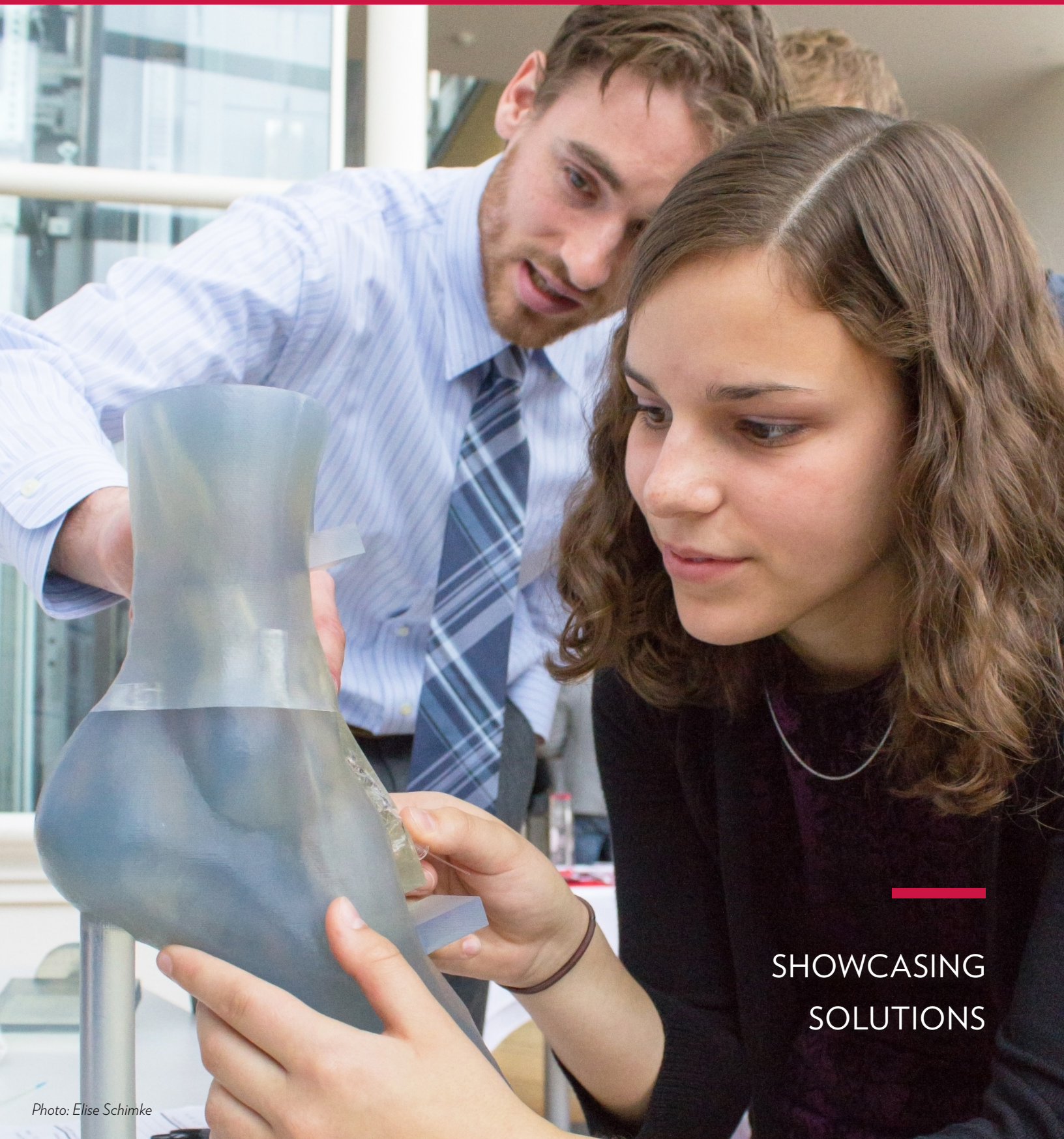
SPRING 2018

BIOMEDICAL ENGINEERING

UNIVERSITY OF WISCONSIN-MADISON



SHOWCASING SOLUTIONS

Photo: Elise Schimke

CHAIR'S MESSAGE

Justin Williams

Greetings!

This spring, we celebrate the accomplishments of the Class of 2018. For many of our graduates, commencement will signify the end of their time on the College of Engineering's campus. But it will also mark the beginning of their membership in our growing BME alumni family.

