



BME

Newsletter
Fall 2017

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BIG RED MACHINE: CARDIOVASCULAR ENGINEERING AT CORNELL

MESSAGE FROM THE DIRECTOR: MARJOLEIN C.H. VAN DER MEULEN



While we have quite a few updates to share from the past year, I want to start by looking forward: the Meinig School of Biomedical Engineering has an exciting year ahead as our first

undergraduate class enters their senior year and prepares to move on. Their graduation in May 2018 will be a major milestone for the Meinig School. And, our undergraduate major continues to grow, exponentially! After growing from 19 seniors in our first class to 33 juniors in our second year, more than 70 sophomores have expressed an intent to affiliate as biomedical engineering majors this fall.

Hiring faculty is always one of our most important activities, even more so as we develop our new undergraduate curriculum. This year we welcome several new faculty, including two new senior hires, both of whom contribute to our excellence in cardiovascular engineering, as highlighted in our cover story (p. 4).

Professor Yadong Wang is a

chemist working on innovative biomaterials for cardiovascular regeneration and tissue engineering. Yadong's success at translating basic polymer science to clinical applications is an important addition to our program.

Professor James Antaki works on ventricular assistant devices and blood pumps, and will join us in January 2018. Jim brings strengths in device design that are currently not well-represented in BME.

Adding to our expertise in imaging and neuroscience, Mert Sabuncu joined the Meinig School as an assistant professor with his primary appointment in Electrical and Computer Engineering and 25% effort in BME (highlighted in last year's newsletter). Mert is one of the leaders of the Cornell Neurotechnology NeuroNex Hub, which was recently funded by the National Science Foundation (NSF) (p. 10).

Ankur Singh (p. 15), working on immuno-engineering, joined BME at 25% effort, effective summer 2017. Ankur has been an assistant professor in Mechanical & Aerospace Engineering since 2013. We look forward to Ankur's leadership in the immunology, infection and inflammation research thrust.

Updating you on the accomplishments and recognition of our faculty is always a pleasure, particularly the junior faculty. Ilana Brito, our newest assistant professor, hit the ground running this year with great success. Most notably Ilana was recognized as a 2017 Sloan Research Fellow by the Alfred P. Sloan Foundation in the area of computational & evolutionary molecular biology. As previously



Christopher Sales, MD, MPH, of Weill Cornell Medicine, instructs students on eye anatomy and ophthalmic surgery on a recent visit to the Meinig School's new collaboration and ideation studio (p. 12).

mentioned, the NSF funded the new Cornell Neurotechnology NeuroNex Hub, an effort led by a team of five faculty, including Mert Sabuncu and Chris Schaffer, both faculty in the Meinig School.

As director, laboratory and teaching space issues keep me up at night. We have made progress in planning for the future in a joint effort between the Colleges of Engineering, Arts & Sciences (CAS), and Agriculture & Life Sciences (CALs), as described in this newsletter (p. 12). The CAS and CALs host the Office of Undergraduate Biology, with whom our future teaching space will be co-located in Comstock Hall. Initially Biomedical Engineering will be shifting our administrative offices to the west wing of Weill Hall, pending completion of ongoing renovation of the first floor and basement. In the basement, we are adding much needed design and fabrication facilities. The planning process for the next and longer phases will be initiated this fall. Creating teaching space outside Weill Hall and opening up the first floor will allow us to add faculty laboratories.

As our faculty grows, growth of the graduate program follows. Our Ph.D. students are highly accomplished and go on to do great things. We highlight the recognitions received by our students on pp. 20-21. Recently quite a few Ph.D. alumni have started

THE BME MISSION

To educate students to understand the human body as an integrated system and the mechanisms of disease through quantitative engineering analysis, and to use that understanding to design better therapeutic strategies, devices, and diagnostics to improve human health.

their own faculty careers, several of which are also included (pp. 22-23). Please reach out and update us on your own career progress, we'd love to share your successes.

Finally, I hope many of you will be able to join us June 22, 2018, as we celebrate the achievements of Professor Michael Shuler (p. 16). Few faculty have such broad impact in the College of Engineering: Mike first contributed through his leadership of Chemical & Biomolecular Engineering, and then as the founding chair of Biomedical Engineering. The Meinig School exists due not only to Mike's vision, but also his perseverance. We look forward to an engaging symposium.

Sincerely,



Marjolein C.H. van der Meulen
James M. and Marsha McCormick
Director of Biomedical Engineering
Swanson Professor of Biomedical
Engineering



ABOUT THE COVER

Cover design by Rob Kurcoba

Cover heart graphic is a collage of cardiac research images from the Nishimura (top left); Antaki (top right & bottom left), and Butcher (bottom right) Labs.

Background image reflects the wall design of the new BME administrative suite in Weill Hall, designed by the architect, Levenbetts.

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BIG RED MACHINE: CARDIOVASCULAR ENGINEERING AT CORNELL ENTERS A NEW ERA *by Syl Kacapyr*

After experiencing some mild chest pain, you step into your physician's office for a diagnosis. Your physician uses a laser to observe the cells in your heart and discovers some damaged muscle. A computer analyzes your patient file and quickly offers a menu of solutions, each with a percentage indicating the likelihood the procedure will work. You select the computer's recommendation to have your heart locally injected with specialized molecules to regenerate the tissue, and your physician will 3D print a new valve made of your own living cells and in the shape you need.

While such an experience remains science fiction, research underway at Cornell Engineering is offering a glimpse into the future of cardiovascular care. New tools and techniques promise to change the way heart disease is treated and prevented, and they're being developed in the face of a stark reality: Over 92 million Americans are living with some form of heart disease or the after-effects of stroke, according to the American Heart Association. Heart disease continues to be the leading cause of death worldwide, contributing to one in every three deaths in the U.S.

Much of this research at Cornell is happening in the Nancy E. and Peter C. Meinig School of Biomedical Engineering, which has added two prominent engineers to its faculty, establishing a critical intellectual presence in cardiac technology. The school is also finding new ways to capitalize on partnerships and collaborations around campus, pushing the limits of imagination and breaking the rules to advance cardiovascular engineering.

HEART-ASSIST DEVICES

When James Antaki was 11-years-old, he was determined to repair an old, antique radio sitting in his parents' basement. He bought an electrical engineering book and taught himself just enough to get the radio working. Years later, Antaki would find himself as a graduate student at the University of Pittsburgh, still repairing broken machines, but this time it would be an artificial heart that was being used by a new university program.

It was there Antaki—who will join the Meinig School in January as the Susan K. McAdam Professor of Heart Assist Technology—pioneered a magnetically levitated rotodynamic heart-assist device, a blood pump dubbed the Streamliner, that became the first of its kind to reach pre-clinical testing.

Like other ventricular devices that came before it, the Streamliner was designed to attach to a patient's heart, helping to pump blood from a weak left ventricle to the aorta. But unlike the first heart-assist devices approved by the FDA in 1994, Antaki's device ditched the unreliable bearings used to suspend the pump's impeller, and replaced it with a magnetically levitating one.

He continued to engineer several

iterations of the device, including PediaFlow, a prototype heart-assist device for infants. "Currently, pediatric surgeons have no options other than a giant refrigerator-size pump that has more blood outside of the baby than inside," explains Antaki, "and they have horrible incidents of stroke and bleeding. Survival is very poor."



Infant with implanted PediaFlow(TM) VAD, an implantable heart-assist device for infants and small children with congenital or acquired heart disease, developed by Antaki.

Today, magnetic levitation pumps are at the forefront of ventricular heart-assist devices, but the technologically-advanced Streamliner is not one of them. Neither is the PediaFlow. While Antaki helped pioneer modern heart-assist devices, intellectual property rights and business decisions that were out of Antaki's hands stifled his ability to bring tech advancements to the market.

Antaki views Cornell as a fresh start. He's in the process of recapturing his patent rights, and points to the words "heart assist

technology" in his title as an example of how Cornell's priorities are aligned with his. He says one of the biggest draws to Cornell was the opportunity for research collaboration. "Cornell's world-class veterinary school is a huge asset," says Antaki. "Having it in my backyard versus having to fly to the West Coast to do experiments—it goes without saying that it will accelerate our pre-clinical testing."

BIOMATERIALS

Pediatric cardiology was thrust into the national spotlight in May of 2017 following



James Antaki



Jonathan Butcher



Yadong Wang



Geoffrey Pitt



Nozomi Nishimura

an emotional episode of the late-night talk show “Jimmy Kimmel Live.” In the episode’s opening monologue, host Jimmy Kimmel, fighting back tears, revealed that his newborn son had just undergone emergency open-heart surgery after he was diagnosed with a rare congenital defect in which a hole existed between his heart’s bottom two ventricles.

Surgeons at Children’s Hospital Los Angeles were able to sew a biomaterial over the hole, “just like you would sew a patch onto a pair of pants,” one surgeon told the *Los Angeles Times*. He noted that Kimmel’s son would need that patch replaced as his heart grows larger. “Hopefully someday we’ll develop materials that will grow and expand over time,” stated the surgeon.

Cornell engineers are doing just that, engineering tissue in the form of living prosthetics.

After watching his mechanical engineering colleagues pioneer a method for 3D printing cartilage in the form of vertebral discs, menisci and even ears, Jonathan Butcher wondered if it would be possible to use the same process to print heart valves. So Butcher, an associate professor and associate director of the Meinig School, began an ambitious project to create an anatomically correct, mechanically heterogeneous, living heart valve with a 3D printer.

The project required the development of cell-friendly hydrogel materials that

could be deposited by a 3D printer and mimic the unique physiological biomechanics of different valve structures. It also required developing a system to cure the deposited material while it was being printed, and computer algorithms to process clinical 3D-image datasets to identify not only the precise valve geometry, but also the different internal material domains within it.

“Over the past 10 years, we have developed the most complex and realistic living human-sized heart valve from scratch. These achievements have the potential to overcome many of the limitations of current tissue-engineered valve technology, and hopefully provide the key needs of biointegration, growth and life-long function,” says Butcher.

While non-living prosthetic valves perform well for elderly patients, the

same isn’t true for younger patients with congenitally malformed valves. The need for a better alternative is compounded when one considers the millions of young patients suffering from valve disease in the Majority World, up to 10 percent of hospital admissions in some communities, according to Butcher.

