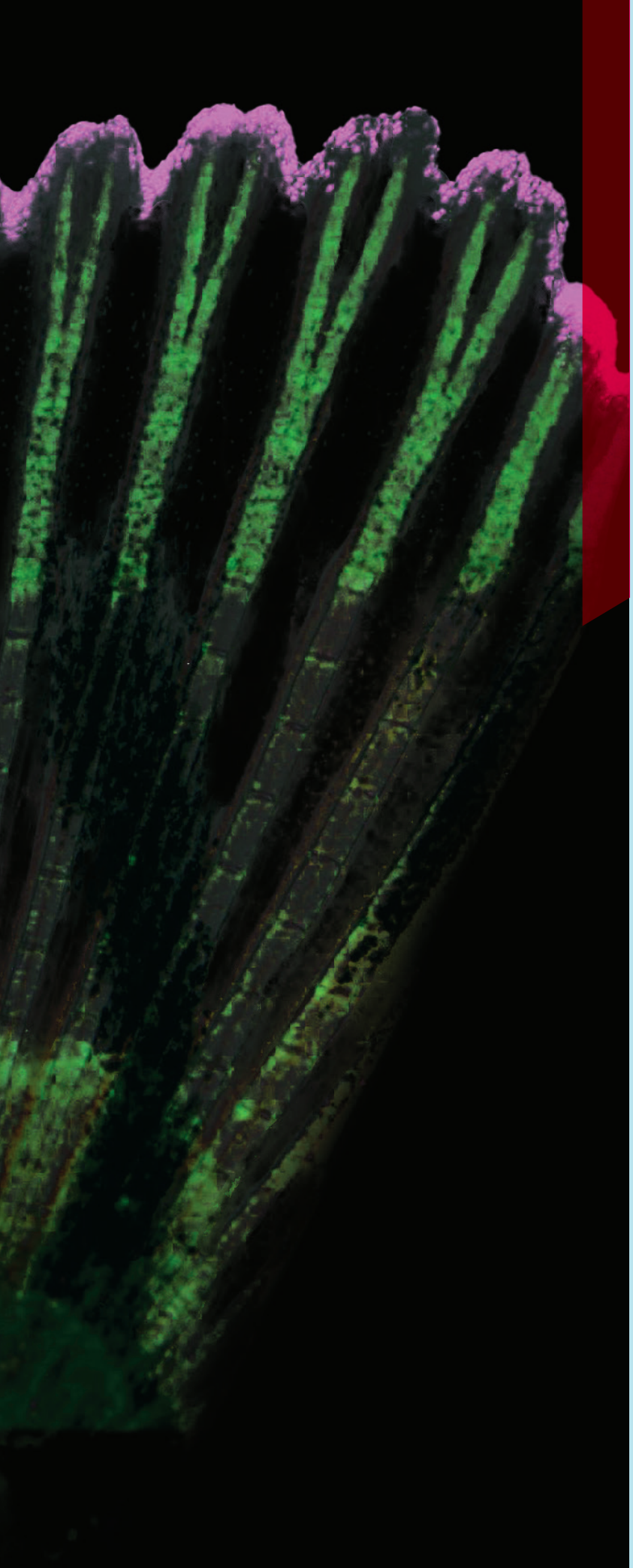
On the wall behind Newmark's desk, there's an image of the planarian nervous system in all its vast complexity. The team has identified a few of the neuropeptides they produce, but they've just scratched the surface. There are so many types of neurons, each producing a different suite of neuropeptides, Issigonis muses. Planarians might seem like a "humble unassuming looking critter on the outside," she says. But just look at that brain. "They're quite complex," she says.

Little fish, big splash

BY MICHAEL PENN

This image shows a regenerating zebrafish tail fin showing regeneration of new bone (green) guided by molecular signals (pink). Morgridge investigator Kenneth Poss is interested in how this fish regenerates damaged tissue throughout its life.

PHOTO CREDIT: SUSHANT BANGRU



Kenneth Poss, Morgridge's newest investigator, studies how zebrafish can restore what is irreparable in humans — including damaged heart tissue

Because Kenneth Poss is a true Badger, born and raised in Green Bay, it's only natural that his scientific journey begins with a fish story.

The tale unfolds in the late 1990s at the Massachusetts Institute of Technology, where Poss is in the grind of thesis research for a Ph.D. in biology. He's part of a team studying mice, trying to tease out the genes involved in learning and memory. But he has friends working in the lab next door, and they're doing something Poss finds strange and wonderful.

The lab, led by MIT biologist Nancy Hopkins, was studying zebrafish as a model for understanding embryonic development. To do this, graduate students would sometimes cut tissue from the fins of adult zebrafish to analyze gene mutations. But whenever they lopped off a fin from one of the inch-long fish, within a few days, the missing parts would start coming back.

"They were kind of frustrated, because the fins would grow back, and they couldn't really identify the fish [they had previously worked on]," says Poss, who is joining the University of Wisconsin–Madison and the Morgridge Institute for Research this fall to lead research on regenerative biology.

“I’ve always been most interested in exploring something that we really don’t know a lot about. Regeneration and zebrafish just seemed like this really open space, where there were so many questions to answer.”

KENNETH POSS

“But I was just really fascinated by the fact that they could regrow these fins.”

Biologists had long known that many fish and amphibians could regenerate lost body parts, but at the time, they still knew very little about why or how. To Poss, who grew up combing the creeks and fields around his Green Bay home in search of interesting creatures, those seemed like questions worth studying.

“I’ve always been most interested in exploring something that we really don’t know a lot about,” he says. “Regeneration and zebrafish just seemed like this really open space, where there were so many questions to answer.”

And so soon after completing his doctorate, Poss convinced his postdoctoral mentor, University of Utah cardiologist Mark Keating, to let him buy a few zebrafish from a pet store and start working out the techniques he’d need to uncover their secrets. He quickly learned that the fish’s extraordinary remodeling skills extend far beyond fin replacement. They can regenerate complex tissue in a host of organs and systems, allowing them to survive injuries that would be fatal for any human. It’s known now that an adult zebrafish can endure having its spinal cord severed or even the obliteration of two-thirds of the tissue in its heart, and it will do ... well, swimmingly. Like a sci-fi supervillain, it gathers its cellular tools and patiently rebuilds.

Poss has observed many thousands of these stunning recoveries in his lab at Duke University, where he has spent the past 20 years studying the fish’s remarkable genetic toolkit. And each one brings him closer to a tantalizing possibility — that those same regenerative abilities are lying dormant in our own DNA, and that we may soon figure out how to turn them back on. Such a breakthrough could lead to revolutionary new therapies, allowing doctors to fix damaged cardiac tissue following a heart attack or restore healthy neurons in a brain ravaged by Alzheimer’s disease.

But let’s not get ahead of ourselves. First, we need to do some more fishing.

Poss’ lab at Duke feels a bit like a very narrowly focused fish store, one with an uncommon enthusiasm for a single species of zebrafish. At any given time, 60,000 or more of the distinctively striped fish live in the lab’s large aquatics facility, darting chaotically around several thousand small tanks. But what the display lacks in visual variety, it makes up for in a less apparent diversity. Most of the fish have been engineered with mutations or transgenic DNA to help researchers see which genes and cellular mechanisms play a part in regenerating different types of fish tissue.

