



BIOMEDICAL ENGINEERING



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Greetings from Madison!

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

Many of our faculty received prestigious new grants this past year, both to their individual labs and also as part of a new National Institutes of Health-funded center based on CRISPR technology. More of our faculty were elected as fellows in the American Institute for Medical and Biological Engineering professional society, where the large majority of our associate and full professors now have been recognized with this honor. Other faculty were elected as fellows of the Biomedical Engineering Society and the National Academy of Inventors.

A common theme among our department activities has been innovation and entrepreneurship. For example, many of our faculty members are highly involved with startup companies based on technology developed in their respective labs. This spirit is particularly embodied in our undergraduate design program, where this year we had a record number of projects. Moreover, we have launched our first design projects in our Biomedical Innovation, Design, and Entrepreneurship master's program. We established this program three years ago and the enrollment has grown robustly. We have asked our industrial advisory board to assist us in identifying and sponsoring additional projects from local companies to support the undergraduate and master's design programs.

We had a record number of first-year students (roughly 240) join our BME program this year. 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 of Engineering. Importantly, the majority of students are women. To reflect our demographics, I increased the size of our industrial advisory board by adding three recent master's and PhD grads (from major companies), and now more than half our board members are women.

We continue expanding our efforts in inclusion, equity and diversity to ensure a welcoming environment for all, working closely with Chris Castro, the college's associate dean for inclusion, equity, and diversity in engineering, to advance our goals for increasing inclusion in the department, the college and across campus. We again are co-sponsoring the Rising Scholars program for career advancement for BME students from historically underrepresented groups, taking place at the University of Minnesota in June 2023. College and department representatives will actively participate in this important event.

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

Stay safe and On, Wisconsin!

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Inventive thinking earns Williams national recognition

A few weeks after visiting Nasdaq headquarters in Times Square to celebrate the success of one company he helped launch, Vilas Distinguished Achievement Professor Justin Williams celebrated another entrepreneurial honor: The National Academy of Inventors selected him in its 2022 class of fellows.

Williams is a pioneer in the field of neural engineering, particularly in developing novel, minimally invasive electrodes and working in concert with physicians to translate them to the clinic.

He's co-founded four companies around devices and technology for recording information from the brain and treating neurological diseases and more. Those include NeuroOne, a company built around flexible, thin-film electrode technology based on the first patent Williams filed after arriving at UW-Madison in 2003.

Williams recalls getting an invitation from then-UW-Madison neurosurgeon P. Charles Garell, now at New York Medical College, to see a new, widely marketed electrode array surgically implanted to treat epilepsy. Williams was stunned by the device's bulkiness—and appalled by the damage it left on the brain when removed after a few weeks.

"It really clicked that there was this huge chasm between what I knew we were capable

of doing from the research and engineering standpoints," he says, "and what clinicians had access to."

He set out to create a true microscale array thin enough to minimize mechanical strain on the brain and flexible enough to mold to the organ's contours. He spent multiple days a week in the operating room with Garell and neurosurgery residents, identifying needs and specifications for such devices. The work led to the launch of NeuroOne in 2009. On November 22, 2022, Williams and other company representatives were in New York to ring the Nasdaq closing bell, marking one year since the company's initial public offering and celebrating its latest U.S. Food and Drug Administration approval.

Williams is working on new devices and strategies to treat neurodegenerative disorders such as Alzheimer's and Parkinson's disease, as well as other minimally invasive methods to electrically stimulate the nervous system to alleviate a host of conditions. He's worked with a slew of collaborators in the UW-Madison School of Medicine and Public Health over the years, including Azam Ahmed and David Niemann, associate professors of neurological surgery.

He's particularly proud of the NAI honor, which he sees as validation of his belief in infusing business thinking, such as regulatory



considerations and consulting with clinical collaborators, early in the research process.

"This is one that really exemplifies my approach to research, balancing and making sure that the things we're doing in the research lab have translational abilities," he says.

NAI fellow status is considered the highest professional distinction given solely to academic inventors. Williams joins William Murphy, Harvey D. Spangler Professor and H.I. Romnes Faculty Fellow, as BME faculty members to earn the honor, along with Professor Emeritus Thomas "Rock" Mackie.

