College of Engineering
UNIVERSITY OF WISCONSIN–MADISON

FALL 2022 NEWSLETTER

BIOMEDICAL ENGINEERING

Teamwork fuels discovery

Greetings!

As we begin a new academic year, I would like to reflect on the successes our BME department has had in the past year and express optimism for the coming year. Due to safety precautions implemented at our university, we had a pretty normal year in 2021-22, where all our classes were in person without any interruptions, including our hands-on design curriculum. It was great to see everyone again in person!

Our researchers continue to receive prestigious new grants, and more of our faculty were elected as fellows of the American Institute for Medical and Biological Engineering (AIMBE) professional society; a large majority of our associate and full professors have been recognized with this honor. We have promoted several of our teaching faculty members to the new teaching professor track in recognition of their continuing efforts to provide high-quality education for both our undergraduate and graduate students.

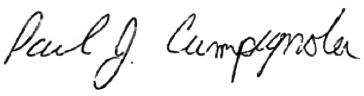
This year we increased enrollment in both our MS and PhD programs. In a significant step, we are implementing a rotation system, where incoming PhD students can explore a few different labs before committing to their thesis lab. This gives our students flexibility and better aligns our practices with our peers. We offered new classes this past year on optics/photonics and cell manufacturing in partnership with UW-Madison's Forward BIO Institute. In 2022-23, we are offering a new lab-based course on CRISPR gene-editing technology. Collectively, these courses provide real-life experiences and better prepare our students for a range of careers.

This year we kicked off our industrial advisory board meetings. Marie Lotto (BS '00, MS '02) is our current chair and is receiving our Distinguished Achievement Award this year in honor of her outstanding career in the medical device industry. Board member Karien Rodriguez (PhD '10) was our Early Career Award winner last year for her work at Kimberly-Clark.

We continue to expand our efforts in inclusion, equity and diversity to ensure a welcoming environment for all. Notably, several of our faculty participated in our college's inaugural WiscProf workshop to help prepare graduate students and postdoctoral researchers from groups traditionally underrepresented in STEM for careers in academia. BME also cosponsored the Rising BME Scholar workshop hosted at Washington University in St. Louis, which covered a broader range of careers for BME PhDs. We will continue to work closely with Chris Castro, the college's inaugural associate dean for inclusion, equity and diversity in engineering.

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

Support ISyE: supportuw.org/giveto/bme

Junior Dhruv Biswas, right, credits PhD student Wihan Adi, left, and Assistant Professor Filiz Yesilkoy for their guidance and mentorship in helping him acclimate to lab research.

Biosensor boosts antibody testing

In the future, with a finger prick and a portable testing device featuring a biosensor, a light source and a camera, you might be able to check your antibody levels against an infectious disease like COVID-19 without leaving home.

The benefits of such a test could be great: Local governments could use community data to inform prevention policies; epidemiologists could draw on data to improve their models of disease spread; clinicians could tailor recommendations about boosters to individual patients based on their antibody levels; and vaccine makers could more easily monitor patient data and better understand their products' effectiveness against different viral variants.

However, that vision requires antibody tests that are both more advanced than those currently commercially available, yet don't require costly and labor-intensive laboratory analysis. Assistant Professor Filiz Yesilkoy is working at the intersection of nanotechnology and photonics to deliver those kinds of tools.

In a paper in *Biomedical Optics Express*, Yesilkoy's lab present a biosensor and imaging approach that delivers a more comprehensive COVID-19 antibody readout than commercially available tests. It's an early-stage demonstration of technology that could power more advanced at-home or point-of-care serology tests.

Whereas most existing serology tests check for any and all antibodies, and antigen tests look for one specific protein on a virus or bacteria, this nanoengineered biosensor delivers a more detailed picture. It's capable of accommodating multiple antigens, and doesn't merely detect the presence of those antigens.