But proving life-saving technology that is safe and effective in children requires a high regulatory burden, including animal and clinical trials. Butcher hopes promising results in large animal models will spur

further investment to bring his dream to fruition. “It is a tough ‘dead zone’ where academic funding often ends, but industry is not yet willing to pick it up,” he says.

To bridge the gap, Butcher is developing a more near-term solution: a bio-hybrid prosthetic valve that also works as a scaffold to hold living cells. The patented device is designed to help the valve regulate normal function within the heart, such as coagulation and protein absorption. He plans to work with Antaki on preclinical testing.

“I want to design solutions that can get into the clinic sooner than the best approach, as many people could still benefit,” says Butcher.

REGENERATION

One of the unique powers of the comic book superhero Wolverine is that he has the ability to regrow parts of his limbs and organs after injury. It’s a remarkable gift that, in real life, is difficult-to-impossible for most mammals to replicate, depending on the organ.

That is partly why heart disease is so deadly for humans. Heart attacks occur after blood flow has been reduced to an area of the heart, causing that area of tissue to be damaged or dead. Because the heart doesn’t have the ability to regenerate, the damage becomes permanent and the victim is left with a weaker heart.

But other parts of the animal kingdom do exhibit the superpower of regeneration. Amazingly, the zebrafish can lose up to 20 percent of its heart before regrowing the tissue in just a matter of days. This piqued the curiosity of Yadong Wang, the McAdam Family Foundation Professor of Heart Assist Technology in the Meinig



A clinically-sized human trileaflet heart valve made in the Butcher Lab using 3D printing of biological hydrogel polymers.

FEATURE: CARDIAC TECHNOLOGY DEVELOPMENT

School, who has been engineering new biomaterials, some of which are used for regenerative medicine.

“Being a chemist by training, I’ve always been really interested in making new things, but mother nature has been doing that for millions of years,” says Wang, referring to the zebrafish’s ability to regenerate its heart. At least part of the secret is in the zebrafish’s extracellular matrix (ECM), essentially a collection of molecules that provide structure and biochemical support to surrounding cells. It’s this ECM that works to repair the heart, although scientists don’t understand exactly how.

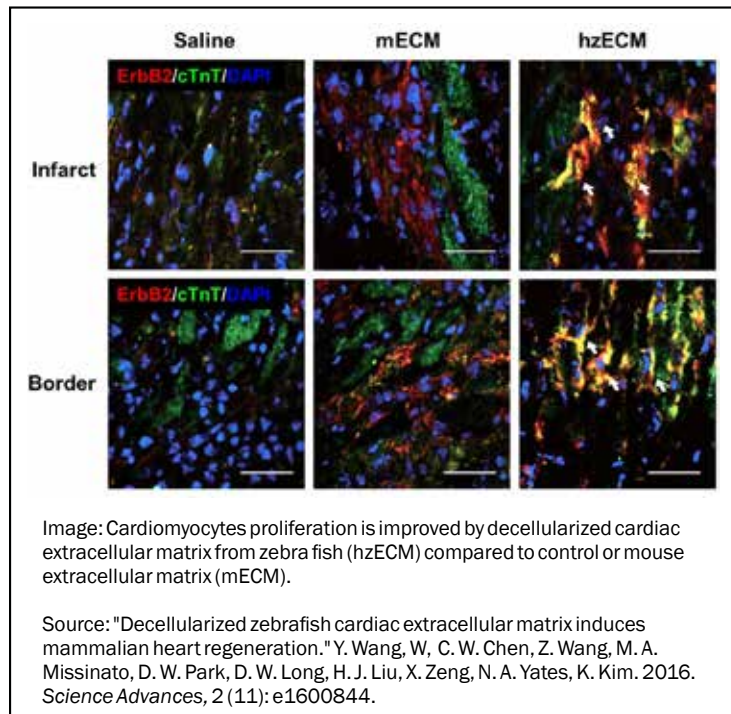
Still, Wang wanted to know how zebrafish ECM would perform in a mammalian heart, so he injected some directly into mice that had suffered a heart attack. What he discovered was the ECM worked to protect myocytes, the specialized cells that make up heart muscle, and within five days he observed an improvement in heart performance in many of the mice. While less than 1 percent of the myocyte was affected, Wang says it’s enough to demand more research. “It’s a start. There’s something there,” he says.

SCAFFOLDS

Wang has also engineered grafts and scaffolds that not only serve as an artificial component of a heart, but also attract and activate cells that can help the heart regenerate.

“We need to design the signals in our scaffold so the immune system recognizes it as a relatively benign material,” says Wang, adding that the wrong type of material could be rejected too quickly by the recipient’s body. “While the immune system is slowly degrading this material, the cells are homing in and making tissue.”

But recruiting the cells is only the first step. The biomaterial the scaffold is made of must also activate the cells to perform the correct tasks. The trick is getting monocytes—a type of white blood cell—that encounter the biomaterial to differentiate into the proper mix of macrophages.



Wang has discovered a number of materials that don’t negatively interact with monocytes. The most promising, he says, is a biodegradable elastomer material he has nicknamed “biorubber.” It looks like silicone, but is actually a polyglycerol sebacate that has successfully been implanted in animals to help them regenerate bone, cartilage, blood vessels and heart tissue.

Wang, who just began his first semester at Cornell, says “I haven’t been to a university that has a veterinary school.” He expects the ability to collaborate with the College of Veterinary Medicine to accelerate his research and allow him to have a better view of how his biomaterials are performing. He also plans to revisit his roots in chemistry through his new colleagues in the Robert F. Smith School of Chemical and Biomolecular Engineering and the department of Chemistry and Chemical Biology.

COMPUTATION

As part of the University of Pittsburgh team experimenting with heart-assist devices, Antaki encountered a problem that

threatened to jeopardize the entire program. It was the mid 80s and the blood inside the valve of an implanted heart pump clotted. Little was understood about the underlying cause of how and why blood clotted inside prosthetic organs, and so Antaki became determined to develop a computational model that could explain.

Years later,

Antaki says “we now have a computer simulation that works remarkably well under certain conditions.” His model worked well enough to earn a National Institutes of Health grant for the next four years to attempt to predict circumstances under which blood will clot in heart-assist devices.

Modeling something as complex as blood flow is no easy task, but the benefits are numerous. Not only can the data help engineer better ventricular devices, but it can simulate risks for individual patients and help manage their post-surgery recovery. For example, Antaki’s statistical model aims to advise patients on whether or not they should get a device, and if so, which one. It can also dictate how patients should manage their diet to reduce the risk of stroke, bleeding and other adverse consequences of receiving an implant.

When it comes to heart disease, computation is showing great promise in its application to precision medicine as well. When used in conjunction with the human genome, it can be a powerful tool to predict the most effective medication for

an individual patient, and to identify which risk factors need to be considered most aggressively.

"There's been some recent studies that have used large genomic data sets to begin to get predictive algorithms for patients that are more likely to develop coronary artery disease or atherosclerosis. And in particular, which patients will benefit from taking one of the statin medications that lower cholesterol," says Geoffrey Pitt, director of the Cardiovascular Research Institute at Weill Cornell Medicine. "There is a separate effort in looking at trying to predict patients that will be subject to atrial fibrillation, which is an arrhythmia that's much more common in elderly patients."

This type of precision medicine has not been as prevalent for predicting and treating heart disease as it has been for cancer, but it's an initiative Pitt plans to bring to the forefront through his institute, which launched in 2016 with the idea of building a larger cardiovascular research program that combines Weill Cornell Medicine's outstanding clinical care with its growing research infrastructure.

Pitt, who has collaborated with Butcher on several research grants, hopes to use the institute to encourage more collaboration, especially with the Ithaca campus and Cornell Tech, both of which provide leading expertise in engineering the types of algorithms needed to analyze large sets of genomic data.

"So we're thinking we can bring this quickly to the clinic if we get the right collaborations."

IMAGING

Another priority area for the Cardiovascular Research Institute is to understand the way small molecules interact with larger biological systems in cardiovascular disease. Luckily, the institute has to look no further than their engineering colleagues in Ithaca for some of the most advanced imaging tools and techniques that science has to offer.

Recently, a team of Cornell researchers imaged, with single-cell resolution, an

in-vivo beating heart. The team was led by Nozomi Nishimura, assistant professor of biomedical engineering, who says looking at how individual cells function inside a live, beating heart has been a major challenge for scientists. "The main problem is that the heart is moving while it is pumping blood and so it's actually been very difficult to get a picture of the underlying cellular behavior," says Nishimura. "The heart is a very dense, blood rich tissue and it's very opaque. So to study blood flow inside the heart wall you really need previously unattainable depth of imaging."

Nishimura was able to achieve the unprecedented microscopic view using three-photon microscopy, a technique developed in Cornell's Department of Applied and Engineering Physics that uses high-intensity lasers to non-invasively excite and image at a point of interest, such as a single cell. Originally engineered with neuroimaging in mind, Nishimura adapted the microscope for a mouse heart by speeding the imaging rate. "We're finally at the point where we can reliably image how the many aspects of heart physiology work together. These include blood flow, cardiomyocyte action potentials, as well as the immune and the inflammatory cells within the living heart," says Nishimura, noting the imaging technique will be important for understanding how heart attacks propagate and the cellular basis behind heart failure.

Nishimura's lab is using lasers not just for imaging cells, but also for manipulating them. Imagine a scalpel not only capable of slicing off a small portion of a cell, but doing so inside a living animal without

having to touch any other part of its body. This is what Nishimura has achieved using a powerful femtosecond laser that blasts photons at its target using pulses that flicker at mere millionths-of-billionths of a second. Using this technique, Nishimura can induce small blood clots or hemorrhages

to mimic aspects of cardiovascular disease.

