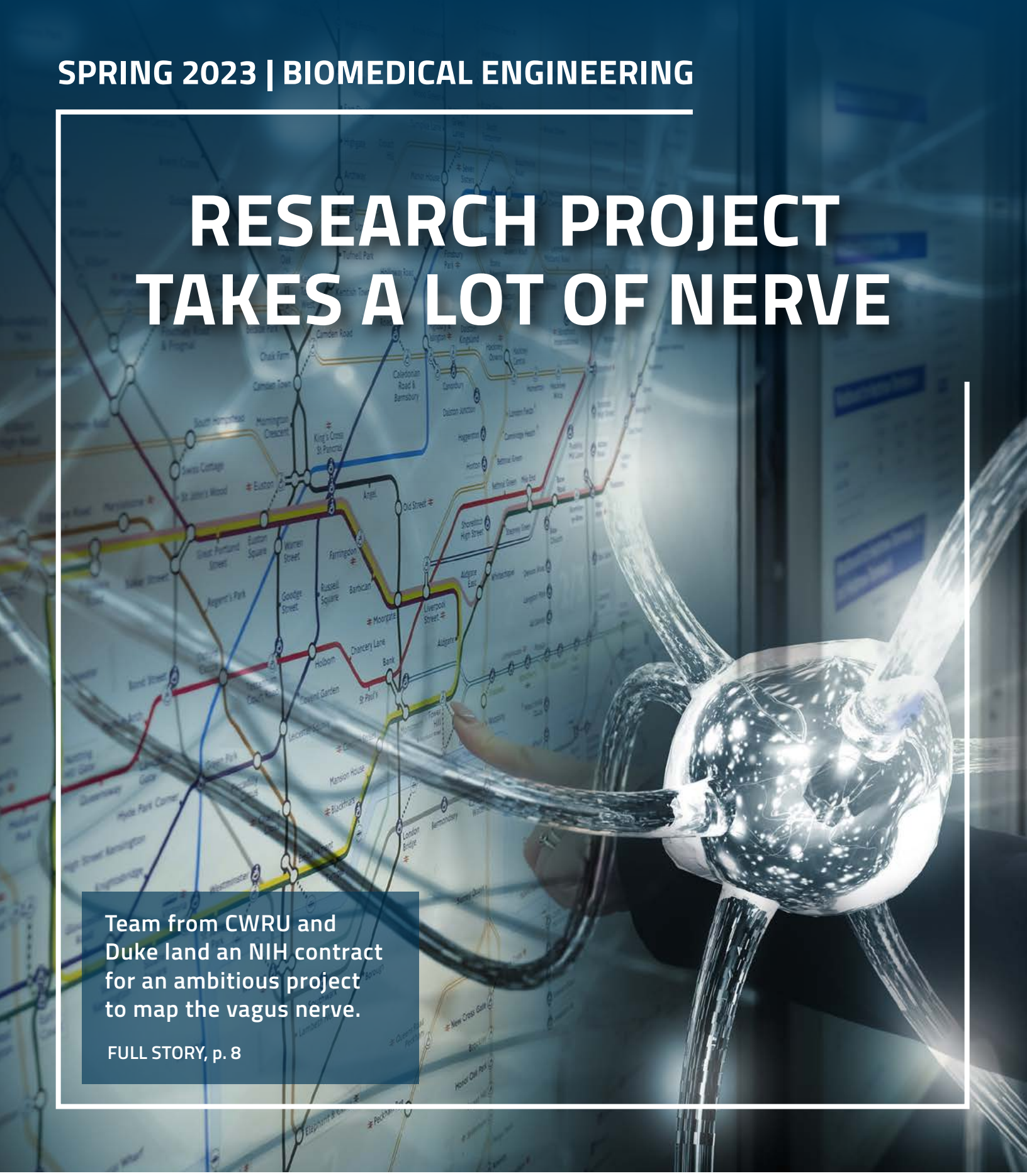
SPRING 2023 | BIOMEDICAL ENGINEERING

RESEARCH PROJECT TAKES A LOT OF NERVE



Team from CWRU and Duke land an NIH contract for an ambitious project to map the vagus nerve.

FULL STORY, p. 8

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Biomedical Engineering Alliance

Cleveland Clinic

IN THIS ISSUE

The Biomedical Engineering Alliance at Case Western Reserve University and Cleveland Clinic

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The Spring 2023 Newsletter has been created by the BME Alliance Publicity Committee.

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A core mission of the Biomedical Engineering Alliance between Case Western Reserve University and Cleveland Clinic is to provide cutting-edge research opportunities and hands-on translational research experiences. Our success in achieving that mission is on display in this issue of the departmental newsletter.

Two feature articles highlight NIH grants totaling more than $23 million awarded to staff from the Department of Biomedical Engineering. Assistant Professor Andrew Shoffstall and colleagues from Duke University landed a $15.75 million contract to map the fibers from the vagus nerve to their target organs, which could ultimately lead to better designed devices and procedures to regulate the nerve's pathways. A team of researchers at Case Western Reserve University and Cleveland Clinic, led by Michael Jenkins, associate professor of biomedical engineering, received a $7.3 million grant to identify new technology, methods and models to study the impact of inflammation and pain on eye health.

Both projects point to the multidisciplinary, collaborative nature of research within the Biomedical Engineering Alliance. They are at the intersection of neural engineering, imaging, biomechanics and artificial intelligence and require close partnerships among researchers and clinicians. Such collaboration helps pave the way to technology translation, some of which is presented in the article on the 2022 Case-Coulter Translational Research Partnership (CCTRP) Awards.

The CCTRP invests more than $1.3 million annually in direct funding and support services to help research teams from Case Western Reserve and its partner institutions advance products from the laboratory to the marketplace, where they can improve patient care. Nine cutting-edge biomedical technologies were selected for program funding in 2022.

You can learn about other research, publications, presentations and achievements of faculty at both Case Western Reserve University and Cleveland Clinic in the Faculty and Staff Highlights of this newsletter. We'd like to draw your attention to a few that bolster our commitment to research:

- Steve Fening, a professor in the Department of Biomedical Engineering and managing director of the Case-Coulter Translational Research Partnership, was appointed associate vice president for research at Case.
- Xiaojuan Li, a staff scientist in Cleveland Clinic's Lerner Research Institute Department of Biomedical Engineering, was awarded a 5-year grant from the Arthritis Foundation to build the Osteoarthritis Imaging Center at Cleveland Clinic.
- Will Grissom joined Case Western Reserve University as a professor of biomedical engineering. His research team strives to reinvent conventional imaging techniques to maximize their information content and value.
- The Cleveland Clinic Consortium for Pain, founded by Carl Saab from the Lerner Research Institute Department of Biomedical Engineering, received an NIH grant for more than $13 million to study ocular pain and stem cell therapy for chronic pain.

There is so much energy, excitement and activity around biomedical research on the campuses of Case Western Reserve University and Cleveland Clinic. We hope you take the time to read about the work of our staff, researchers and students in this issue. And check back in the fall when we present updates and more ground-breaking projects.

STUDENT SPOTLIGHT

Shruti Raghunathan

Students Awarded AHA Fellowships

Two PhD candidates in the Department of Biomedical Engineering have received fellowships from the American Heart Association. Shruti Raghunathan, a doctoral researcher in the Sen Gupta Laboratory, has been awarded an AHA fellowship for her research project focused on thromboinflammation targeted therapeutics for treating venous thrombosis. Yuran Zhu was awarded a two-year predoctoral fellowship to study glymphatic function changes in post-stroke brain using magnetic resonance fingerprinting methods. "Yuran's application received a score that put her in the top 0.28%, which is a record in my lab," says Xin Lu, F. Alex Nason Professor II of Biomedical Engineering, who mentors Zhu.