More than 25 years after meeting his first zebrafish, Poss is still a huge fan of the versatile species, which are native to river basins in India and common in home aquariums. They began to take favor in the 1990s as a model organism for studying embryonic development,

▲ "It's a big goal but we are hopeful that we can leverage discoveries from zebrafish to help make heart muscle cells divide under control in humans." – New Morgridge Investigator Kenneth Poss. *PHOTO CREDIT: ANDY MANIS*

mostly because they are easy to care for and make lots of little zebrafish, as well as the scientifically useful quirk that their embryos are initially transparent. But Poss was among the first to start hunting the genes that adult fish deploy in regeneration.

"I was fortunate just to be there early, to make some of the foundational findings in the field," says Poss, who even after 30 years away from Wisconsin still talks with a characteristic Midwestern soft-spoken amiability. "It was just a great opportunity to be part of those early explorations and make an impact."

In the early 2000s, Poss published the first research showing that zebrafish regenerate heart muscle after injury, findings that helped establish the fish as a central model for the emerging field. His lab, which at Duke comprised more than 20 staff, postdoctoral researchers and students, has made significant discoveries on regeneration in several of the fish's organs and systems, including regrowth of fins, scales, skin and nerves in the spinal column. They have also studied tissue repair in pigs and mice. But the heart of the team's work remains in the zebrafish's tiny, miraculous heart.

Barely a microliter in volume, the adult zebrafish heart has an extraordinary talent humans lack: the ability to order up new muscle cells to restore heart function after an injury. When they sense damage, specialized genes orchestrate a strikingly ordered response, instructing waves of cells to proliferate and migrate around the site of the injury to produce the tissue types needed for repair. The process plays out over several weeks, but once it's complete, there's almost no sign anything was wrong.

Using advanced imaging and florescent molecules that light up specific gene activity and cell types, Poss' team has figured out how to spy on this cellular dance in real time, documenting every genetic signal and cell movement. Their goal, Poss says, is to make a "full-length movie" of the key events involved in fixing a broken heart (and other tissues) — something that could essentially become a how-to video for researchers attempting to do the same for humans.

"More than anyone else, Ken has beautifully documented, in fine detail, the way that cells migrate, interact and ultimately give rise to the complex functions of the heart," says Eric Olson, a molecular biologist who directs the Hamon Center for Regenerative Science and Medicine at the University of Texas Southwestern Medical Center. "And he's been able to convey that excitement to the broader community of biologists."

Olson, who is studying how neonatal mice produce new heart cells after an injury, notes that many mammals have the ability to regenerate heart muscle in early stages of life, only to lose it as adults. Understanding the levers that zebrafish use to launch regenerative responses can help scientists develop interventions that could reawaken those tools in humans, he says.

Poss agrees. "These animals that regenerate really well, they don't have magic genes that we don't have. It's more how they control the genes," he says.

“I think that’s what makes science the most exciting job there is — the opportunity to have a new path very quickly, and to follow it. I think that’s what we are supposed to do.”

But control isn't just about turning the genes involved in regeneration on; it's equally important to know how to turn them back off again, which is essential to prevent unwanted cell division that could lead to cancer. Poss' team has identified the switches that appear to do that naturally in zebrafish — DNA sequences that he calls "tissue regeneration enhancer elements," or TREEs. Even more encouragingly, the group reported in 2023 that those same elements are also able to control genes in pigs and mice, suggesting they could be adapted to direct a targeted regenerative response in mammals.

"You're not going to be able to just take a pill that floods the system," Poss says. "What you really want is to deliver something to the right place, just in the injured tissue, keep it there for the right amount of time, and then shut it off."

Poss, whose academic home at UW–Madison will be in the School of Medicine and Public Health's Department of Cell and Regenerative Biology, expects UW–Madison's strengths in molecular biology and clinical research will help accelerate the study of these gene regulators in larger mammals, a key step toward developing therapies that could help reduce scarring and restore function following a heart attack.

"It's a big goal but we are hopeful that we can leverage discoveries from zebrafish to help make heart muscle cells divide under control in humans," he says.

Regenerative biology is no longer the uncharted frontier it was when Poss started collecting fish. Many dozens of labs now study regeneration in zebrafish, including some led by Poss' former trainees, and many others are focusing on salamanders, flatworms, fruit flies and mice. He currently leads the Duke Regeneration Center, an interdisciplinary group of scientists from across biology and medicine who are studying the topic. In 2021, he co-founded the field's first professional organization, the International Society for Regenerative Biology, as a forum for the growing community.

But even with the influx of new talent and energy into the field, many aspects of regeneration remain mysterious. Scientists don't have a good handle yet, for example, on the specific mechanisms a zebrafish uses to rebuild its spinal cord, a complex rewiring job that allows a fish to go from complete paralysis to full movement in less than two months. And so, while Poss says it's critically important for regenerative biology to start delivering clinical applications, "it's also critically important to continue to learn how these things work."

One advantage of joining UW–Madison, he says, is that it gives him the chance to do both. While he expects the team's more advanced work on heart regeneration to move toward clinical applications, his affiliation with the Morgridge Institute affords him the flexibility to entertain more open-ended explorations.

"A place like Morgridge very clearly supports the idea of not necessarily doing what you wrote on a grant application four years earlier, but going after what you think is the most important thing to do that day," he says. "I think that's what makes science the most exciting job there is — the opportunity to have a new path very quickly, and to follow it. I think that's what we are supposed to do."

That's an ethos that permeates Poss' team, several of whom will join him in Wisconsin. He encourages students and junior researchers to chase down whatever makes them curious and to embrace the inherent uncertainty in their work. "He's always telling us, don't worry if you are getting positive or negative results. Whatever you find, you can learn something," says Fei Sun, a postdoctoral researcher who began working with Poss as a graduate student in 2015.

Sun, who has also accepted a position at Morgridge, says it's a standard Poss equally applies to himself. "I always see him exploring new areas and seeking out new collaborations," she says. At Duke, for example, Poss' team includes a nephrologist studying how zebrafish regenerate kidney tissue and a plastic surgeon interested in applications for skin and soft-tissue reconstruction.

"He's very supportive of [people on his team] exploring new things, even if they aren't the things he is known for," Sun says.

It's no surprise, then, that Poss is approaching his move to UW–Madison with the same sense of open-minded possibility. While he is enthusiastic about the opportunity to come home and to further establish the Midwest as a destination for cutting-edge biological research, he is cautious about laying out too proscriptive an agenda for his lab. He'd rather see what paths suggest themselves in a new environment.

"Any move like this is an experiment," he says. "I can't really predict what direction our research goes, but that's part of the excitement."

But Poss has given thought to one new direction his return to Wisconsin may take him. Still an outdoor enthusiast who loves hiking and exploring nature, he's considering taking up ice fishing. "I've only been once, and I loved it," he laughs. And as he says this, it's easy to see him out there on a frozen lake, enjoying the contemplative quiet. Like science, it's a pursuit that tends to reward the patient, the ones who are content to wait for the fish to reveal themselves.

