College of Engineering
UNIVERSITY OF WISCONSIN–MADISON

FALL 2023 NEWSLETTER

BIOMEDICAL ENGINEERING

ILLUMINATING POSSIBILITIES

Greetings from Madison!

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. Our faculty continue to receive prestigious new federal grants, and more of our faculty were elected as fellows of the American Institute for Medical and Biological Engineering (AIMBE) professional society, where a large majority of our associate and full professors have been recognized with this honor. In addition, six of our faculty have received prestigious UW-Madison professorships or faculty fellowships.

Collectively, the last two years have seen the largest entering classes for our PhD program in many years. In a significant step, we've implemented a rotation system where incoming PhD students are able to explore a few different labs before committing to their thesis lab. Many students have taken advantage of this opportunity. Our initial offering of a new optics/photonics lab course was highly successful, and we obtained philanthropic support from local industries to expand the number of students in the class. This coming year, we will offer a new lab-based course on CRISPR technology. Collectively, these courses will provide real-life experiences and better prepare our students for a range of careers. Our MS programs have had continued strong enrollment, and rank second in the Big Ten in program size.

We are proud to announce the hire of three new faculty members, who collectively will expand upon our research strengths and further our teaching mission. Assistant Professor Joshua Brockman starts this fall and specializes in mechanobiology studies in cancer. Professor Randy Bartels, hired through a collaboration with the Morgridge Institute for Research on campus, comes from Colorado State, bringing expertise in developing new imaging technologies. Aarushi Bhargava will join us an assistant professor starting fall 2024 and specializes in therapeutic uses of ultrasound technology.

We continue to expand upon our efforts in inclusion, equity and diversity to ensure a welcoming environment for all. Notably, several of our faculty participated in the second WiscProf workshop, which aims to prepare graduate students and postdoctoral fellows for careers in academia. Our department also co-sponsored the second Rising BME Scholar workshop hosted at the University of Minnesota, which covers a broader range of careers for BME PhDs.

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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Shedding light on cells' stress-induced self-talk

When a cell contends with changes in its environment, it takes action to respond. Signals travel through its internal circuitry, turning various cellular machinery on and off, expressing some genes while repressing others.

One class of proteins—transcription factors, which bind DNA and regulate gene expression—plays a key role in enabling responses tailored to each stress.

Now, UW-Madison biomedical engineers have uncovered a more nuanced understanding of how cells use those transcription factors to transmit different signals and alter gene expression. They describe their findings in a paper published in the journal *Cell Reports*.

"Cells can actually encode information in how these transcription factors turn on and off over time, and the genes themselves are capable of decoding this information in order to respond appropriately to different stresses," says Kieran Sweeney (PhD '22), who led the work and is now a postdoctoral researcher in Associate Professor Megan McClean's lab.

Photo: Joel Hallberg.

In order to fulfill their job in this intracellular game of telephone, transcription factors juggle messages from multiple signaling pathways, which converge on them in a bowtie pattern. So how exactly does one transcription factor relay all that information?

To answer that question, Sweeney employed light-controlled mutants of the transcription factor Msn2 in yeast (part of the optogenetic toolkit McClean's research group has created to study biological signal processing), in tandem with high-throughput microscopy and computational modeling.

His work bolsters previous evidence of the downstream effects of transcription factors' movement in and out of the cell's nucleus, the duration of their stay (think Morse code) and pulsing behavior, all of which Sweeney controlled with light. Importantly, he also characterized how manipulating the proteins' ability to bind DNA affects the signal decoding behavior of downstream genes. As McClean puts it, that's essentially discovering additional knobs for tuning a signal.

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FOCUS ON NEW FACULTY

Brockman reckons with force of immune system

Cells are the bedrock of life as we know it, carrying out essential biological functions across organisms.

But, as Joshua Brockman is quick to note, cells are also mechanical entities, exerting and sensing physical forces as they try to understand and act on their surroundings. And Brockman is eager to probe those mechanical outputs for clues that could inform and improve healthcare treatments, such as cancer immunotherapy.

Brockman has brought his work at the intersection of mechanobiology and immunotherapy to BME, joining as an assistant professor in fall 2023.

"Very rarely when developing therapies do we think about cells as mechanical," says Brockman, who comes to Madison after spending three years at Harvard University's Wyss Institute for Biologically Inspired Engineering as a postdoctoral researcher. "I want to understand mechanical forces in more natural systems, and I want to use them as a design principle to improve therapies across the board."