Yuran Zhu

Senior Design Teams Win Poster Awards

Two senior design teams from the Department of Biomedical Engineering were recognized for their outstanding poster presentations at Case Western Reserve University's Intersections: SOURCE Poster Session in December. There were more than 185 posters at the multidisciplinary event, which highlights undergraduate research and creative projects in arts and humanities, engineering, life sciences, physical sciences and social sciences. Aaron Rodrigues, Eric Chen, Shifra Narasimhan, Jeremiah Ukwela and Lauren Zukowski won second place in the Engineering and Computer Science category for their project, "Development of an At-Home Electroencephalogram Device." Sonia Kumar, William Austin, Emma Hampson and Yumeng Li earned second place in the Schubert Center competition for child-focused research for their project, "Healthy Baby Monitoring."

George Hoeferlin

Student Wins Three Minute Thesis Competition

George Hoeferlin, a doctoral student in the Department of Biomedical Engineering, won Case Western Reserve University's Three Minute Thesis (3MT™) competition in February. Developed by the University of Queensland and now held at more than 900 institutions, 3MT celebrates the research conducted by graduate students around the world. Hoeferlin presented his thesis on characterizing the connection between the gut microbiome and performance of intracortical microelectrodes in the brain. By manipulating the types of bacteria present in the gut microbiome, Hoeferlin has observed changes to the function of brain implants as well as the immune response surrounding the implant in the brain.

"Outside of papers, it's not often that a graduate student's work gets recognized," says Hoeferlin, who works in the lab of Jeff Capadona, a professor in the Department of Biomedical Engineering. "So the 3MT event meant a lot to me, just to see all of the work that I have put into both preparing for the competition and working toward my research pay off."

Students Help Form New Training Alliance

BME and CBTA Holiday Party 2022

Case Western Reserve University's Biomedical Engineering Graduate Student Association collaborated with the Cleveland Clinic Lerner Trainee Association and Cleveland State University Association of Biomedical and Chemical Engineers to form the Cleveland Biomedical Trainee Alliance (CBTA). The multi-institutional alliance strives to provide meaningful programs, training experiences and networking opportunities for students in the fields of engineering, medicine and science.

60 POTENTIAL PHD CANDIDATES ATTEND OPEN HOUSE

The Department of Biomedical Engineering held an in-person open house February 24 and 25 for potential doctoral students. Following informational webinars about the program and research areas, as well as virtual interviews in January, 60 students from 55 universities traveled to Cleveland for the event. The open house included faculty meet-and-greets, student-run orientations and campus and department tours. Candidates also attended a student-only reception at the Cleveland Botanical Garden.

"Our ability to continue to attract top-notch candidates from around the globe is a testament to our faculty and the outstanding training environment we provide for biomedical engineering students," says Satish Viswanath, assistant professor in the Department of Biomedical Engineering and director of graduate admissions.

Send updates to bme-news@case.edu to be considered for the newsletter, website highlights and social media.

FACULTY & STAFF HIGHLIGHTS

Jay Alberts

Jay Alberts, staff, Lerner Research Institute Department of Biomedical Engineering, was featured in a Nov. 26, 2022, article in the Washington Post entitled, "Parkinson's patients and researchers search for exercise 'prescription.'" He shared insight from his 20-plus years studying the effects of cycling on Parkinson's disease.

Suneel Apte

Suneel Apte, staff, Lerner Research Institute Department of Biomedical Engineering, published two journal articles. He co-authored an article in Cell Chemical Biology entitled, "Visualizing *Staphylococcus aureus* pathogenic membrane modification within the host infection environment by multimodal imaging mass spectrometry." He also co-authored an article in the American Journal of Physiology, Cell Physiology, entitled, "Proteolysis: a key post-translational modification regulating proteoglycans." Timothy Mead, MD, assistant professor in Case Western Reserve University's School of Medicine and a former research associate with the Lerner Research Institute Department of Biomedical Engineering, was also a co-author of the journal article.

Kathleen Derwin

Kathleen Derwin, department vice chair, Lerner Research Institute Department of Biomedical Engineering, was selected as an Orthopaedic Research Society (ORS) Fellow. ORS Fellows demonstrate exemplary service and leadership, substantial achievement, expert knowledge and significant contributions to the ORS, its governance and the field of musculoskeletal research. Derwin is director of the Musculoskeletal Research Center at Cleveland Clinic, which investigates ways to improve healing and long-term outcomes for patients who have had rotator cuff surgery. The lab also studies how the extracellular matrix – the mesh-like substance that provides structure to tissues – might be used to enhance healing after surgery.

Steve Fening

Steve Fening, a professor in the Department of Biomedical Engineering at Case Western Reserve University and managing director of the Case-Coulter Translational Research Partnership, was appointed associate vice president for research at Case. He will focus on driving growth in the university's research enterprise by leveraging partnerships with industry and federal agencies.

"Steve is a proven leader who will help us achieve [CWRU] President Kaler's ambitious goals," says Michael Oakes, senior vice president for research. "His appointment is a key to our university's efforts to substantially accelerate research growth and impact."

Chaitali Ghosh

Chaitali Ghosh, staff scientist, Lerner Research Institute Department of Biomedical Engineering, was selected as a speaker for the 35th International Epilepsy Congress in September 2023 in Dublin, Ireland. Her presentation on BBB receptors and epilepsy will be part of the Neurobiology Symposium entitled, "New frontiers in blood brain barrier regulation and epilepsy."

Ghosh also co-authored a September 2022 article in Frontiers in Neurology entitled, "Genetic and molecular features of seizure-freedom following surgical resections for focal epilepsy: A pilot study."

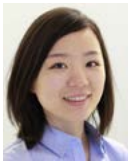
Vinod Labhasetwar

Vinod Labhasetwar, staff, Lerner Research Institute Department of Biomedical Engineering, was elected to the American Institute for Medical and Biological Engineering (AIMBE) College of Fellows. AIMBE Fellows represent the top 2% of medical and biological engineers in academia, industry, education, clinical practice and government. For more than 25 years, Labhasetwar's lab has focused on both basic and translational nanomedicine, with specific interest in cancer imaging and therapy, cardiovascular diseases and neuroprotective treatments for central nervous system injuries.

Xiaojuan Li

Xiaojuan Li, staff, Lerner Research Institute Department of Biomedical Engineering, was awarded a 5-year grant from the Arthritis Foundation to build the Osteoarthritis Imaging Center (OIC) at Cleveland Clinic. The OIC will serve as the imaging coordinating center for multicenter osteoarthritis clinical trials conducted by the Arthritis Foundation Osteoarthritis Clinical Trial Network and will develop a scalable and sustainable image repository to provide osteoarthritis and post-traumatic osteoarthritis images and data for interested researchers.

The first stage of the award is a $2.5 million multi-principal investigator grant between Li and Carl Winalski, MD, from Cleveland Clinic's Department of Diagnostic Radiology, to build the center's infrastructure. They will collaborate with several other physicians from Cleveland Clinic, including Kurt Spindler, MD, from the Department of Orthopaedic Surgery, and Po-Hao Chen, MD, Faysal Altahawi, MD, and Naveen Subhas, MD, from the Department of Diagnostic Radiology.



Dan Ma

Dan Ma, assistant professor in the Department of Biomedical Engineering at Case Western Reserve University, received two grants. The first is a $3 million, 5-year grant from the National Cancer Institute for a magnetic resonance fingerprinting based quantitative imaging and analysis platform (MRF-QIA) for brain tumors. Ma serves as the contact principal investigator. The second is a $1.5 million, 2-year grant from the national funding agency UK Research and Innovation. Ma is co-principal investigator on the project, "Making the invisible visible: A multi-scale imaging approach to detect and characterize cortical pathology."

