In a Different Vein

The idea of engineering organs still astounds, but Laura Niklason is making it a reality

A School for Dreamers

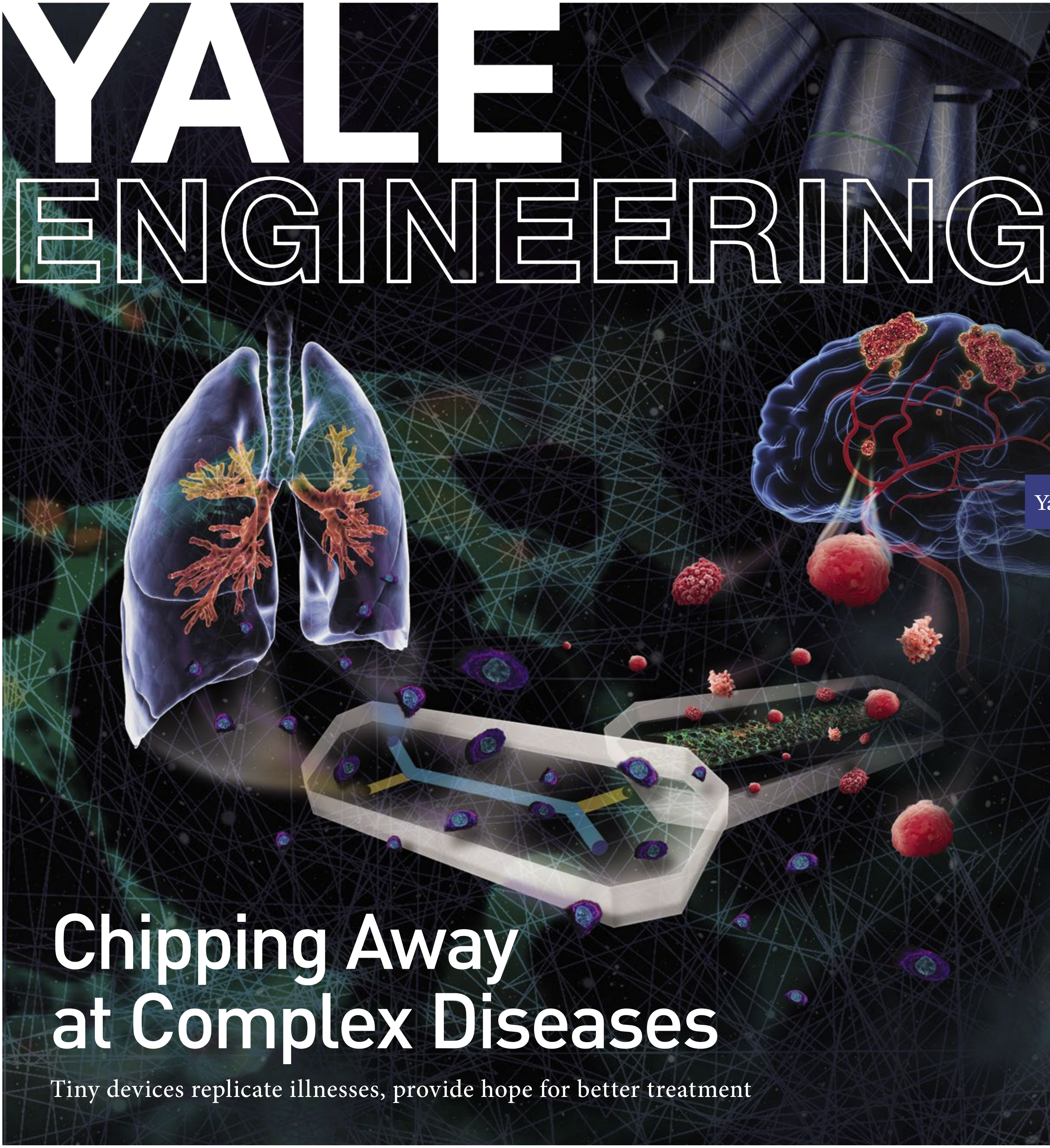
A Yale-Afghanistan collaboration creates a "symbol of hope"

3D Printing to Help Tortured Bones

A Yale surgeon's modern approach to improving medical care

2019-2020

YALE ENGINEERING



Chipping Away at Complex Diseases

Tiny devices replicate illnesses, provide hope for better treatment

The Publication of Yale's School of Engineering & Applied Science

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FEATURES

Front Cover: *"Lab-on-a-Chip" devices recreate living environments and allow researchers to directly observe human physiology. Biomedical engineers Andre Levchenko and Rong Fan have recreated the microenvironments of asthma and brain tumor cells on a chip.*

EDUCATION · INTERDISCIPLINARY · MEDICAL INNOVATION · SUSTAINABILITY · TECHNOLOGY

YALE ENGINEERING 2019-2020

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Message From the Dean

As one of the newest members of the Yale School of Engineering & Applied Science, it has been a pleasure to meet with members of the SEAS community over the last few months and learn how their contributions make this university a singularly special place. One of my first official duties as Dean was to welcome the incoming class of first years and introduce them to the "culture of engineering" we have at Yale. It is a culture of collaboration, innovation and big thinking, where chance encounters and one-off conversations lead to surprising partnerships between scholars from across the sciences, social sciences, and humanities.

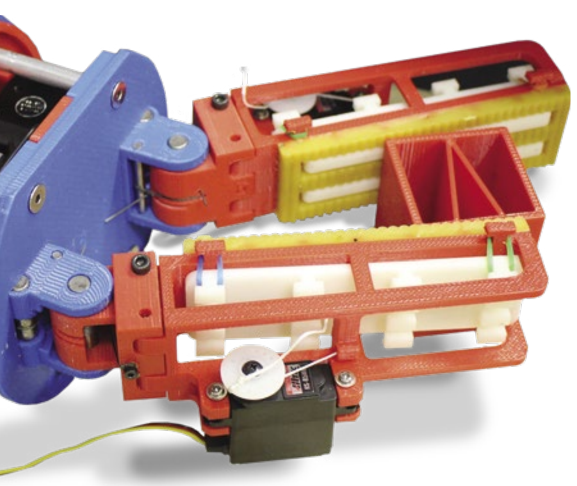
Engineering's impact extends far beyond our corner of Hillhouse Avenue. As you'll read in this year's edition of *Yale Engineering*, we have faculty working on medical breakthroughs at the School of Medicine and on West Campus, and our graduate students have been recognized in a campus wide competition for the artistic quality of their research images. Externally, our faculty are developing instruments to study the air quality of microenvironments in Baltimore, and our undergraduates are sharing their coding knowledge with New Haven middle schoolers in their spare time. Globally, we have worked to ensure water quality in the developing world, and we partnered with colleagues at the School of Architecture and the Macmillan Center to design the Dreamer Institute, a campus and makerspace for high school girls in Afghanistan.

