20

20 YEARS OF EXCELLENCE

Columbia | Engineering

Department of Biomedical Engineering

2000–2020

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Cover image (Front to Back): Gliding microtubules (red) self-assemble into bundles within the confines of a microfabricated 2 μm-deep channel pattern by assembling kinesin-1 motor proteins (green) from solution. The microfabricated Columbia Engineering crown pattern is just 261 μm at its widest, smaller than a grain of caster sugar; Close-up image of gliding microtubules, average length of 20 μm, self-assembling into bundles in an unconfined environment. Images courtesy of Shilpika Chowdhury and Stanislav Tsitkov, under the guidance of Professor Henry Hess in the Columbia Biomedical Engineering Laboratory for Nanobiotechnology and Synthetic Biology.

Opposite: Fluorescently stained section of the small intestine in a developing chick embryo. Mechanical constraints provided by differentiation of smooth muscle fibers (red) drive buckling of the inner surface to form villi, finger-like projections that vastly enhance the absorptive surface area of the gut; tissue morphology visualized by staining for cell nuclei (blue). Image courtesy of Professor Nandan Nerurkar, Director of the Morphogenesis and Developmental Biomechanics Laboratory.

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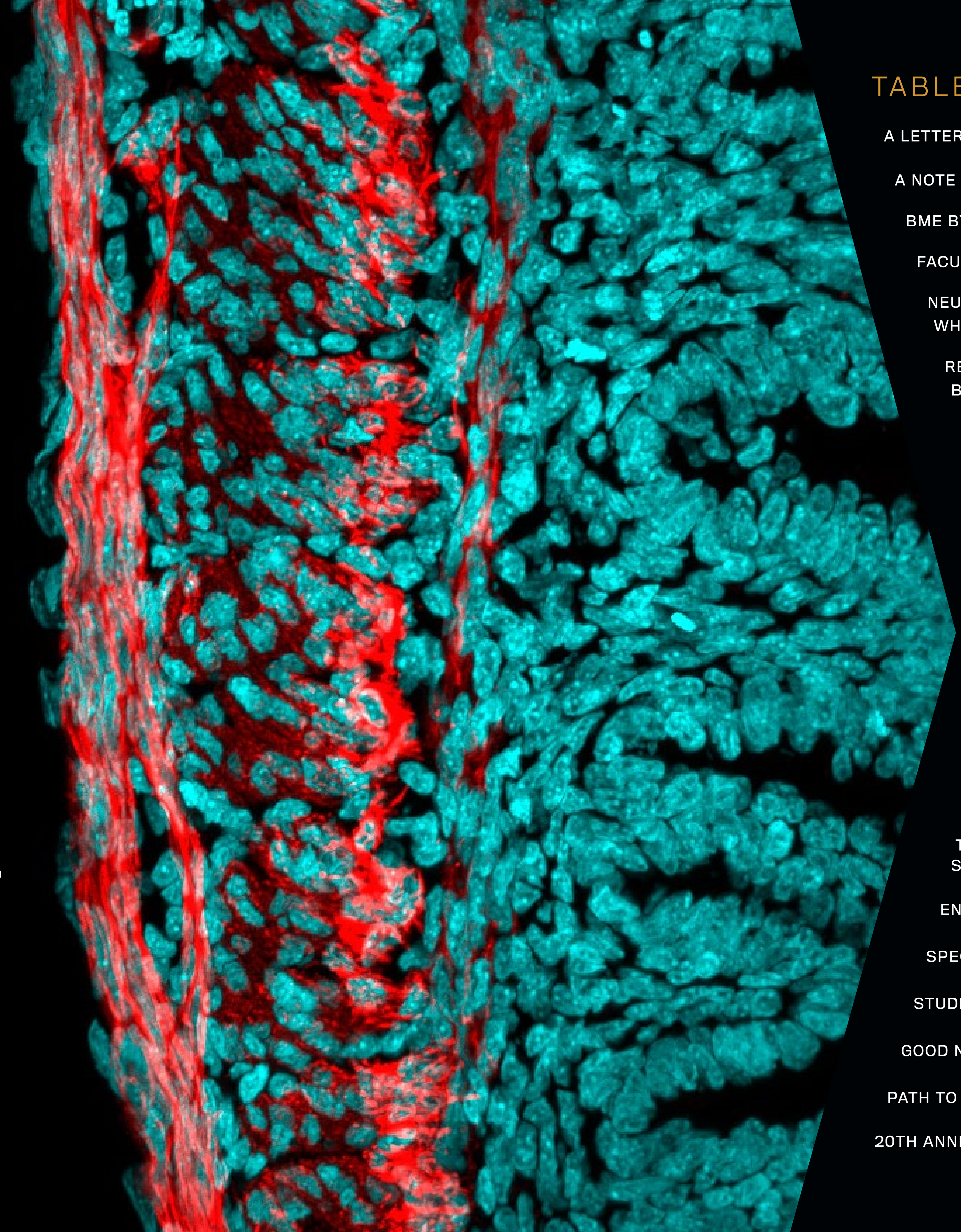

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A LETTER FROM THE DEAN

The history of the Biomedical Engineering Department at Columbia is one of remarkable accomplishment and path-breaking discovery. In 2020, we marked 20 years of advances that have brought significant benefit to society, pioneering engineering frontiers in health and medicine and translating these to practice.

In fact, our history of engineering research and technology for medical applications has roots early in our school. We can trace it back to Michael Pupin, Class of 1883 and a popular professor, who was an early pioneer in the use of x-ray imaging to guide surgery.

From methods for the mass production of penicillin and uncovering the mechanics of blood flow, to the design of artificial organs and collaborations at the Columbia University Irving Medical Center, interdisciplinary research has been a hallmark of engineering advancing health and medicine at Columbia. In 2000, the Board of Trustees approved the establishment of a formal department under the leadership of Professor Van Mow.

Over the years, our program's reputation for excellence has grown and it is now recognized as one of the top ten biomedical engineering departments in the nation. It continues to be at the forefront of every new and emerging frontier in health-related research–from regenerative medicine, tissue engineering, single cell genomics, and neural engineering, to biomedical devices for diagnostics, and therapeutic and medical engineering. We are also addressing the challenges and opportunities brought on by big data and machine learning. And we are translating these findings to clinical settings where they can make the biggest impact.

In the future, biomedical engineering at Columbia will continue to break new ground as advances in materials, sensors, devices, and artificial intelligence pave the way for the next era of discovery that will transform how we prevent, diagnose, and treat disease, injury, and degeneration.

We continue to expand our collaborations with the Medical Center, including our ongoing partnerships with the Institute for Genomic Medicine, the Herbert Irving Comprehensive Cancer Center, the new Irving Institute of Cancer Dynamics, and the Zuckerman Mind Brain Behavior Institute. To support this growth in biomedical engineering and across our departments, we are committed to increasing our investment in resources and facilities and to growing our faculty of world-renowned researchers and investigators.

In keeping with our school vision to be Columbia Engineers for Humanity, the department upholds one of our key pillars—to employ engineering as a means to bring about a healthier humanity. Our faculty, research scientists, students, and alumni embody this vision every day through their contributions to foundational research, innovative scholarship, and entrepreneurship. I congratulate Chair Ed Guo and the entire Biomedical Engineering Department on reaching this notable milestone as we look forward to more discovery and impact in the next 20 years and beyond.

MARY C. BOYCE, PHD
Dean of Engineering
Morris A. and Alma Schapiro Professor

A NOTE FROM THE CHAIR

When we first started working on this 20th anniversary magazine, we imagined publishing it in March 2020. We could never have imagined that instead, we'd be grappling with a world upended by the explosive spread of SARS-CoV-2—the greatest threat to human health in more than a century. The world is watching as scientists, physicians, healthcare workers, civic leaders, and everyday citizens work together to limit the spread of the virus while developing vaccines and treatments. Compared to the real-time drama of life in these uncertain times, the achievements of a single university department can seem insignificant. Yet the progress we are witnessing today is the result of decades of cumulative innovation across all areas of science, including biomedical engineering. In that light, it is even more important to celebrate the innovators and changemakers that push science forward. This is where we find hope.

Our faculty and students leapt into action at the start of the pandemic, developing platforms for rapid COVID-19 testing, researching methods for sterilizing masks, devising strategies for maximizing the utility of ventilators, along with many other efforts. This crisis has united the global scientific community as never before, and I couldn't be more proud to see our department join the fight.

The spirit of collaboration comes naturally to our faculty, as biomedical engineering has always been an interdisciplinary field. Our work is fueled by partnerships between engineers, physicians, and scientists from areas including physics, neuroscience, mathematics, materials science, and computer and data science. This year, we made a commitment to ensure that our faculty and students are as diverse as the work we do. Our newly established Diversity, Equity & Inclusion Committee is just one element of a broader mission to address discrimination and ensure that every aspect of our department reflects our belief in equality in the sciences, and in the world at large.

Over the past 20 years, we have grown from a small group of dedicated founders into a dynamic department making field-changing breakthroughs in six areas of strength: Neuroengineering, Regenerative Medicine, Orthopedics, Biomaterials, Mechanomedicine, and Biomedical Imaging. Our faculty has doubled in size, and our class and degree offerings now include MD-PhD and MS-MD programs alongside the BS, MS, and PhD degrees. Columbia BME is home to about 85 undergraduate students, 150 master students, and 155 doctoral students.

Since 2019, the Department has ranked among *U.S. News and World Report*'s top 10 biomedical engineering departments. Much of the credit for this achievement lies with our esteemed faculty. Our professors are editors in chief of leading journals in their fields. They are recipients of the PECASE, NSF CAREER award, the ASME Medal, and other accolades. They are members of the National Academy of Engineering, National Academy of Medicine, National Academy of Inventors, The American Academy of Arts and Sciences, and The American Institute for Medical and Biological Engineering. The Department leads the nation for National Institutes of Health and National Science Foundation funding per faculty member, and in the past seven years alone, BME students and faculty have launched 17 startup companies to commercialize therapies and devices developed at Columbia.

This special anniversary magazine celebrates our present and salutes our past. While 2020 has taught us all to accept a sense of unpredictability about the future, I couldn't be more excited about what lies ahead for the Department. Now more than ever, I am inspired by my colleagues—their ingenuity, persistence, and pursuit of techniques that heal, restore, and improve patients' lives.

Best regards,

X. EDWARD GUO, PHD
Chair and Stanley Dicker Professor of Biomedical Engineering at Columbia University
Professor of Medical Sciences (in Medicine)
Director, Bone Bioengineering Laboratory

30 COMPANIES STARTED BY BME FACULTY AND STUDENTS

4 FACULTY WINNERS OF THE ASME VAN C. MOW MEDAL

3 EDITORS IN CHIEF OF JOURNALS

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9 **RANK IN U.S. NEWS AND WORLD REPORT**

1:4 RATIO OF STUDENTS TO FACULTY

85 NUMBER OF UNDERGRADS

BME BY THE NUMBERS

309 NUMBER OF GRADUATE STUDENTS

4 FACULTY ELECTED TO THE NATIONAL ACADEMY OF ENGINEERING

1 MEMBER OF THE NATIONAL ACADEMY OF SCIENCES

4 FACULTY ELECTED TO NATIONAL ACADEMY OF MEDICINE

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9 FACULTY RECIPIENTS OF THE NSF CAREER AWARD

16 AIMBE FELLOWS

2,000+ TWITTER FOLLOWERS

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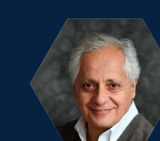

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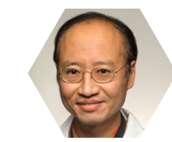

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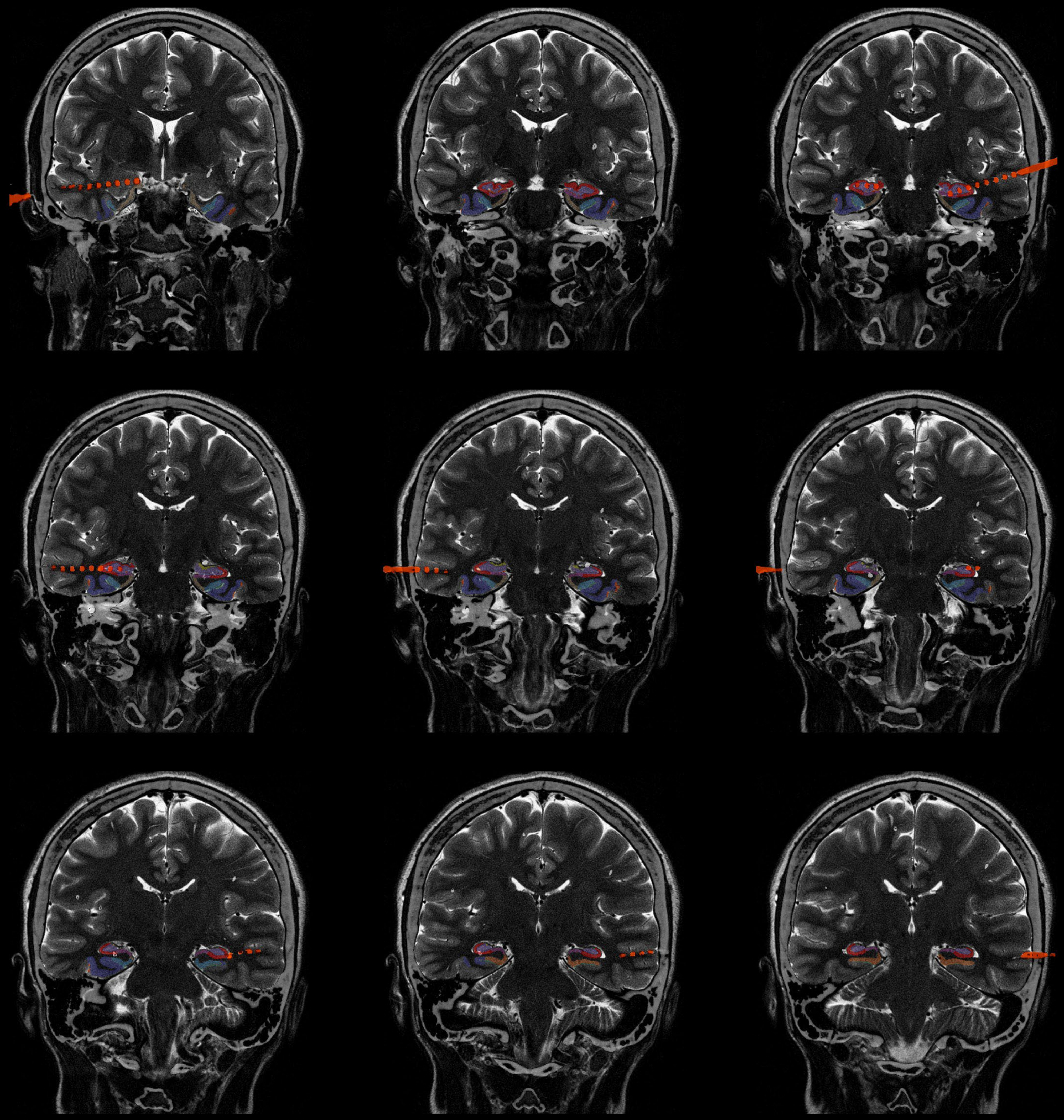
Adjunct Professor of Biomedical Engineering



Single-unit activity recorded from epilepsy patients during spatial navigation found that firing rates of neurons varied with the locations of spatial targets, heading direction, and serial position. Recording sites where electrodes were implanted are shown in red. Image by Brian Jacobs.

WHERE MIND MEETS MACHINE

Columbia neuroengineers are demystifying the workings of the human brain, finding new methods for optimizing and protecting the most complex machinery on Earth

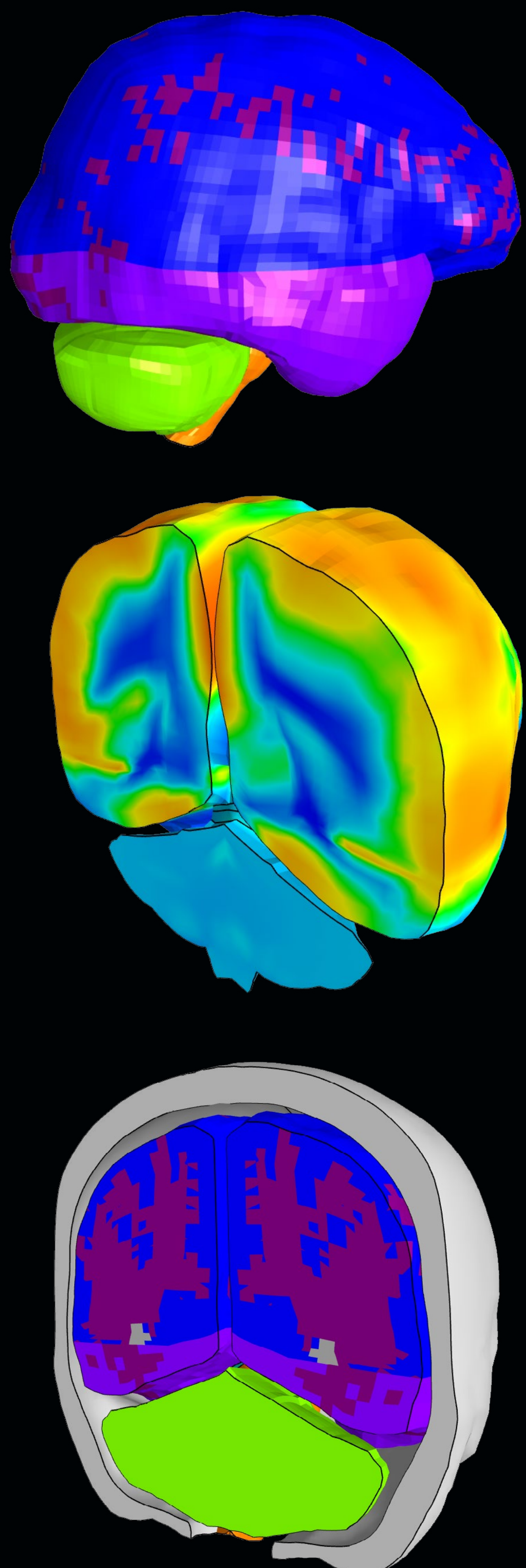
The human brain may be the most advanced computer on Earth, but Qi Wang wants to make it better. "As humans, we're far from perfect, and our behavior is usually not optimal," Wang said, describing how quotidian routines such as a morning cup of coffee or a sugary late-afternoon snack are simply attempts to regulate changes in brain state that can impact alertness, perception, and cognition. While a boost of caffeine is a surefire chemical fix for a sagging mood or waning attention span, the benefits are temporary. Since his arrival at Columbia in 2013, Wang has investigated the neural pathways that underlie cognition and sensory perception, aiming to develop longer-term strategies, including brain-machine interfaces, for optimizing behavior and addressing imbalances in sensory processing due to disease or injury.

Neuroengineering was a new discipline when the department of biomedical engineering was founded 20 years ago. In fact, when Vice Chair Paul Sajda joined the faculty in 2003, he was the only neuroengineer in the building. These days, he's in good company. In addition to Wang, Sajda works alongside half a dozen BME faculty and others from SEAS, Columbia University Irving Medical Center, and the Zuckerman Institute in a quest to understand neural coding and processing and develop novel therapeutic devices and brain-computer interfaces. Advances in computer science, neural imaging, chip and electrode design, and computational modeling have enabled a surge of interest and investment in neuroengineering over the past decade, spurring a steady stream of breakthrough findings about the workings of the humblingly complex circuitry within us.

DECODING DECISIONS

People make tens of thousands of individual decisions each day, most of them within a fraction of a second. Whether it's the simple choice to click an online advertisement or the high-stakes, split-second maneuver of a military fighter jet, Paul Sajda wants to know what underlies it. By studying neural activity during specific tasks using MRI and EEG, as well as tracking physical markers including heart rate and eye movement, Sajda has begun to identify some of the neural correlates of human decision-making. With the help of machine learning algorithms, his lab is building brain-computer interfaces capable of shifting arousal states and augmenting an individual's performance in rapid decision-making scenarios. "Imagine this as kind of a cognitive orthotic," Sajda says, explaining that these technologies could have wide-ranging applications, from assisting a pilot landing on an aircraft carrier to honing the process by which baseball players recognize a pitch and time their swing in mere milliseconds. The latter application is already being commercialized by a startup company, deCervo, founded by two of Sajda's former doctoral students.

Discovering the markers of decision-making in healthy brains has led Sajda to pursue therapeutic applications of brain-computer interfaces in patients whose judgment is impacted by obsessive-compulsive disorder, schizophrenia, or major depressive disorder. In collaboration with colleagues at the Medical University of South Carolina, Sajda's lab is testing a closed-loop system to precisely synchronize the delivery of neuromodulatory therapy—in this case, transcranial magnetic stimulation—with the natural oscillatory rhythms of brain regions implicated in certain diseases.



Top to bottom: Finite element mesh of the brain in FEBio used to study edema; Contour map of relative volume in the brain using FEBio following an automobile-pedestrian impact. Swollen areas (edema) shown in orange and red, compressed inner brain structures shown in blue; Frontal plane cut of the finite element mesh of the brain and skull in FEBio used to study edema.