"We can actually quantify how many antibodies, because our sensor enables that," says Yesilkoy. "The number of antibodies we have may correlate to how well we're protected. It's also important to understand what antigen these antibodies are specific to so that we can identify cues relating to medical conditions and disease protection. Our sensor can do that, and it can do it in a very simple way."

"I have zero regrets," says Ashley Hiebing. "I feel like I am where I need to be, and every step that I've taken to get here were the steps that I needed to take when I took them."

Change of heart

PhD student takes unconventional route to grad school

If Ashley Hiebing is being honest, the questions and insecurities still rattle around her head.

Am I good enough?

Am I smart enough?

Am I *anything* enough to be doing what I'm doing?

Hiebing, a PhD student, is far from alone in grappling with imposter syndrome, especially among women in science, technology, engineering and math fields.

Not only is Hiebing a first-generation college student from a working class family; she's also rebounded after two scrapped attempts at college and worked her way up from Algebra 1 to conducting computational modeling of cardiovascular growth over the past nine years.

"I think even now I'm still trying to prove to myself that I can do this," she says.

And yet there is ample external proof that Hiebing can indeed succeed as a scientist, including earning a prestigious National Science Foundation Graduate Research Fellowship to support her doctoral studies. By Hiebing's own admission, it was an improbable achievement for someone who felt aimless after high school and worked a string of minimum-wage jobs between brief stints at Herzing University and Madison College.

"I wasn't ready for it. I wasn't mature enough to handle the college courseload," says Hiebing, who at age 23 decided to give college a third try.

She set her sights on biomedical engineering, a field that would allow her to help people from behind the scenes while proving to herself that she could conquer a totally unfamiliar challenge.

First, though, she needed to complete a whole host of basic prerequisites, so she returned to Madison College in 2013 and rebuilt her math skills over three years before transferring to Milwaukee School of Engineering (MSOE). She earned membership in two engineering honor societies at MSOE, completed an undergraduate research experience, and made the dean's list all six years across both schools.

"I felt like I knew where I wanted to go and I knew what I needed to do to get there," says Hiebing.

She originally envisioned that destination being the neural tissue engineering field, until a MATLAB programming course at MSOE hooked her. She pivoted from modeling neurological processes after hitting it off with Assistant Professor Colleen Witzenburg, who uses a combination of mechanical experimentation and computational modeling to study cardiovascular tissue structure and function. In particular, Witzenburg is applying her work to hypoplastic left heart syndrome (HLHS), in which children are born with one side of the heart crucially underdeveloped.