George Muschler

George Muschler, MD, staff, Lerner Research Institute Department of Biomedical Engineering, was selected as an American Association for the Advancement of Science (AAAS) Fellow. He was recognized for his work as both an orthopaedic surgeon and researcher with lifetime contributions to the biological sciences, primarily encompassing reconstructive surgery, stem cell research, tissue engineering and regenerative medicine. Since 2007, Muschler has served as vice chairman of the Orthopaedic and Rheumatologic Institute at Cleveland Clinic and co-director of the Armed Forces Institute for Regenerative Medicine (AFIRM), which is now an integrated national network of leading scientists and clinicians at 28 other institutions dedicated to developing new methods for treating battlefield injuries sustained by U.S. service members.

Christopher Nguyen

An article by Christopher Nguyen, staff, Lerner Research Institute Department of Biomedical Engineering, entitled, "A soft robotic sleeve mimicking the haemodynamics and biomechanics of left ventricular pressure overload and aortic stenosis" was the cover story of Nature Biomedical Engineering in October 2022.

Ela Plow

Ela Plow, associate staff, Lerner Research Institute Department of Biomedical Engineering, gave a presentation entitled, "Repetitive TMS for stroke motor recovery – challenges and barriers" at the 5th International Brain Stimulation Conference hosted by Elsevier in February in Lisbon, Portugal.

Carl Saab

The Cleveland Clinic Consortium for Pain (C3P), founded by Carl Saab, staff, Lerner Research Institute Department of Biomedical Engineering, and scientific director of C3P, received a $13 million grant from the National Institutes for Health to study ocular pain and stem cell therapy for chronic pain. The project will be led by Michael Jenkins, associate professor of biomedical engineering at Case Western Reserve University, and Jianguo Cheng, MD, professor of anesthesiology and director of the Cleveland Clinic Multidisciplinary Pain Medicine Fellowship Program.

Saab was also interviewed by the Migraine Science Collaborative in an article entitled "Body and Mind, Emotion and Suffering, Consciousness and More: Pain Never Comes in a Pure Form – A Chat with Carl Saab." He discussed the challenges surrounding development of an objective pain diagnostic, the nature of pain and his vision for the future of migraine research and treatment.

Anirban Sen Gupta

A team of researchers at Case Western Reserve University, led by Anirban Sen Gupta, Leonard Case Jr. Professor of Engineering in the Department of Biomedical Engineering, is part of a $46.4 million, 4-year contract award from the Defense Advanced Research Projects Agency (DARPA) to engineer and optimize fully biosynthetic whole blood. The project lead is Allan Doctor, MD, from the University of Maryland School of Medicine. Other Case collaborators include Harihari Baskaran, professor and chair of the Department of Chemical Engineering, and Umut Gurkan, associate professor in the Department of Mechanical and Aerospace Engineering.

In addition, an article co-authored by Sen Gupta on his lab's research outcomes on new generation artificial platelets, "Platelet mimicking procoagulant nanoparticles augment hemostasis in animal models of bleeding," was featured in Science Translational Medicine.

Sen Gupta also joined the American Society for Hematology (ASH) Working Group on Hemostasis and Thrombosis for a two-year term. The working group, which reports directly to the ASH Executive Committee, reviews ASH's current programs and recommends changes or additions that underscore the society's commitment to the hematology community.

BME Welcomes New Faculty

Will Grissom Seeks to Reinvent Imaging Techniques

Will Grissom joined Case Western Reserve University as a professor of biomedical engineering after serving in the same position at Vanderbilt University.

"The Biomedical Engineering Department here is one of the first and most successful in the country, and unique features like the Case-Coulter Translational Research Partnership and integration with Cleveland Clinic make it really stand out as a place you can get purchase on ambitious ideas with clear and established pathways to clinical translation," he says.

Grissom's research team strives to reinvent conventional imaging techniques to maximize their information content and value. The group is currently working in two primary areas:

- **Low-Field MRI** – The team has two NIH grants in this space, one in collaboration with Mark Griswold, a professor in the Case School of Medicine and the Department of Biomedical Engineering. The project integrates advancements in radiofrequency (RF) pulses using novel RF coils with magnetic resonance fingerprinting methods to enable new MRI scanner designs that are flexible, silent and low cost.
- **Neuromodulation Using MR-Guided Focused Ultrasound** – With another two NIH grants in this area in collaboration with colleagues from Vanderbilt, Grissom's team has developed and preclinically validated a system that uses MRI guidance to target an ultrasound focus to interact noninvasively with specific circuits in the brain. It further uses functional MRI to see what effect that ultrasound modulation has on brain function. In the next phase, the team will perform first studies in patients with the goal of creating a tool to treat neuropathic pain without opioids.

Grissom is excited at the opportunities his appointment at Case facilitates in these pursuits.

"Case has arguably the best relationship with Siemens MRI of any university in the U.S., which historically has meant that inventions developed at Case can quickly make it to product," says Grissom. "Case also has a unique MRI research setup and emphasis on translational imaging developments. The research scanners are located in the same space as the clinical scanners, which means it is easy to get patient data right away when testing new ideas."

Christopher Nguyen to Conduct Patient-Focused Research

Christopher Nguyen joined Cleveland Clinic with dual appointments as associate staff and director of the Cardiovascular Innovation Research Center and with the Department of Biomedical Engineering. He previously served in similar positions at Harvard University and the Massachusetts Institute of Technology.

"I came to Cleveland Clinic so that I could leave the lab and have the opportunity to focus on the patient," says Nguyen. "I had this existential quandary: I am building these things, studying these things, but is it helping anyone? I wanted to be in a place where I could break the barrier between the research and the clinical setting – where I can work directly with patients, while conducting patient-focused, translational research."

Nguyen's research interests surround the clinical translation of novel biomedical engineering technologies, including advanced imaging, digital twins, artificial intelligence, soft robotics and 3D printing. His research team spans numerous institutions, institutes and departments, including all levels of scientists and researchers with multidisciplinary specialties that range from computer simulation and medical imaging to molecular work. His group is working in areas such as:

- **Medical Imaging** – Nguyen has developed new cardiac techniques, such as microstructural imaging, which allows researchers to look at the fiber structure and architectures in vivo. This technique will open up a new way of looking at the heart for his research team, simulating the heart and its levels of tissues from a very mechanical point of view. It can be used as a blueprint for 3D printing of new medical devices, among other potential future applications.
- **Metabolism Imaging** – Nguyen and his team are studying ATP, creatine and f-creatine and how they metabolize over time. With this technique, researchers will be able to visualize metabolically driven diseases, which currently have no way to clinically measure. As this novel technology is developed, Nguyen hopes to eventually discover biomarkers that can detect metabolic dysfunction far earlier than is currently possible.

Nguyen is excited for the opportunity to focus less on high-end, lab-centric research and start developing novel technologies for rapid clinical translation.

"The overarching theme and driving passion behind my research, from day one, has been education – its importance and how to ensure the most underserved of our communities have access," he says. "I think about the millions of people who have been touched by the technologies I have studied, collaborated upon and developed over my career, and it's what fuels and drives everything I do."

60 Minutes Features FES Technology Developed by BME Faculty

Advancements in functional electrical stimulation, implanted devices and prosthetics were highlighted in a segment entitled, "Feeling of Feeling" on the March 26, 2023, episode of 60 Minutes. A. Bolu Ajiboye, associate professor of biomedical engineering, and Dustin Tyler, Kent H. Smith Professor II of Engineering at Case Western Reserve University, discussed innovations to restore function and feeling to people with spinal cord injuries and prosthetic limbs.

