UNIVERSITY OF WISCONSIN–MADISON
COLLEGE OF ENGINEERING

FALL 2021 NEWSLETTER

BIOMEDICAL ENGINEERING

A STEP FORWARD

New teaching lab expands opportunities

Chair's Message

As we enter a new academic year, I would like to reflect on the successes our BME department has had in the past year, despite the challenges faced from the pandemic.

Many of our faculty received prestigious new grants this past year, and several were elected as fellows in professional societies, including the American Institute for Medicine and Bioengineering (AIMBE) and the Biomedical Engineering Society (BMES) in recognition of continued excellence. Our *U.S. News and World Report* graduate program ranking increased from 24 to 21 this year, and we are taking steps for continued improvement by showcasing the important and dynamic research emerging from our faculty, graduate students and other researchers.

Our new undergraduate and graduate teaching labs are now fully open in the Engineering Centers Building. These new facilities are well-equipped and reconfigurable to serve our student needs, including dedicated space for tissue engineering work, basic chemistry, electronics, motion capture capabilities and optical design. This space is now used for lab components of lecture courses as well as for the undergraduate design sequence and new standalone modular lab courses that were funded through our college's education innovation program. We have also continued to serve our students by expanding our two accelerated master's programs, where we have substantially increased enrollment over the past two years.

We are also continuing and expanding our efforts on inclusion, equity and diversity to ensure a welcoming environment for all by actively engaging all stakeholders in the department and college. As one starting point, we have begun to dedicate department seminars to the advancement of this goal.

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
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Devising new strategies to treat growing threat

Antimicrobial-resistant (AMR) infections are predicted to kill 10 million people each year by 2050—up from 700,000 in 2019—and force 24 million people into extreme poverty as early as 2030. Yet, the pharmaceutical industry has divested from the antibiotic resistance crisis, investing instead in more lucrative types of drugs.

Increasing AMR and the lack of industry interest have led some research groups to pursue new tools to assist current approaches. One of these methods is nanomedicine, which has been extensively studied for targeted cancer therapy and diagnoses. Nanoparticles, typically smaller than 200 nanometers in diameter, can be used to deliver drugs and treat disease.

Vilas Distinguished Professor Shaoqin "Sarah" Gong has reported an application of nanomedicine to treat antibiotic-resistant pathogens in *Advanced Materials*.

The dextran-coated stimuli-responsive nanoparticle Gong's group developed contains several components that target infected tissue and bacteria in vitro and in mouse models. Once inside infected tissue, disease-specific stimuli trigger the release of an antibiotic and cationic polymer to eliminate the AMR pathogens.

Gong also received an exploratory/developmental grant from the National Institutes of Health to develop antimicrobial polymer-drug conjugates. Her group will engineer a biocompatible cationic polymer, paired with already-approved antibiotics using chemical linkers that respond to specific characteristics of the infected tissues, allowing for disease-specific drug release.

BEYOND THE BENCH:

New course will put grad students a step ahead in biotech industry

Biomedical engineering PhD students Katie Mueller (middle) and Dan Pham (right) speak with Mary Haak-Frendscho, president and CEO of Spotlight Therapeutics, during the Forward BIO Institute's 2019 annual member meeting. Photo courtesy Forward BIO Institute.

William Murphy

While his colleagues nodded along confidently, Phil Keegan scribbled furiously in his notebook, trying to keep up with the onslaught of acronyms and regulatory terminology being bandied about.

As the sole scientist at a small medical device company and a newly minted PhD in biomedical engineering, he quickly realized how much he needed to learn in areas that went far beyond bench science to make projects succeed. There was the business side, with potential market size and health insurance reimbursement; regulatory hurdles to clear for FDA approval; intellectual property considerations; and manufacturing logistics.

Now, seven years later, Keegan is helping prepare UW-Madison graduate students, including those in biomedical engineering, to navigate the intricacies of the fast-growing biotechnology industry, which includes cell and gene therapies, tissue manufacturing, biopharmaceuticals and more. Keegan, the public-private partnership lead at the Forward BIO Institute at UW-Madison, is one of the architects behind a new graduate-level course in biotechnology and innovation housed in BME.

The course, which will launch in spring 2022 with Professor William Murphy as its instructor, will be built in collaboration with industry partners such as Promega, 3M, Catalent, and UW-Madison's University Research Park, which houses numerous early stage and more established biotech companies on the city's west side.