Mechanobiology, an interdisciplinary field that hooked Brockman as an undergraduate student at Ohio State University, explores the effects of mechanical forces on cell behavior, development and disease.

As a PhD student at Georgia Tech and Emory University, Brockman built molecular tension sensors out of DNA and other polymers, creating bobby-pin-like probes that translate the mechanical forces exerted by individual proteins on a cell's surface into light—allowing researchers to see and take images capturing that information. Taking that work even further, he developed techniques to measure the orientations and locations of those receptor forces, which are at the Piconewton scale—roughly one-trillionth the amount of force required for a human hand to hold an apple, Brockman says.

Now, he hopes to leverage those tools to bolster immunotherapy, augmented by the knowledge of the immune system and biomaterials he gained from working in the lab of Harvard Professor David Mooney, who's a UW-Madison chemical engineering alumnus, Madison native and National Academy of Engineering member.

"I have this deep conviction, backed by the literature, that physical forces are really important in the way the immune system works, including the way the immune system combats diseases like cancer," says Brockman, whose postdoctoral work was funded by a National Cancer Institute grant. "One of the things that I hope to do is merge mechanobiology with immunotherapy in a way that just really hasn't been done before."

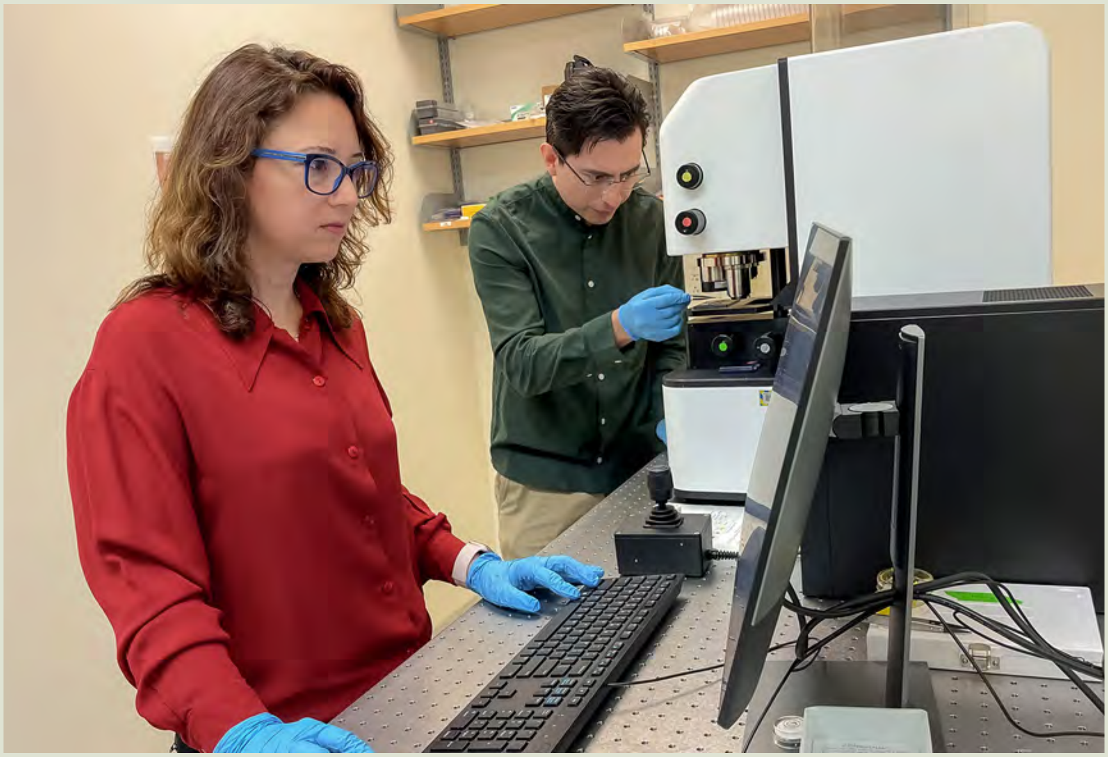
For example, Brockman says, the T-cell receptors on the surface of the immune system's enforcers are mechanically active. But it's unclear whether the same is true of the recognition machinery on genetically engineered chimeric antigen receptor (CAR) T cells, one of the leading cancer immunotherapies. Brockman hopes to find out and then explore ways to potentially modify receptor mechanical functionality to bolster efficacy of immunotherapies.