This image (left) captures a section of a regenerating zebrafish spinal cord, showing a 'tissue bridge' that grows between two severed ends. *PHOTO CREDIT: VALENTINA CIGLIOLAE*

NEXT GEN

MORGRIDGE ALUMNI PUSH THE FRONTIERS OF SCIENTIFIC CAREERS.

DANIELLE LOHMAN

Working to end proliferation of biological weapons

By Dennis Chaptman

Danielle Lohman's scientific career was nurtured at the lab bench at the Morgridge Institute before morphing into a diplomatic role working to prevent the spread of biological weapons.

"Science, communication, and teaching are something you learn as part of your job as a researcher," says Lohman, a foreign affairs officer at the U.S. Department of State. "Today, I'm doing that all the time with international diplomats, scientists, and U.S. government officials."

A native of small-town North Carolina, Lohman earned a bachelor's degree in biochemistry at the University of North Carolina at Chapel Hill in 2011 before coming to the UW–Madison to earn her doctorate.

In Madison, she worked — first as a graduate assistant and then as a Morgridge Postdoctoral Fellow — with researcher Dave Pagliarini, using structural, biochemical and computational approaches to study the protein COQ9 and the role of mitochondrial dysfunction in disease.

A 3D model of the protein still sits on her desk at the State Department's headquarters in the Foggy Bottom section of Washington, D.C.

"I like the idea of having a social contract between the scientist and the rest of society, and that was so apparent at Morgridge," Lohman says. "It made me understand that discoveries are absolutely necessary, but they're not sufficient. If you want to apply the discoveries, and turn them into inventions, it requires a lot more than intellectual discovery."

She adds: "Morgridge is a place where the scientists feel valued. It was very clear that the mission is to do good research to make good discoveries."

In Lohman's second year of graduate school, she attended a career fair and met a scientist who worked at the State Department promoting chemical security. That meeting helped shift Lohman's career path from basic science to science policy.

While Lohman was at Morgridge, she attended a workshop on congressional science and engineering advocacy. And, she interned for the nonprofit Health Security Partners, helping other nations to promote biosecurity and biosafety.

In 2019, she landed a prestigious American Association for the Advancement of Science fellowship working in the Office of Biological Policy in the Bureau of International Security and Nonproliferation.

And she stayed with the bureau in a full-time role. One of her primary duties is helping to oversee a treaty signed by more than 180 nations that bans biological weapons, working with international diplomats to keep the treaty's purpose front and center globally.

"There's a quote in the preamble that's so perfect. It says basically that these weapons are repugnant to the conscience of mankind," Lohman says. "We want to keep the treaty alive and live within its text. Otherwise, it's just a piece of paper someone signed 50 years ago."

Early in her State Department career, Lohman also recognized the commonalities between fine-tuning cellular systems in the lab and influencing the complex workings of government.

"In the lab, if you make a small change to their genetics, they behave differently in significant ways. It transforms things," she says. "I started to think of government as an organism. That helped me make the pivot a little easier, because you're using the same critical thinking as in the lab. Today, I don't find pivoting as scary as it used to be."

JOSE AYUSO

Bringing collaborative science to the dream of precision medicine

By Dennis Chaptman

Growing up in Madrid, Jose Ayuso's parents, both bank clerks, often puzzled over how he acquired such a deep passion for all things science.

But his thirst for science and mathematics was insatiable, transcending disciplinary lines.

At Spain's Autonomous University of Madrid, he earned a biochemistry degree, and stayed to pursue a master's in biophysics. Finally, Ayuso earned a doctorate in biomedical engineering at the University of Zaragoza.

"I like the predictive nature of math," says Ayuso. "I wanted to work in a field where you could bring those equations to the table. That's biophysics or biomedical engineering."

It's not surprising that, with that perspective, Ayuso wound up at the Morgridge Institute, a global leader in cross-cutting, collaborative research.

As a promising Morgridge Postdoctoral Fellow and later as a scientist working with researchers David Beebe, Melissa Skala and Kari Wisinsksi, Ayuso spent more than five years at Morgridge. They worked to generate advanced microfluidic cell culture platforms to recreate the architecture of tumors.

"Melissa is an expert in biology and physics, Dave is an engineer, and Kari is an expert in clinical care," Ayuso says. "That gave me a multidisciplinary foundation allowing me to tackle these projects using new tools to answer questions that help people in the clinic. You cannot easily achieve that without access to those experts."

Although science is moving in more collaborative, less siloed, directions, Morgridge is a trailblazer. In 2022, Ayuso carried Morgridge's collaborative ethic to his current post as assistant professor in UW–Madison's Department of Dermatology.

"The Morgridge experience helped me because today I am working on a daily basis with physicians who are working with patients, and basic scientists who are all working to cross that gap between basic science and medicine," he says.

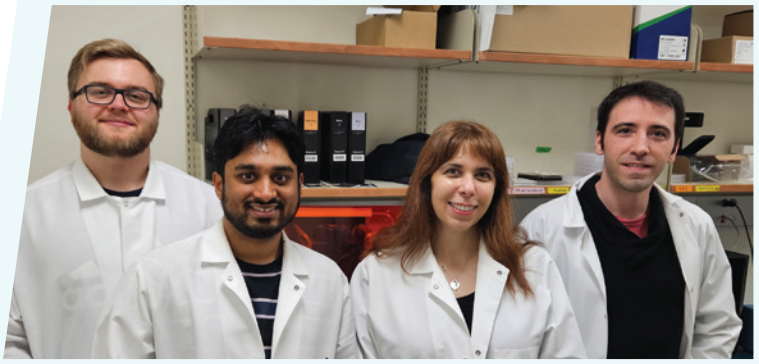
The Ayuso lab uses advances in microfabrication, 3D printing, bioprinting and other tools to fabricate lab-grown skin tissue to tap the promise of precision medicine.

"Maybe we have a patient with skin cancer and need to identify the best therapy," he says. "We don't have the time or ability to test 100 drugs on that patient. So, we use that patient's cells to build and reproduce a small fragment of the skin so we can test which therapies work."

Ayuso, who has also taught molecular and environmental toxicology and a dermatology seminar, takes special pride in helping students with his shared hunger for science to succeed in the lab and the classroom.

Sometimes they return from the lab with sensational data, and often they learn to troubleshoot when their experiments fall flat, Ayuso says. No matter the outcome, Ayuso buoys them with his infectious positivity and unfailing energy.

"It's so rewarding to see them growing from the day they walk in," Ayuso says. "When they challenge your ideas and they are right, that's exciting. When they reach that day, when they challenge you and know more than you do, that's super cool."



KAYLA HUEMER

Mastering the 'spirit of frugal innovation'

By Dennis Chaptman

A line from Apple founder Steve Jobs' 2005 Stanford University commencement address carries special meaning for Kayla Huemer as she ventures out into Africa, committed to advancing global health development through technology.

"He said, 'You can't connect the dots of your life looking forward; you can only connect them looking backward,'" Huemer says. "Looking back, the starting dot for me was working at the Morgridge Institute for Research. The skills I learned there, the mentors I gained and the opportunities I was given — they were the starting dot that got me to where I am today."