Nishimura has been able to advance her work through an ongoing collaboration with Provost Michael Kotlikoff's research lab in the College of Veterinary Medicine, which has engineered calcium-sensitive proteins needed to make her imaging techniques work. Her lab is also developing optogenetic tools to stimulate the electric

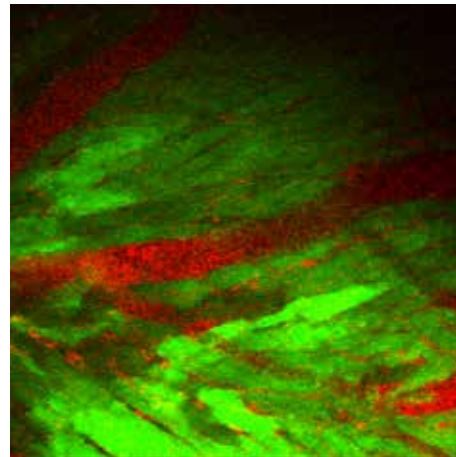
activity of hearts. "We

basically get first crack at trying some of these new tools, so this is a very exciting collaboration," says Nishimura.

THE FUTURE

Emerging trends and technologies in cardiovascular research are providing new hope in the fight against heart disease. The addition of Antaki and Wang to the Meinig School's talented faculty expands its intellectual footprint and uniquely positions the university to be a leader in cardiac technology.

"It's an exhilarating time for cardiovascular research at Cornell," said Marjolein van der Meulen, director of the Meinig School. "We are fortunate to have attracted these two senior leaders who complement our existing strengths, and I look forward to the opportunities and synergies created as these groups build new connections and collaborate with physicians and industry."



Multiphoton microscopy of the mouse heart in the Nishimura lab. Cardiomyocytes in green and blood vessels in red. Red blood cells can be seen with the vessels as dark spots.

WELCOME NEW FACULTY

JAMES ANTAKI



James Antaki, with harmonica

James Antaki will join the Meinig School in January 2018 as the Susan K. McAdam Professor of Heart Assist Technology.

The majority of Dr. Antaki's professional career has been devoted to development of blood-wetted medical devices. He has contributed to the development of several heart-assist devices used clinically, including the Heartmate-II, Novacor, Ventracor, TandemHeart, and Levacor. In 1997, he directed a multidisciplinary team that produced the Streamliner heart-assist device—the world's first magnetically levitated rotodynamic blood pump to

be tested in-vivo, and which in 2001 received the IEEE Control System Technology Award.

Equally important as the devices themselves, Antaki's research focuses on the methodology by which they are designed and used clinically. For example, his team was one of the pioneers in physiological feedback control of implanted ventricular assist devices. He also developed one of the first decision-support programs for identifying heart failure patients who could potentially recover with the acute mechanical circulatory assistance.

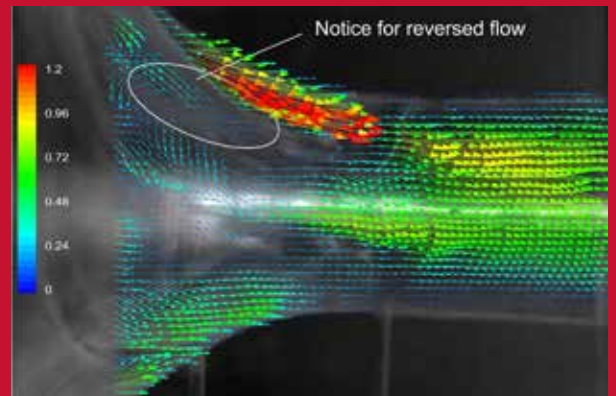
Although his interests and experience are diverse, they share a common theme of improving healthcare through biomedical engineering. Antaki's current research involves five application areas: circulatory support systems for children, decision-support tools for severe heart failure, diagnostic technology for the home and point-of-care to improve patient engagement, multi-scale modeling of thrombosis in artificial circulation, and development of medical devices for global health. A nascent, overarching project aims to accelerate medical innovation by professional networking between physicians, medical product designers and patients.

In addition to his many healthcare contributions, Antaki is an avid harmonica enthusiast and developer. In 1996, he founded TurboHarp (now a part of AntakaMatics, Inc.), a musical instrument technology company, to develop and commercialize harmonicas. TurboHarp's innovative harmonicas are the result of Antaki's ongoing pioneering studies on the acoustics of harmonicas since 1990.

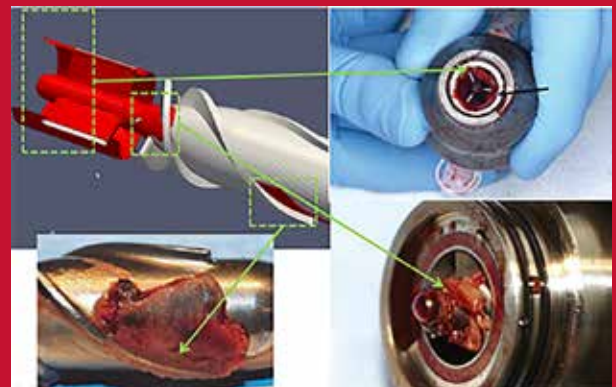
Dr. Antaki received B.S. and Ph.D. degrees in mechanical engineering at Rensselaer Polytechnic and the University of Pittsburgh, respectively. He holds over 16 patents related to artificial organs, harmonica technology and other fields.



Inside view of Pediaflow pump for heart assist that is barely the size of a U.S. quarter.



Antaki brings leading-edge fluid dynamics analysis methods to the development and understanding of cardiac devices.



Blood clots accumulating on pumps endanger patients.

YADONG WANG



Yadong Wang

Yadong Wang joined the Meinig School in the summer of 2017 as the McAdam Family Foundation Professor of Heart Assist Technology. Dr. Wang's research focuses on creating biomaterials that present controlled chemical, physical and mechanical signals to cells, tissues and organs, with an ultimate goal of controlling how the human body interacts with these materials. He is especially interested in applications of biomaterials in the cardiovascular, nervous and musculoskeletal systems. Wang's current projects include vascular grafts, controlled

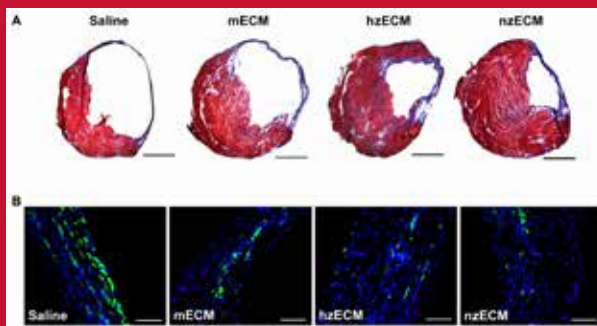
release of proteins and microfabrication of biomaterials.

Dr. Wang's team enjoys collaborating with other scientists and clinicians who share the same passion in translational research. He looks forward to initiating a project in collaboration with computation experts and polymer scientists at Cornell to create biomaterials with more precise control over properties and more diverse functions.

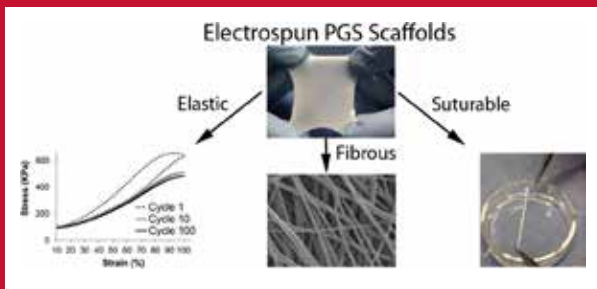
Clear guiding principles in biomaterials design and development are still elusive. A strong materiomics project that couples computation and experiments will advance this aspect of biomaterials science. He believes that the biomaterials field has sufficient data on materials-biology interfaces that computational models will provide useful guidance on materials design.

In addition to academic research, Wang is also very active in technology translation. He co-founded two companies to translate the technologies developed in his laboratory. Several of his inventions are licensed, and one polymer he invented, marketed under the trademark Regenerex™ —the first biodegradable elastomer introduced to the market—is now commercially available and approved for clinical use.

Dr. Wang received his Ph.D. from Stanford University and performed his postdoctoral studies at MIT. He joined the Bioengineering Department at University of Pittsburgh in 2008 after serving as an assistant professor at the Georgia Institute of Technology for five years. He has published high-impact articles at every stage of his academic career in journals including *Science*, *Nature Biotechnology*, *Nature Medicine* and *PNAS*. For his contribution to biomaterials and regenerative medicine, he was inducted into AIMBE in 2014 and awarded the Carnegie Science Award in 2015.



(A) Scarring of the heart at 6 weeks post-MI is revealed by the blue stain in transverse sections of hearts. The zebrafish heart matrix treated groups had less scarring. (B) Detection of chronic inflammation at 6 weeks post-MI in transverse sections of hearts. The zebrafish heart matrix treated groups are less inflamed.



Highly elastic and sutureable electrospun poly(glycerol sebacate) fibrous scaffolds. Poly(glycerol sebacate) (PGS) is a thermally-crosslinked elastomer suitable for tissue regeneration due to its elasticity, degradability and pro-regenerative inflammatory response.



Regenerex™, a polymer invented by Dr. Wang, is the first biodegradable elastomer introduced to the market and now commercially available and approved for clinical use. (image copyright: Secant Group)

INTERCAMPUS COLLABORATION ON BRAIN IMAGING

\$9M GRANT WILL CREATE NEUROTECH RESEARCH HUB

by Syl Kacapyr (originally published in the Cornell Chronicle)

As neuroscientists examine challenging questions about the complexities of the central nervous system, new tools to be developed at Cornell will provide them with an unprecedented glimpse into the inner workings of the brain thanks to a five-year, \$9 million grant from the National Science Foundation.

The grant will establish the Cornell Neurotechnology NeuroNex Hub, which will focus on researching, developing and disseminating new optical imaging tools for noninvasive recording of neural activity in animals. It will also establish the Laboratory for Innovative Neurotechnology at Cornell, where engineers and biologists will collaborate on developing and testing the tools.

The hub aims to overcome three barriers faced by neuroscientists:

Deep imaging of intact brains

Multiphoton microscopy, invented at Cornell, has allowed neuroscientists to record the activities of individual neurons up to approximately 1 millimeter deep into a mouse brain. However, the mouse brain is about 8 millimeters thick, and even thicker in larger animals. The hub will optimize a recently developed three-photon microscope and focus on making the tool widely available.

Imaging of large and multiple neural regions

The best whole nervous system images have come from laval zebrafish, but existing imaging tools cannot holistically view larger brains, even at the scale of an adult zebrafish. Using a combination of two- and three-photon microscopy, the hub will develop a new tool to simultaneously observe neurons in different regions of the mouse brain and the spinal cord.