He also plans to translate his work measuring cellular receptor forces to viscoelastic surfaces that replicate the human body's tissues—partially elastic, but also continuing to deform over time under sustained force.

"I don't feel like we understand very well how viscoelasticity alters the immune system's ability to execute its functions," he says. "If you have a tissue that's both soft and highly viscous, will that really hurt the ability of your immune system to fight off that tumor, for example? And if that's the case, maybe there's something we can do."

At UW-Madison, he's eager to collaborate with colleagues who are experts on the extracellular matrix that surrounds tumor cells, such as Vilas Distinguished Achievement Professor Pamela Kreeger, and leading imaging researchers like Associate Professor Kevin Eliceiri, Professor Melissa Skala, and Peter Tong Department Chair and Professor Paul Campagnola.

"For me, this was a match made in heaven," he says.



Assistant Professor Filiz Yesilkoy, left, and PhD student Samir Rosas have devised a system that leverages the lab's expertise in tissue imaging and nano photonics. Photo: Tom Ziemer.

Small nanoengineered surface shows big picture of tissue changes

When pathologists examine tissue samples for signs of disease, they rely on their trained eyes to spot changes in specific biomarkers that indicate abnormalities.

Before those alterations become visible on chemically stained samples, though, disease-related manipulations occur at the molecular level.

A new imaging system featuring a novel application of engineered plasmonic metasurfaces, devised by UW-Madison biomedical engineers, can chemically map tissues, providing a more detailed, quantitative and representative picture. In addition to enhancing clinical histopathology capabilities, it could aid toxicology studies and reveal new clues into the origins and early markers of various diseases.

The researchers, led by Assistant Professor Filiz Yesilkoy, demonstrated their approach by imaging brain tissue; they published their research in the journal *Advanced Materials*. By pairing advanced microscopy tools with their unique nanofabricated metasurface to boost mid-infrared imaging capabilities, Yesilkoy and PhD student Samir Rosas can detect a wider range of biomolecules while overcoming any bias caused by the thickness or heterogeneity of a given tissue sample.

"We are eliminating the correlation to the physical bulk tissue properties. We are just confining and quantitatively analyzing the tissue material in the nanoscale," says Yesilkoy. "There are lots of diseases where, first of all, we don't have the biomarkers specific to stain the tissue against. So in that case, we need to understand the overall chemical composition of the tissue. And with today's artificial intelligence and machine learning algorithms, if we have this vast amount of chemical information that is resolved spatially, then we can benefit from this data science analytics."

Their method harnesses the unique properties of the plasmonic metasurface Rosas developed in the college's Nanoscale Fabrication Center over the course of two years. The collective effect of almost three million gold resonators adorning the metasurface allows it to cover a wider range of frequencies, and thus, biomolecules, when tissue is placed atop it.

"The plasmonic metasurface has several remarkable features," says Rosas, citing its abilities to cover the desired spectral range, extract molecular information from ultra-thin tissue, and yield information from the same diffraction-limited spot. "Furthermore, our method is completely label-free."

Yesilkoy and Rosas can even image tissue regions that wouldn't otherwise be visible, as well as detect the specific structural alignment of proteins. The latter capability could prove particularly useful for studying neurodegenerative diseases, such as Alzheimer's and Parkinson's, which are characterized by a buildup of misfolded proteins.

"We see a lot of prospects for studying neurodegenerative diseases, because it has that niche where the protein structure can be studied using this method, contrary to other brain imaging and tissue imaging methods," says Yesilkoy.

She and Rosas plan to continue working with collaborator Xinyu Zhao, a professor of neuroscience at UW-Madison whose lab provided tissue samples for the work, to examine brain tissue from mice that have been genetically modified to carry autism. The researchers will use their new technique to create chemical maps of the brains of mice at different ages and identify physiological changes.

"When we don't know what we're looking for," says Yesilkoy, "looking for everything and just feeding that into the data processing pipeline can actually illuminate it."

Tiny antennas open door to injectable electronics for brain monitoring

By creating a miniscule device that translates brain activity into radio waves, UW-Madison neuroengineers have taken a key step toward enabling injectable sensors for wireless, localized recording in the brain.