Over the past year, I've had the pleasure of seeing the work of our BME students, faculty and staff recognized within our university and beyond. Our undergraduate and graduate programs, for example, both earned top-25 rankings from *U.S. News & World Report*.

As at any institution, resources and research are important ingredients for our academic success. I'm grateful our more than 600 students have opportunities to use facilities such as the 12,000 square feet of design space in our college's new makerspace and to study alongside scientists collaborating on initiatives like the National Science Foundation's $20 million Engineering Research Center for Cell Manufacturing Technologies (CMaT). What makes UW's BME education truly outstanding, however, is the emphasis we place on using our knowledge to strengthen our communities.

In this newsletter, you'll read about the ways in which BME Badgers apply engineering ingenuity to solve problems faced by healthcare professionals and consumers. From establishing a mentoring culture in Madison to creating affordable tuberculosis testing in Africa, our faculty and students' work has taken them across the globe—but their dedication to improving the lives of others connects them wherever they travel.

It is this strong sense of community that sustains our department's continued excellence in academics, research and outreach. I thank you—our dedicated alumni and donors—for your continued commitment to improving healthcare by supporting BME, and look forward to what the future holds.

Be sure to keep in touch online (@UWBME on Facebook and @UWMadison_BME on Twitter) and pay a visit the next time you're in Madison!

ON, WISCONSIN!

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TRIO JOINS NEW NSF CELL MANUFACTURING RESEARCH CENTER

William Murphy

Randolph Ashton

Krishanu Saha

Three biomedical engineering faculty members are part of a national effort to transform the use of medical therapies using living cells.

Harvey D. Spangler Professor William Murphy and Assistant Professors Randolph Ashton and Krishanu Saha are part of the UW-Madison team that will contribute to the new National Science Foundation (NSF) Engineering Research Center for Cell Manufacturing Technologies (CMaT).

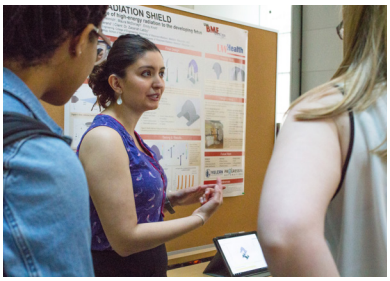
The NSF awarded nearly $20 million to a consortium of universities to support the center, which will develop transformative tools and technologies for the consistent, scalable and low-cost production of high-quality living therapeutic cells. Such cells could be used in a broad range of life-saving medical therapies now emerging from research laboratories.

Working closely with industry and clinical partners, CMaT could help revolutionize the treatment of cancer, heart disease, autoimmune diseases and other disorders. UW-Madison was selected as a major partner for its pioneering efforts in stem cell engineering and a long history of collaboration between the College of Engineering and the UW School of Medicine and Public Health, says Sean Palecek, the Milton J. and A. Maude Shoemaker Professor in chemical and biological engineering who is the project's associate director for research.

The UW-Madison researchers will focus on two disease applications: induced pluripotent stem cells for making heart muscle and engineered T cells to combat cancer.

"The opportunity for collaboration across multiple disciplines and institutions is very exciting," Palecek says. "In addition, our regular interactions with companies that are on the front line of making these cells mean that they may sponsor additional research efforts and offer internships to our students, ensuring that this kind of public-private partnership will truly be a win-win for everybody."

MORE: www.engr.wisc.edu/uw-madison-major-partner-20-million-research-center-expand-use-therapies-based-living-cells/

SOLVING PROBLEMS THROUGH DESIGN

Patient-removed intrauterine devices, virtual reality pain management and a thyroid exam simulator: all part of a day's work in BME design.

BME undergraduate students showcased the fruits of a semester's labor at the end of the fall semester: 61 unique healthcare solutions for 61 unique client problems were on display at the biannual design poster session.

"It was incredible to see this semester's work come to fruition in our biggest and most diverse design poster session ever," says John Puccinelli, associate chair of the undergraduate program. "I say this every year, but the students continue to impress more and more."

Since 1998, teams of BME undergraduates enrolled in the major's six-semester design curriculum have paired with representatives of campus, medical corporations and the Madison community in search of innovative healthcare solutions. They're tasked with developing or improving a prototype by the end of the semester.

The versatility of the biomedical degree allows prospective clients to submit project ideas from a spectrum of medical specialties ranging from oncology to obstetrics. In the case of senior Savannah Kuehn and her team, their automatic intraventricular drainage system was designed to assist Joshua Medow, a professor of neurosurgery in the UW School of Medicine and Public Health, in pursuit of a less complicated process for draining cerebrospinal fluid in patients with increased intracranial pressure.

