MORGRIDGE
INSTITUTE FOR RESEARCH

FALL 2024

YOU MAKE A DIFFERENCE

INSIDE

A special report for supporters of the Morgridge Institute for Research

BRAD'S UPDATE

People at Morgridge — bright, committed, and curious — follow scientific evidence to propel our work in new directions, fulfilling our mission.

So, when we hired two new Morgridge investigators, regenerative biologist Ken Poss from Duke University and virologist Megan Spurgeon from the University of Wisconsin–Madison's McCardle Laboratory, all of those traits mattered.

Ken and Megan join me in recognizing you, whose crucial support enables our efforts to improve human health and inspire scientific curiosity.

Ken delves into how organisms regenerate damaged heart and spinal cord tissue, and his research has potential application to humans. He will also serve as our director of regenerative biology. Megan studies tumor-causing viruses, including human papillomavirus — the leading cause of cervical cancer — and hepatitis B. She will work in the John W. and Jeanne M. Rowe Center for Research in Virology.

The research Ken and Megan conduct is promising, important, and fascinating. But I think the character and the attributes of these individuals are just as important as what they work on. They are individuals with a never-ending curiosity. Their addition to the Morgridge community is another important step on the pathway to being the kind of research institution we have envisioned. Thanks to your support, these scientists can launch their new labs and research endeavors at Morgridge.

We seek out scientists who are driven by an unquenchable need to find out new things — people who get up in the morning and say, "I can't imagine doing anything other than this." Society distrusts celebrity for celebrity's sake, but likes that old-fashioned idea that curiosity and persistence can trigger accomplishment. And if recognition follows, great.

That stamp of character runs through our institute, from undergraduates to postdoctoral scholars to scientists and investigators.

THANK YOU

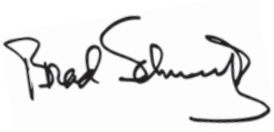
Your vision and support attract talented researchers who power the Fearless Science that helps improve human health.

They all add to the vibrancy of our scientific community and help us live up to society's highest ideals of what science should be doing.

You are an essential part of this story of commitment. Your vision and support help us attract gifted researchers and allows them to unleash their creativity as they solve the riddles that will advance human health. Just as important, your support also helps us realize our outreach and education efforts, to extend the influence and understanding of science.

You have given us your trust, your investment, and your inspiration and we work each day to make you inspired. In this report, you'll read about some of the great work you make happen as donors.

Thank you for being part of our community,



Brad Schwartz, M.D.

Carl Gulbrandsen Chair
Chief Executive Officer
Morgridge Institute for Research

P.S. What's on the cover? Meet Kim Huggler, a graduate research assistant working in the lab of Morgridge Investigator Jason Cantor. The team studies how environmental factors impact cell physiology.

INTRODUCING KEN POSS

HEART REGENERATION PIONEER

Investigator, Morgridge Institute

Professor of Cell & Regenerative Biology, UW–Madison

A biologist who explores the potential life-saving mechanisms that organisms use to regenerate damaged heart and spinal cord tissue joined the Morgridge Institute for Research this fall.

Kenneth Poss comes to Madison from Duke University, where he was the James B. Duke Professor of Regenerative Biology. He researches an area that has grown tremendously in the years following James Thomson's landmark discoveries in human stem cells.

With Thomson's retirement in 2022, Morgridge and the School of Medicine and Public Health at UW–Madison teamed up to recruit another international pioneer to bolster Wisconsin's leadership in this biomedically important field.

Morgridge CEO Brad Schwartz says that Poss was the ideal candidate — not just as a great scientist but as someone who wants to build community and strengthen his entire field.

"At Morgridge we are very committed to curiosity-driven research and fundamental mechanisms of biology, and that is really attractive to Ken," Schwartz adds. "Because that's how he got to where he is today, by following these intrinsically fascinating questions."

His work at Morgridge is supported by donors like you who value the concept of Fearless Science.

Poss, a Green Bay native who spent 21 years at Duke, studies how some animal species are capable of regenerating virtually any damaged tissue in their body. The Poss Lab uses zebrafish, a model species that is uniquely suited to reveal mechanisms of regeneration. He was the first to demonstrate how zebrafish regenerate their heart muscle cells in response to injuries that would be lethal to mammals, including humans.