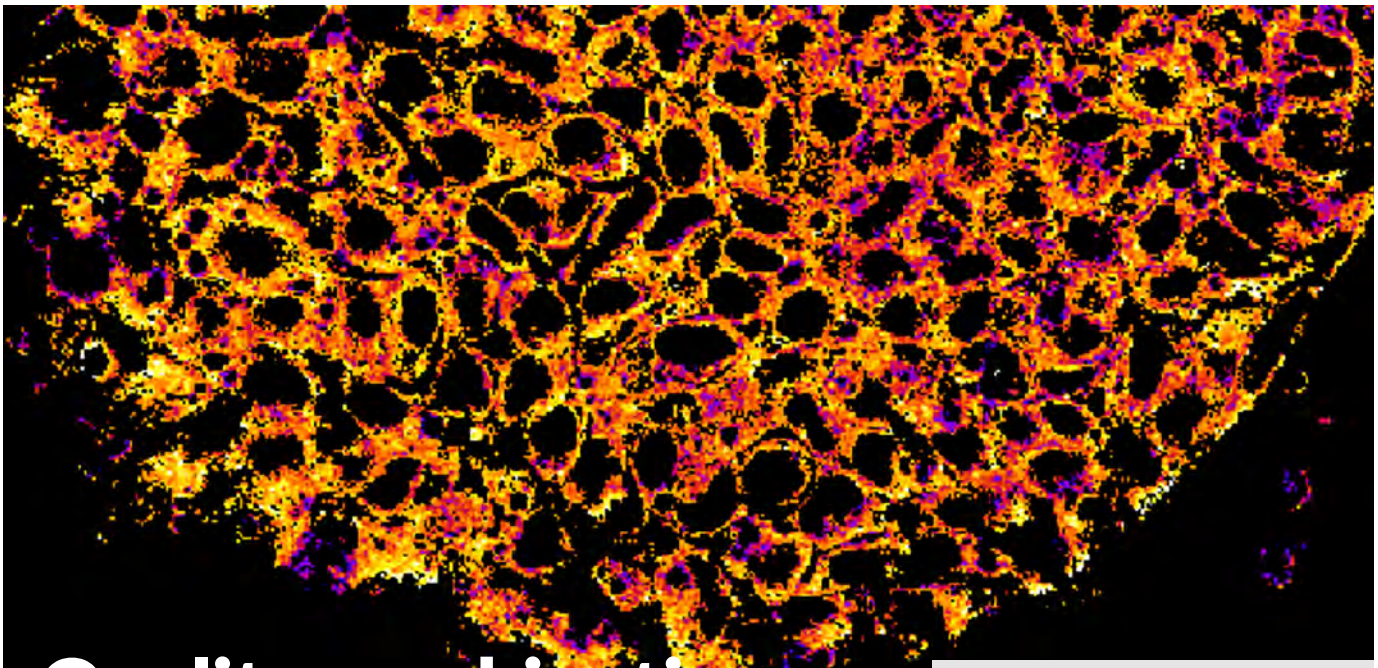
Hiebing has poured herself into studying up on HLHS, setting up Google Scholar alerts for terms like "single ventricle" and reading about treatment plans and surgical techniques. She even got an anatomically correct heart tattooed on her left arm.

Children born with HLHS require a series of three surgeries before age 3, rerouting the blood flow from their hearts to buy them time for a heart transplant. But the timing of the second surgery in particular is crucial to safeguarding the overtaxed right ventricle.

In Witzenburg's lab, Hiebing is helping to build a modeling tool that would allow clinicians to predict the dimensions of a patient's heart, enabling them to more precisely plan the timing of the surgeries for each child.

"I love making computational models," says Hiebing. "I think being able to break a complex process down into a computer simulation, into binary values, zeroes and ones, that's amazing to me. It's like painting the Sistine Chapel with crayons, but I enjoy the challenge."

Inspired by PhD student Ashley Hiebing's wife, Lili Hernandez, who was diagnosed with a rare type of cancer, the Witzenburg Lab participated in the Race to Cure Sarcoma to help fund sarcoma research in July 2022.



Quality combination

Label-free imaging, plus data science, improves biomanufacturing of stem cells

The colors in this image of induced pluripotent stem cells indicate the relative oxidation-reduction state of cells, allowing the researchers track metabolic changes during the reprogramming process. Submitted photo.

Krishanu Saha

Melissa Skala

By reprogramming cells from a patient to yield induced pluripotent stem cells, scientists and clinicians can wield a fertile and versatile resource for personalizing patient healthcare via regenerative medicine, cell therapy or disease modeling for drug testing.

But this reprogramming is far from a neat-and-tidy process; not all cells follow the desired pathway, and sifting through batches to pick out those precious stem cells generally requires techniques that are slow, laborious and oftentimes destructive to the cells themselves.

A team of BME researchers has devised an innovative method that leverages micropatterning, label-free imaging and machine learning to enable real-time, noninvasive monitoring of reprogramming. Their proof-of-concept, presented in a paper in the journal *GEN Biotechnology*, offers a high-throughput option for quality control in biomanufacturing of induced pluripotent stem cells (iPSCs), which can in turn be used to develop cutting-edge personalized therapies and disease models.

