partnership REPORT 2022

Prepared for WARF and Morgridge Trustees, UW–Madison leaders and friends of the institute.

MORGRIDGE INSTITUTE FOR RESEARCH

WISCONSIN UNIVERSITY OF WISCONSIN–MADISON

WARF Wisconsin Alumni Research Foundation

Partnerships
built on a shared vision

At the Morgridge Institute, we believe in Fearless Science. This means we are willing to take risks and press against boundaries. We aim for science that we can't currently imagine.

As an independent institute, we have the freedom to move quickly and decisively, to follow interesting and important questions, wherever they may lead — especially if they lead to uncharted territory. But we are unique in that we have the best of two worlds. We are deeply engaged with one of the world's preeminent public research universities and work strategically with the biomedical research community at UW–Madison.

What are the elements that make this model work?

Our benefactors, John and Tashia Morgridge, were farsighted and expressly built into our endowment a component that allows us to invest in new initiatives. Yet we are not simply another funding source on campus. We evaluate new ideas within light of our own programs, with a process for deciding when to participate.

We have a focused mission and are committed to the importance of curiosity-driven research. We don't try to cover the entire waterfront. We have specific themes, which means we say no to some projects, and our colleagues on campus understand that. They also recognize that we have picked fundamental areas that overlap with a wide spectrum of biomedical research.

We also exist in a unique culture. The Wisconsin way of doing things is different from many other places, where policy and direction are often determined top-down. People here build coalitions to get new ideas off the ground, and that's a good thing. It may take longer, but it results in strong, grassroots support.

These are more than coalitions or collaborations; they are true partnerships. We've put a little bit of ourselves on the line. There is an enormous amount of trust that is required in a partnership, a willingness to assume the same risk with a commitment to see things through to the success or the failure of a shared goal. We genuinely have each other's backs.

In the following pages, you will see highlights of how this works in practice.

- Our mass spectrometry team has broadened its curiosity to include cancer research.
- We support the technology and talent that helped establish a leading center for Cryo-EM technology.
- The campus metabolism initiative, modeled on the stem cell community we helped create, draws from nearly two dozen science disciplines.
- Our research computing team has helped more scientists extract value from data-intensive research and helped expand research computing campuswide.
- We are combining the research and practice of science engagement to better understand how to depolarize public debate about science.

All of these partnerships are thriving because they are based on trust, transparency, and a shared vision. We believe they will unleash the best ideas to advance our knowledge of human health.

Sincerely,

Brad Schwartz
CEO, Morgridge Institute for Research

BY THE NUMBERS

50+
New research ventures launched between Morgridge postdocs and UW–Madison investigators since 2015

500+
Number of campus scientists who belong to the Morgridge Metabolism Initiative, a collaborative hub for metabolism researchers since 2015

82
Number of academic departments and programs that have employed high-throughput computing in their research since 2017

30,000+
Number of Wisconsin K12 students who have participated in science field trips at Discovery since 2011

36
Number of UW–Madison scientists who have employed the Cancer Metabolomics and Proteomics (CAMP) resource, led by Joshua Coon, in their research

$5.7 million
Investment from the Morgridge Strategic Fund in scientific technology deemed a high priority at UW–Madison, such as electron tomography, mass spectrometers and cryo-EM microscopes since 2014

500+
Number of UW–Madison faculty who have participated in public science programs through Discovery Connections since 2011

John Maufort, James Thomson Lab

Laura Knoll (left) and Dawn Davis

Graduate student Kyle Flickinger, Jason Cantor Lab

Graduate students Steve John and Emily Britt, Jing Fan Lab

The Morgridge Metabolism Initiative:

A blueprint for collaboration

The Morgridge Institute's role in advancing stem cell research at UW–Madison is a well-known story.

The institute helped keep stem cell pioneer Jamie Thomson in Wisconsin and the privately funded biomedical research institute became a nucleus for the stem cell community.

That approach helped UW–Madison become a world leader in stem cell research. It also became the model for what could be accomplished in other fields of science. Most notably, Morgridge has become the hub for a thriving university-wide metabolism community.

The institute didn't set out to prioritize metabolism. We approached their mission with a broader question: "What can we do that will help the campus?" recalls Brad Schwartz, who became CEO in 2013. They held several symposia for researchers to speak about their work. Compared to other topics, the enthusiasm and energy around the metabolism gathering was palpable. "It was pretty clear we ought to do this," he says.

Often called the chemistry of life, metabolism provides the energy for all the activity within every cell in the body. So perhaps it was no surprise to learn there were hundreds of people on campus whose research involved metabolism, each working in their own little orbit. It seemed clear that if we could bring them together into one solar system, they could identify common needs and help find solutions.

The timing couldn't have been better. Not long ago, people felt metabolism was a closed book; the pathways were identified and it was all figured out. Now there is a Renaissance of science in metabolism, as researchers realize there is a great deal they still don't know.

One of the gaps the Morgridge Institute quickly identified was the ability to analytically identify and quantify molecules that are part of the metabolic pathways, an emerging field called metabolomics.

Joshua Coon, a biochemist on campus, had the expertise and interest to run the kind of analyses this would require, but not the funding to take it on. Morgridge partnered with UW–Madison's biochemistry department, a birthplace of metabolism research in the United States, to hire staff and secure the hardware he needed to launch a metabolomic center, now self-sustaining and in high demand.

These collaborations are already have an impact on fighting disease. Laura Knoll, professor of medical microbiology and immunology, was studying a parasite that scavenges metabolites from cells to get the nutrients it needs. This mutant parasite was making mice morbidly obese, but she didn't know why.

She was able to work with several different researchers in the campus community to understand the basic science and run experiments to find ways to stop the parasite from tricking the metabolism of the host cells. The result? An FDA-approved drug that inhibits this pathway and kills the parasite.

"Science is all about collaboration," says Knoll. "To really do cutting-edge science, especially in a complex field like metabolism, you have to be able to collaborate, communicate, and get along with people."

