



MORGRIDGE
INSTITUTE FOR RESEARCH

FALL 2026



YOU MAKE A DIFFERENCE

DISCOVERIES ACROSS THE INSTITUTE INSIDE, PLUS:

- 1 A parting thank you from Brad Schwartz
- 3 Meet incoming CEO Eric Perreault
- 7 Summer science opens doors

A special report for
supporters of the
Morgridge Institute
for Research



BRAD'S UPDATE

Feeding the virtuous cycle of curiosity-driven research

What's the first thing that comes to mind when you hear the word "curiosity?"

For me, I immediately think of a young kid in awe of the things he or she sees in the world, peppering their parents with questions about how things work. Kids are in a constant state of discovery, and for good reason. Curiosity turns them into little learning machines who process information, build memory and draw connections.

A 2021 study of classroom learning found that typical kindergarteners ask more than two dozen questions every hour. For middle schoolers, that number dwindles down to about a few per hour. It's puzzling why this innate desire tends to get under-expressed with age. Is it our increasing (and misleading) sense of certainty about things? Or a fear of not knowing something we're supposed to know?

Whatever the answer, it's an important issue in the world of biomedical research. Of all the outstanding scientists I have ever known, the one common attribute is they continue to ask questions in the same way that little kids do. When they ask a question, it often comes from an unshakeable sense of wonder about the world: "This strange phenomenon fascinates me, and I think research could tell us more."



At the Morgridge Institute for Research, we value that trait in every single one of our scientists. It's the foundation of everything we do. It allows us to pursue big, challenging, intractable questions in science that have eluded us for generations, and it allows us to pursue questions whose outcomes are uncertain. It leads to the kind of discoveries that are not expected, and discoveries that dramatically improve our lives.

As esteemed Morgridge Investigator Paul Ahlquist has reminded us: **"Science is about what we don't know."**

Importantly, this is where you are making the biggest impact at Morgridge. We could not be conducting fearless science — our unique brand of curiosity-driven research — without your tremendous support for our scientists. These types of questions take time to get right. They can lead to dead ends or contradictory data that need to be unraveled and decoded. Sometimes they require technology that hasn't even been created yet. And quite often, they can be deemed by traditional science support frameworks as a bit "too risky" for funding because the outcome can't be guaranteed ahead of time.

Plainly put, you enable us to take advisable risks into the scientific unknown. Once given the green light, we put everything we have into the challenge: Deep domain expertise, rigorous methods, cutting-edge technology, and relentless collaboration with others, especially our core partners at the University of Wisconsin–Madison. Above all, we're committed to following the data and getting it right — something society rightfully expects from us, and we intend to deliver.

But it all begins with curiosity. And with you.

I am feeling an especially profound gratitude for all of you today, as I near my retirement from Morgridge next spring after 14 amazing years at this remarkable institution. Together, we have

built something very special and unique here, one of the most renowned independent biomedical research institutes in the US.

I am pleased to tell you that this legacy of fearless science will be in very accomplished hands with our incoming CEO, Eric Perreault. The Morgridge Board of Trustees chose Eric in August after an exhaustive national search for someone who shares our core values of serving society, following the science wherever it takes us and, together with our UW–Madison, WARF, and national partners, pursuing interdisciplinary discoveries.

In the pages ahead, you can read more about Eric's impressive academic and research leadership track record at Northwestern University, another Midwestern jewel of research and education.

Let me leave you with another thought about the virtuous cycle of curiosity and progress. You will also read about the 20th anniversary of the Morgridge Summer Science Camp, our signature program for inspiring STEM careers in Wisconsin youth, especially those from rural areas of the state that may have less exposure to the world of research.

One of the first things they see in the lab is a whiteboard with this prompt:

"Ask questions. Be curious. Imagine your future here."

And that's how the cycle continues ...

My best,

Brad Schwartz, M.D.

Carl Gulbrandsen Chair
Chief Executive Officer
Morgridge Institute for Research

MEET

Eric Perreault, incoming CEO of the Morgridge Institute for Research



This September, we announced Eric Perreault — a research executive, academic leader and biomedical engineering professor at Northwestern University — as the third chief executive officer of the Morgridge Institute for Research.

The Morgridge Institute Board of Trustees selected Perreault in August after a national search. His tenure will begin early 2027, coinciding with the retirement of Brad Schwartz.

Our north star has not changed: we exist to advance fearless science, a model that lets us think beyond short-term metrics so that our researchers can ask big questions and be able to pursue their answers. We believe this is a critical path to advancing human health and strengthening society.

Over more than two decades with Northwestern, Perreault has taken on increasing responsibilities in research administration, most recently as Northwestern's vice president for research from 2023 to 2026. Perreault has also been associate

dean for research in the McCormick School of Engineering and chair of the school's Department of Biomedical Engineering, where he has served on the faculty since 2002.

"The science done at Morgridge and the resources that enable it are outstanding," Perreault says.

"I look forward to building on the strong foundation that Brad Schwartz and the Morgridge team have established and working to expand collaborations with the university for mutual benefit and impact. Together, we can have Morgridge recognized as a destination where the world's best scientists want to come and stay, because of the talent it supports, the community in which it is embedded, and the model it presents for how great science can be done."

Perreault says he is inspired by the institute's extensive research partnerships with UW–Madison and the Wisconsin Alumni Research Foundation (WARF). Both Morgridge and WARF can provide an "amplifying effect" on the world-class research taking place across campus.

Perreault's research career has brought him on a fruitful quest in search of the mechanisms that contribute to the neural control of posture and movement. Through long-term interdisciplinary partnerships, his laboratory has made fundamental discoveries that have furthered our ability to treat mobility impairments resulting from limb loss, spinal cord injury, and stroke. His Northwestern homes have included the departments of Biomedical Engineering, Physical Medicine and Rehabilitation, and the Shirley Ryan AbilityLab.

Perreault's commitment to collaborative, interdisciplinary science extends beyond his laboratory and was a major focus of his tenure as Northwestern's vice president for research — including through a campus-wide visioning process that produced the Northwestern Network for Collaborative Intelligence and the establishment of new centers in the biosciences that draw on expertise from several disciplines.