Keegan is not only working with those partners to craft a curriculum that's relevant to the current state of the biotech sector, but subject-matter experts from different companies also will lead discussions on a mix of business, legal, regulatory and technical topics and consult directly with students on opportunities related to their graduate research.

The course will build toward a showcase event where students will present a value proposition around their research to industry representatives. And it will also give both sides a chance to connect about internships and job opportunities.

"We want those students to finish up their time at UW-Madison capable of making an immediate impact in the biotech industry," says Murphy, who, in addition to being the Harvey D. Spangler Professor and H.I. Romnes Faculty Fellow, is director of the Forward BIO Institute and founder of several successful startup companies. "We want them to understand a whole lot more than a typical trainee from an academic institution would. We want them to be a step ahead."

That same spirit drove the Forward BIO Institute to create its Innovators in Training program in 2019, giving graduate students and postdoctoral researchers experience with core biotech topics. The new course is an extension of that program, and Keegan says he's also hoping to build a companion course for undergraduates in fall 2022.

RISING RESEARCHER THRIVING IN CONSUMER PRODUCTS INDUSTRY

Karien Rodriguez (PhD '10) used her graduate training in BME to pivot from chemical engineering and launch her career in the consumer products industry with Kimberly-Clark.

As a research technical strategist, she leads global research on healthy infant and adult skin for the company's major brands like Huggies, Kleenex, Cottonelle and Depends. She's also served as chair of Kimberly-Clark's Latin American Network for Diversity Employee Resource Group.

BME honored Rodriguez for her achievements with a College of Engineering Early Career Award. She shares insights from her BME education in this Q&A.

How did your experience in the College of Engineering shape your career path?

It set the trajectory for a fulfilling career. I apply the skills I sharpened at UW-Madison daily. The program set a strong foundation for critical thinking and teamwork. Also, working in a research group with people from different backgrounds and experiences helped me to tap into the diversity within teams. I was not only an individual researcher, but I worked with a lot of undergrads and became a leader within my research group.

Who has played the greatest role in your achievements?

I had several great mentors throughout my career. I had a professor at the University of Puerto Rico-Mayagüez who encouraged me to pursue graduate studies. It wasn't something that I was considering, but making that decision was life-changing. Another person who has been instrumental in my success has been my PhD advisor, Professor Kristyn Masters. She's an amazing educator, researcher and encourager! The fact that she believed in me and my potential helped me become a stronger researcher.

What are among your best memories from your time at UW-Madison?

Not only did I meet many of my closest friends, but I developed long-lasting relationships with professors and mentors. My husband and I always reminisce about how much fun we had, especially spending Friday afternoons at the Memorial Union Terrace, cheering for the Badgers, going hiking and camping, and just getting together with friends.

Undergrad wins top campus honor

Over the course of his four years as an undergraduate at UW-Madison, Ani Srinivasan learned to navigate—and, eventually, appreciate—both the incremental triumphs and the frustrating setbacks inherent to performing research.

The biomedical engineering student persevered and emerged inspired to continue challenging himself by pursuing an MD/PhD degree after graduating in May 2021. That tenacity, along with a resume packed with three majors (biomedical engineering, history and neurobiology) and a slew of volunteer work, earned him the 2021 Theodore Herfurth Award for Comprehensive Undergraduate Excellence, one of the oldest and most prestigious student awards at UW-Madison. It's the second straight year a biomedical engineering student has won the award.

While balancing his heavy academic load, Ani spent all four years working in the lab of Bikash Pattnaik, an assistant professor in the School of Medicine and Public Health's Department of Pediatrics. Ani co-led a project exploring the effects of an anti-epileptic drug on the retina.

In 2020, he also joined the lab of Andrew Quanbeck, an assistant professor in the Department of Family Medicine and Community Health, to help develop tools that assist patients who are tapering off opioid prescriptions by better connecting them with their healthcare providers. He's also worked with the consultancy Jump at the Sun to study the use of menthol cigarettes in African-American communities and inform public health campaigns.

He says those experiences align with his broader career ambitions.

"I plan to focus on developing and delivering accessible healthcare technologies to reduce the impact of socioeconomic status on health outcomes," he says.

STEM CELL-DERIVED FACIAL CARTILAGE CELLS SHOW PROMISE FOR JOINT REPAIR

Cartilage is a prevalent but precious commodity in the human body, cushioning our joints to absorb impact for protection and providing a nearly frictionless surface for smooth movement. But when it deteriorates—as those with aging knees can attest—it doesn't regrow like other tissues.