Yale's engineering community inspires me daily. The sense of potential and possibility is everywhere evident, and everyone — from faculty to staff, from students to alumni — shares a passion for the place we work, and the work we do. I'm inspired to bring that passion to bear on our biggest challenges, and to embrace this turning point in Yale's history to enrich and propel our School of Engineering & Applied Science to new vitality, energy, and impact.

Jeffrey F. Brock
Dean, School of Engineering & Applied Science
Dean of Science, FAS
Professor of Mathematics

Year in Review

A look back at some of the news stories from the Yale School of Engineering & Applied Science over the last academic year



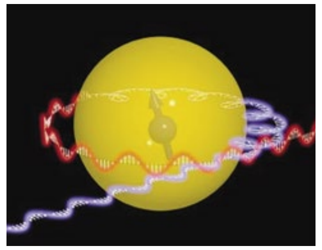
2018: September

A Helping Hand

Picking up a pen is a lot harder than it seems, and this is especially true for robots. So the lab of Aaron Dollar, professor of mechanical engineering & materials science, created a robotic hand that employs variations in friction of finger surfaces. It combines a surface made of soft urethane (high-surface friction), hard 3D-printed plastic (low-surface friction), and some rubber bands to suspend one surface behind the other. The results are promising and the researchers have made the design open-source so others can expand on it.

2018: October

Harnessing Quantum Computing's Spooky Power

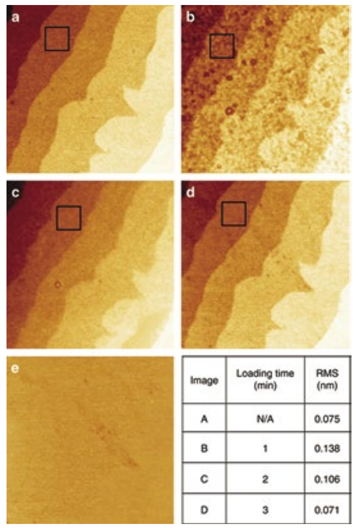


A team of researchers from SEAS and Yale's Quantum Institute was selected by the U.S. Department of Energy to develop the core quantum computing and networking components that would make the uncanny world of quantum physics realistic for computing. Led by Hong Tang, the Llewellyn West Jones, Jr. Professor of Electrical Engineering, the project focuses on finding new materials for the hardware of quantum computing. The three-year, $3.6 million grant was awarded in conjunction with the White House Summit on Advancing American Leadership in QIS.

2018: November

It's All in the Details

The lab of Udo Schwarz, professor and chair of mechanical engineering & materials science, developed a procedure that can replicate surface structures at the atomic scale. The researchers were able to recreate all the details of a mold's surface, right down to minute, atomic-scale features. Key to the breakthrough was choosing strontium titanate for the mold's material. Besides answering some long-standing mysteries about the nature of the glassy-liquid state of certain materials, the innovation could lead to better catalysts and improved data storage among other things.



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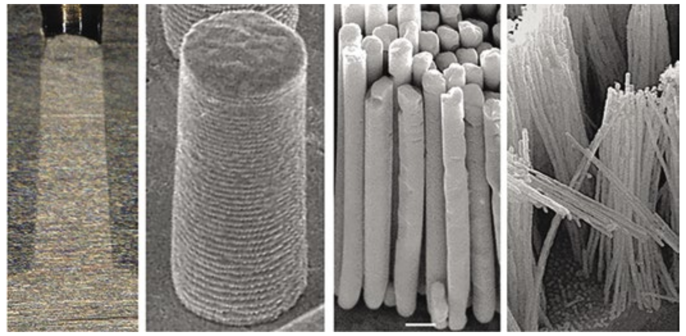
B	1	0.138
C	2	0.106
D	3	0.071

2018: December

3D Drawing Catches On

For bringing sketching into the 21st century, Frederick W. Beinecke Professor of Computer Science Julie Dorsey won Microsoft's first Female Founders Competition, which focused on companies transforming enterprise technology. Dorsey, founder of the digital drawing company Mental Canvas, received $2 million in venture capital funding and access to additional resources. Mental Canvas is a software company that reimagines sketching for the digital age by augmenting it with spatial strokes, 3D navigation, and free-form animations.



2019: January

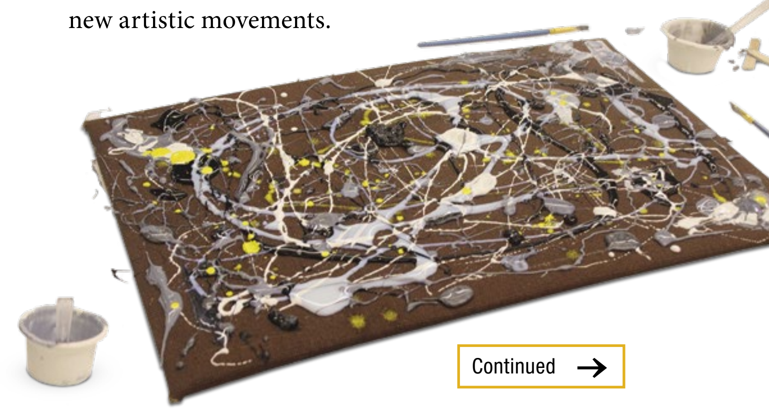
Shaping Metal at the Nanoscale

The lab of Jan Schroers, professor of mechanical engineering & materials science, developed a method known as thermomechanical nanomolding that allows molding crystalline metals into shapes as small as a few nanometers in diameter. The breakthrough could lead to new technologies in fields such as sensors, batteries, catalysis, biomaterials, and quantum materials. It could also open the door for numerous new metals and alloys that would be ideal for specific nanoscale applications, from solar energy to microelectronics.

2019: February

More Than Splattering Paint

A Jackson Pollock painting may look chaotic, but there's science to all that abstract expressionism. At the Yale Center for Engineering Innovation & Design, research scientist Kate Schilling and paintings conservator Cindy Schwarz led a workshop on the physics of Pollock and Helen Frankenthaler paintings. Attendees learned how rheology and such processes as surface tension, capillary action, and diffusion help created the artists' visual styles. Schilling, who teaches the Materials Science of Art — a SEAS-Art collaboration — noted that paint technology has long informed the emergence of new artistic movements.