"I think it's interesting that students at our age are able to delve into a project and figure it out on our own," says Kuehn.

She describes her team's creation not as a class project but as the product of a mutually beneficial partnership: the students sharing their eye for design with Medow and the latter lending his expertise on neuroscience and fluid dynamics.

This chance to apply classroom theory to real-world problems is something junior Bobby Weishar and his teammate, sophomore Jessica Zola, have come to value after working with Randall Kimple, an assistant professor of human oncology. For their project, they created an alternative method to measure tumor volume in mice involving water displacement and sensors.

"It's a lot different from a homework assignment that you turn in and never see again," says Zola. "You can have an impact."

Indeed, many BME designs have evolved into successful spinoffs and startup companies. Last April, for example, two BME graduates and co-founders of EnsoData received approval from the Food and Drug Administration for an automated sleep analysis product. The technology will help doctors more efficiently treat patients with sleep disorders.

Other designs have a more immediate, personal effect: Junior Desiree Fluoro and her team spent the semester with 10-year-old Aubrey, a patient with the genetic condition spinal muscular atrophy (SMA) type 1, and her physical therapist, Karen Patterson.

The two came to Fluoro's team with a paradox: though SMA had destroyed Aubrey's motor neurons (interrupting her muscle communication and immobilizing her), to be eligible for two new gene therapies, she needed to demonstrate substantial muscle development. After a few trips to the hardware store, the team delivered a PVC pipe exercise device to Aubrey's home, fashioned to elevate and swing her legs gently from her wheelchair to increase the strength in her legs.

"The look of happiness on her face was amazing," says Fluoro.

MINDFUL OF MENTORING

Left to right: BME graduate student Amani Gillette, high school students Isabel Jones and Ava VanDommelen, and BME Associate Professor Melissa Skala. *Photo: Renee Meiller.*

A good mentor can make all the difference for finding the right career path. For biomedical engineering graduate student Amani Gillette, that difference was so striking that she wanted to give back to the mentored research program that had been critical for homing in on her own professional niche.

So when Gillette was just starting her graduate training in 2016, she asked her PhD advisor, Associate Professor Melissa Skala, if she could mentor a high school student in the Biotechnology Youth Apprenticeship Program. Gillette had participated in it as a senior at Madison La Follette High School six years earlier.

Skala happily agreed. Since January 2017, Gillette has mentored Ava VanDommelen, from nearby DeForest, Wisconsin, in developing optical technologies for personalized cancer treatment.

Skala says the program, which is run by the Biopharmaceutical Technology Center Institute in Madison, has a much more rigorous design—requiring 900 hours in the lab—than typical six-week programs aimed at giving high school students early exposure to a research lab.

> **"Mentoring is both the best and the hardest part of being a professor. Nothing else brings me as much satisfaction as seeing a student reach their career goal and knowing I was a part of that process."**

"If they start as juniors, they're in the lab for a few hours every day after school and then much longer in the summer," Skala says. "I think this sustained 18-month commitment, combined with structured mentoring and a well-defined project, is key for creating a valuable experience for both students and mentors."

Part of the reason a longer program is valuable, Skala says, is that it gives young students enough time to get up to speed with lab equipment and protocols. Once they have become productive, they are more likely to experience the fun part of research that involves asking—and answering—interesting questions.

VanDommelen's research contributions were so greatly appreciated that Skala had no trouble finding a second mentor a year later, when program coordinator Barbara Bielec asked if she would like to take on another youth apprentice. Isabel Jones, a junior at Verona Area High School, began working with senior scientist Alex Walsh in January 2018.

But Skala is not the only BME professor who takes mentoring seriously. Her colleague Kristyn Masters, a Vilas Distinguished Professor and H.I. Romnes Faculty Fellow, is the faculty co-director of the Women in Science and Engineering (WISE) program, a supportive residential and learning community of female undergraduate students with science, technology, engineering and math (STEM) majors.

In addition to talks, networking and a variety of other social and enrichment activities, WISE pairs students with older female peer mentors in STEM majors—an approach that is highly effective in helping women succeed in technical fields, according to a 2017 study by researchers at the University of Massachusetts, Amherst.

Masters and Associate Professor Pamela Kreeger recently co-authored an article in the journal *PLOS Computational Biology* titled "Ten simple rules for developing a mentor-mentee expectations document."

Masters and Kreeger, both of whom also regularly work with Madison high school students, believe the piece is a helpful addition to the individual development plans that are required for managing the professional development of federally funded trainees.