Principal investigators for the Cornell Neurotechnology NeuroNex Hub. From left: Chris Xu, professor of applied and engineering physics; Joseph Fetcho, professor of neurobiology and behavior; Nilay Yapici, assistant professor of neurobiology and behavior; Chris Schaffer, associate professor of biomedical engineering; Mert Sabuncu, assistant professor of electrical and computer engineering and of biomedical engineering.

“AT THE CORNELL NEURONEX HUB, WE WILL CREATE, OPTIMIZE AND DISSEMINATE THE NEW TOOLS THAT WILL ENABLE BIOLOGISTS TO ATTACK SOME OF THE IMPOSSIBLE PROBLEMS IN NEUROSCIENCE.”

—Dr. Chris Xu, professor of applied and engineering physics

Faster imaging for volumetric recording

To record large numbers of neurons, high-speed imaging will be achieved through the development of an adaptive illumination microscope in which the sample becomes an integral part of the imaging system. By leveraging prior

knowledge of the sample, optimum laser exposure will be used to record the activities from a large number of neurons.

Within five years, the hub aims to integrate the three tools to demonstrate the deepest, high-resolution, large-scale neural activity recording ever achieved.

“It is well recognized that neurotechnology development is essential to push the envelope of neuroscience.

At the Cornell NeuroNex Hub, we will create, optimize and then disseminate the new tools that will enable biologists to attack some of the impossible problems in neuroscience,” said Chris Xu, professor of applied and engineering physics, and principal investigator for the hub.

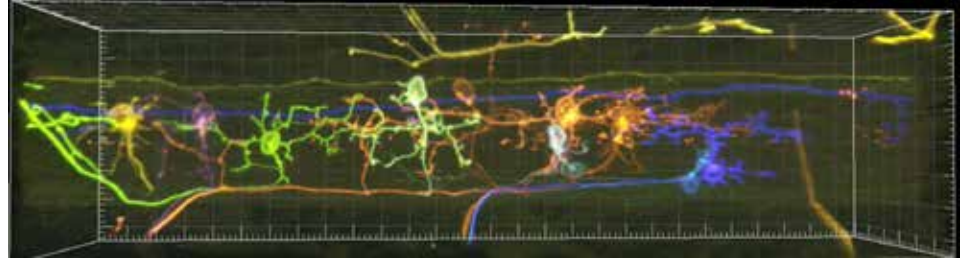
Using the technology, biologists hope to explore unanswered questions, such as how animals consciously switch from autonomous locomotion to deliberate limb placement.

“Behaviors emerge from interactions of neurons widely distributed in brains, but we do not yet have the tools we need to simultaneously monitor single-cell activity widely in the brains of diverse species,” said Joseph Fetcho, professor of neurobiology and behavior, and a senior investigator for the hub.

The hub is part of the larger Cornell Neurotech program launched with a multimillion-dollar gift from the Mong Family Foundation in 2015 with the same goal of encouraging cross-disciplinary research to develop new tools for neuroscience. The hub will also educate

“[CORNELL] IS AN IDEAL PLACE TO MAKE GREAT DISCOVERIES IN NEUROTECHNOLOGY AND NEUROSCIENCE. WE NOT ONLY HAVE THE COLLABORATIVE ENVIRONMENT, BUT WE HAVE A PROUD HISTORY OF PIONEERING NEW TECHNOLOGIES.”

—Lance Collins, Joseph Silbert Dean of Engineering



Labeling with combinations of fluorescent proteins with a method called “Brainbow” enables the visualization and tracking of motoneurons with complex branching patterns in the zebrafish spinal cord. (source: Fetcho Lab)

the next generation of scientists by involving graduate and undergraduate students who will learn to collaborate across such disciplines as biology, computer science, engineering, medicine and physics.

“In many ways, Cornell Neurotech has been growing at a rate faster than we could have anticipated,” said Gretchen Ritter ‘83, the Harold Tanner Dean of Arts and Sciences. “This trajectory is prompted both by the leading-edge imaging work of its researchers, as well as the attention that Cornell’s investment in neurotechnology has been generating more broadly.”

Added Lance Collins, the Joseph Silbert Dean of Engineering: “It’s been

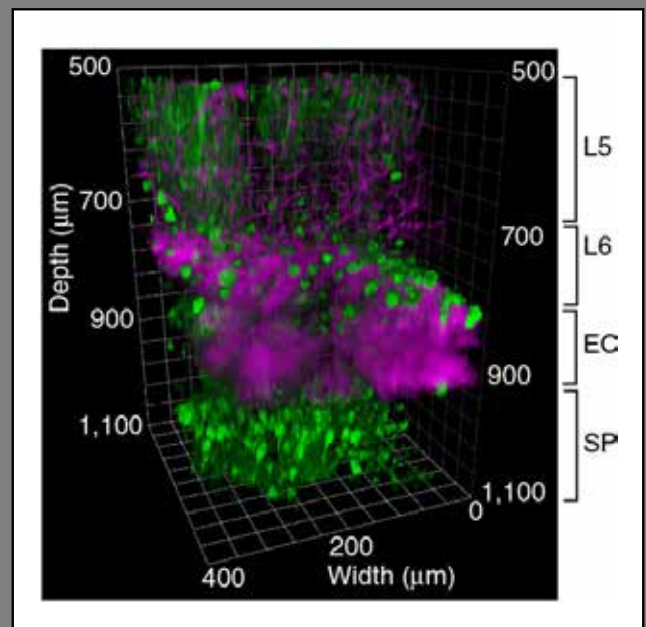
exciting to see this Neurotech initiative blossom here at Cornell, which really is an ideal place to make great discoveries in neurotechnology and neuroscience. We not only have the collaborative environment, but we have a proud history of pioneering new technologies.”

A large number of academic and industry partners across the nation have already signed on to participate in the hub, which will be led by Xu, Fetcho, Chris Schaffer, associate professor of biomedical engineering, Nilay Yapici, assistant professor of neurobiology and behavior, and Mert Sabuncu, assistant professor of electrical and computer engineering and of biomedical engineering.

DEEP THOUGHTS WITH THREE-PHOTON MICROSCOPY

Hippocampus, a brain region critical for memory formation, has been imaged in the mouse in the past by removing overlying brain tissue. However, the Xu Lab has demonstrated imaging in this deep region of brain with three-photon microscopy without disrupting any part of the brain. The ability to go deeper is not just an exciting technical feat, it enables neuroscientist to study regions of anatomy previously inaccessible.

In this image, neurons expressing GCaMP6s are shown in green and third harmonic generation which shows myelin is shown in magenta. Neural activity was recorded from neurons in the SP layer of the hippocampus.



A NEW SPACE

CHANGING SPACES

This summer the Meinig School began a major renovation of Weill Hall as part of a multi-year, three-phase plan to develop new space for its growing research and teaching programs. Included in the projects are renovations to Weill and Comstock Halls. Designed by Levenbetts and executed by the general contractor Edger Enterprises, the \$3 million phase one project began in May with all three phases expected to be finished by 2023.

The first phase of the plan, underway since May 2017, will create a more prominent home for Meinig School administration in the Weill Hall west wing space formerly occupied by a conference room and Synapsis Cafe. Included in the administrative suite will be a reception area with two workstations, a kitchen area, six private offices (some shared), a 12-person meeting room and a multi-purpose room that seats up to 49. The basement area directly below this

administrative suite, which originally contained facilities and dining storage rooms along with an M.Eng. design lab, will now contain several new spaces to serve the student programs, including a collaboration and ideation studio twice the size of the original, a project room/wet lab, a fabrication lab, a computer lab and technician office. The project team expects the design/ideation lab ready for use by September 15, with the remainder of the first-phase space ready by mid-October.

The second phase, expected to begin in the fall of 2017, "will be substantially more challenging due to the complications of renovating space currently occupied by active programs and the multitude of project stakeholders," said Todd Pfeiffer, Weill Hall facilities director. Phase two involves consolidating Biological Statistics and Computational Biology (BSCB) and the Department of Statistical Science (DSS), currently located in Weill Hall and several other facilities, into a new addition

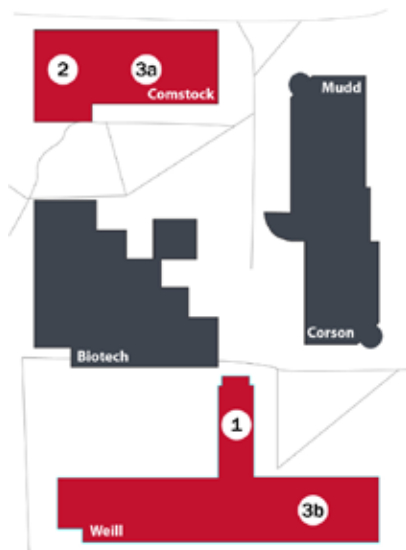
that includes two new stories above the south wing of Comstock Hall. Phase two also involves adding some new teaching and laboratory space on the first floor of Comstock Hall for Meinig School classes as well as renovations to existing teaching lab spaces to be shared with Introductory Biology teaching labs.

Phase three of the project will add faculty research laboratories in the first-floor north wing area of Weill Hall vacated by Meinig School administrative staff and BSCB staff during the first two phases. Also during phase three, the existing basement BME teaching lab spaces will be converted to BME faculty research laboratories.

"After a lot of careful planning, we are excited to see the first phase underway," said Meinig School Director Marjolein van der Meulen of the project. "The plan gives us much needed space and equipment to strengthen and expand our growing research and teaching programs."

Project Phases Schematic:

Biology Quad buildings including Weill and Comstock Halls with project phase locations (indicated in circles).



Phase 1: A New School Home

Design of the new Meinig School administrative suite (A-C), as rendered by the architect, Levenbetts, and the student collaboration and ideation studio (D) open to BME students in September 2017.



NEW DEVICE COULD MAKE CLOSING SURGICAL INCISIONS A CINCH by Bridget Kuehn (originally published in the Cornell Chronicle)



Jason Spector



David Putnam

Like many surgeons, Dr. Jason Spector is often faced with the challenge of securely closing the abdominal wall without injuring the intestines. If the process goes awry, there can be serious consequences for patients, including bowel perforations or a hernia

at the incision site. Often, repairing these complications requires additional surgeries.