Poss mainly investigates the biological rules that allow zebrafish to regenerate their organs. But his work raises exciting questions about whether similar capabilities could one day be unlocked in humans. Human heart tissue does not repair and regenerate itself after a heart attack, leading to scarring and often debilitating loss of function for millions of people.

Several years ago, the Poss lab discovered that genetic "enhancer elements" switch on regeneration programs in zebrafish — and in 2023, the lab showed that they can also work in mammals. These enhancer elements guided repair of damaged tissue in studies in mice and pigs. Most importantly, Poss says, the regeneration responses were restricted just to the injury site, and the enhancers shut down naturally over time.

"It's a strong proof-of-concept study," Poss says. "Factors that can turn on regeneration are often very potent factors that if mutated or over-expressed could cause cancer. We will need to engineer them in ways that will have the very tightest control only in a specific cell type for a specific time."

"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. That's what makes science the most exciting job there is."

— KEN POSS, WHOSE APPOINTMENT WAS MADE POSSIBLE THROUGH YOUR SUPPORT

INTRODUCING MEGAN SPURGEON

EXPLORES LINK BETWEEN VIRUSES, CANCER

Investigator, Morgridge Institute

Assistant Professor of Oncology, UW–Madison

Anywhere between 15 and 20 percent of all cancers are known to be caused by viruses. But with millions of different viruses living on or inside the human body, have we only scratched the surface of our understanding of how viruses impact human health?

New Morgridge Institute Investigator Megan Spurgeon would answer "yes." Her lab — established thanks to your critical support — provides a powerful case in point. Spurgeon studies the newest identified human tumor virus, called Merkel cell polyomavirus. This virus was discovered only about 15 years ago but is increasing in frequency and is implicated in a rare and deadly form of skin cancer.

You are making this work possible. Your support will help unravel more viral mysteries.

Spurgeon's research will fit right in at in Morgridge's John W. and Jeanne M. Rowe Center for Research in Virology. The center has an important track record of researching viruses with oncogenic potential — the tendency to cause cancerous tumors — including human papillomavirus (HPV) and hepatitis B. Spurgeon joins Morgridge from UW–Madison's McArdle

THANK YOU

Your support unlocks the power of research benefitting human health.

Laboratory for Cancer Research, where she was a senior scientist in viral oncology.

"As the power of sequencing and bioinformatics continues to evolve, I think that — similar to Merkel cell polyomavirus — we're going to discover that viruses, whether they're new, or we just haven't discovered their oncogenic potential yet, contribute to other human cancers," Spurgeon says.

Merkel cell polyomavirus is a virus virtually every human gets during infancy, and at the time produces no known symptoms or side effects. Yet it's the driver for Merkel cell carcinoma, which impacts about 3,000 Americans annually and is five times more deadly than melanoma.

Spurgeon also studies HPV — a virus widely known as the leading cause of cervical cancer but also implicated in several other cancer types. Like Merkel cell polyomavirus, HPV belongs to the family of small DNA tumor viruses and integrates its DNA into human cells. That is an important precursor to developing cancer.

"The Rowe Center identified tumor virology as the pivotal area for our latest investigator search because of its dramatic human and scientific impacts," says Morgridge Investigator and Rowe Center Director Paul Ahlquist. "In that already high-value context, we're particularly delighted to have recruited Megan, who, in just the last few years, has produced multiple major advances with small DNA tumor viruses."

"Since getting the position here, I've thought a lot about what fearless science means to me. And it's really about challenging scientific dogma, which I think can be one of the biggest impediments to scientific progress. Your support enables that."

— MEGAN SPURGEON

THE YEAR IN DISCOVERY

THANK YOU

Your support makes a profound impact on science. We cannot make these important, curiosity-driven discoveries without you.

1

Genetic blueprints of creatures great and small

Size doesn't matter in genome sequencing, as a team of Morgridge Institute researchers illustrated when assembling two new reference genomes — one from the world's largest mammal — the blue whale — and one from one of the smallest, the Etruscan shrew.

Researchers published both genomes. Interest in them began with James Thomson, Morgridge's emeritus director of regenerative biology and his research on the biological mechanisms behind the "developmental clock." Generally, larger organisms take longer to develop from a fertilized egg to a full-grown adult than smaller creatures, but the reason why remains unknown.

"It's important just for fundamental biological knowledge from that perspective. How do you build such a large animal? How can it function?" says Yuri Bukhman, a computational biologist in the Ron Stewart Computational Group.

