College of Engineering
UNIVERSITY OF WISCONSIN–MADISON

SPRING 2024 NEWSLETTER

DEPARTMENT OF

BIOMEDICAL ENGINEERING

Greetings from Madison!

As we near the end of this academic year, I would like to reflect on the successes our department has had in the last 12 months.

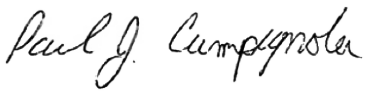
Many of our faculty received prestigious new grants this past year. More of our faculty were elected as fellows in the American Institute for Medical and Biological Engineering (AIMBE) professional society, where the overwhelming majority of our associate and full professors have now been recognized with this honor. Other faculty were elected as fellows into the National Academy of Inventors (NAI).

We had a near-record number of first-year students enter our program this year (more than 200). For historical context, when I joined the department in 2010, there were fewer than 200 total students. We are now the third-largest undergraduate program in the college. Importantly, the majority of students are now women. We are proud of our students, who are conscientious, community-minded young people who break the typical engineering mold by pairing technical knowledge with communications skills. They are curious and well-rounded, allowing them to meet the needs of all types of stakeholders and make a difference in peoples' lives.

We continue expanding our efforts in inclusion, equity and diversity to ensure a welcoming environment for all. We again are cosponsoring the Rising Scholars program for career advancement for historically underrepresented BME students, and our faculty members will actively participate at this year's program hosted by the University of Illinois Chicago. Our faculty also continue to participate in our college's own WiscProf event, where we invite underrepresented students from across engineering to learn about academic careers.

I hope you and your loved ones are well, and I thank you for your support of our department.

Stay safe and On, Wisconsin!



Paul J. Campagnola
Professor and Peter Tong Department Chair
Kellett Faculty Fellow
pcampagnola@wisc.edu

On the cover: In Biomedical Engineering 602: *CRISPR Genome Editing and Engineering Laboratory*, students like undergraduate Carley Schwartz get the chance to work directly with the revolutionary gene-editing toolkit. Photo: Tom Ziemer.

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Photo: Tom Ziemer

CRISPR lab course puts revolutionary gene editing tool into students' hands

As a researcher in a genomics lab, Carley Schwartz is much more familiar with the gene-editing tool CRISPR than the vast majority of the roughly 4,800 undergraduate students in the college.

"That's all I do in lab," says the senior BME major, who hopes to one day work in the biotech industry.

But that level of experience isn't a prerequisite for students in Biomedical Engineering 602: *CRISPR Genome Editing and Engineering Laboratory*, a new course designed to give upper-level undergraduates like Schwartz and graduate students the practical, essential skills to use the tool. They learn the basics of cell culture and differentiation, imaging techniques, strategies for designing genomic edits, and how to sequence and analyze DNA while working with mouse cell lines.

Associate Professor Krishanu Saha has been using the genome editor in his research lab since shortly after its 2012 discovery and teaching about it in classes and workshops for the better part of a decade. But he wanted to create a dedicated, semester-long, lab-based course to allow students to work directly with the technology and get a firsthand look at its possibilities and limitations. He says he only knows of a handful of other similar courses across the country.

Krishanu Saha

"People see the illustrations, they see how it works, they see the impacts on publications and companies being launched, but many people ask, 'Well, how do you actually do it? What are the steps? How do you get CRISPR into the nucleus? Where do you get your reagents? Is it hard?'" says Saha, who's part of the National Institutes of Health Somatic Cell Genome Editing Consortium and the National Science Foundation Center for Cell Manufacturing Technologies. "These are the questions that I think, in particular, engineers ask, because they're thinking of how to refine the process and make it more efficient and scale up and make the technology more accessible and widespread."

Saha's lab uses the CRISPR-Cas9 editor to engineer T cells to attack cancer, as well as in emerging treatments for several eye diseases and other cell therapies. But students rarely get the chance to use the so-called "genetic scissors" unless, like Schwartz, they work in a research lab that deals with genomic editing.

"I didn't have anything like this in my undergrad. We were not doing gene editing," says Madeline Smerchansky, a PhD student in BME and one of the three Saha lab members who helped develop the course and are serving as teaching assistants. "It doesn't seem like a lot of people get that opportunity unless you're in a CRISPR lab."

