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The Brief

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ENGINEERING FOR GLOBAL IMPACT AT **NORTHEASTERN UNIVERSITY**

New Mechanobiology Research Effort with Initial Focus on Aging

From The Dean

Aging brings a host of complications and challenges to our lives. That's why Northeastern University has brought together interdisciplinary expertise to research Mechanobiology with aging as its initial focus. The effort will both deepen our understanding of fundamental phenomena involved in aging and innovate new technologies and therapies to improve human health and wellbeing.

Faculty experts in engineering, biology, physics, physical therapy, and more are investigating the role of force and mechanics in biological systems, from the molecular level to the whole body. Their combined expertise will point the way to new treatments and therapies for cancer, coronary disease, osteoporosis, dementia, and many other conditions that arise as we grow older.

Read on to learn more, and I invite you to reach out with ideas for collaboration and for more information.

Kind regards,

Gregory D. Abowd, D.Phil.
Dean of the College of Engineering
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WHAT'S INSIDE

Editorial credits and contributions: Northeastern College of Engineering and Northeastern Global News

New Research Focus on Mechanobiology to Advance Human Medicine and Health

Widely believed to be the "missing science," mechanobiology can provide the critical link between a variety of pathologies and their root causes, leading directly to the development of effective therapeutics and prevention strategies for many currently untreatable and debilitating medical conditions. To accelerate mechanobiology discovery and technology to advance human medicine and health, Northeastern University has launched a new interdisciplinary research focus on mechanobiology–one of only a few in the world specifically dedicated to mechanobiology study and innovation.

Ning Wang, a professor of bioengineering who joined Northeastern in July 2023, is leading the new mechanobiology research effort, which is made up of faculty experts from the College of Engineering, College of Science, and Bouvé College of Health Sciences. The research will investigate the role of force and mechanics in biological systems, discover the root causes of mechanobiological pathologies that negatively affect quality of life, design interventions and sensors to alter mechanical inputs and biological outputs, and pursue mechanotherapeutics that restore function or slow the progression of diseases.

"I'm excited about this," says Wang, "It's a matter of concentrating effort. The faculty all have the same goal: we're driven to solve societal problems that we could not before. But now, with a mechanobiology research focus, we can get closer to that goal."

Focus on aging

Initially, the primary mechanobiology research theme will be aging, with faculty investigating several interconnected sub-areas, from cardiovascular, musculoskeletal, neurological, and immune systems to mechanotherapeutic technology and methods, to mechanobiological rehabilitation devices, and more. Thoroughly understanding the aging process and its implications for health and wellbeing is increasingly imperative as the Baby Boom generation grows older. The number of Americans over 65 is projected to reach 80 million in 2040 according to the Urban Institute, with the number of adults 85 and older–the group most often needing help with basic personal care–more than doubling between 2020 and 2040.

Although aging is a natural phenomenon, the accompanying decay of tissue function can give rise to debilitating disorders like osteoporosis, a loss of bone density that often results in increased fractures in older adults. If such conditions are mitigated, it could increase the quality of life–the so-called "health span"–for millions of elderly people. Research on translating mechanobiological discoveries into therapies that reverse such pathology has the potential to make a profound impact, not only on this growing population, but on the healthcare sector and the economy at large.

Wang's enthusiasm for inquiry and innovation in the realm of aging is evident in the boundary-pushing questions he poses.

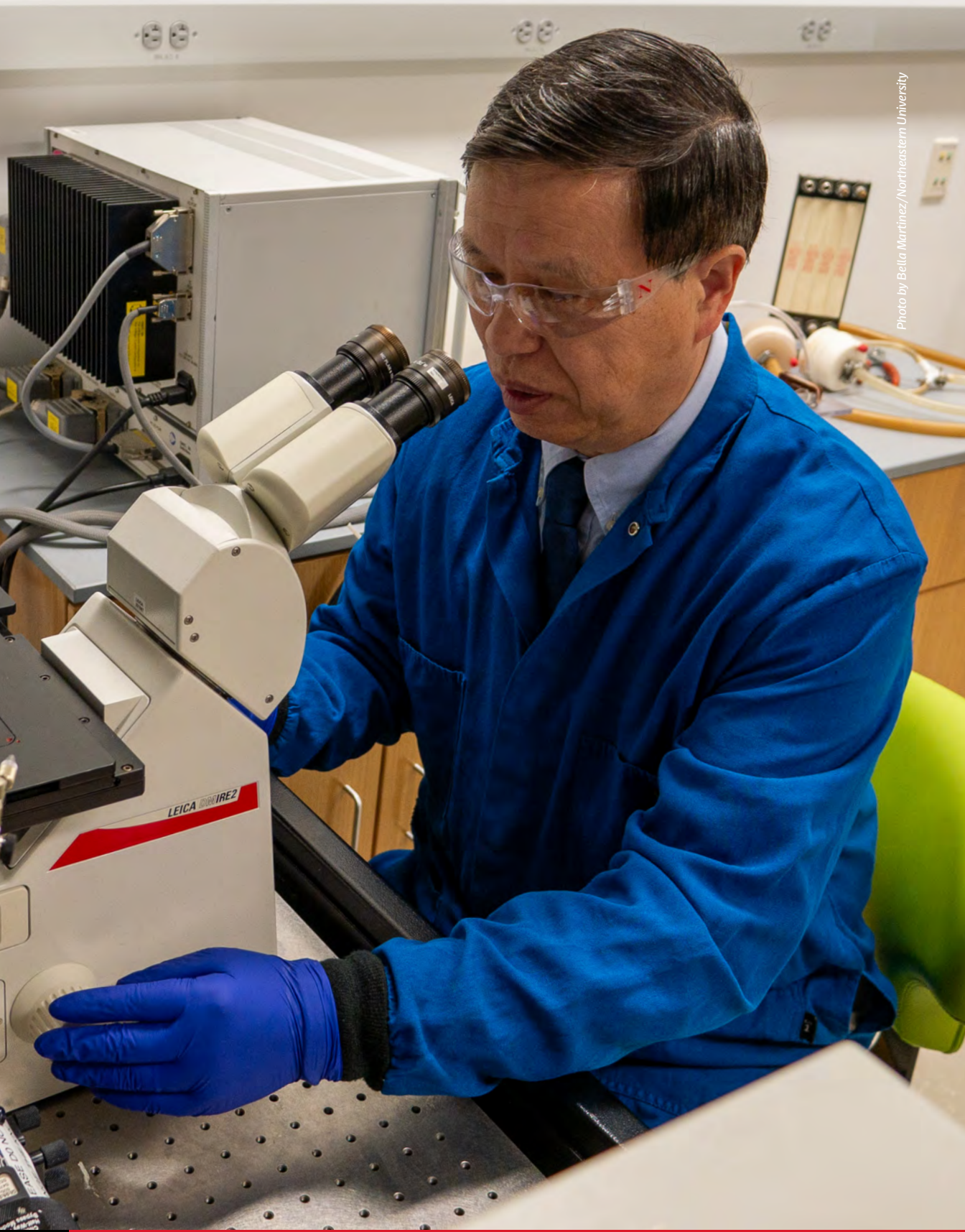


Photo by Bella Martinez/Northeastern University

A research focus on translating mechanobiological discoveries into therapies that can reverse debilitating disorders like osteoporosis has the potential to make a profound impact on the healthcare sector and the economy at large.

"What sets the limit on a human lifespan?" he asks, pointing out that there are animals and plants that routinely live well beyond a century. "Why do we only live until 80 or 100? I've been thinking about this for many years, and faculty members at Northeastern are also very interested in this."

One of Wang's top priorities is to augment its research capabilities with talented and motivated students.

"In my vision, what's huge for mechanobiology is young people," he says. "We have to train the next generation—the PhDs, the master's degree students, and the undergraduate students. We will have undergraduate students work with faculty members, get them excited about this research, and see the promise of it."

Impact of mechanobiology discovery

Mechanobiology links mechanics and biology—an investigation into the role of mechanical forces in biological processes beginning at the most fundamental level: the cell. There are more than 200 distinct cell types in the human body, each type carrying out its unique function by producing specific proteins. Genes housed in a cell's nucleus contain the "instructions" for making those proteins. When the human genome was first fully sequenced in 2003, Wang explains, it was believed that researchers had all they needed to understand and manipulate gene expression in cells to combat disease or enhance natural biological functions. It turned out that there was more to learn.

"The majority of diseases—like cancer, diabetes, cardiovascular diseases—are complex," says Wang. "They're not caused by a single nucleotide mutation or substitution. That's the fundamental issue that's been missing in the field."

All cells, he explains, can sense two basic signals: chemical and mechanical. While biochemical signaling is well understood today, mechanical processes within and among cells represent a less-explored realm. Mechanical forces at the cellular level—how a cell is pushed, pulled, or sheared—have been shown to affect gene expression in cells, altering the proteins they produce.