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2019: March

Run, Robot, Run!

Designing a robot to run on rough terrain — an incredibly complex process — is a tricky thing, but Madhusudhan Venkadesan, assistant professor of mechanical engineering & materials science, offers some guidance in a published study. Using mathematical analysis and computer simulations, his research team found that the way your foot hits the ground plays a major role in stability. Also, it's the changes in the slope of the terrain — not in height — that cause the most problems. The study drew inspiration from videos of animals and humans running.

2019: April

Pondering the Future of AI

Artificial intelligence (AI) algorithms are deciding everything from Facebook posts to court defendants' bail. But there are still crucial questions about the technology. "AI, Ethics, and Society @ Yale," a daylong event that brought together speakers and panelists from across campus, took on many of these issues. The conference, the first of its kind at Yale, was organized by Nisheeth Vishnoi, professor of computer science. Vishnoi said Yale is uniquely positioned to tackle these questions, due to its diverse schools and the many collaborations between them.

2019: May

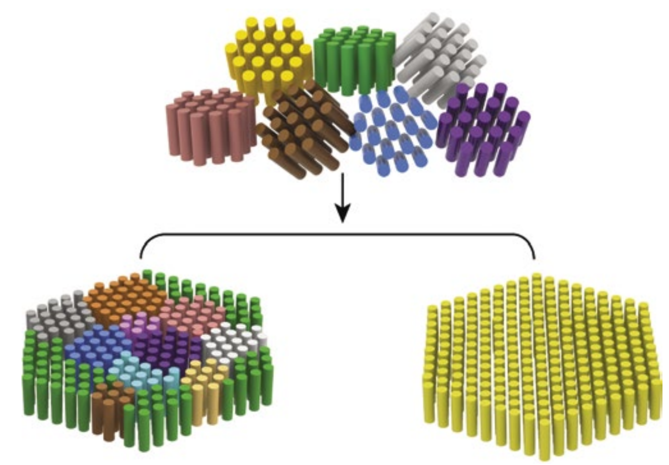
Speedy (but Complicated) Science

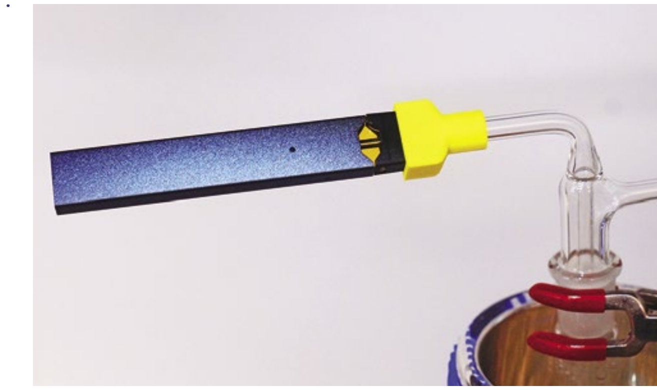
Explaining research that combines neuroscience, statistics, and data science *and* challenges conventions in each of those fields isn't easy, but Mehraveh Saleh did so in three minutes — a feat that earned her first prize at the first Ivy Three-Minute Thesis. Ph.D. students from Yale, Brown, Columbia, Cornell, Dartmouth, Princeton, and UPenn had one slide and three minutes to present their research. Salehi, in the lab of Amin Karbasi, assistant professor of electrical engineering and computer science, focuses on brain maps that can show differences in the brain from one state of mind to another.

2019: June

Making Single Crystal Textures

A team of researchers, including Amir Haji-Akbari and Menachem Eliemelech, both professors of chemical & environmental engineering, demonstrated a method creating single crystal textures in a self-assembled soft material. It's a boon for researchers because the intrinsic properties of materials are best understood in this state. The unique properties of many devices often depend on preparing such materials as single crystals. The microelectronics industry, for example, requires the ability to create wafers of single crystal silicon, to be used for fabricating microelectronic chips. Also, modern aviation depends on single-crystal turbine blades that enable modern jet engines.





2019: July

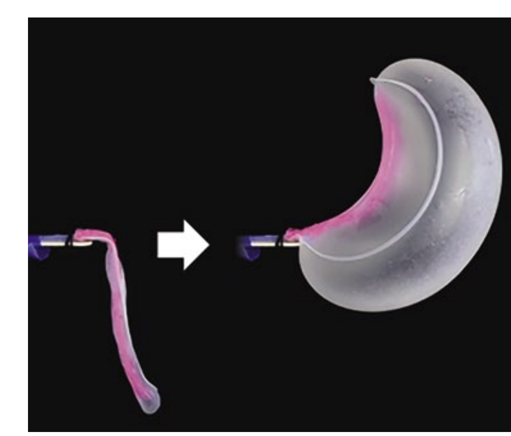
Vaping Hazards Exposed

Despite the popularity of vaping, little is known about the chemical composition of the products. The lab of Julie Zimmerman, professor of chemical & environmental engineering and forestry & environmental studies, published a study showing that when it comes to e-cigarettes, the ingredients listed are not all that users are consuming. Specifically, they found that chemical reactions in flavored liquids can create unexpected chemicals that can irritate users' airways. The researchers used a "vaping machine" custom-built in Zimmerman's lab to analyze the chemical makeup of various flavors.

2019: August

A Bending, Twisting Robot

The lab of Rebecca Kramer-Bottiglio, the John J. Lee Assistant Professor of Mechanical Engineering & Materials Science, built a robot inspired by muscular hydrostats — that is, tongues, elephant trunks and octopus arms. One of the many soft robots that the Kramer-Bottiglio lab has produced, it features a balloon, fibers, and actuators. Not only can this robot expand and elongate, it can twist and bend. With the specially designed actuators made in the lab, the roboticist team can reuse the balloons, quickly modifying them to move in different ways.



Yale

A New Dean at the Helm

A Q&A with Jeffrey Brock

In August, Jeffrey Brock '92 was named dean of the Yale School of Engineering and Applied Science (SEAS). Brock, who also serves as dean of science in the Faculty of Arts and Sciences (FAS), is an internationally recognized data scientist and mathematician with numerous collaborations with computer scientists and engineers. "By serving simultaneously as the dean of SEAS and FAS dean of science, Jeff will be in a position to lead strategic thinking about the connections across science and engineering," President Peter Salovey said. Before coming to Yale in 2018, Brock was the founding director of Brown University's Data Science Initiative and served as the chair of the mathematics department.