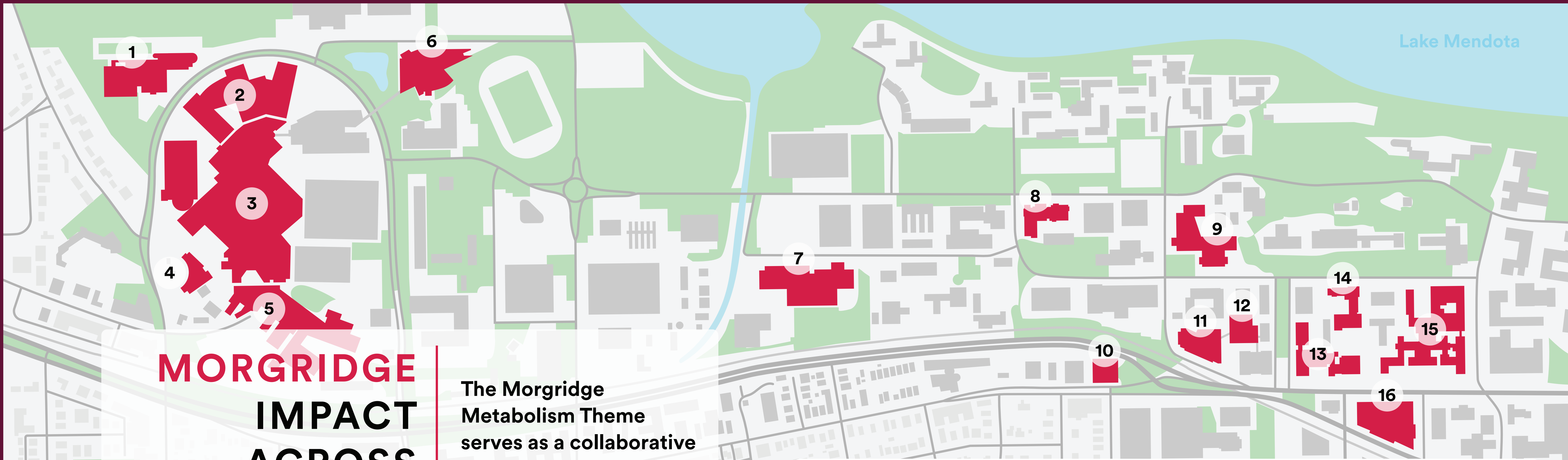
Collaboration is especially critical on a complicated disease like diabetes, a huge public health issue affecting 11 percent of the population that leads to increased risk for many other diseases. Diabetes and metabolism are deeply intertwined: metabolism is how the body extracts energy from food, but when diabetes reduces insulin levels, it can inhibit the energy from being stored.

When Dawn Davis, professor of endocrinology, diabetes, and metabolism, set out to build a diabetes center on campus a few years ago, she was able to build on the collaborations already brewing within the metabolism community to establish the center in early 2020. "If we all work in our little silos on the one thing we know, we never really can push the boundaries of what we want to learn," says Davis.

The Metabolism Initiative has grown into a diverse community of more than 500 researchers who reside in more than two dozen UW–Madison departments. In addition to the fellowship program, Morgridge sponsors an annual symposium (paused during the pandemic), a seminar series, and "MetaLunches" where professors from around campus talk about their work. Monthly online meetings also give trainees experience presenting their work and fielding questions.

This amazing diversity of science thrives because the initiative is a true collaboration, not backed by a formal metabolism department.

While this may seem like a drawback, it is actually an advantage. As Davis notes: "Bringing together multiple departments and schools working on metabolism increases the interactions and the ability to form new directions and collaborations — and helps all of us do better science."



MORGRIDGE IMPACT ACROSS UW–MADISON

The Morgridge Metabolism Theme serves as a collaborative hub for more than 500 scientists on campus

Metabolism Impact Footprint

Talent Recruitment
Jing Fan, Jason Cantor

Programming Support
MANTP – Seminar series and professional development for trainees
American Aging Associate AGE 2021 Meeting Sponsor
ASBMB Meeting on "CoA and CoA-derivatives" 2023 Meeting Sponsor

Instrumentation Investment
Laboratory for Biomolecular Mass Spectrometry
Small Animal Metabolic Phenotyping Facility

Morgridge Metabolism Interdisciplinary (MMI) Fellowships
2018 - Fellow - Prasanth Kumar
i. Graduate Student with Andrew Buller in the Dept. of Chemistry
ii. Current Position - Scientist I at Generate Biomedicines in Boston

2019 - Fellow - Bruno Martorelli Di Genova
i. Postdoctoral Fellow with Laura Knoll in Medical Microbiology and Immunology
ii. Current Position - Assistant Professor in the Dept. of Microbiology and Molecular Genetics at the University of Vermont

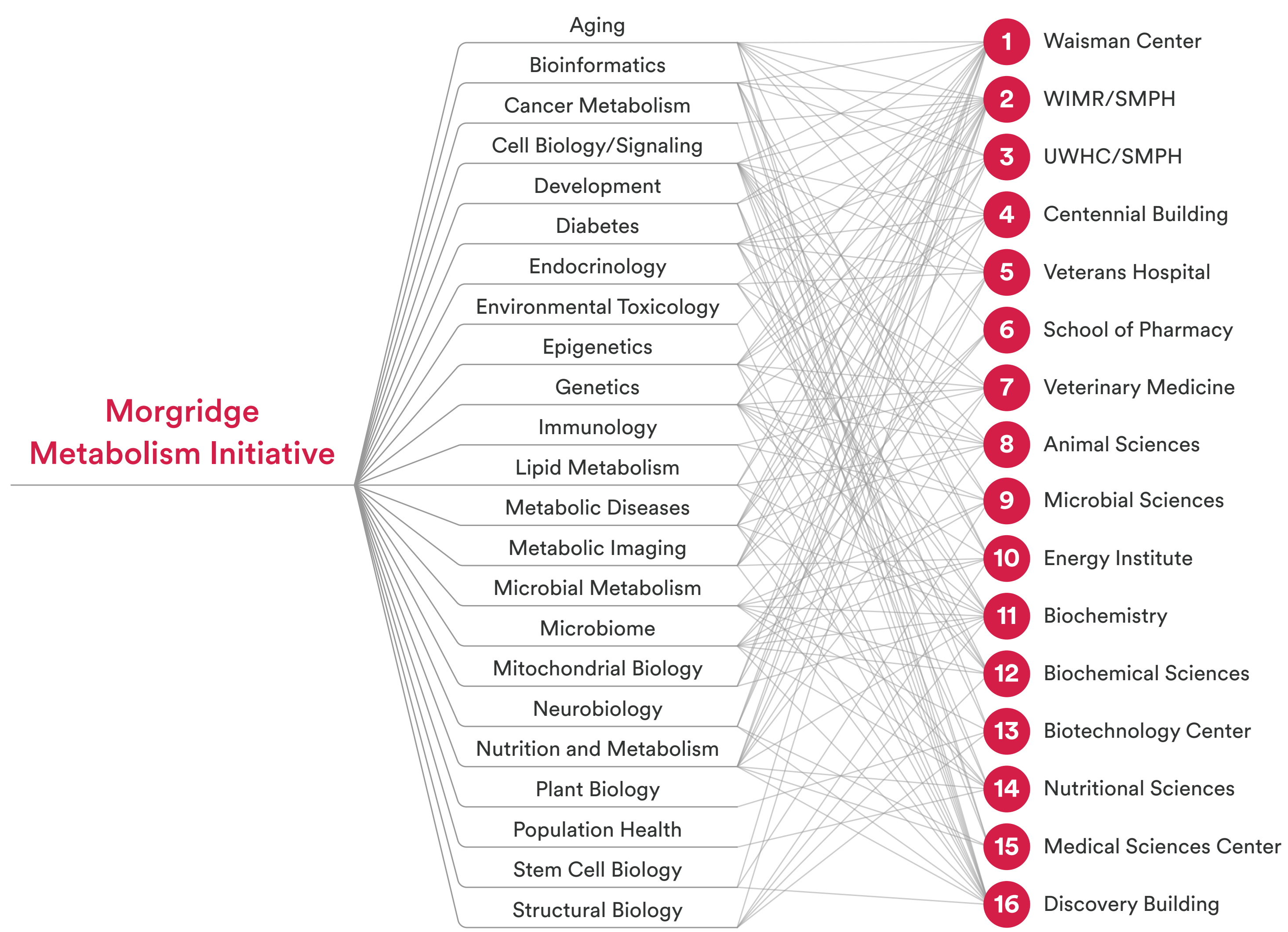
2020 Fellow - Kaitlin Fisher
i. Postdoctoral Fellow with Chris Hittinger in Genetics
ii. Current Position – Assistant Professor in the Dept. of Biological Sciences at SUNY-Oswego