Raised in Mount Horeb, Wis., Kayla earned her biomedical engineering degree at the UW–Madison while conducting research at Morgridge. She worked as a BerbeeWalsh Prototype Pathway student in the Fab Lab on fabrication of a zebrafish live imaging device along with researchers Kevin Elicieri, Robert Swader, George Petry and Ben Cox.

"One of the most valuable skills I gained from my time at Morgridge was the collaborative aspect of bringing people together from different disciplines and not being intimidated that someone else was an expert in their field," she says. "I learned to see the intersection of my skills and their expertise as an opportunity to create something novel. That's what I found most exciting."

As an undergraduate, Huemer went to India for a research internship at the Indian Institute of Science in Bangalore. Using the engineering and design skills she honed at Morgridge, Huemer developed a prototype of a "Smart Shoe," wearable device for diabetic patients to aid in the therapy of foot ulcers often experienced by patients with diabetes.

"Through my experience at Morgridge's Fab Lab, I often worked with doctors and biologists. Then in India, I felt myself directly building on that confidence to work with doctors there."

Her experience helped her earn a U.S. Fulbright research grant to continue developing the device at India's CMC Vellore Hospital the year following her UW–Madison graduation.

"While in India, I saw the way people were so resilient and creative in the way they solved problems when something would break," she says. "There's a Hindi word for it — jugaad — which means 'the spirit of frugal innovation.' I had found a gem of a concept many people back home struggled to relate to. It's a mindset you use for solving problems when resources are strained."

Huemer returned to Morgridge in 2019 as a visiting fellow exploring the use of machine learning to pull novel insights out of data she collected in India.

This set her on the path to graduate school at Stanford to study artificial intelligence in healthcare, global health, and design. There, she earned a master's in bioengineering, honing her love of low-resource engineering.

Her Morgridge experience helped inform her work across the African continent. Based in Nairobi, Kenya, she worked as a product manager for the social-impact organization Medtronic LABS. She helped accelerate healthcare access through technology for underserved communities in Kenya, Ghana, Tanzania, and Sierra Leone.

This June, she transitioned to a role as head of product for Jacaranda Health, which works to strengthen maternity and child health. She works with PROMPTS, an AI-enabled digital health service that, through two-way text message exchange, empowers Kenyan women to seek care at the right time and place, ask questions, and provides information and greater agency in the health system.

"The ability to work with people from several fields to align on technology's value and opportunity for innovation is something I began learning in Morgridge's collaborative environment," she says.

The 'immortal' organism teaching us about stem cells

Celina Juliano, associate professor of molecular and cellular biology at the University of California Davis, talked to *Fearless Science Magazine* about her fascination with the model organism hydra, and science's deep dive into the golden age of regenerative biology.

How did you get involved in studying hydras?
I love studying hydras because they are so simple yet have remarkable capabilities. A freshwater organism about 10mm long, hydras are made up of two tissue layers and comprise a head and a foot. Cut it in half and both ends grow back. It's basically a bag of stem cells that renew continually, so every three weeks you essentially have a new organism.

Looking through a microscope at an animal that doesn't age or die brings out the curious eight-year-old kid in all of us. I saw a seminar on them during graduate school and immediately knew I had discovered my passion. After studying them as a postdoc at Yale, I now run my own lab at the University of California, Davis.

What would you consider to be one of your most impactful findings?
An important piece of work in our lab was to sequence every cell in the organism. We published a cell atlas in 2019 as a resource for the entire hydra community. You can go on our

Celina Juliano, Ph.D., is Associate Professor of Molecular and Cellular Biology and Chancellor's Fellow at University of California, Davis.

website and see exactly where all the genes are expressed. There weren't many surprises — we learned the hydra works the way that we think it works. And that was really satisfying, because the early studies were done by excellent scientists without the tools of today and it turns out they were correct.

You could consider this a golden age for regenerative biology. New genomics approaches that allow us to collect massive amounts of data can be combined with techniques like CRISPR to genetically modify the organism. With modern tools, we can go beyond mouse models and make substantial discoveries in these more offbeat organisms that regenerate.

What are you most excited about in your work right now?

One of our most exciting contributions so far involves the nervous system. The original data set enabled us to start defining the number of different types of neurons that hydra have. Now we're in the process of determining how many neurons they have, where they're all located, and where neurons might differentiate from one type to another so we can map out what happens. Hydras can regenerate a whole nervous system from even a single stem cell. We've been able to image it as it's regenerating and see at what point the newly regenerated neurons integrate into circuits and recover their activity. We aim to understand the nervous system from molecules all the way to behavior to establish it as a strong model for nervous system regeneration.

Understanding why some animals regenerate and some don't is really what we're after, and I'm super excited about moving forward with comparative approaches. Most researchers are studying one species of hydra, but I would like to start cutting up every hydra we can get our hands on to see the differences in regenerative ability across the whole genus. We are writing grants to start building tools and getting the genomic resources up and running for 10 species and will start comparing their nervous systems as well.

▲ The freshwater Hydra is famous for being in a continual state of self-renewal. Credit: Jan Huisken

Do you feel free to pursue curiosity-driven research, to follow knowledge for its own sake, or are you pressured to meet certain expectations to secure funding?

Curiosity is integral to who I am as a scientist. It's of course more challenging to get funding for anything that's not directly going to help human health, but I wouldn't want to change what I'm doing — following knowledge for its own sake. I try to emulate Phil Newmark, the eminent planarian researcher at the Morgridge Institute. He was the outside reader of my Ph.D. thesis and continues to support my career with letters of recommendation. I never worked in his lab, so he gets no credit for helping me, it's out of kindness. And he has really high standards for his own exceptional science.

What is your dream outcome for your work 20 years down the road?

I'd love to be able to understand all the parameters of regeneration, including of the nervous system, at such a level of detail that we could program a computer to simulate it. Then we could understand and predict how breaking different parts of the organism might affect it.

What we do is important, but it's a small piece of the bigger scientific enterprise. I think we'll provide interesting insights and help the field go forward, but I don't think I'm going to solve regeneration. My greatest contribution is likely to be in the scientists that I train, and the students I get to work with and influence. That's really the thing I'm most proud of, and where I believe I will make the biggest mark on the world.

You could consider this a golden age for regenerative biology. New genomics approaches that allow us to collect massive amounts of data can be combined with techniques like CRISPR to genetically modify the organism.

