FALL 2018 | BIOMEDICAL ENGINEERING

CELEBRATING 50 YEARS

50

OF DISCOVERY

BIOMEDICAL ENGINEERING
CASE WESTERN RESERVE UNIVERSITY

A joint department between the Case School of Engineering
and Case Western Reserve University School of Medicine

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A LOOK INSIDE

Biomedical Engineering
at Case Western Reserve University

50th Anniversary Edition

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THANK YOU
FOR 25 YEARS

Sheryl Dugard

Manager, Academic Administration
Department of Biomedical Engineering
Case Western Reserve University

"Sheryl continues to be a mainstay of the department and a great source of institutional history. She has been a pleasure to work with!"

- Robert F. Kirsch

FROM THE CHAIR

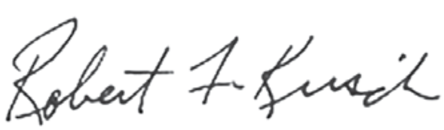
The Department of Biomedical Engineering at Case Western Reserve University turns 50 years old this year! The department was established at the very dawn of the field and worked with other pioneering departments to foster a discipline that now boasts more than 130 programs nationwide. Our biomedical engineering department is unique in that it was founded jointly in the Case School of Engineering and the Case Western Reserve University School of Medicine, and it has evolved into a vibrant department that seamlessly combines the strengths of the two schools (and our medical center affiliates) into a dynamic whole.

Our department has been and continues to be a national leader, setting the standard for education and research. Our faculty make discoveries, translate those breakthroughs into real-life innovations, work with industry and entrepreneurial partners, and train new generations of outstanding biomedical engineers. Our graduates move into increasingly diverse and successful professional careers and become leaders in society. We are proud of our 50 years of accomplishments and of the impact they have left on the world.

The future of the Department of Biomedical Engineering at Case Western Reserve University is also very bright. Faculty research continues to be highly innovative and impactful, and our faculty have secured funding at a record-breaking pace. Likewise, many of our PhD students have been awarded prestigious fellowships to pursue their research projects. Our Case-Coulter Translational Research Partnership propels discoveries into future products and has generated more than $150 million in subsequent industry investments and faculty research grants. Last year, a major gift from long-time supporters, Bob and Brenda Aiken, enabled transformative enhancements of our graduate program and the development of new cutting-edge research programs. At $20 million, it was one of the largest donations in the history of Case Western Reserve University.

We continue to innovate and improve our department. During the summer of 2018, we formed a new bomedical engineering alliance with Cleveland Clinic that will grow our faculty numbers by nearly two-thirds and expand and deepen our research strengths. The biomedical engineering alliance will also provide unique opportunities for research and training of our students, and will contribute to the economic strength of the region.

In closing, I hope that you can sense the excitement and confidence within the Department of Biomedical Engineering at Case Western Reserve University. Our departmental tag line, "Engineering Better Health Since 1968," has never resonated more strongly!



Robert F. Kirsch
Allen H. and Constance T. Ford Professor
Chair of Biomedical Engineering
Case Western Reserve University

FACULTY HIGHLIGHTS

Bolu Ajiboye and Robert Kirsch

Bolu Ajiboye, assistant professor of biomedical engineering, and Robert Kirsch, the Allen H. and Constance T. Ford Professor and Chair of biomedical bngineering, received first place in the 2018 International Annual Brain Computer Interface (BCI) Research Award for their project entitled "Restoring functional reach-to-grasp in a person with chronic tetraplegia using implanted functional electrical stimulation and intracortical brain-computer interfaces."

Zheng-Rong Lu

In collaboration with the Foundation Fighting Blindness and Alzheimer's Drug Discovery Foundation, The Harrington Discovery Institute at University Hospitals announced Zheng-Rong Lu, the M. Frank Rudy and Margaret Domiter Rudy Professor of Biomedical Engineering, is a 2018 Gund-Harrington Scholar for his work in nonviral gene therapy for Stargardt disease, the most common form of inherited juvenile macular degeneration.

The Harrington Discovery Institute, part of the Harrington Project for Discovery & Development, collaborates with the Foundation Fighting Blindness on the Gund-Harrington Award to accelerate therapies for retinal degenerative diseases. It collaborates with the Alzheimer's Drug Discovery Foundation to advance the development of drugs to prevent and treat Alzheimer's disease, according to a news release.

Anant Madabhushi

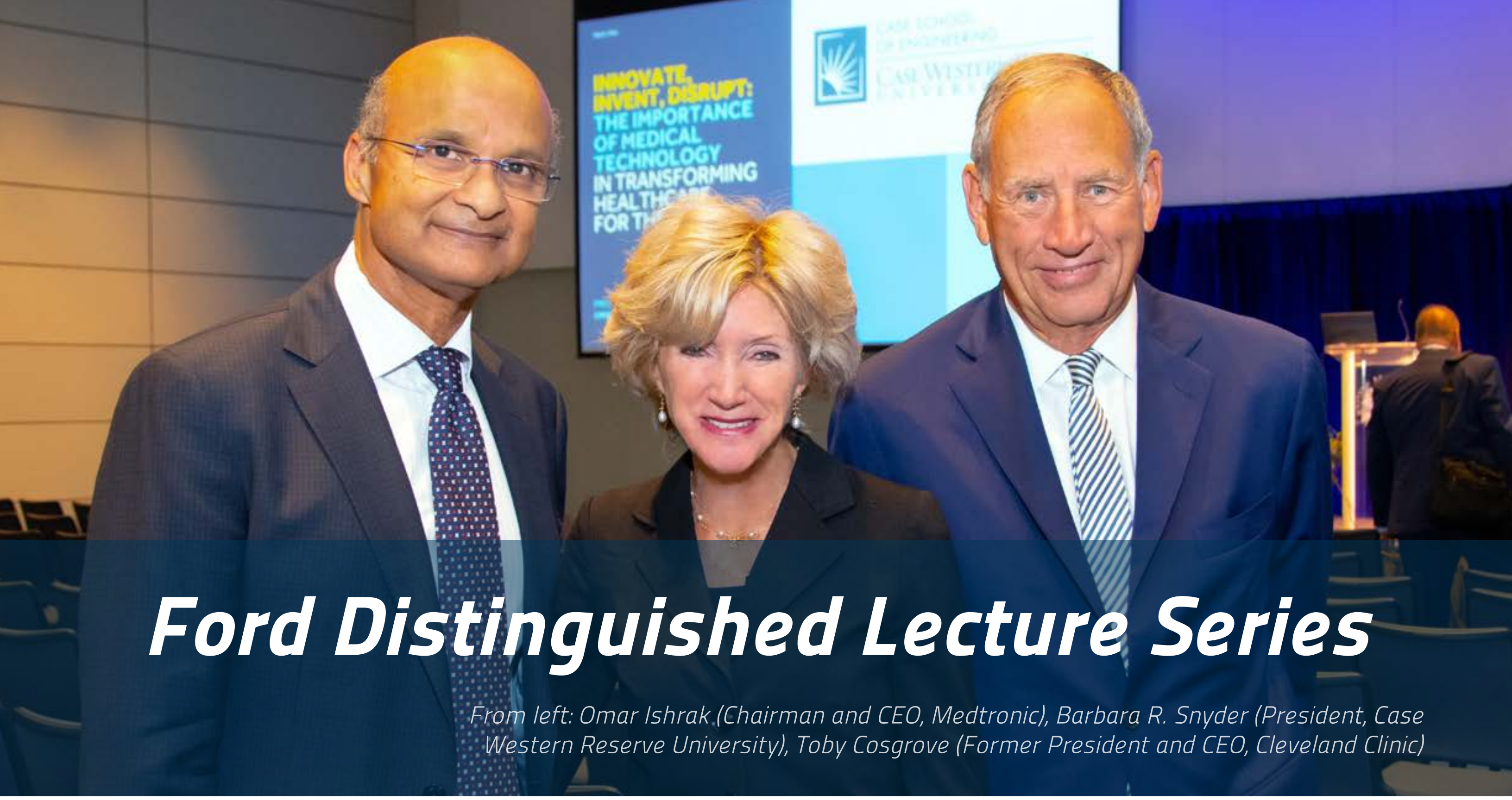
Researchers from the Center for Computational Imaging and Personalized Diagnostics (CCIPD) had 8 patents issued in the first half of 2018. While the patents are on a diverse group of diseases from breast cancer to lung cancer, and include various modalities such as CT scans and tissue slides, their primary focus centers around using sophisticated and novel computerized analytical tools to best predict not only diagnosis of diseases, but also prognosis, prediction of outcome and prediction of response to various treatment paradigms. The CCIPD is led by Director Anant Madabhushi, the F. Alex Nason Professor II of Biomedical Imaging. To date, the center has garnered more than 60 patents issued or pending in the areas of computational imaging, artificial intelligence, and machcine learning applied to radiographic and digital pathology images.