In principle, Wang notes, these changes could be profound. It might even be possible to manipulate mechanical forces in such a way that a cell's function changes entirely, transforming from a fat cell, for example, into a muscle cell. More likely applications in the nearer term include using mechanobiological approaches to combat diseases like cancer, perhaps enhancing the effectiveness of immunotherapy treatments. Wang offers the example of causing cancer cells to stiffen by applying specific forces to them, making them easier for a patient's immune cells to latch onto and destroy; this method is already in clinical trials. He also imagines implantable devices that induce changes in cells through mechanical stimulation, avoiding both the diffusion of injected chemical treatments and their potential side effects.

While mechanobiology holds great promise as a way of understanding and fighting disease, it can also offer insight into natural processes that have never been fully understood—for example, how a single, spherical fertilized egg transforms into a recognizably shaped fetus. A recent project of Wang's, published in *Science Robotics*, uses magnetic microrobots to quantify the phenomenon of force oscillations in mouse embryos only a few days old, the first time such activity has been observed.

"We believe that these huge force oscillations can help dictate or change the shape of the embryo," says Wang. "If we understand that, we can understand the process of differentiation, which could help us understand factors that control aging. How do cells become different as they age, and how can we reverse that process?"

Ning Wang, professor of bioengineering and director of mechanobiology research

Photo by Bella Martinez/Northeastern University

Mechanobiology leader

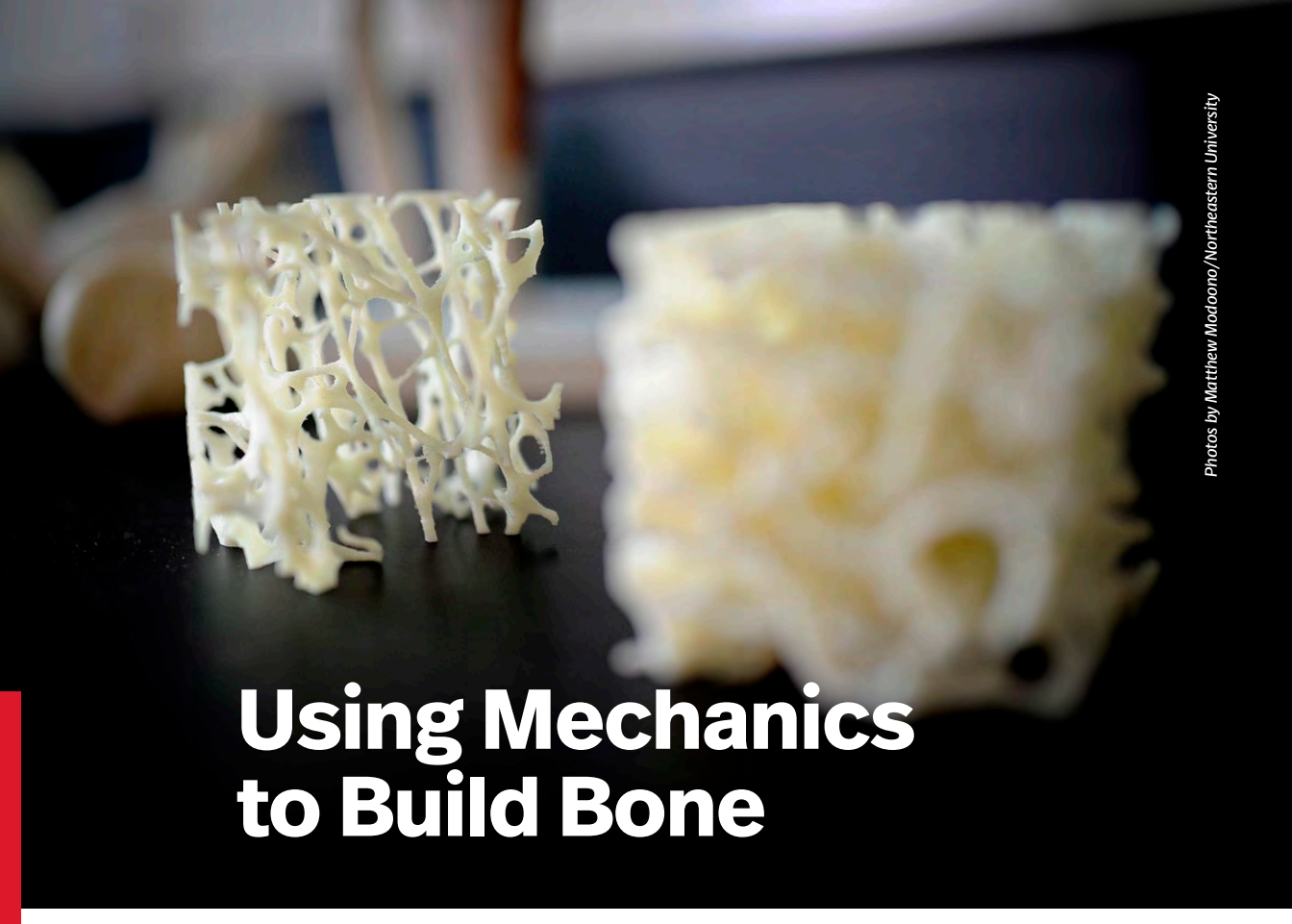
Wang comes to Northeastern's Department of Bioengineering from the University of Illinois Urbana-Champaign, where he was an endowed professor in the Department of Mechanical Science and Engineering. Prior to that, he was an associate professor of physiology and cell biology at the Harvard School of Public Health.

The son of an engineer and a chemist, Wang has been inspired by science and technology for most of his life. As an undergraduate student majoring in biomechanics at Huazhong University of Science and Technology, he was deeply impressed by a visit to his school from Y.C. Fung–sometimes called the "father of biomechanics." This piqued his interest in understanding living tissue from a mechanical point of view. He went on to earn a master's in biomedical engineering at Huazhong, then a doctoral degree in physiology from the Harvard School of Public Health. During a seminar, Wang met Don Ingber, founding director of the Wyss Institute for Biologically Inspired Engineering at Harvard University. The two collaborated on a seminal mechanobiology paper published in *Science* in 1993, "Mechanotransduction Across the Cell Surface and Through the Cytoskeleton." For Wang, this was the beginning of 30 years of increasing specialization in the field.

Since then, he has continued to explore, innovate, and distinguish himself, authoring over 140 publications in the field of cell mechanics, mechanotransduction, and mechanobiology, and receiving several patents for his work. His focus in this area has advanced the understanding of phenomena like mechanomemory–a cell's response to force that persists long after cessation of the force. Published in the *Proceedings of the National Academy of Sciences*, a recent paper of his describes mechanomemory even within the nuclei of cells, where it had not previously been observed.

Wang's new move to Northeastern to lead interdisciplinary research in the area of mechanobiology is a challenging task, he says, but one he is eager to tackle.

"Throughout my career I've collaborated with different scientists from different fields," he says. "When I came to Northeastern, I was really impressed. It's very open, its leadership and faculty. They are all very supportive. Some people say the sky's the limit. I think for us, our wisdom is the limit–we have to use our wisdom to have great ideas and put those ideas into practice." N



Photos by Matthew Modoono/Northeastern University

Using Mechanics to Build Bone

Sandra Shefelbine, professor of mechanical and industrial engineering, and bioengineering, is fascinated by bones–their structure and composition, their mechanical properties, the ways they respond to mechanical signals, and how they adapt to loads placed on them. It's an area of focus with significance to all, she points out–nearly everyone, if they live long enough, will experience some degree of osteoporosis, osteoarthritis, or other bone deterioration.

"People don't often die from musculoskeletal diseases," she says, "but musculoskeletal problems are the primary causes of functional disability. And once you can't move around, everything else starts declining," giving rise to conditions like obesity, diabetes, and heart disease. "Bones have a huge impact on quality of life."

Together with **James Monaghan**, professor of biology, Shefelbine is leading a $650,000 National Science Foundation grant to analyze bone at the tissue, cellular, and molecular levels, and gain insight into how it's formed. Their learnings could potentially lead to more effective and targeted physical therapies to combat bone loss due to disease, injury, or aging.

Analyzing bone at the tissue level

"Bone is a smart material," says Shefelbine. "It actually gets stronger the more load you put on it. It adapts to its mechanical environment."

To learn precisely how this happens, she and her research team use mice as a living model, measuring bone formation in response to applying a mechanical load on the mice's shins every other day over two weeks.

Researchers know that several mechanical phenomena happen during the application of a load. The extracellular matrix–a mesh of proteins and molecules that cells reside in–stretches, which cells feel as mechanical strain. Fluid between cells also moves in response to the load and creates shear, a different kind of force. Separating these force types is key to understanding their effects on bone formation.

"We can apply the load very slowly," says Shefelbine, "so we don't get much fluid flow, but we still get a lot of stretch in the matrix. Or we could do it very fast, so we get the same amount of stretch with a lot of fluid flow."

She and her team discovered that the latter technique enhanced bone formation, clearly demonstrating for the first time that the rate of load is at least as important as level of strain in the load.