Want to answer a big question in science? Ask a bigger one

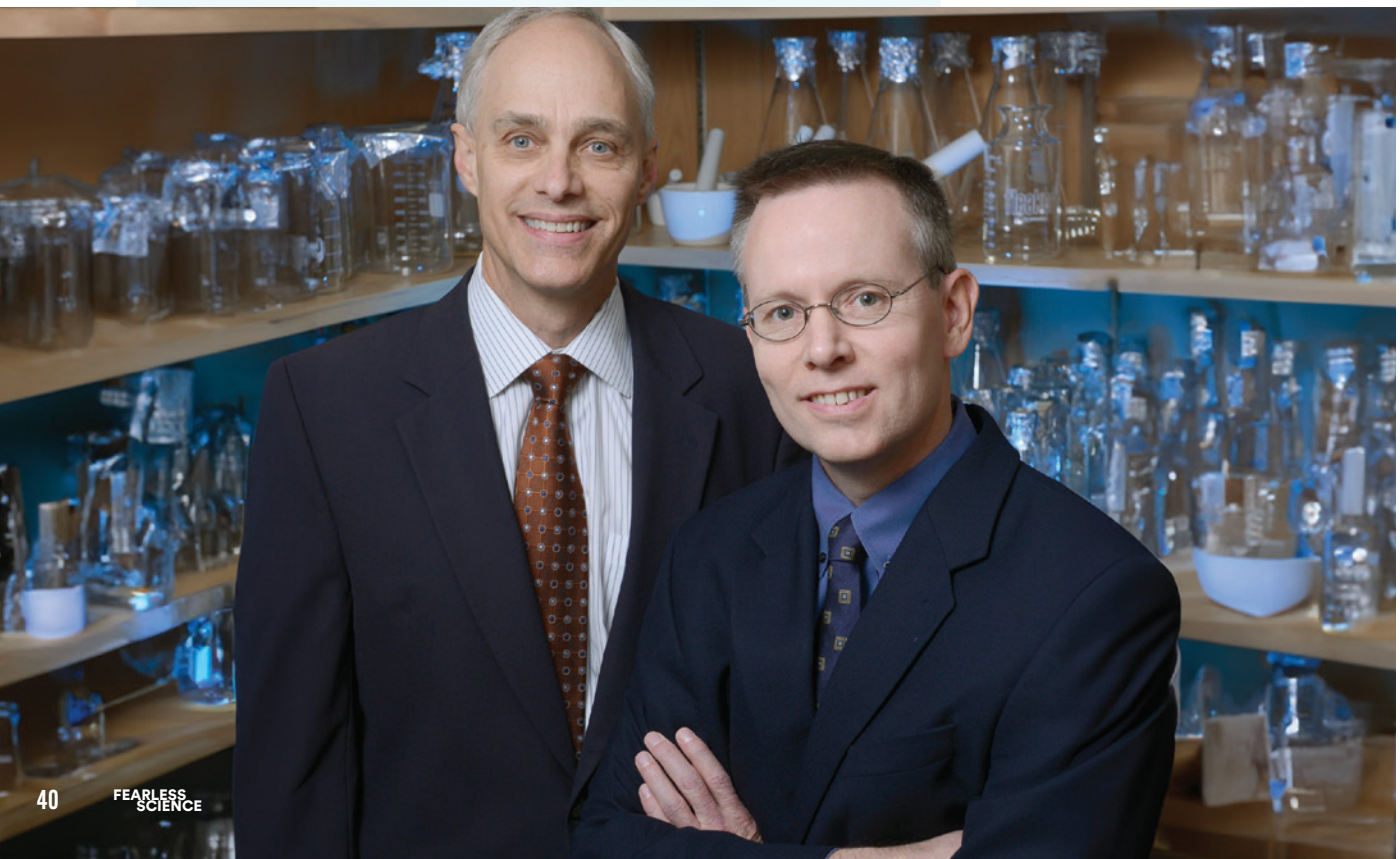
David Mangelsdorf, professor and chair of pharmacology at the University of Texas Southwestern Medical Center, talked to *Fearless Science Magazine* about his lifelong fascination with big, high-risk challenges in science. That fascination has led him to understand the role of an "orphan" nuclear receptor in liver metabolism — and the development of drugs that target liver disease.

When did you realize metabolism and nuclear receptors would be your scientific path?

As a graduate student I worked in a laboratory at the University of Arizona that discovered the vitamin D receptor — a protein in the nucleus of the cell that helps regulate calcium metabolism. I credit my mentor, Mark Haussler, a scientific rock star who made science fun. In his lab, we had to join a journal club where we took turns presenting papers and one was on the new technique of cloning genes. That sparked my interest to clone the vitamin D receptor. My philosophy at the time was, I'm going to take the riskiest project that I can think of, knowing that if it fails, it fails, but I will have learned a lot. Or this could be something that would transform the field, which it did.

How did that philosophy influence your career?

For my postdoc I went to Ron Evans' lab at the Salk Institute. He was this guru molecular biologist wizard who is one of the most cited scientists in the life sciences, and he had this



David Mangelsdorf (left) and Steve Kliewer are long-time collaborators in nuclear receptor research.

same philosophy. The first time I met him, he said to me: To answer a big question, you have to ask a big question. So I decided to ask: Are there any more of these nuclear receptors? It was a high-risk project, but that's what I did.

I have a high tolerance for risk. I call it making the meal or cleaning it up. Cockroaches do a great job of cleaning up the meal. I don't want to do cockroach science. You could be very successful building on what others have done, but I wanted to be the person writing the stuff that's going into the textbooks.

How did you build on your knowledge of receptors to reach your breakthrough on liver treatment?

At Ron Evans lab, I discovered what were called orphan receptors, proteins that looked like nuclear receptors, but we had no idea what they did. It turns out there are 48 of them, and when I came to the University of Texas Southwestern Medical Center, I worked on one that turned out to be very important in liver metabolism and cholesterol homeostasis. The bile acid receptor that we discovered is now an FDA-approved drug target for diseases of the liver, and we were off to the races.

What is a current area of focus for you and your lab partner Steven Kliewer?

Steven Kliewer was a postdoc with me, I later recruited him to UT Southwestern where we run a joint laboratory. We were working on the downstream targets of the nuclear receptors we had discovered. One was a receptor in the liver that responds to nutrient stress, such as starvation, or too little protein, or too much sugar. This kind of stress activated a protein called FGF21. The one stress that really drew our attention was alcohol, because it seems to have an effect in humans as well as mice.

In animal models we found that FGF21 sends a signal to the brain to stop drinking more alcohol. If you knock out FGF21 receptors in the brain, or you knock out FGF21, they'll drink more than they normally would, but if you give it as a drug, they have an aversion to alcohol. We also noticed they will drink three or four times as much water as normal, which is important because alcohol dehydrates you. We don't know if this would work in humans, but in mice it also creates body heat, which can prevent hypothermia caused by alcohol.

Does FGF21 have the potential to be like what Narcan does for opioid overdose?

Another outstanding question was whether FGF21 can also regulate how long an intoxicated animal remains unconscious. We gave mice a binge dose of alcohol after eliminating FGF21 from the body and they remained unconscious two to three times as long. Remarkably, if you do the same experiment and instead give a therapeutic dose of FGF21, the animals wake up three to four times faster. We figured out the brain mechanism that FGF21 works through to have this effect. And now we're studying whether this mechanism can reverse binge drinking suppression of breathing and heart rate.

Clinically it could be very useful. If a person comes into the emergency room unconscious from alcohol, having a compound to give as a shot that wakes them up faster could potentially save their life. And it could save millions of dollars by not keeping them in the emergency room for as long. We're exploring this now with a new startup biotech company.

What is the impact you think this work can bring to the world?