That frustrating reality has led millions of patients to undergo total joint replacement surgeries and spurred the medical field to explore different treatments, including cartilage transplantation.

"But these methods don't lead to long-term satisfactory outcomes," says Wan-Ju Li, a professor of biomedical engineering and orthopedics and rehabilitation.

Li is among the researchers worldwide working toward a different approach: using stem cells to regenerate hyaline cartilage, the type of connective tissue found in knee and hip joints and the nose. But producing viable, functional chondrocytes, the specialized cells that make up hyaline cartilage and also direct formation of the tissue's extracellular matrix, has proven elusive.

In a study published in *Science Advances*, Li's lab and collaborators in the Department of Chemical and Biological Engineering compared chondrocytes derived from human induced pluripotent stem cells (hiPSCs) through two of the body's developmental cell lineages, revealing new details that could inform future cartilage regeneration strategies. Ming-Song Lee, a PhD student in biomedical engineering, was first author on the paper.

Notably, the researchers found that chondrocytes from the ectomesodermal/neural crest lineage, which naturally develop into facial cartilage, actually repaired cartilage more effectively than those from the mesodermal lineage, which generates the cartilage in the joints of our limbs.

That seemingly paradoxical result backs up work from the University of Basel in Switzerland, in which researchers have taken chondrocytes from the nasal septum and engineered cartilage grafts for patients' knees.

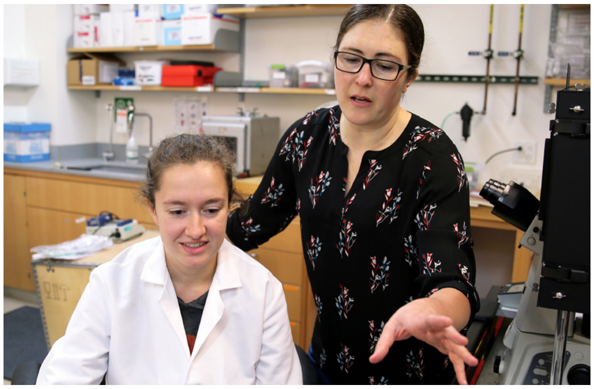
"Our study demonstrates the novel finding of stem cell-derived facial cartilage for knee repair and also provides the solid scientific evidence to explain what the Swiss group has done, including in clinical trials," says Li, whose work centers around osteoarthritis. "That's why this is so interesting. Everything seems to match together."

In their study, Li and his collaborators used hiPSCs reprogrammed from blood cells to derive genetically identical chondrocytes from the two developmental lineages. They implanted the chondrocytes in rats with joint defects and found that after 16 weeks, the ectomesodermal-lineage chondrocytes repaired more—and better—cartilage. And, in a battery of molecular analyses, those chondrocytes also displayed more biomarkers of hyaline cartilage, including greater expression of collagen type II and aggrecan. The chondrocytes also didn't express collagen type X, a hypertrophy marker indicating cartilage turning into bone over time, a problem that has vexed many potential stem cell therapies for cartilage repair.

Li's lab continues to explore why the ectomesodermal-lineage chondrocytes produced more hyaline cartilage. He plans to implant them in larger animal models in hopes of collecting enough data to eventually carry out a human trial.

"I really think it's very important to understand the differences we have found," he says, "and identify what molecular determinants govern the differences to develop effective stem cell therapies for osteoarthritis patients."

McClean to use NSF CAREER Award to explore nongenetic heterogeneity in microbes



Genetic mutations, as the rise of SARS-CoV-2 variants has demonstrated, can cause major ripple effects, making a virus more infectious or resistant to drugs. To devise strategies to counter those genetic alterations, researchers can sequence the genome of the organism in question to track down a specific mutation.

But differences between cells among a population can also derive from sources other than their DNA, emerging from factors such as the ages of cells or what stage they're at in the cell cycle.

And that nongenetic heterogeneity can also influence things like disease progression, stress tolerance and drug resistance.

"We can see this nongenetic heterogeneity, but what causes it is more poorly understood," says Associate Professor Megan McClean.

McClean hopes to illuminate one of the mechanisms behind nongenetic heterogeneity—and how that individual variation can affect traits and behaviors at the population level—through a National Science Foundation CAREER Award, while also preparing students to work on topics that intersect biology and engineering.