Anirban Sen Gupta

Anirban Sen Gupta, a professor in the Department of Biomedical Engineering, has developed synthetic nanoparticles that can mimic platelets' abilities to clot at the site of a bleeding injury, called SynthoPlate. This technology was recently issued two patents.

Case Western Reserve University and Cleveland-based biotechnology company Haima Therapeutics LLC have signed a two-year option to license the technology and advance it to prevent and treat bleeding complications from trauma, low platelet counts, and surgery. The agreement, managed through the university's Technology Transfer Office, will allow for pre-clinical testing of SynthoPlate. Haima Therapeutics has received two Phase I SBIR grants (from NSF and DoD) to carry out these studies.

Ford Distinguished Lecture Series



From left: Omar Ishrak (Chairman and CEO, Medtronic), Barbara R. Snyder (President, Case Western Reserve University), Toby Cosgrove (Former President and CEO, Cleveland Clinic)

In celebration of the biomedical engineering department's 50th anniversary, the Ford Distinguished Lecture Series featured a talk by Medtronic Chairman and CEO Omar Ishrak, *"Innovate, Invent, Disrupt: The Importance of Medical Technology in Transforming Healthcare for the Future."*

The lecture included remarks from biomedical engineering Professor Emeritus John Thomas Mortimer, who spoke about the history of the school's relationship with Medtronic, the world's leading medical technology company. He explained, "The environment at Case Western Reserve was characterized by a type of collaboration between engineers and physicians where the traditional boundaries have been broken down to an unusual extent." The relationship between the university and Medtronic began in 1966 when Mortimer acquired a radio frequency antenna from a young Medtronic. He went on to describe a collaborative research effort between the two institutions that led to new knowledge on the mechanism of tissue injury.

This continued relationship was illustrated by the next speaker, Medtronic's Chairman and CEO. Ishrak's talk was on the future of the biomedical engineering industry, the future of the healthcare payment model and Medtronic's operations.

Much like Apple and Microsoft, Ishrak said that Medtronic started out of a garage; its original product was the first ever battery-powered pacemaker. Medtronic is currently the largest medical device company in the world and is worth about $30 billion. It has been working toward the mission statement "to alleviate pain, restore health, and extend life" for almost 70 years.

Robert Kirsch, chair of the Department of Biomedical Engineering said, "The event was fantastic; we showed Medtronic a good side of the university, and I think we got to interact a lot with people from Medtronic very effectively as well." He reflected on how the biomedical engineering department has evolved over 50 years: "We started off with a pretty tight focus on just stimulation devices with a handful of faculty, and now we have 30 faculty at the university and about another 20 at the Cleveland Clinic."

Moving from the past to the future, Ishrak also spoke about the future of biomedical engineering at large. He said, "It's got a long runway, it's got unlimited problems to solve and it can make a real difference in patients' lives, and it can contribute to creating economic benefit as well by having more healthy people."

Despite a packed schedule, Ishrak specifically wanted to speak at Case Western Reserve to showcase his company's technology with hopes of inspiring future engineers to pursue a career with Medtronic. More importantly, he wanted to showcase the ways which Medtronic is leveraging expertise from all fields to create new therapies to benefit patients around the world.

The Ford Lecture was endowed by Allen H. Ford and his late wife, Constance.

CELEBRATING GRADUATE STUDENT FELLOWSHIPS

Jacob Antunes

National Cancer Institute
F31 Predoctoral Fellowship
"Rad-path-omic tools for rectal cancer treatment evaluation"
Mentors: Satish Viswanath, Anant Madabhushi

This project will develop novel computational imaging tools for accurate identification and assessment of pathologic complete response to neoadjuvant chemoradiation (NAC) via routine multiparametric MRI in rectal cancers.

Nathanial Braman

National Cancer Institute
F31 Predoctoral Fellowship
"Radiogenomic tools for prediction of breast cancer neo-adjuvant chemotherapy response from pre-treatment MRI"
Mentor: Anant Madabhushi

Braman plans to develop radiogenomic tools for pre-treatment prediction of response to neoadjuvant chemotherapy to enable the non-invasive guidance of therapeutic approach without requiring an initial treatment period in breast cancers.

Peter Bielecki

National Science Foundation
Graduate Research Fellowship
"Immune-stimulant nanoparticles as a potent therapy to combat tumor immunosuppression"
Mentor: Efstathios Karathanasis

This project aims to use nanoparticles to deliver immune agents directly to the tumor site. This treatment may more effectively overcome the suppressive microenvironment that keeps tumors hidden from local and systemic immuno-surveillance in order to shift immunity towards an anti-tumor response.

Erika Cyphert

U.S. Department of State and the J. William Fulbright Foreign Scholarship Board
Fulbright Fellowship
"Drug delivery spacer for treatment of large bone defects in bone cancer patients"
Mentor: Horst von Recum

Cyphert will conduct research at Warsaw University of Technology as part of a project to develop a dual antibiotic/chemotherapeutic drug delivery spacer. This spacer will be used in a two-part therapeutic and regenerative system for the treatment of bone cancer.

Elizabeth Heald

Craig H. Neilsen Foundation
SCI Research on the Translational Spectrum
"Training of activity of muscles below the injury level in complete SCI for neuroprosthetic control"
Mentor: Hunter Peckham

This project will explore the use of an intensive biofeedback training paradigm for human subjects with spinal cord injury with the goal of significantly improving the myoelectric signal response from below-injury muscles that show evidence of weak volitional control.

Shuying Huang

National Science Foundation
Graduate Research Fellowship
"Parallel transmission (PTx) hardware development in magnetic resonance imaging (MRI)"
Mentor: Mark Griswold

The purpose of this project is to develop digitally controlled, compact, high efficiency on coil transmit chain in MRI with real-time feedback. This would allow implementation of high-density PTx coil arrays with individual transmit elements which will mitigate transmit in-homogeneity and other dynamic errors.

Patrick Leo

National Science Foundation
Graduate Research Fellowship
"Population-specific machine learning models for high-accuracy, low-cost prostate cancer biochemical recurrence prediction: Precision medicine for minority populations"
Mentor: Anant Madabhushi

The project proposes to develop a technology to predict a patient's biochemical recurrence risk of prostate cancer immediately after surgery based on computerized analysis of the prostate tissue.

Brooke Odle

National Science Foundation
Craig H. Neilsen Postdoctoral Fellowship
"Novel control systems to auto-regulate standing balance after SCI"
Mentor: Ron Triolo

The purpose of the project is to develop and implement new control systems to automatically regulate standing balance after spinal cord injury with neuroprostheses utilizing functional neuromuscular stimulation.

Anisha Rostagi

National Institute of General Medical Sciences
F30 Predoctoral National Research Service Award
"Evaluating neural force modulation and force-controlled intracortical brain-computer interfaces"
Mentor: Robert Kirsch

This project aims to investigate force-related information from the brain as a potential control signal for a brain-computer interface (BCI) system. The end result of this work will move the technology toward enabling patients with tetraplegia to interact with and grasp objects, thus increasing their independence and quality of life.

Kathleen Young

American Heart Association
Predoctoral Fellowship
"Drug-refillable stent coatings for use in preventing restenosis"
Mentor: Horst von Recum

This project proposes to develop a biocompatible cyclodextrin polymer drug-eluting stent coating to provide sustained drug delivery via drug refilling doses that can both prevent and treat restenosis, without removal of the initial stent implant.