Improving our understanding of early spinal cord development



Randolph Ashton

Associate Professor Randolph Ashton is part of a UW-Madison team developing the means to turn stem cells into a wide range of specific types of spinal cord neurons and cells in the hindbrain, paving the way for improved prevention and treatment of spinal cord disease.

In a study published in *Science Advances*, Ashton and colleagues described a new protocol for differentiating human pluripotent stem cells into nearly the full spectrum of neuronal cell types that arise during early hindbrain and spinal cord development—important, because neuronal cells have so many different, specialized jobs within the body. The study also used new bioinformatic analyses to capture previously unknown information about their development in humans.

The work combined Ashton's expertise in neurodevelopment and stem cell bioengineering with Biostatistics and Medical Informatics Associate Professor Sushmita Roy's experience with machine learning and gene regulatory networks. Their labs developed a unique resource mapping the gene expression changes that mark differences between neuronal cell subtypes along the hindbrain and spinal cord.

"This is something that we, as scientists, really haven't had good access to before, but stem cells are allowing us to start exploring this," says Ashton, who's also associate director of UW-Madison's Stem Cell & Regenerative Medicine Center. "With this paper we can start to fill in those gaps of understanding of how human development occurs in the hindbrain and spinal cord and provide a really nice tool that essentially can lead to a very standardized and scalable protocol to manufacturing regenerative cell transplants."

With access to subtypes of neuronal cells and information about how they develop and interact in different regions of the spinal cord, Ashton expects researchers will soon be able to manufacture specific cell types for any damaged region of the spine for transplantation and effective post-injury regeneration.

Alums find rhythm at design program spinoff

Five years after graduating, Matt Knoespel and Phil Terrien are co-founders and the engineering backbone of a medical device company that's collected an array of awards since spinning out of a BME design project.

Atrility Medical is also filling a crucial need in post-operative care for newborns with serious heart defects and starting to establish itself in children's hospitals around the country.

If the two Green Bay, Wisconsin, natives are being honest, though, all that success has emerged from a design assignment that wasn't even their first choice.

Each semester in the BME design program, student teams select client projects to pour themselves into for three months. After missing out on their preferred option, Knoespel, Terrien and their groupmates reluctantly grabbed what would turn into the company's AtriAmp device from the list of assignments that hadn't yet been claimed.

"It turned out to be a life-changing selection that was thrust upon us, to some degree," says Knoespel, who, like Terrien, earned his BME bachelor's degree in 2017. "When doors close, new ones open, and sometimes you don't expect that."

Along with three classmates, they quickly shook off their disappointment, dove into learning about the heart, and set to work creating a prototype of a device capable of both passing on cardiac signals to a bedside monitor and interfacing with an external pacemaker. Their creation won the Tong Biomedical Design Award, the top prize in the BME design program each year, and the first in a series of honors the device-turned-company has collected over the past six years.

The AtriAmp, which secured U.S. Food and Drug Administration (FDA) approval in 2020, bears little resemblance to that first prototype, but the basic

premise is the same: The device displays continuous signals from surgically placed temporary wires on the intensive care unit monitor. It also connects to a pacemaker, which is vital in case the heart slips into an arrhythmia after surgery.

Nicholas Von Bergen, an associate professor of cardiology at UW-Madison, turned to the BME design program after identifying the need for such a device in his work with infant patients. Von Bergen and Pete Lukszyz, a lecturer in the Wisconsin School of Business, are Atrility's other co-founders. While the AtriAmp works with adult patients as well, pediatric care has been Atrility's initial focus, and more than 15 children's hospitals across the country are either using the device or planning to soon.



Phil Terrien, left, and Matt Knoespel first worked on the prototype that became the AtriAmp in spring 2016. It's now gaining traction in hospitals, and Atrility Medical is devising other technologies that could improve patient care in the wake of surgeries.

In the four years between completing their design project and celebrating FDA approval, Knoespel and Terrien sharpened their product design to incorporate regulatory and manufacturing considerations, as well as additional safety features. But, as part of a small startup, they also had to dabble in strategic forecasting, accounting, sales support, marketing and more.