Just ask Michelle Bretl, a PhD student in communication sciences and disorders minoring in BME who came into the course with only cursory knowledge about CRISPR. Now, she's eager to apply it to the tissue engineering and regenerative medicine work she's doing in the lab of BME affiliate faculty member Susan Thibeault in the Department of Surgery.

"I'm excited by the fact that it is something that people from a lot of backgrounds can do, and I think that will benefit patients in the future," says Bretl. "It's not this specialized thing. So much of medicine is so specialized and can cost a ton of money. This feels like we could be moving toward more accessibility."

Saha says the equipment in BME's recently renovated teaching lab on the first floor of the Engineering Centers Building makes it possible to offer a course where students can work on mammalian cells. That's significant, because it means the skills and techniques they're learning will directly translate to human cells.

"We're fortunate to have fantastic facilities, which I think reflects the commitment of both the college, the department and the donors who provided the funds and equipment to build out this space," he says. "It takes biosafety cabinets, it takes incubators, it takes specialized equipment to work with these cell lines that are probably the most relevant for these types of therapeutic applications."

Professor William Murphy and PhD student Joshua Choe. Photo: Tom Ziemer

Mineral coatings could enable shelf-stable mRNA therapies

The rapid development of mRNA-based vaccines against COVID-19 was a game-changer in the global pandemic. The vaccines employ messenger RNA to direct cells to produce a protein from the surface of the virus—triggering an immune response that preps our body for the real thing.

These vaccines are the result of decades of incremental mRNA research (some of which earned two scientists the 2023 Nobel Prize in medicine). Multiple estimates show the preventative treatments have saved millions of lives.

There's just one problem: COVID vaccines, as well as other mRNA-based therapies for cancer, require cold-chain storage to maintain their potency.

"It sounds like a trivial problem, but it's actually quite a tremendous problem," says William Murphy, the Harvey D. Spangler Professor and H.I. Romnes Faculty Fellow. "If you're trying to get these to sub-Saharan Africa, you're going to have substantial challenges."

Murphy and his lab members believe they've found a viable alternative that could allow mRNA therapeutics to be stored at room temperature. In a paper in the journal *Acta Biomaterialia*, the researchers detail how using mineral coatings can maintain mRNA activity for up to six months. With that kind of preservation, mRNA therapeutics—including vaccines against infectious diseases and emerging treatments for cancer and tissue regeneration (the latter another Murphy lab project)—could be stored on the shelf at local clinics, allowing them to reach lower-resourced communities across the country and world.

Study lead author Joshua Choe, an MD/PhD student in Murphy's lab, screened 40 different mineral compositions to optimize their ability to maintain the mRNA stability in simpler formulations than clinically deployed vaccines. In the end, he identified a composition with the suitable amount of citrate and fluoride that maintained the potency of freeze-dried mRNA complexes. He's now applying the approach to similar lipid nanoparticles used in COVID vaccines, with promising early results. The group has submitted a provisional patent based on the work through the Wisconsin Alumni Research Foundation.

"All the way to six months, you're maintaining that activity, whereas without using our mineral to store those mRNA therapeutics, you lose quite a bit of the activity after two weeks, and then it declines to almost nothing," says Choe, who hopes to work as an orthopedic surgeon and researcher after graduating.

The approach draws inspiration from ancient fossils' documented ability to preserve DNA and proteins. Scientists successfully extracted DNA to analyze the genome of "Denny," an estimated 90,000-year-old hominin whose remains were found in a Russian cave in 2012. In another find in Tanzania, researchers found intact proteins in ostrich eggshells that date to 3.8 million years old.

Murphy's lab has been using minerals to stabilize biological molecules for various biomedical applications for about 15 years, and Choe saw an opportunity to apply the tactic to mRNA therapeutics while working in the lab during the lockdown days of winter 2020.

In addition to further demonstrating their approach's effectiveness with mRNA vaccines, Murphy and his group are pursuing its use for tissue regeneration, particularly for treating spinal cord injuries, wound healing and regrowing cartilage, muscle and bone.