"People don't often die from musculoskeletal diseases, but musculoskeletal problems are the primary causes of functional disability. And once you can't move around, everything else starts declining. Bones have a huge impact on quality of life."

Sandra Shefelbine
Professor of Mechanical and Industrial Engineering, and Bioengineering

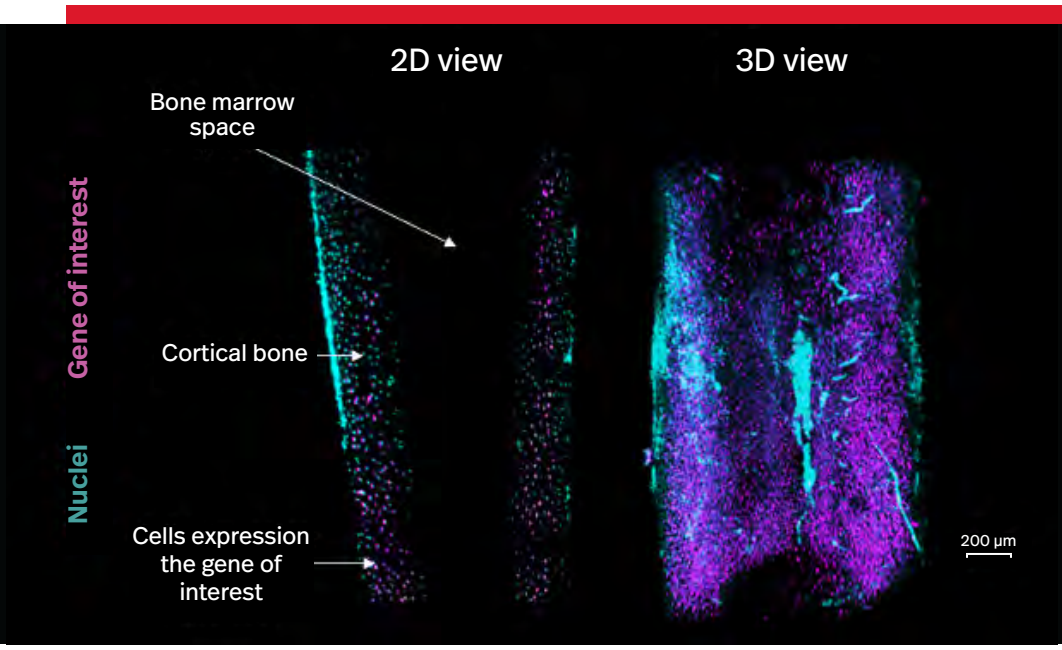
"You can apply a lower-level load as long as you do it really fast," she says. "Translating that into the clinic, it's probably better for bone formation to do jumping jacks than to go on the elliptical. You really need that impact to get the bones to signal."

Watching bone form at the cellular and molecular levels

Observing the cellular and molecular details of bone formation presents a challenge as most of those processes take place inside the bone, where they can't easily be seen. Traditional 2D microscopy and sampling techniques can't reflect the relative positions of cellular signaling molecules, which Shefelbine maintains are crucial to understanding mechanically induced bone formation.

To capture this information, her team combines fluorescence microscopy with whole-mount imaging, which examines intact tissues instead of thin slices. The result is a complex 3D image of fluorescently labelled signaling molecules that illustrates the spatial location of bone-building signals in the tissue. This innovative technique generates much more data than traditional methods, so the researchers are leveraging machine learning tools to analyze the trove of information they're collecting.

"Being able to examine bone tissue on this minute scale reveals a fundamental mechanobiological phenomenon in action," says Shefelbine. "We're watching the process of cells translating mechanical signals into a biological response." N



Whole-mount image of a mouse tibia showing the locations of mechano-sensitive signals (in pink) at the cellular level.

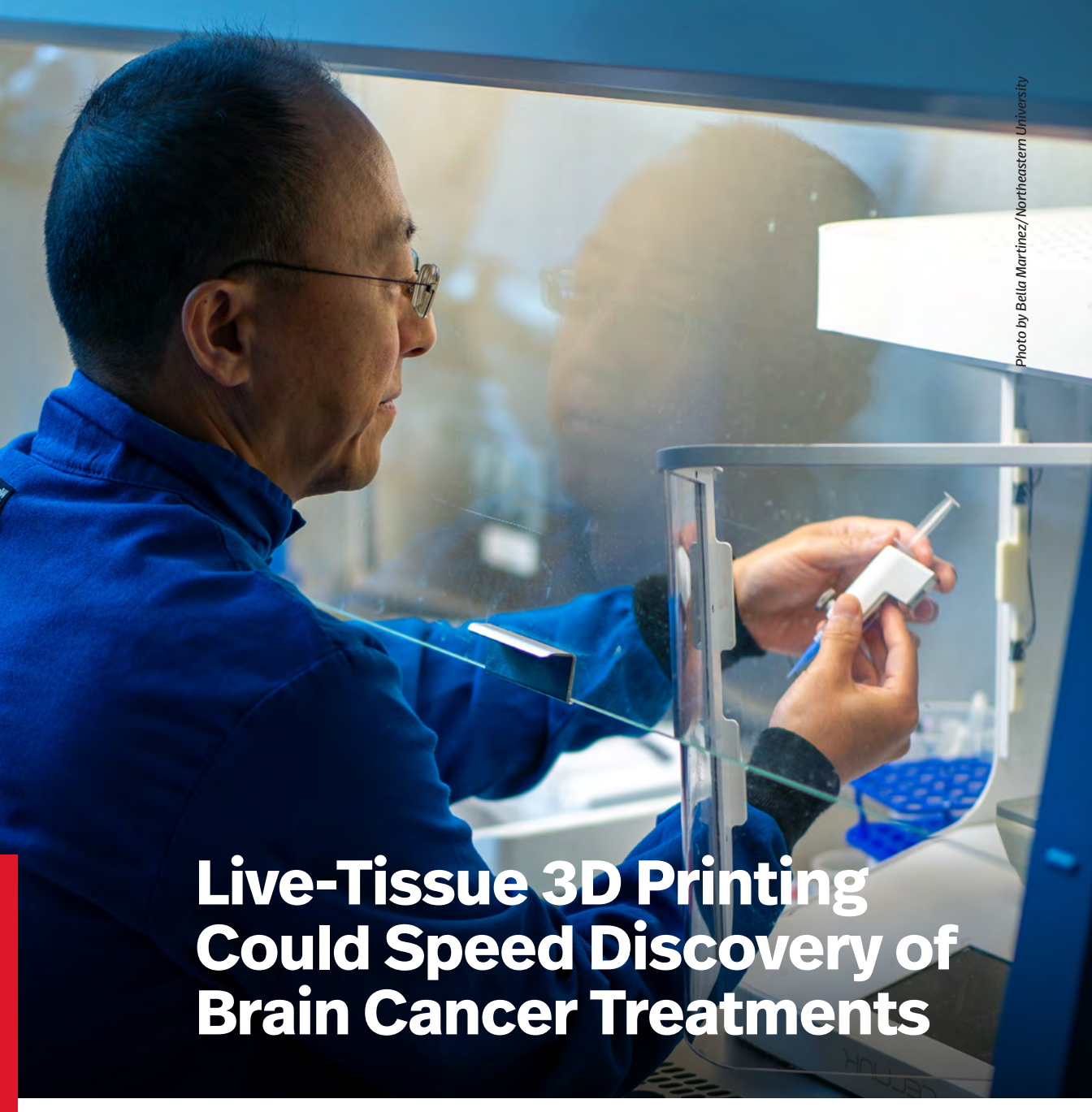


Photo by Bella Martinez/Northeastern University

Live-Tissue 3D Printing Could Speed Discovery of Brain Cancer Treatments

Glioblastoma is the deadliest form of brain tumor—less than 10 percent of people who are diagnosed with it will survive more than five years.

A group of researchers has devised a new way to study this rapidly spreading cancer, using a three-dimensional structure made of an agglomeration of human brain cells and biomaterials. Their work, published in *Science Advances*, could help medical professionals better understand how the tumor grows and speed up the discovery of new drugs to fight it.

"This is a very difficult brain tumor to treat," says **Guohao Dai**, professor of bioengineering and an author of the study. "And it's also difficult to do research on the brain tumor, because you cannot really see what's happening."

Inside a living brain, researchers can't directly observe how tumor cells grow and respond to treatment. Studies are typically done in mice or rats, and the animals must be dissected to understand the tumor's development. Animal studies are expensive and time-consuming, Dai says, and they don't allow for day-to-day observations of the same tumor in living tissue.

To be able to study glioblastoma more directly, Dai, whose lab specializes in 3D printing live tissue, grew a three-dimensional model to act as brain tissue for tumor cells to infiltrate.

"We use human brain blood vessel cells, and connect them with all the neurons, pericytes, astrocytes, the major cell types in the human brain," Dai says. A water-based substance known as a hydrogel serves as a matrix to hold these cells in place. "Then we use 3D printing to stack them in a three-dimensional fashion."