The work, detailed in the May 2023 issue of the journal *Sensors and Actuators B: Chemical*, is essentially a proof-of-concept for using minimally invasive sensors that wirelessly harvest power and transmit data to external imaging hardware operating on radio frequency, such as magnetic resonance imaging (MRI) scanners.

PhD student Suyash Bhatt, left, and undergraduate Emily Masterson use an MRI machine, obtained through a Defense University Research Instrumentation Program (DURIP) grant from the Office of Naval Research, to validate the Hai lab's minimally invasive sensors. Photo: Tom Ziemer.

"Right now, in order to get brain recordings of any description, you've got to have either a wired probe or a wireless probe with bulky hardware on top of your head," says PhD student Suyash Bhatt, co-first author on the paper along with recent graduate Emily Masterson (BS '23). "In our case, you can actually inject this into the brain, look at what's going on in MRI. The MRI provides the power, and you don't even need anything else in terms of circuitry. So that's a pretty big step forward."

While the sensor is broadly applicable, it would be particularly useful for diagnosing and monitoring neurological conditions, including epilepsy, Parkinson's disease and traumatic brain injury.

The research is part of Assistant Professor Aviad Hai's quest to create dramatically less invasive technologies that yield more detailed, granular and comprehensive data from across the brain.

The Hai lab is creating milliscale sensors that consist of an inductor and capacitor—which form a resonator, essentially acting as an antenna that can absorb electromagnetic energy from an outside transmitter—along with an ion-sensitive field effect transistor. That transistor, powered by the resonator, detects the rapid flow of ions in the brain, which corresponds to neural activity.

To validate their prototype, the researchers surgically implanted it in the brains of rats and then electrically stimulated one of their hind paws, causing a neural response.

"Nothing like this has been shown in the living brain," says Hai.

Bhatt has already fabricated a microscale version of the device using tools in the college's Nanoscale Fabrication Center. At less than a square millimeter in total area, the sensors are small enough to fit in a 16-gauge needle.

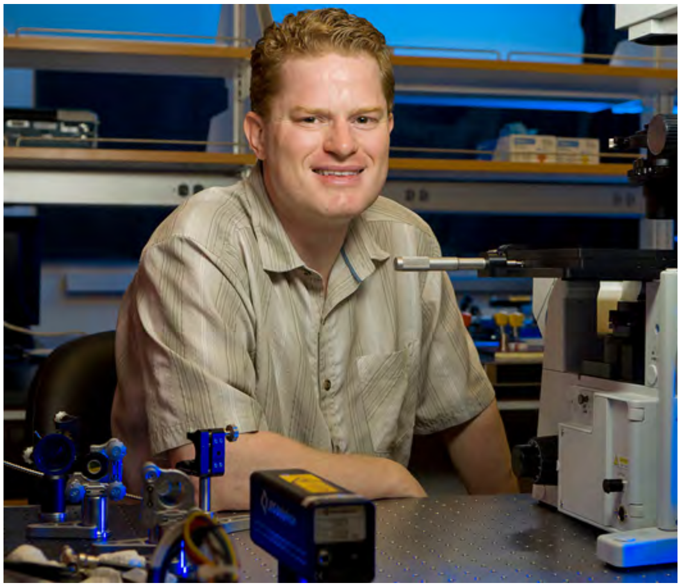
"These are basically just the equivalent of dust," says Bhatt.

The group also can track specific neurotransmitters—dopamine, for example—by coating the transistor with different chemicals.

Hai hopes to eventually translate the research to clinical use. "There's no reason not to. We're using purely biologically compatible materials that have been used for other technologies that are FDA approved," he says.

For Masterson, claiming a co-first author credit on a paper—a rarity for an undergraduate—is a satisfying reward to more than three years in the lab. After graduating, Masterson started a full-time position at Medical Murray, a medical device contractor.

"My research experience has given me the opportunity to accomplish something meaningful and advance the field of neuroscience," says Masterson. "Moving forward, I hope to leverage my experience in research to add a different perspective to any conversation."



"I think true innovation has to be collaborative, built on conversations across disciplines and lots of trial and error."

FOCUS ON NEW FACULTY

Bartels pushes limits of imaging

Randy Bartels is chasing innovation in imaging technology while building collaborations with researchers across the biological sciences.