TIME, SPACE, MEMORY

Joshua Jacobs has spent the better part of a decade mapping the neural basis of spatial navigation and memory. The subjects of his experiments—hospitalized epilepsy patients—may seem like an unusual research cohort, but many have turned their illness into an opportunity to help Jacobs understand how we find our way in the world. Methods for monitoring brain activity typically rely on external electrodes placed on the surface of the skull. Jacobs' subjects, however, had electrode arrays implanted within the brain to localize seizure activity prior to surgery. The circumstances offered a rare chance to collect exquisitely sensitive direct recordings of brain activity.

As patients played a virtual-reality video game requiring both spatial navigation and object memory tasks, Jacobs discovered that individual neurons target specific memories during recall. These "memory-trace" neurons are activated during location-specific memory tasks, and Jacobs' team was able to track shifts in activity between single neurons when participants recalled different objects by location. They also discovered key differences between the processes that encode spatial memory in rodents and humans. "We know there are neurons that represent specific locations where you're trying to go during movement," Jacobs said. "In rats, those cells usually represent the current location. In humans, the memory system is more flexible, and those neurons represent where you are trying to go."

Thanks to direct brain recording, Jacobs has also observed previously unknown patterns of neural oscillations. Last year, he reported the discovery of "traveling waves"—signals that propagate across the entire brain during cognition. "The more consistently these waves move across space, the better the subject is performing a memory task," said Jacobs. "This suggests that part of the brain working efficiently is the ability to coordinate and move all kinds of memory information across different regions of the brain."

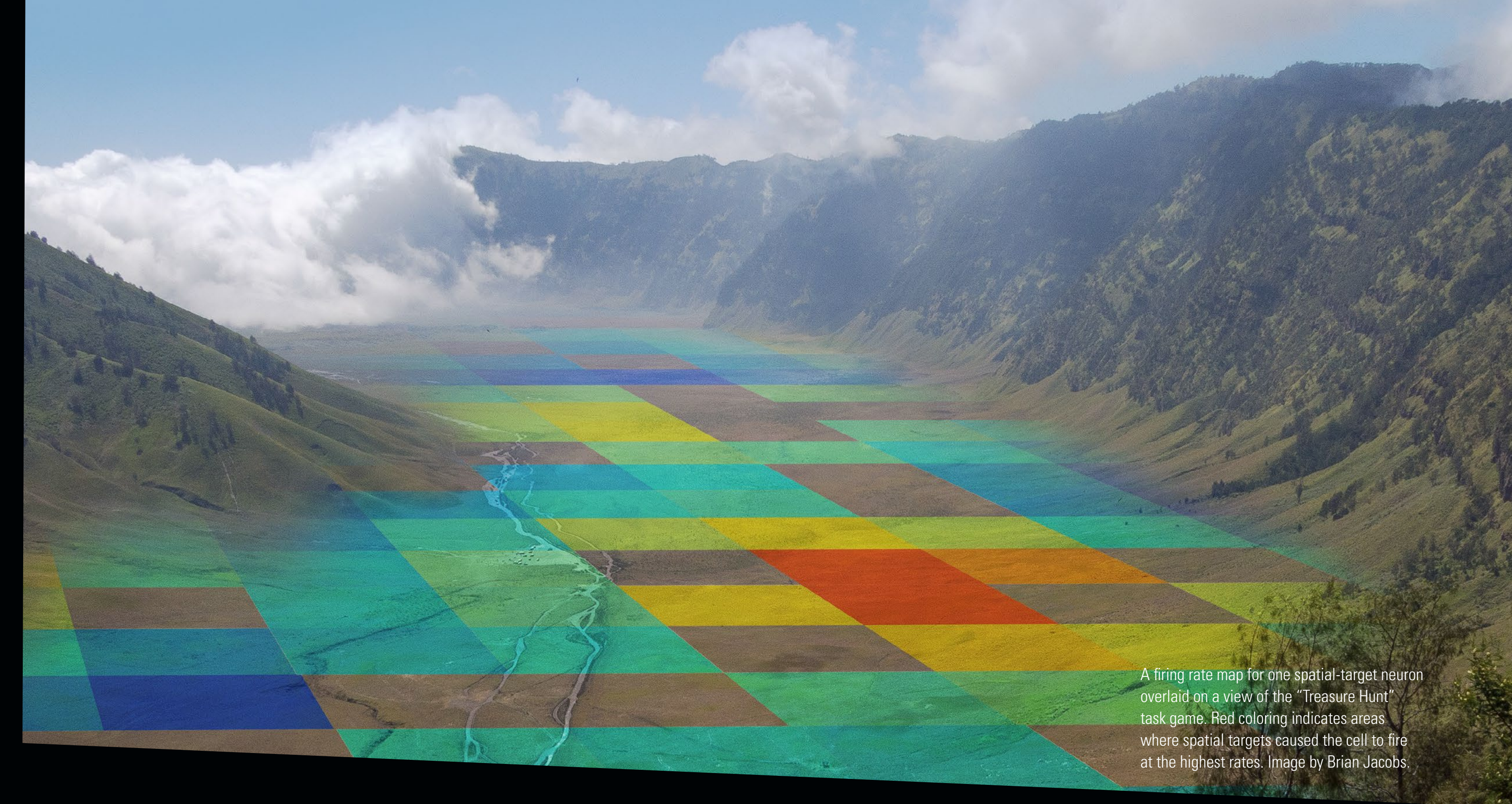
These findings may ultimately inform clinical efforts to understand, and perhaps even treat, memory loss associated with age or Alzheimer's disease, or to simply improve memory in otherwise healthy minds.

FROM TRAUMA TO TREATMENT

Barclay Morrison's primary research interest is, in his words, "a messy subject." For 20 years, he has studied the mechanisms of traumatic brain injuries (TBI) and worked to devise strategies for preventing them. From the crash of a linebacker to a shock wave from an explosive, Morrison is analyzing how the brain responds to injurious forces to better understand how to protect it. "It's a little bit like taking a hammer to a computer, then trying to figure out how to put it back together so it works again," Morrison said. More than two million people suffer traumatic brain injuries every year, yet there was little public awareness of the problem until news media began spotlighting the impact of brain injuries in the military and professional sports. "It was a silent epidemic, but not anymore," said Morrison.

Through years of subjecting brain tissue samples to various mechanical stimuli, Morrison has teased out the different material and viscoelastic properties of white matter compared to gray matter, and of the tissues that comprise different areas of the brain. His lab has developed widely utilized tolerance criteria for the human brain—metrics that quantify how much of a specific type of force the brain can withstand, and at what duration and frequency, before damage occurs. This information is essential fuel for the computational models that have largely replaced crash-test dummies in accident simulations and are being used to boost the safety of cars and helmets. Tolerance criteria may also impact "return to play" protocols for athletes following concussion or other head injuries.

Morrison's lab is also exploring therapeutic approaches, testing existing drug compounds for their potential to prevent long-term complications, such as cognitive impairment, that often follow traumatic brain injury. "We're hoping to break the progression from stimulus to outcome," he said.

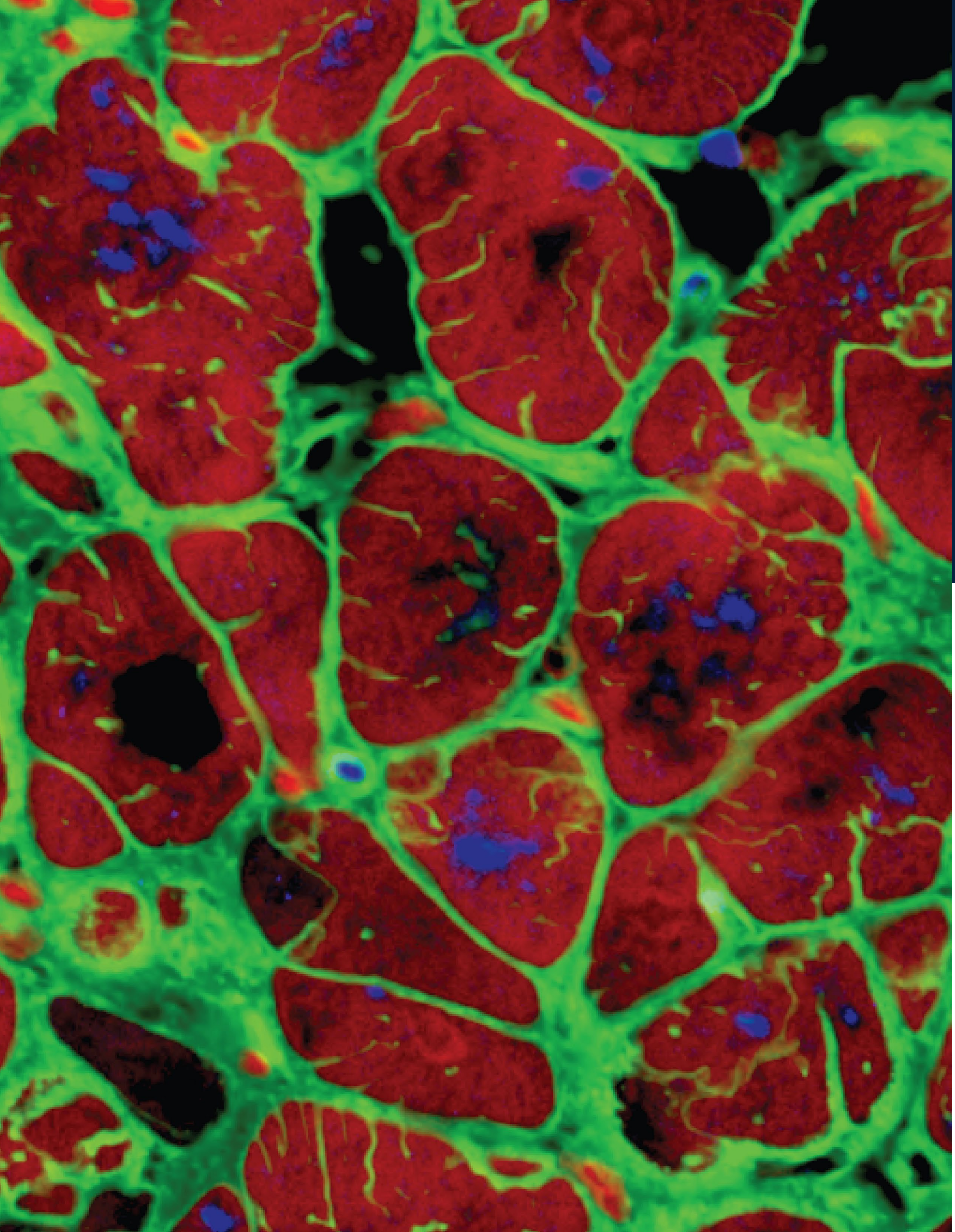


A firing rate map for one spatial-target neuron overlaid on a view of the "Treasure Hunt" task game. Red coloring indicates areas where spatial targets caused the cell to fire at the highest rates. Image by Brian Jacobs.

TUNING IN

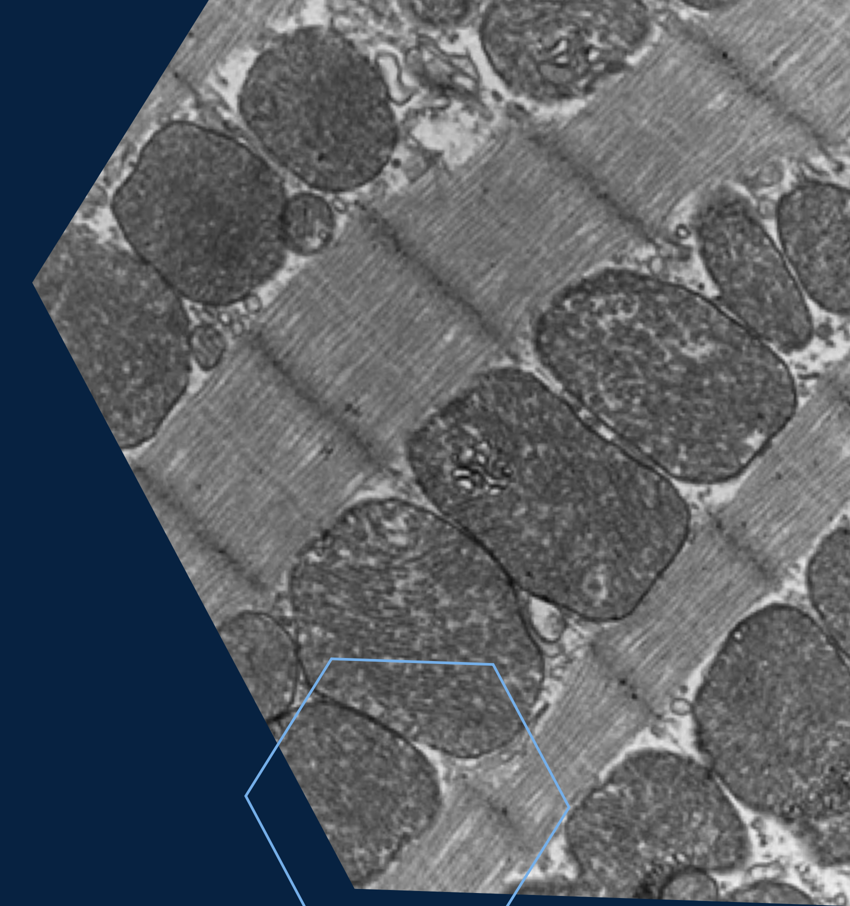
Beyond elaborate brain-computer interfaces, single-neuron monitoring, and computational models of brain deformation, neuroengineering research can serve up elegant explanations of processes so fundamental they may be taken for granted. One example is the combination feat of engineering and physics that governs the fine-tuning of frequencies in the human ear. Thanks to ultra-sensitive microsensors that measure motion in the sensory tissue of the cochlea, Elizabeth Olson—the only biomedical engineer with a joint appointment in otolaryngology at the Vagelos College of Physicians and Surgeons—is parsing out the intricate process by which the ear sorts the frequencies of incoming sound waves.

As Olson explained, the mechanics of cochlear amplification make correcting hearing deficits far more complex than addressing vision issues. Her lab has partnered with researchers at Massachusetts Eye and Ear Infirmary and MIT to develop a flexible intracochlear microphone—one component of a fully internal cochlear implant. A biomechanical approach to resolving hearing loss is "the next frontier" said Olson, although her cochlear implant is still early-stage. As she reflects on a career of decoding the mechanical complexities of human hearing, her description of the process is one that could easily apply to the brain itself. "We're trying to figure out how this all works together—it's an amazing machine," she said.



REGENERATIVE MEDICINE

BUILT FROM SCRATCH



Cell and tissue engineers are ushering in a new era of healing and repair

Harry Potter fans will remember the scene when Hogwarts' resident nurse is tasked with re-growing the bones in Harry's arm following a mishap with a magical spell. At her direction, he downs a foul draught of potion and emerges whole, mended, and no worse for the wear. Science fiction and fantasy stories are rife with tales of healing and restoration. In the natural world, salamanders, starfish, worms and many other animals perform astonishing feats of regeneration. Nothing quite as flashy is likely to materialize for humans, but the advances in regenerative medicine emerging from the labs at Columbia are no less remarkable.

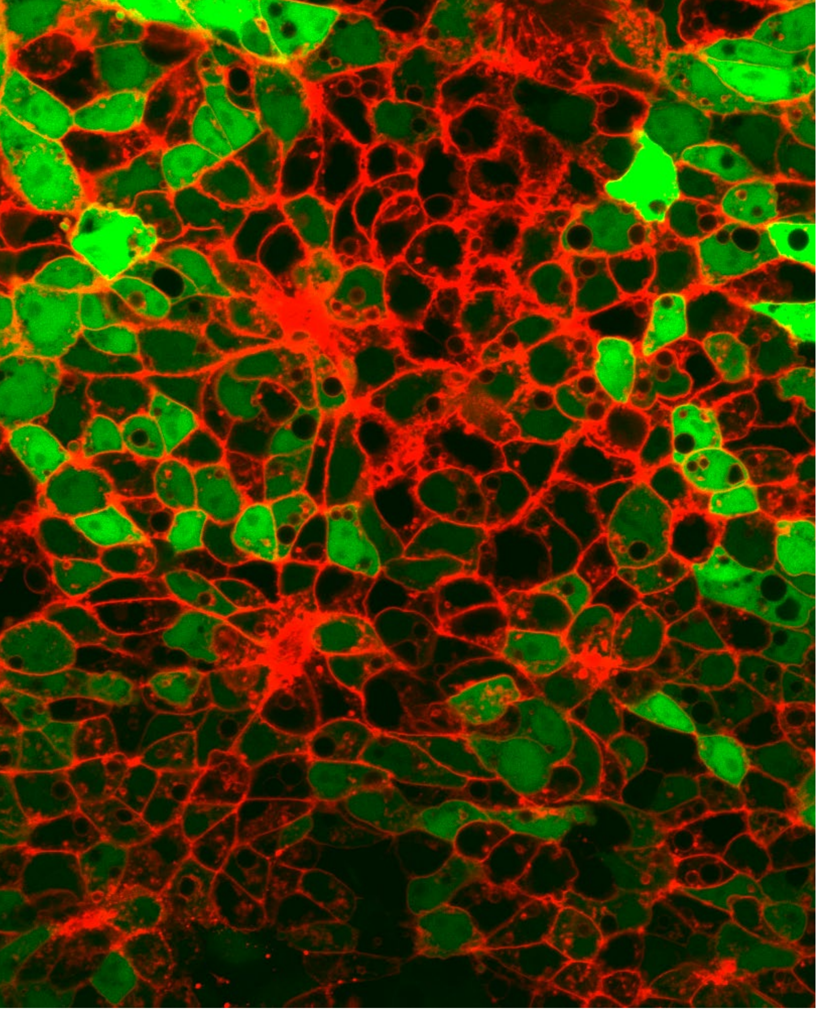
Faculty and students are using tissue engineering not only as a means to grow functional tissues to repair injuries, but also to create three-dimensional models of human disease for drug screening and development. They are generating field-changing insights and techniques that are bringing the true future of re-generation and precision medicine into view.

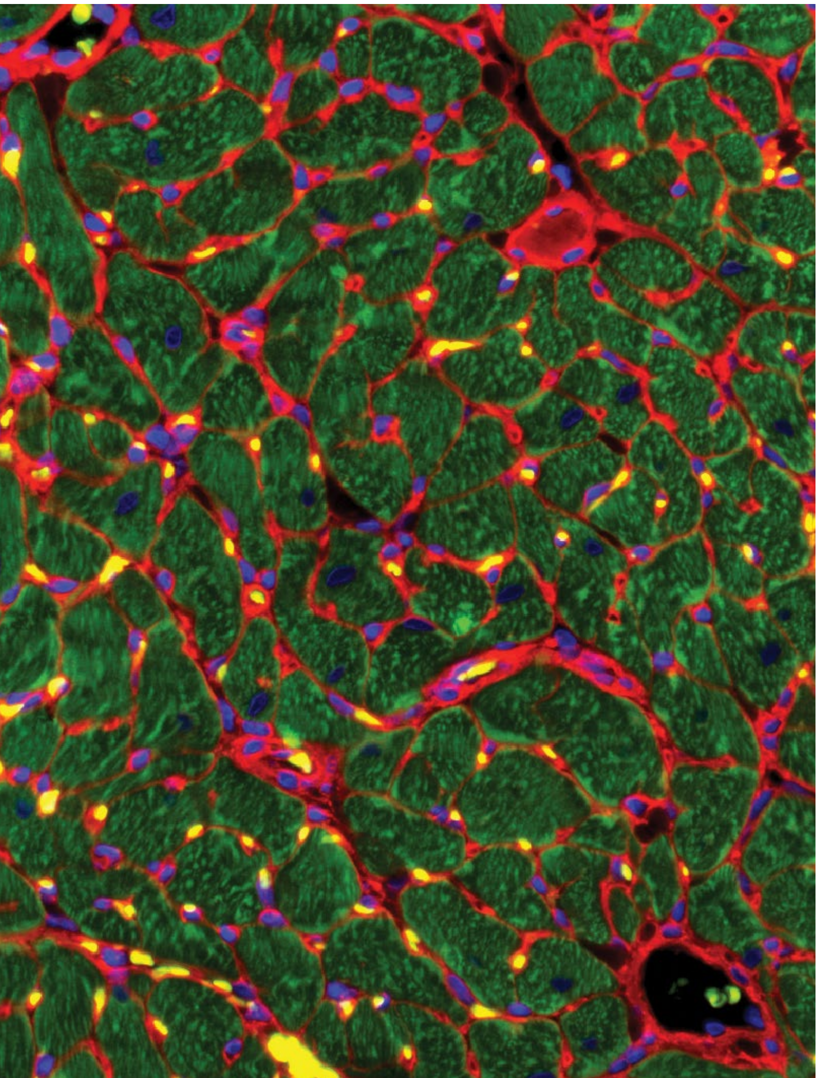
Opposite: Cross-section of engineered human heart muscle. Ronaldson-Bouchard et al., *Nature* 2018.

Above: Ultrastructure of human heart muscle grown in the lab

FROM LAB-GROWN BONES TO MIRACULOUS CELL MODELS

Some of the most impactful breakthroughs in regenerative medicine in the country have come from Columbia's Laboratory for Stem Cells and Tissue Engineering. Its leader is Gordana Vunjak-Novakovic, Mikati Foundation Professor of Biomedical Engineering and Medicine and the only University Professor within SEAS. Her collaborations are so numerous and her contributions to the field so significant that she has become something of a one-name celebrity at Columbia. "She's the Cher of regenerative medicine," one faculty member joked. To discuss her research is to catch some of Vunjak-Novakovic's infectious enthusiasm for the work that has occupied her for decades, as well as her reverence for the dedicated students who carry it out. The past 20 years have yielded fundamental findings about the precise conditions human cells need to function in their native environments, and how to recapitulate those *in vitro*. Vunjak-Novakovic's lab is tapping those insights to create practical applications of cell and tissue engineering to meet pressing clinical needs.