In the middle of the structure, which is only a few millimeters thick, the researchers place glioblastoma tumor stem cells collected from brain tumor patients.

“We can observe how the brain tumor cells aggressively invade, just like what we see in patients,” Dai says. “They invade everywhere.”

Putting chemotherapy to the test in 3D models

To get an accurate picture of what’s happening inside the 3D model without disrupting it, the researchers used a laser to scan the sample and quickly create a three-dimensional snapshot of the cellular structure.

This combination of techniques allowed them to evaluate the effectiveness of a commonly used chemotherapy drug, temozolomide.

“We treated the tumor with the same kind of drug you give to a patient when they undergo chemotherapy,” Dai says. “We monitored this chemotherapy over two months. And what we found was the chemotherapy was not able to kill the tumor.”

Temozolomide had been able to kill glioblastoma cells in two-dimensional models. When used in the three-dimensional model, however, the tumor merely shrank in response to the drug, then rebounded swiftly and aggressively. The drug did not work in the long term, which lines up with the experience of patients with glioblastoma.

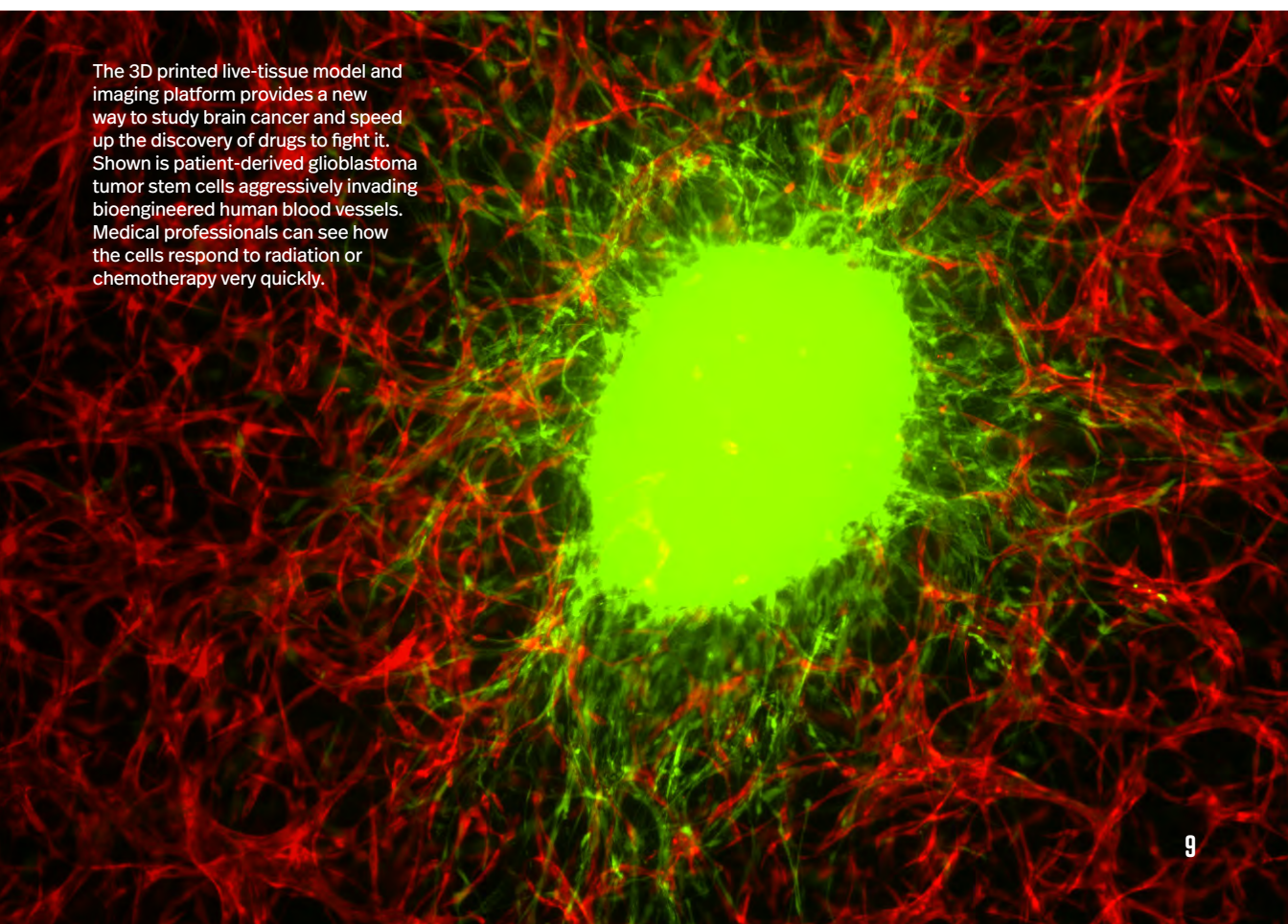
“This particular chemotherapy is not effective for the brain tumor,” Dai says. “We need to develop and screen other chemotherapy drugs.”

This model may be able to speed up that process, weeding out unsuccessful drugs early and ensuring that only the most promising ones move to animal, and eventually human, trials.

“You have a tremendous amount of time and cost associated with animal research,” Dai says. “With our 3D glioblastoma model and imaging platform, you can see how the cells respond to radiation or chemotherapy very quickly.” N

View journal paper in *Science Advances*

Mehmet S. Ozturk, Vivian K. Lee, Hongyan Zou, Roland H. Friedel, Xavier Intes, and Guohao Dai, High-resolution tomographic analysis of in vitro 3D glioblastoma tumor model under long-term drug treatment. Science Advances VOL. 6, NO. 10 (2020) DOI: 10.1126/sciadv.aay7513



The 3D printed live-tissue model and imaging platform provides a new way to study brain cancer and speed up the discovery of drugs to fight it. Shown is patient-derived glioblastoma tumor stem cells aggressively invading bioengineered human blood vessels. Medical professionals can see how the cells respond to radiation or chemotherapy very quickly.

Modeling Cancer to Boost Immunotherapy

In recent decades, immunotherapy has joined surgery, chemotherapy, and radiation therapy as a viable method of cancer treatment. Immunotherapeutic drugs stimulate or enhance the body's natural immune response to help it attack and kill tumor cells. However, while immunotherapy can be effective against some types of cancer, in many cases tumors are able to stymie immune cells in a deceptively simple fashion–with a physical barrier.

Herbert Levine, University Distinguished Professor of physics and bioengineering, focuses on examining cancer progression, metastasis, and interaction with the immune system. Many tumors, he explains, surround themselves with a dense network of fibers as a defense against immune cell attack. Even with the help of immunotherapeutic agents, an immune cell has little hope of affecting a target it can't reach. Levine has spent much of the last decade researching the characteristics of these fibrous regions.

Mathematical modeling and computational techniques could one day help predict whether or how an immune cell might move through fibrous barriers to reach cancerous tumors. Modeling an immune response before introducing a drug to a patient could increase therapy efficiency and lower patient risk.

"It's in some sense a mechanics problem," he says. "You have these fibers, they attach to each other, they can be bent–they're not rigid–and there are spaces that cells can try to sneak through. We're interested in what determines how cells of various kinds are able to navigate through this jungle of fibers that surround tumors."

In an effort to understand these complex dynamics, Levine and his research collaborators are creating sophisticated computational models of tumor fibers that build off of years of prior study of cell movement in controlled laboratory settings.

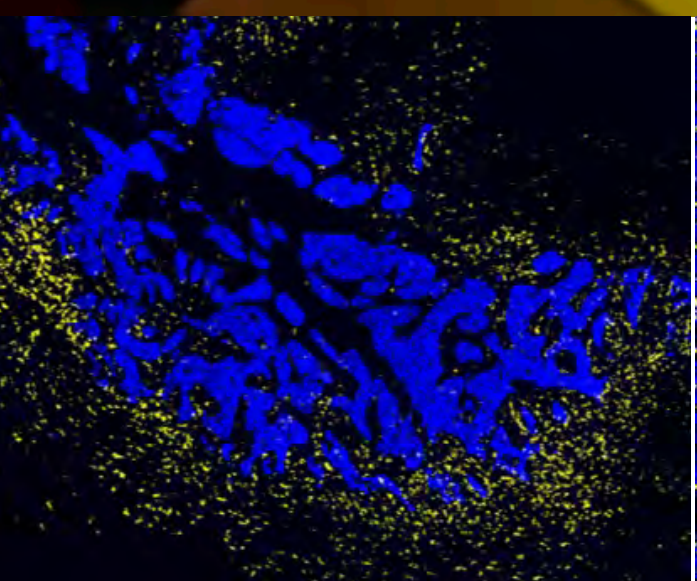
"That was done for very simple cases," Levine says of this earlier research, "for cells crawling along flat surfaces with no obstacles in the way. Now, the work has progressed to the point where we can begin to study how they move in these much more complicated geometries. There's friction with the materials, and the shape of the cell gets deformed to fit through those holes, so you actually have to solve for a flexible mechanical object. And you can put all those things together into a relatively complicated mathematical model and try to see how far we get."