That they exhibited that kind of agility is no fluke; cultivating it is one of the aims of the BME design program's open-ended format.

"It's much more resemblant of what you see in the real world," rather than typical coursework, says Terrien. "You face a lot of challenges that are not answerable via a textbook or a previous test. You're kind of paving your own course. Having those experiences is helpful, because that's what the startup world is, and more broadly, that is what the real world of engineering is."

Atrility is one of at least nine companies to grow out of BME student design projects over the past 15 years.

Atrility Medical earned a 2022 Wisconsin Innovation Award, one of two winners with BME roots. Stem Pharm, a company co-founded by Professor William Murphy that produces 3D human brain organoids for neurological drug discovery and pre-clinical research, also received the honor.

mRNA therapy could break down treatment barriers for spinal cord injuries



William Murphy

In the wake of a spinal cord injury, a protective scar forms to allow the central nervous system to heal. It's not unlike the body's reaction to a run-of-the-mill wound, but there's a significant downside in this case.

While the resulting glial scar helps to stabilize the compromised area, it also walls it off—preventing the regrowth of nerve fibers that could enable renewed motor function like walking.

A range of treatment options for spinal cord injuries are under development, but they're predominantly focused on the acute phase, covering the days or weeks that follow when the glial scar still hasn't fully formed. After that, patients run out of viable therapies.

A team of UW-Madison researchers, led by William Murphy, the Harvey D. Spangler Professor & H.I. Romnes Faculty Fellow, is developing a novel method for breaking down the glial scar and paving the way for motor function recovery in patients with long-term spinal cord injuries.

Murphy's group, in collaboration with the lab of Amgad Hanna, a professor of neurological surgery, is using mineral-coated microparticles to nonvirally deliver messenger RNA (mRNA) to direct production of an enzyme that can degrade the glial scar and potentially also drive new axon growth to restore movement. The team detailed its successful results in rat models in the journal *Advanced Healthcare Materials*. Alumnus Andrew Khalil (PhD '17) was the paper's first author.

"My hope is this opens up an opportunity to treat patients who have chronic spinal cord injuries," says Murphy, whose lab develops biologically inspired materials for regenerative medicine applications. "That's a patient population that really doesn't have options right now."

Through an injection directly into the glial scar, the microparticles carry mRNA that causes cells in the area to "overexpress" an enzyme called Chondroitinase ABC (ChABC), which can break down a key component of the glial scar.

Previous studies have demonstrated ChABC's effectiveness in doing so. But the enzyme is unfortunately rather unstable, meaning its activity—its ability to catalyze a chemical reaction—drops rapidly. Synthetically produced ChABC is also less active than the version created in the body, and when injected, it's transported away from the site.

The UW-Madison team's solution is the first to use mRNA delivery to encode ChABC production, which results in a natural, more active version of the enzyme that's released slowly over time and remains at the site of the scar.

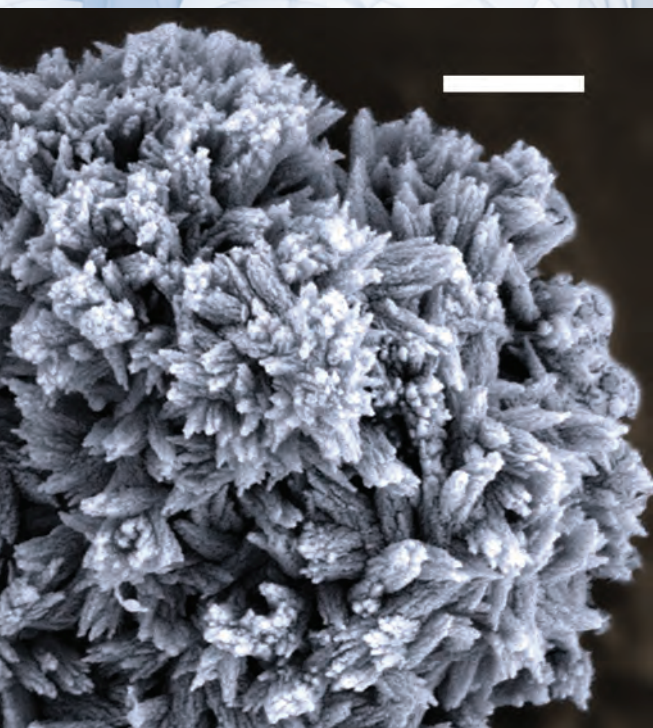
"It's a one-delivery system, so you don't need repeated injections," says Dan Hellenbrand (MS '10), a researcher in Hanna's lab who sustained a spinal cord injury in 2003, leaving him paralyzed.