Some successes have made headlines, including a technique for growing fully functional bone and cartilage segments from a patient's own stem cells. That technology, now in clinical trials, forms the basis of Epibone, one of four startup companies that Vunjak-Novakovic has founded to commercialize therapeutic breakthroughs from her lab.

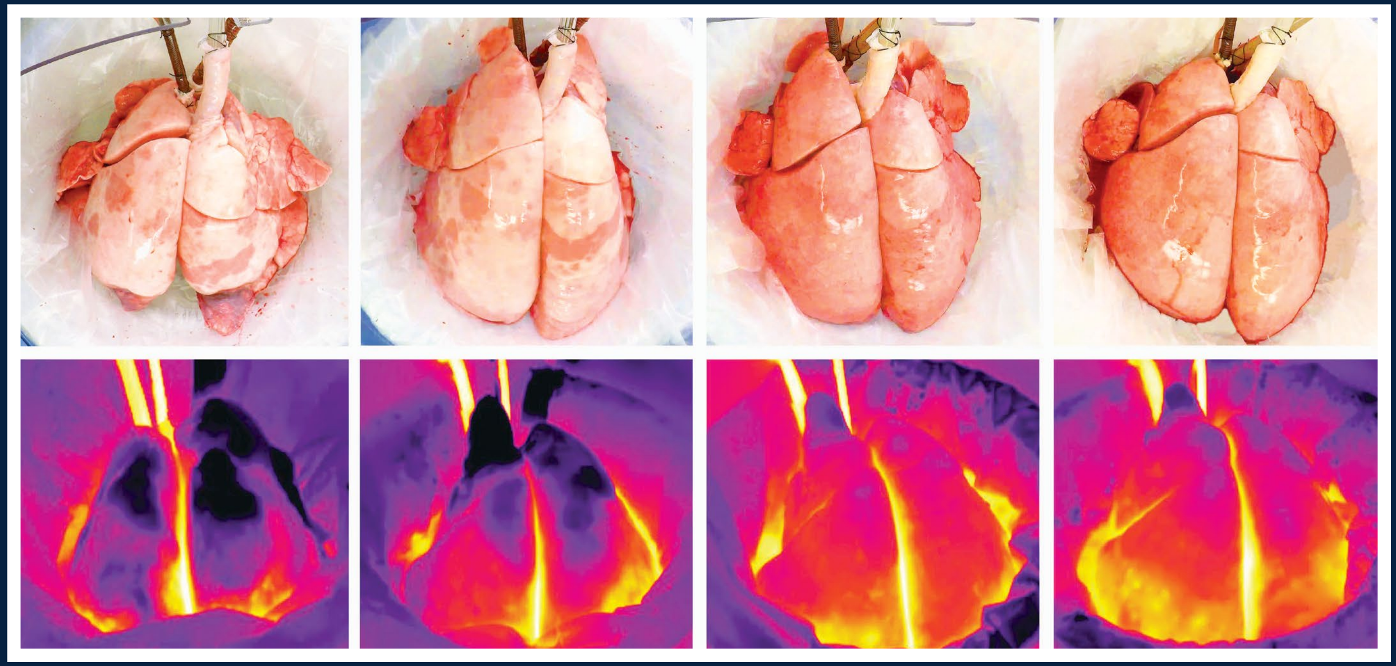
Another standout technique addresses the ongoing shortage of healthy organs available for transplant. "Four out of five lungs that come in for transplant are rejected, and it's often due to localized areas of injury in the epithelial tissue," explained Vunjak-Novakovic. Working with colleagues at Columbia University Irving Medical Center and Vanderbilt University, her team developed a cross-circulation system that maintains the organ's integrity for four days—enough time for therapeutic interventions that reduce inflammation and regenerate epithelial tissue, rendering the organ suitable for transplant.

On a far smaller physical scale, Vunjak-Novakovic has demonstrated the powerful clinical relevance of cultured human tissue models, often referred to as "organ on a chip." Her lab uses these platforms to model cancer, inflammation, autoimmune and cardiovascular diseases, and to test the efficacy of new and existing drug therapies. Such systems can even help predict notoriously unpredictable processes, such as cancer metastasis. "Breast cancer can metastasize into different organ systems, and where it goes depends on genetics and the makeup of the cancer cell subpopulations," said Vunjak-Novakovic. "Now we are starting to model this process on an individual basis, for any given patient, in collaboration with our CUIMC colleagues."

Vunjak-Novakovic is one of two Columbia lab directors engaged in an NIH-funded effort to develop *in-vitro* disease models using human tissues. The other is Kam Leong, Samuel Y. Sheng Professor of Biomedical Engineering. He's best known for developing nanoparticles for gene editing and drug delivery, but also spends nearly half his time building and studying cerebral organoids—three-dimensional aggregates of neural cells that can faithfully replicate the pathophysiology of neuropsychiatric disorders in a dish. Even amid major advances in neuroimaging, "access to the living brain at the molecular level is pretty much zero right now," Leong said, "so when we develop drugs to treat disorders like depression, it's almost like we do it in a black box."

Top to bottom: GFP-expressing endoderm cells (green) in the chick embryo, counterstained to visualize cell boundaries (red)

Exosomes secreted by therapeutic cells promoted recovery of infarcted heart muscle in a rat model of myocardial infarction. (Liu et al., *Nature Biomedical Engineering*. 2018).



Brain organoids have demystified this process, becoming valuable stand-ins for living brains for both drug screening and studies of disease pathogenesis and progression. Leong creates organoids from cells with known genetic mutations, linking them to a system of engineered blood vessels and a blood-brain barrier interface. Thus a system the size of the tip of a crayon becomes a microcosm of a human brain, one that Leong hopes will lead to new therapeutic directions for neuropsychiatric disorders based on increased understanding of their molecular pathways. "I'm very passionate about this area of my work—these disorders are so misunderstood," he said.

REGENERATION MEETS REPAIR

Most tissues in the body are naturally capable of some degree of healing, a process that typically involves both regeneration and replacement. Cartilage is a notable exception. "It doesn't heal, period," said Gerard Ateshian, Andrew Walz Professor of Mechanical Engineering and professor of biomedical engineering. Through a decades-long partnership with Professor Clark Hung, Ateshian learned to grow "the best lab-grown cartilage there is," an accomplishment he describes with a paradoxical mix of pride and humility—the former, because replicating the properties of cartilage *in vitro* is no small feat, and the latter because despite "tremendous progress," lab-grown cartilage is likely to remain inferior to native tissue for at least a decade.

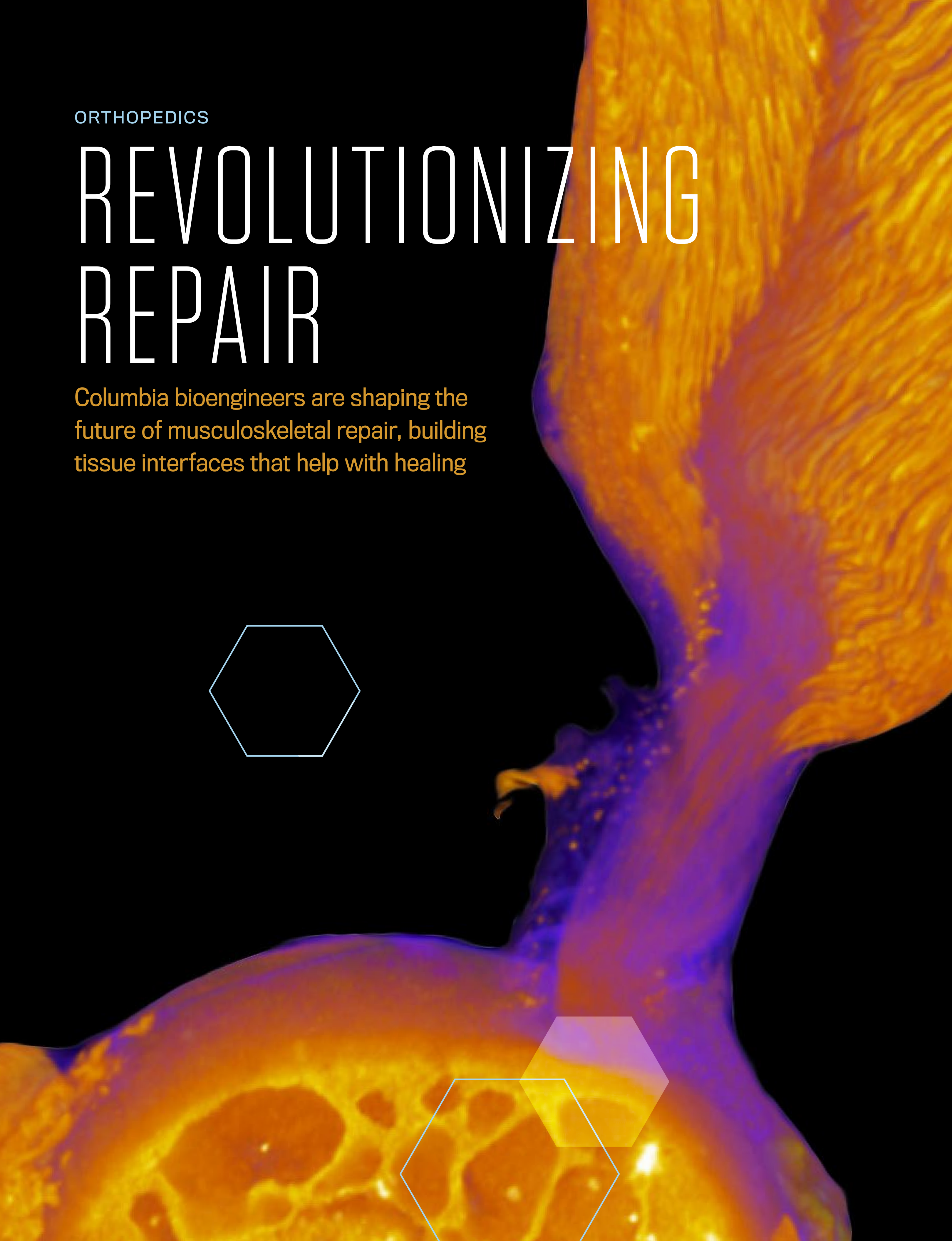
In the meantime, Ateshian has developed a parallel track of research with near-term benefits for patients. While Hung and Ateshian were refining their method of growing cartilage, tissue banks were making dramatic improvements in preserving cadaver cartilage for use in surgical repairs. During the same period, joint replacements became commonplace, and today they dwarf osteochondral allograft procedures by a factor of forty. Ateshian saw an opportunity within this new reality, one that channeled his unique expertise in cartilage mechanics into a revolutionary form of joint repair. In collaboration with Dr. Melvin Rosenwasser, a hand surgeon at Columbia University Irving Medical Center, Ateshian patented a process for cutting and shaping bendable osteochondral allografts for use in parts of the body where joint replacement is ineffective, notably the thumb. "After a few attempts in the lab, we found a reliable way to cut grooves into the bone in just the right way, just the right amount, so the tissue cells remain alive after you bend the cartilage," Ateshian said. He emphasized that this method could be adapted for other fingers, or to repair partial joint injuries.

If the technique takes off, Ateshian believes that demand for such allografts could skyrocket as the population ages, straining tissue banks' supply. By then, he's hopeful that lab-grown cartilage will have matured enough to make it to market—a research thread come full circle. "None of the research you do goes to waste," he said. "I always feel like the discoveries we make will help us at some point."

Above: Recovery of lungs damaged by ischemia by cross-circulation technology (O'Neill et al., *Nature Biomedical Engineering*. 2017).

REVOLUTIONIZING REPAIR

Columbia bioengineers are shaping the future of musculoskeletal repair, building tissue interfaces that help with healing

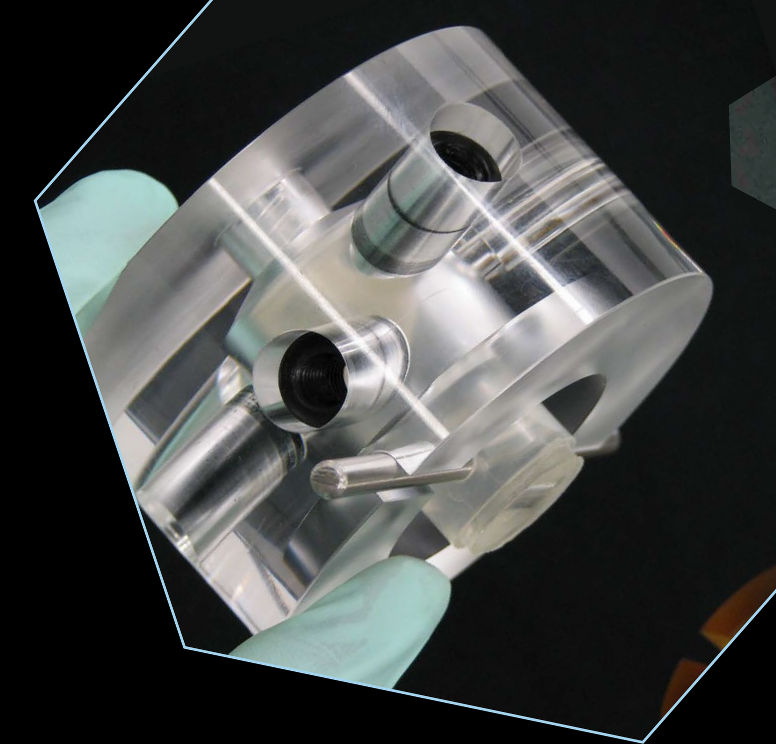


When Steve Thomopoulos talks about reattaching a torn tendon to bone, he doesn't mince words. "Imagine driving nails through a piece of rope into a block of cement and hoping for the best," he says, describing the attempt to rejoin two materials with such drastically different properties that only nature could devise a strategy for bonding them. More than half of the 33 million musculoskeletal injuries reported in the US each year involve tendons, many of which are repaired through surgical procedures with surprisingly high failure rates. The prognosis for ligament injuries is somewhat better, but restoring the ties that bind muscle to bone and bones to each other presents both biological and mechanical challenges. It's just one task that Thomopoulos and a cohort of orthopedics researchers at Columbia are tackling as they explore the mechanics of tendons, bones, cartilage, and muscle cells in a quest to develop new techniques for understanding and repairing injuries, promoting healing, and preventing new injury.

Orthopedic biomechanics has strong roots at Columbia. Department founder Van C. Mow was already internationally recognized for breakthrough discoveries in cartilage mechanics when he came to Columbia in 1986, and X. Edward Guo and Helen Lu, the current chair and vice chair of the department, along with founding faculty Gerard Ateshian and Clark Hung, are all renowned orthopedics researchers. Today, Columbia is home to one of the largest groups of musculoskeletal researchers in the country.

Opposite: The tendon attaches to bone across a mineralized fibrocartilage transition called the enthesis (from top to bottom: muscle, tendon, enthesis, bone).

Above: Bioreactor for engineering anatomically shaped human bone (Grayson et al., PNAS. 2010).



BONE DEEP

Healthy and strong or weak and brittle, bones are a subject of longstanding fascination for BME Department Chair and Stanley Dicker Professor of Biomedical Engineering X. Edward Guo. His work probes the fundamentals of bone biomechanics, from the process by which bone mass changes in response to mechanical loading to the microstructural shifts associated with degenerative diseases such as osteoporosis and osteoarthritis. Fifteen years ago, Guo and his collaborators in the Bone Bioengineering Lab pioneered Individual Trabecula Segmentation (ITS), a software providing high-resolution, three-dimensional visualization of bone microstructure. Since that time, researchers around the world have utilized ITS to derive new, clinically relevant insights. Guo's work with ITS has identified specific bone changes that could impact management of osteoporosis, including data that could be used to make more accurate predictions of fracture risk and methods for evaluating the efficacy of osteoporosis treatments. ITS has also spotted early structural bone changes that precede cartilage degradation in osteoarthritis patients. Guo envisions a day when these insights, paired with increased understanding of osteocyte mechanobiology, could be used to develop therapeutics to restore or halt bone loss.

Guo's lab recently published findings that highlight the impact of genetics on bone strength and shed light on a well observed, but poorly understood phenomenon. "Chinese-American women have lower bone mineral density than Caucasian women, but they have lower incidence of fracture," Guo explained. Using ITS, Guo and his team learned that Chinese-American women have comparatively stronger bone microarchitecture, which may explain this resilience. Humans have been studying bones for centuries, "but the surprises keep coming," said Guo.

> “We’re shifting the focus from mechanical fixation to biological healing”

INTERFACE INNOVATION

Every time we take a step, grasp an object, throw a ball, sit down, or make any of the other tens of thousands of movements of an average day, we rely on the perfect synchrony between soft and hard tissues in the musculoskeletal system—tendons, ligaments, cartilage, and bone. Most people give little thought to the sites throughout the body where these distinct tissue types interface, allowing knees to bend, shoulders to rotate, fingers to flex. Helen Lu is not most people. For two decades, she has studied the junctures that facilitate movement, aiming to elucidate the mechanical and cellular interactions between tissues at these interfaces. “We want to understand how the body maintains tissue interfaces, and how they regenerate following injury,” she said. These mutually reinforcing research directions have yielded seminal insights into the relationship between interface structure and function, as well as field-changing tissue engineering techniques that are revolutionizing injury repair.

Tears to the rotator cuff and anterior cruciate ligament (ACL) are among the most common musculoskeletal injuries in the country, accounting for more than 700,000 surgeries each year. However, many of these repairs remain vulnerable to re-tearing, due in part to a lack of tissue regeneration at the repair site. Lu’s lab has developed integrative solutions that stand to transform the repair process. In partnership with William Levine, Chair of Orthopedic Surgery at Columbia University Irving Medical Center, Lu fabricated biomimetic nanofiber scaffolds to facilitate healing of the tendon-to-bone interface in the rotator cuff. Tuned to mimic the natural variations in architecture and porosity found at the interface, the scaffold includes precise cellular cues to coax the regeneration of multiple tissue types. Syntegrity Biomedical, a startup company founded by Lu and Levine, has licensed this technology and is advancing it to clinical trials. Similar scaffolds have also been successfully deployed to promote integrated healing of ACL tears.

Opposite: The tendon enthesis develops from a unique population of progenitor cells, shown in green (tendon: top of image, bone: bottom of image).

More recently, Lu has set her sights on tackling the longstanding problem of integrating cartilage grafts with native cartilage and bone in osteoarthritis patients. Among other innovations, her lab is testing a novel nanofiber cup designed to promote integration and restore cartilage integrity and function. “We’re shifting the focus from mechanical fixation to biological healing,” she said.

FROM CELLULAR CUES TO UNDERWATER GLUE

Steve Thomopoulos directs the Carroll Laboratories for Orthopedic Surgery, a hub for multidisciplinary musculoskeletal research at Columbia University Irving Medical Center. His work probes human developmental biology, materials science, and even the features of other animal species to better understand and recapitulate the formation of what he deems “the really elegant attachment structure” between tendon and bone.

Thomopoulos has homed in on the molecular and biophysical signals that guide enthesis construction during fetal development, along with identifying key progenitor cells and growth factors. He hopes to infuse crucial elements of this process into cell therapies capable of transforming wound healing from a scar-mediated process to a regenerative one. He’s also tapping the animal world for biomimetic solutions to improve surgical repair outcomes, finding inspiration in creatures both humble and fearsome.