"There are billions of dollars being invested in stem-cell-derived cell products, and a bottleneck has been to identify high-quality stem cells that would be appropriate for subsequent manufacturing toward injectable cell therapies," says Associate Professor Krishanu Saha, senior author on the paper. "Therefore, a real-time, label-free tool to track cell state in these heterogeneous stem cell cultures is very important. With this tool, we have gained unprecedented insights into reprogramming biology and heterogeneity."

The project was a collaboration between Saha's lab in the Wisconsin Institute for Discovery and Professor Melissa Skala's group in the Morgridge Institute for Research, both housed in the Discovery Building on the UW-Madison campus.

Kaivalya Molugu, a recent PhD graduate in biophysics from the Saha lab and the paper's first author, had previously used high-resolution imaging of cells' nuclei to predict reprogramming outcomes. That method, though, necessitated halting the cells' growth. With support from the UW-Madison Stem Cell and Regenerative Medicine Center, Molugu integrated imaging techniques from Skala's lab that track metabolic changes based on the natural fluorescence of several molecules found in cells, rather than relying upon an added dye or other invasive labeling method that could unintentionally alter the cell.

"Cells, as they get reprogrammed into stem cells, change the way they produce energy substantially, and that's something we can trace with molecules that naturally give off light in the cell," says Skala, who envisions eventually integrating optical equipment into an incubator or bioreactor for true real-time monitoring of cell cultures.

Using a micropatterned substrate, Molugu tracked islands of cells during the 22-day reprogramming process, identifying signatures in both the metabolic and nuclear imaging data, and used machine learning algorithms to predict cells' reprogramming trajectories. Her models classified iPSCs with 95% accuracy while greatly reducing the time required for identification.

"You can just image the reprogramming cells, run it through our machine learning process and identify the stem cells immediately so that you can use them for downstream applications," says Molugu, who's now a scientist at the biotechnology company Editas Medicine in Cambridge, Massachusetts. "It's really an attempt to reduce the time between getting the cells from the patient and trying to get them back into the patient for stem cell-based therapies."

Saha says the project reflects a growing emphasis on incorporating data science into the stem cell biology field. He has already introduced Molugu's work into his BME 520: *Stem Cell Bioengineering* course for upper-level undergraduates and graduate students.

Undergrads persevere to build tandem bike for autistic adult

As an 8-year-old, Noah would pedal around the cul-de-sac in his Madison, Wisconsin, neighborhood, showing off hard-won biking skills his mom had patiently taught him over the course of multiple years.

"He loved it," says Noah's mom, Lucille Marchand. "And then one day, he said he was done."

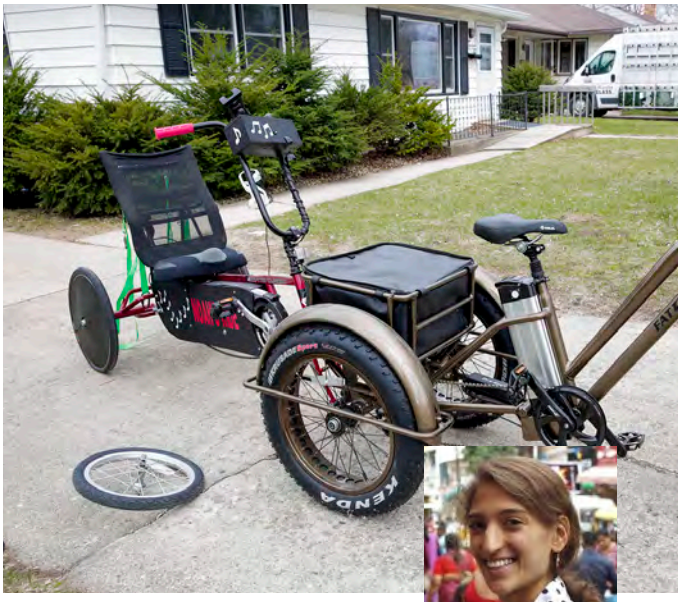
But Noah's sudden change of heart went beyond what might seem like the typical fickle nature of childhood interests. Noah, now 28, is autistic, with limited verbal expression, leaving his mother to speculate about his reasons. An avid biker, she was devastated to lose both a connection point with her son and a way for him to explore his surrounding community.