Perreault sees that same spirit at work across Morgridge research areas in both fundamental biology and cutting-edge technologies.

“The collaboration network that these complementary domains of expertise have fostered both within Morgridge and in partnership with the rest of the university is inspiring and demonstrably productive.”

And as a leader, Perreault sees a critical need for scientists to communicate more effectively with the public about science's role in society. Institutions around the country are getting on board with that mission, he says, but Morgridge has walked for two decades.

When Perreault was getting to know the institute this past summer, his interview with Morgridge co-founders John and Tashia Morgridge was especially memorable.

“I asked them what they want the next CEO to keep in mind so that their vision of Morgridge continues, and they came back with one word: Fulfillment. Their single word nicely summarized the enthusiasm, commitment, and productivity I had been observing, and what I will work to persevere as Morgridge's next CEO.”

HEAR FROM LEADERS IN THE NATIONWIDE SEARCH THAT LED TO THIS SIGNIFICANT MOMENT:



Eric's commitment to fearless science, interdisciplinary discovery, and serving our public and scientific communities makes him an inspiring choice to lead Morgridge into its next decade. What an important moment for the Morgridge Institute. We are delighted to bring Eric to Wisconsin.

— Jacquelyn Fredrick, Morgridge
Board Chair



Eric Perreault embodies a core ethos of the Morgridge Institute: rigorous science paired with a genuine drive to see it have significant impact outside the lab. His work bridging neuroscience, biomechanics and rehabilitation technologies is a model for the interdisciplinary, curiosity-driven research Morgridge was built to advance and he understands the institute's vital role in complementing UW–Madison's excellence.

— Erik Iverson, CEO of WARF



Megan Spurgeon: How a mild-mannered virus becomes a cancer culprit

The study of tumor viruses — viruses known to trigger cancer — dates back to a century-old discovery of a virus that caused cancer in chickens. Researchers have since discovered seven tumor viruses that impact humans, including well-known names like hepatitis B and C, and human papillomavirus (HPV). Today tumor viruses are implicated in as many as 20 percent of all human cancers. Yet many of their oncogenic mechanisms remain shrouded in mystery.

Megan Spurgeon, an investigator at Morgridge's Rowe Center for Research in Virology, studies HPV

as well as the latest addition to this perilous list: Merkel cell polyomavirus (MCPyV). While this virus is incredibly common and usually harmless, it can trigger a rare and deadly form of neuroendocrine cancer in the skin called Merkel cell carcinoma (MCC). About 3,000 Americans are diagnosed annually, although MCC incidence is rising.

Spurgeon discussed her lab's approach to studying this virus, including the development of preclinical models that can help better understand the virus-host interactions that could ultimately give rise to the devastating disease.

How did Merkel cell research come on your radar, and how much do we know about MCPyV?

When I joined UW–Madison Professor Paul Lambert’s lab at the McArdle Laboratory for Cancer Research in 2010 to study human papillomavirus, MCPyV had just been discovered in 2008. At the time, my postdoc challenge was to look into this expanding repertoire of virus-associated cancers. I was tasked with developing a mouse model to study if and how the MCPyV T antigens — the viral proteins that the virus expresses — give rise to Merkel cell carcinoma in a mouse model. It has been valuable to have my experience in other tumor viruses because we’re learning there are a lot of parallel pathways these viruses use in how they cause cancer.

With MCPyV, we know the virus is ubiquitous from antibody screening studies. By swabbing the skin of healthy individuals, we know that it seems to be a part of the natural communities of microorganisms that make up our skin flora, and that we acquire it early in childhood. It seems to be asymptomatic, even when first infected with it. And that’s consistent with other microbes that are part of our flora — usually we don’t even know they’re there.

Do we understand the paradox between the virus being literally everywhere, but its related cancer remaining extremely rare?

We don’t know why the associated cancer is rare, but we do know the integration of viral DNA [into the host genome] is really a dead end for viral replication. If you think about it from the virus’s perspective, there’s really no benefit integrating into the host. And if there was benefit, we would be in much bigger trouble. So it’s actually an accident, quote-unquote, that the virus integrates.

But when the viral genome integrates, you no longer make new virus, but you still have these viral proteins with functions that are doing everything that would cause cancer, such as cell proliferation and dysregulation of the cell cycle. Integration is usually thought to be one of the last straws before these viruses ultimately give rise to cancer.

What are the challenges of studying a rare disease like MCC?

Obviously, funding is always going to be an issue, but there is also a lack of technical resources like reagents, antibodies or other tools that we would use in the lab. Another aspect of rare cancer research is the difficulty of accessing samples.

Models are also important. My lab has developed and we continue to advance preclinical in vitro models, as well as in vivo models, to study specifically how this virus and its proteins cause cancer and lead to the development of Merkel cell carcinoma. As with many other kinds of neuroendocrine cancers, we’re hoping we can find good early MCC biomarkers to help detect these cancers before they become advanced. We’re also using the virus itself as a tool to learn about pathways in the cells and tissues that it infects.

Are virus-associated cancers on the rise?

I think it depends on the virus and the type of cancer. The incidence of Merkel cell carcinoma is rising, in Wisconsin and the United States and worldwide. There could be a lot of different reasons for that. One is, people are living longer. They’re being exposed to more UV radiation from being out in the sun. There are oropharyngeal carcinomas caused by HPV that are increasing as well. And in the case of HPV, there are prophylactic vaccines, but it’s not always accessible in other parts of the world or taken in those parts where it is. As a whole, I would say, yes, across the world, they are increasing, but there’s some nuance there between the different viruses and different cancer types.