Dhruv Seshadri

2018 Grenoble Innovation for Advanced New Technologies Summer Fellowship
"Wearable Electroceutics Target the Skin Microcirculation for Wound Healing"
Mentor: Colin Drummond

Seshadri's work on bioelectronics to study microcirculation for wound healing with Jean-Luc Crakowski, Matthieu Roustit, a team at the Centre Universitaire Hospitalier and researchers at CEA-Leti in Grenoble, France, has continued upon his return to Case Western Reserve University. Seshadri is teaming with Christian Zorman in the department of electrical engineering and computer science and Kath Bogie at the Louis Stokes Cleveland VA Medical Center to focus on wearable devices.

STUDENTS ON T32 FELLOWSHIPS

PI: Robert Kirsch
Nabeel Chowdhury
Nicholas Couturier
Douglas Crowder
Christopher Delianides
Paul Gloth
Youjoung Kim
Platon Lukyanenko
Leah Roldan

PI: David Wilson
James Ahad
Jacob Antunes
Prathyush Chirra
Andrew Dupuis
Robert Halliday
Morgan Lorkowski

PI: Eben Alsberg
Felicia He

PI: Andrew Rollins
Brecken Blackburn

PI: Anirban Sen Gupta
Michelle Cruz

AIKEN FELLOWSHIP RECIPIENTS

Sarah Carney
Andrew Dupuis
Yuning Gu
Tyler Johnson
Mohammadhadi Khorammi
Patrick Leo
Emily Mugler
Sid Nanda
Ruchika Verma
Lu Wang
Hao Wu
Kathleen Young

POSTDOCTORAL TRAINING GRANTS

Catherine Jayapandian

Center for Computational Imaging and Personalized Diagnostics at Case Western Reserve University and the Cleveland Clinic

NIH NIDDK Ruth L. Kirschstein NRSA

"Establishing innovative computational and data science analytics approaches for multi-centric evaluation and risk stratification of nephrotic syndrome study network"

PI: Anant Madabhushi

Jayapandian is involved in developing novel imaging approaches to facilitate a more thorough quantitative interrogation of renal parenchyma than previously possible, as decision support to pathologists and nephrologists for better risk assessment. The ability of these tools to identify complex visual and sub-visual image features associated with normal and pathologic kidney structures from tissue images may enable discovery of prognostic biomarkers.

Stephan Nieuwoudt

Cardiovascular Research Institute of Case Western Reserve University

NIH T32 Cardiovascular Research Training Program

"Establishing the central roles of extracellular matrix and soluble factor release in models of diabetic cardiomypathy and exercise therapy"

PI: Sam Senyo

The primary research objective under this training grant is to identify novel cellular mechanisms that impart the benefit of exercise in diabetic cardiomyopathy, which the Senyo Lab presumes to occur via Extracellular Matrix remodeling and cell-cell communication within the myocardium. In vitro, alongside engineered microfluidic platforms, and pre-clincal models will be used to investigate potential mechanisms with the help of resources and guidance from the Cardiovascular Research Institute and its member labs.

Nathan Rohner

Digestive Health and Research Institute of Case Western Reserve University and the Cleveland Clinic

NIH T32 Postdoctoral Training Grant

"Research of polymer synthesis and characterization to deliver therapeutics in treatment of pre-cancerous esophageal lesions"

PI: Horst von Recum

The project researches polymer synthesis for long-term therapeutic esophageal drug delivery. It will be developing and validating alternative methods for treating esophageal cancer and fibrosis. Through the use of their local, affinity-based delivery technology, previously ineffective or systemically toxic drugs will be re-purposed to combat difficult to treat fibrotic and precancerous conditions of the digestive system.

Rui Tang

Cardiovascular Research Training Program

NIH T32 Postdoctoral Training Grant

"Three-dimensional, self-assembled tissue regeneration with exogenous stimuli-free vascularization"

PI: Eben Alsberg

Rui Tang is working on construction of three dimensional microenvironments with controlled cell-cell and cell-matrix interactions for regulating and enhancing vasculogenesis, chondrogenesis and stem cell maintenance. He and his advisor filed two provisional patents on this work in 2018.

Emily Graczyk

DARPA Riser

PI: Dustin Tyler

Emily Graczyk, who earned a PhD in biomedical engineering from Case Western Reserve University in May, was one of 50 early-career engineers and scientists chosen as a Defense Advanced Research Projects Agency (DARPA) Riser. Graczyk and the others were identified by DARPA Program Managers as possible future superstars with expertise that could be important to national security and presented posters on their research to a panel at D60, DARPA's 60th anniversary symposium in September.

Among that distinguished group, Graczyk was one of only three chosen to present her work to more than 1,900 D60 symposium attendees at the DARPA Riser Plenary Session. The title of her talk was "Electrical activation of the nervous system to investigate and augment sensory perception." She shared research conducted in Case Western Reserve's Functional Neural Interface Lab on restoring natural sensation to upper limb amputees with prosthetics.

"I was very honored to present to the entire assembly," says Graczyk, a research associate in the Department of Biomedical Engineering. "Spreading the word about our research can not only further our work, but also inform people about what's possible with sensory feedback. That will start the wheels turning and get people excited about the technology and what we can do in the future."

Since earning her doctorate, Graczyk has expanded the scope of her research to examine the modality and types of sensation elicited by electrical stimulation. She also is working on a pain study utilizing electrical stimulation with Jonathan Miller, director of the Functional and Restorative Neurosurgery Center at University Hospitals Cleveland Medical Center.

"Spreading the word about our research can not only further our work, but also inform people about what's possible with sensory feedback. That will start the wheels turning and get people excited about the technology and what we can do in the future."

— Emily Graczyk

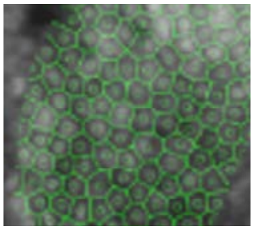
Capitalizing on Opportunities in Medical Imaging

Researchers in the Biomedical Imaging Laboratory are developing innovative technologies across disease areas.

It's been a banner year for David Wilson, the Robert J. Herbold Professor of Biomedical Engineering at Case Western Reserve University, and his colleagues in the Biomedical Imaging Laboratory. So far in 2018, Wilson has obtained five grants totaling more than $5 million for his work on computational biomedical imaging and microscopy.

"My success hinges on the great ability at Case to work with collaborators. So many different opportunities present themselves just by walking the halls here," says Wilson. "There are some biomedical engineering departments that are relatively isolated from medical schools and hospitals. Our proximity to the School of Medicine and world-renowned hospitals makes us unique."

Partnering with clinicians and biomedical researchers, Wilson and his team have created computational tools for image segmentation, registration and quantitative analysis. They also conduct work in 3-D visualization, machine learning and imaging physics. One of their greatest successes is development of a cryo-imaging system that serially sections and images the block face of a frozen specimen, providing ultra-high resolution RGB and fluorescence volumes. The system, which is now being commercialized by the startup company BioInVision, allows preclinical researchers to view unparalleled levels of detail – down to an individual cell.