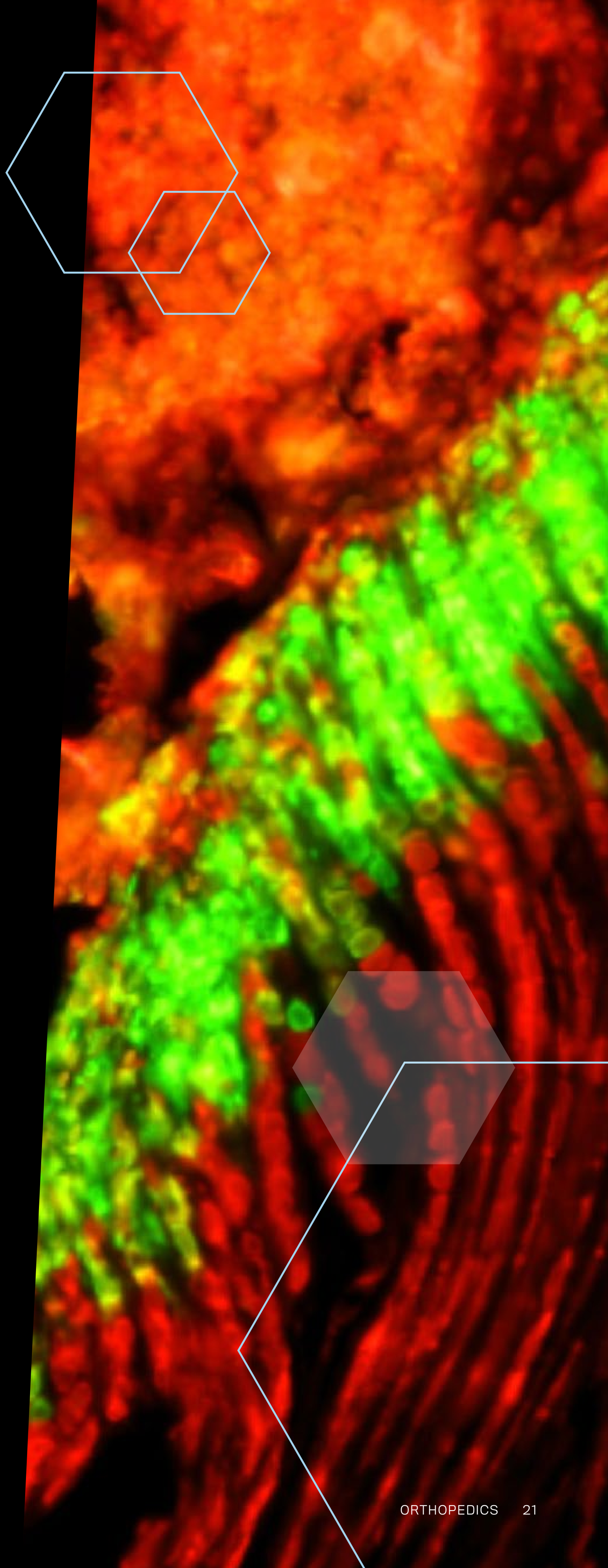
In collaboration with a polymer chemist, Thomopoulos is developing an adhesive for tendon repair based on the remarkably strong underwater “glue” that binds marine mussels to rocks. Deployed in a surgical environment, this adhesive could augment the sutures used in tendon repair. “This approach is more mechanically advantageous,” Thomopoulos said. “The entire surface is adhered, which spreads out the forces.” Another innovation, a device based on the curvature of python teeth, could be surgically placed at the juncture of tendon and bone. Sporting an array of “teeth” optimally designed for grasping, the device, which is currently under patent review, could further secure and stabilize tendon repairs.

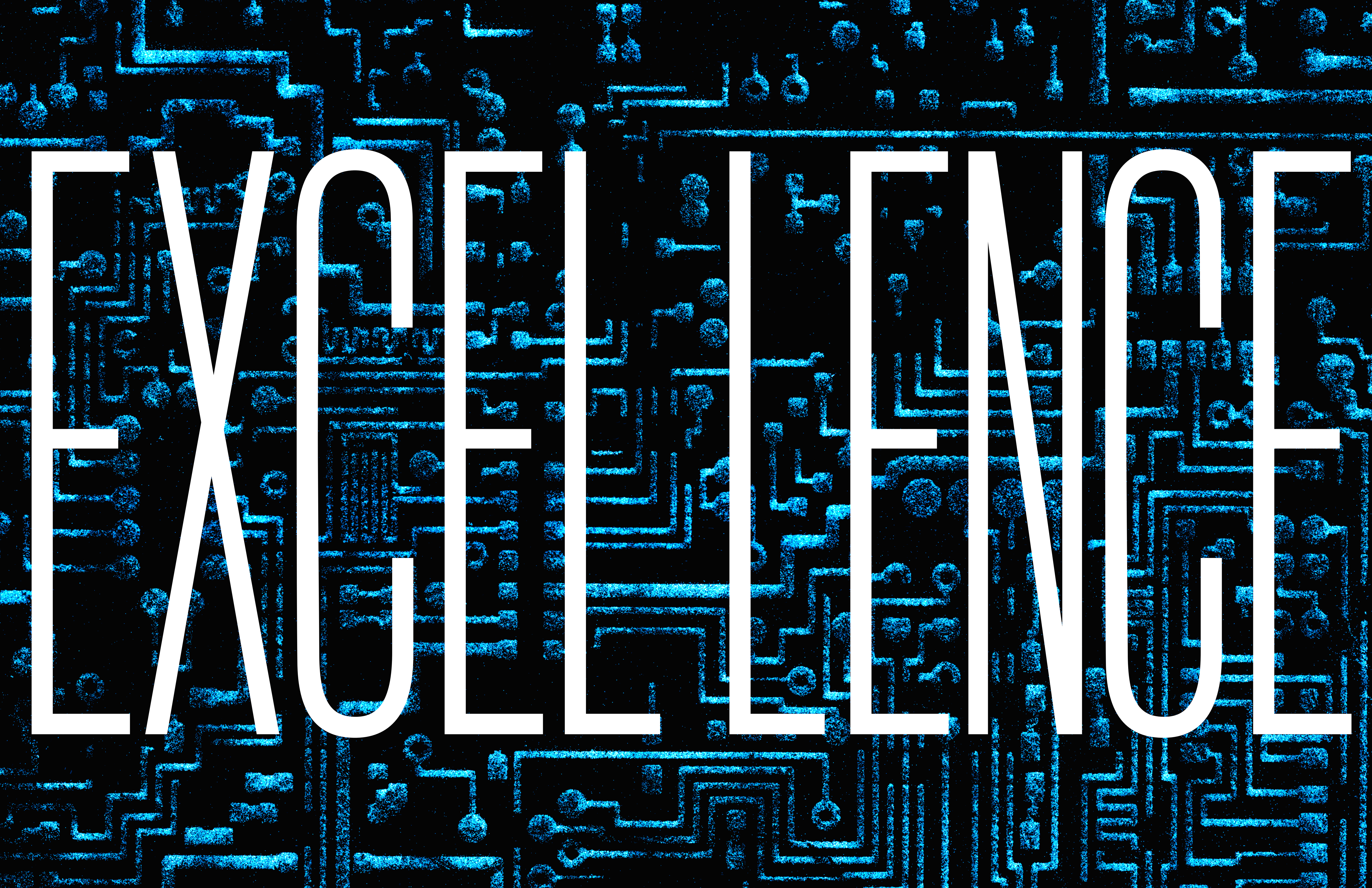
LEARNING FROM INFLAMMATION

Not far from Thomopoulos’ lab, Associate Professor of Biomechanics Nadeen Chahine is tackling one of the leading causes of disability and lost productivity worldwide: back pain. Despite its prevalence, intervertebral disc degeneration and other causes of back pain are often treated based on a clinician’s intuition. “Physicians still don’t have a good method for predicting who will respond to treatment,” she said. “The best data suggest about a 50% response rate, like flipping a coin.” Chahine and her collaborators want to improve those odds, and they’ve found a promising path through the study of another injury-associated process: inflammation.

A degenerating disc is, literally, a hotbed of pro-inflammatory cytokines, compounds which researchers and clinicians have long known trigger pain and negatively impact healing. Chahine’s lab has shown that inflammation is more than a chemical nuisance, however—inflammatory compounds actually alter cell mechanics, impeding their ability to respond to mechanical loading. In animal models of intervertebral disc degeneration, inflammation alone is enough to trigger degeneration. “Even without a traumatic injury, we see that inflammation impairs the cells’ ability to handle mechanical stress, which perpetuates the degeneration process,” according to Chahine. Her lab is testing pharmacologic approaches that may inhibit these pathways locally, while other studies are uncovering a surprising use for measures of systemic inflammation—one that may empower clinicians to make more informed treatment decisions.

An ongoing study of hundreds of patients shows that in addition to local inflammation, back pain sufferers have systemic inflammation that varies based on their specific type of disc disease. “Someone with herniation has a different inflammatory profile than someone with degeneration,” Chahine said, noting that some profiles respond better to certain treatments, such as epidural injection, than others. “This allows us to more accurately predict the likelihood of treatment response,” she said, explaining that this information is being used to develop a patent-pending predictive algorithm for clinical use. “Patients are suffering, and we want the first treatment plan to be their best chance at a positive outcome,” she said.




EXCELLENCE

HINDSIGHT

A Brief History of Biomedical Engineering at Columbia

Columbia has been a hub for innovation in engineering, biology, and medicine for more than a century. Transformative breakthroughs in the 19th and 20th centuries—including those that extended the range of long-distance phone calls, powered the first nuclear submarines, ushered in the era of FM radio, and contributed to the creation of the New York City subway system—came to light in Columbia's engineering labs. In 1896, more than 60 years before the emergence of the field of biomedical engineering, Columbia professor Michael Pupin used a cutting-edge technology called x-ray to conduct the first image-guided surgical procedure. In 1949, Columbia alum Elmer Gaden detailed a method for mass-producing penicillin and other antibiotics, just one of many achievements that would earn him the moniker "the father of biochemical engineering." In 1958, the National Institutes of Health awarded the first-ever bioengineering grant to chemical engineering professor Edward Leonard in support of work that culminated in his founding of the Artificial Organs Research Laboratory, which he still directs today.

In 1962, Gaden, then a professor of chemical engineering, established the Committee on Bioengineering at Columbia, creating the first formal links in what would become a well-traveled bridge between the School of Engineering and Applied Sciences (SEAS) and the College of Physicians and Surgeons (P & S). The Committee conferred master and doctoral degrees in bioengineering, and undergraduate students earned bachelor's degrees in bioengineering through the department of chemical engineering.

By the early 1970s, administrators and faculty recognized the importance of creating a university-wide platform for collaboration between physicians and engineers. Columbia President Grayson Kirk and P & S Dean H. Houston Merritt formed the Columbia Bioengineering Institute, and named Dr. William Nastuk, professor of physiology at P & S, director in 1974. Four years later, Nastuk passed the baton to Richard Skalak, chair of the department of civil engineering and engineering mechanics. Skalak's longstanding research partnership with P & S Professor of Physiology Shu Chien was emblematic of the kind of co-equal interdisciplinary partnership the Institute aspired to foster among faculty. Yet the Institute never gained traction, and ceased activity shortly thereafter.

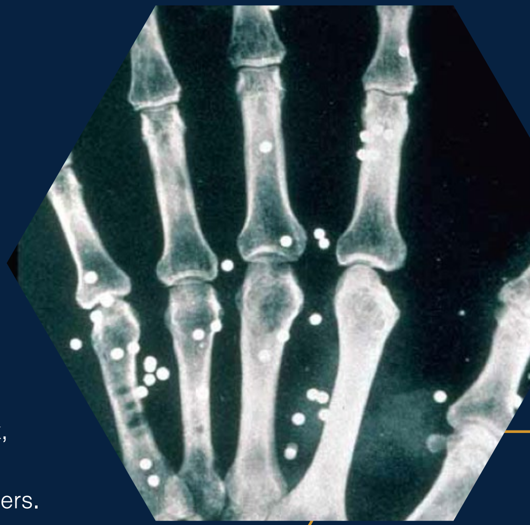
Other initiatives soon took its place, starting with the first joint faculty appointments between SEAS and P & S. In 1986, Columbia recruited Van C. Mow, professor of engineering at Rensselaer Polytechnic Institute and a renowned orthopedic biomechanics researcher. Mow had a track record of interdisciplinary collaborations, including a stint as a visiting scholar at Harvard Medical School. Mow joined Columbia as the Anne Y. Stein Professor of Orthopedic Bioengineering. Michael Lai, a professor of mechanical engineering at RPI and Mow's longtime collaborator, soon followed him to Columbia.

In the mid-1990s, with support from Columbia President George Rupp, Provost Jonathan Cole, and Vice Provost Michael Crow, Professors Mow and Lai teamed up with Edward Leonard and Gerard Ateshian, then an associate professor in mechanical engineering with expertise in cartilage mechanics, to develop a new biomedical engineering program at SEAS. Launched in 1995, the Center for Biomedical Engineering was a critical step toward the development of a standalone department. With university funding and a planning grant from the Whitaker Foundation, the program added staff in several key areas—biomechanics, medical imaging, and cellular and tissue engineering.

Over the next five years, the biomedical engineering program secured additional funds and established offices in what was once the grants and contracts office in the Engineering Terrace adjacent to the Mudd Building. On January 1, 2000, the Columbia University Board of Trustees approved the founding of a new Department of Biomedical Engineering, with Van C. Mow at the helm. By 2006, the department had appointed 11 more assistant professors—a trajectory of steady growth that has continued—and expanded the department's areas of research to include regenerative medicine, neuroengineering, and translational research. Mow remained chair until 2011, retiring in 2018 as one of the most celebrated bioengineers in the world. Several BME faculty are recipients of the ASME accolade that bears his name—the Van C. Mow Medal for excellence and leadership in biomedical engineering. Mow was succeeded by Andrew Laine until 2017, when X. Edward Guo took over leadership of the department.

Previous Page: E. coli bacteria micropatterned into a motherboard pattern; Credit: Tal Danino

1896 Columbia professor Michael Pupin, Class of 1883, conducts the first image-guided surgical intervention when he uses x-ray to map buckshot in a patient's hand.



1949 Elmer L. Gaden's doctoral dissertation in chemical engineering details a more efficient way to produce penicillin. The National Academy of Engineering hails him as "the father of biochemical engineering."

1958 The NIH awards its first bioengineering grant to Columbia Professor Edward Leonard, who pursues path-breaking research in the engineering and design of artificial organs.

1974 The Bioengineering Institute is established under Dr. William Nastuk, Professor of Physiology at the College of Physicians and Surgeons, to facilitate collaboration between engineering and bioengineering researchers.

1986 Van C. Mow becomes the first joint faculty appointment between Columbia's engineering and medical schools. He is elected to the National Academy of Engineering, and later to the Institute of Medicine, for his work in orthopedic bioengineering.

1995 Van C. Mow, W. Michael Lai, Gerard Ateshian, and Edward Leonard join forces to develop a new program in biomedical engineering.

1997 A Whitaker Foundation Special Opportunity Award enables Columbia Engineering to hire tenure-track faculty in biomechanics, cell and tissue engineering, and biomedical imaging.

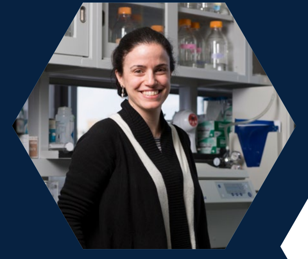
2000 The Columbia University Board of Trustees approves the founding of a new Department of Biomedical Engineering, with Van C. Mow as founding chair.

2003 Barclay Morrison, Lance Kam and Elisa Konofagou join Columbia BME.

2005 Michael P. Sheetz and Lance C. Kam lead Columbia's efforts to establish the Nanomedicine Center for Mechanobiology, advancing regenerative medicine and immunotherapy.

2005 The American Society of Mechanical Engineers (ASME) creates the Van C. Mow Medal, an annual award honoring mid-career bioengineers for excellence and leadership.

2005 Elisa Konofagou uses focused ultrasound to noninvasively penetrate the blood- brain barrier, once a vexing challenge for drug delivery.



2008 Van C. Mow and X. Edward Guo launch the journal *Cellular and Molecular Bioengineering* for the Biomedical Engineering Society.

2008 The Columbia Stem Cell Initiative launches with grants from New York State, the Helmsley Foundation, and the NIH.

2009 Clark Hung assumes editorship of the *Journal of Orthopaedic Research & Reviews*, is elected a Fellow of the American Institute for Medical & Biological Engineering (AIMBE) and a year later, of the American Society of Mechanical Engineers.

2009 Henry Hess joins BME. His Laboratory for Nanobiotechnology and Synthetic Biology is designing nanoscale motors that enable new approaches to biosensing and drug delivery.

2009 President Barack Obama presents Helen Lu with the Presidential Early Career Award for Scientists and Engineers (PECASE) for her pioneering work on interface tissue engineering.

2010 Sam Sia travels to Rwanda to test the mChip, a microfluidic "lab on a chip" that can diagnose HIV and other diseases. He is recognized as one of MIT Technology Review's 35 Innovators Under 35.

2011 Paul Sajda is elected editor in chief of the IEEE journal *Transactions on Neural Systems and Rehabilitation Engineering*.

2011 Elizabeth Hillman receives the Adolph Lomb Medal for Young Investigators from the Optical Society of America for her *in-vivo* optical imaging and microscopy techniques.

2011 The Columbia-Coulter Translational Research Partnership is founded with funding from the Wallace Coulter Foundation, SEAS, and Columbia Medical School. It is later renamed the Columbia Biomedical Engineering Technology Accelerator, or Columbia BiomedX.

2012 Gordana Vunjak-Novakovic becomes the first woman at Columbia elected to the National Academy of Engineering.

2013 Sam Sia develops Harlem Biospace to support entrepreneurial ventures in bioengineering. The project is sponsored by the New York City Economic Development Corporation.

2013 Andrew F. Laine, a pioneer in sophisticated wavelet analysis of medical images, is elected president of the IEEE's Engineering in Medicine and Biology Society.

2014 Steve Thomopoulos joins the faculty as director of the new Dr. Robert E. Carroll and Jane Chace Carroll Laboratories for Orthopedic Surgery.

2016 J. Thomas "Tommy" Vaughan, Jr. joins Columbia as director of magnetic resonance research and founder of the Columbia MR Research Center.

2016 Tal Danino founds the Synthetic Biological Systems Laboratory, pioneering the use of programmed bacteria for cancer treatment.

2017 Gordana Vunjak-Novakovic is named University Professor—the first Columbia Engineering faculty to attain the University's highest academic rank.

2017 Aaron Kyle wins Columbia University's Presidential Award for Outstanding Teaching in recognition of teaching excellence at the undergraduate and graduate levels.

2017 X. Edward Guo is named chair of the Department of Biomedical Engineering.

2019 Columbia BME is ranked among the top 10 biomedical engineering programs in the country by *U.S. News and World Report*.

2019 Paul Sajda is awarded the Vannevar Bush Faculty Fellowship from the U.S. Department of Defense.

2020 Kam Leong elected to National Academy of Medicine

2020 Columbia BME celebrates 20 Years of Excellence.

Q & A
ELISA KONOFAGOU

Elisa Konofagou leads the Ultrasound Elasticity and Imaging Laboratory at Columbia, where she and her collaborators develop novel ultrasound-based techniques for imaging and therapeutic applications. Her work is transforming the possibilities for using ultrasound for early detection of cardiovascular disease and stroke, as well as early cancer detection and treatment. Last year, Konofagou's group published the first study using ultrasound-facilitated drug delivery across the blood-brain barrier to restore neural pathways damaged by Parkinson's disease.

Q: Ultrasound is primarily an imaging technique, but your lab uses it to understand much more than anatomy. What else can ultrasound tell us?

Konofagou: Ultrasound generates thousands of images in real time, but there's no functional information in those pictures—no way to understand the electrical activity of a muscle or the mechanics of a moving heart. Our work goes beyond the anatomy to understand more about how different organs function and how diseases progress.

My lab is at the juncture of imaging and signal processing, so we use signal processing algorithms to pick up information from ultrasound that the eye can miss. This kind of quantitative imaging gives us important information about the mechanical properties of tissues.

Q: Heart disease is a leading cause of death in the Western world, but it's very challenging to diagnose in the earliest stages. How are you using ultrasound to detect early signs of cardiovascular disease?

Konofagou: There's a real need for non-invasive cardiac imaging geared toward early detection. A good analogy for this is mammography, which can spot very early breast cancers. Right now, physicians can only detect problems with the heart when they reach a level that's more severe. Many detection methods are invasive, and while interventions like stents are helpful, they are irreversible and only used when disease is fairly advanced. What if we could detect coronary stenosis at 20 percent or 40 percent, instead of 80 percent? We could potentially avoid invasive interventions, and treat patients with drugs, diet, and exercise. That's what we're striving for.

My lab has developed signal processing algorithms that can look at a cardiac ultrasound and detect small changes in the contraction of the heart muscle. It's so sensitive that we can see even very small areas of ischemia—spots where there are issues with coronary perfusion.

We can also use ultrasound for early detection of events that can precede myocardial infarction. For example, we can identify tiny, transient electrical disruptions in the heart—events that take place in just milliseconds, which is far too fast for our visual perception. Signal processing algorithms allow us to analyze these disruptions. We're also very excited about a paper recently published in *Science Translational Medicine* where we showed that our ultrasound techniques can map arrhythmias and atrial fibrillation more accurately than 12-lead electrocardiography, which is the clinical gold standard.

Q: How do these techniques apply to stroke detection?

Konofagou: Stroke is another area where prevention is key. Ultrasound has long been used to image plaques in the carotid arteries, but it's difficult to correlate plaque size to stroke risk. You can have a big plaque that never ruptures, or you can have a small plaque that breaks and leads to a stroke. We're working on a method of using the elasticity, or compliance, of the plaque as a biomarker for stroke risk. If the plaque is elastic, it's a bit easier to break, which leads to a higher probability of stroke. We are conducting a longitudinal study to see if we can predict potential stroke events in patients, and we hope to have some results in the next few years.

Q: Elasticity is also a factor in detecting cancer with ultrasound. What methods are you working on for improving cancer diagnosis?

Konofagou: Similar to stroke plaques, we can also image the elasticity, or the mechanical properties, of cancer tumors. This technique applies to superficial tumors like breast cancer, or deeper ones such as pancreatic tumors. We probe the tissues with the ultrasound beam, which causes them to vibrate, and through signal processing methods, we can see which tissue vibrates more or less. Tumors typically vibrate less because they're harder.

This method is useful for early detection, but we can also use it to gauge the effectiveness of treatment. In pancreatic cancer patients, ultrasound can detect changes in interstitial fluid pressure in tumor cells soon after treatment. Tumor cells lose fluid before they shrink, so this is an early marker that treatment may be working.