"I've done a lot of incisional hernia repairs on people who've had two, three or more hernia repairs," said Spector, professor of surgery (plastic surgery) and of plastic surgery in otolaryngology at Weill Cornell Medicine, an adjunct professor in the Meinig School of Biomedical Engineering and a plastic surgeon at NewYork-Presbyterian/Weill Cornell Medical Center.

Unsatisfied with the existing tools to help prevent these poor outcomes, Spector turned to his long-time collaborator David Putnam, associate professor in the Meinig School. Spector asked for material that would be strong enough to protect the intestines from a needle puncture and bendable enough to insert through a laparotomy incision that would quickly dissolve in the body.

As it turned out, Putnam's then graduate student Nicole Ricapito had created and was testing a material that met those specifications. In a study published

May 31 in *Acta Biomaterialia*, the collaborators and their colleagues demonstrated that the compound was strong enough to protect mice intestines during suturing of the abdomen and quickly dissolved in the body.

"It was bendy and stretchy and degraded really fast," Putnam said. "It was a match made in heaven."

The compound is made up of polyethylene glycol, a chemical compound used in laxatives and many personal care products, and dihydroxyacetone (DHA), a natural byproduct of the breakdown of glucose in the body. The U.S. Food and Drug Administration has approved the use of DHA in nutritional supplements and spray tanners. The polyethylene glycol lends flexibility to the device and DHA adds strength, Putnam said. Both break down when exposed to water in the body.

In the study, the material was used in lieu of plastic or metal devices called retractors that surgeons typically use to protect the intestines. Traditional retractors must be removed before the incision is completely closed, leaving the surgeon to carefully make the final stitches without protection for the intestines. But Spector and Putnam's device is left behind in the abdominal cavity, allowing the final sutures to be made with protection still in place. The study found that the device dissolved within three hours of the surgery, leaving no scarring or signs of toxicity.

The next step for the collaborators will be to try to replicate the results with further preclinical testing. If further study of the device shows it to be safe and effective, Spector and Putnam hope to

THE DEVICE



A standard for abdominal fascia closure needle engaging the device, a rubbery elastomer that degrades rapidly in the presence of water. The device shield is flexible and handled easily (seen with surgical forceps) with sufficient resistance to inadvertent needle puncture.

pursue commercial development. Cornell University has filed a patent for the device.

If all goes well, Spector said this flexible material might one day help surgeons more confidently and securely close abdominal incisions.

"I hope it will lead to fewer incisional hernias," he said. "In addition, the implantable device could be used in a multitude of situations where surgeons want to protect vital structures from inadvertent needle puncture, but using a removable retractor would prove difficult or impossible."

Read more:

"Transient phase behavior of an elastomeric biomaterial applied to abdominal laparotomy closure," Kaymakcalan OE, Jin JL, Sun Z, Ricapito NG, Clare McCorry M, Morrison KA, Putnam D, Spector JA. *Acta Biomater.* 2017 May 30. (17)30344-6.

NEW ORGAN TRANSPLANT MONITORING PROMISES BETTER PATIENT CARE by Syl Kacapyr (originally published in the Cornell Chronicle)

Using a combination of DNA sequencing and computer science, a team of researchers has developed a new method for monitoring the health of organ transplant patients—one that promises to provide life-saving clues to diagnose organ rejection at an early stage.



Iwijn De Vlamincq

More than 180,000 people live with organ transplants in the U.S., and many undergo costly and risky biopsies to determine if their body is accepting or rejecting an organ. An alternate method demonstrated by Iwijn De Vlamincq, assistant professor of biomedical engineering at Cornell University, found that cell-free DNA (cfDNA), essentially fragments of dead cells derived from an organ, can be detected in a patient's bloodstream and used as a proxy for the organ's health. The more cfDNA that is discovered, the greater the likelihood the organ is failing. But without knowing the donor's DNA—which is often the case—doctors have no reference to identify the cfDNA.

Now a research team from Cornell and Stanford University has demonstrated a method for identifying cfDNA without the donor. To address the issue, the team developed a computer algorithm that can estimate the donor-derived cfDNA and can predict heart and lung rejection with an accuracy similar to that in cases where donor information is available. The method is detailed in the paper "Quantification of transplant-derived circulating cell-free DNA in absence of a donor genotype," published Aug. 3 in the journal *PLOS Computational Biology*.

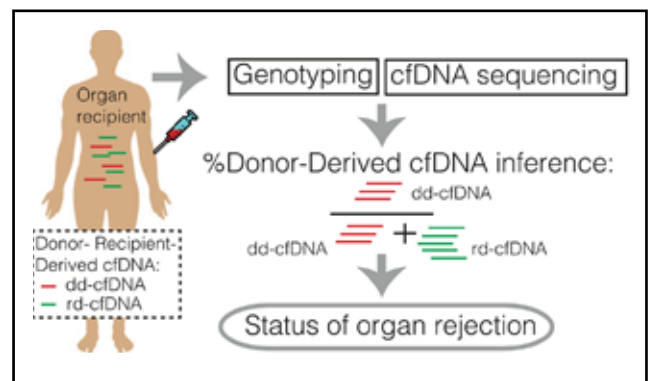
"Our method can be easily adapted to monitor the health of other transplanted organs such as liver and kidney," said De Vlamincq, adding that the paper details a refined algorithm to address closely related recipients and donors, a scenario that is common in bone marrow and kidney transplantations.

The algorithm uses publically available genotypes and techniques of relationship inference to model which cfDNA fragments are most likely from the organ. "Specifically, the model infers the donor's most probable ancestral population and accounts for close relationship by detecting DNA segments that are identical due to close descent," said Eilon Sharon, a Stanford postdoctoral researcher and co-author of the paper.

The findings alleviate a major barrier to using cfDNA detection—also known as genome transplant dynamics—instead of biopsies, and researchers hope the computer science-based method will help save lives. Accurate monitoring of organ health is essential to a patient's long-term survival; the median survival rate for a heart transplant patient is 11 years and only 5.3 years for recipients of lungs.

"We are excited about the multiple applications for this method in transplantation medicine and we are looking forward to seeing it used in clinical settings," said De Vlamincq.

The study was funded by the National Institutes of Health and EMBO (European Molecular Biology Organization) Long Term Fellowships.



THE APPROACH

Monitoring the health of the allograft is a critically important component of post-transplant therapy. De Vlamincq and collaborators demonstrated that cell-free DNA (cfDNA) enables diagnosis of post-transplant rejection. In this approach, genotyping of the recipient and the donor together with shotgun sequencing of cfDNA are used to quantify the proportion of donor-derived cfDNA (dd-cfDNA). This approach offers key advantages over the current practice of organ biopsy, which is invasive, costly, and risky. However, the difficulty and cost of establishing a pure reference donor genotype is a major barrier to its widespread clinical implementation. This new paper describes a computational approach that enables an accurate estimation of dd-cfDNA levels without the need for a donor genotype, as well as an application of cfDNA in the noninvasive diagnosis of Graft Versus Host Disease, a serious and difficult-to-diagnose complication of allogeneic bone marrow and stem cell transplantation.

Read more: "Quantification of transplant-derived circulating cell-free DNA in absence of a donor genotype." Sharon E, Shi H, Kharbanda S, Koh W, Martin LR, Khush KK, Valentine H, Pritchard JK, De Vlamincq I. *PLoS Comput Biol*, 2017 Aug 3;13.

TAILORED ORGANOID MAY HELP UNRAVEL IMMUNE RESPONSE MYSTERY

By Tom Fleischman (originally published in the Cornell Chronicle)

What if you could design an adaptable, biomaterials-based model of an organ to track its immune response to any number



Ankur Singh

of maladies, including cancer, transplant rejection and the Zika virus? The lab of Ankur Singh, assistant professor in the Sibley School of Mechanical and Aerospace Engineering and Meinig School of Biomedical Engineering, has asked—and begun to answer—that very question.

Singh and a team of researchers from the Meinig School of Biomedical Engineering and Weill Cornell Medicine have developed a modular immune organoid that can replicate the anatomical structures found within lymph nodes. The organoid mimics the early stages of a germinal center, where B cell differentiation and initiation of immunological responses take place during infection.

By manipulating the components of the organoid, the researchers are able to dictate the action of the immune-cell response and demonstrate, for the first time in a controlled manner, the role of the lymph node’s environment in immune cell activation. And as opposed to two-dimensional models, the 3-D organoid enables much quicker and more plentiful replication of B cells, which are antibody-producing lymphocytes.

“This method presents the first lab-made 3-D immune tissue that allows you to change things found in immune organs once you get infected—the altered extracellular matrix, cell-cell interactions—and control the pace at which immune

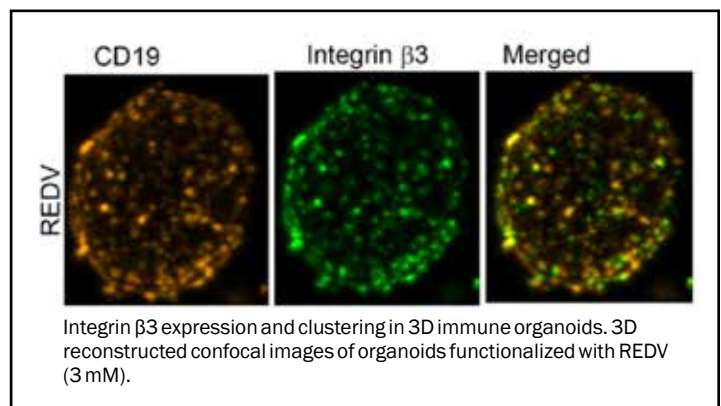
cells respond,” Singh said.

Their paper, “Modular immune organoids with integrin ligand specificity differentially regulate ex vivo B cell activation,” was published Dec. 13 in the American Chemical Society journal *Biomaterials Science & Engineering*.