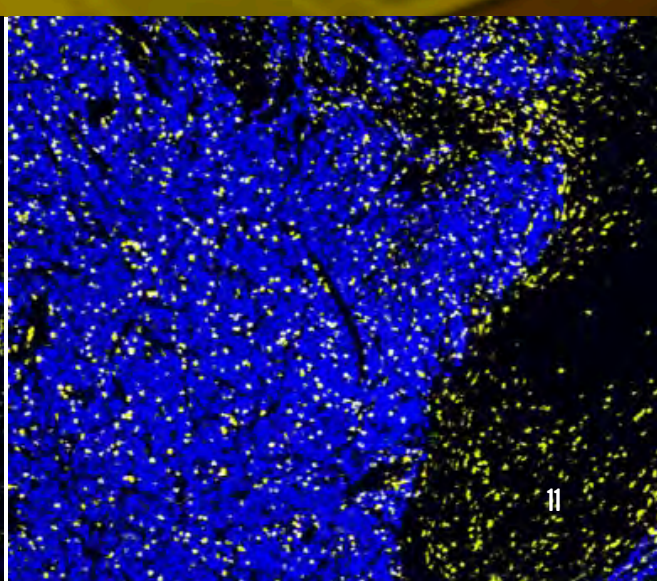
Though currently used to describe very fundamental principles, Levine's mathematical modeling and computational techniques could one day help predict more reliably whether or how a cell might move through these fibrous thickets to reach tumors. Such insights could be used to help doctors make better informed decisions about which immunotherapy drugs might benefit a patient.

"Immunotherapy drugs are known to have severe side effects," Levine points out. "In typical solid tumors, there's no current method for deciding in advance if a patient would benefit from these drugs." Modeling an immune response on a specific type of tumor before introducing a drug to a patient could help make more efficient use of the therapy while lowering the risk to patients. N

Photo by Ruby Wallau/Northeastern University

Herbert Levine, University Distinguished Professor of physics and bioengineering (left), and **Shubham Tripathi**, doctoral student. **BELOW**: Interactions between tumors (in blue) and immune cells (in yellow); Depending on a variety of factors, immune cells may infiltrate the tumor (right) or be excluded (left). Infiltration is a necessary condition for the effectiveness of modern immunotherapy.





A New Key to Asthma Treatment

Asthma affects more than 25 million people in the United States according to the Cleveland Clinic. Despite its widespread impact, little is known about its underlying causes and mechanisms, making effective and universal medical treatment difficult.

Harikrishnan Parameswaran, associate professor of bioengineering, is researching how the smooth muscle tissue of the airway detects irritants and generates force at the cellular level, leading to debilitating asthma attacks. In addition to Parameswaran, the interdisciplinary research team includes **Erin Cram**, professor of biology, as well as bioengineering and biology doctoral students.

Like any organ in the human body that requires constriction, the airway is lined with smooth muscle that aids in its contraction. When asthmatics inhale a low concentration of an irritant like dust, smoke, or pet dander, their airways hyper-constrict, leading to breathing difficulties. Healthy individuals need to inhale a significantly higher concentration of irritant to have their airways narrow the same way.

Smooth muscle cells are supported by a complex scaffold of proteins called the extracellular matrix. This extracellular matrix undergoes substantial changes in asthma. Parameswaran's research has discovered that when smooth muscle cells from healthy human donors are placed on a synthetic substrate mimicking diseased extracellular matrix, even a tiny dose of an irritant molecule is perceived as a high dose and causes an increased contraction response.

The most curious finding, however, is that this abnormal reaction doesn't occur in single smooth muscle cells, but only within groups of cells–meaning the cells are somehow communicating and responding to inhaled irritants as a collective.

"When inhaled irritant molecules bind to the smooth muscle, the smooth muscle cells communicate with each other using calcium waves," explains Parameswaran. "These calcium waves are frequency modulated–just like those used in radio communications–and, together like a committee, these cells decide the amount of inhaled irritant molecules. This method of sensing inhaled irritants is fundamentally different from what is currently known. It brings up the intriguing possibility that the individual smooth muscle cell might not be at fault in asthma. Instead, the problem might be in how these cells talk to each other in an asthmatic airway."

The discovery of how cells coordinate collective behavior in the airway is something that scientists have previously not been able to see. "These cells respond differently as a collective than they do as individuals," says Cram. "If you think about the cells of your airway, they're all interacting together," she says. "You don't have a cell here and a cell there–the whole thing is lined with cells. This is a much more realistic picture of what's probably actually going on."

While they don't fully understand the mechanisms that underlie the cellular communication process yet, the team knows that it relies heavily on mechanical forces transmitted through the extracellular matrix: When they mimic a healthy extracellular matrix in their lab experiments, this hyper-reactive communication stops.

The research team first described this phenomenon in a paper in *Science Advances* in 2020. In 2021, Parameswaran received a CAREER Award from the National Science Foundation, which is continuing this research by studying real-time mechanical interactions between cells.

The ultimate goal is to provide better treatments for severe asthmatics for whom the only current option might be a dramatic therapy called bronchial thermoplasty, in which the smooth muscles of the lungs are heated up and thinned out–an often effective but daunting procedure.

Parameswaran says, "If we're able to understand better how the underlying matrix modulates intercellular communication, we may be able to learn more about what drives the disease of asthma and develop methods to target the cause and not the symptoms of this disease." N

Photos by Matthew Modoono/Northeastern University

Photos by Bella Martinez/Northeastern University

"If we're able to understand better how the underlying matrix modulates intercellular communication, we may be able to learn more about what drives the disease of asthma and develop methods to target the cause and not the symptoms of this disease."

Harikrishnan Parameswaran
Associate Professor of Bioengineering

Erin Cram, professor of biology (right), and bioengineering PhD student **Fereshteh Sadeghian**

View journal paper in *Science Advances*

S.E. Stasiak, R.R. Jamieson, J. Bouffard, E.J. Cram, and H. Parameswaran. Intercellular communication controls agonist-induced calcium oscillations independently of gap junctions in smooth muscle cells. Sci. Adv. 6, eaba 1149 (2020). doi:10.1126/sciadv.aba1149

Photo by the National Park Service

The Impact of Wildfire Smoke on Human Health

Wildfires continue to burn out of control while an ever-growing number of people live in their paths. That's why two Northeastern bioengineering professors have set out to determine the health risks associated with prolonged wildfire smoke inhalation.

The intense heat of wildland fires produces fine and ultra-fine particles that can penetrate deep into the lungs and enter the bloodstream, thereby damaging organs beyond the pulmonary system. And when the fires sweep through abutting neighborhoods, they ignite a host of household materials that produce airborne toxins.

Little is known about the long-term effects of wildfire smoke inhalation, according to **Jessica Oakes**, associate professor of bioengineering. Oakes and **Chiara Bellini**, associate professor of bioengineering, are co-leading a $3.4 million grant from the National Institute of Environmental Health Sciences through a prestigious Outstanding New Environmental Scientist award. The ONES award is given to select young investigators who have demonstrated excellence in environmental health research.

"The focus of our study is not just the impact of burning vegetation, but also the health risks associated with the combustion of common household materials," says Bellini. "We expect to find that these materials are even more dangerous than the smoke from burning vegetation."

"Most studies focus on short-term exposure of a week or two," says Oakes. "We want to know if there is a cumulative effect to repeated exposures."

Oakes and Bellini use complex computational modeling and conduct live experiments on mice using a smoke mixture that mirrors the composition of wildfire smoke in the forests and chaparral of California. In addition to burning trees and brush, the experiments focus on two highly toxic household items–plastics and the polyurethane foam common in furniture and bedding.

Oakes has focused her career on the pulmonary system, concentrating on computational fluid dynamics and controlled animal studies. Bellini, in turn, has focused on the cardiovascular system, combining experimental and computational tools. They have filled out their multidisciplinary team with a fire protection engineer at the University of California-Berkeley and a statistician at the Tufts University Medical School.

The ultimate goal of the study is to make policy recommendations on issues such as evacuations and the types of materials that should be avoided in new construction in the wildland urban interface. N

Jessica Oakes, associate professor of bioengineering (left), and **Chiara Bellini**, associate professor of bioengineering

Photo by Adam Glanzman/Northeastern University

The focus of the study is not just the impact of burning vegetation in the wildland urban interface, but also the health risks associated with the combustion of common household materials. The ultimate goal is to make policy recommendations on issues such as evacuations and the types of materials that should be avoided in new construction in the wildland urban interface.

Can a Modified Gait Ease Knee Pain?

One of the first randomized controlled trials examining the relationship of gait modifications and knee pain in older adults

For many, knee pain is an inevitable part of growing older, as these joints are subjected to decades of use–and sometimes misuse–due to work, athletic activity, or physiological disorders. Abnormal joint loading is a known risk factor for osteoarthritis (OA), the breakdown of cartilage between the bones in joints.