Morgridge/UW–Madison Metabolism Symposium
2018, 2019, 2021

Morgridge Metabolism Colloquium
34 invited speakers since 2015

Frontiers in Metabolism
2018, 2019

UW–Madison Diabetes Day
Sponsor/Administrative Support; 2019, 2021, 2022



Research partnership brings gene editing promise to eye disease

Skala Lab contributes imaging expertise

Melissa Skala

David Gamm

Kris Saha

In order to tap the tremendous potential of CRISPR gene editing technology for reversing human disease, Wisconsin scientists are working with a star pupil.

The human eye — though one of the body's most complex and intricate structures — happens to be an ideal early candidate for treatments that incorporate CRISPR, the Nobel Prize-winning tool that may help precisely target and alter sequences of DNA associated with disease.

David Gamm, director of UW–Madison's McPherson Eye Research Institute (McPherson ERI) and professor of ophthalmology and visual sciences, describes a number of important attributes. Eyes are a self-contained, compact system. They are readily accessible to treatments, unlike the brain or other organs. They are somewhat immune privileged, making them less prone to tissue rejection. We have two of them — in case something goes wrong.

And there's major clinical momentum, Gamm says. A gene therapy called Luxturna — used to treat a rare inherited form of vision loss — recently became the first gene therapy approved in the U.S. that targets a disease caused by mutations in a specific gene.

That interest has coalesced at UW–Madison through an interdisciplinary partnership involving scientists at the McPherson ERI, the Morgridge Institute and the Wisconsin Institute for Discovery (WID). The team is organized around a variety of techniques to identify the safety, reproducibility and efficacy of gene editing targets in the eye.

Gamm, whose expertise is in cell-based therapies to fight diseases of the retina, started exploring the idea of CRISPR-based therapies about a decade ago with Kris Saha, a biomedical engineer at WID and member of the NIH's Somatic Cell Genome Editing Consortium. Saha has pioneered new gene editing technologies.

They were joined by Morgridge Investigator Melissa Skala, Carol Skornica Chair in Biomedical Imaging, who provides non-invasive ways to measure off-target effects of gene editing. The team also includes Sushmita Roy at WID, who is an expert in computational methods for genome network analysis.

Their NIH-supported project, now in its fourth year, uses stem cell-derived retinal organoids (or tiny 3D retinal tissue cultures) created in the Gamm Lab to replicate the cellular makeup of eye diseases in a dish.

Gamm notes there are more than 250 different genetic diseases that cause human blindness, so creating organoids en masse allows the team to test literally thousands of gene editing combinations to identify beneficial effects and unforeseen safety issues.

"The vast majority of human eye diseases do not have animal models," Gamm says. "In the case of gene editing, you need to work within the human genome to know if your therapy will be safe and on-target."

The Skala Lab contributed a technique called autofluorescence lifetime imaging — which can track the natural fluorescence produced during cellular activity. The technology is highly sensitive to retinoids, which are pigments in the eye that change conformation during visual cycles.

The experimental approach designed by Skala Lab Assistant Scientist Kayvan Samimi successfully tracked the dynamics of cellular changes across these organoids. Importantly, it provides a way to confirm whether changes are occurring as a direct result of the gene editing. Right now, getting that validating proof is one of the major challenges of CRISPR technology.

"It came out of left field," Skala says. "We all knew that retinoids were in the eye and that they fluoresce, but we thought they weren't useful to identify function. Kayvan discovered how he could image different conformations of retinoids that were meaningful in determining the function of the cell. So, that was a really fun journey."

The next step in the journey, Saha says, is to build on the current work to actually develop an investigational new drug based on gene editing of the retina within a patient, rather than treating cells outside the body and returning them. It would represent a monumental step forward, not only in preventing eye diseases but providing gene-editing proof of concept for other diseases.

"This is a great example of team science and working across colleges and disciplines," Saha says. "I could tell that we were pushing the boundaries when we first sketched out the project. We were constantly asking: 'What did you mean by that? What is that term?' That's a signal that we're really bringing together people who normally don't talk to one another."

Gamm says the project reflects how the McPherson Eye Research Institute approaches basic research. It draws on talented scientists from across the university — many of who have not worked within the eye before — out of the recognition that one field of research won't have all the answers.

"We're tapping into what's already the greatest resource that the UW–Madison has, which is that all of its talented people actually like to work with one another," Gamm says. "Researchers here are excited to get outside of their own swim lane, and working together is like having a noodle to hang onto as you venture into the deep end."

Engaging the science-curious public

In partnership with the Wisconsin Alumni Research Foundation, the Morgridge Institute inspires and engages society through its Discovery Connections science outreach programs.

Programs are available in-person in Madison, at the Discovery Building, but many others are available in new digital platforms or are hosted at schools, community centers, libraries, and museums throughout Wisconsin and beyond.

Here are some vital statistics, sprinkled with images from our signature programs, the Wisconsin Science Festival and Saturday Science at Discovery.

80,000+
PEOPLE HAVE ATTENDED SATURDAY SCIENCE

IN A TYPICAL YEAR, WE WELCOME 700,000+ PEOPLE TO THE DISCOVERY BUILDING

THE WISCONSIN SCIENCE FESTIVAL:
HAS ATTRACTED
393,000+
STATEWIDE ATTENDEES SINCE 2011

WE HAVE ACTIVE PROGRAMMING ACTIVITY IN AS MANY AS
44 COUNTIES
EACH YEAR

WE HAVE WORKED WITH
500+ FACULTY
ON PUBLIC ENGAGEMENT PROGRAMS

Training the next generation of science leaders

Scientific training is much more than learning experimental methods or interpreting data. When postdoctoral trainees enter the workforce, they will require management, leadership, collaboration, and communication skills to be successful.