"Touch is about connection – connection to the world, connection to others and connection to yourself," said Tyler on the program.

Watch full episode here

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Woodside Park
West Finchley
Mill Hill East
Finchley Central
East Finchley
Highgate
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Upper Holloway
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Kentish Town
Camden Road
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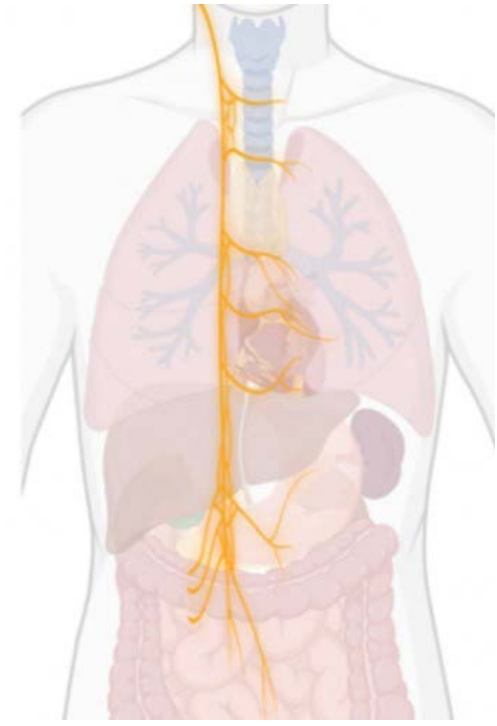
Hackney Central
Homerton
London Fields
Cambridge Heath
Bethnal Green
Shoreditch High Street
Whitechapel
Stepney Green
Mile End
Bow Road
Seven Sisters
Tottenham Hale
Kentish Town West
Gospel Oak

RESEARCH PROJECT TAKES A LOT OF NERVE

Team from CWRU and Duke land an NIH contract for an ambitious project to map the vagus nerve.



Various innervation sites of the vagus nerve in humans. Organs innervated by the vagus nerve include the heart, lungs and gastrointestinal system. Image created with Biorender.

Vagus nerve stimulation (VNS) offers hope for people living with a variety of conditions. It's been FDA-approved to control epilepsy, manage depression and obesity, and aid in stroke rehabilitation. In addition, researchers are studying VNS for many other uses, ranging from blood pressure regulation to rheumatoid arthritis treatment. But there's a snag related to basic understanding of the vagus nerve, the longest of 12 pairs of cranial nerves that innervates many organs.

"It's shocking that our knowledge of the vagus nerve and all its pathways is not 100% known," says Andrew Shoffstall, assistant professor of biomedical engineering at Case Western Reserve University. "There are individual variants among people and potentially new branches of the vagus nerve that don't have names yet, none of which is captured in standard anatomy textbooks."

Shoffstall and colleagues from Duke University landed a three-year, $15.75 million contract from the National Institutes of Health in September 2022 to precisely map the fibers from the vagus nerve to their target organs, which could ultimately lead to better designed devices and procedures to regulate the nerve's pathways.

"If we can provide an atlas of the vagus nerve, then we might be able to create more selective, effective ways to interface with it."

Andrew Shoffstall, assistant professor of biomedical engineering at Case Western Reserve University

"The NIH is contracting us to build an image repository – a subway map of 100 vagus nerves [left and right] from 50 cadaveric donors," says Shoffstall. "That's certainly not an easy task considering no one has done it even one time, let alone 100 times."

An Extension of Earlier Work

The contract builds on a previous NIH SPARC award (Stimulating Peripheral Activity to Relieve Conditions) that supported collaboration among Shoffstall's team and researchers from Duke and the University of Wisconsin to better understand and improve neuromodulatory stimulation treatments.

"The way the electrodes are used right now to treat epilepsy, for example, is by wrapping them around the vagus nerve and stimulating the entire nerve, which can be effective," says Shoffstall. "But when you look at the clinical data, it's a bit of a coin flip – only about half of the patients achieve 50% reduction in seizure frequency."

Under the SPARC award, the researchers experimented with moving cuff electrodes to various spots up and down the vagus nerve, then functionally mapping the responses. The team from Case created micro-CT images of the vagus nerve, the group from Duke used those images to perform computational modeling and researchers from the University of Wisconsin conducted in vivo studies and measured the effects.

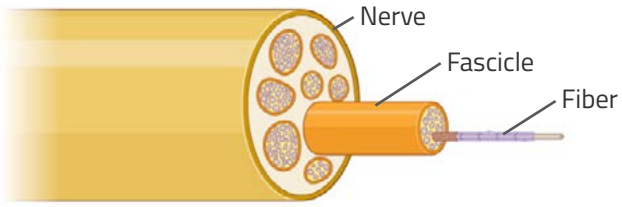
Multiscale Examination of the Nerve

Under the new contract, which is within the SPARC program, the researchers will conduct multiscale imaging of vagus nerves procured from cadavers donated to the Case School of Medicine's Anatomical Gift Program using numerous technologies, including a new technique for 3D microscopy with ultraviolet surface excitation called 3D-MUSE.

The 3D-MUSE imaging microscope was developed under a separate NIH R01 grant by David Wilson, the Robert J. Herbold Professor of biomedical engineering, and Michael Jenkins, associate professor of biomedical engineering, at Case, and Richard Levenson, MD, at the University of California, Davis. The method combines 3D microscopy with an imaging system that serially sections and images the block face of a specimen, providing ultra-high resolution fluorescence volumes across the long length of the vagus nerve.

The complexity of the vagus nerve requires the team to move beyond a zoomed out examination of its topology.

"The vagus nerve is surrounded by the epineurium membrane, then inside that are fascicles, which are groupings of fibers," says Shoffstall. "So, we will be looking at three different scales – the nerve level, fascicle level and fiber level."



Cross sectional view of a peripheral nerve. Image created with Biorender.

It's a monumental undertaking that requires a multidisciplinary team. Representatives from Case Western Reserve University include Jenkins, Wilson and

Ken Gustafson, associate professor, from the Biomedical Engineering Department, as well as members of the Department of Materials Science and Engineering, Departments of Radiology and Anatomy at the School of Medicine and the Cleveland Institute for Computational Biology at CWRU.

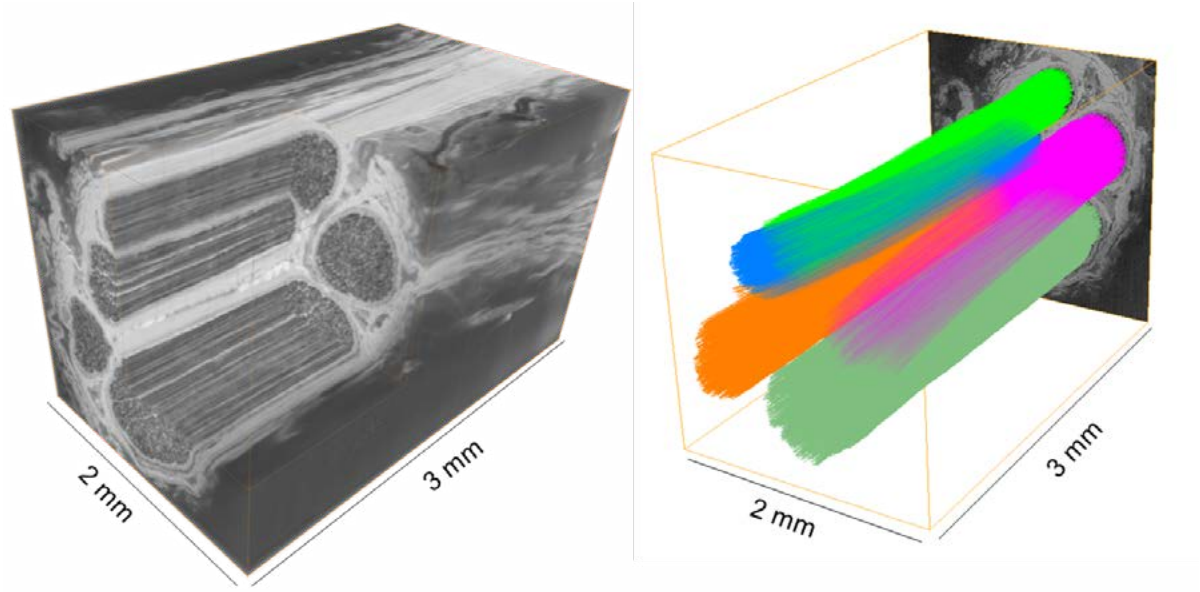
Partner institutions include:

- Duke University – Co-investigator Nikki Pelot, research director in the Grill Lab, and Warren Grill, Edmund T. Pratt, Jr. School Distinguished Professor of Biomedical Engineering
- The University of Wisconsin – Kip Ludwig, co-director of the Wisconsin Institute for Translational Neuroengineering
- The University of Pittsburgh – Curtis Tatsuoka, researcher in the UPMC Hillman Cancer Center
- Louis Stokes Cleveland VA Medical Center – Jeff Capadona, a researcher at the VA and a professor in Biomedical Engineering at Case

Boundless Clinical Potential

The team hopes that performing a comprehensive imaging analysis of the human vagus nerve and creating an image repository for the NIH isn't merely an academic exercise. In time, it could significantly impact clinical care.

"The vagus nerve innervates most of our major organs and controls a lot of functions of the parasympathetic nervous system," says Shoffstall. "If we can provide an atlas of the vagus nerve, then we might be able to create more selective, effective ways to interface with it. And that has the potential to help people with a panoply of conditions, from post-traumatic stress disorder to gastrointestinal disorders and heart failure."

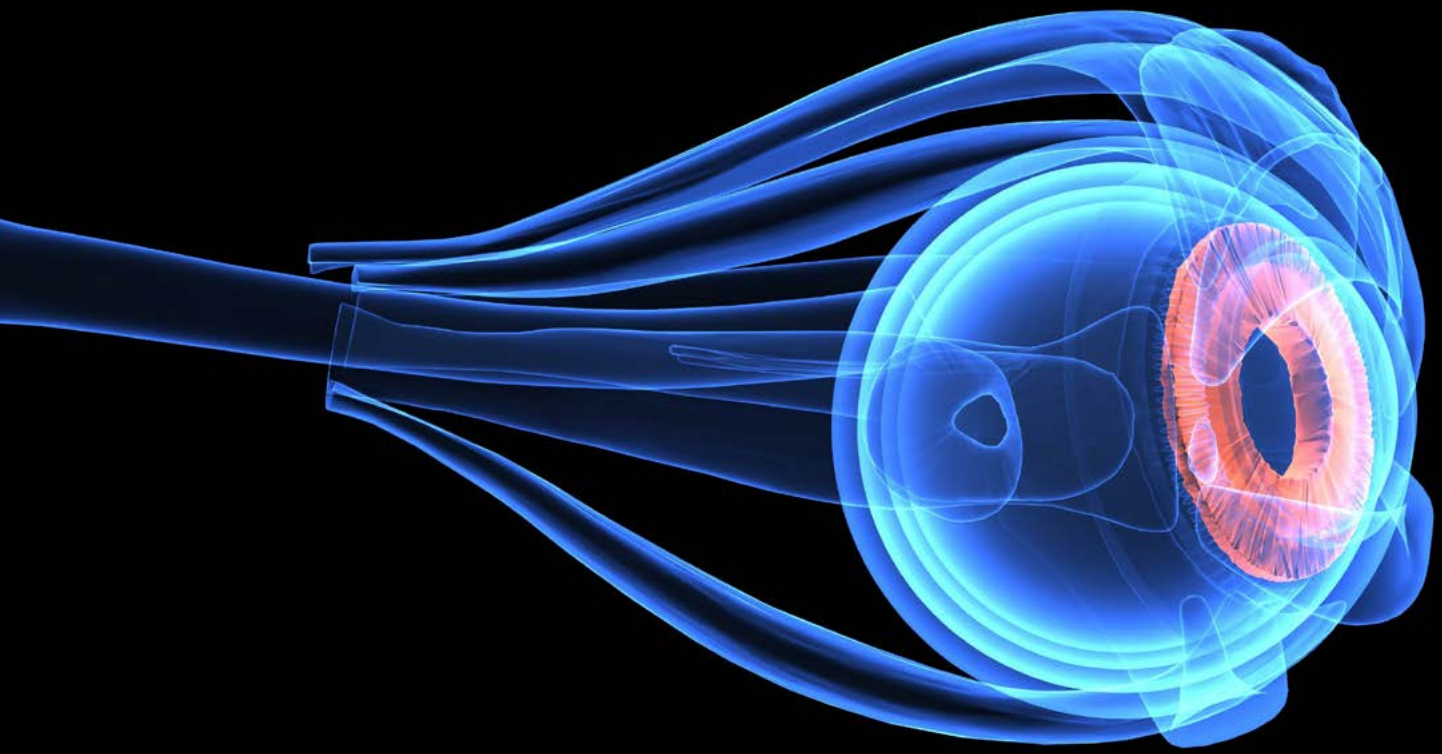


Left: Volume rendering of 3D-MUSE data of a nerve sample, illustrating multiple fascicle bundles and fibers.

Right: Tractography generated from the 3D-MUSE data, where all tracts originating from a specific fascicle bundle are given a unique color.

TEAM SETS ITS SIGHTS ON EYE HEALTH

Researchers and clinicians collaborate on grant to study neural control at the eye's surface.



"We are developing tools to properly assess what's happening within the nervous system."

— *Michael Jenkins, associate professor of biomedical engineering at Case Western Reserve University*

Eye pain is associated with a host of conditions, ranging from corneal ulcers to dry-eye disease. However, despite its high prevalence, eye pain isn't well understood. A team of researchers at Case Western Reserve University led by Michael Jenkins, associate professor of biomedical engineering, hopes to change this.

Last October, the National Institutes of Health (NIH) awarded Jenkins and his associates at Case and Cleveland Clinic a five-year, $7.3 million grant to develop and apply new technology, methods and models to study the impact of inflammation and pain on eye health. The team's goal is to unravel how the nervous system maintains eye health.

"The cornea is the most densely innervated tissue in the body, and it's tied to a lot of diseases, including dry-eye disease, diabetes and more. However, we have a poor understanding of how structural and functional integrity is maintained at the eye surface," says Jenkins, who also serves as the Dr. Donald and Ruth Weber Goodman Professor of Innovative Cardiovascular Research at the School of Medicine. "Understanding neural control at the eye's surface is a critical step to developing better treatments for many diseases."

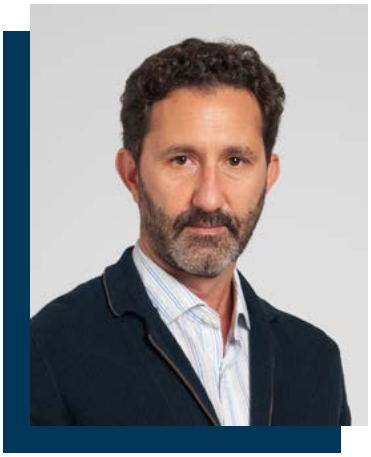
Making the Move into Eye Health

Jenkins' interest and move into eye health was serendipitous. One of the focal points of his lab is the development and application of novel neuromodulation tools and techniques for investigating diseases of the peripheral nervous system. Several years ago, Matt McPheeters, a student in the lab who was struggling to image vagus nerve activity, discussed the project with Brecken Blackburn, a friend in another lab studying corneal biomechanics.