"Knee OA is a huge public health problem," says **Joshua Stefanik**, assistant professor of physical therapy, movement, and rehabilitation sciences. Aside from being a leading cause of functional limitation and disability, knee OA is responsible for more than $81 billion annually in healthcare expenditures across the United States, according to a 2019 study–a financial burden similar to that of cancer.

Stefanik, a physical therapist, is investigating the mechanisms that contribute to knee OA to understand and manage the disease and the pain that comes with it. With funding from the National Institutes of Health, he and his research team are conducting a pilot clinical trial in which subjects experiencing knee pain learn to reduce the stress placed on their knees by modifying their gait.

The process starts in Stefanik's lab, which is equipped with in-ground force plates, motion-capture cameras, and a treadmill with force plates under its belt. The researchers use this equipment to measure and record subjects' gait mechanics and establish their baseline values.

Subjects are then divided into two groups. Members of both groups are asked to walk in the lab for eight sessions, with walking duration increasing from 10 to 30 minutes. One group is fitted with an inertial measurement unit that tracks how fast their legs accelerate toward the ground as they walk. If this movement speed rises above 80% of the subject's baseline, it triggers an audio cue telling the subject to slow the impact of their feet on the ground.

"The faster the foot accelerates toward the ground, the greater the impact you're going to get," Stefanik explains. "Those forces are translated up to the knee. So, we're trying to decrease that loading rate."

Over the course of eight sessions, as subjects in this group internalize the movements needed to walk more softly, the audio cues are phased out.

Stefanik has collected data this way from 46 subjects. Still, he points out, these measurements of gait mechanics–ground reaction force and movement data–are indirect, not measurements of the forces experienced in the knee joints themselves. For that insight, he turns to **Sandra Shefelbine**, professor of mechanical and industrial engineering, and bioengineering. She and her team use computational modeling to determine which muscles are being used in the modified walking technique and what forces they place on bones and joints.

Photos by Bella Martinez/Northeastern University

> *"We're trying to avoid medication, avoid knee replacement. If we can get older adults to be more active without exacerbating their symptoms, it will lead to a healthier aging process."*
>
> **Joshua Stefanik**
> Assistant Professor, Physical Therapy, Movement, and Rehabilitation Sciences

OPPOSITE, LEFT: **Corey Lanois**, PhD student, uses ultrasound imaging to assess the health of a subject's knee cartilage prior to a walking trial. **OPPOSITE, RIGHT**: Reflective markers placed on a subject's shoulders, hips, legs, and feet are monitored by the lab cameras tracking the movement of the body. **ABOVE**: **Joshua Stefanik**, assistant professor of physical therapy, movement, and rehabilitation sciences, evaluates the gait of a research participant, using a treadmill with force plates under its belt. Realtime movement and forces are visualized on the TV monitor.

Stefanik is currently combining Shefelbine's mechanical analysis with qualitative feedback from the study subjects to determine the efficacy of the training regimen.

"Does change in muscle and joint forces correlate to change in pain?" Stefanik asks. "And, is just walking okay, or do you need some kind of feedback on how you walk? Maybe it's just being active that's important, versus how you're being active."

While this gait modification technique has been studied previously in runners, Stefanik's study is one of the first such examinations in walking by older adults. He hopes it will help show the way to a higher quality of life for this growing population.

"We really need to get these people more active and decrease their pain," he says. "We're trying to avoid medications and knee replacements. If we can get older adults to be more active without exacerbating their symptoms, it will lead to a healthier aging process." N

From Stem Cell to Neuron: Aging in the Human Brain

Photos by Bella Martinez/Northeastern University

Mechanical connections help determine stem cells' fate

People don't often think of the brain as a center of mechanical activity in the body. It doesn't move–it isn't part of the musculoskeletal system. It doesn't expand or contract as the stomach, esophagus, or intestines do. And yet, mechanical principles can have a highly significant impact at the cellular level.

"The idea of mechanobiology having influence beyond those typical tissues we look at–bone, muscle, things you'd expect to have mechanical responses–is really on the leading edge of where we are with mechanobiology," says **Rebecca Willits**, professor and chair of the Department of Chemical Engineering. She and her research team are examining how mechanobiology influences aging in the human brain, looking at neural stem cells and how they are influenced by their environment.

"The brain changes with age," says Willits. "It changes with disease. And the elements of the brain that change then interact with our stem cells."

The body has reservoirs of stem cells that can either remain stems cells or differentiate into a specific cell type–in the brain, they can become neurons. Understanding what causes a stem cell to either retain its "stem-ness" or transform into a new cell type that can help maintain or renew tissues in the body is a key focus of Willits' research.

"We know that stem cells are not as vibrant a contributor to maintenance over time," she says. "So we're trying to link some of those changes that happen in the brain to the stem cells that do not respond in the way we would expect in a younger person."

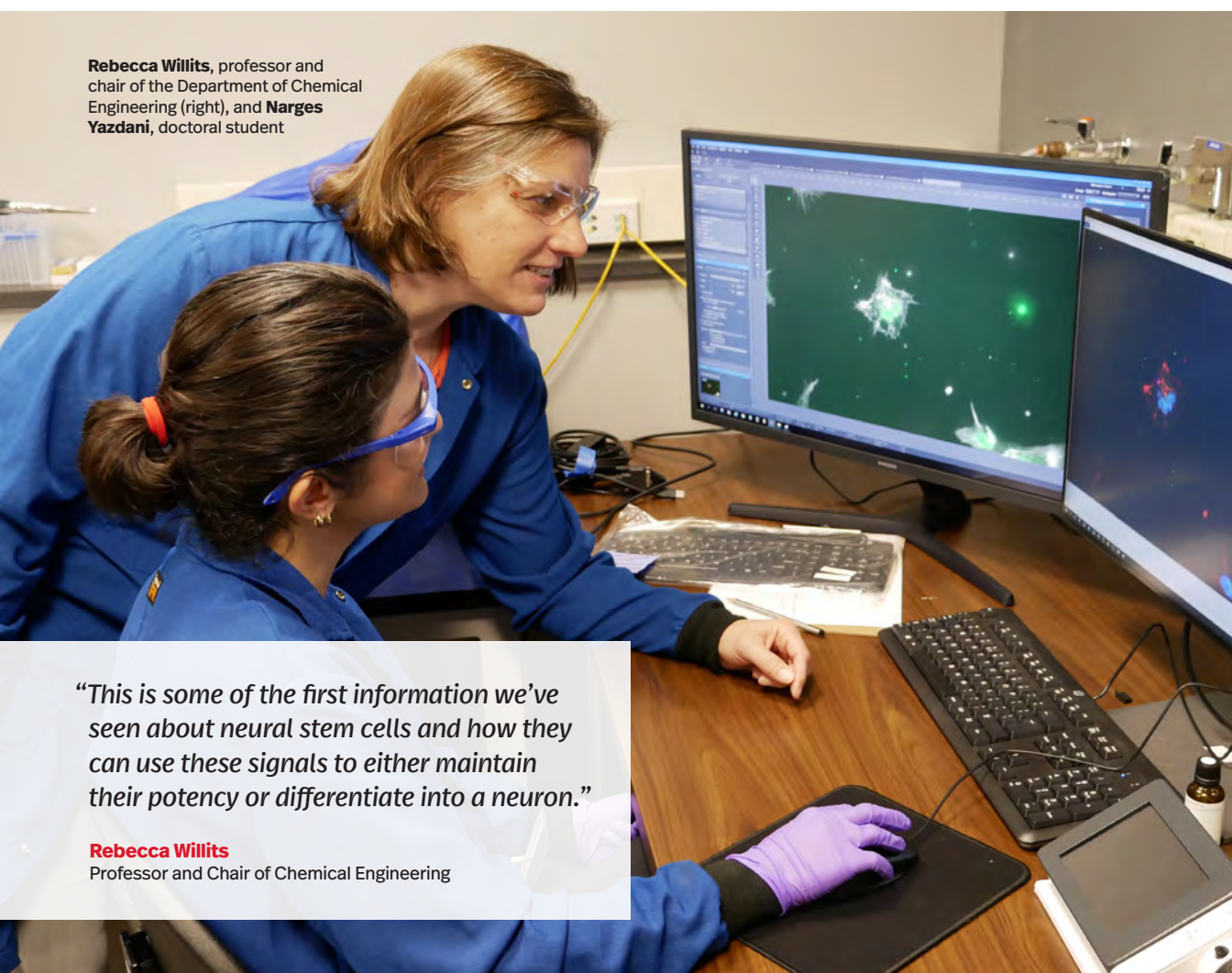
Willits explains that neural stem cells can experience two types of mechanical connections: they can bind with their surrounding environment, a scaffold of proteins called the extracellular matrix, or they can bind to one another in a cell-cell interaction. To investigate these interactions, she and her team created artificial matrices and binding sites to observe how changes in those bonds affect adult human stem cells. They discovered that different interactions can make a big difference in the fate of a stem cell.