The Morgridge Institute is committed to fostering growth of "whole scientists," with scientific training that prepares them as science leaders. And, because of our close affiliation with UW–Madison, the institute is committed to enhancing the research and educational mission of the university.

We not only press the boundaries of biomedical research — we also mold the next generation of fearless scientists who will carry that mantle in the future.

Morgridge fellowships promote new connections with UW–Madison

In 2015, we created the Morgridge Interdisciplinary Fellowship designed to promote new collaborations between institute investigators and UW–Madison faculty. To be eligible for the fellowship, the candidate must be advised by a Morgridge investigator and a UW–Madison faculty member who have not worked together before, and the project must be a new line of inquiry for the team.

The program has been wildly successful: More than 50 new linkages have been created between investigators who had not worked together before. These projects have connected Morgridge to more than 20 departments throughout the university in seven schools and colleges. To date, the 21 fellows have produced almost 80 unique publications. Today, 18 of the projects are still active, many having received additional funding.

"Morgridge is an essential partner in the success of postdoctoral training across UW–Madison," says Imogen Hurley, director of the UW–Madison Office of Postdoctoral Studies.

Postdocs appreciate flexible approach

After completing training, Morgridge postdocs have landed faculty positions, founded companies, landed prestigious AAAS fellowships, entered government service, entered industry, and more. When asked, our trainees commonly cite three reasons why they chose a Morgridge postdoctoral position:

- **Research flexibility:** Because their scientific activities are less constrained to the specific aims of grant funding, they have more freedom to go where the science takes them.
- **Support for entrepreneurship:** The institute's recognition of the importance of entrepreneurial pathways is cited as an influencing factor.
- **Interdisciplinary approach:** The ability to learn across disciplines is frequently cited, especially regarding imaging expertise. Several of our postdocs are excited to learn multiple hardware systems, and most express enthusiasm for finding new training collaborations.

TESTIMONIALS FROM POSTDOC ALUMNI

José Ayuso
Assistant Professor of Dermatology at UW–Madison

I think it's a fantastic experience. Now, I have so many collaborators I met through my mentors. I had access to a lot of people, and I was exposed to many different fields. That's why now I have a network of colleagues that I ask questions about or who can help me. If you work without these connections, your research would be more limited. I work in dermatology now, but because of my connections, I know researchers focusing on epithelial cancers, neurosciences, human oncology, immunology, surgery, organ transplantation. Those are very different departments!

Something that I really like about Morgridge is that they try to go for bolder things. 'Fearless science'... that's kind of true! Morgridge researchers all seem to share that attitude, and I really liked that."

Kalpana Raja
Assistant Professor of Research at UTHealth Houston

"Being a postdoc at Morgridge was a wonderful opportunity! It was always very easy to approach colleagues, and Ron Stewart is a great mentor. I learned how to be a mentor from him.

He gives space for the student to suggest whatever approach they have in mind, irrespective of whether it is correct or wrong. It allowed me to think and offer ideas without hesitation. Of course, we can refine it later, but there is the freedom to come up with whatever you have in mind. So we always had the freedom to talk to Ron and say whatever we think in our mind, especially about our research.

I loved Morgridge and Madison. I didn't want to leave!"

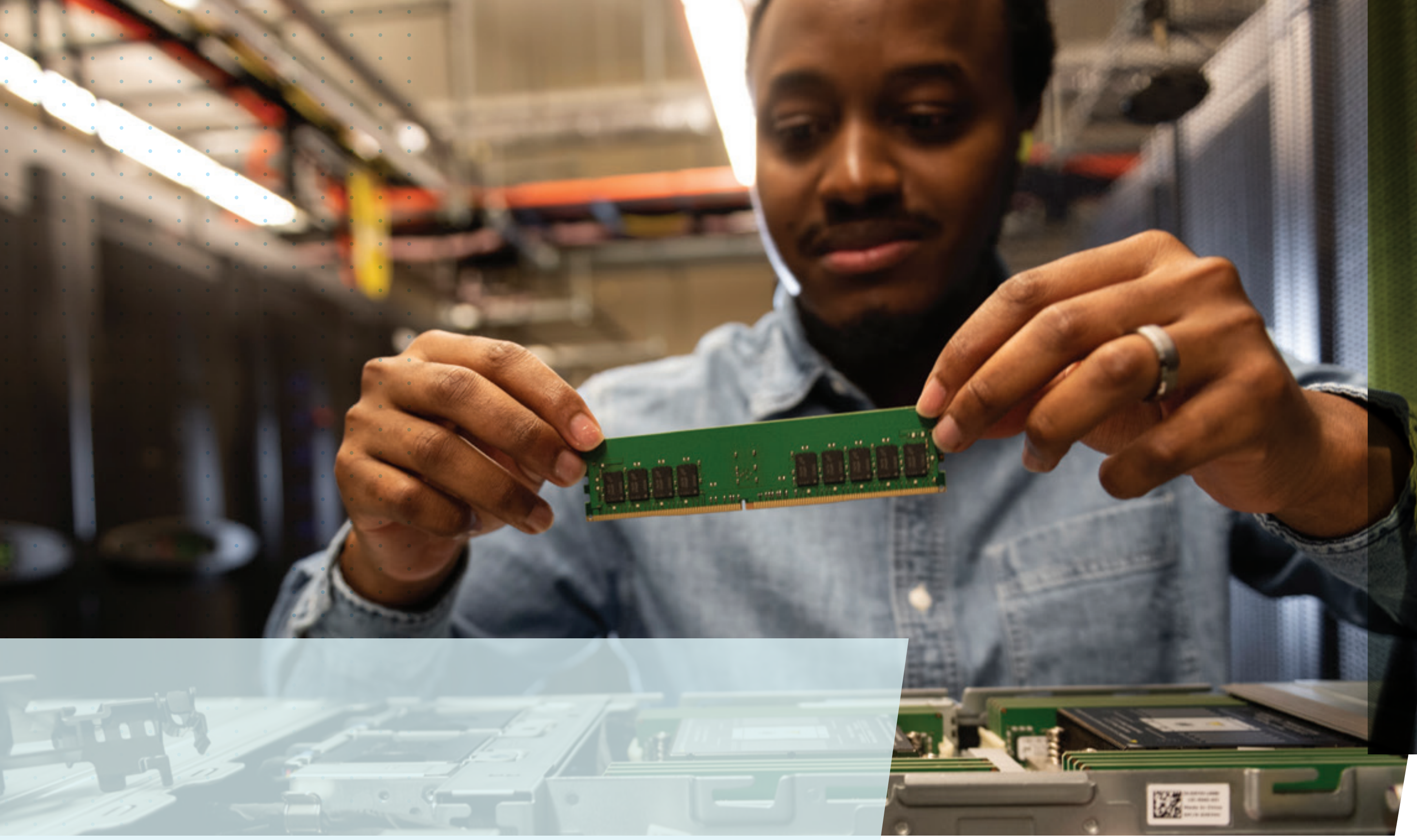
Finn Kuusisto
Founder of FANTM

"I've always based career path decisions on just wanting to do cool stuff and do things that I can be excited to talk about with family and friends. At Morgridge I could say we are growing brains in a dish! And then we're doing drug toxicity testing ... just sci-fi level work.