So he should fit nicely in BME, whose faculty and students routinely work with colleagues across the UW-Madison campus to develop new tools for the research lab and the clinic.

Bartels, an expert in creating technologies that shed light on unseen worlds in biology, joined BME and the Morgridge Institute for Research in summer 2023. He's spent the past 20 years on the faculty of Colorado State University, specializing in the development of light microscopy and laser technology for applications such as ultra-deep imaging of tissues and vastly improved resolution of cell populations.

"I've been working in the space of biomedical imaging for more than 15 years, but Morgridge and UW-Madison will offer an opportunity to work with a wider range of collaborators in biology," says Bartels, who will initially serve as a visiting faculty member in BME before joining full time in 2024. "I think true innovation has to be collaborative, built on conversations across disciplines and lots of trial and error. I'm really excited to work with biologists who want to push what we're capable of imaging."

Two current Bartels research projects have captured the attention of the "Frontiers of Imaging" program at the Chan Zuckerberg Initiative (CZI). In 2020, Bartels received CZI support for a project to image more deeply into tissue by developing ways to suppress scattered light and increase resolution. And in 2022, Bartels partnered on a CZI project to develop a laser technology that can illuminate large populations or regions of cells at much faster speed and higher resolution than conventional techniques.

Bartels has earned high honors for his work. He was awarded the Adolph Lomb Medal from the Optical Society of America, a National Science Foundation CAREER award, a Sloan Research Fellowship in physics, an Office of Naval Research Young Investigator Award, a Beckman Young Investigator Award and a Presidential Early Career Award for Science and Engineering.

A self-described "science nerd" in his youth, Bartels was a first-generation undergraduate student when he attended Oklahoma State University in the early 1990s. His curiosity about research was helped along by his exposure to an early iteration of the internet called "Gopher," created by the University of Minnesota. Long before search engines became ubiquitous in modern life, Bartels jumped on Gopher (designed mostly for academic researchers) to explore what summer research projects might be open to undergraduates.

The search led him to a summer research opportunity at the Ames Research Lab at Iowa State University, where he worked on semiconductor thin film growth. The next year, he landed a summer research gig at the University of Michigan's Center for Ultrafast Optical Science. There he met the scientists who would become his PhD mentors.

While Bartels' academic training is almost exclusively in physics and engineering, today he is most at home at the intersection between physical sciences and biology.

"These days, I spend a lot more time reading biology papers than I do physics papers, because I want to understand some of the problems that we really need to solve," he says. "And also, I'm not naive enough to think that I come in with a technology, and it's just going to solve problems on its own."

One class of experiments Bartels plans to pursue in Madison is developing optical correlative imaging with cryo-EM and MRI. In the case of cryo-EM, he will exploit unique properties of his new fluorescent super resolution imaging technique. In particular, the microscopy can image large sample volumes, even when optical aberrations are present.

Bartels is excited to develop innovative new biomedical microscope technologies that will open new lines of inquiry by being able to quantitatively address questions that cannot be systematically studied with current technologies.

Faculty News

Associate Professor Kevin Eliceiri received an H.I. Romnes Fellowship from UW-Madison. The award provides honorees within six years of promotion to a tenured position with flexible funding. Eliceiri, who holds the Retina Research Foundation Walter H. Helmerich Research Chair, also earned a Wisconsin Alumni Research Foundation Accelerator Big Data Challenge Grant.

Associate Professor Krishanu Saha also received a Romnes Fellowship.

Assistant Professor Aviad Hai landed a Defense University Research Instrumentation Program (DURIP) grant from the Office of Naval Research to install a new MRI machine in his lab. Hai also received a Vilas Faculty Early Career Investigator Award, which provides three years of flexible funding to recognize research and teaching excellence among early career faculty.

Professor Pamela Kreeger earned a Vilas Distinguished Achievement Professorship from UW-Madison in recognition of her distinguished scholarship and outstanding teaching and service. The award provides five years of flexible funding.

William Murphy, a Harvey D. Spangler Professor and H.I. Romnes Faculty Fellow, won the Society for Biomaterials Clemson Award for Applied Research.

Justin Williams, a Harvey D. Spangler Professor and a Vilas Distinguished Achievement Professor, earned a Kellett Mid-Career Award from UW-Madison. The award offers flexible funding to faculty promoted to tenured positions within seven to 20 years.