We're also developing a way to treat tumors at the point of detection, with the same ultrasound beam used to vibrate the tissues. If we increase the intensity, it's possible to burn and destroy the tumor from the outside, with no other damage. Our vision is a treatment that would take 15 minutes, then the patient can go right back to living their life!

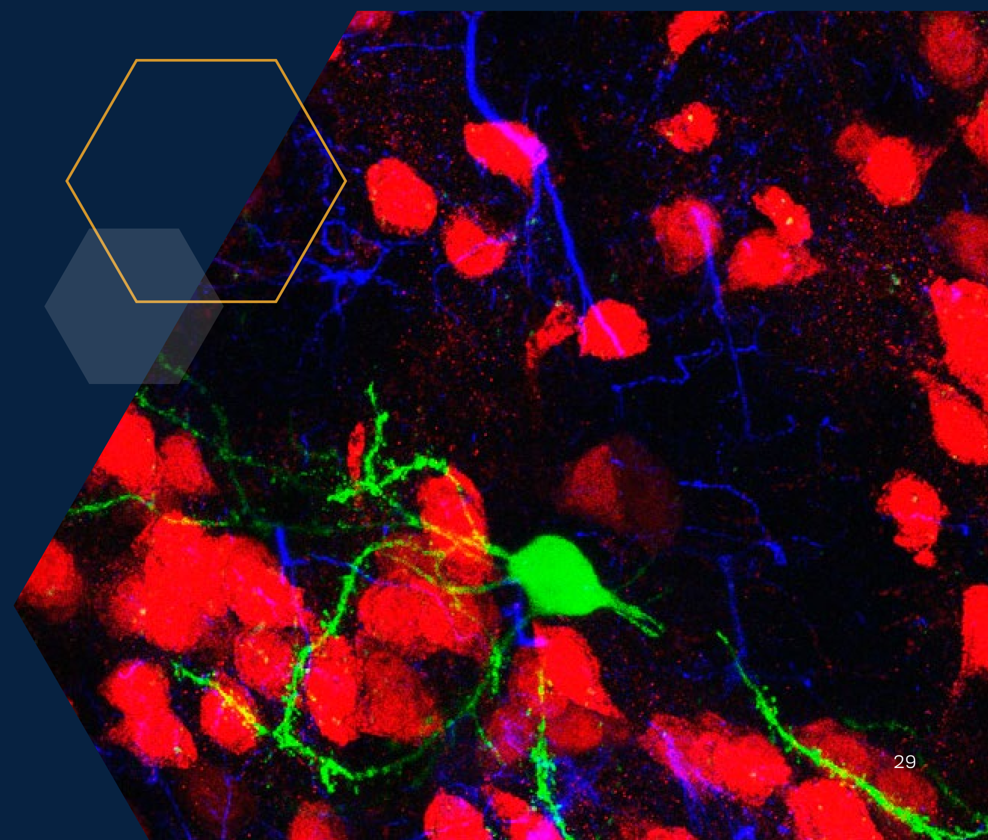
Q: Your lab receives a lot of attention for your work on drug delivery to the brain and neuromodulation. What are some of the most exciting things you're working on?

Konofagou: Drugs designed for the brain often don't work because the brain has an amazing defense system: the blood-brain barrier. If you're a Parkinson's patient or a glioblastoma patient, that system works against you. For the past 15 years, my lab has been temporarily lifting the blood-brain barrier using ultrasound. We place a transducer on the scalp and we can focus on precise regions of the brain, sparing everything else.

We're using this technique for early treatment of Alzheimer's and Parkinson's, as well as brain tumors. Parkinson's and Alzheimer's are focal diseases that originate deep in the brain, so a non-invasive approach is really desirable. Using ultrasound, we can deliver drugs directly into the affected region of the brain, and we can even restore function to the dopaminergic pathways in mice with early Parkinson's. For Alzheimer's, we can reduce the amount of tau protein in the mouse brain, and this improves cognition. We recently received FDA approval to test ultrasound-induced opening of the blood-brain barrier in a small group of people with Alzheimer's. It's very exciting.

Q: You've been at Columbia BME since the early days of the department. Any thoughts on the 20th anniversary?

Konofagou: Our founding chair, Van C. Mow, chose the early members of the department carefully, and he did so with an eye toward collaboration. He knew that it wasn't just about the research, it was about how well people gel together. That cohesion and camaraderie is still present in the department today, and that's a big part of Van's legacy. It's a real testament to his vision.



Right: Mouse neuron transduced by an adeno-associated vector expressing green fluorescent protein after crossing the ultrasound-induced opening of the blood-brain barrier.

Left: *Microbial Rainbow*, 2019,
Engineered soil bacteria on petri dish.
Courtesy Tal Danino

BIOMATERIALS

INTERFACING WITH LIFE

Novel biomaterials and engineered biological systems are enabling new paradigms in disease treatment, health monitoring, and drug delivery

The medicines in Tal Danino's Synthetic Biological Systems Laboratory are alive, and they are devious. In his hands, even benign bacteria can be engineered to kill, their sights set on a universal enemy: cancer. Danino is a pioneer in synthetic biology, a newly emergent field borne of decades of cumulative progress in genetic engineering and cell and tissue engineering. Thanks to a deep understanding of the function of gene sequences, Danino and others in the field are building novel biological systems precisely programmed to perform specific tasks in certain environments.

For Danino, the environment of interest is the tumor interior. Sequestered from the immune system, bacteria naturally flock to solid tumors, invading and replicating with little impact on either the tumor or the host. Danino's experiments upend that paradigm, sending armies of genetically modified bacteria directly into tumors—Trojan horses by the millions. Once inside, the invaders carry out their orders—usually the production of a small molecule followed by mass lysis, which releases those molecules within the tumor. "We've engineered bacteria to produce nanobodies that target checkpoint inhibitors, cytokines, and chemokines," he said, noting that the technique can be tailored to different types of cancer. "If it's a drug you can make in bacteria, we can probably make it inside a tumor," Danino said.

Danino's lab has achieved complete regression in mouse models of lymphoma. This early success represents a potentially thrilling frontier in cancer immunotherapy, a subject dominated most recently by CAR-T cell therapy. "There's a long history of trying to use bacteria to stimulate the immune system to fight cancer," Danino said, "But it wasn't until we developed engineering approaches that allowed us to control the bacteria that people really started getting excited about the idea again."

A range of clinical disciplines increasingly rely on engineered biological systems and biomaterials to advance therapeutic treatments, diagnose disease, enable next-generation implantable devices and sensors, and transform drug delivery.

TINY BUT MIGHTY

If Kam Leong, Samuel Y. Sheng Professor Biomedical Engineering, could stake a "claim to fame," as he described it, the honor would go to his lab's success creating biocompatible nanoparticles for drug delivery and gene editing. Targeted, tunable, and tiny, nanoparticles offer tantalizing advantages over traditional drug delivery systems, and hold significant potential for nonviral gene editing. From Leong's standpoint, these mini materials represent nearly infinite possibilities for improving treatments that already exist, as well as facilitating new therapeutic pathways. One compelling example is Leong's efforts to develop the first dual-purpose nanoparticle-based system for cancer treatment. In a mechanism he describes as "push-pull," the system would deliver targeted chemotherapy drugs while also inhibiting disease progression by binding to, or "scavenging" cellular waste associated with metastasis.

CRISPR-based systems have made precise gene editing more feasible than ever, but delivering the elements within certain tissues—especially brain tissue—remains a challenge. It's here too that Leong sees a transformative role for nanoparticles. He and fellow BME professor Elisa Konofagou are among a select few research teams developing methods for gene editing in the brain under the NIH's Somatic Cell Genome Editing Program. Their work merges Konofagou's expertise in focused ultrasound, an effective method of opening the blood-brain barrier, with Leong's work in nanoparticle design. Together, they are optimizing a nanoparticle-based CRISPR delivery system targeting Alzheimer's and Parkinson's. Leong sees a future of orally-delivered nanoparticle CRISPR therapeutics designed to withstand the harsh environment of the GI tract. His lab is already at work on an oral CRISPR-based therapy to safeguard the hematopoietic system from radiation damage in cancer patients, or as a potential treatment for Acute Radiation Syndrome.

Left: Coexistence 001, 2019,
Bacillus bacteria on petri dish.
Courtesy Tal Danino

A WI-FI CONNECTION TO THE BRAIN

Integrated circuits are ubiquitous in smartphones and computers, but in Ken Shepard's lab, CMOS chips have a very different destination. "Our technology basically allows us to establish a wi-fi connection to the brain," Shepard said, describing a breakthrough that feels decidedly futuristic. Not only is his system real, it's capable of revealing detailed information about neural processes, including vision. Building on decades of progress fabricating ever-smaller, more powerful integrated circuit chips, Shepard and his collaborators have created a flexible, biocompatible brain implant barely the size of a pea and one-third as thick as a human hair. At that thickness, the material, which Shepard can modify in a variety of ways to increase its biocompatibility, is unusually pliable. "It's just like a sheet of paper," he said. Placed directly on the brain's surface, the chip's 65,000 electrodes transmit neural activity data wirelessly to an external device. Shepard is mapping and stimulating the visual cortex in animal models, with the ultimate goal of creating a "visual prosthetic" that may someday restore human sight following optic nerve injury. A somewhat similar device is in human trials right now, but Shepard is quick to point out that it features just 64 electrodes. "Animals can't tell us what they see, so once we get to human trials, we'll be able to understand the richness and visual perception that may be possible with a dramatic increase in the number of electrodes," he said.

MINIATURE DEVICES, MAJOR IMPACT

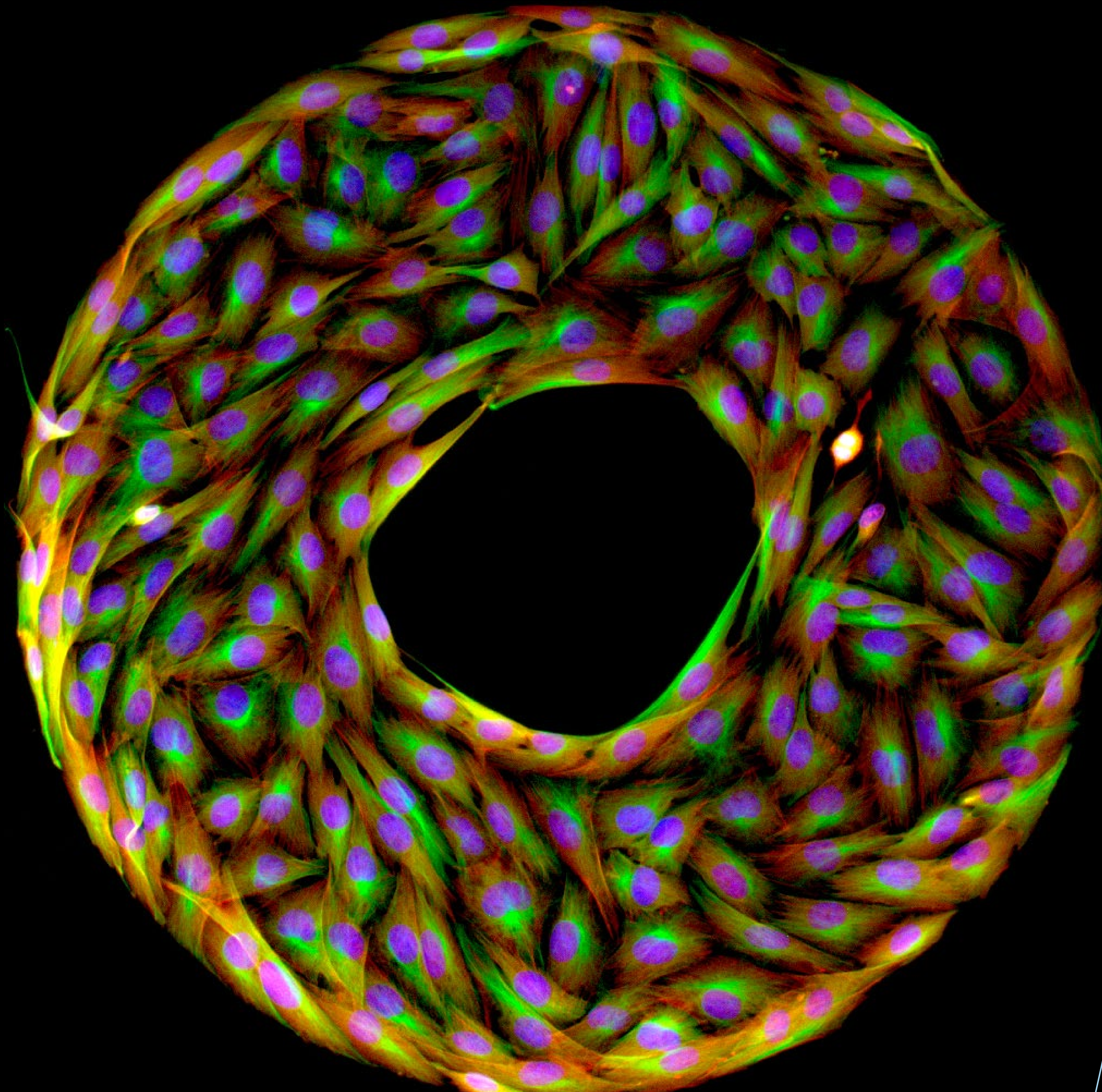
"At some point we'll have sensors we can use to collect health information anywhere, anytime, or even all the time, if needed." That's part of Sam Sia's vision for the future of diagnostics and health monitoring, and he's not leaving the work to other people. Utilizing innovative materials and design schemes, Sia's lab is designing minimally invasive biosensors and microfluidic devices that are advancing both digital health and global public health.

Sia's lab has garnered a steady stream of attention for designing devices that rely on microfluidics and nanoparticles to replicate complex laboratory assays in a low-cost unit that can be used in point-of-care settings. A microfluidic HIV and syphilis test requires just a drop of blood, and, paired with a smartphone, can provide reliable results in 15 minutes. A similar platform has been adopted for the first microfluidic test for Lyme disease, which affects 300,000 people each year and can cause long-term neurologic and other complications if left untreated.

More recently, Sia published the results of his lab's efforts to design a biosensor patch to monitor analytes in interstitial fluid. While existing biosensors perform similar functions—continuous glucose monitors are one example—Sia notes that most systems rely on silicon or metal microneedles, which can be painful for patients. Sia's patch uses arrays of biocompatible hydrogel microfilaments that are stiff in their dehydrated state for easy insertion, then soften on contact with fluid beneath the skin. The filaments are chemically conjugated to fluorescent sensors to facilitate detection of changes in analyte levels. While the technology is still in its early stages, Sia sees this novel adaptation of existing materials as a key step toward "closing the loop," linking health monitoring with timely interventions. "It's one thing to collect the information, then we can work on responding, perhaps by coordinating a drug release," he said. "As we move more towards personalized medicine, we're always thinking about how we can find out what's happening in the body, then take action in real time," Sia said.

FROM HUMAN MUSCLE TO NANOMOTOR

Nanorobots have long been envisioned as the ultimate future technology for drug delivery and disease treatment. "There was always this idea that we would build tiny submarines that would enter the bloodstream, find cancer cells, then kill them with lasers," said Henry Hess. "But that's probably not going to happen." Hess leads the Laboratory of Nanobiotechnology and Synthetic Biology, home to a microscopic fleet of nanoscale motors that may represent a more feasible approach to using biocompatible nanomachines in a variety of fields, including drug delivery, biosensing, and even environmental sensing. "We use the same motor proteins that drive muscle contraction in the body to create nanoscale transporters," he said, explaining that when placed in synthetic environments, these proteins can be controlled and utilized to collect or move cargo. In a sensor application, this approach could take the form of millions of ingestible or implantable nanosensors that can detect analytes in the body or toxins, such as anthrax, in ambient air. The advantages of such hybrid bio-nanodevices are significant, especially in medicine. Hess' lab is exploring paths to overcome the engineering challenges—including energy efficiency—that stand between concept and reality.



MECHANOMEDICINE

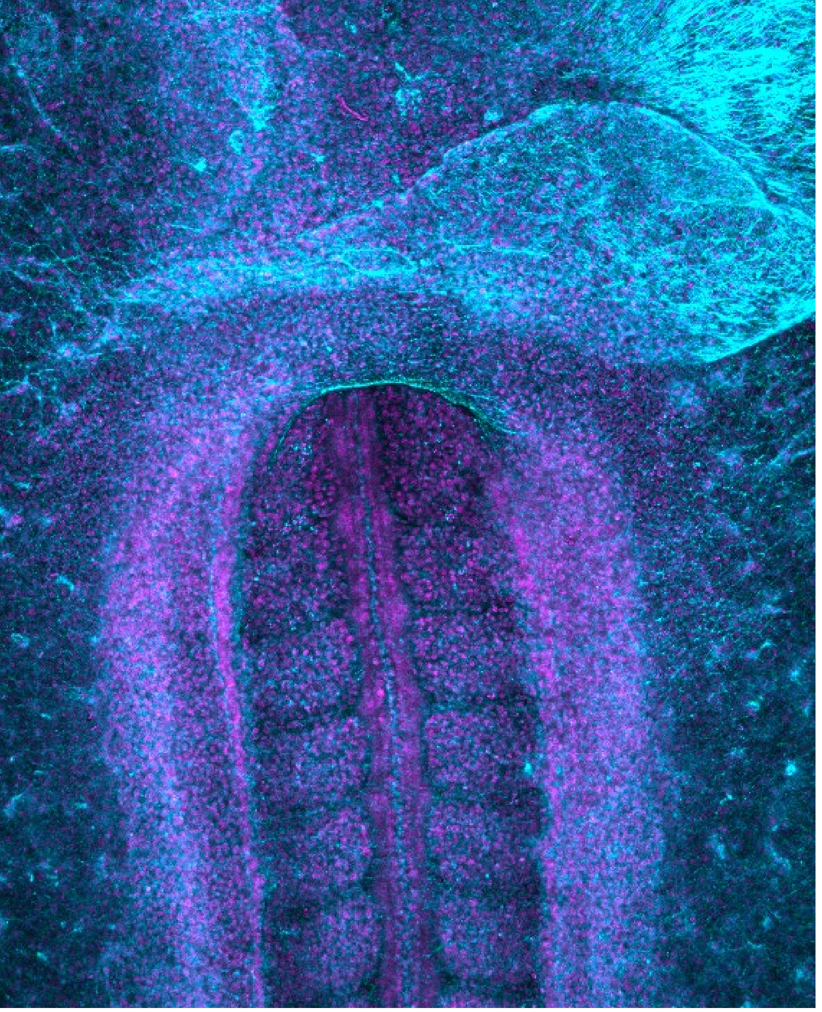
FORCES OF NATURE

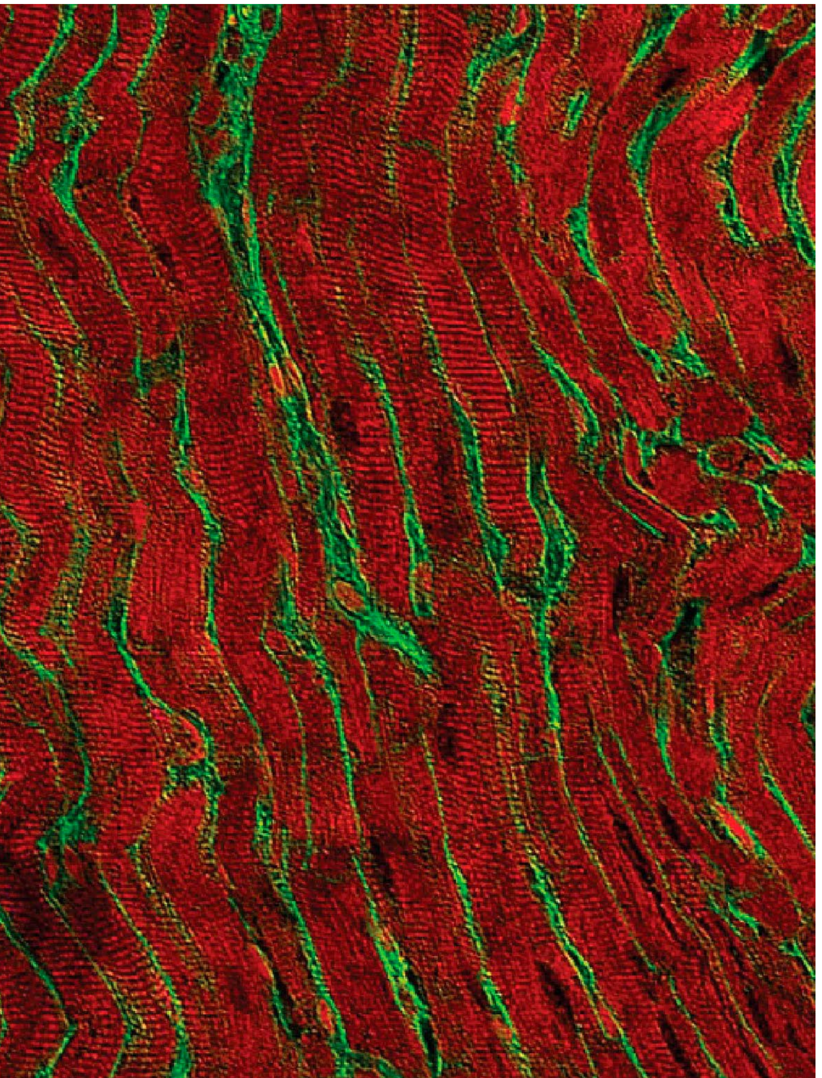
Understanding the interactions between cells and their physical environment is leading to new therapeutic approaches

Human T cells are the special ops forces of the adaptive immune system: highly specialized, targeted, lethal. But they're not all tough, as Columbia bioengineers Lance Kam and Helen Lu learned when they began testing a new method for culturing T cells, which are in high demand for use in cancer immunotherapy. "We found that if we used a softer substrate instead of the typical hard plastic laboratory dishes, we could dramatically increase the growth of functional T cells," Kam explained. The implications are significant and immediate: one of the key bottlenecks to using T cells therapeutically, whether for CAR-T or other adoptive T cell therapies, is limited access to sufficient numbers of cells.