My advisors were always very positive, and that was helpful. I always had a lot of freedom in what I worked on, and I had a pretty good experience with my advisors.

The benefits at Morgridge are outstanding, too. I had major surgery during my postdoc, and the insurance provided by Morgridge was outstanding.

But when I think about Morgridge, it's the intangible stuff that's the biggest sell. It's a research institute doing basic science, but it also has interest in the entrepreneurial world. I think I learned a lot working with bench scientists, too. I'd tell my friends you got nerds walking around like in lab coats, and I'm the computer scientist working in the office next door. Before my postdoc, my medical experience was with electronic health records work. Morgridge opened my mind to more medical applications."



The Morgridge Research Computing Team (from left): Christina Koch, Emile Turatsinze, Miron Livny, Rachel Lombardi, and Brian Bockelman

High-throughput computing:

Fostering data science without limits

Biology and big data are now completely inseparable. Most modern biology produces data sets too massive to manage by conventional standards, and the challenge will increase exponentially as the sophistication of the science grows.

The Center for High Throughput Computing (CHTC), a joint partnership of UW–Madison and the Morgridge Institute, sees this onslaught of data and says: *Bring it on.*

"We have established a goal of never letting the amount of data limit the experimental approach of the scientists," says Miron Livny, the founder of high-throughput computing (HTC). Livny has been championing HTC for more than three decades as a UW–Madison computer scientist, and more recently as the Morgridge Institute's lead investigator of research computing.

HTCondor is a task-scheduling software approach that essentially breaks larger computational tasks into smaller pieces, allowing researchers to analyze more data. The key is to enable a project to be done more quickly — hence the term "high throughput." The team now handles 250-300 projects a year, double that of five years ago, and uses hundreds of millions of hours of computing time.

And that's just at UW–Madison. The global Open Science Grid provides HTC resources to the world, where it is the backbone system for Nobel Prize-winning projects such as detecting gravitational waves and discovering new subatomic particles. Just this year, it made a splash for its contribution to the discovery of a massive black hole in the center of our galaxy.

This service is gaining adherents on campus because scientists are learning that it is more than someone asking, "What technology do you need?" Research computing is a collaboration, and the people HTC brings to the equation are more important than the technology.

Livny says the HTC Facilitation Team is a great example. The emphasis on facilitators was way ahead of its time, almost unheard of in computer science circles. These are the translators who can work their magic between the technology and the bench experiments — finding the best way to maximize the data for the scientists.

Livny uses a hospital metaphor. Like a hospital ER room, HTC is not dedicated to one disease or one family of health challenges. It takes all comers — whether it's particle physics or brain science or COVID-19. The facilitators help decide: What is the right computational "medicine" for each individual?

The UW–Madison and Morgridge side of HTC work together seamlessly — by design, one can't tell where one begins and the other ends. But there is a unique ingredient Morgridge provides. Livny says the institute's hiring flexibility allows the group to hire unconventional talent who might not be optimal fits for tenure-track roles, but are perfect for advancing HTC as a core service.

Brian Bockelman came on board in 2019 as a Morgridge research computing investigator, having decades of HTC experience with big physical science projects such as the CERN Collider in Switzerland and IceCube in the South Pole. He has been able to apply that experience to the massive computational needs we are now seeing in biological research. For example, he led development of the data management platform for the new cryo-electron microscopy (cryo-EM) center on campus. As a technology that provides both large-scale data and processing challenges, cryo-EM will keep the research computing team busy for years to come.

"Research computing's real success is when researchers change the way they do science because of questions we ask, as well as the computing we provide them, opening their eyes to things they didn't know were possible," Livny says. "Ultimately, established scientists are able to think differently about the science itself, rather than just solving one distinct problem."

Katie Overmyer and Evgenia Shishkova, Coon Lab scientists

Josh Coon and Howard Bailey

Mass spec provides new pathways for fighting cancer

When biochemist Joshua Coon, Thomas and Margaret Pyle Chair in Metabolism at Morgridge, first started developing scientific instruments to measure molecules in living systems, his criteria for finding partners on campus at UW–Madison were simple and clear. "We were technology people interested in making better measurements, and we needed cool projects to help us push the technology," he recalls.

Fifteen years later, that approach has completely flipped on its head. Coon's Lab is the nexus of a prolific network of collaborations on campus, drawing on world-class technology to help push the science.

One of his most prominent partnerships is with the Carbone Cancer Center, using mass spectrometry to help researchers find new ways to prevent and treat cancer.

Mass spectrometry uses instruments to measure the mass of molecules and tell you the chemical structures. When studying cancer, scientists look for molecules, or proteins, that change when cancer cells appear. They try to prove whether those changes in these targets have a direct role in cancer development. And if so, they test ways to stop it.

The seeds of the partnership were planted about a decade ago during a series of meetings aiming to bring tech and cancer people together. Then seven years ago, thanks to investments by the Morgridge Institute, the Coon Lab began measuring lipids and metabolites, in addition to proteins. With the potential for even more specific studies and potential solutions, "we deliberately sought him out," says Howard Bailey, who directs the cancer center.

Mass spectrometry is not a commodity technology like DNA sequencing, with scientists paying a set fee for a package of services. The tech teams work with each collaborator to help them design their experiments. That takes a lot of back and forth and it can be one to two years from the first handshake to getting results that are actionable and publishable. "Those deep collaborations are really what makes things work," says Coon.

More than 30 different Cancer Center members have joined mass spectrometry projects that range from basic questions like "What is this protein doing?" to studying more clinically relevant patient samples and everything in between.

Emery Bresnick, for example, works on discovering mechanisms that cause blood cancer predispositions. When his team has an intriguing molecule, they bring it to the Coon Lab to better understand what it does, to whom, and how, and mass spec tools can provide a short list of possible leads. "It's essential to have that technology," says Bresnick. "The data sets open up new doors that otherwise sometimes open through serendipitous discovery, but sometimes they never open."