Alumna Christa Wille (BS '12, PhD '23) has joined BME as a teaching faculty member. She's also part of the team at the college's Center for Innovation in Engineering Education.

Assistant Professor Filiz Yesilkoy received a Trailblazer R21 Award from the National Institute of Biomedical Imaging and Bioengineering to support her work developing an innovative cancer detection platform.

Remembering John Webster

John Webster, a pioneering and renowned researcher and educator in the field of biomedical instrumentation, died March 29, 2023. He was 90.

Webster first joined the UW-Madison faculty in 1967, working in electrical engineering for more than three decades before helping launch the BME department in 1999. He developed and taught the department's signature undergraduate design course sequence, helping to instill the BME ethos of learning through the hands-on creation of medical device prototypes. Webster also experimented with teaching techniques that would eventually be called flipped classrooms or blended learning decades before they were in vogue.

Webster, who remained active as a teacher and researcher even after retiring from full-time work, published more than 250 journal articles and wrote or edited more than 25 books. The latter figure includes the 3,000-page *Encyclopedia of Medical Devices and Instrumentation* and *Medical Instrumentation: Application and Design*, one of the most-used textbooks in biomedical engineering education around the world. He also edited the 24-volume *Encyclopedia of Electrical and Electronic Engineering,* featuring hundreds of authors.

Among a host of other honors, Webster was a fellow of the Institute of Electrical and Electronics Engineers, the International Society of Automation, the American Institute of Medical and Biological Engineering, and the Institute of Physics. In 2019, the Institute of Electrical and Electronics Engineers awarded him its 2019 James H. Mulligan Jr. Education Medal for his career contributions.

Travelle Franklin-Ford Ellis

Kelly Stevens

Outstanding alums

BME celebrates two exceptional alumnae as part of the college's 2023 Engineers' Day festivities: Travelle Franklin-Ford Ellis (PhD/MD '13), health equity director at biotech company Exact Sciences, and Kelly Stevens (BS '02), associate professor of bioengineering at the University of Washington.

Both drew inspiration for their career paths by founding student organizations and holding leadership roles during their time as BME students.

Ellis, who's receiving the college's Early Career Achievement Award, was one of the inaugural hires in Exact Sciences' health equity program.

"This idea of educating communities and people on the fundamentals of why or how to be healthy or how to improve their lives has really had an impact on me," she says.

Stevens, who holds the James Chao-Yao Koh and Maria Lee Koh Endowed Engineering and Medicine Career Development Professorship, is among the college's Distinguished Achievement Award honorees. In addition to pioneering approaches to mapping and replicating human tissues and organs to work toward regenerative therapies, she's a national leader in efforts to improve representation in the biomedical engineering research community.

"I enjoy that I can spend each day doing work that I believe is important for our broader society and world," she says. "That means both doing science, as well as doing activities to improve diversity, equity, and inclusion in our profession."

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BME duo helping develop gene editing therapy to treat blindness

Vilas Distinguished Professor Shaoqin "Sarah" Gong and Associate Professor Krishanu Saha are part of a team of UW-Madison researchers advancing innovative therapies for a pair of eye diseases through a $29 million National Institutes of Health grant.

Sarah Gong

Krishanu Saha

Over the next five years, the collaborative project will merge new drug delivery systems with advanced genome CRISPR technology, targeting Best Disease (BD) and Leber Congenital Amaurosis (LCA), both of which are currently untreatable hereditary diseases.

Saha views the grant as a crucial step toward advancing gene editing therapy and drug development on campus.

"The genome editing piece of it is a game changer," Saha says. "The opportunity to execute it in a safe and meaningful way for patients, specifically Wisconsin patients currently diagnosed with one of these diseases, would be a nice fulfillment of why we do the work and why it's publicly funded."

Gong will lead the development of one nonviral delivery system for the CRISPR gene editor, leveraging nanotechnology.

"Developing a safe and efficient delivery system for the CRISPR genome editor is essential for clinical translation," says Gong, whose work focuses on a new family of nanoparticles that can carry genome-editing tools into target organs or cells around the body and then harmlessly dissolve.

"It's a long road from the design stage of paper and pencil to formulating effective therapeutics with a lifetime impact," says Saha. "It takes lots of investment. The fact that we are piecing together the resources and the people here in Madison makes that really exciting and meaningful."