Two decades later, a team of recent BME graduates is helping Marchand offer Noah a new way to bike. As part of BME's hands-on design curriculum, the group built half of a tandem bike that attaches to the back of an electric bike and offers him the experience of biking while ensuring his safety and security.

"Noah's Ride" features a resistance mechanism, repurposed from an exercise bike, to simulate the physical work of biking and a Bluetooth speaker that connects to Noah's iPod and only plays when he pedals.

The students—team leader Callie Mataczynski (BS '20), Eric Arndt (BS '20), Mengizem Tizale (BS '21) and Aaron Wagner (BS '20)—incorporated a number of features tailored to Noah's needs into their design. The straps on Noah's seat match the ones from his van, keeping him secure. Plastic coverings on the wheels and chain safeguard his hands. And while his handlebars can turn slightly and his pedals spin, the electric bike, ridden by a caregiver, has full control of steering and speed.

But the students had to navigate a string of logistical challenges during and after the project's allotted two semesters, including a workshop flood, the COVID-19 pandemic, manufacturing delays, and a debilitating illness for Mataczynski.



Callie Mataczynski

"I worked on projects for the BME department every single year that I was in college, and never did I have to deal with this many roadblocks. And never have I actually had a product that turned out so well," says Wagner, who's now a product development engineer at Kimberly-Clark.

Alana Stempien (PhD '22) is planning to pursue a career in research and development in the biotechnology industry.

Cell mechanics offers new clue in genetic heart disease

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a mouthful of a heart disease that's essentially an invisible ticking time bomb for the estimated 1 in 10,000 people who have it. Often, the rare genetic disease goes undetected; those who carry it have hearts that appear structurally and functionally normal under typical circumstances.

But physical or emotional stress can trigger a life-threatening irregular heart rhythm, leading to a diagnosis that can arrive tragically late.

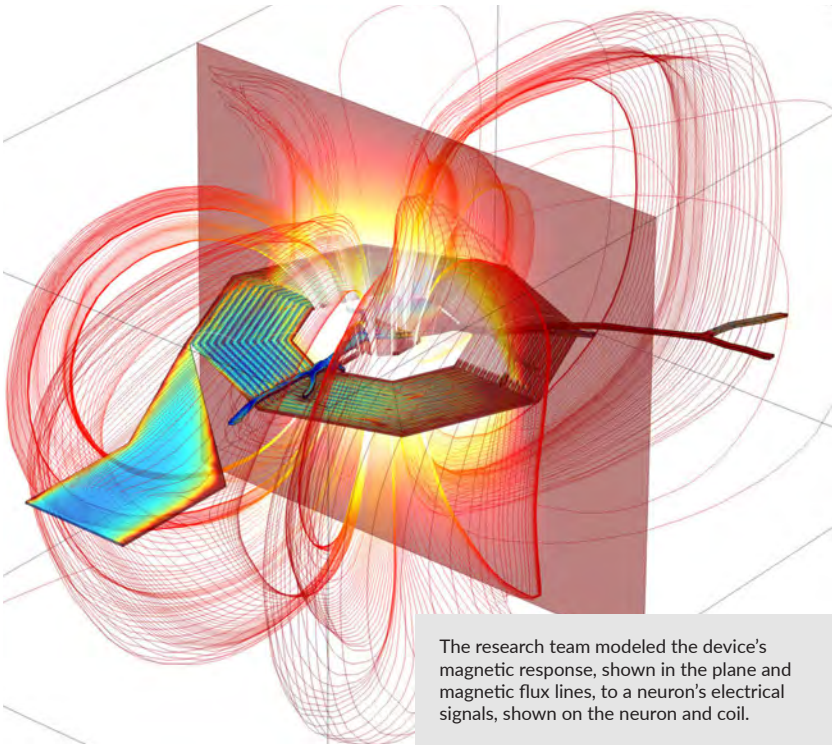
"If you don't have a known family history of the disease, the first appearance of the disease could be a sudden-death event," says Alana Stempien (PhD '22).