"If you have really strong reactions between the cellular receptors, the cell-cell type of interaction, the cell is more likely to differentiate and to change from its stem cell state to a neural state," says Willits. "Whereas if we're using a solid matrix and it's binding to the matrix, the cell maintains its stem-ness, remaining a stem cell."

"This is some of the first information we've seen about neural stem cells and how they can use these signals to either maintain their potency or differentiate into a neuron."

The discovery could have implications for the laboratory study of neurodegeneration, allowing scientists to mimic a disease state in vitro and then attempt to manipulate that state using drugs or other methods. It might even point the way to new therapeutic approaches to debilitating conditions like Alzheimer's disease.

"If we understand that the cells interacting with this specific receptor or that specific binding site differentiate into neurons," says Willits, "and you need neurons, you can probably deliver molecules and materials that have those binding sites, and that would then force the interaction." N



Rebecca Willits, professor and chair of the Department of Chemical Engineering (right), and **Narges Yazdani**, doctoral student

"This is some of the first information we've seen about neural stem cells and how they can use these signals to either maintain their potency or differentiate into a neuron."

Rebecca Willits
Professor and Chair of Chemical Engineering

Photos by Bella Martinez/Northeastern University

Repairing Blood Vessels at the Cellular Level

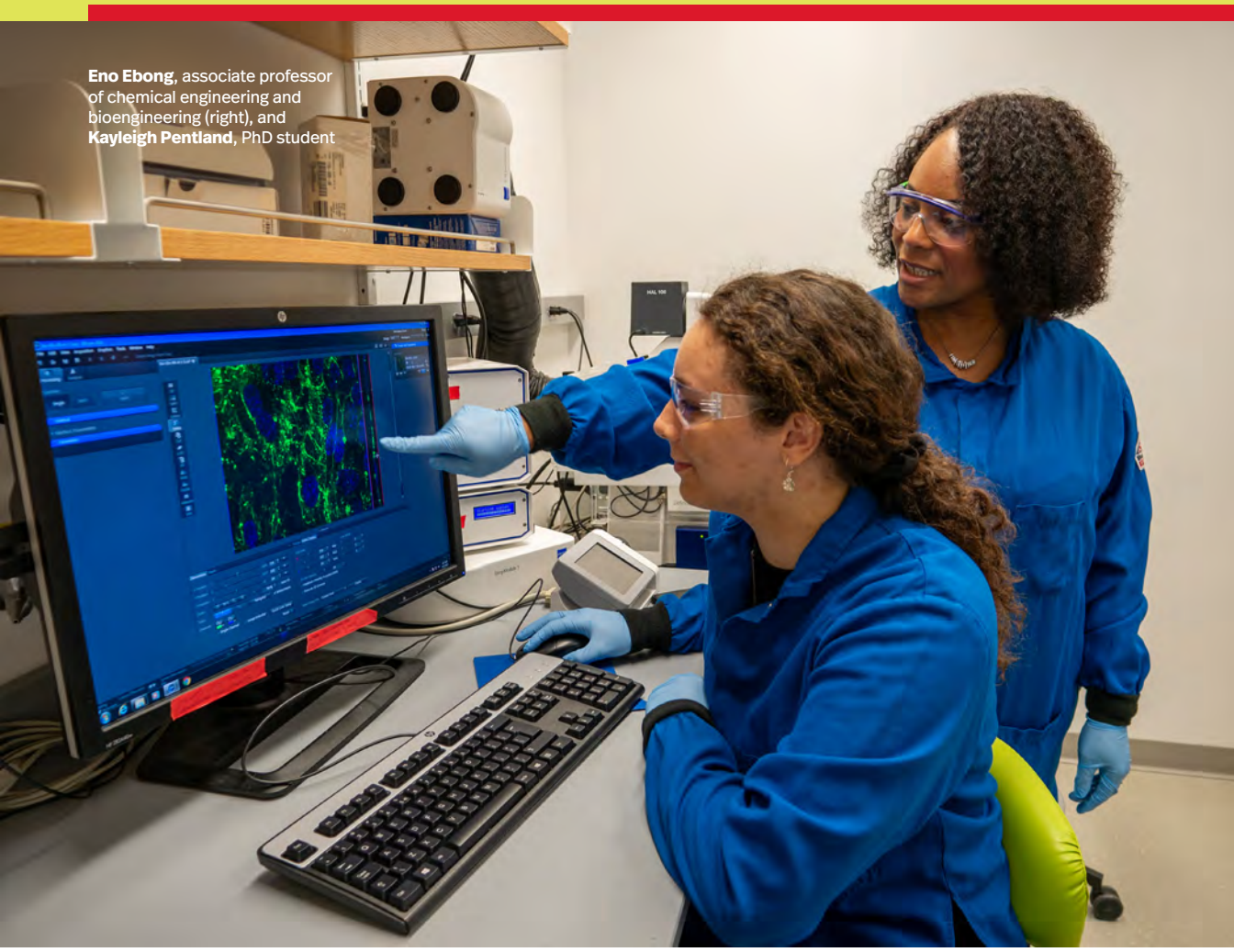
Endothelial cells line our blood vessels and guard them from dysfunction that lead to diseases like atherosclerosis, cancer metastasis, and neurodegeneration. **Eno Ebong**, associate professor of chemical engineering and bioengineering, investigates how the mechanical forces of blood flow and tissue stiffness affect these endothelial cells. In 2019, she received a prestigious CAREER award from the National Science Foundation to examine how fluid and solid mechanics affect an endothelial cell structure called the glycocalyx.

The glycocalyx is a mesh of sugar chains that surrounds cells and serves multiple functions; in the endothelium, it can regulate vascular permeability and aid mechanical signal transduction through cells in vessel walls. While the impact of blood flow forces on endothelial cells have been well studied, Ebong's research is the first to examine the combined effect of flow and tissue stiffness on the endothelial glycocalyx.

"Typically, when you look at the glycocalyx's response to flow in disease settings, its dimensions are diminished," Ebong says. Her research team found that the glycocalyx isn't degraded in this way by mechanical stimulation due to combined flow and tissue stiffness. The types of sugars that comprise the glycocalyx are altered, a change that could have implications for disease susceptibility. "The component that gets upregulated has a lot of binding sites for inflammatory cells and pathogens," Ebong says, noting that the discovery lays the groundwork for exploring direct causal links between glycocalyx alteration and vascular disease.

Building on these recent and prior findings, Ebong has embarked on a new project funded by the National Institutes of Health aimed at repairing and regenerating damaged endothelial glycocalyx. By adding chemical components to cell samples in the lab, she and her team have discovered that they can restore important functions to the glycocalyx.

The discovery of the ability to restore important functions to the glycocalyx could prove significant for treating atherosclerosis—an erosion of blood vessel walls that can lead to heart attacks, strokes, aneurisms, and other serious disorders—earlier in the progression of disease than current methods allow.



Eno Ebong, associate professor of chemical engineering and bioengineering (right), and **Kayleigh Pentland**, PhD student

"We were initially doing that experimentally," Ebong says, "trying to modify the glycocalyx and see if it had an effect. But we found that if it can be done in a controlled way it can actually be therapeutic." Not only was the team able to repair the filtration function of the glycocalyx, but they were also able to control signaling activities that affect the elasticity of blood vessel walls.

This achievement could prove significant for treating atherosclerosis, an erosion of blood vessel walls that can lead to heart attacks, strokes, aneurisms, and other serious disorders that affect millions worldwide. Crucially, such treatments could be applied much earlier in the progression of disease than current methods allow.