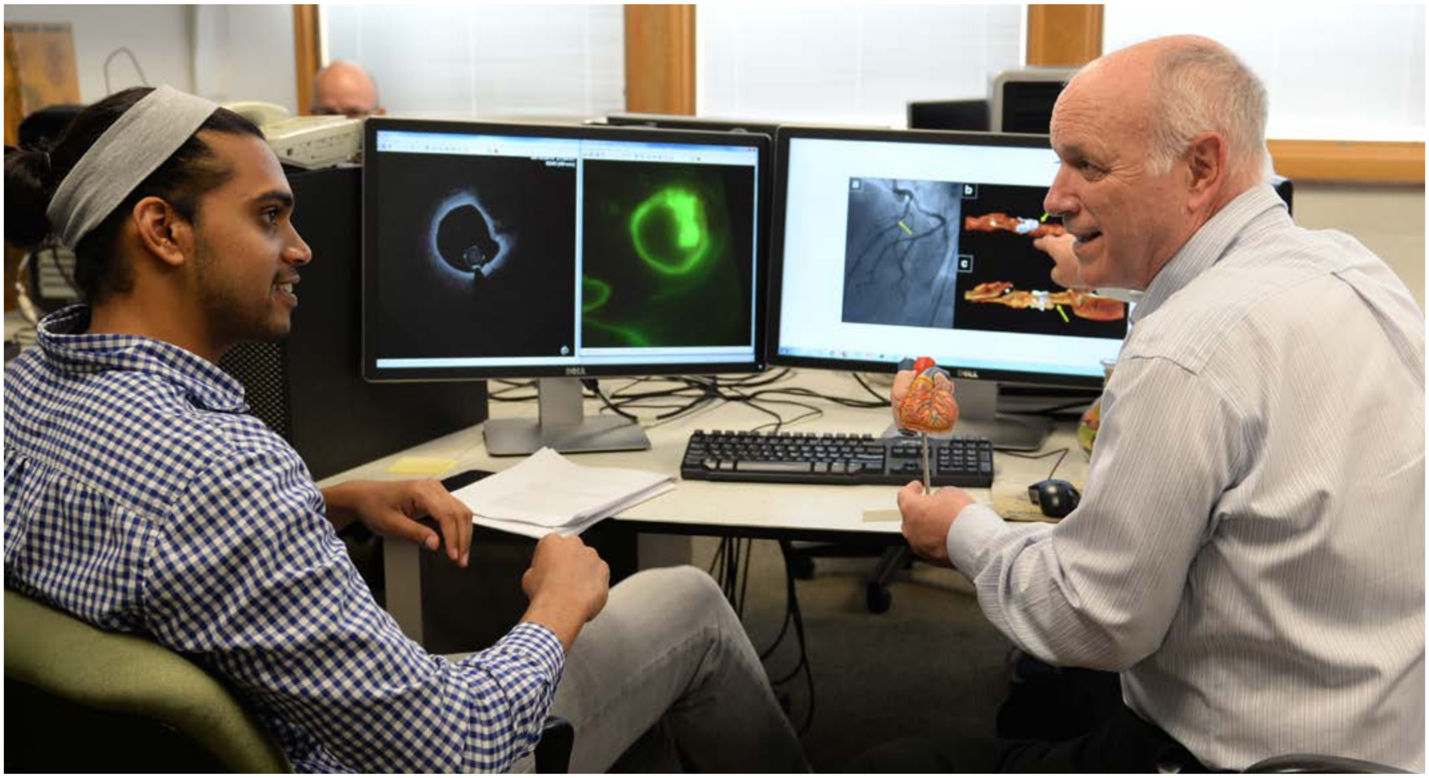


This year's grants will allow the Biomedical Imaging Laboratory to advance projects in three different disease areas – cardiovascular, cancer and ophthalmological conditions – as well as a new 3-D microscopy technique. "Some bioengineers focus on one disease. I've opted to focus on the technology – the software and instrumentation side," says Wilson. "As a result, I'm not married to one application versus another. Instead, I look for opportunities."

Opportunities certainly abound for the Biomedical Imaging Laboratory.

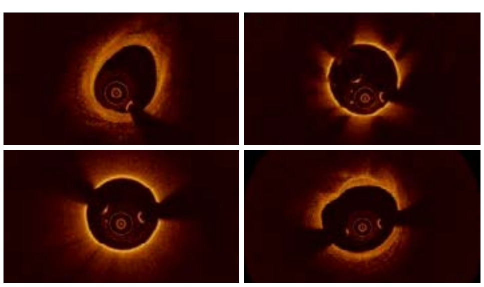
Developments in Cardiovascular Imaging

Wilson is the principal investigator on two new grants in the cardiovascular field. The first, an R01 award from the National Institutes of Health (NIH), focuses on computer-assisted coronary artery stent intervention



David Prabhu, left, discusses cardiac images with David Wilson in the Biomedical Imaging Laboratory.

planning. The team utilizes optical coherence tomography (OCT) during catheterization. "You insert the catheter, with the imaging device on the tip, through the vasculature to obtain microscopic images inside the coronary arteries," says Wilson. "There is no way you can do this from outside the body with this kind of resolution."



Wilson and students in his lab have developed methods for identifying the types of atherosclerotic plaque in blood vessels using deep learning techniques. "Recently, we have focused on calcified plaque because cardiologists cannot readily apply stents if there is a lot of calcium," says Wilson. The technology created by the Biomedical Imaging Laboratory will allow clinicians to locate calcifications and decide where to place stents or adopt a plaque modification approach.

"Our proximity to the School of Medicine and world-renowned hospitals makes us unique."

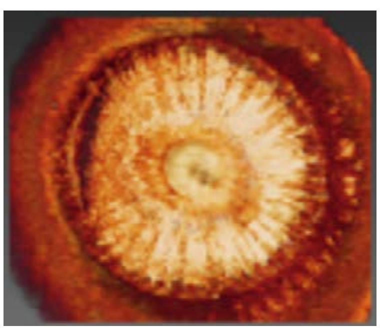
— David Wilson

"With this grant, we're going to be doing a lot of biomechanical experiments and imaging," says Wilson. "We have a great team aimed at trying to understand how best to deploy stents in the presence of calcifications." Among those working with Wilson is Hiram Bezerra, associate professor of medicine in the Case Western Reserve University School of Medicine.

Wilson's second award related to cardiovascular research is an NIH Small Business Innovation Research (SBIR) grant with BioInVision, where he serves as chief technology officer. The team will use computed tomography (CT) perfusion imaging, parameter estimation and deep learning to examine blood flow in the myocardium, a procedure that has traditionally been done with positron emission tomography (PET) or single proton emission computed technology (SPECT) nuclear imaging.

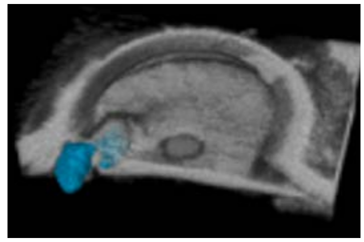
There are several advantages to using CT, says Wilson. It's more readily available and allows clinicians to do CT angiography to examine the blood vessels. "By adding our CT technology, clinicians can look at the blood vessels to see if there's stenosis and also see if there is blood flowing into a specific region of tissue," he says.

Opportunities in Ophthalmology



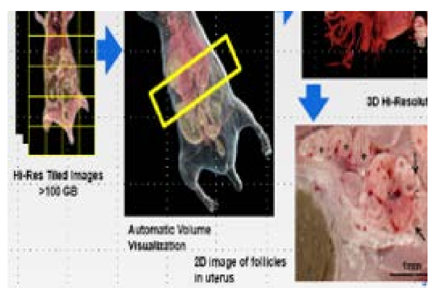
Two years ago, Wilson moved into the ophthalmology space. This year, he was awarded at R21 grant from the NIH to analyze cornea endothelial images using machine learning and determine if the technology can be used to help predict keratoplasty failure. "Corneas are one of the most common tissue implants. If they fail, it's a great expense and increases the chance of blindness in patients," says Wilson. "So the idea is to look at these images and use machine learning to better predict which corneas are at risk and need greater care."

On this project, Wilson is teaming with the Cornea Image Analysis Reading Center (CIARC) at Case Western Reserve University and University Hospitals Cleveland Medical Center. "The CIARC is the premier center in the world for analyzing these images, so it's a perfect match," he says.