The current development plans define big-picture expectations and are effective for achieving long-term career goals, but they lack the nitty-gritty details of daily lab operations that are just as important for ensuring positive and healthy regular interactions between mentor and mentee.

"Mentoring is both the best and the hardest part of being a professor," Kreeger says. "Nothing else brings me as much satisfaction as seeing a student reach their career goal and knowing I was a part of that process. While this is also possible with students I meet through classroom teaching, it is much more intense and tangible with the undergraduate and graduate students who are in my lab for several years."

TRANSFORMING TUBERCULOSIS TESTING

David Beebe

Since the 1970s, millions of women have appreciated the ease of a urine-based home pregnancy test to find out if their family is about to grow.

A diagnostic test that's just as accurate and easy to use would make a big impact in the war on tuberculosis (TB). With more than 10 million affected people worldwide, many of them in Africa, the annual market for such a test is estimated at about 75 million—but only if it costs as little as $2 apiece.

David Beebe and his colleagues think they can deliver on that.

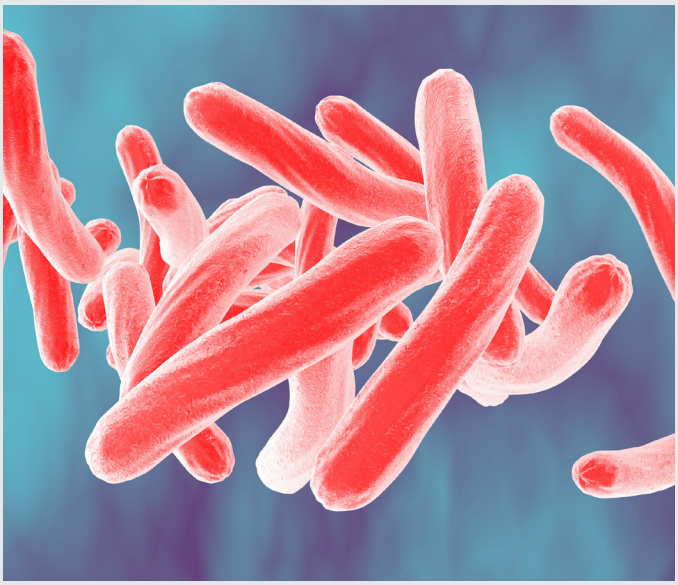
"We've come up with a robust, simple and inexpensive way to increase the sensitivity of an existing TB test by integrating a concentration enrichment step into a protocol that's very similar to the familiar pregnancy test," says Beebe, the John D. MacArthur Professor and Claude Bernard Professor.

"And we think this new technology may soon not only detect TB in urine, but also diagnose many other conditions in both the developing and developed world."

Researchers with Beebe's spinoff company, Salus Discovery, completed much of the intellectual work behind the new technology thanks to a $2.6 million grant from the Bill and Melinda Gates Foundation.

Most current TB tests are DNA-based, time-consuming and expensive—not to mention unpleasant, as they rely on a saliva-and-mucus sample coughed up from a person's respiratory tract. An additional limitation is that many tests only work in HIV-positive patients, who are at greater risk of developing TB.

"But that's a small percentage of all cases, and a broadly applicable triage test is urgently needed to start treatment as early as possible," Beebe explains.



The new diagnostic test is based on a proprietary and innovative sample preparation technology and detects the LAM protein at much lower concentration than existing urine-based tests. The engineers who designed the test also accounted for the environmental conditions in which it might be used in Africa, such as dust, high humidity and hot temperatures, and for the country's limited clinical infrastructure.

For a previous project also funded by the Gates Foundation, Salus Discovery researchers provide training to Uganda-based staff on a new diagnostic test for HIV/AIDS. Field training for the new tuberculosis test began in spring 2018 in Ethiopia and South Africa. *Photo courtesy of Salus Discovery.*

Beebe's next goals are to obtain World Health Organization certification for the new test and to help start a company in Africa to manufacture TB screening kits. Since Salus is a for-profit company with philanthropic tendencies, as Beebe likes to describe it, that approach will create jobs and provide a more sustainable solution than manufacturing the kits in the United States and then shipping them to where they are needed.

The long-term future includes broadening areas of application for tests of this kind.

According to Beebe, this project and others are the culmination of his more than 10 years of experience working with African partner organizations.

"We're excited to lead an exceptionally talented group of international collaborators toward a goal that's incredibly important to global health and has the potential to save at least 400,000 lives a year," he says.