The adaptable microparticles could also serve as a platform to deliver mRNA for production in the body of other difficult-to-produce therapeutic proteins, such as nerve growth factors, needed for spinal cord injury treatment.

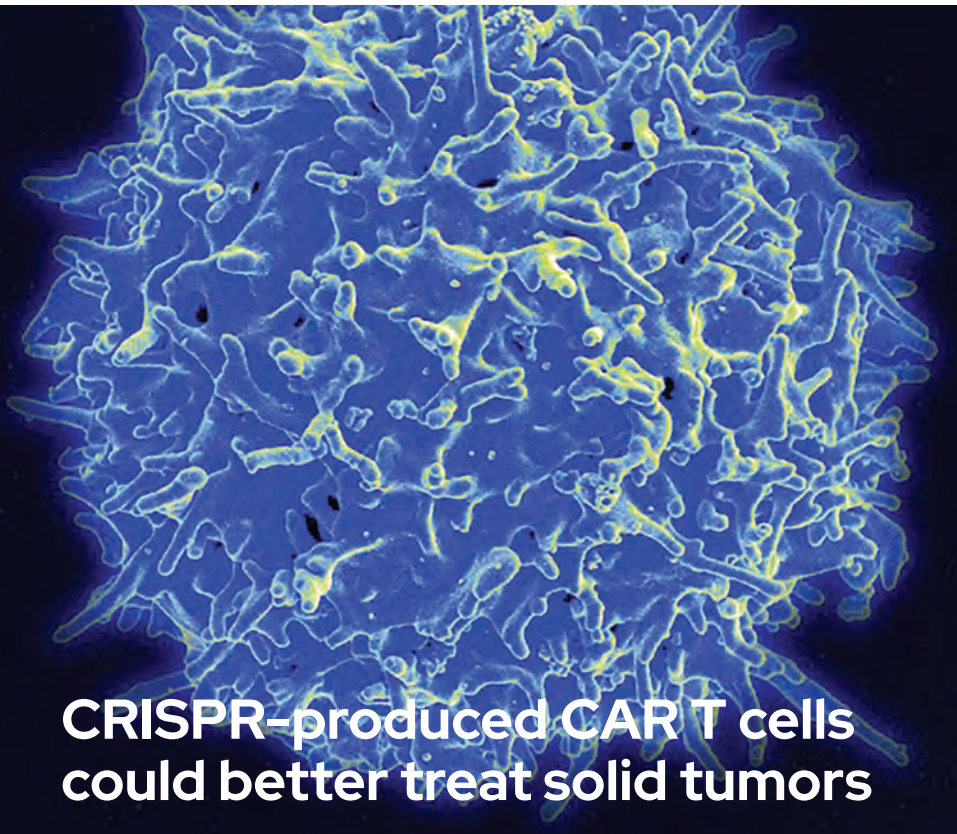
Murphy's lab has previously created mRNA strands that encode for production of neurotrophin-3, a molecule that enhances axon growth. He and Hanna are already pursuing grants to test a combination mRNA therapy with ChABC and neurotrophin-3 in rodent models, with a long-term aim of human clinical trials and commercialization.

It's the sort of research that inspired Hellenbrand to earn his master's degree under the direction of Murphy and Hanna—and with the help and support of his wife, Amy—and continue working in the latter's lab.

"My personal experience with spinal cord injury is the whole reason why I'm researching spinal cord injury and looking for treatments, not just for me, but for future generations," he says.