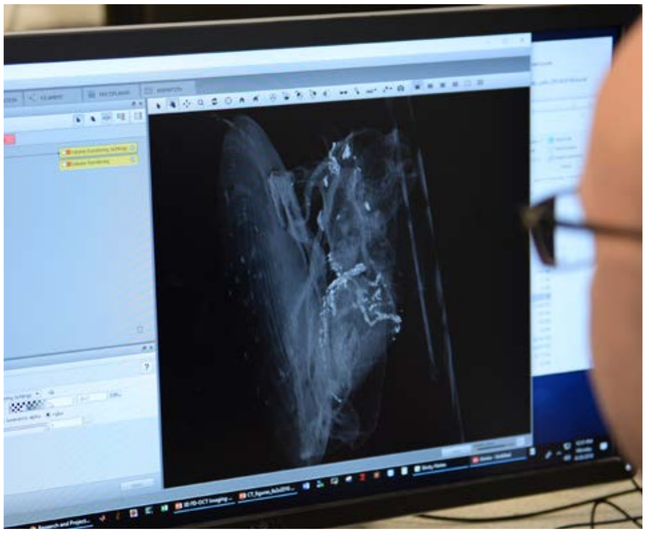
Wilson has a second ophthalmology project with Faruk Orge, a pediatric ophthalmologist at University Hospitals, as well as assistant professor of pediatrics and associate professor of ophthalmology at the Case Western Reserve University School of Medicine. Using a 3D microscopic ultrasound system developed by Orge to image the front part of the eye, they will study the ciliary body (responsible for most of the eye's fluid production) and the drainage system. "This is a great new way to study glaucoma, and we think it could actually lead to image-guided treatment of glaucoma," says Wilson. This project was recently funded by the Case-Coulter Translational Research Partnership (CCTRP).

Studying Metastatic Cancer



A fourth award, related to the patented cryo-imaging system developed by the Biomedical Imaging Laboratory, offers potential in the oncology field. The NIH SBIR Phase II grant with BioInVision will focus on a cancer imaging and therapy analysis platform.

With cryo-imaging, preclinical researchers can take a tissue sample – even an entire mouse – and freeze it in liquid nitrogen. Then, the sample is placed under a cryo-microtome, where there is repeated sectioning and imaging of the block face of tissue. With extremely thin sectioning (thinner than a human hair) researchers can obtain very high resolution imaging of large tissues. "We can do color imaging as well as fluorescent imaging," says Wilson. "So if someone has labeled stem cells or cancer cells with a fluorescent marker, then



Left to right: Yingnan Song, Yazan Gharaibeh, Hao Wu, Yiqiao Liu , and David Prabhu, graduate students in the Biomedical Imaging Laboratory, discuss cardiac images.

we can image all the cells." Wilson's team has created images where they've counted more than 500,000 cells in a mouse.

The new SBIR Phase II award will use cryo-imaging to study metastatic cancer. "We are developing software for better analysis of cancer therapeutics and imaging," says Wilson. "And we are developing new applications for things like immunotherapy in mice."

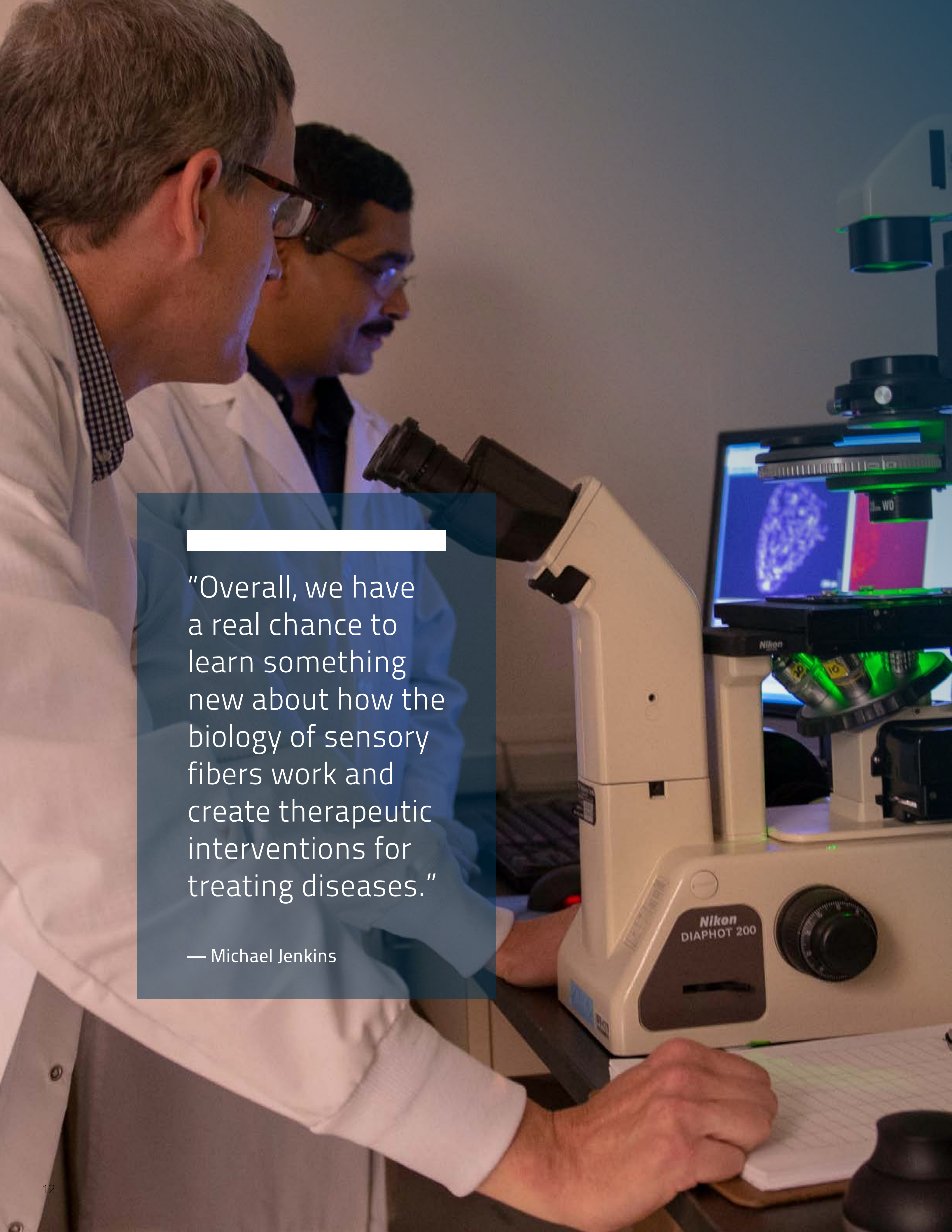
Advances in Microscopy

The final project has significant potential. The idea is to create a new technique for 3D microscopy with ultraviolet surface excitation (3D-MUSE).

A few months ago, Wilson saw Richard Levenson, a pathologist at the UC Davis Medical Center, give a talk to the Case Western Reserve Biomedical Engineering Department on the MUSE microscope he helped create. "When he spoke, the lightbulbs went off in my head and we teamed up," says Wilson. "With 3D MUSE, we are combining our cryo-sectioning machine with his new microscopy technique to get cellular resolution and sensitivity that we really didn't have before. We are building a new system that can easily create terabyte histology of samples."