One practical application of this knowledge is in stem cell-based therapies. To heal an injury, stem cells must differentiate into specialized cell types of the relevant organ or tissue. The speed of this process is controlled by some of the same molecular mechanisms that underlie the developmental clock.

JOURNALS: MOLECULAR BIOLOGY AND EVOLUTION, SCIENTIFIC DATA

2

A new signaling pathway controlling planarian germ cells

Biogenic monoamines — molecules like dopamine and serotonin — are famous for their role as the brain's emissaries of mood, learning and memory, stress mechanisms, and fight-or-flight responses in the body.

But these neurotransmitters existed long before brains popped up in the evolutionary tree. While they are prevalent in plants, bacteria, and single-cell organisms, their functions there are far less understood.

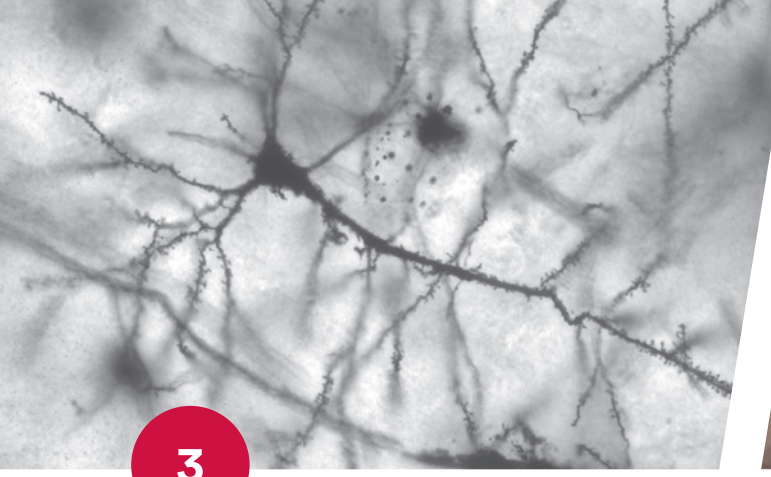
Scientists at the Morgridge Institute have discovered another task for monoamines. They play a key role in the reproductive organs of flatworms called planarians, where they appear to be critical for the development of female and male germ cells, the cells that eventually become eggs and sperm.

A Morgridge regenerative biology team demonstrated that such transmitters are not only signals originating from the planarian brain. They're also highly localized within special "niche" cells that regulate germ cell development.

"We are excited about this because it demonstrates a new paradigm for niche-to-germ cell signaling," says Research Investigator Melanie Issigonis, the study's lead author.

The next step is to understand how these signals function in flatworms and across the animal kingdom — taking us that much further into a mostly unchartered scientific territory.

JOURNAL: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES



3

Understanding stem cell aging in the brain

Researchers can harness the light naturally thrown off by biological specimens to better study the different states of stem cells in the nervous system, thanks to a tool developed through collaboration between Morgridge and UW–Madison scientists.

The tool brightens chances for studying the way stem cells age — and potentially unlocks new knowledge about neurodegeneration.

Darcie Moore, a UW–Madison neuroscience professor, partnered with Morgridge Investigator Melissa Skala to identify and decode the behavior of neural stem cells in mice. They found that the way these cells emit natural light — their "autofluorescent signatures" — can be matched to active and quiescent cell states.

"The quiescent state is very important," says Moore, "Aging and neurological diseases limit the exit from quiescence, so we have a great need to study adult neural stem cells in their different cell states."

By revealing these autofluorescence signatures, Moore and Skala have developed a tool that can aid in studying adult neurological diseases and aging, but potentially also expand beyond neuroscience.

"These natural signals within the cell can reliably identify cell function and identity," Skala says. "It's like nature is trying to tell us all the secrets of life."

JOURNAL: CELL STEM CELL

4

Advanced imaging uncovers a parasitic 'kiss'

Using the power of optical metabolic imaging, Morgridge researchers revealed how a parasite that causes toxoplasmosis affects the metabolism of host cells during the course of an infection.

Toxoplasmosis is a lifelong chronic infection prevalent in about 30% of the human population.

Assistant scientist Gina Gallego-Lopez spearheaded a collaboration between Morgridge Investigator Melissa Skala and Laura Knoll, a UW–Madison medical microbiology and immunology professor.