Stempien and Wendy Crone, her PhD advisor and a professor of engineering physics, worked with collaborators across the UW-Madison campus to uncover new details about the mechanical characteristics of heart cells in CPVT—basic science research they hope might someday inform treatment strategies. They published their findings in the journal *Frontiers in Bioengineering and Biotechnology*.

Stempien and Crone used an engineered, two-dimensional cell culture platform and image tracking technique to compare cardiomyocytes (the cells responsible for heart contraction) derived from a patient with CPVT with those from his mother, who didn't carry a CPVT mutation.

In analyzing the pulsing cardiomyocytes, the researchers found statistically significant differences in two mechanical measures: maximum contractile strain (deformation per contraction) and intrinsic contraction rate (speed of contraction). The patient-derived cells showed a higher strain and a slower rate. While the rate results meshed with previously reported research—validating their approach—the difference in mechanical strain was a new discovery. The mechanical attributes of cardiomyocytes in CPVT as a whole have rarely been explored in human cell cultures; most research has concentrated on the electrophysiology.

"Finding this difference in mechanical function in itself is interesting, but I think it further implies that the mechanical function is something worth understanding more in this disease," says Stempien.



The research team modeled the device's magnetic response, shown in the plane and magnetic flux lines, to a neuron's electrical signals, shown on the neuron and coil.

Wireless nano antennas amp up brain sensing

Jack Phillips

To record brain activity, neuroscientists and physicians must choose between electrodes that require wires running through the skull or noninvasive options like electroencephalography (EEG) or magnetoencephalography (MEG) that track signals from the scalp.

In addition to electrodes' potential to cause injury when implanted, they're limited by where they can spatially reach in the brain. EEG and MEG, unsurprisingly, are prone to weak signals and, like electrodes, collect data from populations of neurons in specific locations. MRI, another option for scanning the brain, merely tracks blood flow as an indirect indicator of brain activity.

In short, each offers a limited picture of the brain, leaving researchers to explore ways to get a more comprehensive look at neural activity. That's why Assistant Professor Aviad Hai's lab is developing technologies to deliver a wider, deeper and more granular view, including a unique nanoscale device capable of forming direct connections with individual brain cells and amplifying their magnetic signals.

"It's an entirely different framework for thinking about brain recording than the current methodologies that are electrode-based," says PhD student Jack Phillips.

Phillips, Hai and other lab members detailed and modeled the capabilities of one such untethered neural sensor in a paper in the *Journal of Neural Engineering*, laying the groundwork for systems capable of detecting signals at the single-cell level across different regions of the brain.

"We miniaturized the interface between brain cells and wireless nano antennas, to the point where now we have antennas that are the size of cells," says Hai. "So we basically have a one-to-one relationship between brain cells and devices that transmit brain activity to the outside."

In the paper, Phillips created a 3D model of their "nano antenna," using a mathematical model developed by undergraduate researcher Mitchell Glodowski (BS '20) to optimize its design. Then, using baseline electric activity measured in cultured neurons, Phillips modeled the enhanced magnetic signal strength. They found that signal was more than 250 times stronger than the neuron's intrinsic signal.

Hai's lab also published a paper in *Scientific Reports* using computer modeling to test the feasibility of one class of injectable magnetic nanoparticles for recording whole-brain electrophysiology via magnetic particle imaging.