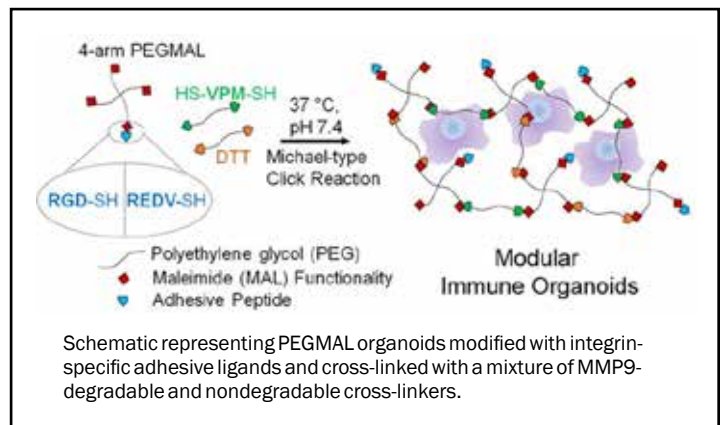
Co-lead authors were doctoral students Alberto Purwada and Shivem B. Shah of the Meinig School. Also contributing were Dr. Ari Melnick, the Gebroe Family Professor of Hematology/Oncology at Weill Cornell Medicine, and Wendy Beguelin, an instructor in the Melnick Lab.

A related paper, “Immuno-engineered organoids for regulating the kinetics of B-cell development and antibody production,” was published Dec. 22 in *Nature Protocols*, a journal geared to bench researchers. Singh and Purwada authored that work.

Germinal centers (GCs) are dynamic structures within lymphoid tissues that develop once B cells receive activation signals from surrounding immune cells in the presence of infection. During the GC process, naïve B cells (unexposed to antigens) differentiate into a specific immune marker (GL7) and then rearrange



Integrin $\beta 3$ expression and clustering in 3D immune organoids. 3D reconstructed confocal images of organoids functionalized with REDV (3 mM).



Schematic representing PEGMAL organoids modified with integrin-specific adhesive ligands and cross-linked with a mixture of MMP9-degradable and nondegradable cross-linkers.

into high-affinity B cell receptors, but the underlying mechanisms of this progression aren’t understood.

Gaining a full understanding of those mechanisms, through the use of a “plug-and-play” system like the organoid that can be tailored to a specific disease, could provide better understanding of B cell biology and responses to a wide range of maladies, including cancer, asthma, arthritis and transplant rejection, along with faster responses to emerging infections such as H1N1 and Zika.

“Up to now, we have not been able to study the earliest steps of malignant transformation of cells in the immune system,” said Melnick, who is also a member of the Sandra and Edward Meyer

Tailored Organoid, continued from p. 15

Cancer Center at Weill Cornell Medicine. “Now we can design experiments that will give us unprecedented understanding of how these tumors form, which will in turn provide critical insights into how to treat these diseases.”

Singh says the organoid—in either a synthetic polyethylene glycol or semi-synthetic gelatin-based platform—offers a quick and robust method for mimicking the GC microenvironment. That eliminates the need to implant the model inside a living creature.

“It’s living tissue that allows you to model certain parameters that you cannot do in vivo,” said Singh, who last week was selected to receive the top young

investigator award from the Society for Biomaterials.

Singh said his group published its findings in *Nature Protocols* because they want the greater scientific community to know about it.

“Our goal was to make this technology available to scientists who can use this to understand immunology in a much better way,” he said. “I have a role and responsibility in advancing the science by putting this forward.”

More work in this area is ongoing, said Singh, who earlier this year was one of five Cornell recipients of a National Science Foundation CAREER award, which helped support this work. But he

noted that the ability to drive immune reactions through the use of organoids will “grant us the ability to reproduce immunological events ... for more rapid development and better understanding of B cells.”

This work was also supported by the National Institutes of Health.

Read more:

“Modular Immune Organoids with Integrin Ligand Specificity Differentially Regulate Ex Vivo B Cell Activation.” Alberto Purwada, Shivem B. Shah, Wendy Beguelin, Ari M. Melnick, and Ankur Singh. *ACS Biomater. Sci. Eng.*, 2017, 3 (2), pp 214–225.

“Immuno-engineered organoids for regulating the kinetics of B-cell development and antibody production.” Alberto Purwada and Ankur Singh. *Nature Protocols.*, 2017, 12, pp 168–182.

SAVE THE DATE



A SYMPOSIUM
honoring the achievements of

Michael L. Shuler
Samuel B. Eckert Professor of Engineering

JUNE 22, 2018
Cornell University
Ithaca N.Y.

shulersymposium.engineering.cornell.edu

Hosted by:
Robert Frederick Smith School of Chemical and Biomolecular Engineering,
Nancy E. and Peter C. Meinig School of Biomedical Engineering
and Cornell Engineering.

Please join us as we honor the achievements of Michael L. Shuler, Samuel B. Eckert Professor of Engineering, during a symposium to be held June 22, 2018 at Cornell University in Ithaca, New York. Featuring a keynote address by George Georgiou (Ph.D. '87), Laura Jennings Turner Chair in Engineering at The University of Texas at Austin.

Contact the symposium organizers with any questions via email at shulersymposium@cornell.edu or phone at (607) 255-6331.

TEACHER-SCIENTIST PARTNERSHIPS IN STEM CELL BIOLOGY

This summer, 10 New York state middle and high school biology teachers spent eight weeks at Cornell participating full time in a new program that pairs teachers with faculty and graduate students for research, learning and curriculum development experiences. Funded by a four-year grant from the New York State Department of Health, the NYSTEM Stem Cell Research Experience for Pre-College Teachers (NYSTEM RET) was awarded to Meinig School associate professors Jonathan Butcher and Chris Schaffer last fall.

"The aim [of the program]," says Butcher, "is to shift the teaching of science from a collection of static book facts to a focus on science as a creative, dynamic process for discovery experienced in professional spheres." As detailed in the grant, the NYSTEM RET program defines three mechanisms for facilitating this shift: by giving teachers authentic research experiences, by putting graduate fellows in classrooms as "resident scientists," and by supporting teachers in creating new curricular materials that engage students in scientific discovery.

Coordinated by the Meinig School of Biomedical Engineering in conjunction with Cornell's Stem Cell Program, the program hosts teachers from upstate New York school districts. This year, teachers from Ithaca, Lansing, Newfield, Cortland, Elmira, Horseheads, Afton and Syracuse took a graduate course on stem cell biology and scientific research, worked with a partnered graduate fellow to create new curricular materials for their classrooms and participated in research on stem cell biology.

Research projects were rooted in a number of different departments on campus, but all had a focus on stem cell research, with participating Cornell faculty and graduate students hailing

from Biomedical Engineering, Biological and Environmental Engineering, Mechanical and Aerospace Engineering, Molecular Biology and Genetics, Biomedical Sciences, Microbiology and Immunology, Nutritional Sciences, and the Baker Institute for Animal Health.

"I couldn't have asked for a more challenging and rewarding educational experience," said Ryan Asmus, a biology teacher at Syracuse Academy of Science, who worked in the Meinig School's Cosgrove Lab on protein signaling pathways in muscle stem cells. "I have learned so much about the biochemistry of stem cells and their importance in the study of cancer and cancer therapies, specifically in cancer and tissue regeneration. These experiences have caused me to refocus on the skills students can develop from inquiry-based investigations. I look forward to integrating this material into my own high school classes."

"It was an eye-opening and rewarding experience all around," said Meinig School Assistant Professor Ben Cosgrove of working with Asmus. "He was a quick learner and valuable contributor to our research team, and we enjoyed working with him on the challenges of translating our stem-cell science to the high school classroom. We look forward to staying connected to Ryan's teaching efforts throughout the next year."

Cosgrove added, "The NYSTEM RET program provides an invaluable opportunity to bridge the research lab-classroom divide and interact directly



Summer NYSTEM RET participant Ryan Asmus works with Ph.D. student Alex Loiben on a STEM research project in the Cosgrove Lab.



Professor Paul Soloway presents a lecture on molecular genetics to NYSTEM RET participants.

with teachers from a variety of classroom environments."

As follow up to the summer program, graduate fellows will make multiple visits to each teacher's classroom during the coming academic year as their new curriculum is implemented, and teachers will also participate in call-back sessions.

With exposure to real-world, cutting-edge experiences like these, teachers can bring research into the pre-college classroom, with an ultimate goal of helping students to see the power of science for addressing real-world problems.

M.ENG. PROJECT BRINGS NON-DRUG SOLUTION FOR MIGRAINES TO LIFE

When the medical technology startup eNeura was ready to take its next generation migraine solution to market in 2013, Cornell BME M.Eng. students were tapped for help. Designing a physical package and user interface became an M.Eng. project that resulted in a product for eNeura. eNeura founders Drs. Robert and David Fischell (B.S. '75, Ph.D. '80 AEP), serial entrepreneurs who had commercialized medical devices before, had ideas for the design but knew the project needed additional resources with knowledge and creativity to make those ideas into prototypes for consideration and testing. David Fischell, an emeritus trustee and the current chair of the Meinig School Advisory Council, recalled being asked to keep an eye out for industry projects that might be suitable for students in the M.Eng. program. eNeura's project seemed a good fit for the request.

"The vision to connect Cornell Engineering M.Eng. students with external sponsors," said David Lipson, then M.Eng. program coordinator and a senior lecturer in biomedical engineering "came from Mike Shuler." Shuler, the Samuel B. Eckert Professor of Engineering and chair of BME at the time, had been integral to establishing the Department of Biomedical Engineering, now the Meinig School, as part of the College of Engineering in 2004, and had long been a proponent for connecting biomedical engineering at Cornell with companies and individual physicians hoping to develop a prototype of a clinical concept. "The specific opportunity with eNeura came about," said Shuler "because of a need and also the Fischells' faith that our students could make real progress on the problem."

Together, the Fischells, Shuler and Lipson defined the project and presented the opportunity to students beginning

the 1-year M.Eng. program. From the interested students who came forward, they assembled a team comprised of Priyanka Venkatesh, Qui Rui, Abvirab Deb, Ji Heng Fei and Rachel Hyder. It was this team that worked concurrently with eNeura's engineers and leadership team operating in California during the 2013-2014 academic year. "The company worked closely with the chosen M.Eng. students—a group of highly motivated individuals," said Shuler, "and David Lipson's supervision was critical.