Steven Kliewer and I are truly 100% equal team, and we've discovered four or five things that turned out to be therapeutic. I've always wanted to strive to make change, not incrementally, but giant leaps forward that require that high tolerance for risk. Howard Hughes Medical Institute has funded my research for three decades, and at the end of every five-year funding cycle they ask: Where would this field be if David Mangelsdorf did not exist? Did you change the trajectory? And so that's been my goal, to change the tr*ajectory.*

The bile acid receptor that we discovered is now an FDA-approved drug target for diseases of the liver, and we were off to the races.

▲ Eric Wright (right) runs as many as 17 million computational jobs each year to analyze bacterial genomes.

Mining millions of genomes for the next powerful antibiotic

Erik Wright, assistant professor of biomedical informatics at the University of Pittsburgh, spoke to *Fearless Science Magazine* about how his quest to discover new antibiotics to counter resistance — and how that pursuit has made him biology's No. 1 user of the Open Science Pool for advanced computing.

How did an electrical engineer end up as a microbiologist?

After a few years working at Apple as an electrical engineer, I decided to go back to grad school and switched to environmental engineering. Studying water and wastewater treatment introduced me to microbes and bacteria and I just fell in love with it. I shifted to microbiology for my Ph.D. at UW–Madison, and the prerequisite classes felt like I was being fed gold nuggets of information. There's this whole invisible universe out there of microorganisms that I was completely oblivious to. I found a little niche for myself doing biology tied to computing. And now I run what I call soggy lab, which is a hybrid wet and dry lab together.

Why did you decide to make antibiotic resistance the focus of your research work?

The bugs evolve resistance to our drugs. It's a really hard thing to counter, and it's especially hard to reverse. I like that it's so difficult, that's probably the main draw. I live and breathe the idea that resistance is something that can be stopped and

We aim to build an ecosystem that will live on the grid, which is a little bit of a wild idea, but it will continuously update and compute new genomes and add them into a giant comparison of all genomes versus all genomes.

reversed. I began to study the natural antibiotic producers, the microorganisms that we get about 70% of our antibiotics from. These organisms have been naturally producing antibiotics for about half a billion years at least, and because they're mostly bacteria, they've also figured out how to resist them.

What are the areas of focus for your lab?
We're one of the few labs that studies what strategies bacteria use to avoid resistance. Then we want to understand how to bring that strategy to the clinic and scale it up.

We are studying durability, to understand why some antibiotics have been able to avoid resistance. And we are exploring how we can prescribe them in a multidrug cocktail such as for HIV and tuberculosis. The vast majority of the antibiotics we give are pure compounds in a high dose, but that's only one hurdle for the bug to jump over, we want to present them with many hurdles.

We're trying to figure out how to work with the existing available pool of drugs to do something that's better than what we currently do. And we think that by changing the way we treat patients — mimicking the biology that currently exists — then maybe we can figure out a more sustainable solution.

You are the number one biology user of high throughput computing with the Open Science Pool. How do you integrate computational approaches to tackle antibiotic resistance?
I had the extreme advantage of being part of the Wisconsin Institute for Discovery at UW–Madison, so I was an early adopter and that has completely changed my career. I've been using the Open Science Pool for 12 years and we simply could not reach the kind of computing capacity we need without it. Because it's open, we don't have to write grant proposals, which allows us to do a lot of exploratory work. I can't overstate how much that is worth to me. It is also set up in a way amenable to my research. Instead of shared memory computing, the OS Pool is set up with a distributed memory. We like to split up our work into tiny compartments that each last an hour, so we hit something like 17 million jobs last year.

Why is your lab so computationally intensive?
The main thing my lab's doing is comparing genomes by processing huge data sets in millions of separate computing jobs on the grid. We have access to about 2 million bacterial genomes, and we have developed software that can draw on thousands of computers to quickly compare new genomes to those that already exist. Then other computers store the data, and thousands more process and analyze the results — all through this gigantic set of grid jobs that is always running.

We end up having groups of genes that are the same gene across different organisms, and then we build software that tells us which genes work together. From that we can do things like find which groups make natural products like antibiotics.

We aim to build an ecosystem that will live on the grid, which is a little bit of a wild idea, but it will continuously update and compute new genomes and add them into a giant comparison of all genomes versus all genomes. What we're ultimately going to do is take those groups of genes that work together, transplant them into a host organism, and then turn them on and see what product they make.

What would a dream outcome look like from the research that you're doing now?
I would like to discover new small molecules that no one has known about. And to find totally new drugs if I could. We've developed ways of finding genes that work together, that nobody's seen before. But we have no idea what antibiotic or other compound that makes. It's on the order of millions of different possible compounds and it's a dream to bring some of those to reality. We have developed ways of handling hundreds of thousands of genomes, approaching millions, so this is very much possible.

‘With current technology, preterm births are rarely preventable’

BY MELISSA SKALA
KRISTIN MYERS
MICHELLE L. OYEN

Pregnancy is an engineering challenge — diagnosing and treating preterm birth requires understanding its mechanics

Why are babies born prematurely? Researchers still don’t really know.

Obstetricians are very good at managing the process of birth. But when it comes to predicting whether a baby will be born in a timely manner, the science is still catching up. Research on the causes of preterm birth is decades behind that of other conditions such as cancer. That means nurses, doctors, midwives and doulas don’t have the tools and resources they need to do the best job possible when babies are born before 37 weeks of pregnancy.

Yet pregnancy is also an engineering challenge because it involves physical forces. Clinicians are dealing with an average 7-pound (3.2 kg) baby in around 1 liter of amniotic fluid held in place with a membrane less than 1 millimeter thick — all within a uterus that started out the size of a fist. That involves forces, pressures and mechanical loads that all can contribute to maternal, fetal and placental conditions that can trigger preterm birth.

In a paper published over 150 years ago, a physician recognized that birth is a mechanical event. But he was using 19th-century technology to measure the pressure per area on membranes that support pregnancy. Only now do researchers have the mechanical, electrical and computational engineering expertise to address the challenges of preterm birth.

But research on preterm birth is still so early that scientists first must build the tools to study it before they can diagnose and treat it. Our team of researchers is working to do just that.

Many complications can cause preterm birth

It's hard to narrow down who is at risk of preterm birth because there is no single cause. Preterm birth can be triggered by multiple factors involving the pregnant person, the fetus, the placenta or the fetal membranes attached to the placenta that connect fetus and parent.

Globally, 1 in 10 live births are preterm, or born before 37 weeks of pregnancy. Of these preterm births, about 30% to 40% are caused by premature rupture of the fetal membranes, and another 1% to 9% by the cervix dilating prematurely.

With current technology, preterm births are rarely preventable. Current screening tools to measure the risk of preterm birth are fairly primitive. Doctors use ultrasound to monitor the size and position of the baby, and they touch the cervix to feel whether it is softening, a normal process prior to labor but problematic if it is happening too soon.

If the baby isn't growing, perhaps because of insufficient blood supply to the placenta, doctors perform preterm C-sections to prevent stillbirth. Preemptive C-sections are also sometimes used to prevent or treat preeclampsia, or dangerously high blood pressure during pregnancy.

In both cases, patients and doctors balance the benefit of an early C-section for the fetus and the parent against the risks associated with preterm birth, including a lifetime of breathing, vision, cardiovascular or other health issues for the child.