Mark Burkard is studying the person-to-person differences in breast cancer to be able to deliver more precise treatments. He worked with the Coon Lab to better understand what mechanisms control DNA getting segregated into daughter cells during cell division. Some of the more effective cancer treatments target this DNA segmentation process because it is highly error prone in cancer cells. With a better understanding of the biology, Burkard's team can use that information to select which patients should receive which drug.

One key strength of the partnership is its decentralized approach. There are a dozen labs on campus with mass spec expertise, and the team has taken on the role of asking what a researcher is trying to do, assessing whether mass spec can help, and then serving as matchmaker to find the best fit. "We're embracing all of the expertise on campus, which is going to be really important for the next five to 10 years of cancer research," says Coon.

His lab even offers micro grants to help get a collaboration started and defray the risk, to get some momentum that will lead to joint publications or grants, while minimizing the burden on the cancer center.

As the tools progress and measurements get faster and better, the hope is to integrate it into tailored patient care.

In every cell, there are 20,000 proteins, several hundred metabolites, and a couple of thousand lipids. When those things get perturbed, bad things can happen, but we don't really know at a molecular level what's changing enough to be able to understand who does well and who doesn't.

"There's a reason why some people do better than others with cancer," says Bailey. "The signals are there; we just have to be able to read and interpret them."

Developing the science of science communication

“We are very excited about a science communication hub at Morgridge becoming an incubator for a broad portfolio of innovative, on-the-ground work with communities in the state and beyond. Many of the challenges we face in Wisconsin at the interface of science and society either forecast or mirror similar challenges for the U.S. or even globally.”

— DIETRAM SCHEUFELE

The first rule of thumb in strategic communications is to know your audience. And if you don’t, you need to do a little research to learn.

Strangely enough, when scientists try to communicate to the public, they often forget to take the disciplined approach they apply to their own work and instead just wing it. Then they are surprised when they cause confusion or are misunderstood.

At UW–Madison, two programs are bringing together the rigor of academic research and the expertise from hands-on fieldwork, collaborating to make science communications more scientific.

At many universities, research in this area is still in its infancy, but the work of the Department of Life Sciences Communication (LSC) is internationally renowned. Across campus, the Morgridge Institute is a national model for running community outreach programs, from summer camps for kids on campus to the annual state-wide Wisconsin Science Festival involving hundreds of scientists in nearly every county.

Deepening this relationship is now a top priority for the institute. Science Advisory Board Chair John Durant, who directs the MIT Museum, sees tremendous opportunity to improve science communications by melding theory with practice in a way that perhaps no other university has done.

“It’s hard to identify a more urgent issue that we, as both scientists and citizens, need to deal with” says Brad Schwartz, CEO of Morgridge. “We want to know — this is what works, this is what doesn’t, and this is why.”

A good example of this partnership is a National Science Foundation grant to explore whether on-the-ground engagement with different publics can depolarize public debates around emerging technologies like CRISPR. How can insights from social science help us create constructive dialogue between scientists and citizens without public debate getting gridlocked by political or value-based disagreements?

Such partnerships require rethinking and humility on the part of scientists as well. Whether the topic is cancer or genetic engineering or vaccines, “we need to make sure we don’t assume to know what people value,” says Dominique Brossard, chair of LSC and an expert in public opinion dynamics related to controversial science.

Information is crucially important, but it’s not enough. The problem comes in throwing information at audiences without context. “We’re often answering questions that we either assume or wish audiences would’ve asked, rather than the questions that they are actually asking,” says Dietram Scheufele, an expert in the fields of political communication, science communication, and science & technology policy.

The same caution applies to understanding to whom people want to listen. “We tend to assume that the science we trust is the science that other people trust,” says Scheufele. “Unfortunately, people are as good at finding the science that confirms their belief as they are in ignoring evidence that doesn’t.”

Actively practicing humility also means scientists must refrain from blaming people for not knowing enough or doing the wrong things, as if they were the problem that needs to be fixed. Instead, we should ask ourselves: How can we change the public’s mindset by answering questions that people really have? How can we address concerns and values?

Brossard and Scheufele are in the process of creating a scaled-up program in which rigorous research in the science of science communication and real-life public engagement inform each other.

In a time when society is deeply fractured and anything can quickly become politicized, scientists must also remember to first do no harm. “We are really concerned about science as a polarizing force,” says Brossard.

Often, it’s based on well-meaning missteps that just produce the wrong outcomes. UW research has shown that efforts to assuage fears of the mRNA vaccines used against COVID-19 by saying, “don’t worry, it won’t change your DNA,” backfired because it elevated fears of other technologies such as gene editing.

Scientists also need to remember that the proverbial mic is always on, especially on social media. You can’t disparage Republicans on Twitter and then ask them to listen to you on climate change. Or mock Christian beliefs and ask religious people to listen to you on stem cells or tissue engineering.

And sometimes it comes down to simply paying attention to how we say things rather than what we say. Scientists speak confidently of their “theories,” but laypeople see that as a weakness, something is “just a theory” that cannot be proven. Vaccine “passports” can sound like government overreach, while vaccine “verification” sounds like an active individual choice.

Using Wisconsin as a test bed, the collaboration between researchers and the practitioners is about to get closer. Brossard and Scheufele will be identified as Morgridge investigators. The university offers minors and certificate programs for both undergraduates and graduate students at UW–Madison.

A hub for this work at Morgridge could offer interesting new models of study, such as a visiting scholar program, workshops in addition to full courses, or weekend executive education opportunities. They aim to focus on helping scientists at all levels — from beginning students to seasoned senior investigators — communicate more clearly.

Elizabeth Wright and Brian Bockelman

From 'blobology' to atomic precision:

Wisconsin's leadership on cryo-EM imaging

Microscopes have come a long way from what many people remember from their high school biology class. Instead of peering through a lens, scientists can now create 3-D images by shooting beams of electrons at protein structures that have been frozen to hold their shape.

This state-of-the-art technology, called cryo-electron microscopy or cryo-EM, drives a promising collaboration between the UW–Madison Department of Biochemistry, Morgridge and other campus entities. Recognizing they risked falling behind, the partners sprinted to build a center that supports a broad range of research on campus and is now a national hub for training and research development.

Cryo-EM is all about getting clearer, more detailed images of the structure of molecules. Scientists need this atomic-level resolution to understand, for example, how proteins malfunction with disease and how to target them when developing a new drug. The specimen is flash-frozen in liquid ethane, which helps reduce the damage that inevitably occurs every time the electrons hit to secure an image.

The technology dates from 1974, but the field began to boom about ten years ago when more advanced hardware hit the market. Like many universities in the country, UW–Madison realized it needed to get serious about cryo-EM or risk becoming obsolete. Investigators at Morgridge and the biochemistry department started inviting the world's best experts to campus to give talks so they could learn how it works and understand what they needed to do.