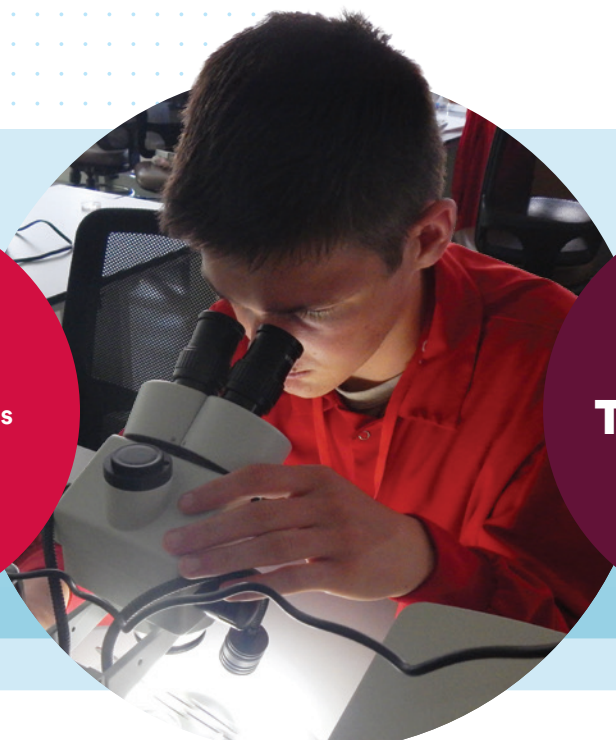
**Because of your support, our
researchers have the freedom to
pioneer new solutions.
THANK YOU!**

A milestone year for Morgridge Summer Science Camp

Every summer for the past two decades, students and their teachers from across the state of Wisconsin have travelled to Madison for the Morgridge Summer Science Camp. There, they meet scientists at all career stages, stay in dorms on campus, and immerse themselves in biology, microscopy, and more at Discovery Building and all across UW–Madison campus.

This year the camp celebrated a major milestone: its 20th anniversary.





Your support
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of students and
future scientists.

THANK YOU!

“I’ve always kind of dreamed of being in a space like this,” rising Platteville High School junior Bryn Larson told Ella Hanley of The Capital Times, who stopped by to profile the camp in its second week. “To me, it’s a surreal experience, but it’s these [researchers’] everyday lives.”

That surreal experience is made possible by donors like you. To lower the barrier to entry, the camp is completely free for participating school districts.

This year, students from Kickapoo, Prentice, and Sturgeon Bay, Wis. kicked off the camp at the Ed Jackson Summer Science Camp Week, a third one-week session made possible through the support of the family of Dr. Ed Jackson. Over the course of three weeks, students experienced nearly 100 hours of hands-on science activities.

A favorite activity for many students this year was the snail dissection led by the Newmark/Issigonis Lab, who uses the snails to gain insight into the life cycle of parasitic flatworms.

In the final week’s session, Caleb Carlsen, a camp alum and now doctoral candidate at UW–Madison studying breast cancer, shared how the camp experience inspired him to do research. “Seeing some of this for the first time ever from Phillips, where we have limited access to resources to do research, was really cool.” Mark Peterson, Carlsen’s teacher who brought him to the camp eight years ago, was returning with a new group of students. Seven are attending or have graduated from UW–Madison.

At the Morgridge Institute, the summer science camp opens the door to equitable STEM experiences. That feat — and those futures that arise from it — is made possible by Morgridge scientists, campus collaborators and donors like you.

The institute’s Community Engagement team is in the midst of a study of camp alumni to measure the camp’s impact over the past 20 years. “Our goal for the camp is to engage students and their teachers in ways that encourage them to pursue a career in the sciences,” Community Engagement Manager Jacques Lowe Nieto says: “Hopefully through higher education at UW–Madison.”

DONOR PROFILE

Patrick Thiele seeks to rebuild opportunity for rural Wisconsin students





THEY CAN NOW SEE THEMSELVES THERE, AND IF THEY'RE ACADEMICALLY QUALIFIED, THEY MIGHT TAKE A SHOT.

For decades, the American conversation about education has focused on funding, curriculum, and standardized testing. But beneath those debates lies a deeper, more cultural challenge — one that is increasingly shaping the country's future: the widening divide between rural and urban America.

Patrick Thiele, a former global insurance CEO who grew up in rural Wisconsin, has watched this story unfold across his lifetime.

"I think it's getting wider," he says plainly.

Raised in the small town of Boscobel, Wis., Thiele graduated in a class of just 65 students. When he headed to the University of Wisconsin–Madison on a scholarship in 1968, the distance between rural life and the state's flagship university didn't feel insurmountable. Seven students from his graduating class ended up attending Madison.

Today, that kind of pathway is far less common.

"Very few of them even think about going to Madison now," Thiele observes. "It doesn't feel like a place where they fit."

For Thiele, that's where programs like the Morgridge Institute Summer Science Camp come

into the picture, and is one of the reasons he chooses to invest in this work.

At first glance, the camp seems simple enough: high school students interested in science spend time on a university campus, exploring research and participating in hands-on scientific activities.

But the experience goes far beyond experiments and lab demonstrations. "It allows the students to see themselves in that environment," Thiele says.

For teenagers from small rural schools — sometimes graduating classes of 20 or fewer students — the experience of spending time at a large research university can be transformative. And whether or not they ultimately pursue scientific careers is almost beside the point.

"They can now see themselves there," Thiele says. "And if they're academically qualified, they might take a shot."

Science, it turns out, is an unusually effective platform for this kind of transformation. Part of its power lies in its process. Science encourages curiosity, experimentation, and the ability to make sense of the world. Students learn to ask questions, gather information, test ideas, and revise their thinking.



“You take all this information, ask the right questions, and come to a conclusion,” he says. “And when it works — when you figure something out — it feels really good.”

Success in science doesn’t require perfection. In fact, failure is often part of the journey.

“If you’re right 51 percent of the time, that’s a great outcome,” Thiele says with a laugh.

Students are not the only beneficiaries of programs like the science camp. Teachers play a critical role as well.

Many educators return from these experiences energized by what they have seen and learned. They gain new examples, new stories, and new ways to connect classroom lessons to real-world applications.

“The teachers are incredibly excited about it,” Thiele says. “They go back and they’re better teachers.”

That excitement has a multiplying effect. A single teacher inspired by a new experience can influence hundreds of students over the course of a career.

Beyond helping students and teachers, Thiele supports the Summer Science Camp because he believes it and programs like it also strengthen science itself. Rural students bring perspectives shaped by different communities, economies, and life experiences. When those perspectives enter scientific spaces, they broaden the conversation and enrich the problem-solving process.

In that sense, expanding access to science is not only about equity — it’s also about improving the quality of scientific inquiry.