A microparticle shown via scanning electron microscopy. Image courtesy Andrew Khalil (PhD '17).



Scanning electron micrograph of a human T lymphocyte (also called a T cell) from the immune system of a healthy donor. Credit: NIH.

CRISPR-produced CAR T cells could better treat solid tumors



Krishanu Saha

Chimeric antigen receptor (CAR) T cells are biological assassins: white blood cells that are specifically engineered to attack cancer cells. Over the past five years, they've become an

established therapeutic option for patients with blood cancer that has withstood standard treatments.

But dueling with cancer cells is taxing work, particularly in solid tumor microenvironments that are resistant to the immune system. With that in mind, a team of UW-Madison researchers is working to produce CAR T cells that could deliver results in solid tumors, using gene editing rather than a viral method to manufacture them.

The group, led by Associate Professor Krishanu Saha and Christian Capitini, an associate professor of pediatrics, has detailed the work in an article published in the *Journal for ImmunoTherapy of Cancer*.

The research builds upon recent breakthroughs from a handful of labs using CRISPR technology to genetically edit T cells, this time in the unique context of treating

solid tumors. While CAR T cell therapies are regularly deployed against blood cancers like leukemias and lymphomas, progress in solid tumors has proven much more stubborn. Currently, no Food and Drug Administration (FDA)-approved CAR T cell therapies exist for solid tumor cancers.

"That's been the holy grail of the field," says Capitini.

To generate CAR T cells specifically tuned to attack tumor cells in neuroblastoma, a rare form of cancer that affects the adrenal gland and nerve cells almost exclusively in children, the research team used CRISPR/Cas9 gene editing to essentially cut and paste a piece of DNA into standard T cells. That DNA, which encodes the CAR, empowers the T cells to specifically target a sugar molecule found on the surface of neuroblastoma tumor cells, as well as some glioblastomas, melanomas and other types of cancers.

But unlike the standard method for manufacturing T cells, in which a modified virus carries the necessary DNA, using CRISPR avoids many safety concerns—by eliminating potential undesired effects of a virus—and delivers a more precise genetic edit.

"It's a much cleaner way to put in our functionality," says Saha, noting the CRISPR method inserts the CAR genetic material in

one specific spot in the human genome—compared to tens of thousands of different spots with a standard viral vector.

That precision approach may improve treatment efficacy, too. In analyzing their CRISPR-generated CAR T cells vs. viral-produced ones, the researchers found theirs were more immature and less prone to exhaustion, traits that have correlated with better treatment results in blood cancers.

CRISPR CAR T cell production also circumvents the viral vector manufacturing bottleneck, a supply chain backlog that worsened during the COVID-19 pandemic. The UW-Madison group isn't the first to use CRISPR to generate CAR T cells—a group at Memorial Sloan Kettering Cancer Center published its results in 2017—but no one had done it when then-PhD student Nicole Piscopo (PhD '20) first took up the project in Saha's lab back in 2015.

Under Saha's guidance, Piscopo and fellow PhD student Katherine Mueller (PhD '22, cellular and molecular biology) built upon the nascent method to tailor CAR T cells to attack solid tumors. Their CRISPR-edited CAR T cells induced solid tumor regression in mouse models with neuroblastoma.

"There's a huge, huge space ahead of us to improve treatments for these cancers that are currently incurable," says Mueller, now a postdoctoral research fellow at Children's Hospital of Philadelphia studying CAR T cell exhaustion.

Saha and Capitini plan to seek FDA approval for an investigational new drug application needed to start a clinical trial for the treatment—ideally in Madison through UW Health's Program for Advanced Cell Therapy—and are exploring collaborations in the biomanufacturing industry through the Forward BIO Institute at UW-Madison and the National Science Foundation's Engineering Research Center for Cell Manufacturing Technologies. They're also pursuing a Cancer Moonshot grant through the National Cancer Institute for further research.

"The challenge in my mind is to get it into the clinic," says Saha. "And we're working night and day on that."