The phenomenon underlying this surprising finding is mechanosensing–the ability of a cell to sense mechanical cues from its environment. Mechanosensing is often associated with cells that bear mechanical loads, such as those of the bones, muscle, and heart, as well as cultured stem cells, which differentiate partly in response to the mechanical stiffness of their substrate. "Our discovery that T cells could also do this was very unexpected," Kam explained. Kam and Lu paired their respective expertise in immune cell mechanobiology and smart material design to create an electrospun fibrous mesh that incorporates a soft silicone elastomer. Deployed as a substrate in T cell culture, the mesh outperforms the current gold standard by "an order of magnitude," according to Kam, and even encourages growth in historically unresponsive T cell populations, such as those harvested from patients with chronic lymphocytic leukemia. This type of cross-disciplinary collaboration is "one of the magic things" about the culture at Columbia BME, according to Kam. "The investigators here are not just willing, but *excited* to talk across boundaries and learn about each other's work," he said.

Opposite: Chirality of muscle cells recapitutulated by micropatterning of cells (Wan et al, PNAS, 2011).





Columbia bioengineers are building upon a rich history in mechanobiology, making new discoveries about the profound role of mechanical forces in shaping human physiology. Through the emerging field of mechanomedicine, these concepts are being applied to clinical challenges.

UNDER PRESSURE

Twenty years ago, *Time* magazine published the hottest jobs of the future. Number one on the list: tissue engineer. Clark Hung remembers that story, along with others from that time, which promised a tantalizingly close future of ready-grow replacement organs. “Most of those ideas still haven’t materialized,” said Hung, and he’s not surprised. The process of learning to grow a comparatively “simple” tissue type, cartilage, was rife with trial and error. Early engineers quickly realized that it wasn’t enough for lab-grown tissue to look native—it had to *perform* like native tissue. “Mechanical inputs are critical for the development of cartilage in the body,” Hung said, “and we now know that bioreactors must incorporate physical forces if we want to grow tissue with the mechanical competence to survive.”

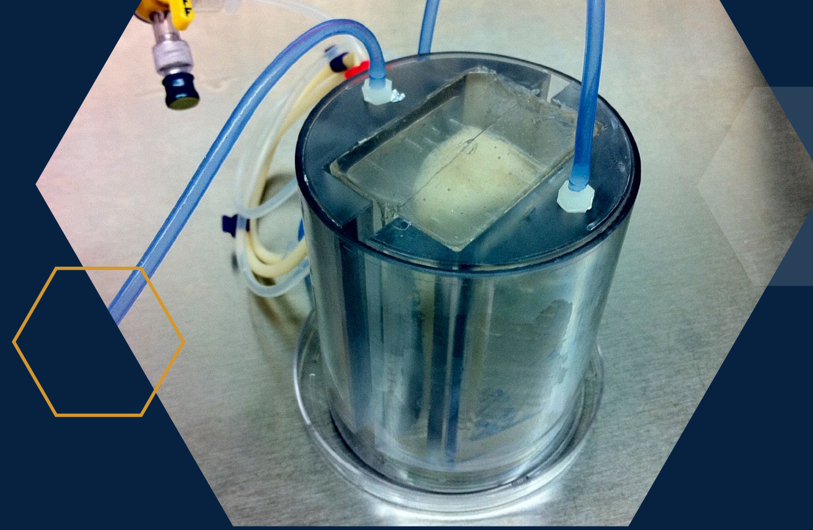
Absent the vascularity that brings nutrient-rich blood to bone and nearly every other tissue in the body, cartilage relies on mechanical loading to absorb nutrients from synovial fluid. Over the course of a 20-year collaboration with BME colleague Gerard Ateshian, Hung has demonstrated how reproducing this force-driven process *in vitro* boosts the growth and development of engineered cartilage replacements. His insights have also enabled the design of three-dimensional engineered tissue models of diseases that impact cartilage, including osteoarthritis. These systems allow researchers to observe disease processes and test new therapeutic approaches.

Despite his enthusiasm for basic research, Hung never loses sight of the practical aspects of his work. He has dedicated much of his career to finding ways to use clinically available techniques and materials to bring new treatment strategies to patients. In 2019, the world’s largest tissue bank, MTF Biologics, licensed a preservation system for osteochondral allografts that Hung developed with a team at the University of Missouri. The system maintains the mechanical integrity of these allografts prior to transplant and extends the window of viability from 28 days to at least 56. More than 150 institutions have transplanted grafts stored using Hung’s system. “Whenever we can, we try to optimize what’s being used clinically now, with the hope of finding a path to translation as quickly as possible,” he said.

Opposite, top to bottom: Fluorescent micrograph of the forming heart and foregut in a developing chick embryo. Human heart muscle grown in the lab using electromechanical conditioning.

Engineered human heart muscle, matured by electromechanical conditioning (Ronaldson-Bouchard et al., *Nature*. 2018).

Right: Bioreactor for cultivation of complex, anatomically shaped cartilage-bone grafts (Chen, Wu et al., *Science Translational Medicine* 2020).



“It wasn’t enough for lab-grown tissue to look native. It had to *perform* like native tissue.”

A GUT FEELING

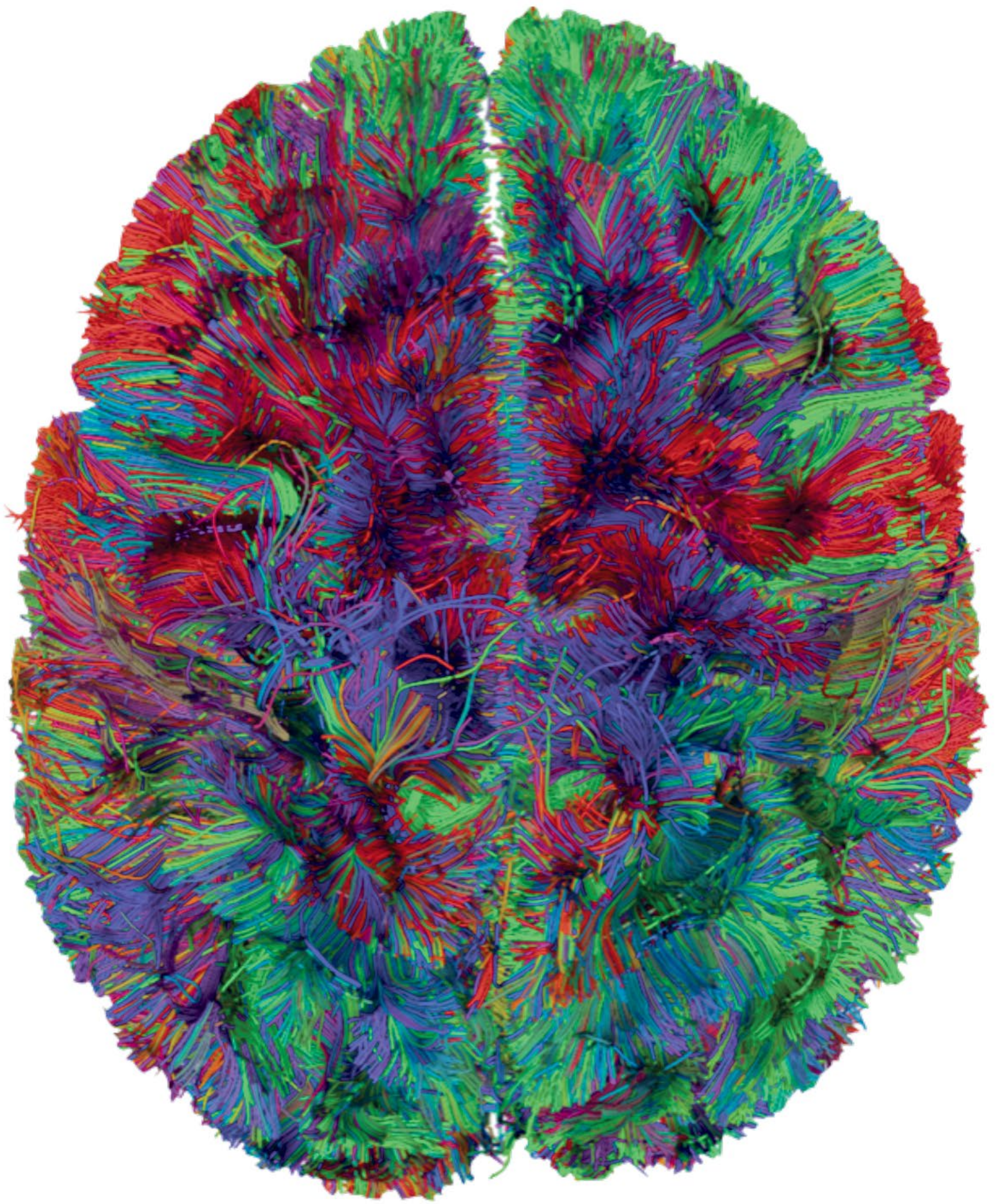
In the earliest stages of life, cells engage in an elaborate process of organization and differentiation. This ancient choreography is dictated by genes, but its success depends on cells generating forces that enable dramatic shape changes as an organism develops. “Cells have to generate exactly the right amount of force, in exactly the right direction, at exactly the right time and place, and these forces need to act on tissues that have exactly the right stiffness,” said Assistant Professor Nandan Nerurkar, whose lab is applying engineering approaches to understand development. “If you change any of those parameters by even five percent, you end up with something that looks quite different.”

Nerurkar is among a growing group of researchers intrigued by the mechanics of embryonic development, a niche of developmental biology once occupied mainly by mathematicians and physicists. Over the past two decades, as major advances in molecular biology have facilitated the study of genes that direct embryonic development, researchers like Nerurkar, who has cross-disciplinary training in engineering and genetics, are increasingly focusing on how the mechanical processes of embryonic development are controlled during the progression from “a seemingly disorganized ball of cells” to a highly complex, functional organism.

Nerurkar’s research, conducted on chicken embryos, has elucidated the signaling pathway by which the initially straight intestinal tube physically buckles into the characteristic looped pattern of the small intestine. The findings have surprisingly broad relevance, as the same pathway may direct this process in human development. During experiments to determine the impact of over-or under-expressing the proteins in this pathway, “we recreated some birth defects that are also seen in humans,” Nerurkar explained. “Knowing these defects are tied to this pathway may give us the opportunity to take a bit more of a guided approach to determining if there are mutations relevant to it,” he said. An increased understanding of the mechanical principles of overall embryonic tissue formation may have implications for regenerative medicine and tissue engineering applications. “When you’re asking these questions in the context of developmental biology, the human health relevance is never very far away,” Nerurkar said.

LOOKING DEEPER

New biomedical imaging modalities and advances in existing ones allow researchers and clinicians to observe the processes of life as never before



In 1896, legendary Columbia professor Michael Pupin performed the first image-guided surgical procedure using x-ray photography. Just over 40 years later, in Pupin's namesake lab, University Professor Isidor I. Rabi discovered nuclear magnetic resonance, which earned him the Nobel Prize and later became the basis for magnetic resonance imaging (MRI). It's likely that neither man could have envisioned the view through a SCAPE microscope. Created by Professor Elizabeth Hillman, SCAPE—short for swept confocally-aligned planar excitation—merges light-sheet microscopy and confocal scanning microscopy, producing three-dimensional images and videos of living or cleared tissues hundreds of times faster than point scanning microscopes. Watching the technique in action on a cleared mouse brain is immersive and astonishingly beautiful, the imagery akin to a video game fantasy world—a thick forest of axons weaving amid a field of cell bodies, bright as stars.

Hillman describes the discovery of SCAPE's wide-ranging potential as "almost an accident." As she and her collaborators at the Zuckerman Institute's Laboratory for Functional Optical Imaging refined the technique, new capabilities and functionalities kept emerging. "We didn't realize how powerful it was," Hillman said, until repeated tests and trials made SCAPE's broad applicability crystal clear. The most recent iteration of the technology, SCAPE 2.0, has captured the firing of individual neurons in live mice, the flow of a single red blood cell through the developing heart of an embryonic zebrafish, and the cellular dynamics of the proprioceptive system within the fruit fly brain, all in real time and three dimensions.

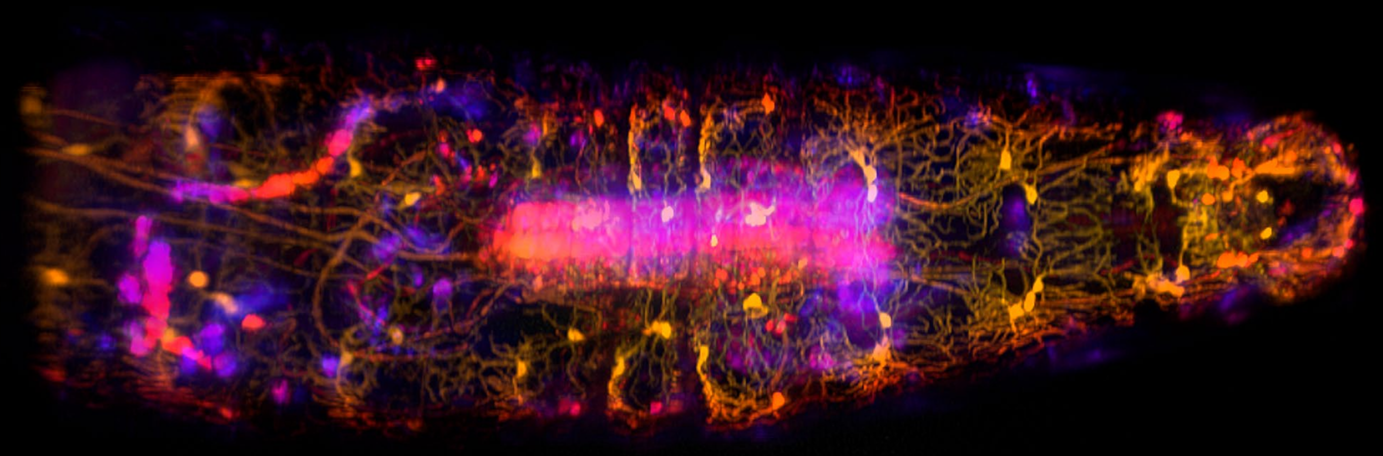
Hillman has a growing roster of collaborators at Columbia and beyond. She has assisted other research institutions in building their own SCAPE systems, and has even packed up the microscope for in-person demonstrations. SCAPE will soon be more accessible than ever, as Hillman's lab recently licensed the technology to Leica Microsystems for commercialization.

With support from the Columbia BiomedX accelerator, Hillman is developing a miniaturized version of SCAPE for *in-situ* histopathology. "In addition to the bench-top applications, we realized SCAPE could be used in medical applications to image people," she said. "You can put the microscope against a kidney, for example, and get high-speed 3D images of the cells without having to remove anything or process the tissue." This information could help determine the viability of donor organs or provide guidance on margin detection during cancer surgery and biopsy procedures.

While most areas of biomedical engineering embrace multiple disciplines, every area relies on some form imaging. In addition to developing new technologies, Columbia researchers are using advances in artificial intelligence and data science to broaden the clinical applications of existing imaging technologies, including ultrasound and MRI.

Opposite: An example of MR tractography. Courtesy GE Healthcare and J. Thomas Vaughan, Jr.

Below: Freely crawling fruit fly larva imaged using high-speed 3D SCAPE microscopy (Hillman Lab). Colors denote different depths into the sample. Fine structures are proprioceptive neurons that tell the larva's brain (center) about its body position.



> "Machines can give us statistically powerful answers to big, complicated questions about health, disease, and the human condition."

THE DISTANT HORIZON

J. Thomas Vaughan, Jr. can see the future—at least as it pertains to MRI. A pioneer whose inventions have enabled every successive leap in magnetic resonance imaging for 30 years, he doesn't hesitate to share his ideas about the yet-unrealized capabilities of MRI. "We're going to ask very big questions of very big data sets," Vaughan said, teasing the potential of a collaboration he's spearheading to unite the major research institutions in New York, "the epicenter of the world in terms of talent in biomedical sciences and especially in neuroscience," under the umbrella of the new Columbia Magnetic Resonance (MR) Research Center.

Vaughan describes himself as a technology developer—"more a telescope builder than an astronomer." He came to Columbia in 2016 as Director of Magnetic Resonance Research with a vision aimed at pushing the university to the forefront of MRI research and application. "I've always been building the most powerful telescope to see the most distant horizon," Vaughan explained. He is charting a course to make MRI more clinically relevant and farther-reaching than ever before, answering deep questions of health and disease, body and mind. Success will depend in part on gathering a trove of data beyond anything previously archived in the history of biomedical imaging. Vaughan has a strategy for this, too.

In 2018, the Columbia MR Center became the first fully cloud-integrated biomedical imaging research facility, linking five Columbia-affiliated sites—and eventually many of the city's major hospitals and research institutions—to a limitless repository of MRI data. "Collecting data is collecting knowledge," Vaughan said. "What we can't use today, we'll use tomorrow, for an experiment we haven't thought of yet." The mission of amassing an unprecedented trove of MRI data runs parallel to Vaughan's desire to expand the accessibility of MRI, which is currently unavailable to more than 90% of the world's population. A portable MRI system he's developing may advance that goal, helping to move MRI beyond the clinical setting and testing its utility to reveal mechanisms of behavior, emotion, and awareness. "Our minds aren't capable of looking at all the correlations, effects, and subtle influences, but machines can give us statistically powerful answers to big, complicated questions about health, disease, and the human condition," Vaughan said.

In the meantime, Associate Professor of Biomedical Engineering and Radiology Christoph Juchem is working to boost the clinical potential of existing MRI and MRS technologies, especially as a means of deriving new insights into neurodegenerative diseases such as multiple sclerosis. Juchem's work is two-pronged—one technological, one translational. His lab has developed novel algorithms and software for studying the brain at 7 Tesla, which uses a far more powerful magnet than typical MRI scanners to produce ultra-high resolution images that require specialized processing methods. Among his major contributions are image processing technologies that improve magnetic field homogeneity to yield more clinically relevant data.

The other arm of Juchem's lab works to apply these technological solutions to solve clinical problems. "Pilots don't develop airplanes, and most clinicians don't develop their own technology," said Juchem, who has established partnerships with clinicians and scientists throughout Columbia. Testing his lab's image processing and analysis methods in the clinical setting is "where the symbiosis comes in," he said. "It's a true win-win."

Juchem's lab is using MRI and MRS to analyze the interplay of metabolites in the brain and spinal cord of multiple sclerosis patients, with the hope of arriving at a method for early detection and even treatments to address specific neurochemical imbalances. "We want to see if we can identify changes that occur before there's cellular damage, spinal cord lesions or even symptoms of the disease," said Juchem. "By the time we see atrophy in the brain, we may be years too late."

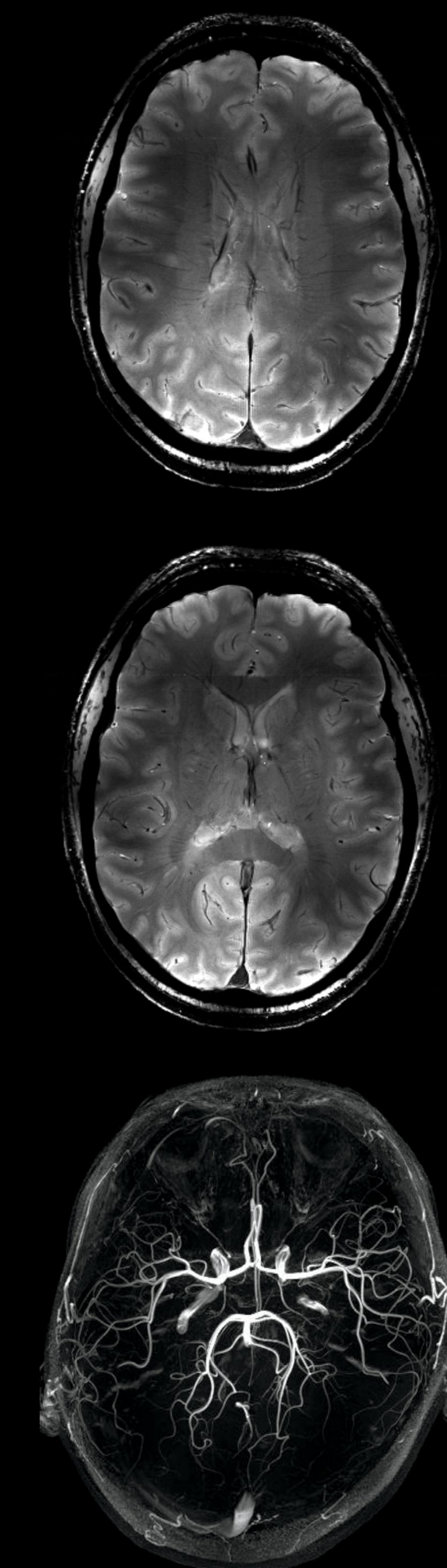
Top, middle: The first human brain images acquired at 9.4 Tesla (Vaughan et al, *Magn Reson Med.* 2006)

Bottom: An example of MR angiography in the brain. Courtesy GE Healthcare and J. Thomas Vaughan, Jr.