"We want to be able to achieve it so you can literally take a treatment off the shelf, apply it to a patient and stimulate tissue regeneration," says Murphy.

First-year BME students create solution to empower woman with MS

A sense of dread washes over Kristan Collins just about every day when it comes time to run errands. It's not that she doesn't enjoy trips to stores like Homegoods. And she loves driving her 2020 Mercedes-Benz GLE 350—her first non-utilitarian vehicle since the mother of four became an empty nester.

From left: Lucas Cramer, Luke Schmelling, Kristan Collins, Lauren Piper and Sydney Smith. Photos: Joel Hallberg

The root of her anxiety is the seemingly simple task of getting behind the wheel.

"Getting into a car seems like a mindless activity, but for me, it's a big challenge," says Collins, a 57-year-old resident of Waunakee, Wisconsin, who lives with multiple sclerosis that limits her ability to lift her right leg higher than 3 inches off the ground. "I really have to hold onto the car with both hands and launch myself into the driver seat."

A team of first-year BME students created a device to alleviate that worry for Collins. The students' project was part of INTEREGR 170, an interdisciplinary, introductory design practicum that's open to first-year students in the College of Engineering. Each semester, groups of students develop prototypes to address challenges for real clients, often local community members contending with health challenges like Collins.

BME majors Luke Schmeling (Holmen, Wisconsin), Ilia Mikhailenko (Mequon, Wisconsin), Sydney Smith (Sheboygan, Wisconsin), Lauren Piper (Eagle River, Wisconsin) and Lucas Cramer (Rochester, Minnesota) fashioned a removable traction pulley system that attaches to Collins' car and helps her lift her right foot high enough to enter the vehicle smoothly and safely.

"I think we all came in with the preconceived notion that we wouldn't be doing anything real-world until maybe our junior or senior year," says Schmeling. "It makes the engineering feel a lot more real, a lot faster."

Collins connected with Assistant Teaching Professor Tracy Puccinelli, who created the course, through her neurologist, Dr. Chris Luzzio. Luzzio, a professor in the School of Medicine and Public Health, has also taught several engineering courses throughout his time at UW-Madison and referred a handful of clients to Puccinelli's class over the years.

The students set about exploring solutions, incorporating advice and feedback from alumnus Scott Schulz (BSBME '16), a lead system designer at GE Healthcare who volunteers as a project advisor. They met virtually with Collins, using some of the communication skills that Puccinelli is keen to instill in them, along with teamwork, self-awareness and technical acumen, to better understand their client's problem. Then they created a decision matrix to weigh competing factors like ease of entry, cost and safety, before presenting three ideas to Collins in mid-October.

She was wowed.

"It's hard to believe that these students are only freshmen," says Collins, a two-time UW-Madison graduate. "I would have expected this from seniors. But they really make me feel like they're doing this for me … not a grade!"

In the end, the students, with Collins' endorsement, opted for the simplest and most adaptable design. Their pulley system, which consisted of a foot loop, rope, pulley and carabiner, won out over a collapsible seat that would slide toward the driver's seat—à la a rowing machine—and a pneumatic balloon.

Collins, who was diagnosed with MS at age 31 during a pregnancy, is hopeful the design could be a prototype for a broader-reaching solution for older adults and others with medical conditions that affect mobility. She's planning to refer a friend to Puccinelli for a future project—giving another set of budding engineers a chance to build their skills while helping someone in the process.

"It's not just for our grade—it's actually going to help somebody with their life," says Mikhailenko. "It's additional incentive to make it as good as we possibly can."

Ashton lab stem cell technology leads to new understanding of autism risks

Technology developed in the lab of Associate Professor Randolph Ashton to grow "rosettes" of brain and spinal tissue gives scientists new ways to study the growing human brain, including a recent study of how genetic mutations linked to autism affect early stages of human brain development.

It's the latest discovery using RosetteArray technology, a screening tool that uses stem cells to generate embryonic forebrain or spinal cord tissue structures called neural rosettes. Neural rosettes are the starting material for generating human stem cell-derived neural organoids—clusters of cells that resemble larger, more complex organs—and can be used to assess whether different genetic makeups or exposure to chemicals increase the risk of neurodevelopmental disruptions.