▸ Kayvan Samimi, an assistant scientist in the Skala Lab, leads a multi-year project to image fetal membrane samples that have been provided by partner hospitals after births. Meriter Hospital in Madison and Intermountain Healthcare in Provo, Utah, collectively provided more than 60 fetal membrane samples for the study, from both vaginal and C-section births.

KRISTIN MYERS,
Professor of Mechanical Engineering, Columbia University

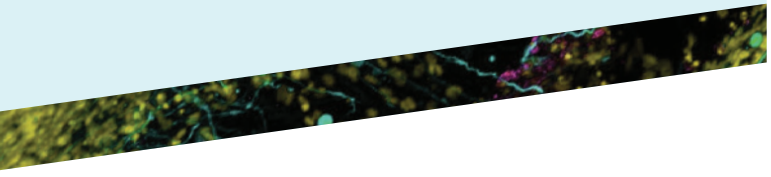
MICHELLE L. OYEN,
Associate Professor of Biomedical Engineering, Arts & Sciences at Washington University in St. Louis

MELISSA SKALA,
Morgridge investigator and Professor of Biomedical Engineering, UW–Madison

Better core understanding of the biomechanical forces at work during pregnancy can give researchers new places to look for diagnostic clues.

“Research on preterm birth is still so early that scientists first must build the tools to study it before they can diagnose and treat it. Our team of researchers is working to do just that.”

MELISSA SKALA —
PROFESSOR OF BIOMEDICAL ENGINEERING,
UNIVERSITY OF WISCONSIN–MADISON



The wide variety of factors that play a role in preterm birth make early diagnosis a challenge. But a better core understanding of the biomechanical forces at work during pregnancy can give researchers new places to look for diagnostic clues.

Tackling the challenge from multiple angles

Pregnancy is essentially a physical process, from the uterus stretching to accommodate the baby to the cervix dilating when labor contractions begin and it’s time for the parent to push. And when something mechanical goes wrong, it can lead to tragic results.

For example, maternal risk factors for preterm birth include rupture of the uterus or preeclampsia. The placenta could also detach from the wall of the uterus, causing the parent to bleed to death. Carrying twins comes with additional amniotic fluid and blood volume that adds an extra load to the placenta, which can trigger preterm labor.

Our team of biomechanical and biomedical engineers is working to understand the underlying causes of preterm birth from different angles, all with a view toward diagnosis and intervention.

One of us, Kristin Myers, studies the biology of tissue remodeling to quantify the biomechanics of pregnancy. Her lab creates computer models to measure how the uterus, cervix and fetal membranes work to carry the mechanical loads that pregnancy generates. She and her team use ultrasound to look at how the uterus grows and stretches and how much mechanical load is on the cervix, predicting whether it will fail too soon. Using the uterus as a pressure gauge for the mechanical environment of pregnancy could help identify problems before they occur.

Another of us, Michelle Oyen, studies the physics and materials science of soft tissues focusing on the mechanical properties of the fetal membranes and nutrient transport in the placenta. Her lab, along with Myers’ team, is applying big data and machine learning to anonymized medical records to create digital twins — or computational models of a given patient’s health data — that could help predict how a pregnancy will unfold. This may help physicians treat or avoid pregnancy complications.

Finally, Melissa Skala uses a noninvasive technique called optical coherence tomography. This imaging method produces 3D images of tissues that can’t be captured by ultrasound or MRI, such as extremely thin fetal membranes. Her lab used this technique to study how fetal membranes rupture under different pressures, providing a baseline of information that can be used to build better digital models of fetal membrane stress. Improved imaging of the fetal membranes and cervix can alert physicians to when these structures are at risk of failing.

Better imaging and better models

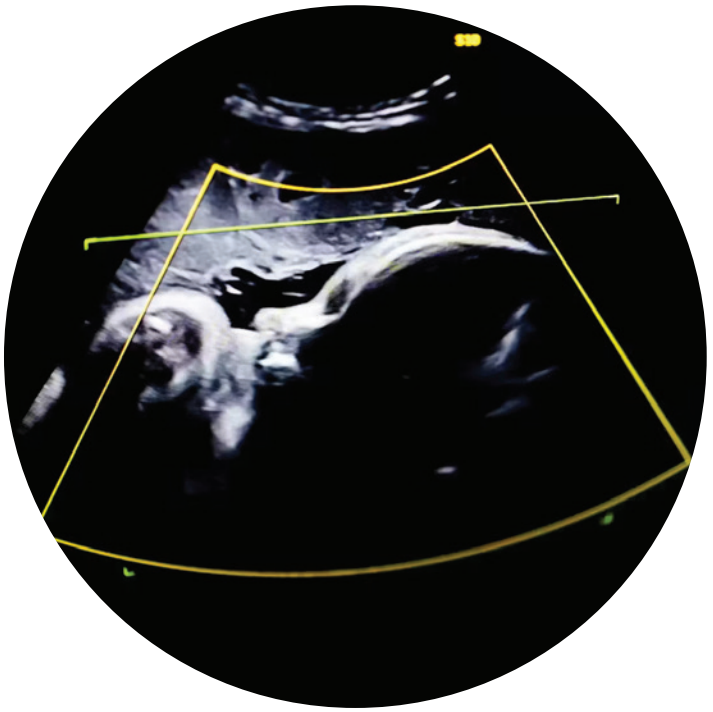
The Holy Grail of preterm birth prevention is early diagnosis. An early warning checklist for preterm birth risk could help protect the health of both baby and mother.

This checklist could look like your doctor ordering an imaging scan as soon as you find out you're pregnant to understand the size of your uterus and cervix. Then they might take a swab of vaginal fluid to analyze biological changes in your cervix.

Better modeling techniques would be able to assess how your pregnancy will progress, and more precise imaging tools could measure changes over time. With a better prediction for when labor will start, doctors and patients can make a more informed decision on whether a C-section is necessary.

An accurate early warning checklist for preterm birth is still years away. But researchers in reproductive biology, epidemiology, bioinformatics and engineering are working hard to better understand in greater detail how babies are born and the many complications that can arise along the way, including preterm birth.

We believe that engineering — creative problem-solving using technology — is a critical addition to the multidisciplinary approach needed to address the complexity of preterm birth.



FEARLESS LEADERS

MESSAGE FROM THE CHAIR, JACQUELYN FREDRICK

The Morgridge Institute practices fearless science, and its board of trustees is extraordinarily proud to elevate and advance this mission.

Our scientists are the top of their field, and we give them the freedom to pursue their ideas wherever they take them.

This concept of curiosity-driven science permeates the organization, right down to the postdocs and undergrads. It's all one team, and they're all so energetic and brilliant.

What also differentiates the Morgridge Institute is our commitment to engage with the public, especially the schoolchildren in the state of Wisconsin. Our researchers truly value interacting with people in our communities to share their love of science.

The role of the board is to uphold our commitment to curiosity-driven research. To achieve this, we bring a diversity of research experience in science from different perspectives. Many of us have a deep underlying commitment to the University of Wisconsin-Madison, and some have gone on to build companies focused on human health, based on our vision of fundamental science. Above all, we have the unique honor of benefiting from the wisdom of our founders John and Tashia Morgridge.