He takes over the position from Kyle Vanderlick, the Thomas E. Golden, Jr. Professor of Chemical & Environmental Engineering, who served as dean from 2008 to 2017 (Mitchell Smooke, the Strathcona Professor of Mechanical Engineering & Materials Science and Applied Physics, served in the interim). Brock graduated from Yale with a B.A. in mathematics and speaks fondly of how his undergraduate experience allowed him to pursue other subjects, including literature and music. His interest in the latter led to his playing bass on the first two albums by Grammy-nominated jazz pianist Vijay Iyer (they were roommates at Yale).

"The beauty of the Yale undergraduate degree is that I had exposure to the top mathematical minds in the world but could also take courses from the great literary scholars which made Yale famous," Brock said. "That's doubly true in engineering — you can bring your ideas to life, but also have these context-building experiences."

We spoke with Dean Brock about the future of SEAS, the value of intellectual exploration and other topics:

How does SEAS fit into the university's overall goals for the sciences?

Yale is currently investing at a historic level in science and engineering, in ways that cut across departments, schools, and areas of emphasis. That allows researchers to reach across these divisions toward larger goals.

Yale's focus on solving the great problems of society places Engineering squarely in the center of these efforts. I want to engage the SEAS faculty in a process where we think through our strategic goals in reference to these priorities and how we can partner across the science departments, the social sciences, the medical school and even the humanities. The benefits go both ways: it's vital for Engineering to play a direct role for the university's science priorities to succeed.

But we also have to think about how our departmental excellence can further our strategic goals — that is, we need to leverage our strengths. Among many examples, we have a top environmental engineering group leading the development of new technologies that help advance sustainability and control environmental impact. These excellent faculty have strong connections to faculty in the School of Architecture, School of Public Health, School of Forestry & Environmental Studies, and in Ecology and Evolutionary Biology.

Our faculty are leading the way to the next generation in computing, whether it's rethinking chip design to realize the next breakthrough in classical computing, or the great work they're doing to bridge classical and quantum computing systems. In Biomedical Engineering, our faculty

Continued →

explore the mechanisms of intracellular communication within the immune system and sit at the vanguard of gene editing technology – these and many other examples will be critical to the implementation of the science priorities.

How should SEAS meet the surging student demand for STEM curriculum (the "E" in STEM in particular)?
We need to meet the students where they are. They're coming here interested in things like design, entrepreneurship, and innovation — not just the engineering "classics." We're developing the Y-shaped engineer — breadth, depth, and purpose — but also honing the creative force that the Yale undergraduate embodies. We have these incredibly creative students, whether they are engineers, artists, musicians, writers, or just deep thinkers, and places like the Center for Engineering Innovation & Design (CEID) and the Tsai Center for Innovative Thinking at Yale (CITY) provide an outlet for that creative force. We need to provide them with a way to realize their dreams and goals.

What are some ways that SEAS can promote entrepreneurship?
One thing we need is a more porous boundary between the university and industry and, more specifically, better opportunities for our students to connect with a new kind of industry. Engineering has traditionally responded to the needs of large-scale engineering-based companies, but there's increasingly more of an emphasis on startups and hi-tech ideation. Those companies want innovative solutions. I'm looking to build a kind of innovation ecosystem around the School of Engineering and give students a chance to interact with industry leaders, innovators, and potential venture accelerators and consider potential startups. That culture is emerging here, but we can enhance it with thoughtful programming and outreach. I want our students to know they have the opportunity to bring forth new ideas and to be able to realize them.

Among faculty, we need win-win arrangements between researchers from industry and academia that don't threaten either's responsibility to their institutional mission. Our departments are desperate for these kinds of relationships, which are critical to recruiting top faculty into engineering. We need to provide them with the kind of ecosystem and intellectual ferment that will draw them away from lucrative offers of companies. Yale Engineering ought to be the place where faculty feel that they can bring their ideas to life while building a culture of innovation and exploration. We need to evangelize what's unique about our culture in regard to startups and to leverage what Yale is known for – deep expertise and scholarship across a range of domain areas.

How can alumni be a part of this effort?
Increasingly, every conversation I have with alumni quickly moves to "How can I partner with you and how can we work together on some project?" I want to establish better communication and networking with our incredible alumni working in industry. Everyone I meet is deeply proud of their engineering degree and they all want to bring their enthusiasm to campus and connect with the students. I would love for our alumni to feel like they could view their relationship with the School of Engineering not just as a philanthropic one, but as one of engagement on an intellectual level. They value so deeply the culture and the community we have here, and they really want to help, so it's a clear win-win collaboration.

You founded the Data Science Initiative at Brown. How does big data come into play in SEAS?
Its role can't be overemphasized. Every device we engineer, every experiment we run, every collaboration we undertake generates vast amounts of data which we need to understand to refine and develop our base of knowledge. Likewise, the tools of machine learning and big data are increasingly vital across engineering and design questions, such as drug design, materials science, wearable devices, and imaging technology. We are increasingly engaged in the question of how data science, machine learning, and artificial intelligence are transforming society. These questions involve Computer Science, Electrical Engineering, Biomedical Engineering, new ways of thinking about algorithms and rethinking how we use data generated by the devices we build. These priorities require new ways to collaborate with leaders in mathematics, statistics and data science to come up with smart solutions. Big data is woven through all of these disciplines.

"When you get to Yale, you find yourself surrounded by all these incredibly creative and smart people, and that drives your own sense of what's possible."