"This technology gives us access to an embryonic model of human central nervous system development that we would otherwise not have access to," says Ashton, who's also associate director of the Stem Cell and Regenerative Medicine Center at UW-Madison. "This is useful, because not only can we now understand more about human development, but we can get an understanding of when it goes wrong."

Ashton and Gavin Knight (PhD '18) developed the technology behind RosetteArrays, which are marketed by Neurosetta, a company they co-founded with support from UW–Madison Discovery to Product and the Wisconsin Alumni Research Foundation's Accelerator Program.

RosetteArray technology played an important role in a study published in *Nature Neuroscience*. The study, led by University of Southern California stem cell biologist Giorgia Quadrato, with Ashton and Knight as co-authors, investigated mutations of a gene called SYNGAP1.

SYNGAP1 mutations have long been associated with risk factors for autism spectrum disorder, epilepsy, neurodevelopmental disability and more, but until now the gene has mainly been studied in animal models and focused on the impact of SYNGAP1 on synapses, the structure at the tips of long brain cells called neurons that allow them to pass signals to neighboring cells.

In their new SYNGAP1 autism study, Quadrato and her lab used RosetteArray technology to grow neural rosettes from healthy human cells as well as from the cells of a patient with a disease-causing variant in SYNGAP1. By analyzing these young, developing neural organoids, Quadrato determined that human radial glia cells—the cells responsible for producing all the neurons in the outer layer of the brain called the cerebral cortex—can express SYNGAP1. When SYNGAP1 is mutated, it leads to disrupted organization of the cortical plate, an early brain structure that gives rise to the cerebral cortex. This shows that SYNGAP1-related brain disorders can arise through non-synaptic mechanisms.

Quadrato and Neurosetta plan to partner on further studies to explore the extent of autism spectrum disorder genetic backgrounds that can be modeled using RosetteArray technology, which Ashton hopes will eventually lead to new precision medicine approaches.

"Simply being able to model early human development, in this case brain and spinal cord formation, gives you a very powerful platform to try to improve human health," says Ashton. "We've been surprised to see the effects of neurological disease-causing mutations in the earliest stages of these tissues' formation. RosetteArrays model approximately four to six weeks post conception, and we're learning that you can start to see markers for autism then, which is a disease that people typically aren't diagnosed with until post 2 years of age. So, the fact that we can see this very early in our model of human development is amazing."

Ashton says researchers using technologies like the RosetteArray are finding that the risk factors for autism spectrum disorder are boiling down to a couple of core pathways, that seem to have roles very early in human brain development, which is helpful information as researchers work on treatments.

Associate Professor Randolph Ashton delivers a "mini pitch" at WARF's Innovation Day as part of Summerfest Tech in June 2022. Photos courtesy of WARF.

Faculty News

David Beebe, the John D. MacArthur Professor and Claude Bernard Professor, was among the National Academy of Inventors 2023 class of fellows.

Beebe (PhD '94), who's also a professor in the Department of Pathology and Laboratory Medicine, leads the multidisciplinary Microtechnology, Medicine, and Biology Lab. He also is a fellow at the Wisconsin Institute for Discovery and a member of the UW Carbone Cancer Center.

Beebe holds 67 U.S. patents and 19 international patents. Of the U.S. patents, 50 have been licensed or optioned to commercial entities, as have 13 international patents.

His research into microfluidic technologies and microenvironments has led to the development of multiple research tools, streamlined point-of-care and lab-based diagnostics, and lowered cost testing for diseases. He is influential in organ-on-a-chip technologies that mimic the functions of organs on a microchip and allow the testing of drugs in a small-scale environment with a goal of improving clinical treatment decisions. His lab research currently includes cancer biology, multi-kingdom interactions, infectious disease and continued small-scale physics and technology development.