"When you see someone on statins, or with a triple bypass, or stents, it's very advanced at that point," says Ebong. "But the glycocalyx changes happen very early on. So, this could be applied after an early diagnosis and keep things from getting advanced." Another potential application might be coating stents and other implanted devices with therapeutic agents based on Ebong's formulation to promote vascular healing after surgery. N

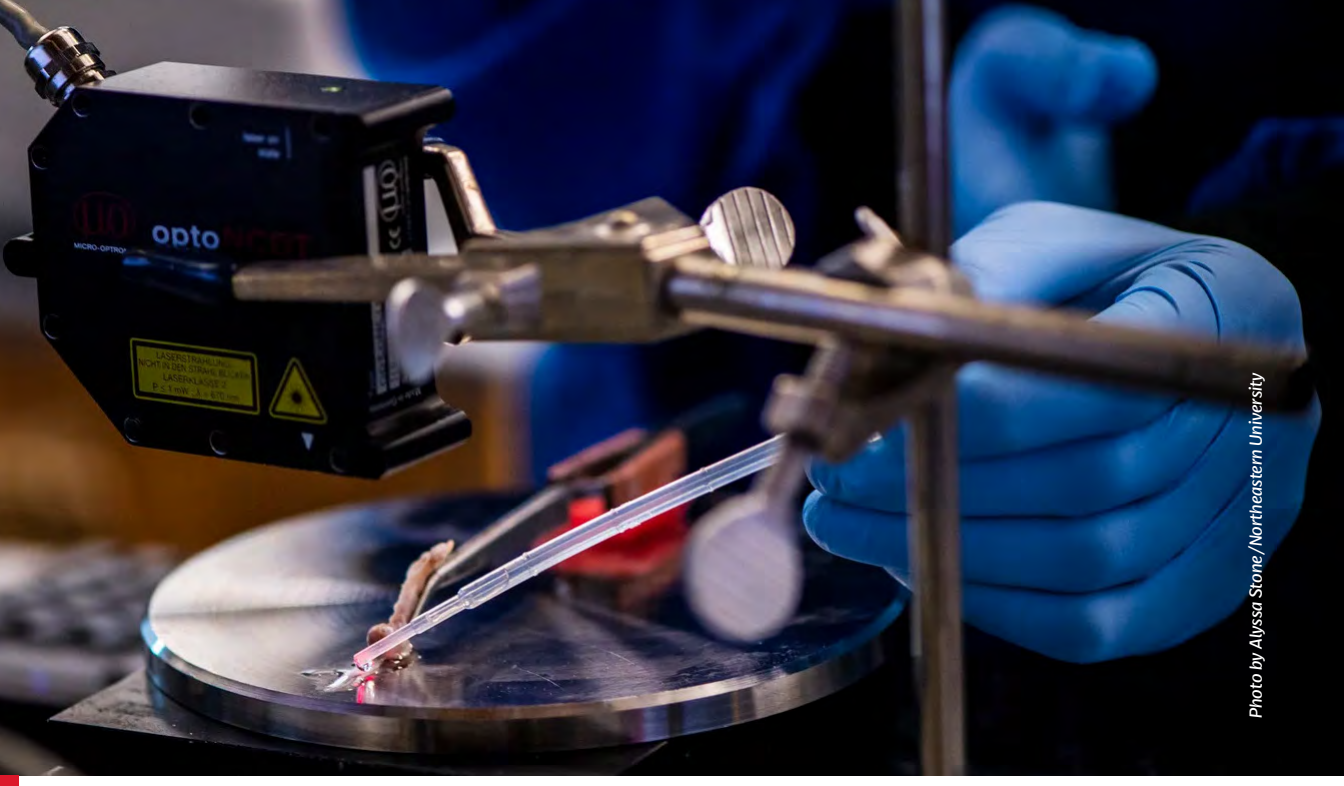


Photo by Alyssa Stone/Northeastern University

Using Collagen to Rapidly Repair and Prevent Tendon Injuries and More

Every year, millions of people suffer from orthopedic injuries such as tears of the ACL, Achilles tendon, rotator cuff, meniscus, or spinal damage. Only a small fraction of these injuries are appropriate for surgical repair, and most are left to heal on their own. With surgery or not, intensive physical therapy is needed, and patients can lose strength and productivity as they heal, as well as risk reinjury.

Jeffrey Ruberti, professor of bioengineering, has been studying collagen since 2004. Collagen is the most abundant protein in the body and the building block of connective tissues such as tendons, ligaments, muscle, skin, and cartilage. Over the years, Ruberti and his students have discovered that when manipulated, collagen can lead to faster recovery times for tendon injury.

“Collagen is the structural molecule in vertebrate animals,” says Ruberti. “In every tissue, it takes different forms, from tendons to corneas. It’s made up of tiny little strands of molecules that assemble into bigger and bigger strands that hold our cells in place.”

Those molecules have special properties. Ruberti found that if you pull on them, they’ll start to snap into place with one another, and form recognizable, string-like structures called fibrils.

“That was a fundamental discovery,” he says. “That means it’s more stable when you pull on collagen molecules than when you don’t.” It is also self-healing, seeking out sites of injury in connective tissues and forming fibers there to repair the damage. If collagen is present someplace it is not needed, it breaks down and clears out.

Ruberti and his research team manipulated collagen into two different forms. The first is a gel-like material called “metastable” collagen, which can supply loose collagen molecules to a wounded tendon. The other is a stable, dense mat of collagen that can wrap around the tendon, holding the gel in place.

Jeffrey Ruberti, professor of bioengineering

The fundamental discovery that collagen, which is made up of string-like molecules, gets more stable when pulled, led to an active liquid crystal collagen that can be directly injected to the injury site to rapidly repair and prevent orthopedic injuries.

Photo by Ruby Wallau/Northeastern University

"Think of a fractured Achilles tendon as a broken rope," Ruberti says. "The stable collagen acts like a piece of tape wrapped around the broken spot, holding the ends together. But inside the tape, we put a highly dense gel of collagen molecules that can help facilitate tendon repair. If we stimulate the calf muscle to contract a little, the tendon may start to incorporate those molecules."

Ruberti's lab invented the liquid crystal formulation needed to deliver collagen as a therapeutic. "There's 10 patents behind us, 25 research papers on the concept and about $6 million from the NIH," Ruberti says.

Offering new supplemental sources of collagen

From this research, Ruberti and his former PhD student **Jeff Paten**, who also received his undergraduate degree from Northeastern, founded BrilliantStrings Therapeutics, a spinout company from their lab. The company produces active human collagen to promote rapid healing of injuries, either by injecting liquid crystal collagen directly into the site of the injury or, for larger tears, using a patch that releases the protein. While there are some supplemental collagen sources on the market, they use inactive collagen, which is difficult for the body to use effectively. BrilliantStrings Therapeurtics' active collagen product can help prevent further degeneration and pain, and enable a full recovery in potentially half the time.

Testing of the technique is currently being conducted in a rodent model; human testing won't be for a while. If successful, Ruberti thinks this new active collagen technology could be invaluable to professional athletes, soldiers, or anyone who relies on keeping their body in peak form in order to do their job. The company made it to the "final four" of the U.S. government's "ARPA-H Dash" health outcomes competition, which identifies revolutionary, evidence-based ideas to transform health.

"The market out there is not just for ligaments and tendons," Ruberti says. If successful, the technology could help heal skin injuries, diabetic ulcers, and burns, even serving as an active ingredient in cosmetics. "There are a lot of places where I believe we can help." N

Cigarettes, Vaping, or Both—What Is Worse?

While recent decades have seen a significant decline in cigarette smoking in the United States, the advent of electronic cigarettes and other "vaping" devices has complicated the issue of smoking and public health. E-cigarette popularity has skyrocketed among young people, as well as those attempting to quit traditional cigarette use. Although these devices were originally marketed as an aid for smoking cessation, many smokers have continued to use both traditional and e-cigarettes.

Very little is known about the health effects of this so-called "dual use." With a $3.8 million grant from the National Institutes of Health, **Chiara Bellini**, associate professor of bioengineering, and **Jessica Oakes**, associate professor of bioengineering, are among the first to investigate the effects of long-term exposure to cigarette smoke and aerosols from e-cigarettes.

While cigarettes and e-cigarettes both raise blood pressure and can cause asthma, Oakes, who focuses on lung function, points out that e-cigarette vapor has been shown to narrow the airway more than cigarette smoke. Bellini, who studies cardiovascular systems, notes that e-cigarettes can cause arterial stiffening that does not occur in cigarette use.

"We know their effects are different," says Bellini. "But if we combined them together, maybe the effect of vaping and smoking will be worse than doing one or the other."

E-cigarettes have not been on the market long enough to recruit long-term users for study, so Bellini and Oakes rely on mice as a preclinical model to test their hypothesis. They expect to see significant cardiopulmonary remodeling, an inflammatory response that can thicken organ tissues, impairing their function. The effects of the smoke and vapor can also extend well beyond these organ systems, Oakes points out.

"It definitely creates a systemic inflammatory response that's observed downstream of the cardiopulmonary system," says Oakes, including in the brain, sperm cells, and other tissues. In collaboration with **Sandra Shefelbine**, professor of mechanical and industrial engineering, and bioengineering, they are also studying the effects of inhaled smoke and aerosols on bone and musculoskeletal systems.

What the team learns from this research may ultimately inform future health policy and product regulation at the national level. "The Food and Drug Administration is really interested in scientific data to drive their policies," says Bellini, noting that a similarly rigorous examination of cigarette smoking was too long delayed. "We could have saved a good 50 years if we'd just funded research to understand the effects of cigarette smoking—we don't want to repeat that. The FDA is really interested in learning what the combined effects of these products are." N

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About the Cover

Eno Ebong, associate professor of chemical engineering and bioengineering, investigates how the mechanical forces of blood flow and tissue stiffness affect endothelial cells–cells that line our blood vessels and guard them from dysfunction that lead to diseases. In 2019, she received an NSF CAREER award to examine how fluid and solid mechanics affect an endothelial cell structure called the glycocalyx. She discovered that important functions can be restored to the glycocalyx, which could prove significant for treating atherosclerosis. *See pages 20-21 for more information.*

Photo by Bella Martinez/Northeastern University

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