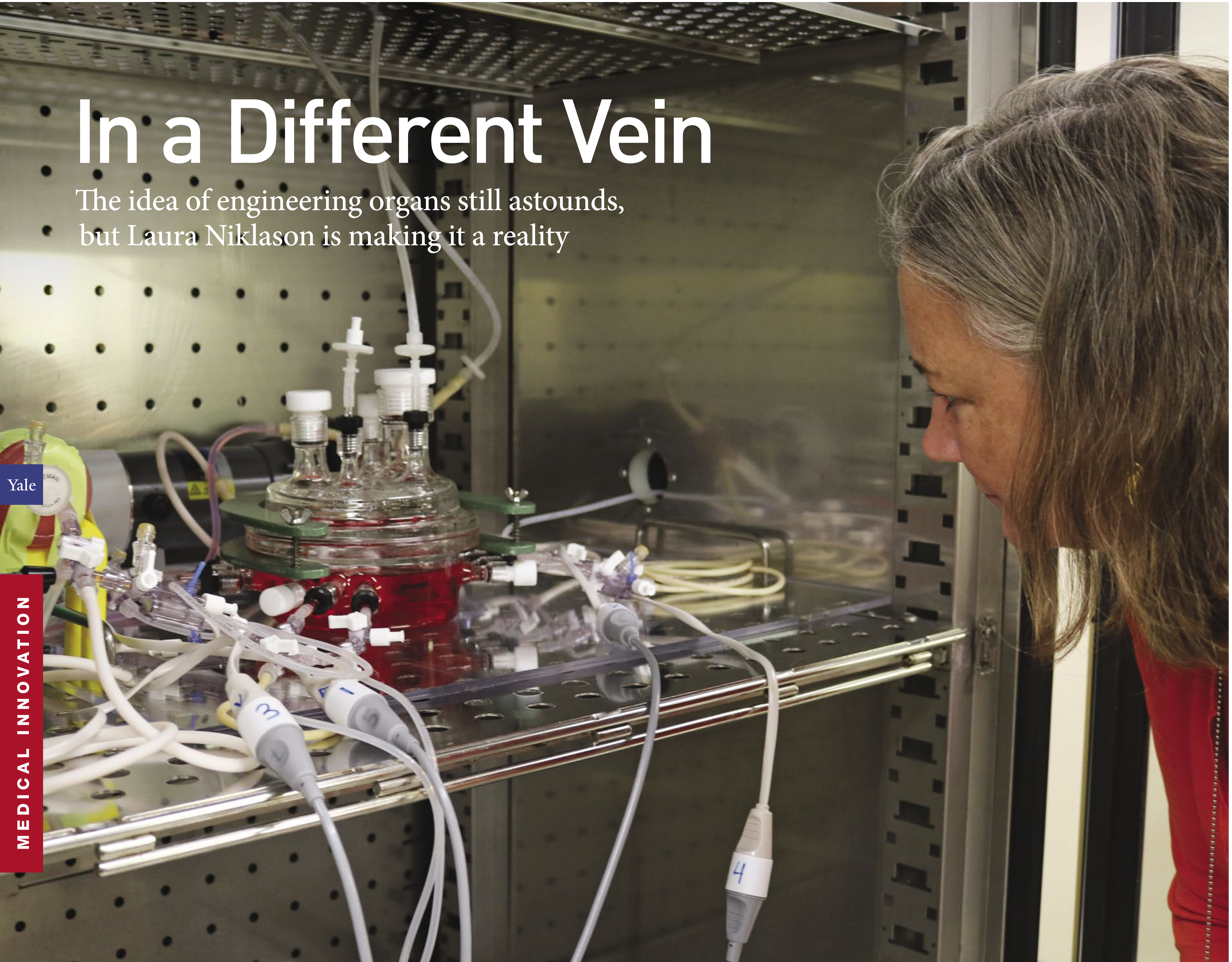
› *Jeffrey Brock, dean of the Yale School of Engineering & Applied Science*

What do you want Engineering students to get out of their experience here at Yale?
When you get to Yale, you find yourself surrounded by all these incredibly creative and smart people, and that drives your own sense of what's possible. I want our students to feel that they can build the foundational knowledge of whatever subject interests them within a broader context. The connections that students can draw from other disciplines to the work in their major is a rich part of the Yale experience. That means a student in Environmental Engineering may do great work on clean water solutions, but also develop an understanding of the history and the cultural context of access to water and its development of new societies. That context is critical; we're in an era when the tools of engineering and the things we create are more socially powerful than ever. The kind of broad understanding that the Yale student can bring to these problems is one of the things that differentiates our graduates from those of other engineering schools.

At Yale we ask questions that run a little deeper: SEAS should be a school that doesn't just train engineers in the traditional sense, but one that shapes our excellent students into future leaders that understand the direction and future of engineering. The world needs Yale and its engineering graduates to lead in this time of deep technological transformation and to ensure that our innovations sit in the service of our most deeply held values as a society.

In a Different Vein

The idea of engineering organs still astounds, but Laura Niklason is making it a reality



It was her experience as a physician in the intensive care unit that pointed Laura Niklason in the direction of making engineered blood vessels for kidney dialysis patients. She worked with countless patients requiring needle injections multiple times per week, whose veins weren't up for the job.

"Some patients had failures over and over and over," said Niklason, the Nicholas M. Greene Professor in Anesthesia and Biomedical Engineering. "They're in the operating room all the time and they get infections and they get hospitalized for those infections. And it's just miserable."

Off-the-shelf engineered blood vessels, on the other hand, could operate the same way that natural ones do but with the durability to withstand the abuse that dialysis requires.

Niklason has been working for more than 20 years on what's known as bioengineered human acellular vessels (HAVs). They're the product that Humacyte — the North Carolina-based company that Niklason founded in in 2004 — specializes in. In addition to dialysis patients, they could also prove to be life-savers for patients with cardiovascular disease. This year, the U.S. military began exploring the use of Niklason's HAVs to treat soldiers who have been injured on the battlefield and need a blood vessel repaired.

Also this year, Niklason and Humacyte realized a major breakthrough: In one of the longest follow-up studies of its kind, researchers found that their specially bioengineered blood vessels evolved into living tissue after human implantation. Beyond the immediate benefits, this transformation from non-living to living is a great sign for the future of regenerative medicine in general.

The results, which were published in *Science Translational Medicine,* showed that the vessels created in her lab — devoid of any cells when they were implanted in patients — had taken on cells, transforming the structures into living tissues