Optical metabolic imaging allows researchers to monitor metabolism within live cells by detecting fluorescent activity in the cells without killing them.

Gallego-Lopez was also curious about metabolic changes associated with a mechanism known as "kiss and spit," where the parasite interacts with the host cells' surface before full invasion.

"One cell may be infected while the cells around it are not; it looks like the parasite 'kisses' those cells and then injects some proteins," she says. Surprisingly, the parasitic kiss created changes on par with full infection.

Ultimately, Gallego-Lopez hopes to establish her own lab to continue studying parasites such as Toxoplasma and Cryptosporidium, a parasite associated with colorectal cancer. "I want to understand how it's possible that these parasites induce changes in the host to be able to induce cancer with time," she says.

JOURNAL: MBIO

5

Imaging approach spotlights cellular secrets

Morgridge's Randy Bartels is using optical imaging to answer complex biological questions by observing previously difficult-to-capture phenomena.

The Bartels Lab and collaborators developed a new approach that looks into biological samples to uncover hidden information within cells and tissues. For the first time, researchers used third harmonic generation holographic microscopy to collect measurements of light.

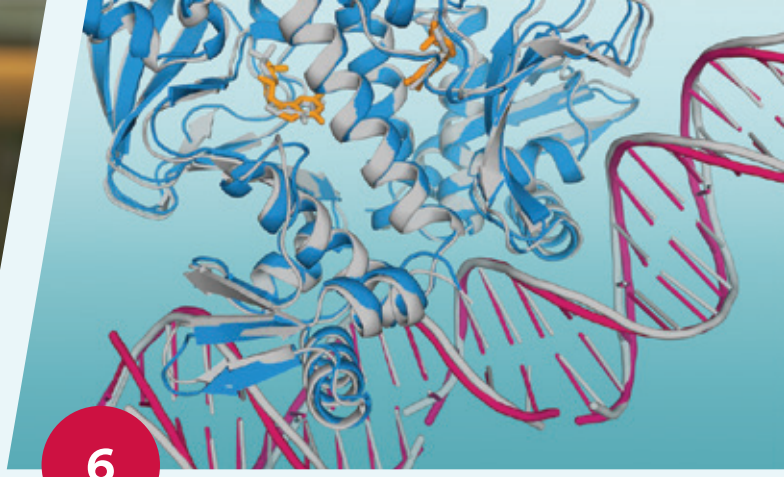
Researchers suggest that information derived from the technique can provide additional details about fundamental biological structures.

"This allows us to access information about the way cells and tissues are organized, which could lead to new way of studying and detecting disease," says Bartels.

"With this information, we can unlock new material properties or solve problems to generate three dimensional images. This opens up the possibility of new applications in biomedical imaging and material science," adds Yusef Farah, a postdoctoral researcher and first author of the published work.

One promising application of this technology is to perform rapid assessments of tumors, to identify biomarkers of cancer within the cells of a biopsy sample. Instead of needing to wait a couple days to prepare and fix slides, this could be performed at a microscope in an operating room while a patient is still in surgery."

JOURNAL: OPTICA



6

Grad student raises open-source conflict with new AI model

As society embraces new technologies, scientists must balance exchanging ideas and preventing public misinformation and polarization.

Bryce Johnson, a computer sciences graduate student in the lab of Morgridge computation biologist Anthony Gitter, activated this idea with an opinion piece about the artificial intelligence software AlphaFold 3 in the digital magazine, Undark.

Google DeepMind, a private research subsidiary of Google, developed AlphaFold. The most recent model, AlphaFold 3, was published in Nature.

"This model claims it can predict the structure of proteins and their interaction with DNA, RNA, and other types of biological molecules," says Johnson. "The ability to know how these molecules interact with a protein can be really useful to revolutionize drug discovery."

Johnson questions how Nature editors seemingly allowed the AlphaFold 3 model to be described without adhering to the journal's usual open-source standards. "It felt like this was more about a promotion for a for-profit company," he says.

"This is a perfect example of the Morgridge mission of having scientists communicate to a broader audience about important issues," Gitter says.

JOURNAL: UNDARK

High school students sample Fearless Science

Part of the mission at the Morgridge Institute for Research is community involvement and building a broader understanding for science.

For three weeks in July, Morgridge welcomed 75 high school students from 13 rural high schools across Wisconsin to participate in hands-on science activities alongside researchers.