In 2018, the field took off in the United States when the National Institutes of Health developed three national cryo-EM centers for single-particle analysis, a sort of plug-and-play approach where a scientist wants a single image to look at a specimen.

UW–Madison decided to establish its own center, focused on an approach called tomography. Similar to a person undergoing an MRI, the specimens are rotated and 120-140 images are taken from every angle to reconstruct the molecule.

Morgridge and biochemistry also joined forces in 2018 to recruit Elizabeth Wright from Emory University, where she had built a similar Cryo-EM center from the ground up. Everything fell into place when the NIH put out a proposal to support cryo-EM tomography centers — UW–Madison applied and won.

The depth of the partnership has been clear from the start. Buying expensive equipment through a state university can require jumping through hoops that can take as long as two years, so the department offered to take on other expenses if Morgridge could secure the microscopes. "We did all the negotiating afterwards, because we trusted each other enough to know that it was going to work, and it did," says Brad Schwartz, CEO of Morgridge.

After heavy renovations of dilapidated rooms, including pouring thick concrete slabs topped by an antivibration table to keep the sensitive equipment still, the first four microscopes were speedily delivered just as the pandemic forced the campus to close in March in 2020.

Ten years ago, scientists were looking at what Wright calls "blobology," when all the pictures taken looked like little blobs of molecules and you couldn't exactly see what's going on. The images of today, by contrast, let you see where all the atoms are positioned — like moving from play dough to tinker toys.

This process generates so much data that normal laptops can't handle the computation required to sort and analyze all the images. This is where the high-throughput computing capacity of Morgridge comes into play, what has become as essential to a lab as lighting. "Without really good computation, the cryo-EM microscopes are just over overpriced paperweights," says Wright.

Brian Bockelman, Morgridge research computing investigator, joined the institute with deep experience working with physicists with massive data challenges. While the science of cryo-EM is drastically different, the computational fundamentals are the same. His computational infrastructure is helping the cryo-EM center extract the particles that interest a researcher to generate the higher-resolution 3-D structures they need.

"I would love it if researchers on campus drowned us with computational and data challenges so they can really start pushing us to think better," Bockelman says.

Morgridge also brings the expertise of Tim Grant, a biomedical imaging specialist who develops algorithms and applies new methods for improving the imaging and its analysis.

The center has talked to a vast number of investigators, and already work with nearly 50 groups spanning many different types of science. In addition to the researchers studying proteins, many are looking at viruses such as SARS-CoV-2 and HIV. Others work with bacteria to understand how to develop new antimicrobials and antibiotics. Some groups want to look more at tissue, such as the eye, or brain tissue to understand different neurodegenerative diseases and brain development.

> **"We're pioneering different aspects of thinking about computation, hardcore algorithm development, and how we use these microscopes to look at challenging biological questions," says Wright.**

Morgridge Bioethics:

Navigating the challenges in cutting-edge biomedical research

What are the ethical tradeoffs of stopping a clinical trial due to COVID safety concerns, when doing so also halts potential medical progress from the trial?

How do researchers navigate consent when studying neurodegenerative diseases such as Alzheimer's, when a patient eventually cannot grant consent on their own behalf?

As more health studies move to home or remote environments, rather than controlled healthcare settings, how do researchers ensure the data is still reliable?

Just because it's legal to use some de-identified patient medical records, does that automatically mean it's ethically sound?

Pilar Ossorio

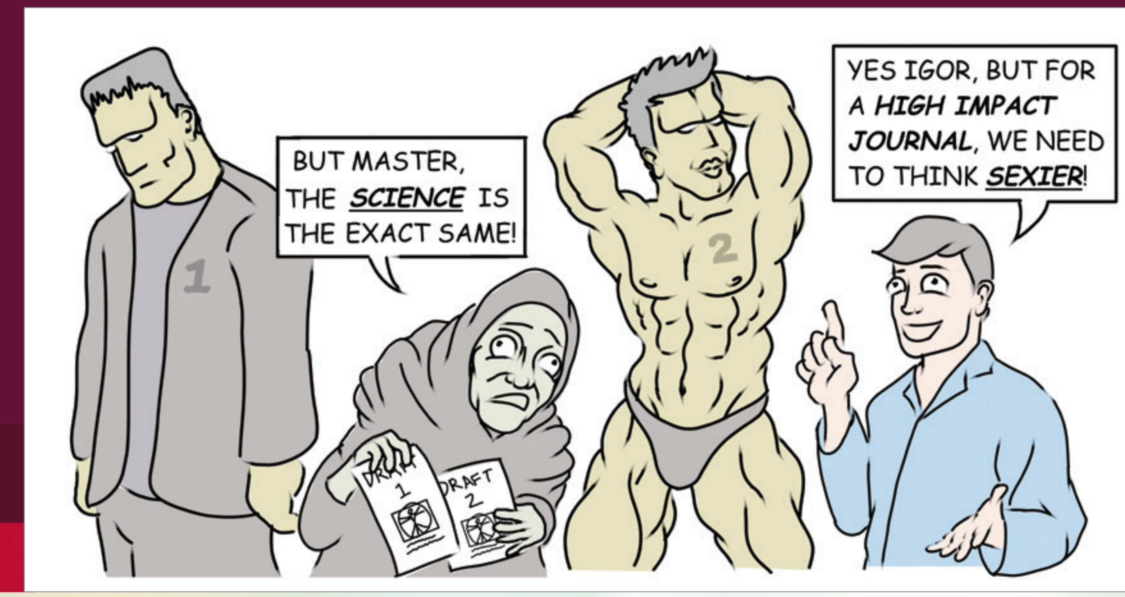
These represent a small fraction of the kinds of issues that reach the desk of Morgridge Bioethicist-in-Residence Pilar Ossorio, a UW–Madison professor of law and bioethics. For the past decade, Ossorio has been offering a suite of programs and services to the Wisconsin bioscience community to help address the increasingly complex ethical issues tied to cutting-edge research.