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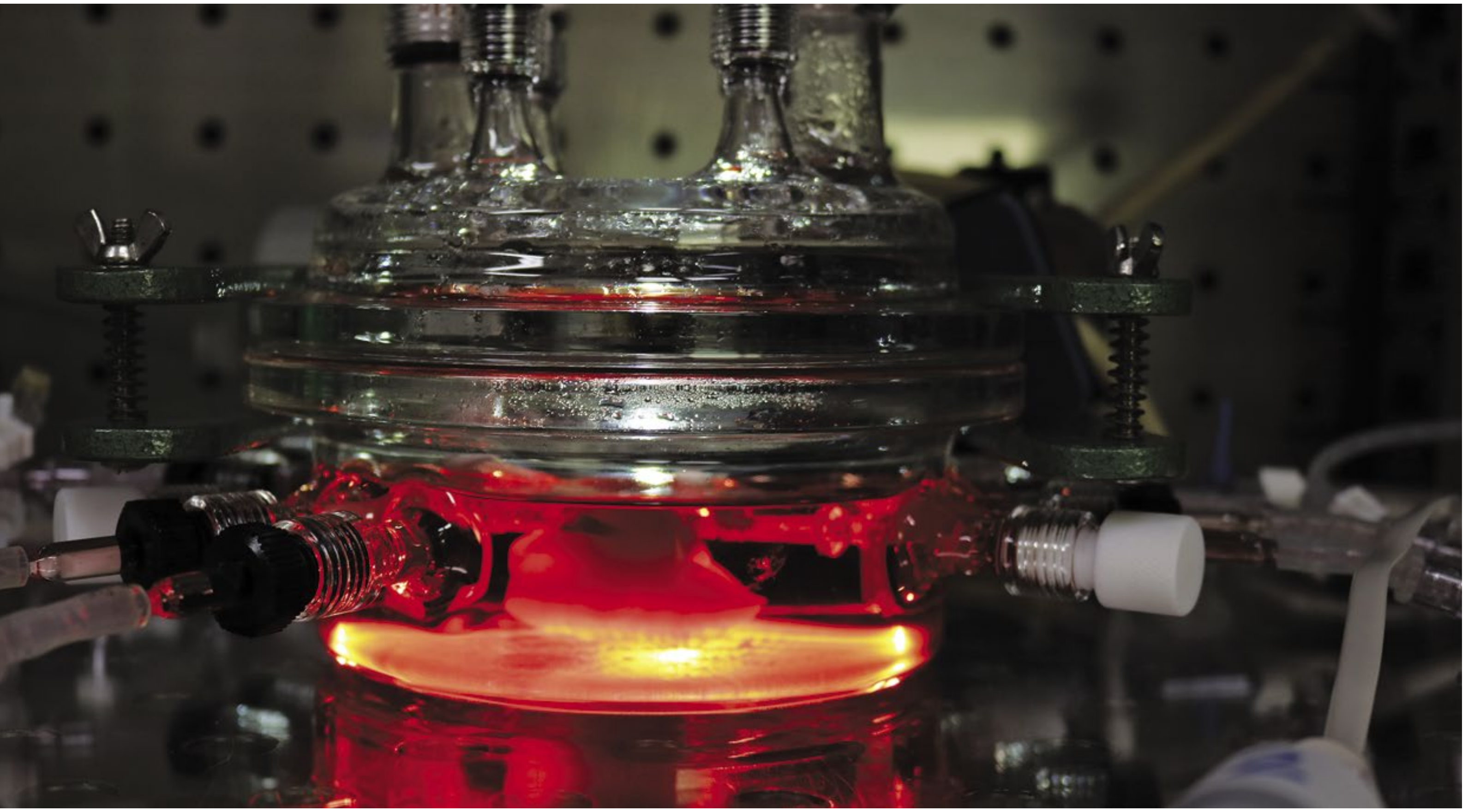


that could transport blood and self-heal after injury. The implants stimulated the recipients' cells to repopulate the vessels and take on all the characteristics expected of cells. They had, essentially, become the patients' own blood vessels.

"For me that's very exciting — we're starting off with a nonliving implant and turning it into living tissue," she said. "We think it's a reason why these vessels work better than synthetic ones, which never become the patient's own tissue, but remain a piece of plastic with a few scar cells on top."

The HAVs for dialysis patients are 42 centimeters long, 6 millimeters in diameter and strong enough to endure a strong tug. Once implanted, they function like arteries from the get-go, and can be repeatedly punctured with needles.

Starting more than six years ago, the researchers began implanting the HAVs in patients with end-stage kidney disease. These patients typically receive hemodialysis three times a week. The procedure, in which a machine cleanses the blood of waste, salts and other materials, is often administered through a graft made from a synthetic material such as Teflon. These grafts, implanted in the arm, carry a high risk of infection, clotting, and scarring so much that the vessel closes up. Up to 40 percent of these grafts fail within one year.

An Astounding Idea Becomes Reality

It was in the mid-1990s when Niklason decided that this was the field she would focus on.

"I wanted to do something interdisciplinary — medicine, engineering, and even some math, where I could combine what I knew about biology and the physical sciences," she said. "I also wanted to work in a field that was new, that wasn't densely populated by many investigators. And tissue engineering at the time certainly fit that bill!"

In fact, she got a lot of confused looks when she told people her plans.

"People laughed at me! They thought it was so funny that I was trying to grow arteries in jars."

Continued →

Top Left: *Engineered rat lung during culture, growing inside a bioreactor designed to mimic physiological conditions.* Top Middle: *Decellularized rat lung; the cells have been removed so what's left is just the extracellular matrix of the lung. This serves as the starting scaffold/platform for making engineered lungs.* Top Right: *A set of bioreactors, each culturing an engineered blood vessel.* Bottom: *Bioengineered human acellular vessels (HAVs) can be stored on a hospital shelf, available for patients in need.*

Illustration courtesy of Humacyte

More than 20 years later, the idea of engineering organs still astounds. But with a remarkable amount of progress, Niklason has brought this once far-fetched notion far along enough to give hope for many patients, including those with kidney failure, heart disease, or in need of certain organ transplants.

She came to Yale in 2006 and quickly gained a reputation as a valuable collaborator. Anjelica Gonzalez, an associate professor of biomedical engineering who also focuses on engineered tissue, said she was "awed and inspired" before meeting Niklason by her ability to apply engineering to advance medicine. Once they began working on various projects, Gonzalez said, she was even more impressed.

"As a mentor and collaborator, she is generous with her time, knowledge and resources," Gonzalez said. "This underscores the idea that she is intensely dedicated to the advancement of science to improve human health."

Niklason's work with engineered tissue began with blood vessels, and about 12 years ago she added engineered lungs to her research. Walking through her bustling laboratory in the Amistad Building on a Monday morning, she stops to point inside a bioreactor to show off an engineered vessel.