Channeling Goldilocks creates lab environment for cells that's 'just right'

David Beebe

Humans breathe in a mix of air containing roughly 21% oxygen—yet, the oxygen levels in our individual cells vary considerably, depending upon their location and function and our body's overall state.

Cells also self-regulate their oxygen levels to suit their activities, consuming more as needed. It's a dynamic environment that adapts to demands and conditions. However, when trying to study cell behavior in the lab, researchers have historically relied upon experimental cell culture setups with decidedly unnatural oxygen environments.

Most research labs run their cultures at the ambient oxygen level of 21%; some use gas regulators to strictly control the level, which still doesn't allow for the homeostatic processes that play out in the body.

Those approaches—standard lab protocols—are akin to studying exercise science by asking humans to work out at dangerously high or low oxygen levels or in a rigidly set oxygen tent, says Professor David Beebe.

Beebe and some of his lab members believe they've found a better way to mimic the body's natural oxygen microenvironment by entrusting the cells themselves to regulate the oxygen level in microscale cell cultures.

In a paper in *Advanced Science*, Beebe, scientist Chao Li and collaborators from UW-Madison and beyond present their solution: an under-oil, microfluidic cell culture system that allows cells to autonomously regulate their oxygen microenvironment, which researchers can dynamically monitor.

"Nobody's ever done this in a way that is so simple. It's really simple for anybody to use this," says Beebe, who specializes in developing straightforward technology for cell culture applications. "We will likely see different biology now, and the argument would be that it will be more relevant biology."

Building upon its previous work with under-oil microfluidic systems, the Beebe Lab's method uses silicone oil to achieve the "just right" level of oxygen permeability (hence the Goldilocks reference in the paper's title), along with an optical sensor and a dye to monitor oxygen concentration at both the cell layer and from within the cultured cells.

Faculty News

Using a Discovery to Product SEED grant, John D. MacArthur Professor and Claude Bernard Professor David Beebe is working with Salus Discovery, a spinoff from his lab, on a tool for studying biological signals and biochemical gradients in 3D microenvironments.

Peter Tong Department Chair Paul Campagnola continues his work investigating pulmonary fibrosis through two new grants from the National Science Foundation and the School of Medicine and Public Health's Wisconsin Partnership Program.

Associate Professor and Retina Research Foundation Walter H. Helmerich Research Chair Kevin Eliceiri was named an Open Hardware Trailblazer Fellow by the Open Source Hardware Association.

The Biomedical Engineering Society named Professor Pamela Kreeger to its 2022 class of fellows in recognition of her work and leadership.

"GATA6 regulates aging of human mesenchymal/stromal cells," a paper authored by Associated Professor Wan Ju Li, was included in the High Impact Research from STEM CELLS collection.

With a $2.5 million National Institutes of Health grant, Associate Professor Kip Ludwig is working to improve a neuromodulation therapy along with co-investigators Professor Justin Williams and Wisconsin Institute for Translational Neuroengineering colleague Aaron Suminski.

Associate Professor Krishanu Saha is leading a team of BME faculty and affiliates on a Research Forward grant project focused on developing a new way to treat brain disorders, injuries and aging via cell therapy.

Student News

Undergraduate Samuel Neuman received a 2022 Barry Goldwater Scholarship, one of the most prestigious awards in the U.S. for undergraduates studying the sciences. Neuman also received a Hilldale Undergraduate Research Fellowship.

The BME Graduate Student Association took home first place in the student organization category at Engineering Expo.

Alumni News

Marie Lotto (BS '02, MS '03) has the honor of being BME's first Distinguished Achievement Award recipient at the College of Engineering's annual Engineers' Day celebration. Working in the medical device industry her entire career, Lotto is now the head of integration for Hologic, a women's health medical device and diagnostics company. She also brings her experience back to BME as the new chair of the department's industry advisory board.

Angelica Lopez (BS '21) received an NSF Graduate Research Fellowship to support her graduate studies. Will Wightman (BS '21) earned honorable mention status.