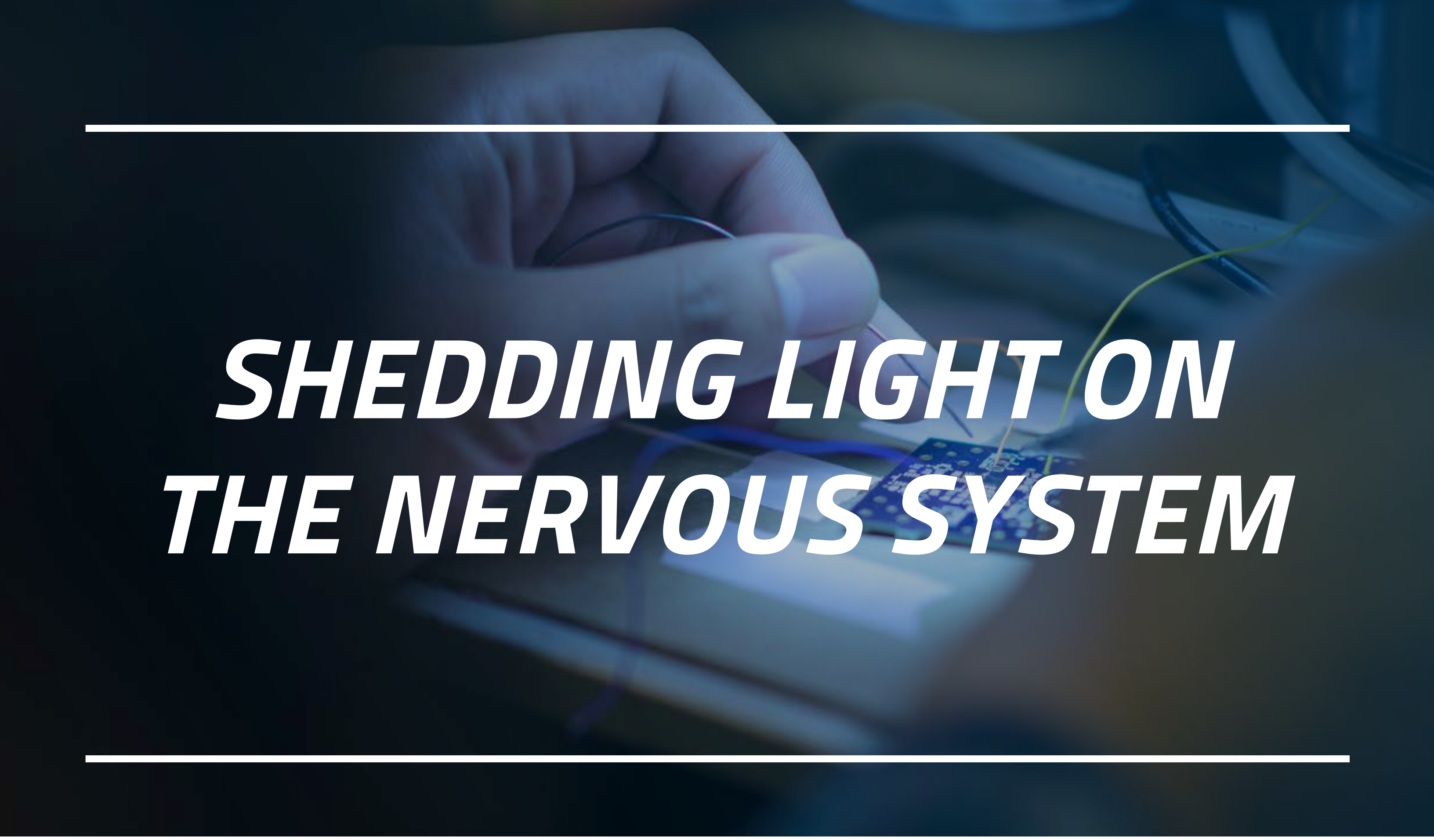
No matter the project, Wilson says success is all about the collaborators – and timing. "Some of these things are serendipitous," he admits. "You just talk to people, and there's the opportunity for a new invention or project." Wilson hopes more new ideas are on the horizon for the Biomedical Imaging Laboratory.

For more information on the Biomedical Imaging Laboratory, please contact David Wilson at David.Wilson@case.edu



"Overall, we have a real chance to learn something new about how the biology of sensory fibers work and create therapeutic interventions for treating diseases."

— Michael Jenkins



SHEDDING LIGHT ON THE NERVOUS SYSTEM

Researchers are harnessing infrared light to modulate, block and excite electrical signals that control organ function.

The first line of treatment for many diseases today, ranging from asthma to cardiac arrhythmias, is prescription drugs. But what if there was a better option?

"Drugs are pretty good at treating diseases, but they typically have lots of side effects," says Michael Jenkins, assistant professor of pediatrics and biomedical engineering at Case Western Reserve University School of Medicine. "Recently, it's been shown that we may be able to treat diseases by modulating the electrical signals that control your organs and your autonomic responses."

Last spring, a multidisciplinary team of researchers led by Jenkins received a four-year, $9 million grant from the National Institutes of Health (NIH) to develop enhanced infrared light technology for potentially treating a variety of diseases, including cardiac arrhythmias, high and low blood pressure, asthma and sleep apnea. Researchers from the Jenkins Lab, Vanderbilt University and the University of Pittsburgh have partnered to create new technologies to precisely send infrared light to nerves and ganglia in animals, watch the ensuing activity and map the molecular components in 3-D with high resolution.

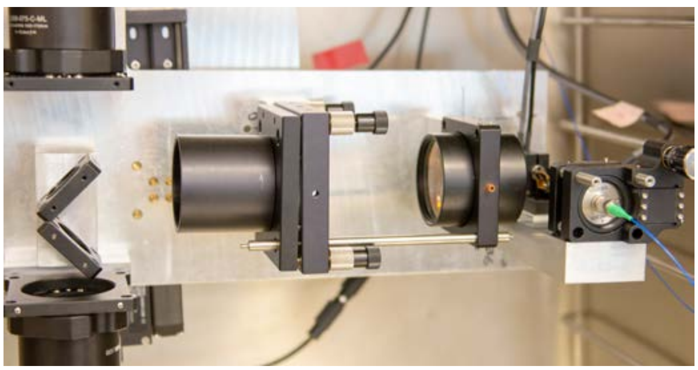
Targeting Sensory Fibers

Modulation of the nervous system often utilizes electrodes for stimulation of large fibers. Jenkins' group uses infrared neuromodulation (IRN) applied to peripheral structures, such as the nodose ganglion in the first cervical vertebra, to induce unique patterns of physiological responses that can't be elicited by electrical current or drugs.

"Our infrared light targets small-diameter fibers preferentially, whereas electrical stimulation tends to target the large fibers," says Jenkins. "Electrical currents are decent for eliciting movement – your arms and legs, for instance. But a lot of sensory fibers that control organs are actually small fibers, so there's an advantage to being able to more easily get at those fibers."

Recent work conducted by Jenkins and his peers indicates that IFN can affect collections of nerve cells that control autonomic function, such as heart rate, respiration, digestion and other visceral functions. "Essentially, we take infrared light, shine it into the tissue and try to specifically target regions of the nodose ganglia," says Jenkins. "We've discovered we can do things like lower blood pressure and affect the breathing rate. At this point, we are just starting to build tools to more accurately map what's going on. But it's exciting to get these different types of responses."

Deciphering How the Technology Works



"The ganglion is like a little brain in the periphery structures, controlling certain autonomic functions," says Jenkins. "If we can control those functions, it could be very valuable both as a tool for learning how the circuitry works, but also as a therapeutic tool."

The goal of the NIH grant is four-fold:

- To create new devices that efficiently and precisely deliver infrared light to nerves and ganglia.
- To assess the safety, selectivity and repeatability of IRN.
- To map the spatial organization of the ganglionic function.
- To develop a deeper understanding of how IRN works.

Because the work is in its infancy, the group will spend time studying exactly how IRN affects autonomic functions. "The electromagnetic spectrum includes visible light and infrared light, which has longer wavelengths than visible light," says Jenkins. "We have chosen to use wavelengths that have higher water absorption properties, and we think some of the responses we're getting are due to transiently heating the tissues."

One of the interesting things about the project, says Jenkins, is that the team has gotten different effects when stimulating the nodose ganglion depending upon the parameters they use. Electrode stimulation typically provokes one response no matter where the electrode is placed on the fiber. "But when we use the light, we actually get different responses depending upon where we place our optical fiber," says Jenkins. "The idea is that perhaps we can get more spatial precision with this technique and target certain types of cells."

The collaborators also will study how long you need to shine infrared light on sensory fibers to achieve results. Some effects occur only when the laser is on, while other responses last for hours after applying IRN for only a few seconds.

Working Toward Real-World Applications

Discovering what IRN is capable of doing, creating models for how it works and developing advanced optical systems to facilitate the technology requires a multidisciplinary approach. The research team includes collaborators in seven labs across three universities. The primary biomedical engineers are Jenkins, who earned his PhD in biomedical engineering from Case Western Reserve University in 2008, and E. Duco Jansen, professor of biomedical engineering at Vanderbilt University and one of the inventors of IRN. Other researchers include Hillel Chiel, a biology professor at Case Western Reserve University with a secondary appointment in biomedical engineering, and Stephen Lewis, professor of pediatrics at Case Western Reserve University's School of Medicine.