The 18th annual Summer Science Camp gave students a chance to learn about the depth and breadth of career opportunities in science and engineering.

Students explored the structure of proteins, learned about fruit fly genetics and their role in studying human disease, observed the biology and chemistry involved in cheese making, learned about the cutting-edge technology that drives discovery, and much more.

The camp also affords students a taste of university life. They lived in dorms during their stay and receive personalized advising from UW–Madison admissions and student financial aid.

Participants were part of Upward Bound, a federal program that provides support to low-income or first-generation high school student in preparation for college entrance.

Students who took part were enthusiastic about the experience. Ana, a student at Tri-County Area Schools, says she enjoyed being immersed in innovation, discovery and experimentation.

“Your support made it possible for me to explore fascinating scientific concepts, conduct hands-on projects, and develop a deeper appreciation for the wonders of our world.”

— ANA, A HIGH SCHOOLER AT OUR DONOR-SUPPORTED SUMMER SCIENCE CAMP

The experience was also embraced by Natasha, a Westfield Area High School student. “I learned a lot about stem cells and cardiomyocites,” she says. “What I learned here taught me not only about science, but about communication and that failure is the best way to learn, especially in science.”

Help Wanted:

DEEPEN RELATIONSHIPS WITH FEARLESS SCIENCE TOURS

Our new donor-hosted tours of the Morgridge Institute for Research provide avenues to spotlight the institute's work for new groups, building awareness, support, and understanding of its mission.

Called Fearless Science Tours, they are a new Morgridge initiative to introduce new people and groups to the institute.

We need your help. Come in for a tour, or host one. Tour hosts are Morgridge donors or sponsors who work with staff members to select tour content, dates and create invitation lists.

During the tours, small groups get a host-curated sampling of what makes Morgridge a leader in discovery-driven research, meet researchers and hear about their work, visit laboratories, and take part in Q-and-A sessions.

Rebecca Sikes, Morgridge's donor engagement manager, says the tours help spread knowledge of Morgridge's role, its researchers, and its work.

"This is an opportunity for current donors to connect their networks to our organization with a highly efficient tour. It's also an opportunity for donors themselves to refamiliarize themselves with our scientists and get a more personal look at the latest work our scientists are doing," Sikes added.

This is your chance to get involved as a tour host and introduce your friends and networks to our fascinating and crucial research. For more information, contact Sikes at rsikes@morgridge.org or (608) 910-0657 or Chief Development Officer Bill Swisher at bswisher@morgridge.org or (608) 316-4364.

THANK YOU

For supporting our efforts to increase public understanding of science and its vital role in society.

Rising Sparks:

MEET KASIA WIECH

MAKING SCIENCE MATTER IN EVERYDAY WALKS OF LIFE

As the first wave of millions of Ukrainians arrived by train in Poland, fleeing the Russian invasion in February 2022, Kasia Wiech was on a crowded Warsaw train-station platform helping get refugees daily supplies and housing.

“All of Poland was involved in some way in the response,” says Wiech, who was juggling volunteer service with her work as a Fulbright student researching neural networks at the University of Warsaw.

Working alongside evacuated U.S. Fulbright scholars from Ukraine, she raised more than $2,000 for basic and medical supplies.

The daughter of Polish immigrants, Wiech grew up in south Florida and is driven to tie science to society — whether through providing soap, baby shampoo, and other basic supplies to refugees or through her planned career in science policy or diplomacy.

"I think scientists need to make more efforts to show up in public spaces regularly, not just when there's a crisis. That really brings a culture that recognizes the value that science brings into our lives."

— KASIA WIECH

As a child, disaster piqued Wiech's interest in science.

"When Hurricane Wilma hit in 2005, and we didn't have power for two weeks, my dad and I would lay on our roof and watch the stars. That got me interested in physics," she says. "And my sister loved to play school when we were kids. She was seven years older, and I remember her using science books as part of her lesson plans."

She went on to earn a physics degree at the University of Florida but was motivated to link people with science.

"My research experience has given me a deep understanding of what the research enterprise looks like, how to think like a scientist and interact with scientists," says Wiech, who worked in Melissa Skala's biomedical imaging lab at Morgridge before graduating with a master's degree in biomedical engineering in August.

"As much as I love research, for me, the human part of everything in science has been really important. Where I shine and where I'm happiest, is in the middle," she says.

Working as a National Science Foundation graduate research fellow, Wiech researched autoimmune disorders, especially lupus.