Promising new approach to sepsis treatment

Sarah Gong

Sepsis, the body's overreaction to an infection, affects more than 1.5 million people and kills at least 270,000 every year in the U.S. alone. The standard treatment of antibiotics and fluids is not effective for many patients, and those who survive face a higher risk of death.

In research published in the journal *Nature Nanotechnology*, the lab of Vilas Distinguished Professor Shaoqin "Sarah" Gong reported a new nanoparticle-based treatment that delivers anti-inflammatory molecules and antibiotics.

The new system saved the lives of mice with an induced version of sepsis meant to serve as a model for human infections, and is a promising proof-of-concept for a potential new therapy, pending additional research.

The new nanoparticles delivered the chemical NAD+ or its reduced form NAD(H), a molecule that has an essential role in the biological processes that generate energy, preserve genetic material and help cells adapt to and overcome stress. While NAD(H) is well known for its anti-inflammatory function, clinical application has been hindered because NAD(H) cannot be taken up by cells directly.

"To enable clinical translation, we need to find a way to efficiently deliver NAD(H) to the targeted organs or cells. To achieve this goal, we designed a couple of nanoparticles that can directly transport and release NAD(H) into the cell, while preventing premature drug release and degradation in the bloodstream," says Gong, who led the interdisciplinary project along with postdoctoral fellows Mingzhou Ye and Yi Zhao.

The lipid-coated calcium phosphate or metal-organic framework nanoparticles designed by the Gong lab can be used to co-deliver NAD(H) and antibiotics. This technology may pave the road for the development of a new clinical therapy for sepsis that could also be applied in other inflammation-related scenarios, such as COVID-19 treatment. An additional benefit of this therapy is the ability to treat infection with lower amounts of antibiotics, which reduces their overuse.

College of Engineering
UNIVERSITY OF WISCONSIN–MADISON

engineering.wisc.edu/bme

Department of Biomedical Engineering
1550 Engineering Dr., Room 2130
Madison, WI 53706

Spinoff safeguards developing brain, spinal cord from toxic threats

Amid his usual day-to-day of meeting with students, writing research papers and grant proposals, and overseeing experiments in a productive lab at the Wisconsin Institute for Discovery on the UW-Madison campus, Associate Professor Randolph Ashton is polishing his pitch.

Ashton is co-founder of Neurosetta, a startup company built around technology for modeling human brain and spinal cord development that emerged from his research lab. Launching the company in 2021 has meant adding entrepreneurial skills to his repertoire—understanding market research, clearly defining the technology's applications, and presenting it all in a way that resonates with potential investors.

"It's a different side of your brain and a different way to look at things," says Ashton, who co-founded the company along with lab alumnus Gavin Knight (PhD '18) and former UW-Madison colleague Rebecca Willett.

Neurosetta's platform, which also employs computational image analysis to rapidly assess neural cells derived from stem cells cultured on microchips, is particularly useful for prescreening chemicals and pharmaceuticals for neurotoxic effects. But it can also be used for disease modeling to enable drug discovery and to investigate genetic mutations that increase the risk of neurodevelopmental disorders.

Ashton and Knight say their modeling technology offers superior reproducibility and processing rate compared to existing screening options. They're initially targeting agrochemical companies that create new herbicides and pesticides, based on market guidance they received from UW-Madison's Discovery to Product (D2P), a program that provides mentorship, education and other resources to faculty, staff and students with entrepreneurial ideas.

Associate Professor Randolph Ashton and alumnus Gavin Knight (PhD '18) participated in the Wisconsin Alumni Research Foundation's Innovation Day as part of Summerfest Tech in June 2022. Photo courtesy of Wisconsin Alumni Research Foundation.

D2P is one of several campus resources the group has leveraged to turn Neurosetta from a benchside research lab tool into a company. The company also received a $1.7 million FastTrack Small Business Technology Transfer grant from the National Institutes of Health.