We are aided by our independent and engaged scientific advisory board. I consider them an integral part of our leadership. They bring not only a perspective of how to achieve our mission, but also the knowledge of what is going on in the broader ecosystem of high-level research institutes, giving us greater confidence in our judgment of scientific quality.

Each of us on the board embraces three elements that are core to who we are: our values of collaboration, freedom, and a focus on excellence; our dedication to social responsibility around research and science with the greater public; and our deep connection with UW–Madison.

Our measure of success is clear. The board's number one priority is to ensure that the vision and mission of our founders are well grounded as we bring in new generations of people, whether they're new board members, scientists, or partners at the UW. To have lasting impact, we must continue to hold ourselves accountable to this goal.

Morgridge scientists have great passion for the young people they teach. Entire generations of great scientists are being developed and mentored here, and I think that's one of the more amazing parts of our story.

JACQUELYN FREDRICK

"The board's number one priority is to ensure that the vision and mission of our founders are well grounded as we bring in new generations of talent."

JACQUELYN FREDRICK

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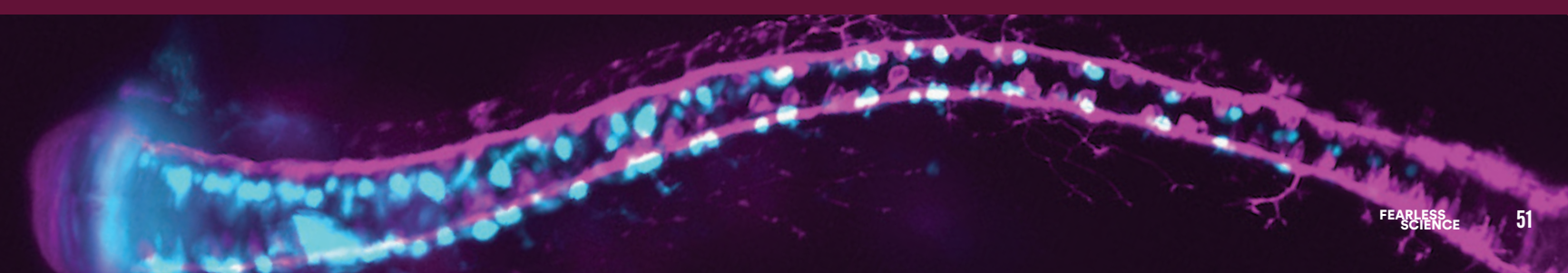

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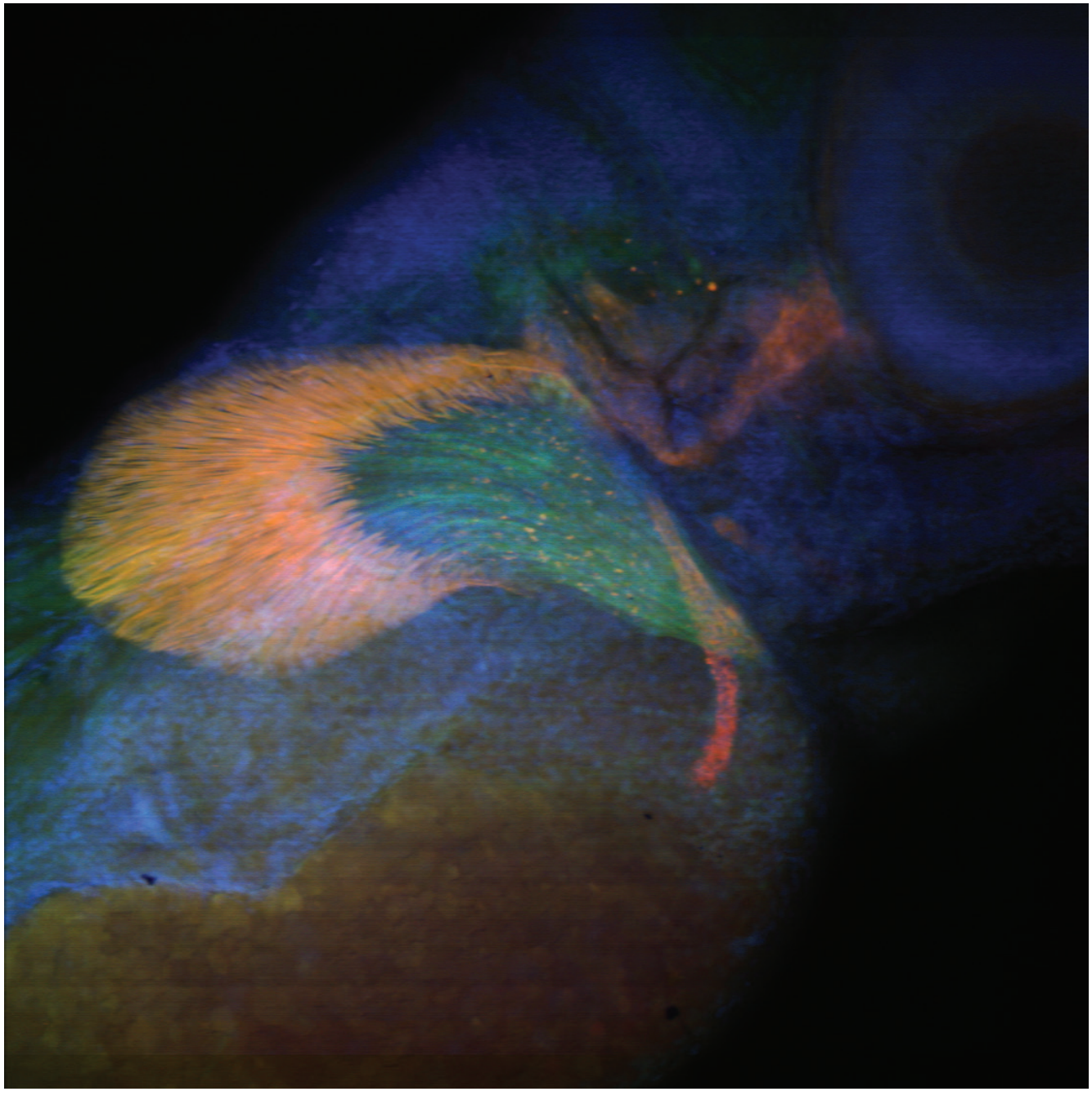

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MAKE A GUESS, EARN A PRIZE

“The important thing is to not stop questioning. Curiosity has its own reason for existing.”

— ALBERT EINSTEIN

Ignite Tomorrow's Discoveries

YOUR GIFT IS THE KEY

In the world of science, the greatest breakthroughs don't come from asking "safe" questions. Discoveries emerge when daring minds support fearless exploration. That's why our scientists pursue the uncharted frontiers of biology, health and medicine.

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When you make a gift to the Morgridge Institute, you empower pioneering scientists. Your support helps develop new disease prevention, discover innovative treatments and launch breakthrough diagnostic technologies.

Let's improve human health together.

Join us with your gift of support — together we'll discover the next big breakthrough. Make your gift of any size today.

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Contact us:

Bill Swisher
(608) 316-4364
bswisher@morgridge.org