She used patient samples to isolate T-cells and examine them with high-tech microscopes to view metabolic and chemical reactions. Her work was aimed at determining differences between people with inactive forms of lupus and those with more severe symptoms.

While doing that research, Wiech won a grant from SPIE, the international society of optics and photonics, to create an escape room-themed science outreach program for high school students at the Morgridge Summer Science Camps.

"It inspires the next generation of scientists," she says. "I think scientists need to make more efforts to show up in public spaces regularly, not just when there's a crisis. That really brings a culture that recognizes the value that science brings into our lives."

Wiech also earned a graduate certificate in life science communication. "Whether it's through diplomacy, policy outreach, communication, or advocacy, I want to help make sure that people feel like science is about them and for them," she says.

Wiech's Morgridge experience was crucial to her academic path and her future career.

"Working at Morgridge has been a fantastic experience," she says. "It really gives students the opportunity to explore their full selves and all of their interests by providing mentorship and funding. That's something that's unique and really beautiful."

THANK YOU

For supporting Fearless Science and expanding the limits of science.

Rising Sparks:

MEET RAISON DSOUZA

DSOUZA'S 'WHERE'S WALDO' QUEST FOR PROTEIN IMAGES

Raison Dsouza's parents hired tutors to help him take the exams needed to gain entry to engineering or medical schools in his native India. But the 15-year-old had a different goal.

Intent on becoming a physicist, he ditched his prep school studies, hung around cyber cafes, and played pick-up basketball.

"I didn't do well on the engineering and med school exams, and I had no option but to do a bachelor's in science," says Dsouza, who today is an assistant scientist in Morgridge's John W. and Jeanne M. Rowe Center for Research in Virology. "And my parents were fine with it. They supported me no matter what."

Dsouza's interest in physics bloomed after a teacher gave him a copy of Stephen Hawking's "A Brief History of Time" a couple of years earlier.

As an undergraduate, he was an insatiable reader, even winning a prize at St. Aloysius Degree College in Mangalore, India for borrowing the most books

from the library in a year. From there, he earned a master's degree in physics from the National Institute of Technology Karnataka.

With a hunger for learning abroad and proceeds from a scholarship in his pocket, Dsouza was attracted by Germany's Max Planck Institute for the Structure and Dynamics of Matter for doctoral studies.

During his work as a research fellow studying the superconducting properties of graphene, Dsouza's mentor left, and Dsouza's appointment was in jeopardy. Through luck and resourcefulness, Dsouza managed his way through the crisis.

"In Germany you have the beer-garden culture, where people go out and have a beer in the afternoon in the summer," he says. "Another researcher says, 'You do simulations. You're a computer guy. We have a problem we need to fix.'"

He first agreed to work with lasers and tissue ablation, then moved to another project in the same lab as a theoretical physicist looking at the behavior of proteins' role in photosynthesis. "It turned out to be a good thing because while I couldn't get a unifying theme in my Ph.D. thesis, I was able to tackle three or four problems, which my boss and I thought it was a win," Dsouza says.

He spent his postdoctoral fellowship at UW-Milwaukee using machine learning to analyze and improve images obtained through electron microscopy. Along the way, Dsouza met a postdoc working with Morgridge researcher Timothy Grant, who encouraged Dsouza to join the institute.

In Grant's lab, Dsouza is developing new computational methods to analyze cryo-electron microscopy images, trying to find specific particles in "noisy," corrupted data.

"It's like playing 'Where's Waldo,' because you have all of these proteins interacting with each other and we need to locate a protein of interest inside of cells," Dsouza says. "We do that through template matching, which is something like facial recognition of proteins."

He thrives in Morgridge's interdisciplinary culture.

"You're making coffee, and you run into another researcher working with flatworms, and they invite you to their lab to see their work and you trade information about papers you've read.

"There are a lot of sections of biology working together. There are so many good things going on here. This is a very special place."

— RAISON DSOUZA

THANK YOU

Your vision gives us new and potent pathways to discovery, gifted researchers, and a chance to strengthen scientific understanding in society.

“Fearless science, as we call it at Morgridge, is partly about our own work, and partly about elevating the next generation of fearless leaders for science and society.”

— DIETRAM SCHEUFELE, MORGRIDGE INVESTIGATOR IN THE SCIENCE COMMUNICATION INCUBATOR LAB

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