McClean will use the five-year, $629,896 grant to examine the role of transcription factors, proteins that regulate gene expression by controlling the transcription of DNA into RNA, in nongenetic heterogeneity among cells. To do so, she'll study the influence of engineered, light-activated transcription factors in *Saccharomyces cerevisiae*, or brewer's yeast. It's an application of some of the optogenetic techniques and technology McClean's lab has developed, using yeast as a model microbe, since she arrived at UW-Madison in 2015.

Heterogeneity can also disrupt microbe performance in biotechnology applications, such as ethanol or pharmaceutical production. McClean says those are also examples of the kinds of promising solutions to global challenges that involve a combination of engineering and biology. As part of her CAREER project, she plans to create a new advanced cellular engineering course for engineering undergraduates who are interested in biological applications and graduate students from both engineering and biological disciplines.

Experimental model of ovarian cancer shows effect of healthy cell arrangement in metastasis

Ovarian cancer devastates more than 20,000 women in the United States every year, due in part to its tendency to evade detection and present after metastatic spread. A key element to slowing metastasis is understanding the mechanisms of how tumor cells invade tissues.

A team led by Professor Pamela Kreeger and Jacob Notbohm, an assistant professor of engineering physics, explained in the journal *APL Bioengineering* how microscopic defects in the way in which healthy cells line up can alter how easily ovarian cancer cells invade tissue. Using an experimental model, where the cellular makeup mimics the lining of the abdominal cavity, the group found disruptions in the normal cellular layout, called topological defects, affect the rate of tumor cell invasion.

"My lab is very interested in identifying ways to slow metastasis. This study is exciting, because it demonstrates a unique role for organization of nontumor cells to either aid or slow that process," says Kreeger. "Identifying factors that regulate this organization could help us to achieve our goal."

The group's model consisted of a single layer of healthy cells, called mesothelial cells, the predominant cell type that covers structures inside the abdomen, where ovarian cancer often metastasizes.

"A common way to fill space is a honeycomb-like packing, in which each 'cell' would be nearly spherical," says Notbohm. "But in our case, the mesothelial cells were elongated, making the honeycomb packing not possible."

Such elongation led to areas of well-ordered cell layers and left other areas with alignment imperfections, causing the topological defects.

The researchers seeded ovarian cancer cells on top of the mesothelial cell layer and compared what effect the arrangement of the mesothelial cells had on how the tumor cells passed through this barrier. The patterns of cell flow were different near the defects, with certain defects causing inward cell flow, toward the center of the defect. At those locations of inward flow, the cancer cells passed through the mesothelial barrier more slowly.

In addition to pursuing the impact of topographical organization in cancer cell metastasis, the group is looking to investigate the cause of topological defects, with the hopes of finding ways to direct cell patterning in uses such as tissue engineering.

—Story by AIP Publishing

Faculty News

Associate Professor Randolph Ashton and three lab members won the 2020 Wisconsin Alumni Research Foundation (WARF) Innovation Award contest for their work using stem cells to derive improved brain and spinal cord tissue models.

Associate Professor Kevin Eliceiri was elected fellow by The Optical Society for outstanding research in cellular microenvironment imaging and bio-image informatics. Eliceiri will help lead an initiative to develop and advance light sheet microscopy technology through a five-year, $1.2 million grant from the Arnold and Mabel Beckman Foundation.

Vilas Distinguished Professor Shaoqin "Sarah" Gong is part of a UW-Madison team developing and testing a new therapy for restoring vision in patients with severe visual impairment or blindness due to certain kinds of retinal disorders through a five-year, $7.7 million award from the National Eye Institute.

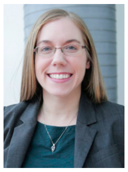
Assistant Professor Aviad Hai earned a National Institutes of Health (NIH) Director's New Innovator Award, which consists of a five-year grant of nearly $2.3 million. His project aims to develop injectable, wireless electronics that could offer a global look at the actual electrical activity of the brain, all without the need for surgical procedures.

Vilas Distinguished Professor Kristyn Masters coauthored a commentary in the journal *Cell* calling upon the National Institutes of Health to address documented disparities in the agency's funding of Black researchers.