SEEING IS HEALING

Medical imaging typically helps make diagnoses or inform treatment strategies. But in the hands of Elisa Konofagou, Robert and Margaret Hariri Professor of Biomedical Engineering, an imaging technology can *become* a treatment strategy. Konofagou is known for pushing the boundaries of ultrasound, developing novel methods for detection and assessment of malignant tumors and atherosclerotic plaques (see Q & A, page 28). She half-jokes that "ultrasound can do anything," and her forays into therapeutic use of the modality only builds her case. Konofagou is testing high-intensity focused ultrasound ablation therapy for small breast cancer tumors, a technique she envisions may someday produce a "non-surgical method for detecting cancer and treating it non-invasively, on the spot, in 15 minutes."

In 2014, she discovered the mechanisms that enable ultrasound-induced opening of the blood-brain barrier, a technique that has become a promising avenue for delivering small molecules and gene editing components directly to the brain. Since then, Konofagou and collaborators at Columbia University Irving Medical Center have demonstrated the potential for using ultrasound to aid the treatment of neurodegenerative diseases including Parkinson's and Alzheimer's. In 2019, she was the first to achieve partial restoration of damaged dopaminergic pathways in early Parkinson's patients following the delivery of existing drugs across the blood-brain barrier. That same year, Konofagou and Lawrence Honig, a neurologist at Columbia's Taub Institute of Alzheimer's Disease and Aging, received FDA approval for the first clinical trial testing a focused ultrasound device to open the blood-brain barrier in a small group of early Alzheimer's patients. Konofagou hopes the trial, which began in early 2020, will soon be expanded to a larger cohort.



TRANSLATION

STARTUP ENGINE

A steady stream of startups and a curriculum steeped in entrepreneurship result in a vibrant culture of innovation

Above: Neopenda testing its infant vital signs monitor at a hospital in Uganda

In some situations, success looks like an exit sign. "When ideas that can really impact human health stay within the university, they're not getting any closer to patients," said Katherine Reuther, senior lecturer in design, innovation, and entrepreneurship, who has watched more than a dozen teams of entrepreneurs take flight during her six years at Columbia. Reuther leads the Master's program in biomedical engineering and directs Columbia BiomedX, a biomedical engineering technology accelerator that provides funding, mentorship, and other support to advance the development of early-stage innovations.

When asked to describe their work, the majority of Columbia BME faculty emphasize practical research directions with clear commercial or clinical applications. Over the past decade, and especially in the last five years, Reuther has witnessed "a palpable shift in the entrepreneurial mindset and ecosystem at Columbia," reflected both in the department's curriculum as well as the University's vast network of training and educational resources. "Innovation and entrepreneurship are now major strengths of our programs," Reuther said. "We're really supporting students who want to pursue this career path." The numbers confirm her assertion—since 2015, BME faculty and students have founded a record 17 startup companies.

From entrepreneurship bootcamps to the department's renowned undergraduate Senior Design course—a full-year immersion during which students identify and address unmet biomedical device needs—BME course offerings aim to cultivate "a translational educational mindset," said Aaron Kyle, senior lecturer in biomedical engineering design and leader of the undergraduate program. "Not every project makes sense for a startup company, but every project has to have a real-world tie-in," he said.

This hunger for impact is a driving force behind the steady flow of commercially relevant innovations from the department. Faculty and students are upending the traditional "bench-to-bedside" translational paradigm, forging a new process that's "bedside to bench, then back to bedside," according to Gordana Vunjak-Novakovic, University Professor and Mikati Foundation Professor of Biomedical Engineering and Medicine. "Clinicians are increasingly identifying problems and coming to us to collaborate and, hopefully, find solutions."

Vunjak-Novakovic has spun four companies out of her lab since 2008. All are helmed by former students, three of them women. The first, Epibone, recently entered early human trials of a proprietary technology for growing custom bone grafts using patients' own cells. Two others, Tara Biosystems and Xylyx, are using cell culture and tissue engineering methods to facilitate drug discovery. The most recent addition to the portfolio, Immplacate, is working to bring a potent stem cell therapy for immune disorders to market.

Other startup superstars include Professor Sam Sia who is commercializing low-cost microfluidic diagnostic devices for HIV and syphilis in developing countries through one of his companies, Junco Labs. Another, Rover Diagnostics, is fast-tracking development of an ultraportable PCR platform aimed at providing rapid COVID-19 testing. Sia's first company, Claros Diagnostics, was acquired by pharmaceutical company Opko in 2012. Its core technology, a point of care diagnostic test for prostate specific antigen, recently received FDA approval. He's also the founder of Harlem Biospace, an incubator for local biotech companies.

STUDENT SUCCESS

BME students have no less impressive startup stats. Two former doctoral students from Paul Sajda's Laboratory for Intelligent Imaging and Neural Computing, Jason Sherwin and Jordan Muraskin, co-founded deCervo in 2015 to commercialize methods for improving decision-making capabilities in professional sports. Sajda's own startup, Neuromatters, which uses EEG to gauge consumer engagement with marketing and advertising messages, was acquired in 2019.

Ideas hatched during coursework or university-wide design challenges have become the basis of several recent startups addressing global health and maternal and infant mortality. Kinnos, founded by undergraduate alum Jason Kang, is commercializing Highlight, a patented color additive that mitigates human error when using disinfectants and has been implemented by hospitals and humanitarian agencies to prevent infections. Luso Labs, founded by Jahrane Dale, Olachi Oleru, Ritish Patnaik, and Stephanie Yang, has developed and deployed a specialized camera and smartphone algorithm for improving interpretation of cervical cancer screening tests in lower and middle income countries, where more than 50 percent of the world's cervical cancer deaths occur. Inspired in part by the long-ago death of a family member, Mikhail Kamal—now a medical resident—founded Jibon Health, and is testing a low-cost device for stemming postpartum hemorrhage, a leading cause of maternal mortality. Neopenda CEO Sona Shah had never considered starting a company until she enrolled in Professor Reuther's Masters Biodesign class in 2014. Six years later, she and fellow BME alum Teresa Cauvel are launching their company's first product in Uganda—a low-cost newborn vital signs monitor based on the initial concept they created in class. Shah, Kang and others credit the mentorship they received as crucial to their success. "Columbia has been so supportive in our journey—the guidance we've received goes far beyond the classroom," Shah said.

Right: The Fire Department of New York using Kinnos' Highlight technology for decontamination during an Ebola response simulation.

ENTREPRENEURSHIP AND OPPORTUNITY

Professors Gordana Vunjak-Novakovic and Sam Sia on startups, students, and the pursuit of science for the sake of humanity.

Why is biomedicine such a hot area for innovation and entrepreneurship at Columbia?

Gordana Vunjak-Novakovic: For everyone in our department, translation or application of science is as important as the science itself. We do basic science research, but the real goal is to benefit people, and this is a more important goal in biomedical research than in many other areas. If something is significant or innovative, it's very obvious and highly motivating. Another huge advantage of our field is that some of the greatest talent is attracted to this area—young people want to save the planet, and they believe they can have real impact in an area of such universal importance.

Sam Sia: I agree—we're at a time where the opportunities for biology and medicine are unprecedented, and we have great institutional support for entrepreneurship here at Columbia. Also, our faculty are strong in many leading areas—not only biomechanics, biomaterials, tissue engineering and imaging, but neuroengineering and synthetic biology as well.

How have students' attitudes and interests in entrepreneurship and translational research changed over the past 20 years? Do you see students entering the department with a specific interest in starting a company?

GVN: First, I want to say that so much of the department's success in this area is due to the dedication and interest of our trainees. They're really the story here. There's a lot of interest in entrepreneurship, in part because there are many more opportunities today for students and fellows to learn about business and the components of translation as part of their scientific training. Those opportunities didn't exist even 10 or 15 years ago. Many students, postdocs, and clinical fellows from my lab have completed entrepreneurship boot camps and workshops that helped build their business knowledge and confidence. I'm sorry I'm not a graduate student today—they're having a lot more fun than we did!

SS: Educationally, what we're doing in the department on things like design and entrepreneurship, even starting with the undergrad level, is really impressive. We've got great instructors like Aaron Kyle and Katie Reuther, and students can adapt the curriculum to their interests. I think the students who visit here and see our program know that this is an area where we're really strong.

What are the advantages of doing translational research in New York? There was no technology startup sector when the department was founded, but that's certainly changed.

GVN: Starting a biotech company in New York City was science fiction even 15 years ago, so there's been a big shift there, for sure. But the biggest advantage is that New York is much more than a city: it's a microcosm of the world. We don't have to travel far to develop technologies that are applicable in developing countries—we have communities here, our neighbors, that are underprivileged in many ways and need solutions that work for them.

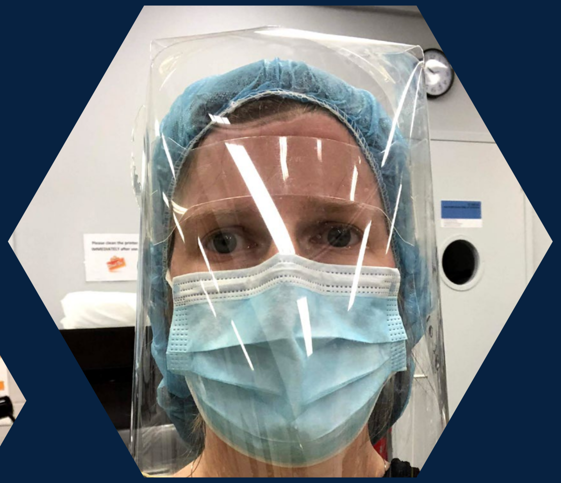
SS: Exactly, it's impossible to get away from the connection between our work and its potential impact on humanity and society when you're living in New York City. Nothing happens here in isolation.

GVN: Sam has done amazing work in this area, designing diagnostic devices for parts of the world with limited access to healthcare. But you can test these ideas here and get really valuable feedback from local communities.

How has this interest in socially responsible work changed your approach to getting research innovations out of the lab and into patients?

GVN: We are increasingly focused on how to make the development process from lab to application safer and shorter. In many cases, you take a concept from the lab, test it in an animal model, and then sometimes, but rarely, move into tests in people. But the process is slow and expensive. More and more, we find that we can transfer knowledge gained during research to make clinical trials easier, cheaper or faster, because it's important that it reaches the patients. The vision is medicine for the masses, not innovations that come only to a select few who can afford them.

Right: Cover image of the *iScience* special issue on bioelectronics, depicting the positive acrylic mold used to fabricate hydrogel microfilaments for intradermal biosensing.



INNOVATING IN REAL TIME

Amid the worst public health crisis in a century, BME faculty join the fight against COVID-19

It started with an email on a Tuesday night in March 2020, shortly after New York began a historic shutdown to halt the spread of the novel coronavirus SARS-CoV-2. The message, written in all capital letters from a physician at Columbia University Irving Medical Center, shouted from the screen of Professor Elizabeth Hillman's computer. The plea was urgent: the hospital was desperate for N95 face masks. Could Hillman create them using a 3D printer, and if so, was it possible to make one million masks by the weekend? "I realized that I'm sort of a professional problem solver," said Hillman, "so I started researching it." Days later, through a flurry of emails and dozens of conversations, a group of Columbia faculty coalesced, determined to find a solution to protect their hospital colleagues. "We quickly realized that N95 masks are made of specialized material, and 3D printing didn't seem to be the answer. Instead, we locked onto face shields as something that could really help," Hillman recalled.

Fast and furious virtual collaborations followed, with Hillman and others prototyping face shields "in our basements or on the living room floor every night until 3 a.m.," cramming what would typically be a lengthy product design and testing process into mere weeks. Driven by what Hillman described as "a burning desire to do anything we possibly could to help," the team navigated multiple logistical challenges—including a global shortage of elastic—to produce a shield cut from a single sheet of recyclable plastic that can be rapidly manufactured, flat-packed, and assembled in seconds. Their design, along with others created by teams spanning several departments at Columbia, are freely available for license, and are being manufactured for use by healthcare workers in New York and elsewhere.

Face shields are just one example of the kind of real-time, rapid response innovation and mobilization that has become part of the new normal for BME faculty and students since the start of the pandemic. Within months, the drive to respond to the fast-changing needs of physicians and patients had altered the way students and faculty teach, learn, and collaborate. "If there's one positive to this, it's that it has broken down silos tremendously–it's incredible how much we've all come together," said Katie Reuther, senior lecturer in design innovation and entrepreneurship.

Reuther, Hillman, and Senior Lecturer in Biomedical Engineering Aaron Kyle are among the core faculty leaders of the Columbia COVID Tech Innovation Group, a task force formed in the early weeks of the pandemic to centralize COVID-19 research throughout SEAS, facilitate communication and collaboration between Columbia physicians and engineers, and help speed commercialization and deployment of products and devices. Teams are tackling pressing challenges for healthcare workers and patients, including devising safe sterilization methods for N95 masks and optimizing intensive care equipment, such as ventilators.

Some faculty have received financial support through Columbia BiomedX, the technology accelerator program Reuther leads, which rolled out a Fast Grants program to support prototyping and implementation of COVID-19-related innovations. As the pandemic seeped into all aspects of life and conversation, so too did COVID-19 work its way into the BME curriculum. Among the SEAS Summer 2020 Design Challenges was a pandemic-themed challenge, "Safer Medical Care and COVID-19," co-led by Reuther. The six-week program tasked students with rethinking the healthcare environment within the framework of the pandemic, devising products or processes to boost the safety of clinicians, patients, families and communities. "We're trying to prepare now with the expectation that this could rebound," said Reuther. "We don't want to get hit like we did last time."

By the time the World Health Organization declared COVID-19 a pandemic, demand for diagnostic testing had outstripped both supply and laboratory capacity around the world. Faulty assays and a shortage of test swabs compounded an already challenging testing landscape—one in which patients lucky enough to get tested waited a week for an appointment and just as long for results. Professor Sam Sia knew that part of the issue was that RT-PCR, the gold standard method for infectious disease diagnostics, is time-consuming and requires specialized lab equipment. Sia's company, Rover Diagnostics, was months into developing a rapid, portable RT-PCR platform when COVID-19 reached the United States. As local caseloads grew, the team pivoted to focus on detection of SARS-CoV-2.

During a Columbia webinar in April, Sia stressed the importance of rapid, decentralized testing technologies, correctly predicting that current PCR platforms couldn't keep pace once COVID-19 began spreading widely. "If we're going to test 100 million Americans, it's simply impractical to be funneling everything through a small number of labs," he said. Less than 8 weeks later, cases were surging beyond New York, with test sites in Florida, Texas, Arizona and other states facing near-crippling demand. At the same time, public health experts began to emphasize the need for surveillance testing—population-level testing to monitor the status of the outbreak—in order to reopen businesses and schools.

Rapid antigen tests entered the market in May, bringing speedy—but less reliable—results. The Rover team's platform aims to match the speed of rapid tests without the reliability concerns. "We're working to make a test that's as accurate as what you'd get from a lab, but can be used to deliver results in minutes at pharmacies, businesses, schools or in transport hubs," Sia said. In September, Rover was one of about 30 companies chosen to advance in the National Institutes of Health Rapid Acceleration of Diagnostics Initiative (RADx), which helps develop and commercialize rapid COVID-19 testing technologies.

While the COVID-19 pandemic will ultimately end, most experts agree that the virus itself is here to stay. So too is the commitment, ingenuity, and spirit of collaboration this crisis has ignited in the scientific community at Columbia and around the world. "I feel a sense of responsibility," said Professor Hillman. "We should tell the world what we've learned and keep leveraging all the skill sets and expertise we can offer to help solve this problem."

Columbia engineers designed a flat-fold face shield that can be assembled in seconds

> "If there's one positive to this, it's that it has broken down silos tremendously–it's incredible how much we've all come together."

$1M GIFT ADVANCES RESEARCH TO FIGHT COVID-19

Three research teams at Colombia received a boost in their efforts to beat the pandemic, thanks to a $1M gift to the University from SEAS alum and Columbia Engineering member of the Board of Visitors Dr. Bing Zhao (‘92, ’94). The gift, announced in April 2020, supports work within Columbia Engineering and the Mailman School of Public Health in three key areas: rapid diagnostics, therapeutics, and public health outreach.

BME faculty member Sam Sia is using his portion of Zhao’s gift to advance the development of rapid diagnostic tests for COVID-19 that deliver lab-quality accuracy in a point-of-care setting. “This is an unprecedented challenge, and I felt it was imperative to contribute in any way I could,” said Zhao. “Columbia University has been on the front-lines since this crisis began, addressing the urgent need for therapeutic inventions, rapid diagnostics and assistance for developing nations with the world’s most fragile health-care systems.”

This generous gift also supports the work of Jingyue Ju, Samuel Ruben-Peter G. Viele professor of chemical engineering, who is developing protocols for using existing drugs as COVID-19 therapeutics, and Wafaa El-Sadr, director of ICAP at Columbia University, as she spearheads urgent COVID-19 response efforts in sub-Saharan Africa.

THE FAST TRACK TO RAPID DIAGNOSTICS

Elaine Kim (M.S. ’21) never imagined she’d spend her final summer at Columbia supporting efforts to create diagnostic tests for a new pathogen. But when Professor Katherine Reuther encouraged BME students to consider joining a federal effort to speed innovation in COVID-19 diagnostics, Kim pounced on the opportunity. At that time, “so many people were unable to get tested, and I wanted to do whatever I could to help,” she said.

Kim is one of two BME graduate students working with the National Institutes of Health Rapid Acceleration of Diagnostics (RADx) initiative. RADx is a “shark-tank”- style competition designed to accelerate the development and commercialization of rapid COVID-19 testing technologies. Participating companies vie for a share of $500M allocated to fund production and deployment of the most promising technologies.

Along with Carter Usowski, (M.S., ’21), Kim is a RADx assistant project facilitator, offering administrative and logistical help to up to four teams of developers at a time. “Our work really differs depending on who we’re paired with,” said Usowski, explaining that teams hail from well-established companies hoping to commercialize late-stage technologies as well as startups trying to get fledgling platforms off the ground. To date, about 30 teams—including one led by BME Professor Sam Sia—have moved into advanced stages of development.

The experience has brought a once-in-a-lifetime global health crisis home for Kim and Usowski, neither of whom had previously considered working in diagnostics. “I’ve been geared toward research and development, but everything I’m learning is super interesting to me,” Usowski said.

Rapid testing is widely considered critical for controlling the spread of COVID-19 and facilitating a safe return to public life. For Kim, RADx is more than just a way to help accomplish that goal. Amid the many challenges of 2020, the program is “a reason for hope,” she said.

BME Responds to

BLACK LIVES MATTER

Following the brutal killing of George Floyd, public outrage over racially-motivated violence against the Black community boiled over, resulting in what is arguably the largest protest movement in U.S. history. As Black Lives Matter marches brought systemic racism into the stark light of day—and into the streets of pandemic-stricken America—the Columbia University community stood in solidarity with protestors, students, and family and friends of those targeted by attacks against the Black community and communities of color. Alongside a University-wide affirmation of equality and diversity, the Department of Biomedical Engineering vowed to address discrimination and injustice in our educational programs. We called on our students to channel despair and outrage into change and progress, and to join with us to forge an equitable path forward.

We established the Committee on Diversity, Equity & Inclusion, a new initiative with a mission to identify, address, and overcome discrimination in any form in our research, educational programs, and hiring practices. In partnership with students, the Committee, co-chaired by Professors Henry Hess and Elisa Konofagou, is creating continuing education and mentorship opportunities, forging strategic partnerships, and spearheading community outreach. We are also committed to improving the diversity of our graduate program, in part through focused recruiting at Historically Black Colleges and Universities.

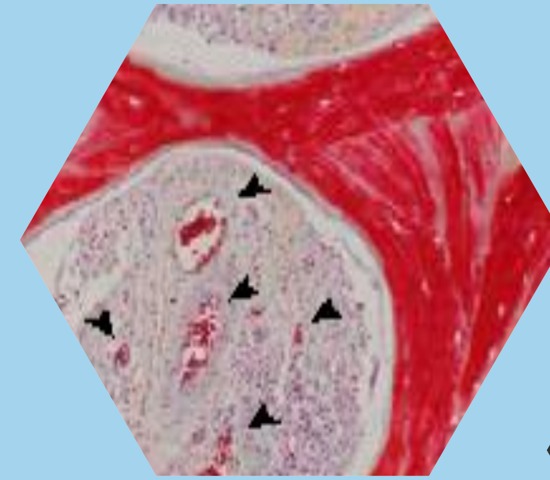
Together, we are striving to create a diverse, inclusive environment to advance education and research in science, engineering, and medicine.

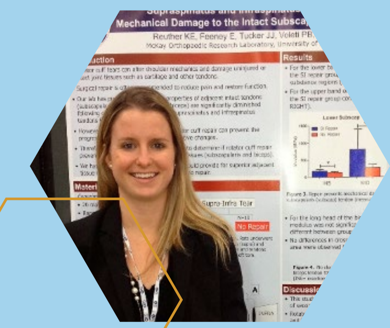
To learn more about the Committee on Diversity, Equity & Inclusion, please visit **bme.columbia.edu/diversity-equity-inclusion-bme**.