"Imaging peripheral nerve activity is challenging because peripheral nerves scatter light significantly, which degrades the signal. But the cornea is fairly transparent," says Jenkins. "So, the two students thought, 'Maybe we should see what we can do together?'"

Researchers in the Jenkins Lab landed an R21 Exploratory/Developmental Grant from the NIH to develop technology to image calcium signals in the corneal nerves. That has since snowballed into a multidisciplinary effort among researchers and clinicians with expertise in advanced 3D microscopy, pain, immunology, neuroscience, machine learning and more.

Colleagues from the Case School of Medicine working alongside Jenkins on the latest NIH grant include Marcin Golczak, associate professor in the Department of Pharmacology; Patricia Taylor, assistant professor in the Department of Ophthalmology and Visual Sciences; and David Wilson, professor in the Department of Radiology with a dual appointment as the Robert J. Herbold Professor of Biomedical Engineering. Collaborators from Cleveland Clinic include B.J. Dupps, MD, and Rony Sayegh, MD, from the Department of Ophthalmology and Carl Saab, staff scientist in the Lerner Research Institute Department of Biomedical Engineering.



"Synergy allows a creative process of discovery."

— *Carl Saab, staff scientist in the Lerner Research Institute Department of Biomedical Engineering and director of the Pain Science Technology And Research (STAR) Lab*

"The less we know about a healthcare condition, the more we need to work collaboratively with a multidisciplinary team so we can start wide and hone in closer on the pathology and mechanisms," says Saab, director of the Pain Science Technology And Research (STAR) Lab. "This is the case for the little understood condition of eye pain, where a team with very focused expertise working alone might miss the obvious when starting a project of this magnitude."

Taking On a Multipronged Investigation

Saab adds that "synergy allows a creative process of discovery." Synergy will certainly be required to achieve the NIH's goal of better understanding neural control of the ocular surface.

The eye controls blinking, tearing and maintenance of the corneal surface, among other things, in response to sensory feedback from the corneal nerves. This chain can be disrupted by damage to corneal nerves, which can further deteriorate eye function and lead to additional degradation of the nerves in a "feed-forward loop," says Jenkins.

The research team's investigation will be three-fold:

- Map the structure, molecular expression and function of the corneal nerves and supporting cells.
- Investigate how corneal signaling at the eye's surface is linked to signaling in the brain's pain centers.
- Investigate eye surface control under different inflammatory and pain conditions, such as dry-eye disease, diabetes and bacterial keratitis, to better understand how treatment options affect the eye surface control system.

The work requires numerous tools, some of which already exist and others that the team is building. For example, researchers in the Jenkins Lab have developed a method for imaging calcium signaling that can be used as a surrogate to indicate when action potentials are firing on the corneal surface to better understand neural activity. Calcium reporting will be combined with a mouse model of a pain detection assay developed by Saab's team that enables investigations into single cell, neural dynamics underlying pain processing in the central nervous system of awake animals.

"We developed a model, in collaboration with colleagues at Brown University, where the mouse is trained to lick from a waterspout only in response to a sensory stimulus, so that when licking occurs it constitutes an unbiased self-report akin to the human condition," says Saab. "This model is fully automated and uses advanced analytics as well as optogenetic, cell-specific sensory stimuli."

Advanced Tools Are Key Component

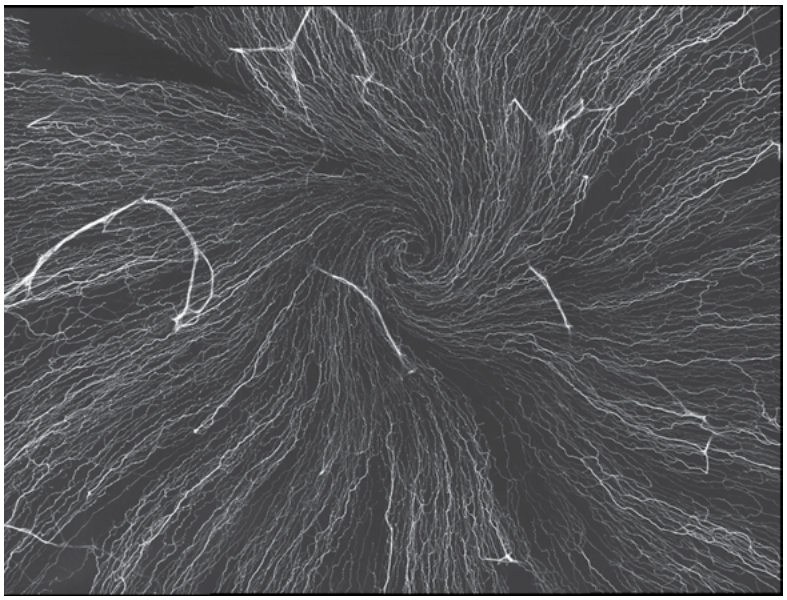
While the NIH grant supports basic research related to neural control at the eye's surface, the project could ultimately benefit patients.

"We hope to map neural circuits of pain in the eye so we can better understand healthy and pathologic conditions and hopefully develop new therapies," says Saab.

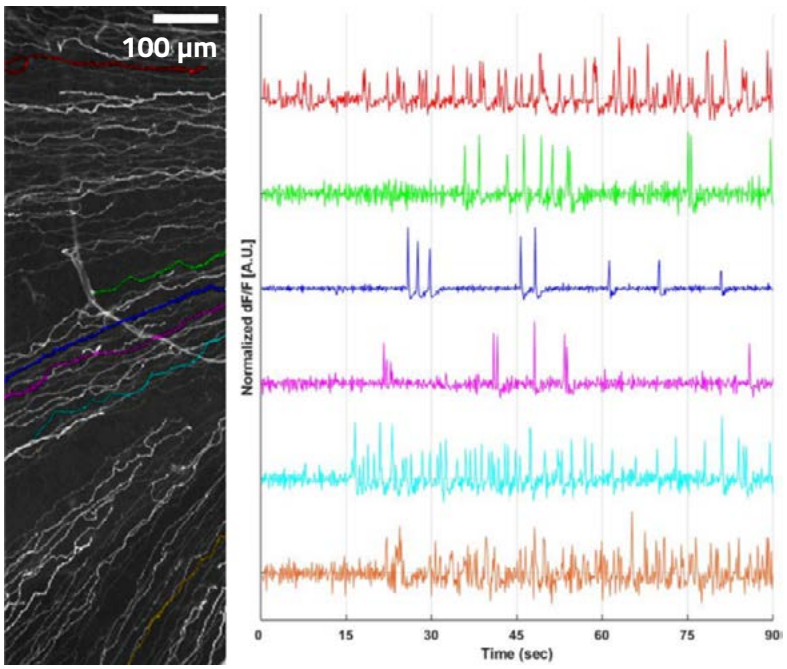
And the technologies developed by the multidisciplinary team – from advanced 3D microscopy to pain assessment tools and animal models – are key to translation from the lab to clinical settings.

"People are looking at therapies such as nerve growth factor even though they don't exactly know what it's doing – they don't have the tools to really understand it," says Jenkins. "We are developing tools to properly assess what's happening within the nervous system."

Ki-Soo Jeong, PhD candidate (left), and Bihua Bie, MD, PhD demonstrate the optical stimulation that activates specialized receptors.