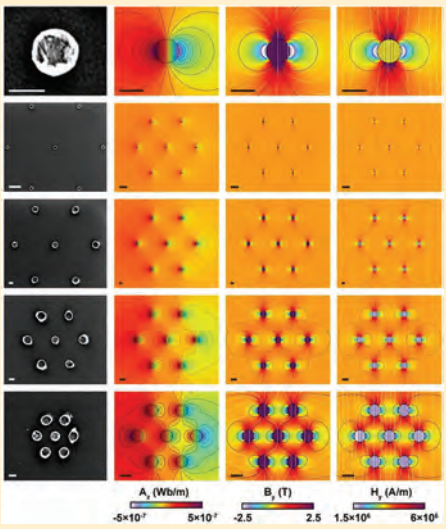
In addition to collaborating with established life sciences companies such as Gilson, Beebe is a serial entrepreneur, having founded or served on the board of Ratio, Tasso, Lynx Biosciences, Onexio Biosystems, Salus Discovery, and Flambeau Diagnostics. Beebe's current work with Flambeau Diagnostics was in response to the COVID-19 pandemic. The company's mobile, rapid testing platform can be performed in lab-equipped vans and adapted for different infectious diseases.

Associate Professor Kevin Eliceiri, the Retina Research Foundation Walter H. Helmerich Chair, earned a spot on the Clarivate Web of Science Highly Cited Researchers list for 2023.

Associate Professor Megan McClean received renewed funding from the National Institute of General Medical Sciences for her work elucidating the processes by which cells sense and respond to their environments. The five-year, more than $2 million grant is a continuation of her Maximizing Investigators' Research Award.

Professors David Beebe and Melissa Skala collaborated on a paper in the journal *Communications Biology* presenting a new microfluidic platform that better mimics the complex microenvironment in the body's tissues. In the paper, they demonstrate its usefulness in studying cancer progression.

A research paper from the lab of Assistant Professor Filiz Yesilkoy garnered the cover image on the September 2023 issue of the journal *Sensors & Diagnostics.* In the paper, Yesilkoy's team used a machine learning model to sharpen a biosensor to detect COVID-19 vaccination and past infection status from blood samples.



A figure from the paper shows the range of magnetic fields in proximity to nanoparticle clusters of different orientations. Image courtesy Hai lab.

Neuroengineers prove longstanding MRI theory

It started out as a side project, a repurposing of the nanopatterning techniques that PhD student Ilhan Bok has fashioned in Assistant Professor Aviad Hai's neuroengineering lab.

Bok and Hai were curious: Could they use their nanofabricated particles to experimentally test longstanding computational theory about how particle clustering, size and geometry affects signaling in magnetic resonance imaging (MRI)?

"We discovered that we were doing something that hasn't been done before," says Hai.

Their efforts paid off. Hai and Bok, with help of lab mate Alireza Ashtiani (PhD '16), an assistant scientist, and Beth Rauch, an instrumentation specialist in the Department of Medical Physics, were able to validate computational simulations that date to the early 1990s.

They published their results in the journal *Magnetic Resonance in Medicine*, which flagged the paper as a "rapid communication," signifying its importance for the field.

"This is something really basic that a lot of this science relies on, but no one really went as far as just to test this exact effect," says Bok (BS '20).

By using innovative nanolithography techniques, Bok produced arrays of iron oxide nanoparticles with a variety of geometries, allowing the group to prove the nonlinear relationship between the size of an aggregation of nanoparticles and the MRI signal strength. Nanoparticles are frequently used as contrast agents with MRI to enhance the signal.

Hai says the project forms a basis for developing any type of MRI sensor that relies on aggregation of particles.

Department of
Biomedical Engineering
UNIVERSITY OF WISCONSIN–MADISON

1550 Engineering Dr., Room 2130
Madison, WI 53706
engineering.wisc.edu/bme

Excitement is building

Our engineering campus is getting a facelift. With formal approval of state funding for a new 395,000-square-foot building, we're continuing our growth initiative.

The seven-story building will span parts of the existing Engineering Mall and the space currently occupied by 1410 Engineering Drive (which will be demolished), and feature refreshed green space and indoor and outdoor gathering spaces.

The $347 million facility, funded through $150 million in private giving and $197 million from the state of Wisconsin, will be a catalyst for research while allowing the college to educate many more exceptional students.

Explore more, follow along with the building's progress, and support the project at engineering.wisc.edu/new-building.

All images by Continuum Smithgroup. Artist's concepts of the new building.