What’s happening in Wisconsin is hardly unique. Across the United States, the cultural distance between rural and urban communities has grown more pronounced in recent decades. Economic shifts, media ecosystems, and political polarization have all contributed to the divide.

Programs like the Morgridge Summer Science Camp cannot solve those challenges on their own. But by creating opportunities for students to cross geographic and cultural boundaries, they remind young people that the world is larger — and more accessible — than it might appear from their hometowns.

And sometimes, that realization is all it takes to change a life trajectory.

“Just one or two students,” Thiele says thoughtfully. “If you can make a difference for them — that’s a big deal.”

Editor’s note: Patrick Thiele sat down with us this summer to share his perspective in our Rural Roots, Research Futures project recognizing the 20th annual Morgridge Summer Science Camp. This profile has been adapted from that conversation.



▶ **Learn more about the project here**

A photograph of two children in a classroom setting. A young boy with dark hair, wearing a grey t-shirt, is smiling broadly and holding up a large, handmade airplane made of cardboard. A girl with blonde hair, wearing a red t-shirt, is partially visible in the foreground, also smiling. They are sitting at a white table. The background shows a classroom with shelves and other students.

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we serve.

RESEARCH UPDATES

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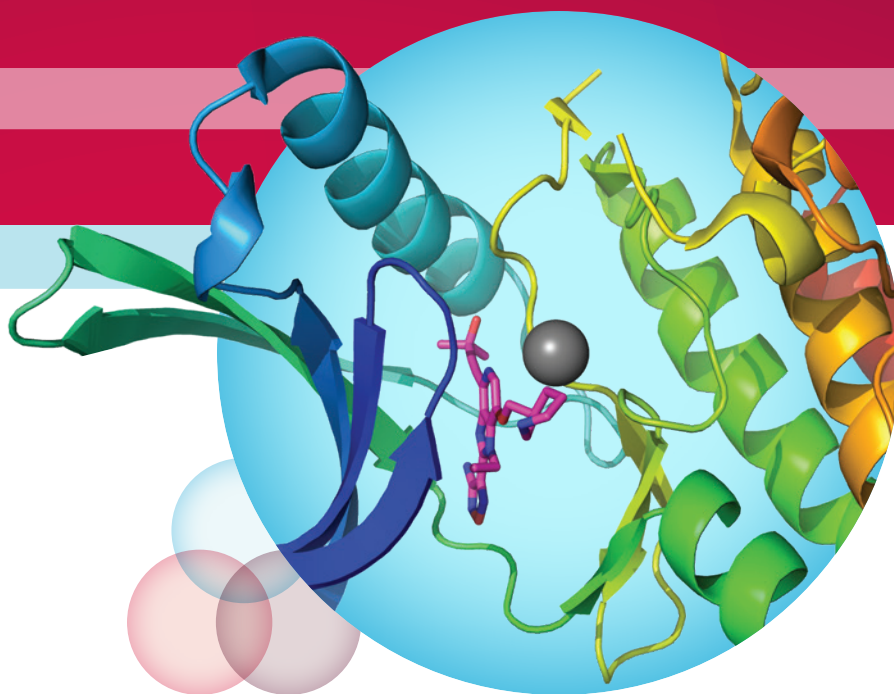


Using cryo-EM to illuminate bacterial genome replication

In nearly every attempt to copy their genome, bacteria encounter some kind of glitch or obstacle that throws the process off. Remedying a would-be lethal error, finely tuned proteins race to the site of the break and repair it on the fly. This “replication restart” process is a little-understood but essential activity for bacteria. This spring, **Tim Grant**, a Morgridge investigator who pioneers cryo-electron microscopy techniques, and James Keck, a professor of biomolecular chemistry at UW–Madison, revealed a more complete look at the DNA replication machinery in *E. coli*. One of the most striking discoveries is the apparent parallel between a replication restart protein and a canonical replication initiation protein, suggesting a conserved mechanism.

“Since the process driven by the proteins in our complex occurs in all bacteria via similar mechanisms, and is not found in human cells, the structures are excellent potential targets for antibacterial therapeutic development,” Keck says. Grant notes that these are fascinating structures from a cryo-EM perspective, given that they are both heterogenous and dynamic — and could never be captured by X-ray crystallography: “The final model really demonstrates how complex the arrangement of all the components is and highlights the power of cryo-EM in solving the structures of dynamic samples.”

► **JOURNAL: NATURE COMMUNICATIONS**



Disarming tuberculosis with microbiology and machine learning

Tuberculosis (TB), considered the world's oldest infectious disease, stubbornly maintains its hold as a leading infectious killer. Nathan Wlodarchak at the Rocky Mountain Regional VA Medical Center and **Tony Gitter** at Morgridge have teamed up to combine microbiology with machine learning to find new drugs that could jam the signaling pathways TB uses for basic function. Wlodarchak's primary focus is on two proteins, PknB and PstP, that play a big role in building TB's fortress-like cell walls. No studies to date have explored whether PstP, like PknB, could suppress TB growth. Starting with a screen of more than 100,000 chemicals, the team ultimately identified four that actively inhibit both PstP and bacterial growth. The compounds provided additive benefits when teamed with other treatments.

For Gitter, modeling the PstP biochemical activity was a rich challenge from a data science perspective. Rather than creating algorithms to train on existing databases, this was a chance to apply techniques to an emerging idea where the data is all fresh — and highly relevant to human health. “That has really informed entire new ideas that my group's working on now about how we can do that even better.”

► **JOURNAL: JOURNAL OF BIOLOGICAL CHEMISTRY**



Revealing secrets of viral genome replication

Behind the immense global health impact of viruses lie tiny molecular machines fueling viral replication. Earlier this year, Morgridge scientists revealed the outsized role of a surprisingly small part of this machinery. Using a model positive-strand RNA virus, the lab of **Paul Ahlquist** zeroed in on a short, rigid sequence of just 17 amino acids within the virus's replication protein, protein A. Like an arm crooked at the elbow, the region cradles other domains of the protein. Their experiments unearthed not just structural contributions but major responsibilities for turning on protein A's two enzymatic functions: polymerase, essential for RNA synthesis, and RNA capping, essential for stability and expression of the new RNAs. **"Many insights from this work have implications for understanding and potentially controlling other viruses,"** Ahlquist notes.