Faculty News



Associate Professor **Randolph Ashton** has been elected to the American Institute for Medical and Biological Engineering's College of Fellows for his work modeling brain and spinal cord development using stem cells. Members represent the top 2% of medical and biological engineers. Ashton's induction gives BME 15 AIMBE Fellows on its faculty.



Associate Professor **Kevin Eliceiri**, who holds the Retina Research Foundation Walter H. Helmerich Professorship, was selected for the Clarivate *Web of Science* Highly Cited Researchers list for 2022. The honor is reserved for scientists who ranked in the top 1% of cited papers over the last decade.



Professor **Kristyn Masters** earned the UW-Madison Slesinger Award for Excellence in Mentoring.



Professor **Pamela Kreeger** is co-principal investigator on a National Science Foundation grant to study the causes and effects of friction in how biological cells move in collective groups, which is an essential process in cancer invasion, tissue development and wound healing.



Professor **Melissa Skala** was named the Carol Skornicka Chair at the Morgridge Institute for Research. The Skornicka Chair provides a reliable source of funding for the Skala Lab's work in biomedical imaging.



Assistant Professor **Colleen Witzenburg** is a co-principal investigator on a grant from the UW-Madison Institute for Clinical and Translational Research to examine untreated post-surgical coarctation of the aorta and assess early stent intervention using a novel growth stent.

Student News



Parker Esswein, a senior and member of Professor Paul Campagnola's research group, is the 2022-23 recipient of the Joshua Zelmanowitz Plantz Scholarship.

Alumni News



Rebecca Alcock (BS '18, MS '20), now a PhD student in the Department of Industrial and Systems Engineering, was named among the "2022 Rising Tech Leaders to Watch" by *Milwaukee Business Journal*.



Ludwig improving neuromodulation safety testing

As neuromodulation therapies for treating a growing number of conditions proliferate and advance, they've rapidly outpaced knowledge and methods for proactively understanding the safety of electrical stimulation of the nervous system.

But those kind of underlying insights could accelerate development—and U.S. Food and Drug Administration approval—of therapies.

With that in mind, Associate Professor Kip Ludwig is leading a five-year, \$1.8 million project to create a new benchtop testing framework to predict safety issues concerning a wide range of electrodes. The funding is part of the National Institutes of Health (NIH) Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) Initiative.

James Trevathan, a research scientist in Ludwig's lab in the Wisconsin Institute for Translational Neuroengineering (WITNe), is a co-investigator on the grant, which is among a number of projects for which Ludwig's lab has received funding in recent months.

He's part of a collaboration led by Case Western Reserve University and Duke University that landed a \$15.75 million contract from NIH to map the human vagus nerve—a key pathway for many neuromodulation treatments—in unprecedented detail.

Ludwig, who is the neuroengineering lead for the college's Grainger Institute for Engineering and co-director of WITNe, is also leading a \$2.5 million NIH project to optimize a class of neuromodulation therapies called baroreflex activation therapy. And he's serving as a co-investigator on a Duke-led NIH grant to develop new waveforms for blocking nerve activity, which could have implications for treating hypertension, heart failure and cardiac arrhythmias.

Ludwig's group is also working with industry partners Abbott Laboratories and the Alfred Mann Foundation to better understand the neuroanatomy to inform electrode design and improve therapeutic effects while minimizing side effects.

Lastly, through a Wisconsin Alumni Research Foundation Accelerator award, Ludwig's lab is conducting further testing of a noninvasive stimulation strategy of a cranial nerve to encourage blood flow and the clearance of metabolic waste products. The therapy could represent a preventative treatment for neurodegenerative diseases such as Alzheimer's and Parkinson's.



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Rowing in a new direction

One of our undergraduate design teams hopes to make exercise more inclusive. From left, Josh Andreatta, Annabel Frake, Tim Tran, Samuel Skirpan and Roxi Reuter are working with fitness manufacturer Johnson Health Tech to design an adaptive rowing machine for people who use wheelchairs. While a few adaptive machines exist, Andreatta notes they're not convertible between standard and adaptive setups—functionality that would be especially useful in a gym setting. “Maybe our design will inspire someone else to also add more inclusive gym equipment to their line of products,” says Reuter.