MORE: www.engr.wisc.edu/bringing-cheap-accurate-tuberculosis-tests-africa/

CRISP AND CLEAN GENE EDITING

Assistant Professor Krishanu Saha (back) and graduate student Jared Carlson-Stevermer have modified the CRISPR/Cas9 gene editing technology to make it more precise and reliable. *Photo: Stephanie Precourt.*

For the past five years, CRISPR-Cas9 technology has revolutionized the field of gene editing due to its ease and low cost. But although this technology reliably finds and cuts the targeted stretch of DNA sequence, fixing that cut as desired has been something of a hit-or-miss process. Error rates as high as 50 percent are a particular problem when the goal is to correct typos in the DNA that cause genetic disease.

Now, a team of researchers led by Assistant Professor Krishanu Saha has made the fix less error-prone.

Compared to standard CRISPR technology, the new method improves the likelihood of rewriting the DNA sequence exactly as desired by a factor of 10. The researchers achieved this much greater precision by taking advantage of a molecular glue, called an RNA aptamer, to assemble and deliver a complete CRISPR repair kit to the site of the DNA cut.

"The kit provides not only the molecular scissors, but also the correct template for the cell machinery to fix the DNA cut with," Saha says. "Since the RNA aptamer is strong and very stable, everything we need is getting to the right place within the cell in one fell swoop."

In standard CRISPR technology, the bacterium-derived Cas9 protein (the scissors) and a guide RNA molecule (to locate the targeted DNA sequence) are delivered to the cell. When the scissors cut open the DNA molecule, the cell mends the gap with nearby DNA templates, but more faithful rewriting results from attaching the desired templates to the Cas9/RNA package with the molecular glue.

The new method has several other advantages. First, the off-the-shelf kit contains only non-viral reagents, which simplifies the manufacturing process and reduces safety concerns for clinical applications of genetic surgery in the future. Second, attaching an RNA aptamer to the kit is much easier than modifying the Cas9 protein and provides greater flexibility.

MORE: **www.engr.wisc.edu/one-repair-kit-makes-crispr-gene-editing-precise/**

NEW HOPE FOR UNDERSTUDIED HEART DISEASE

The diminutive size of our aortic valve—just shy of a quarter—belies its essential role in pushing oxygen-rich blood from the heart into the aorta, our body's largest vessel, and from there to all other organs. Yet for decades, researchers have focused less on damaged valves than on atherosclerosis, the gradual hardening of the blood vessels themselves.

But scientists now are catching up on understanding the roots of calcific aortic valve disease (CAVD).

"For a long time, people thought CAVD was just the valvular equivalent of atherosclerosis," says Vilas Distinguished Achievement Professor Kristyn Masters. "Today we know that valve cells are quite unique and distinct from the smooth muscle cells in our blood vessels, which explains why some treatments for atherosclerosis, such as statins, don't work for CAVD and why the search for drugs has to start from scratch."

A team led by Masters has jumped a longstanding hurdle in that search with a study published in the journal *Proceedings of the National Academy of Sciences*. The researchers teased apart, for the first time, the early cascade of events that may eventually cause stenosis, a severe narrowing of the aortic valve that reduces blood flow to body tissues and weakens the heart.

The only current treatment for stenosis is valve replacement, which typically requires risky and expensive open heart surgery.

"Our study sheds new light on the differences between atherosclerosis and CAVD, especially in terms of bottleneck events that we can target with drugs," Masters says. "With a better understanding of how the disease progresses from early to later stages, we may eventually be able to stop CAVD in its tracks and avoid valve replacement surgery."

MORE: **www.engr.wisc.edu/new-hope-stopping-understudied-heart-disease-tracks/**

SPECIAL DELIVERY: NANOPARTICLES SAFELY CARRY DRUGS

Attacking cancer cells with anti-cancer drugs is one of the best tools in the fight against the disease. However, many promising anti-cancer treatments—from chemotherapy to gene therapy—have not been pursued clinically due to their low treatment efficacy and high systemic toxicity.

Vilas Distinguished Professor Shaoqin (Sarah) Gong has thus focused her research on the field of nanomedicine, in which she is working to more safely deliver a variety of drugs to treat cancer, heart disease and even blindness.

"We engineer nanoparticles to deliver all sorts of payloads for medical purposes, including small molecular drugs, proteins, DNAs, RNAs and CRISPR-based genome editing agents and so on," Gong says. "They allow the delivery of drugs more specifically to the target organ or cells while enhancing their stability during circulation in the bloodstream."