The study is the most detailed in vivo analysis of function in a viral RNA replication organelle to date. Its insights into structure and function provide valuable foundations for opening new avenues in science and medicine. These include the development of broad-spectrum antivirals that target essential, conserved features shared across many viruses — features that are much harder for the virus to mutate under the genetic selection of antiviral treatment.

► **JOURNAL: NUCLEIC ACIDS RESEARCH**



Making advanced image analysis easier for all

Modern fluorescence microscopy can generate images of living cells as stunning to look at as they are informative to study. For techniques like fluorescence lifetime imaging microscopy (FLIM), those images provide a window into cell metabolism, helping scientists study cancer treatment, autoimmune disease and more. But for these researchers, the image is just the beginning. To draw any biological insights, researchers need to guide massive amounts of data through a maze of software analysis tools and scripts, ensuring careful quality checks throughout the journey. Data analysis becomes a major roadblock for experts and can fully exclude non-experts.

Morgridge scientists in the **Skala Lab** are tackling this challenge head-on. They developed a new open-source, user-friendly data analysis platform, FLIM Playground, designed to make FLIM analysis easier, faster and more reproducible. The name reflects the interactive analysis and visualization tools that allow users to “play” with their data, says Wenxuan Zhao, first author of the study and lead developer of the platform. The team tested the full pipeline — from data extraction to analysis — on datasets from different types of biological samples and fluorescence lifetime systems. FLIM Playground performed consistently across systems, successfully recognizing expected biological differences such as metabolic responses in pancreatic cancer cells.

► **JOURNAL: CELL REPORTS METHODS**

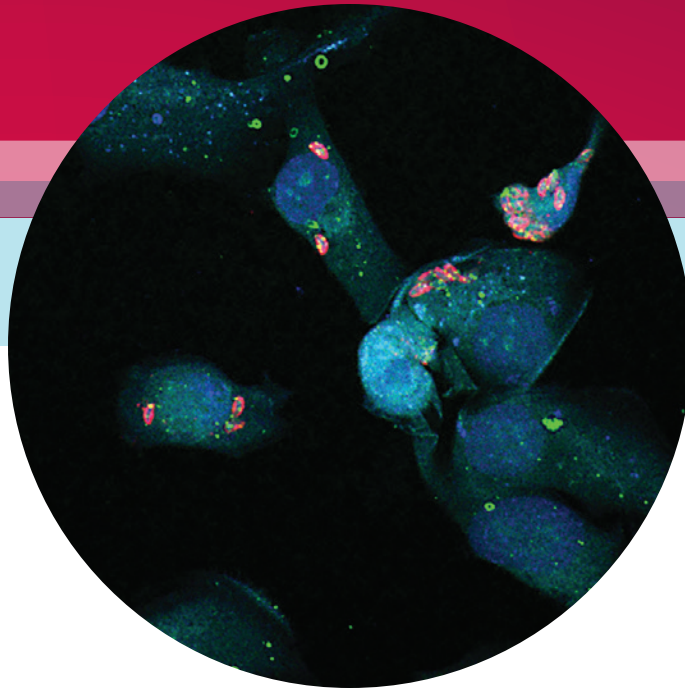


Searching for relevance in a sea of 39 million scientific papers

Biologist Sydney Brenner, in his 2002 Nobel Prize lecture, cautioned that science is now **“drowning in a sea of data and starving for knowledge.”** The online database PubMed, which contains more than 39 million abstracts and counting, is a case in point. A Morgridge Institute team is tackling this challenge with a hybrid solution that combines two different “flavors” of machine learning algorithms. The first is “literature-based discovery,” which helps researchers search for unexpected connections in past findings to inform new directions, and the second is a large language model, or LLM, which helps interpret results to get “at the actual mechanistic relationship between these biomedical terms,” according to first author on the study Jack Freeman. Nodding at its hybrid nature, the team dubbed the resulting tool SKiM-GPT.

The results reveal a one-two punch for evaluating millions of journal articles to inform hypotheses plausibility. Every hypothesis run through SKiM-GPT will come back with three key findings: a scored hypothesis; the rationale used to evaluate the question; and specific citations of all abstracts used in the review. And it does all this 97 percent faster than a human researcher could, with 93 percent concurrence with the human results.

► **JOURNAL: BMC BIOINFORMATICS**



Chasing down the infection that causes toxoplasmosis

Around the world, chances are 1 in 3 that you've been infected with a single-celled parasite called *Toxoplasma gondii*. While for most of us infection is a non-event, it poses a major concern for pregnant and immune-compromised people. A team of researchers led by Morgridge scientist **Gina Gallego-Lopez** uncovered more details about what happens when the parasite first approaches the host it seeks to invade. The study, published this summer, brings together the metabolic imaging expertise of Morgridge's Melissa Skala Lab with the medical microbiology expertise of Laura Knoll's group at UW–Madison.

After “kissing” the host's plasma membrane, the parasite “spits” out the contents of special secretory organelles into the host cytoplasm. But then what? The team found that those contents start remodeling the host cell's metabolism, allowing it to hijack the nutrients it needs to replicate — in effect creating a biochemical domino effect that leads to the purine nucleosides the parasite cannot make on its own but needs to survive. Current treatment options for toxoplasmosis are limited and target parasite rather than host metabolism. This work lays the foundation for new anti-parasitic drug development targeting the metabolic pathways that *T. gondii* requires but a healthy uninfected host cell does not.