Mouse cornea nerves imaged with confocal microscopy. In healthy eyes, the nerves have an impressive organization, forming a "whorl" pattern. These patterns can be disturbed or completely lost in diseased eyes.



Corneal nerve activity. The left panel shows corneal nerves from the subbasal nerve plexus. The right panel shows calcium transients that represent nerve activity from select nerves of the identical color in the left panel. The activity was stimulated with high amounts of potassium. Calcium traces are plotted as the change in fluorescence over the baseline fluorescence (dF/F).

CASE-COULTER TRANSLATIONAL RESEARCH PARTNERSHIP AWARDS

Cutting-edge biomedical technologies receive more than $1.7 million in funding and support.

Case Western Reserve University EST. 1826 | Wallace H. Coulter Foundation
Translational Research Partnership

JobsOhio

The Case-Coulter Translational Research Partnership (CCTRP), with the support of the JobsOhio Cleveland Innovation District, has announced more than $1.7 million in funding and support for biomedical technologies.

Nine projects were selected for full program funding, which ranges from $50,000 to $200,000. Several additional pilot projects have or will be awarded pilot funding by the end of the year. All projects are partnerships between a clinician and a biomedical engineer and are focused on solving areas of unmet healthcare needs.

The 15-year-old CCTRP invests more than $1.3 million annually in direct funding and support services to help research teams from Case Western Reserve and its partner institutions advance products from the laboratory to the marketplace, where they can improve patient care.

Funding focuses on preparing projects for commercialization, such as demonstrating technical feasibility, deciphering the business opportunity and gauging market feasibility and industry interest. Sixty-nine full projects have been supported to date, which has led to 42 licenses, 33 startup companies and delivered 41 technologies to patients. The technologies supported by the program have gone on to receive an additional $547 million of investment, mostly as at-risk capital.

"The Case-Coulter Translational Research Partnership continues to be a cornerstone of our department, filling an essential gap to transition university biomedical technologies from research to products, where they can significantly improve the health of our society," says Robert Kirsch, the Allen H. and Constance T. Ford Professor and chair of the university's Department of Biomedical Engineering.

The Case-Coulter oversight committee reviewed 24 proposals during this cycle. Projects must have the potential to advance to a commercial entity within 12 to 30 months.

"As a group, the quality of the evaluated technologies continues to improve each year, demonstrating the robustness of the biomedical research-based technology pipeline," says Steve Fening, CCTRP managing director. "Even with the infusion of additional capital from JobsOhio, we still had many more proposals that were deserving of inclusion into the program than we were able to accommodate, making the selection process as challenging as ever."

Enteric Conduit for Fistulas or Leaks

Steve Schomisch, Jeffrey Marks

People sometimes develop a pathological connection from their intestine to their abdomen. This complication is incredibly debilitating and costly. Loss of intestinal contents causes dehydration and malnutrition, and digestive fluids cause injury to the skin and muscle. There is currently no way to stop the leak, and wound management is challenging. The team is developing a novel strategy to greatly reduce the leak to help these patients recover faster and reduce the associated costs.

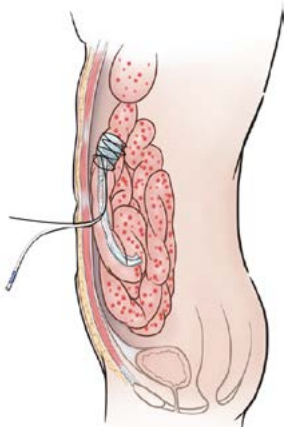


Illustration by Amanda Mendohlsen

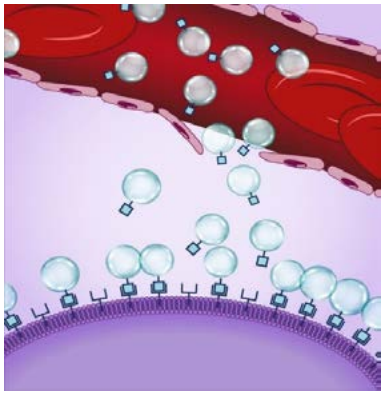


Illustration by Erika Woodrum

Nanobubble Agents as a Therapeutic Technology for Management of Prostate Cancer (TNT)

Agata Exner, David Wald, James Basilion

The team has developed a novel drug-free, low toxicity cancer treatment using nanobubbles (NB) targeted to a biomarker overexpressed on tumor cells. The NBs are injected into the bloodstream and seek out the cancer cells. Once the NBs are inside the cancer cell, a noninvasive exposure to ultrasound (US) results in on-demand collapse of the bubbles, leading to a precise, highly focused disruption of structures inside the cells and target cell death. The approach, which the team calls TNT – targeted nanobubble therapy – destroys only the target cancer cells and not the surrounding healthy cells. Because it does not contain a toxic drug, TNT can treat tumors without any off target side effects.

MRP-14 Antibodies for Treatment of Inflammatory Disease

Yunmei Wang, Xin Yu

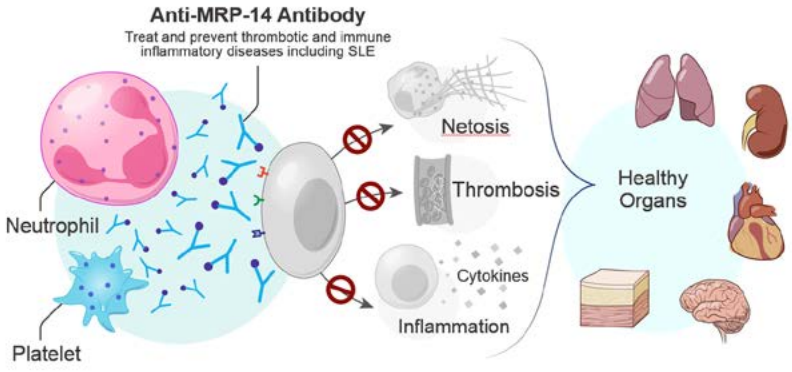


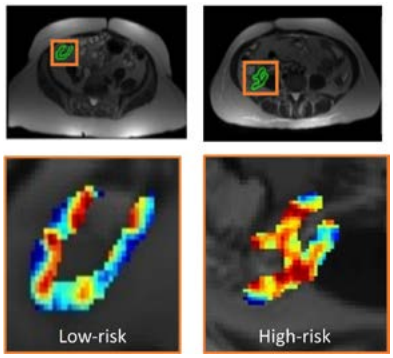
Illustration by Erika Woodrum

Myeloid-related protein 14 (MRP-14, aka S100A9) is a key signaling protein that acts as a potent driver of inflammation. Published and unpublished work from Wang, Yu and others have demonstrated a critical role of MRP-14 in the pathogenesis of several human diseases, including COVID-19, systemic lupus erythematosus (SLE), thrombosis, atherosclerosis, vasculitis, acute lung injury (ALI) and cancer. To target MRP-14-driven diseases, the team has developed and validated novel monoclonal antibodies {mAbs) against human MRP-14, and they are currently working on antibody (Ab) optimization for clinical studies.

Salivary Blocking for RLT

Zhenghong Lee, Norbert Avril, James Basilion

Recent developments of targeted radioligand therapy (RLT) have shown remarkable clinical results for treating patients with late-stage prostate cancer who have already exhausted all approved options. However, the intolerable toxic side effect of treatment-induced dry mouth has prevented RLT from becoming a frontline therapy. The team has identified the mechanism of the side effect through machine learning: the radioligands hit a non-tumor target in the salivary glands to cause dry mouth. They discovered that a small molecule inhibitor can block the target and prevent dry mouth during RLT of prostate cancer.