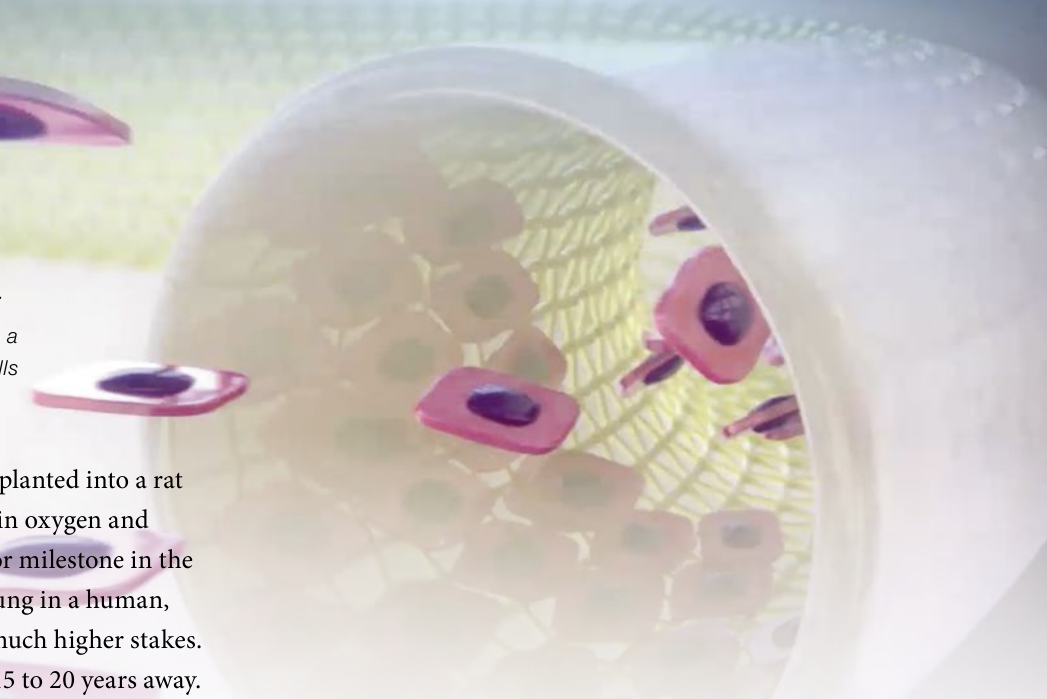
Above: *Niklason's lab transplanted into a rat an engineered lung that was able to take in oxygen and breathe out carbon dioxide.*

It sits on a rotating platform that allows it to achieve a gas exchange — essentially, to breathe.

A few aisles over, she points to another bioreactor, this one housing a set of rat lungs. Because a lung is a much more complicated tissue, it requires a much more complicated set-up. Numerous tubes run from the lungs to the machine, each facilitating a different function that a lung would naturally do on its own. There are pumps to control arterial perfusion and oxygenation, and one to essentially feed it and remove waste at the same time.

"It's our attempt at artificial homeostasis," said Micha Sam Raredon, a graduate student in Niklason's lab. "We're trying to control the whole milieu."

Both the lungs and the vessels rely on the use of donor cells to repopulate the tissue, but the key is getting the cells to act accordingly once they're there. In the case of lungs, that's particularly tricky. "It's not mature or functional now — that's what we're trying to get to," she said of the engineered lung. "It's living, but it's disorganized."

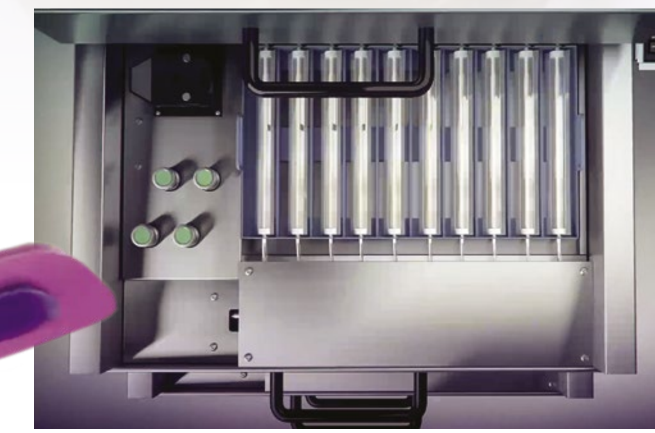


Top: *Smooth muscle cells are placed on a tubular scaffold to form a vessel.*

Bottom: *Vessels are grown and monitored in a bioreactor system for eight weeks until all cells are removed and ultimately form HAVs.*

In 2010, Niklason's lab successfully transplanted into a rat an engineered lung that was able to take in oxygen and breathe out carbon dioxide. It was a major milestone in the field. Getting a functioning engineered lung in a human, though, is complicated and comes with much higher stakes. Reaching that goal, she figures, is about 15 to 20 years away.

Off-the-shelf blood vessels, on the other hand, could be available in just a few years. "There's a lot of caveats and stuff that we can't control — how the trials turn out and what the FDA thinks, for instance — but we would hope to be on the market by 2021."



Illustrations courtesy of Humacyte

How They Work

Years ago, Niklason had originally conceived the HAVs for use in heart bypass procedures. But she also considered the realities of the FDA approval process, and the clinical trials required for such a high-risk procedure as a heart bypass — as if growing brand new tissues in the lab wasn't already fraught with its own complications. Instead, they decided to concentrate on using them for grafts for dialysis patients — a direction with lower patient risk, and one that would allow them to move forward quicker. "It was a way that we could study these things safely but also in a way that had a big potential for benefit."

The HAVs are formed by placing human donor cells from smooth muscle tissue onto a tubular scaffold. They remain in a bioreactor for eight weeks, growing *in vitro* into an extracellular matrix, which is the structural support for the cells. All cells are then removed and the structures are cleansed of anything that could trigger an immune response. What's left are mechanically robust, rope-like structures made from collagen and 40 to 50 other proteins in the matrix, a makeup that's pretty consistent among humans — that's key to why the patients' bodies accept the vessels.

"We use someone else's cells to make this great matrix and then take the cells away and implant that into the patient," she said. "The patient doesn't know it's not him, so his cells repopulate that tissue.

In some ways, it's like tricking the new cells into believing that this has always been their home.

"I think of the extracellular matrix being the apartment building, and this apartment building has the right ceilings and wall color, so that when cells crawl in, they say 'OK, this is a blood vessel — I'm supposed to behave like a blood vessel cell.'"