► **JOURNAL: mSPHERE**

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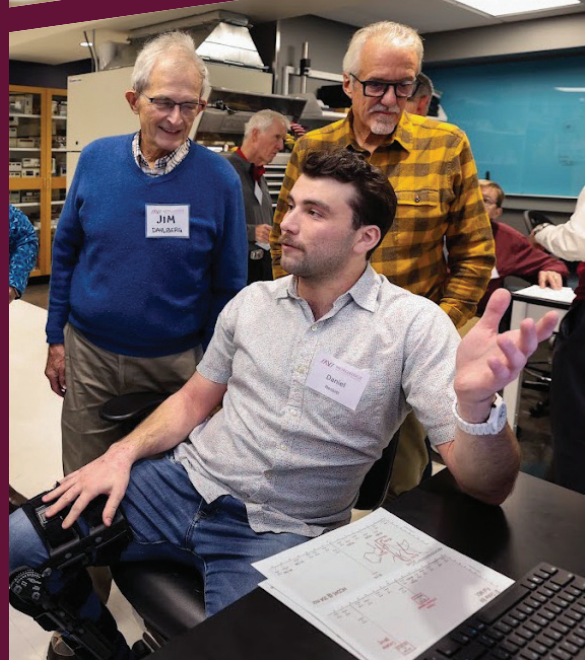
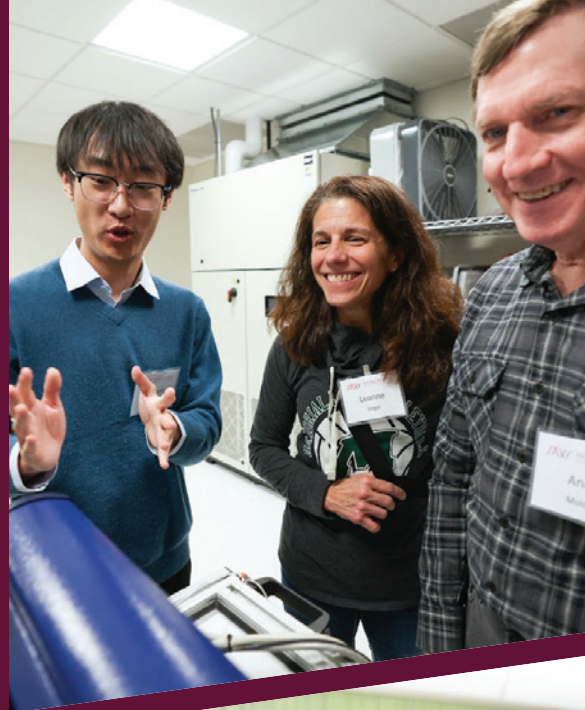
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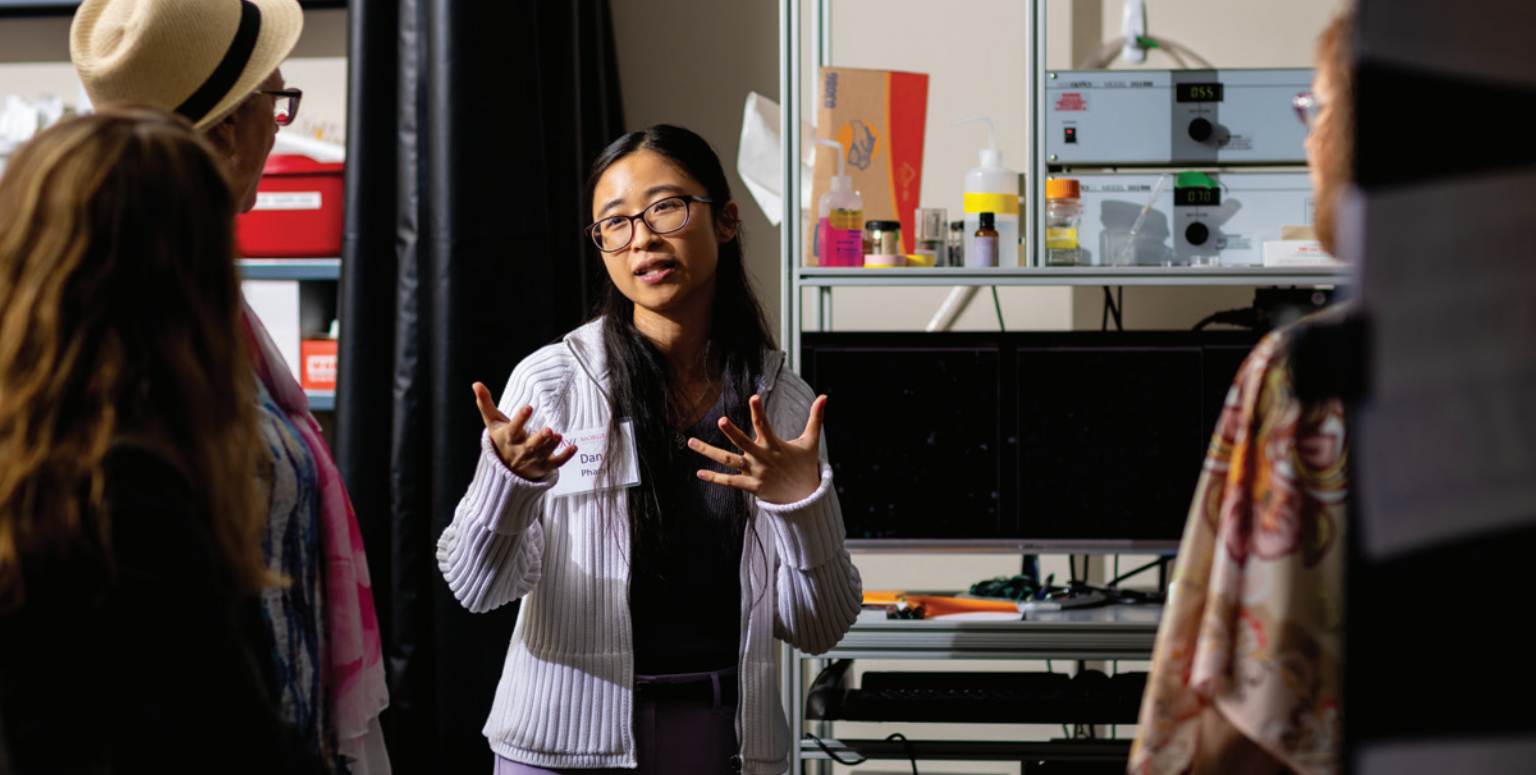
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- ▶ Meet some of our scientists,
hearing their personal stories
and learning more about their
research, *and*
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Improving cancer immunotherapy with advanced metabolic imaging

Chimeric antigen receptor (CAR) T cell therapy is transforming cancer care for patients with cancers of the blood. But it has proven especially challenging to develop against solid tumors. Those solid tumors — and the spread of those tumors throughout the body — cause the vast majority of cancer deaths.