The nanoparticles Gong and her research group engineer are effectively tiny cages that house the various payloads. The nanoparticles can be designed with different structures and chemical features. These differences allow the nanoparticles to be tailor-made for the type of payload and the type of disease being targeted.

Imaging probes can also be incorporated so researchers, and eventually clinicians, can monitor if the nanoparticles are reaching the tumor while avoiding healthy tissues.

Most nanoparticle research currently being conducted uses particles made up of multiple molecules, but a concern is they do not have adequate stability in the bloodstream and can lead to premature release of the payloads and loss of their targeting specificity. Instead, the Gong lab is focusing on engineering "unimolecular" nanoparticles.

"Our nanoparticles are unique because they are formed by one single molecule, and thus are much less likely to fall apart during circulation in the bloodstream," Gong says.

MORE: **www.engr.wisc.edu/small-mighty-nanoparticles-can-deliver-types-drugs-safely/**

FACULTY NEWS

Assistant Professor **Randolph Ashton** received almost $800,000 from the National Institute of Neurological Disorders and Stroke, part of the National Institutes of Health, to continue a five-year research study of Lou Gehrig's disease after successfully completing its first phase. Ashton also received the college's Equity and Diversity Award in recognition of his efforts introducing underrepresented minority students to engineering.

Vilas Distinguished Professor **Shaoqin (Sarah) Gong** landed a Kellett Mid-Career Award, a UW-Madison honor that supports faculty who are seven to 20 years past their first promotion to tenured positions. The awards provide $75,000 to be spent over five years.

Professor **Paul Campagnola** and a team of collaborators won a 2017 best manuscript award from the American Heart Association's *Circulation Research* journal.

DEPARTMENT NEWS

A paper co-authored by alumnus **Jason Chiang**, MD-PhD '16, Associate Professor **Christopher Brace** and other UW-Madison collaborators was selected as a distinguished laboratory investigation by the editors of the *Journal of Vascular and Interventional Radiology*.

STUDENT NEWS

Undergraduate students **Taylor McKenna Marohl**, **Hunter Johnson** and **Kiersten Haffey** received National Science Foundation Graduate Research Fellowship awards. The program recruits high-potential scientists and engineers and supports their graduate research training in STEM fields.

Undergraduate **Will Flanigan** won best poster in the cell and developmental biology, immunology and microbiology category of the undergraduate poster contest at the American Society for Biochemistry and Molecular Biology's 2018 annual meeting.

Undergraduates **Kayla Huemer** and **Hannah Lider** received Fulbright awards to study and conduct research in India during the 2018-19 academic year.

LEARNING BY MAKING

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Complex human joints are a challenge to visualize. Textbook figures may be helpful, but they only offer a static, two-dimensional view. Meanwhile, real-life joints in actual humans are difficult to gain access to, unless you're an orthopedic surgeon—not to mention that they're inevitably obscured by a mess of blood and body tissue.

So, what is an engineering student interested in orthopedic joints and implants to do? For starters, they could sign up for *Design of Orthopedic Implants*, which makes innovative use of cutting-edge learning technology in the College of Engineering's new makerspace, the Grainger Engineering Design Innovation Laboratory.

Seniors and graduate students in the course use the makerspace's enormous interactive touchscreen and virtual reality headset to study bone joint anatomy. They use the technology to study computed tomography (CT) scan data from the National Library of Medicine, which provides the basis for the total joint replacements they'll develop using computer modeling. The students can then use the visualization tools to examine their implant models before they finally print them, also at the makerspace, with a 3-D printer.

Molly Scott, a senior BME student, is part of a team working on modifications to the standard knuckle joint replacement. She and her group want to develop an implant with titanium sleeves at either end that are mounted onto the bones and make implant replacement quick and simple.

Scott says she'll likely pursue a career in the field. Her experience in the course has confirmed her enthusiasm for it.

"I've been like a kid in a candy shop with everything here in the makerspace," Scott says. "Nothing is ever engineered in a vacuum, so it's a lot cooler to see the implants we're developing physically and be able to study the joints with the vis lab screen and the 3-D models. We actually get to put the information we're learning into action and test it."

MORE: www.engr.wisc.edu/new-makerspace-helps-students-visualize-creations/

Complex human joints are a challenge to visualize. Students in the *Design of Orthopedic Implants* course use the makerspace's interactive touchscreen and virtual reality headset to study bone joint anatomy.

Photos: Renee Meiller