"One of the exciting things about working in larger groups to solve problems is that you bring together expertise from a number of different areas," says Jenkins. "It's imperative to get a lot of viewpoints if you want to move your science along quickly." And advancing the science of IRN has the potential of helping millions of people with an array of conditions. Consider just two possibilities:

- Diarrheal diseases account for one in nine child deaths worldwide, making diarrhea the second leading cause of death among children under the age of five, according to the Centers for Disease

Michael Jenkins studies images created using infrared neuromodulation.

Control and Prevention. Using IRN, clinicians may be able to target the part of the nodose ganglion that controls peristalsis, which pushes ingested food through the digestive tract toward its release at the anus. "By slowing peristalsis down, we can stop diarrhea from taking a fatal tool on people, especially young children in less developed countries, who are particularly susceptible to death from dehydration," says Lewis.

- More than 4 million Americans suffer from recurrent arrhythmias, according to the American Heart Association. Some undergo cardiac ablation to prevent abnormal electrical signals from entering the heart, thereby stopping the arrhythmia. However, there can be unwanted side effects. "Ablation can lead to other problems because no ganglion control just one thing. So people may develop a droopy half of their face or other significant side effects," says Jenkins. "What if you could modulate the signal with infrared light instead of ablating it?"

While these real-life applications remain on the horizon, Jenkins is excited by the potential for IRN. "With this grant, we'll learn how it works and map the types of responses we are getting. In the future, we'll move toward better ways to deliver the light to the tissue," he says. "Overall, we have a real chance to learn something new about how the biology [of sensory fibers] work and create therapeutic interventions for treating diseases."

BIOMEDICAL ENGINEERING ALLIANCE

Case Western Reserve University and Cleveland Clinic have launched a new partnership to advance research and education in biomedical engineering across greater Cleveland's growing health innovation ecosystem.

This biomedical engineering alliance capitalizes on the synergistic strengths of both institutions' nationally renowned biomedical engineering departments to create a unique program with an extensive portfolio of laboratory breakthroughs that led to life-changing treatments for patients.

Additionally, the alliance increases opportunities for trainees at all levels — from high school to postdoctoral education — to study with renowned scientists, physicians and engineers whose expertise ranges from nanotechnology and neural engineering to imaging and regenerative medicine.

"This agreement furthers northeast Ohio as a biomedical hub," says Geoffrey Vince, chair of biomedical engineering at Cleveland Clinic Lerner Research Institute. "After many years of close collaboration, this formal alliance will push forward the teaching and research mission of our institutions."

The alliance includes more than 50 researchers with primary appointments in biomedical engineering, as well as another Case Western Reserve 80 researchers located in such disciplines as cardiology, ophthalmology, orthopedics and precision medicine. In 2017, Case Western Reserve's biomedical engineering researchers alone received nearly $20 million in federal, industry and nonprofit support.

"Our departments' researchers have long partnered on projects where combining their experience and expertise could lead to better and faster results," says Robert Kirsch, chair of Case Western Reserve's Biomedical Engineering Department. "This new model creates a framework to catalyze joint efforts in a more intentional manner, rather than relying on individual relationships or chance encounters to spark collaborations."

Celebrating its 50th anniversary this year, Case Western Reserve's biomedical engineering department is among the first-ever founded in the U.S. The department is home to about 500 undergraduate and

[Left to right] Geoffry Vince (Biomedical Engineering Chair, Cleveland Clinic); Serpil Erzurum (Chair, Cleveland Clinic Lerner Research Institute), Pamela Davis (Dean, Case Western Reserve University School of Medicine), Robert Kirsch (Biomedical Engineering Chair, Case Western Reserve University), James Young (Executive Dean, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University).

150 graduate students and pursues research to develop new technologies and apply them to a broad range of clinical conditions.

The university's department also is active in entrepreneurial efforts, as illustrated by the Case-Coulter Translational Research Partnership (CCTRP) and several educational programs focused on translational research and commercialization. "Over the last 13 years, our Coulter program has supported more than 80 technologies," says Stephen D. Fening, Director of the CCTRP. "More than a third of these projects have been licensed and in total have raised more than $150 million in follow-up funding, mostly from professional investors." Six innovative projects that received the latest round of funding from the CCTRP are highlighted in this newsletter on page 18.

Cleveland Clinic's biomedical engineering department is renowned for its commitment to investigation, innovation and translation of scientific discoveries to enhance patient care. Cleveland Clinic biomedical engineering researchers are leaders in several major NIH grants, including the $14 million NIH Center for Accelerated Innovations.

The hospital's biomedical engineering department has several international research affiliations, including the Center for Transformative Nanomedicine, a global partnership with Hebrew University of Jerusalem that is focused on nanotechnology through education and research. The department also has an alliance with the University of Technology and Engineering in Lima, Peru.

"Our departments' researchers have long partnered on projects where combining their experience and expertise could lead to better and faster results."

— Robert Kirsch, chair of biomedical engineering

CASE-COULTER TRANSLATIONAL RESEARCH PARTNERSHIP AWARDS

Translational Research Partnership

$1.1 MILLION IN FUNDING AND SUPPORT FOR PROMISING BIOMEDICAL ENGINEERING UNIVERSITY TECHNOLOGIES

The Case-Coulter Translational Research Partnership, which helps to commercialize projects by clinicians and biomedical engineering faculty that improve human health and well-being, has awarded more than $1.1 million in financial backing and other support for the most recent round of funding.

For more information, please visit bme.case.edu/cctrp.

Sickle Cell Disease Biochip Blood Cell Adhesion Test for Emerging Anti-Adhesive Therapies

Umut Gurkan, Jane Little

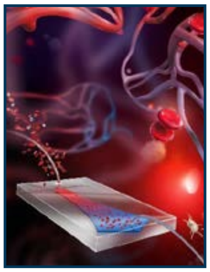
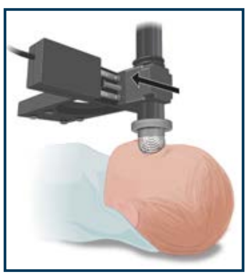


Image Credit: Grace Gongaware

Sickle Cell Disease Biochip technology is a new microfluidic blood test that measures the stickiness of blood cells to blood vessel walls. This new blood test can be used as a companion diagnostic test platform for emerging anti-adhesive therapies to enable effective, personalized treatment and care for patients living with sickle cell disease.

3-D Ultrasound Imaging for Ophthalmology

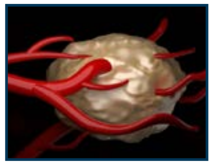


Faruk Orge, David Wilson, Rich Helms

This technology will be the first high-resolution 3-D microscopic ultrasound system to provide unique visualizations of eye structures to better understand pathophysiology, plan treatments, and assess treatment results. Ultrasound is unique among ophthalmic imaging modalities in its ability to see structures behind the iris, including the lens and ciliary body, as well as key portions of the aqueous outflow system. This region of the eye plays a critical role in glaucoma, a disease affecting over 2.7 million people in the United States alone, and cataract, which are leading causes of reversible and irreversible blindness.

LunIOTx©: Decision Support Technology for Predicting Response to Immunotherapy in Lung Cancer

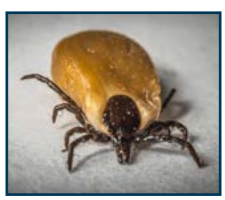
Anant Madabhushi, Vamsidhar Velcheti



LunIOTx is a non-invasive decision support technology that uses patented artificial intelligence and pattern recognition algorithms on routine CT scans to identify lung cancer patients who will or will not respond to immunotherapy. By identifying patterns on CT scans associated with response, LunIOTx can enable early identification of lung cancer patients in whom expensive immunotherapy can be avoided and who might be better candidates for chemo or radiation therapy.