At the start of the project, the M.Eng. team was asked to create a design to meet user requirements provided by eNeura. After brainstorming around those requirements and details with the eNeura team, the Cornell M.Eng. team divided tasks based on individual skills and set to work.

"The students got to develop the user interface for this device for a discriminating customer," said visiting lecturer Jack Thompson, who advised part of the project. "A common challenge for the design engineer (or team) is to refine the sometimes unclear vision of the product manager into a demonstrable embodiment. But when the product manager says 'this is exactly what I had in mind!' the vision has been distilled into a definition that can be detail engineered and produced. This is valuable experience and a glimpse into how new products are developed."

"This project was an invaluable introduction to industry—and the highlight of my time in the M.Eng. program," said Rachel Hyder, a student member of the team who worked on the electronics for the interface. "The partnership meant direct access to eNeura's engineers and founders. It also meant a very tangible end goal, a design used in an FDA-approved, marketed medical device—kind of a pipe



The second generation TMS device from eNeura (top); an intermediate picture of the electronics developed by the Cornell BME M.Eng. team (middle); and the final design (third generation device) that was presented to eNeura (bottom).

dream for a 22-year-old BME student." Hyder recalled the experience also helped develop effective communication skills necessary for working with a cross-functional team—a guarantee in today's biotech industry. She said frequent update meetings with the eNeura engineers kept the project moving forward; quick feedback and advice kept the project from

derailing. "The current device design, the sTMS mini (shown right)," said Hyder, is very similar to the one we developed." The mini, approved by the FDA in 2016, is now being rented to patients around the U.S.

Hyder's involvement with the eNeura-Cornell partnership led her to join another Fischell company, Angel Medical Systems, as Field Clinical Engineer after graduating in 2014. She spent a rewarding two years there before moving on to Regeneron Pharmaceutical where she currently works as a validation specialist, qualifying large scale manufacturing equipment and managing validation projects.

Of the eNeura-M.Eng. collaboration, David Fischell said, "My dad (Robert) and I were extremely impressed by the creativity and engineering of the student team."

With the device now available to migraine sufferers through prescription, the collaboration appears to be a success, and projects with external sponsors remain a cornerstone of the Meinig School's M.Eng. program.

The Project:

"One of the challenges," said Thompson, "was the user interface." To operate effectively, the device needed to be in contact with a specific place at the back of the head during treatment, which meant its design had to accommodate a comfortable and effective grip that allowed for placement accuracy for treatment. Because a user couldn't see the device when in use, it also meant that a typical graphic/LED interface was not useful for indicating treatment progress.

For the physical packaging, the team proposed an approach that distributed the components (circuit board, treatment coil and two large capacitors) and would fit the patient's hands comfortably. They prototyped several iterations of this shape using 3D printing with a high-quality material/method to achieve a smooth and pleasing prototype surface executed by an

external 3D print service.

For the device's user interface, the team simulated operation of the device using an Arduino board to emulate the device microcontroller. Next they built a prototype of a user interface consisting of buttons, a speaker and LEDs to indicate battery charge, system readiness and status. The final interface incorporated a pushbutton start that progresses through an aural system of tones that increases in tempo as treatment progresses toward completion. Lastly, they programmed the Arduino to demonstrate the interface concept packaged in the 3D-printed case. This user interface and geometric prototype was presented to Fischell and other supporting personnel at eNeura, who were impressed with the result.

About Migraines:

In the U.S., over 36 million people are affected by migraine, with an estimated annual cost to the country of over \$24 billion. However, 70% of patients are currently dissatisfied with current treatment options, with most patients citing side effects or lack of efficacy as their primary concerns. The eNeura sTMS mini has the ability to provide life-changing therapy for the 5.5 million Americans who suffer from migraines but cannot take medications. As migraines primarily affect people between 20 to 55 years of age, treating the disease without side effects is crucial.

Migraine can result in lost personal time, lost family time, lost days of work, co-morbid psychiatric disorders, and lost productivity for employers. There have been no new acute treatment options for migraine since the 1990s. Triptans are commonly used but can produce severe side effects (tightness in chest/throat, fatigue, drowsiness, difficulty concentrating, GI problems) and

many patients are not candidates for these drugs.

BOTOX® is currently used to treat approximately 200,000 chronic migraine patients, growing at 20%+ per annum. The Migraine Research Foundation estimates that U.S. employees take 113 million sick days per year with migraines, creating an annual loss of \$13 billion.

THE PRODUCT

eNeura's SpringTMS (sTMS) mini is a portable, non-drug option for treating migraines. The device operates based on the concept of single-pulse, transcranial magnetic stimulation (sTMS), which uses sub millisecond magnetic pulses of 1 Tesla intensity to electrically stimulate neurons in the brain. eNeura markets its sTMS device as the world's only safe, clinically proven, non-drug migraine treatment for both prevention and acute treatment of migraine. sTMS has none of the side effects associated with medications, is FDA and European CE Mark approved, and is currently available by prescription in the United States and United Kingdom.



The current product, the sTMS mini, as shown on the eNeura website. www.eneura.com

HONORS & AWARDS

CORE FACULTY



Assistant Professor
Ilana Brito

Participated on a panel at the World Economic Forum; awarded a Sloan Fellowship and a \$25,000 grant from the Internationalizing the Cornell Curriculum Competition.



Professor Adjunct
David Fischell

Elected a National Academy of Inventors 2016 Fellow.

Julia Chen, a Ph.D. student in the van der Meulen Lab, received a Young Investigator Travel Grant award from the American Society of Bone and Mineral Research.



Associate Professor
Jonathan Butcher

Awarded a patent (No. 9,629,713) that describes a biomedical implant for use in fluid shear stress environments.



Assistant Professor
Nozomi Nishimura

Awarded a 2017 Cook Award for commitment to women's issues.

Benjamin Cohen, a Ph.D. student in the Bonassar Lab, received a Scientist Award for his presentation at the TERMIS-AM 2016 Conference.

Peter DeNero, a Ph.D. student in the Fischbach-Teschl Lab, was awarded a K. Patricia Cross Future Leaders Award.

Liz Feeney, a Ph.D. student in the Bonassar Lab, won a Poster Teaser Presentation Award at the 2017 meeting of the Orthopaedic Research Society.



Assistant Professor
Ben Cosgrove

Selected a 2017 Young Innovator of Cellular and Molecular Bioengineering.



Associate Professor
Chris Schaffer

Awarded the Mr. & Mrs. Richard F. Tucker Teaching Award from Cornell Engineering.

Yunye Gong, a Ph.D. student in the Doerschuk Lab, won a Google Ph.D. Fellowship in machine learning.

Frank He, a Ph.D. student in the Fischbach-Teschl Lab, was inducted into Bouchet Graduate Honor Society.

Rebecca Irwin, a Ph.D. student in the Bonassar Lab, was awarded a grant from the Arthroscopy Association of North America (AANA).



Associate Professor
Chris Hernandez

Elected Fellow of the American Society of Mechanical Engineers (ASME) and awarded the Zellman Warhaft Commitment to Diversity Award.



Assistant Professor
Ankur Singh

Awarded the 2017 Young Investigator Award from the Society for Biomaterials; received the U.S. Department of Defense Career Development Award.

Mary Clare McCorry, a Ph.D. student in the Bonassar Lab, won 2nd place in the Podium Presentation Award at the 2017 meeting of the Orthopaedic Research Society, published a cover article in *Connective Tissue Research*, and was accepted to AIMBE's FDA Scholars Program.

Zeinab Mohamed, a Ph.D. student in the Daniel Lab, won an NSF fellowship.



Associate Professor
Claudia Fischbach-Teschl

Awarded a grant from the Human Frontiers Science Program to study breast cancer's effect on bone composition, and a Research Excellence Award from Cornell Engineering.

STUDENTS & POSTDOCS

GRADUATE STUDENTS

Alexander Boys, a Ph.D. student in the Bonassar Lab, received a travel award from the International Conference on the Chemistry and Biology of Mineralized Tissue (ICCBMT).

Alberto Purwada, a Ph.D. student in the Singh Lab, won the 2017 Society for Biomaterials STAR Award.

Shivem Shah, a Ph.D. student in the Singh Lab, received the Rising Star Award from the Society of Asian Scientists & Engineers.

Adrian Shimpi, a Ph.D. student in the Fischbach-Teschl Lab, won an NSF fellowship.

Madhur Srivastava, a Ph.D. student in the Freed Lab, received travel awards from the Shared EPR Network, the Cornell Graduate School, the International Conference on Electron Paramagnetic Resonance Spectroscopy and Imaging of Biological Systems, the CALS Alumni Association Academic Enrichment, the ISMAR 2017 conference, and was selected to attend CGI-U 2017 at Northeastern University in October.

Erik Zavrel, a Ph.D. student in the Doerschuk Lab, received the Three-in-Five Competition Grand Prize (\$500) at the 2017 Design of Medical Devices (DMD) Conference.

Ph.D. students **Carolyn Chlebek** (van der Meulen Lab), **Korie Grayson** (King Lab), **Zeinab Mohamed** (Daniel Lab), and **Josue Santana** (Hernandez Lab) each received awards at the Diversity Programs in Engineering 2017 banquet.

M.Eng. students **Manel Djeflal**, **Aya Gaballa** and **Zeyad Saleh**'s team Resilia received honorable mention at the 2017 Health Tech Hackathon.

UNDERGRADUATE STUDENTS

Jordan Harrod, an undergraduate student in the Bonassar Lab, received an award at the Diversity Programs in Engineering 2017 banquet.

Shannon Hugard, an undergraduate student in the van der Meulen Lab, finished 31st in her debut at the NCAA track & field championships.

Katherine Phillips, an undergraduate student in the Butcher Lab, won best poster presentation in Molecular and Cellular Biology at the Cornell Undergraduate Research Board (CURB) spring research forum.

Jane Wei, an undergraduate student in the Fischbach-Teschl Lab, won a 2017 BMES Student Design and Research (Extended Abstract) Award.

POSTDOCS

David Small, a postdoc in the Schaffer-Nishimura Lab, won an American Heart Association Postdoctoral Fellowship for his project titled, "The influence of hypoxia on cardiovascular precursor cells following injury using in vivo multiphoton microscopy."