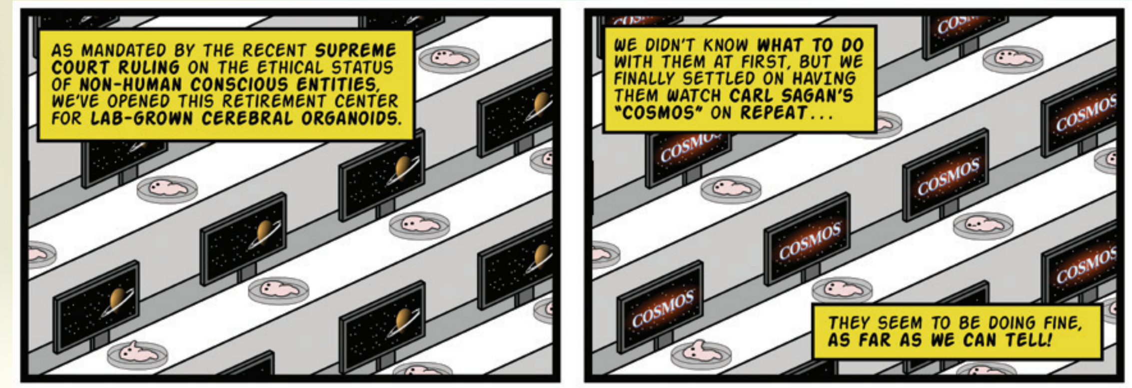
Through her Research Ethics Consultations Service (RECS), launched in 2014, Ossorio has tackled more than 60 inquiries on bioethical concerns large and small. Some of them she describes as "curbside consulting," where the answers have been well-addressed in the current literature, and she can simply connect scientists to the critical consensus. Then there are other challenges thorny enough to warrant multi-year involvement, and lead to scholarly papers of their own.

Ossorio says the demand has remained quite steady over the years. What's frequently most satisfying about the work is it not only helps clear certain ethical hurdles, it can ultimately make the science stronger and the results more useful. And it can make research proposals more competitive on the front-end.

"UW–Madison has a department of medical history and bioethics, and we have fabulous bioethicists there, but most of those bioethicists are not really applied ethicists," Ossorio says. "They're more sort of traditional academics who are advancing the scholarship, rather than dealing with the nitty-gritties of doing the research. So I think the applied research ethics component of what we do is really critical, and that makes us a good partner for the scientific community."

While the RECS program most often is helping scientists with unforeseen challenges that arise during research, many other groups are seeking Ossorio's help in the grant writing process.





The 2022 first prize (top) went to Logan Keding, School of Medicine and Public Health, Endocrinology and Reproductive Physiology Program; second place went to William Mayner, School of Medicine and Public Health, Neuroscience Training Program.

"At NIH and NSF, a growing number of programs require some attention to ethical, legal and or social issues as part of an application," she says. "Applicants are often not fully prepared to address that, even when they don't require it."

Ossorio says scientists are encouraged to look forward, past the planning and funding stages, to the implementation stage of their research, and seeing the ethical considerations through the entire course of the work. "The more we become known as a place for applying ethics expertise, even when it's not required, the more it improves the competitiveness of Wisconsin science."

When Morgridge was first chartered in 2006, it contained a few features that are not always evident in independent research institutes. For example, the founders made public outreach a core part of the Morgridge mission, and it created a program devoted to the professional development of trainees. The founders also wanted to have bioethics be a topic infused across all research areas, while providing an additional ethics resource for campus partners.

One of the guiding principles of the Bioethics-in-Residence program is "promoting a culture of responsible science," where it is not a box that gets checked, but an everyday way of thinking about the scientific process. One of the creative ways Ossorio's team has fostered this is through the annual Bioethics Cartooning Contest, now in its fifth year.

"People often think of research ethics as focusing on what researchers can't do. It's framed in the negative, it's all finger-wagging," says Ossorio. "We wanted to do something that would bring some humor to the whole subject area, and let people be creative when thinking about their ethical problems and ethical issues that they confront."

TESTIMONIALS FROM PARTNERS

"Morgridge is a significant contributor to the success of the UW-Madison Office of Postdoctoral Studies. Morgridge staff played a central role in the development of a Postdoctoral Training Course in Scientific Leadership by convening a faculty focus group, recruiting course co-instructors and sharing training expertise in the creation of training materials. The course, now entering its seventh year, will continue to improve through the integration of more inclusivity and equity training."

— IMOGEN HURLEY, DIRECTOR OF THE UW–MADISON OFFICE OF POSTDOCTORAL STUDIES

"The Morgridge Institute for Research will serve as a test bed for novel interactions between biology and data science that will support the goals of the new Data Science Building."

— STEVE ACKERMAN, VICE CHANCELLOR FOR RESEARCH AND GRADUATE EDUCATION

"It's always helpful to have opportunities to nucleate collaboration. Morgridge was able to fund both a graduate student and a postdoc in my lab, and it led to a new collaboration between Morgridge Investigator Melissa Skala and myself. That has been fantastic for my lab."

— LAURA KNOLL, PROFESSOR, MEDICAL MICROBIOLOGY AND IMMUNOLOGY

"Diabetes is a huge public health problem that affects at least 11 percent of the population. Several years ago, I started working with folks at the School of Medicine on creating a comprehensive diabetes research center on campus. Morgridge has been a really instrumental partner with administrative support and in leveraging these connections and communities that already existed in the Morgridge metabolism space. We have more than 100 members now in the center."

— DAWN DAVIS, PROFESSOR, DEPARTMENT OF MEDICINE

"With the new Cryo-EM center, when you're building something of this magnitude and complexity, it's valuable to have partners across the campus. The Morgridge partnership was important to me because it allowed for certain flexibilities to be able to happen with respect to computation and to hiring talent. And the flexibility of acquiring some of our hardware through Morgridge enabled us to speed the process forward."

— ELIZABETH WRIGHT, DIRECTOR, UW–MADISON CRYO-EM RESEARCH CENTER

"The latest black hole image is a remarkable feat in the world of astronomy — only the third such black hole imaged in this way by the Event Horizon Telescope. And it was made possible with the help of UW–Madison high throughput computing (HTC). My job here is to inspire you all with a sense of the discoveries to come that will need to be enabled by HTC."

— ERIC WILCOTS, DEAN, COLLEGE OF LETTERS AND SCIENCE, DURING HIS KEYNOTE FOR HTCONDOR WEEK 2022

Investigators

Paul Ahlquist, John W. and Jeanne M. Rowe Center for Research in Virology

Brian Bockelman, Research Computing

Jason Cantor, Metabolism

Joshua Coon, Thomas and Margaret Pyle Chair in Metabolism

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Laura Heisler, Discovery Outreach

Miron Livny, Research Computing

Phil Newmark, Regenerative Biology

Pilar Ossorio, Bioethics Scholar in Residence

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Deane Mosher, Metabolism

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Chad Reinstra, Metabolism

Dietram Scheufele, Science Communication

Igor Slukvin, Regenerative Biology

Andreas Velten, Biomedical Imaging

Justin Williams, Biomedical Imaging

Elizabeth Wright, John W. and Jeanne M. Rowe Center for Research in Virology

Ming Yuan, Virology

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"Morgridge is an example of what a university should be kind of rolled into one building, one conceptual process. It's diversity of thought, diversity of expertise brought to bear on various topics of concern of society. How do we think more creatively? How do we try and move past our various developed bureaucratic and disciplinary walls to move things forward?"

— Howard Bailey, Director, Carbone Cancer Center

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