GOOD NEWS

During a year of unprecedented challenges, BME faculty continued the Department's history of excellence. Our colleagues have given us many reasons to celebrate in 2020, and we salute their remarkable achievements–from promotions, awards, and grants to the establishment of a committee to advance our commitment to equality and diversity.

- HELEN LU is named Percy K. and Vida L. W. Hudson Professor of Biomedical Engineering
- NANDAN NERURKAR wins a National Science Foundation CAREER award
- STAVROS THOMOPOULOS wins the 2020 Van C. Mow Award from ASME
- ELIZABETH HILLMAN is named Herbert and Florence Irving Professor at the Zuckerman Institute
- SAM SIA AND KEN SHEPARD are awarded a $16.4M grant from DARPA to advance the development of an "active" bandage equipped with sensors to monitor and accelerate the wound-healing process.
- AARON KYLE is inducted into the AIMBE College of Fellows, and wins the 2020 Diversity Lecture Award from the Biomedical Engineering Society (BMES).
- X. EDWARD GUO receives double honors from the Biomedical Engineering Society as the winner of the 2020 Christopher R. Jacobs Award for Leadership and a member of the 2020 Class of Fellows.
- QI WANG is promoted to Associate Professor of Biomedical Engineering
- ELISA KONOFAGOU AND HENRY HESS are the first co-chairs of the Diversity, Equity & Inclusion Committee, founded in 2020 as part of BME's commitment to supporting diversity, and addressing and eliminating discrimination in hiring, research, and education.
- TAL DANINO is awarded two prestigious grants to advance his research in engineering bacteria as cancer therapies: a $1.25M Lloyd J. Old STAR program grant from the Cancer Research Institute, and a $600,000 Pershing Square Sohn Prize for Young Investigators in Cancer Research from the Pershing Square Sohn Cance
- GORDANA VUNJAK-NOVAKOVIC is presented with the 2020 Order of Karadjordje Star, Serbia's highest honor.





BME BLAZE

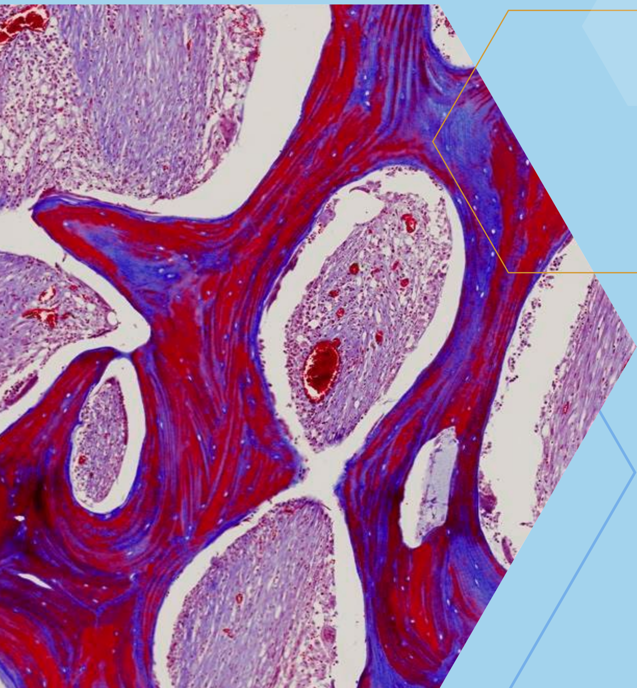
PATH TO PROFESSOR

Sharing stories of the trailblazers of Columbia BME

What challenges have you faced on your path to professor and how did you address them?

ELIZABETH HILLMAN My biggest challenge as a faculty member has been juggling my time, especially since I had two children pre-tenure at Columbia and I have a large research lab at the Mortimer B. Zuckerman Institute. I also support major efforts to share and commercialize the imaging technologies we develop. You have to be incredibly self-motivated to be a faculty member, and as you progress it's challenging to decide where to focus your energy. It's important to take a breath once in a while to enjoy and appreciate what you have.

My path also brought me from a small suburban town in Britain to London, then to Boston and New York. Many great academics were born overseas and have faced prejudice, the insecurity of maintaining visas, and the angst of being apart from family members. I am very fortunate to have a supportive spouse, but finding the ideal position can be a major challenge, especially for female faculty seeking jobs that are a 'best fit' for them.



HELEN LU One of the first challenges I faced was starting at Columbia in 2001 with lots of new ideas, but without students or a lab. The space that is now my lab was a storage dumpster for another division of the university! Kevin Costa, another BME faculty member, generously shared his lab with me while I worked with an architect to design the new lab, which thankfully was completed a year later. A bigger problem than deciphering architectural drawings was that I had no students to do research with, as I missed the regular doctoral student recruitment season. Luckily, word got around that there was a new professor in town, and I was approached by BME junior Kathie Dionisio and then-Masters student Jie Jiang, who later became my first doctoral student. For the first few years, unlike today, my lab had two to three times more undergraduate and MS students than doctoral students. They made a big difference in helping me get started! The lessons I learned through this unexpected beginning are to make the best of any difficult situation, embrace local talent, and appreciate the generosity of others.

ELHAM AZIZI One common challenge in STEM fields is dealing with unconscious biases and a lack of confidence in women to lead successful teams and research groups, let alone to shape and define research fields. This is sometimes rooted in lack of sufficient examples and role models. I was very fortunate to be mentored by Dr. Dana Pe'er during my postdoctoral training, a pioneer and leader in the field of computational biology, whose work in connecting machine learning—a male-dominated field—with biology has largely influenced my path. I am also proud to have joined a department with several female tenured faculty members, all successful leaders in their respective fields and great inspirations to future generations of BME.

BME requires creative collaboration between multiple disciplines. What has been your experience with this?

GORDANA VUNJAK-NOVAKOVIC: Collaboration is an organic component of everything we do. If you are a mathematician or a poet, you may be able to do it on your own. If you are a biomedical engineer, you rely on collaborators from many different areas. In my lab, these include stem cell biology, cancer, surgery, immunology, transplantation, pulmonology, orthopedics, cardiology, dental medicine, systems biology, materials science, and of course many areas of engineering.

BME is incredibly supportive and collegial and makes it easy for a "collaborative phenotype" to thrive. This culture started with our founding chair, Van C. Mow, and the legacy continues among the faculty, staff, and trainees in our growing department. The barriers for collaboration are low across Columbia campuses, and it is easy to cross the boundaries between disciplines, where some of the most exciting science happens today. The spirit of collaboration is one of the two things that drew me to Columbia—the other being the opportunity to build programs and pursue research with incredibly nice and creative people.

KATIE REUTHER This is one of the most exciting parts of BME. In my current role as Senior Lecturer in Design, Innovation, and Entrepreneurship in BME and as Director of Columbia BiomedX, I am fortunate to truly sit at the intersection of engineering, medicine, and business. The overlap between these disciplines allows us to collaborate and work toward developing new technologies and innovations that address real unmet clinical needs and can be implemented to impact human health.

HELEN LU Collaborations are essential for our work, especially when it comes to clinical translation of biomaterials and devices for tissue regeneration—taking an idea from bench to bedside. As biomaterial designers, partnerships with clinicians are essential in order for our technologies to truly benefit patients. We have benefited greatly from the generosity of our clinical collaborators, who have taught us and shared valuable perspectives. Another exciting aspect of collaboration is the continuous intellectual exchange between specialties or fields that these interactions foster, challenging us to move out of our comfort zones and even learn a new scientific language. Team science enables us to work together on bigger problems and provide better solutions. I'm also grateful that many collaborators have become lifelong friends. Working together at midnight on a proposal that is due in just a few hours is a magical bonding experience!

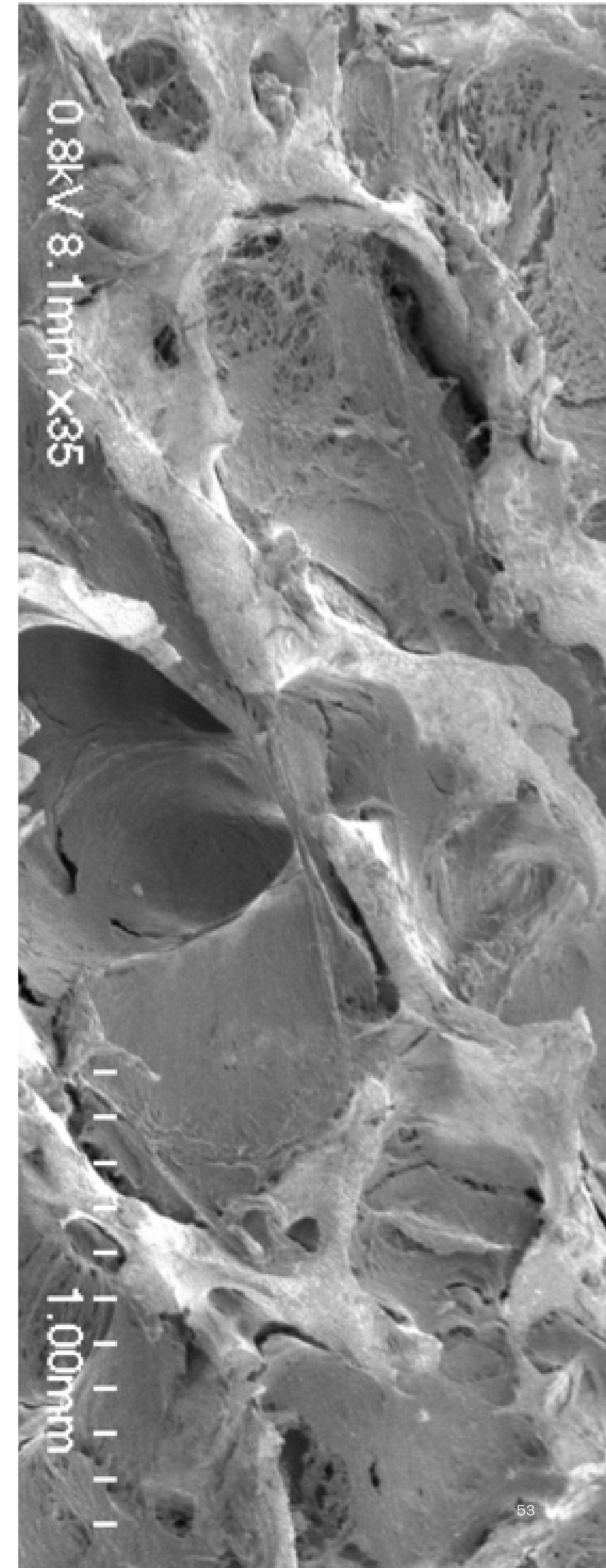
If you could give your 16-year-old self a piece of advice related to pursuing a STEM career, what would it be?

ELISA KONOFAGOU I was a very shy and not always happy 16 year-old, but I loved math and physics. I loved matrix inversions and solving quadratic equations. Physics made me look at the world through a completely different lens, no pun intended! I would tell my younger self that your instincts are correct. You belong in the STEM fields, even if people around you may push you in different directions. I grew up in Greece, and the default for women was not becoming an engineer or scientist—far from it! I would also say that even if you don't see a single female STEM faculty member from high school through college, the only way to change that is by becoming one yourself, so the women after you may see it as a natural thing—which it is, of course.

ELIZABETH HILLMAN At 16, I wanted to be an astronaut, but I herniated a disc in my back doing gymnastics and suddenly experienced a world of medical imaging and physical therapy. I was considering going into medicine when one day I wondered, "wait, who builds these machines?" I think 16 year-old me would not be terribly surprised to see what I am doing now!

The main thing I would have liked to hear is that it's okay to be different. It's not always easy to find other people who understand what matters to you and accept who you are. When I moved from my all-girls high school to a university class of 150 undergraduate physics majors, even though there were only 15 girls, we all had a lot more in common than people I had met before. It is so nice now to find people throughout the world who share my excitement and interests and who appreciate what I do. That would have been pretty hard to imagine at 16.

KATIE REUTHER I found this quote in graduate school but I wish I found it sooner: "The goal is not to be better than anyone else but rather to be better than you were yesterday." I think having this growth mindset and internalizing this desire for continuous improvement and learning has allowed me to overcome some of the "imposter syndrome" feelings often encountered in academia.



What about your BME experience are you most proud of and excited for?

ELISA KONOFAGOU I am most proud of our students and the alumni from my laboratory. One of the things that nobody tells you when you're a stressed, panicky young assistant professor is how rewarding it is to interact with students and fellows that are eager to learn and contribute to scientific research. Our students are so dedicated and hardworking that it pushes me to be better. I am very excited about the future. I am especially excited to see how our technologies can make patients' lives better. Virtually all of our technologies are in the clinic now, and it is so exciting to witness how we, as biomedical engineers, can positively affect the way patients are diagnosed and treated.

ELHAM AZIZI I am most proud of my students' performance during these past months. Our young lab started in January 2020 and the campus was shut down only 2.5 months after. Despite the many challenges that students have faced in the midst of a global pandemic, having to move multiple times across the country and take classes and perform research almost all remotely, they have continued to make great strides in multiple projects building the foundations of our lab. I am very excited about continuing to explore these new directions and expanding our team.

GORDANA VUNJAK-NOVAKOVIC I am most proud of my lab. The successes of our postdocs, students, and scientists are what count the most. They are passionate about science and about working hard, even under the abnormal conditions of the pandemic. After leaving the lab, our alumni continue to be very successful in many different ways. We really are only as good as the people we train, and our trainees need to be better than we are.

To read the full "Path to Professor" interviews, please visit **bme.columbia.edu/bme-blaze-path-professor-sharing-stories-trailblazers-columbia-bme**

ELHAM AZIZI is Herbert & Florence Irving Assistant Professor of Cancer Data Research in the Irving Institute for Cancer Dynamics and Assistant Professor in the Department of Biomedical Engineering at Columbia University. Elham's research utilizes single-cell genomic technologies combined with statistical machine learning techniques to characterize interacting cells in the tumor micro-environment as well as their dysregulated gene circuitry. Elham completed her postdoctoral training at Memorial Sloan Kettering Cancer Center and Columbia University. She received a PhD in Bioinformatics from Boston University, an MS degree in Electrical Engineering from Boston University and a BS in Electrical Engineering from Sharif University of Technology. She is a recipient of the NIH NCI Pathway to Independence Award, the Tri-Institutional Breakout Prize for Junior Investigators and an American Cancer Society Postdoctoral Fellowship.

ELIZABETH HILLMAN is the Herbert and Florence Irving Professor at Columbia University's Zuckerman Mind Brain Behavior Institute and a Professor in the departments of Biomedical Engineering and Radiology. Hillman obtained her PhD in Medical Physics and Bioengineering at University College London. She performed postdoctoral research at Massachusetts General Hospital, Harvard Medical School, and became faculty at Columbia University in 2006.

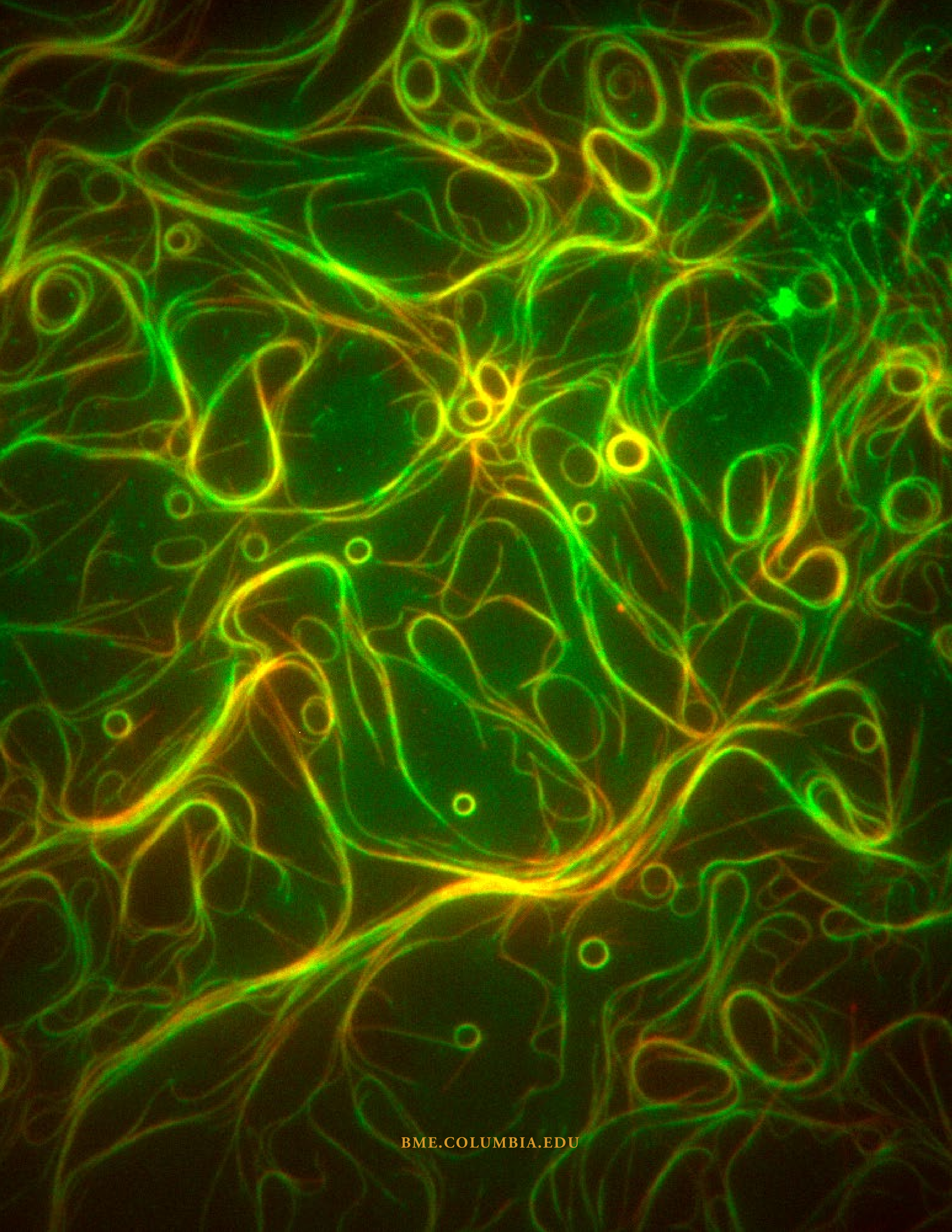
Hillman is a fellow of the Optical Society of America (OSA), the society of photo-optical instrumentation (SPIE) and the American Institute for Medical and Biological Engineering (AIMBE). She received the 2011 OSA Adolf Lomb Medal for contributions to optics at a young age, the 2018 SPIE Biophotonics Technology Innovator Award, a 2020 Royal Microscopical Society Mid-Career Scientific Achievement Award and early career awards from the Wallace Coulter Foundation, National Science Foundation and Human Frontier Science Program.

ELISA E. KONOFAGOU is the Robert and Margaret Hariri Professor of Biomedical Engineering and Professor Radiology as well as Director of the Ultrasound and Elasticity Imaging Laboratory at Columbia University in New York City. Her main interests are in the development of novel ultrasound-based imaging and therapeutic methods. Elisa has co-authored over 230 peer-reviewed research articles and is the recipient of the NSF CAREER award, the NIH Nagy award, the IEEE-EMBS Technological Achievement Award, the SPIE Wellness Award and the IEEE-IUS Carl Helmholtz award. Elisa is also a fellow of the Acoustical Society of America, the American Institute of Ultrasound in Medicine and the Wallace H. Coulter foundation.

HELEN H. LU's research focuses on tissue interfaces, particularly recreating the body's natural synchrony between tissues, a hallmark of the musculoskeletal system and the nexus of human mobility. The body of fundamental knowledge she has uncovered regarding biointerfaces and interface scaffold design has provided blueprints for building organs-on-a-chip as well as total limb regeneration. She has also received tenure at the Columbia College of Dental Medicine and currently serves as Chair of Promotion, Tenure and Faculty advancement for Columbia Engineering. The inventor and co-inventor of more than 25 patents and patent applications, her research has led to the formation of several start-ups for medical devices. Her many accolades include the Presidential Early Career Award for Scientists and Engineers (PECASE) and Columbia's Avanessians Diversity Award. She is an elected Fellow of the American Institute for Medical and Biological Engineering and a fellow of Biomaterials Science and Engineering. Lu received her undergraduate and graduate degrees in bioengineering from the University of Pennsylvania and has been on the faculty at Columbia since 2001.

KATHERINE REUTHER is Senior Lecturer in Design, Innovation, and Entrepreneurship in the Department of Biomedical Engineering at Columbia University, with additional appointments as the Director of the Columbia Biomedical Technology Accelerator (BiomedX) Program and the Director of Master's Studies.

GORDANA VUNJAK-NOVAKOVIC is University Professor, the highest academic rank at Columbia. She is the first engineer in the history of Columbia to receive this distinction. She is the Mikati Foundation Professor of Biomedical Engineering and Medical Sciences and a member of the faculty of the College of Dental Medicine. She has been elected to the Academia Europaea, Serbian Academy of Arts and Sciences, the National Academy of Engineering, the National Academy of Medicine, the National Academy of Inventors, and the American Academy of Arts and Sciences.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