ALUMNI

Ed Bonnevie, a 2016 Ph.D. graduate of the Bonassar Lab, received the ORS Society's 2017 New Investigator Recognition Award.

Casey Kraning-Rush, a 2013 Ph.D. graduate of the Reinhart-King Lab, became a practicing Delaware attorney.

Jenny Puetzer, a 2014 Ph.D. graduate of the Bonassar Lab, accepted a faculty position at Virginia Commonwealth University.

Michael Mitchell, a 2014 Ph.D. graduate in the King Lab, accepted an assistant professor position at the University of Pennsylvania Department of Bioengineering.

Kristen Stoner, a 2010 M.Eng. graduate, won the University of Iowa's Department of Biomedical Engineering's 3 Minute Thesis Competition.

Liz Wayne, a 2016 Ph.D. graduate of the King Lab, was awarded a TED Fellowship for 2017 and her talk was highlighted as a big idea at TED 2017.

Jennifer Weiser, a 2013 Ph.D. graduate of the Putnam Lab, accepted a tenure-track faculty position as professor of chemical engineering at Cooper Union for the Advancement of Science and Art.

MEET THE 2017 NSF FELLOWS



The 2017 NSF Fellows Zeinab Mohamed (left) and Adrian Shimpi (right). Photo by Suzanne Aceti Koehl.

The Meinig School of Biomedical Engineering proudly congratulates Zeinab Mohamed and Adrian Shimpi, who each won a 2017 National Science Foundation (NSF) Graduate Research Fellowship (GRFP), which offers three years of stipend support during a five-year fellowship tenure to applicants selected through a national competition.

Mohamed, a Ph.D. student working with Dr. Susan Daniel (CBE), will study the role of outer membrane vesicles secreted by bacteria in pathogenesis and antibiotic resistance. Specifically she aims to look at how these vesicles affect antibiotic efficacy and hopes to create a platform that allows researchers to study how antibiotics affect these vesicles and how the vesicles interact with cell surfaces.

Shimpi will study how obesity-associated changes in the extracellular matrix through a glycan known as hyaluronic acid contribute to tumorigenesis. Specifically, he will be looking at how these changes in the ECM contribute to changes in a subpopulation of tumor cells known as cancer stem cells.

ALUMNI



Parijat Bhatnagar, Ph.D. 2007

Parijat Bhatnagar completed his Ph.D. in biomedical engineering at Cornell under

the supervision of Prof. Carl Batt on microfabrication of biomaterials. After graduation, he worked in semiconductor manufacturing at Intel Corp. followed by a joint postdoctoral training at the MD Anderson Cancer Center and the Houston Methodist Research Institute before starting an independent research program.

Bhatnagar is currently the Program Director for Cell-based Medicine at SRI International. In 2016, he received National Institute of Health (NIH) Director's New Innovator Award. This award, part of the NIH "High-Risk, High-Reward Research" program, is designed to support scientific investigators with exceptional creativity who are conducting high-impact research.

Bhatnagar's research focus is on the development of a platform therapeutics based on T cells engineered with chimeric antigen receptors (CARs). These CAR T cells are designed to actively seek disease microenvironments, assess the disease burden, and produce a calibrated therapeutic response. To assist the clinical implementation, he is also developing technologies for manufacturing clinical doses of CAR T cells. Additionally, he is also directing his approaches to engineer cells as sensors for use in companion diagnostics and early detection.



Robert DeFeo, M.Eng. 2013

Robert DeFeo received his B.S. in chemical engineering from U.C. San Diego in 2009

and his M.Eng. in biomedical engineering from Cornell in 2013. In between the two degrees, DeFeo worked at Genentech and a medical device startup.

While at Cornell, DeFeo focused primarily on tissue mechanics and worked under Dr. Jonathan Black to help develop a device for measuring ligament tension during ACL repair. DeFeo also enjoyed a variety of courses at the Johnson Graduate School of Management, which led him to pursue medical device operations upon graduation.

Following Cornell, DeFeo moved to the San Francisco Bay Area and joined operations at Boston Scientific as a manufacturing engineer on the Lotus aortic valve replacement system. Leveraging his background in chemical engineering and tissue mechanics, he helped commercialize and scale the Lotus operation. Today, still at Boston Scientific, he manages Lotus valve manufacturing where his team of 80+ employees span engineering, production and supply chain.

DeFeo enjoys staying connected with the BME M.Eng. program, whereby he regularly advises students on career strategy and has presented during the seminar series. Whether you're interested in going into industry, want to learn more about manufacturing or are looking for some operational support, feel free to reach out to him!



Rachel Hyder, M.Eng. 2014

As a senior at East Tennessee State University, Rachel Hyder thought the Cornell M.Eng. program may be

out of her reach. As it would happen, it was the first acceptance letter she opened, and her decision was made that day.

At Cornell, Hyder's M.Eng. project team partnered with eNeura, Inc. to design the third generation of a Transcranial Magnetic Stimulation devices for migraine headache relief. The project was the perfect introduction to the biotech industry and catalyst to hone skills developed throughout her engineering education (see article, pp. 18-19).

The eNeura collaboration led directly to a position as a Field Clinical Engineer for Angel Medical Systems based in her hometown of Knoxville, TN. Hyder spent two years traveling around the eastern U.S. meeting with patients participating in the ALERTS clinical trial to prove the efficacy of an implanted device designed to alert patients at the first physiological signs of heart attack. It was Hyder's job to provide technical guidance during device implant procedures, analyze and alter device programming and be a general resource for patients, nurses and physicians.

After a move to Albany, NY (to join the love of her life—a fellow Cornell alum whom she met during the M.Eng. immersion term), Hyder began work as a Validation Specialist at Regeneron Pharmaceuticals. Here, she validates large-scale commercial manufacturing equipment. The position involves project leadership, cross-functional collaboration and fast-paced learning—all skills refined at Cornell.



Brooke Mason, Ph.D. 2014

Brooke Mason completed her Ph.D. in 2014. Her research in the Reinhart-King Lab focused

on angiogenesis, cellular mechanics, biomaterials and imaging.

After graduating, Mason joined Becton Dickinson (BD) as part of the Technology Leadership Development Program (TLDP). She completed her first TLDP rotation at BD Biosciences where she was the project manager for the development of a clinical flow cytometry product. Her role included concept and requirements generation, technical leadership of instrumentation development, and identification and management of multiple international design partners.

Mason's second TLDP rotation is at the BD Innovation Hub. Located in Silicon Valley, her team is part of BD's Corporate Technology & Innovation organization. She is focused on leading the identification and development of new opportunities aligned with BD growth strategies followed by establishing and leading cross-company teams to design and build sustainable healthcare solutions, leveraging exponential technologies while operating in a lean startup environment. Her work also includes collaboration with strategic marketing to define new areas for BD Innovation and leveraging the Silicon Valley entrepreneurial community for inspiration and partnership.



Luke Perkins, M.Eng. 2007

As an M.Eng. student at Cornell, Luke Perkins researched the mechanical properties of

collagen gels in the Bonassar Lab. After graduation, he relocated to Colorado to work for Covidien Respiratory and Monitoring Solutions (now part of Medtronic) in Sustaining Engineering supporting failure investigations and cost savings projects for several lines of disposable medical devices including tracheostomy tubes, endotracheal tubes and pH-based CO₂ detectors. Here, he also worked a program management rotation supporting the launch of PB980 next generation ventilator.

In 2015, Perkins moved back to the Northeast, taking a role as core team leader at Becton Dickinson, where he is responsible for managing a portfolio of sustaining projects for a product line called PhaSeal™, which is used in the safe preparation and administration of hazardous drugs. His team is responsible for supporting global projects encompassing line extensions, cost savings and failure investigations. He has had the opportunity to work closely with a manufacturing team located in Madrid and regional business leaders in the U.S., Europe, China and Japan.

Last fall Perkins matriculated into the SC Johnson School of Business to pursue an Executive MBA. After graduation, he plans to continue working in leadership roles within the medical device industry.



Jennifer Weiser, Ph.D. 2013

Jennifer Weiser earned her B.S. in chemical engineering from Rensselaer Polytechnic

Institute ('06) and her M.S. ('10) and Ph.D. ('13) in biomedical engineering from Cornell under the mentorship of Dr. David Putnam. In the Putnam Lab, Jennifer leveraged her background in chemical engineering, with her previous experience as an exploratory medicinal chemist for Wyeth Pharmaceuticals, to create polymeric biomaterials for long-term controlled release and wound healing. Weiser also took part in the inaugural year of Cornell's NSF GK-12 program, where she partnered with a high school biology teacher in Elmira, NY.

Post-graduation, Weiser and Putnam worked together again for a year, joining the startup company iFyber with a NIH STTR grant to explore one of their polymeric materials for in vivo testing. In 2014, she began a NIH Ruth L. Kirschstein NRSA postdoctoral training fellowship under W. Mark Saltzman in the BME department at Yale University, where she worked on electrospinning polymer scaffolds for wound healing applications. She also collaborated with the Department of Otolaryngology in the Yale School of Medicine and helped to develop a device for the prevention of pharyngocutaneous fistula. Weiser was appointed a visiting assistant professor in the Department of Surgery there to continue these studies.

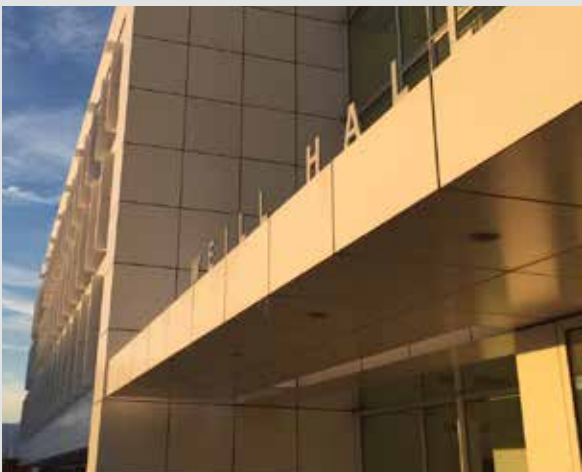
In September 2017, Weiser began as a tenure-track assistant professor of chemical engineering at The Cooper Union for the Advancement of Science and Art in NYC.

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For more information, please contact June Losurdo, 607-254-1643 or JML235@cornell.edu.