Magneto-Optical Diagnosis of Lyme Disease in Blood Samples

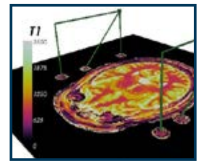
Brian Grimberg, Umut Gurkan, Robert Deissler, Michael Martens, Robert Brown



There is an expanding need for a reliable diagnostic for Lyme disease to identify and treat the over 300,000 potentially infected Americans. Iron labeled antibodies attach to the Borrelia bacteria, which makes it responsive to a magnetic field and can yield a result in 5 minutes as opposed to weeks, and more importantly it functions immediately after exposure to an infected tick instead of having to wait a month for the current test. This early detection can lead to an early cure instead of patients languishing for years without an effective treatment.

Magnetic Resonance Fingerprinting for Target Identification in Deep Brain Stimulation

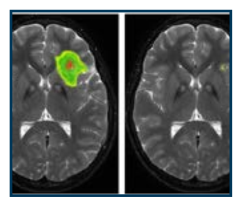
Cameron McIntyre, Mark Griswold, Jennifer Sweet, Dan Ma



The goal of this project is to develop a clinical workflow and computational algorithm that enables integration of advanced MRI acquisitions, known as magnetic resonance fingerprinting, into surgical targeting strategies for deep brain stimulation (DBS) therapies. The inventors are developing a prototype system around subthalamic nucleus DBS for the treatment of Parkinson's disease.

Novel Positron Emission Tomography (PET) Imaging Agent for Tumor Detection & Treatment

Susann Brady-Kalnay, James Basilion, Zhenghong Lee, Norbert Avril



Specific tumor detection is a critically important goal in cancer imaging to avoid unnecessary biopsies to exclude false-positive findings, and it will enable treatment, or redirection of treatment, at earlier stages of disease. Positron Emission Tomography (PET) imaging agents that specifically recognize tumor cells are necessary for improved imaging and subsequent evaluation of therapeutic efficacy independent of their metabolic rates. PTPμ is a novel imageable biomarker that can be used to specifically and more comprehensively detect and monitor aggressive invasive and metastatic tumors.

CHECKING IN WITH ALUMNI

LANCE A. LIOTTA

Lance A. Liotta (GRS '74, MED '76) received his PhD in biomedical engineering from Case Western Reserve University in 1974. Since 2005, he has served as Co-Director and Co-Founder of the Center for Applied Proteomics and Molecular Medicine (CAPMM) at George Mason University. Prior to this appointment, Liotta served as Chief of the Laboratory of Pathology, NCI, Deputy Director of NIH, Co-Director of the NCI/FDA Clinical Proteomics Program, and Director of the Anatomic Pathology Residency Program.

Liotta has invented and patented, along with his laboratory co-inventors, transformative technologies in the fields of diagnostics, cancer molecular therapeutics, microdissection and proteomics that have been used to make broad discoveries in cancer biology, and diagnostics, and therapeutics. The Laser Capture Microdissection prototype is in the Smithsonian Collection.

His team at CAPMM studies the proteomics of human tissue, cultured cells, and body fluids using this set of novel technologies. This research has directly resulted in ongoing clinical research trials applying the technology to the discovery of markers for early stage disease, individualized therapy for metastatic cancer, and adjuvant therapy of premalignant breast cancer.

Liotta is a founder of Theranostics Health and Ceres Nanosciences. He has more than 100 issued or allowed patents and more than 690 publications. He is an ISI highly cited investigator and the recipient of numerous awards for biomedical research, including the 2015 Outstanding Virginia Faculty Award (SCHEV), the Flemming Award for Cancer Research, the Warner-Lambert Parke Davis Award, and the Surgeon General's Medallion.

Photo: Evan Cantwell/George Mason University

MARK A. KNEPPER

Mark A. Knepper (GRS '75, biomedical engineering, MED '76) received his PhD in biomedical engineering from Case Western Reserve University in 1975. He has been a NIH scientist since 1978 and is currently head of the Epithelial Systems Biology Laboratory at the NHLBI. Knepper has received the H.W. Smith Award (the highest award of the American Society of Nephrology), the R.W. Berliner Award at Yale University, the C.W. Gottschalk Award of the American Physiological Society, the Hugh Davson Lectureship of the American Physiological Society, and the D.W. Seldin Lectureship of the American Heart Association (Council on the Kidney in Cardiovascular Disease). He has published over 400 peer-reviewed papers on renal physiology, hypertension, nephrology, and systems biology. His editorial positions have spanned the American Journal of Physiology and the Journal of Clinical Investigation. Knepper is a member of the American Heart Association, American Physiological Society, American Association for the Advancement of Science, American Society of Nephrology, and Biomedical Engineering Society.

Knepper's research concentrates on the physiology and pathophysiology of the kidney, with particular focus on regulation of water and salt transport by the peptide hormone vasopressin. They have pioneered methods for application of phosphoproteomics (using LC-MS/MS) to physiological signaling systems revealing the kinase classes activated and inactivated by vasopressin. Knepper's group is heavily invested in the development of such computational approaches and resulting software. Knepper and his colleagues have produced a number of databases to make the large-scale (proteomic and transcriptomic) data available to scientists worldwide.

To be featured in the next edition of the Biomedical Engineering newsletter, please send your stories to bmedept@case.edu.

ALUMNI COUPLE COMMIT GIFT TO COMPUTER IMAGING LAB

From left: Anant Madabhushi, Harita Patel, and Jayendra (Jay) Patel

For the last 6 years, Anant Madabhushi's lab on the campus of Case Western Reserve University has emerged as a global leader in the detection, diagnosis and characterization of various cancers and other diseases by meshing medical imaging, machine learning and artificial intelligence. This summer, a California couple with an increasing interest in that same intersection of technology and medicine — and who met at the Case School of Engineering in the 1980s — became one of his biggest supporters.

Jayendra (Jay) and Harita Patel have committed to give $500,000 to Madabhushi's lab, the Center for Computational Imaging and Personalized Diagnostics (CCIPD). The funding will help the CCIPD expand its research and bring in a qualified senior researcher to work in a new disease area, Madabhushi says.

"One of the things that Jay and Harita recognized very quickly is that not only are our researchers developing cutting-edge artificial intelligence and machine learning algorithms for aiding in disease diagnosis and treatment response prediction, but we are also uniquely positioned to take advantage of the massive medical enterprise that is located in close proximity to Case Western Reserve University," he says. Collaborations with healthcare partners at Cleveland Clinic, University Hospitals of Cleveland, the Cleveland VA Medical Center and MetroHealth Medical Center have given his center access to massive imaging datasets for developing and validating the center's analytic tools.

Like Madabhushi, the Patels also came to Case Western Reserve from India. They met here as graduate students when thrown together on a project for a computer science class. "We built our first 8-bit microcomputer together at Case Western Reserve," Jay Patel recalls.

Harita Patel, who had until then been mostly interested in physics, only took the course because it was a requirement for her new major in computer science. "But we had to work with a partner on the project and Jay was there, so we did," she says. "There were a lot of long hours together."

Several years later, they were married, moved to California and started a family, raising two sons. They also both took jobs in the early days of Apple computers in the late 1980s. Jay Patel eventually went on to several other companies, but Harita Patel worked at Apple for more than 25 years, retiring several years ago. That's when the couple began to look for a way to give back to Case Western Reserve.

"We found that our passions — education, healthcare, especially cancer research — all came together in Anant's lab," says Jay Patel. "We've had family members who have suffered from cancer, and we now have the means to do something to help combat the problem. And Anant is doing an awesome job in that area."

Since 2015, Madabhushi and his team of about 50 researchers have received more than $15 million from the National Cancer Institute and an additional $2.7 million from the Departments of Defense and U.S. Veterans Affairs to develop computational tools to analyze digital pathology images of breast, prostate, lung, and head and neck cancers.

The Patels' gift is CCIPD's first from private donors who specifically want to help accelerate the center's research. Harita Patel says the couple hopes to help encourage other donors to partner with Madabhushi and the CCIPD.

"We had been on the sidelines watching the progress, but now we're really excited to hear about things happening at CWRU," she says. "We are who we are partly because of what we learned at Case, and we want to be a part of something big there."

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