Researchers at the Morgridge Institute and UW–Madison are using advanced metabolic imaging to better understand how cells function within the tumor microenvironment. Last year, they published new research in the journal *Nature Biomedical Engineering* showing how a technique pioneered by the **Skala Lab**, optical metabolic imaging (OMI), is sensitive to the dynamics of T cell metabolism.

“Metabolism is one of the many factors that affects how T cells function within the tumor microenvironment, and hopefully one of the key factors that could inform what can be made better for these CAR T cells in a solid tumor,”

says Dan Pham, a postdoctoral researcher in the lab of Morgridge Investigator Melissa Skala and first author of the study.

The tumor microenvironment is harsh and suppressive to immune cells with limited oxygen and glucose, both important elements for T cells to perform their function. However, during manufacturing, CAR T cells are grown in an artificial environment with unlimited nutrients and oxygen.

“When we put them in the body, we’re asking them, in a way, to survive in the wild,” says Skala. “Kind of like how you think of a captive lion being released into the wild — they don’t do so well.”

The Skala Lab uses OMI to capture metabolic activity within the cells. A major benefit is being able to image a sample directly across many timepoints. It also analyzes at the single-cell level, which can help differentiate populations that have stronger functional responses.

“This study hopefully supports the application of OMI to fill in the gaps in the analytical tools that people use for CAR T cell manufacturing,” says Pham. “Our measurements complement other metabolic assays from our collaborators so we can be certain in our validation.”

Collaborators include Morgridge metabolism investigator Jing Fan; UW pediatric oncologist and director of the Carbone Cancer Center Christian Capitini; Wisconsin Institute for Discovery biomedical engineering investigator Kris Saha, who uses genomic editing tools like CRISPR CAS-9 to generate CAR T cells; and industry partner Promega Corporation.

The researchers identified several windows of opportunity in the manufacturing process where optimization could result in a better therapeutic product, with a major focus on timing for gene editing.

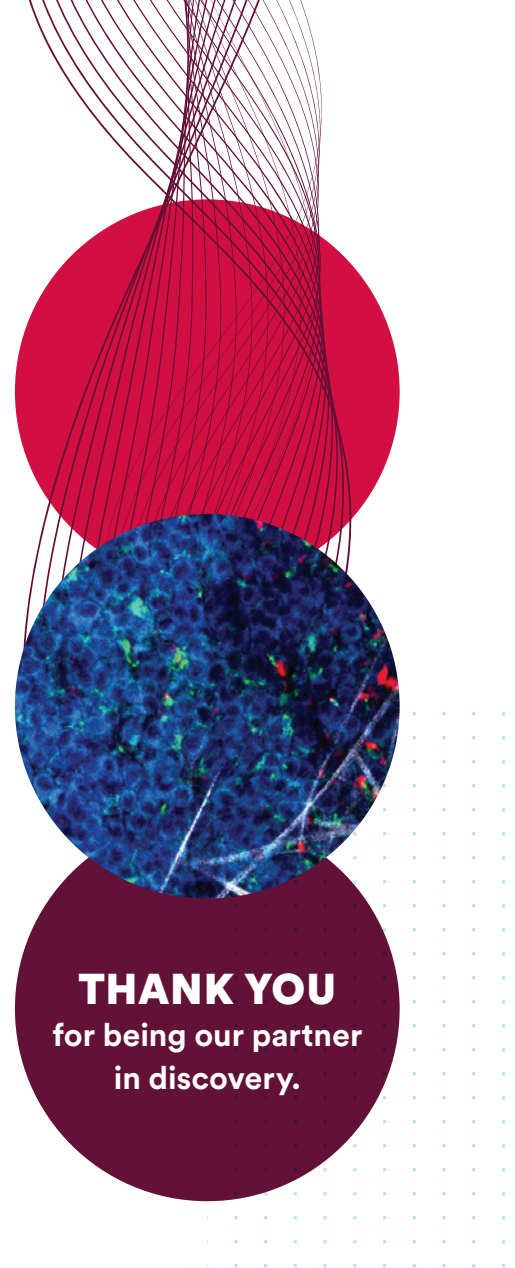
“With OMI, we are able to sense when cells are entering the cell cycle, the optimal time for gene editing,” Pham says. **“Over time, we can identify that peak when metabolism is supporting the cell cycle, and at that point they can do gene editing which would result in a higher percentage of CAR yield.”**

Another area of optimization is in providing the right level of nutrients and metabolites at different manufacturing stages to enrich for the most functional T cells.

And at the end of the manufacturing process, OMI can help identify a product that would be more potent in vivo.

Pham says that this work is very much a proof of concept but ultimately demonstrates that OMI is sensitive enough to pinpoint these areas that could improve CAR T cell manufacturing. Since the technology is adaptable and scalable, there is potential to implement this tool in a large-scale manufacturing setting.

“There’s no point in building all this stuff unless you already know that you can impact the manufacturing process and predict which T cells will do better killing tumors in the body,” says Skala. “You have to establish all of that first, and once you do, then it’s worth building the technologies.”



MORGRIDGE MILESTONES



Quinn Waeiss becomes second bioethics investigator at Morgridge

Despite a push to implement artificial intelligence (AI) to help healthcare providers manage burgeoning workloads, patients have often been left out of the conversation. **Quinn Waeiss**, who became the institute's second bioethics investigator this August, is hoping to change that equation. Waeiss is studying the impact of AI large language models being incorporated into the secure messaging systems between patients and their doctors. This work originates in their postdoc at Stanford University and Waeiss's research will expand to include other projects where greater ethical reflection among scientists and community voices are especially valuable.



Morgridge Chief Technology Officer Miron Livny wins Hilldale Award

Miron Livny was recognized by UW–Madison with a Hilldale Award for his devotion to mentorship, research, and service. Livny created Condor, a landmark distributed computing framework that pioneered the field of high throughput computing, just over 40 years ago. Now HTCondor, this framework serves as the computing backbone for the IceCube Neutrino Observatory and has supported three Nobel Prize awards. Under Livny's leadership, the Center for High Throughput Computing builds an international cyberinfrastructure that harnesses the power of distributed computing capacity to enable and transform science across disciplines.