Images by Prathyush Chirra and Amanda Mendelsohn

EnteroQuant for Crohn's Disease

Satish Viswanath, Florian Rieder

EnteroQuant is a novel computer-based image analysis tool for quantifying subtle details of Crohn's disease on MRI scans to enable clinicians to select the optimal treatment option for patients, toward minimizing nonbeneficial medication and improving patient outcomes.

PReVent for Rectal Cancers

Satish Viswanath, Sharon Stein

PReVent is a novel computerized assay which uses routine MRIs to indicate presence of residual cancer after treatment to assist clinicians in identifying which patients with rectal cancer can be actively followed while avoiding surgery and which will need immediate surgery to ensure optimal survival.

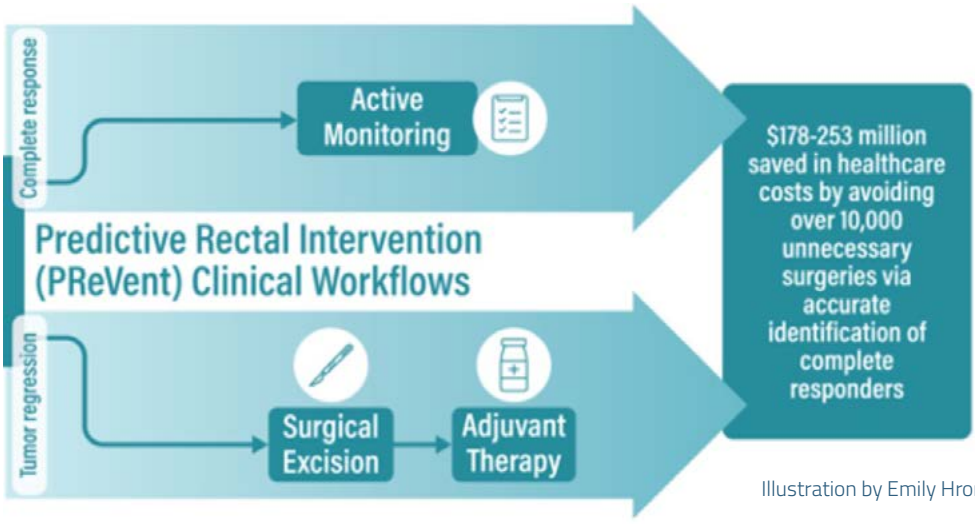


Illustration by Emily Hromi

Non-Contact Sensing During Sleep

Kenneth Loparo, Reena Mehra

Loparo and Mehra developed a non-contact device that does not disturb patients and monitors important vitals and sleep to assist with in-home clinical diagnostics. The prototype device measures heart rate and respiration, and the next step is to determine sleep and wake from the available data.

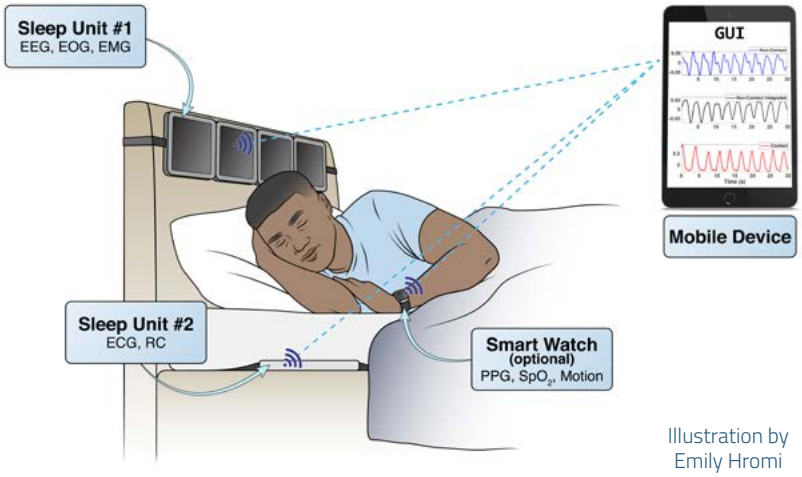


Illustration by Emily Hromi

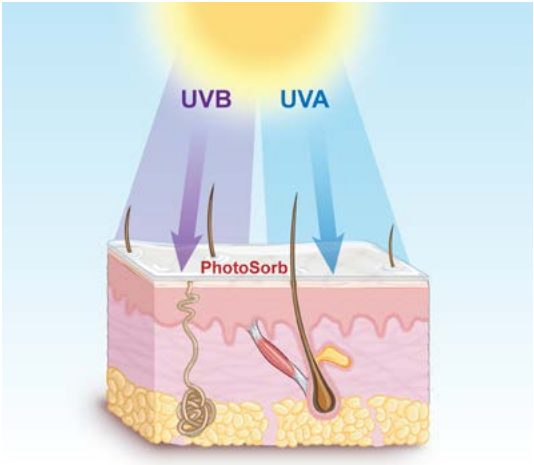


Illustration by Amanda Mendohlsen

PhotoSorb: Novel Sunscreen Active Ingredient

Vijay Krishna, Edward Maytin

Skin cancer is the most prevalent cancer, outnumbering the total number of all other cancers combined in the United States. Current sunscreens are effective for only a short duration, cause photo-allergy and coral bleaching, and have questionable safety, with the FDA removing 12 out 14 active ingredients from the GRAS (generally recognized as safe) list. PhotoSorb is a single, multifunctional sunscreen that can prevent skin cancer and is safe for humans and the environment.

KeyGrip: A Simple System for Hand Grasp

Megan Moynahan, Harry Hoyen, Chong Kim

KeyGrip is a system that provides hand function to paralyzed people and allows them to pick up and use small objects, giving them independence in eating, writing and other activities of daily life. KeyGrip has two to three implantable electrodes that can be placed in an outpatient procedure to activate paralyzed muscles. Activation of the implant is achieved through externally placed components. KeyGrip's design is based on conversations with over two dozen researchers familiar with neuroprosthesis applications for hand grasp and represents an idealized "simplest system" that minimizes tradeoffs and improves the value proposition to hospitals and payers.

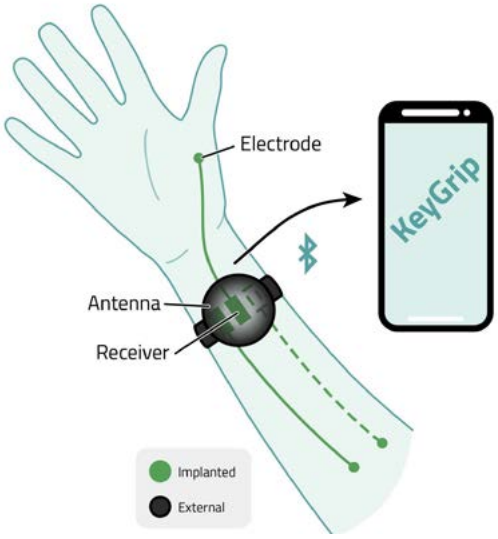


Illustration by Erika Woodrum

CHECKING IN WITH ALUMNI

Ujjal Didar Singh Sekhon

Ujjal Didar Singh Sekhon (GRS '20), who graduated with a PhD from the Sen Gupta Lab, and Dante Disharoon, a postdoctoral fellow at Case Western Reserve University conducting research in the lab, participated in the DARPA Forward symposium held at The Ohio State University on Oct. 4-5, 2022. The symposium was one of six held throughout the U.S. last year to connect DARPA leaders with potential partners, energize innovation ecosystems and fuel breakthroughs in national security. Since graduating from Case, Sekhon has worked as a scientist at Haima Therapeutics LLC, a pre-clinical stage biotechnology company developing platelet-inspired therapeutics to mitigate bleeding and to treat other blood-related disorders where platelets play a key role in their progression.

Send updates to bme-news@case.edu to be featured in the newsletter.

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