Associate Professor Megan McClean and John D. MacArthur Professor and Claude Bernard Professor David Beebe are using a five-year, $3.8 million grant from the National Institute of Allergy and Infectious Diseases to create a new kind of microfluidic system that should reveal new details about the dispersal process in systemic fungal infections. McClean also received a WARF Accelerator Microbiome Challenge Grant for a project to develop a smart probiotic for programming fungal members of the microbiome.

Harvey D. Spangler Professor and H.I. Romnes Faculty Fellow William Murphy received a UW-Madison Kellett Mid-Career Award, which supports faculty members who are seven to 20 years past their first promotion to a tenured position.

Professor Melissa Skala was named the Retina Research Foundation Daniel M. Albert Chair through the McPherson Eye Research Institute at UW-Madison.



Assistant Professor Colleen Witzenburg received a $439,514 grant from the National Science Foundation to support her work quantifying the spatial variance of material properties in soft tissues and predicting points of failure, specifically in ventricular tissue after a heart attack.

Assistant Professor Filiz Yesilkoy will use a Wisconsin Partnership Program grant to create a portable antibody test that could allow for wider COVID-19 immunity monitoring across the state, including in rural and low-income urban settings.

Student News

Graduate student **Ilhan Bok** received a research award from the UW-Madison Global Health Institute to support his work optimizing magnetic particle imaging to monitor brain activity.

Graduate students **Ashley Hiebing** and **Kelsey Tweed** earned National Science Foundation Graduate Research Fellowships. Recent graduates **Laura Guerrero** and **Jennifer Leestma** also received fellowships.

Undergraduates **Ryan Anderson, Thor Larson, Tae Ji Lee, Alex (Ximian) Li, Angelica Lopez, Samuel Neuman, Tsani Rogers, Ruby Salbego** and **Anne Wong** received Hilldale Fellowships to support research projects. Meanwhile, undergraduates **Joshua Andreatta, Emily Masterson, Shrey Ramesh** and **Greta Scheidt** earned Sophomore Research Fellowships.

Two more AIMBE fellows brings total to 12

Professor Walter Block and Associate Professor Kevin Eliceiri were elected to the American Institute for Medical and Biological Engineering's (AIMBE) prestigious College of Fellows in February 2021, giving BME 12 faculty members who have earned the selective honor.

Block received the honor for his work on magnetic resonance imaging (MRI) technology and techniques, including applying MRI to guide brain therapies. Eliceiri, who also holds the Retina Research Foundation Walter H. Helmerich Research Chair in the McPherson Eye Research Institute, was cited for his research on open-source imaging and image analysis tools.

The AIMBE College of Fellows is made up of the top 2% of medical and biological engineers. The other BME members are: John D. MacArthur Professor & Claude Bernard Professor David Beebe; Peter Tong Department Chair Paul Campagnola; Vilas Distinguished Professor Shaoqin "Sarah" Gong; Professor Pamela Kreeger; Associate Professor Kip Ludwig; Vilas Distinguished Professor and H.I. Romnes Faculty Fellow Kristyn Masters; Professor Beth Meyerand; Harvey D. Spangler Professor and H.I. Romnes Faculty Fellow William Murphy; Retina Research Foundation Daniel M. Albert Chair and Professor Melissa Skala; and Vilas Distinguished Achievement Professor Justin Williams.

Professors Emeritus Thomas "Rock" Mackie and Willis Tompkins are also AIMBE Fellows.

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Up and running

While the COVID-19 pandemic disrupted its opening, BME's new teaching lab in the Engineering Centers Building is giving undergraduates like Kristen Schill (right, standing) access to brand-new equipment, including a motion capture sensor and inground force plates.

In addition to biomechanics tools, the lab also includes equipment for tissue engineering applications, such as biosafety cabinets and fume hoods. Assistant Professor Filiz Yesilkoy will also lead a new lab course in the space on optics and biophotonics, in which undergraduates will construct and evaluate a variety of microscopes and work with nanophotonic and bioanalytical devices.

With the lab's opening, BME has more than tripled its teaching lab space and now boasts the kind of multi-use, flexible setup that allows instructors like PhD student and lecturer Christa Wille (right, kneeling) to introduce students to new technology and techniques. Wille teaches a pair of courses, BME 315: *Biomechanics* and BME 415: *Biomechanics of Human Movement*, that will use the lab.

BME undergrads like Schill can also access the lab for their design projects. During the spring 2021 semester, Schill led a team that designed wearable technology capable of collecting knee data to inform strategies to prevent anterior cruciate ligament injuries.