SeLight, LLC enters new chapter with award from National Science Foundation and UW–Madison

SeLight, LLC, led by Morgridge scientist **Amani Gillete**, emerged from research in the Melissa Skala Lab seeking to develop a new way of assessing T cell fitness in patients. Only about half of all patients eligible for transformational chimeric antigen receptor (CAR) T cell therapy have T cells healthy enough to be manufactured into viable cancer-fighting agents, leading to high failure rates. Now, funding from the NSF as well as UW–Madison's SEED fund will help SeLight demonstrate feasibility of a prototype that will fit seamlessly in clinical settings.



Josh Coon recognized with two distinguished professorships

Morgridge investigator **Josh Coon** has received a Wisconsin Alumni Research Foundation (WARF) named professorship — the John E. P. Syka professorship of Biomolecular Chemistry and Chemistry — from the Office of the Vice Chancellor for Research. The award recognizes faculty who have made “major contributions to the advancement of knowledge.” Coon has also been named a Vilas Distinguished Achievement Professor at UW–Madison. The award recognizes exceptional accomplishments in research, teaching, and service and provides five years of flexible funding to support ongoing scholarly and academic endeavors.



Kevin Eliceiri wins inaugural Spencer Shorte Legacy Award

Kevin Eliceiri, Morgridge investigator in biomedical imaging and director of the Fab Lab, received the first Spencer Shorte Legacy Award from Association of Biomolecular Resource Facilities and Core Technologies for Life Sciences “to recognize efforts to uplift the community.” The award will support the establishment of the Illuminating People Program, a platform for matching experienced and early-career researchers that recognizes the “bi-directional intellectual spark that good mentoring has on both the mentor and mentee.” The award honors Shorte’s legacy by recognizing someone who embodies integrity and community-minded values.



Center for High Throughput Computing receives major award to shape the nation’s future data backbone

The Morgridge Institute for Research, along with UW–Madison’s College of Computing & Artificial Intelligence and five other partner universities, was selected to lead one of the two flagship projects awarded by the National Science Foundation in integrated data systems and services. The Fabric for AI-Driven Science (FabAID) is a 5-year, \$24.5 million project that builds a fabric of services to accelerate data-intensive and AI-driven science. The project will be led by investigator **Brian Bockelman** alongside Morgridge colleagues **Anthony Gitter** and **Miron Livny**, among others.



Questions OF THE HEART

Kyle Flickinger builds on biochemistry foundation to reveal the secrets of heart regeneration in zebrafish.

Kyle Flickinger arrived for his first-grade career day as a scientist, wearing a lab coat borrowed from his dentist father, oversized goggles, and toting that powerful child's scientific instrument — a bug jar.

That grade-school curiosity was unshakable. Flickinger's interest in insects, frogs and other animals kicked off a scientific journey that eventually led to the Morgridge Institute for Research lab of investigator Ken Poss, where he works as a postdoctoral research associate in a team searching for the secrets behind tissue regeneration.

His parents, both in the military, moved the family a number of times before settling near Sault Ste. Marie, Mich. "They always encouraged me in science and gave me a lot of little encyclopedias and fact books about animals and helped develop my passion," Flickinger says.

After earning an undergraduate degree in biochemistry at Northern Michigan University in 2019, Flickinger embarked on a PhD program at UW–Madison. Working as a graduate research

assistant in Morgridge Investigator Jason Cantor's lab, Flickinger researched how nutrients influence cancer-cell biology.

"I did a lot of follow-up work that stemmed from high-throughput tests to figure out what genes are important for cancer cells to grow and why some cancer therapies fail. Ultimately, the goal was getting down to a mechanistic level of why some nutrients contained in blood protect cancer cells from the effects of these drugs or the loss of those genes," Flickinger says.

After earning his PhD, Flickinger moved to the lab of Morgridge Investigator Ken Poss, drawn by the challenge of regenerative biology research. There, the postdoctoral research associate works to understand how zebrafish are able to regenerate many types of damaged tissues.

"My central hypothesis is that metabolism coordinates some of this," he says. **"It's challenging as a postdoc to do metabolic research in whole animals, because of the complexity. But that's one of the reasons why it's a good challenge for my postdoctoral training. It's a fun challenge to take on because people sometimes shy away from it because it's hard."**

Flickinger is concentrating on questions involving regeneration of heart tissue. The Poss Lab's research raises exciting questions of whether the zebrafish's regenerative abilities could one day be unlocked in humans to repair heart and other tissues.

The institute's recruitment of Poss and his laboratory to Morgridge two years ago — and now, Flickinger's work in it — is thanks to your ongoing support.

"Heart disease is a leading cause of death among adults and tackling that problem is critical," Flickinger says. "I'm blending the mechanistic biochemistry that I used in Jason's lab with the animal model I work with now, and hopefully that will yield results that can translate to solving a human problem."

The long and demanding grind of graduate school taught Flickinger many lessons about persistence and discovery.

"Someone once told me that medical school was like being dropped into a stormy, foggy ocean, but there's a lighthouse. It's hard and can be a slog, but at least it's very defined. Year one and two have classes and tests, years three and four have clinicals, and then you graduate and move on to residency," he says.

"Graduate school is like being dropped into a similar stormy, foggy ocean, except there's no lighthouse. You just have to pick a direction, start swimming, and figure out what you're swimming toward along the way," he adds.

One key to grad school success is finding an advisor that will let you struggle but who won't let you drown, Flickinger says.



"Struggle and failure can be good teachers. Even if most of what you're doing at the beginning doesn't work, eventually you get traction," he says. "Having a goal of really thoroughly accomplishing one publication-quality thing a week can be helpful. Focus on one experiment, and if everything else fails, at least that one thing shows progress."

As Flickinger worked through his academic career, he built a strong love of teaching.

"For a while, I considered being a high school teacher. But being a professor, you get to be both a teacher and a researcher — which goes back to my lifelong scientific ambition," he says. "My passion really lies in teaching not only undergraduates, but also graduate students."

Fostering a love of learning and a drive to communicate scientific principles are priorities for Flickinger.

"A mentor of mine once told me that to keep a skill, you give it away," Flickinger says. "Not to prove your mastery, but to continue to help you internalize scientific concepts by explaining them to someone else and see them grow, as well."

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