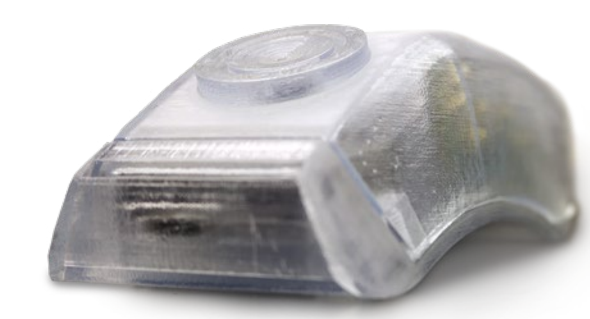
Niklason's company Humacyte is currently finishing up a Phase 3 trial, which compares the HAVs to synthetic grafts. The researchers are also enrolling for a second Phase 3 trial in which the HAVs will be compared to arteriovenous fistulas, another procedure used for dialysis in which an artery is connected to a vein.

What You're Breathing, Right Now

You encounter many types of air over the day. This technology tells you everything about it

Yale

SUSTAINABILITY



Perhaps you're aware of the air quality right outside your home. But that's one data point. What's the air inside your home when you wake up? Or on the mornings when you burn your toast? Perhaps you took a side street on the way to work, instead of the usual main road — how does that change things?

These are the microenvironments you encounter throughout the day. Getting a clear account of the quality of all these microenvironments — from one room to the next — would give us a much more thorough look at the air we're each breathing from day to day, even hour to hour.

Drew Gentner, associate professor of chemical & environmental engineering and forestry & environmental studies, is currently at work on that now with a study that looks at the interiors of homes, workplaces, and vehicles, and out on the streets of Baltimore, Md. In collaboration with researchers at Johns Hopkins University, his lab has set up a stationary air quality monitoring network that will measure more than 50 sites throughout the city, and enlisted 100 people for the study to wear portable air monitors, each for several days.

Continued →

"On any given day, a person is going to different locations — in your home, your car, your office, and different shops," Gentner said. "Outside of the scientific goals of understanding the spatial temporal heterogeneity of exposure to air pollutants, we want to provide people the tools they need to make informed decisions and better personal choices. That's one of the things we're interested in: How do people's personal choices affect air pollution?"

Below: *By deploying both wearable and stationary air sensors, Gentner hopes to learn how the data collected differs from one another. The sensors can detect matter as small as 2.5 micrometers in diameter — the size determined to pose serious health effects.*

Larger cities often have a few stationary sensors to collect air quality data. Gentner's project, though, will provide something much more thorough than the single-point measurements that make up many air reports. It's an idea that technology has caught up with, as the cost of making sensors has decreased even as they become more accurate. The project is part of the Solutions for Energy, Air, Climate, and Health (SEARCH) Center, created by the U.S. Environmental Protection Agency (EPA) with a five-year, $10 million grant. Only one of three centers funded by the EPA, it's designed to study the relationships between air quality, energy policy, climate change, and public health. Michelle

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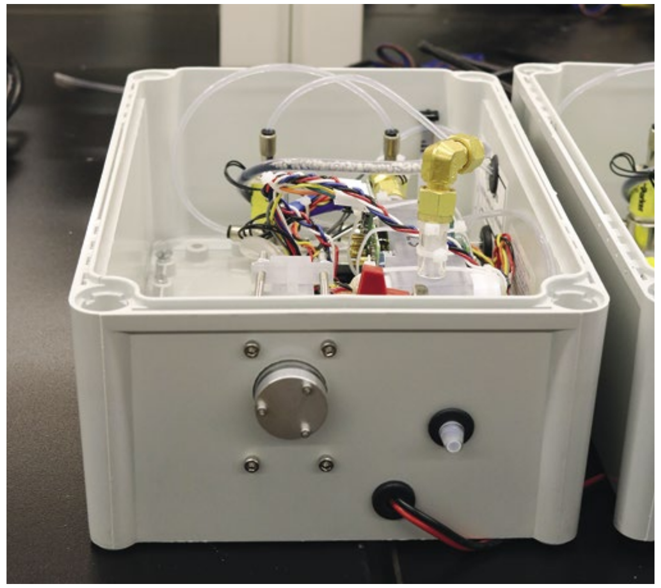
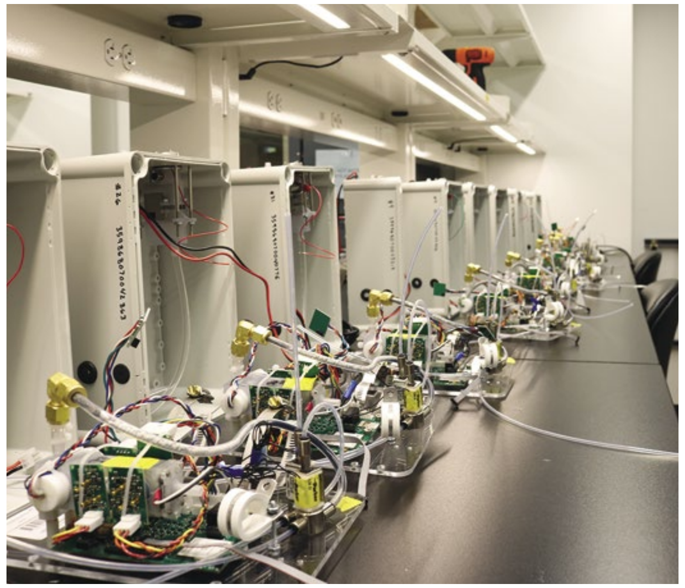
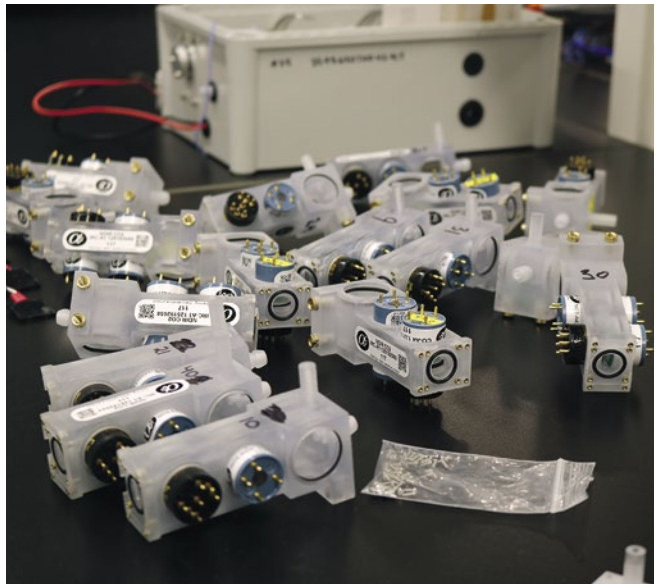
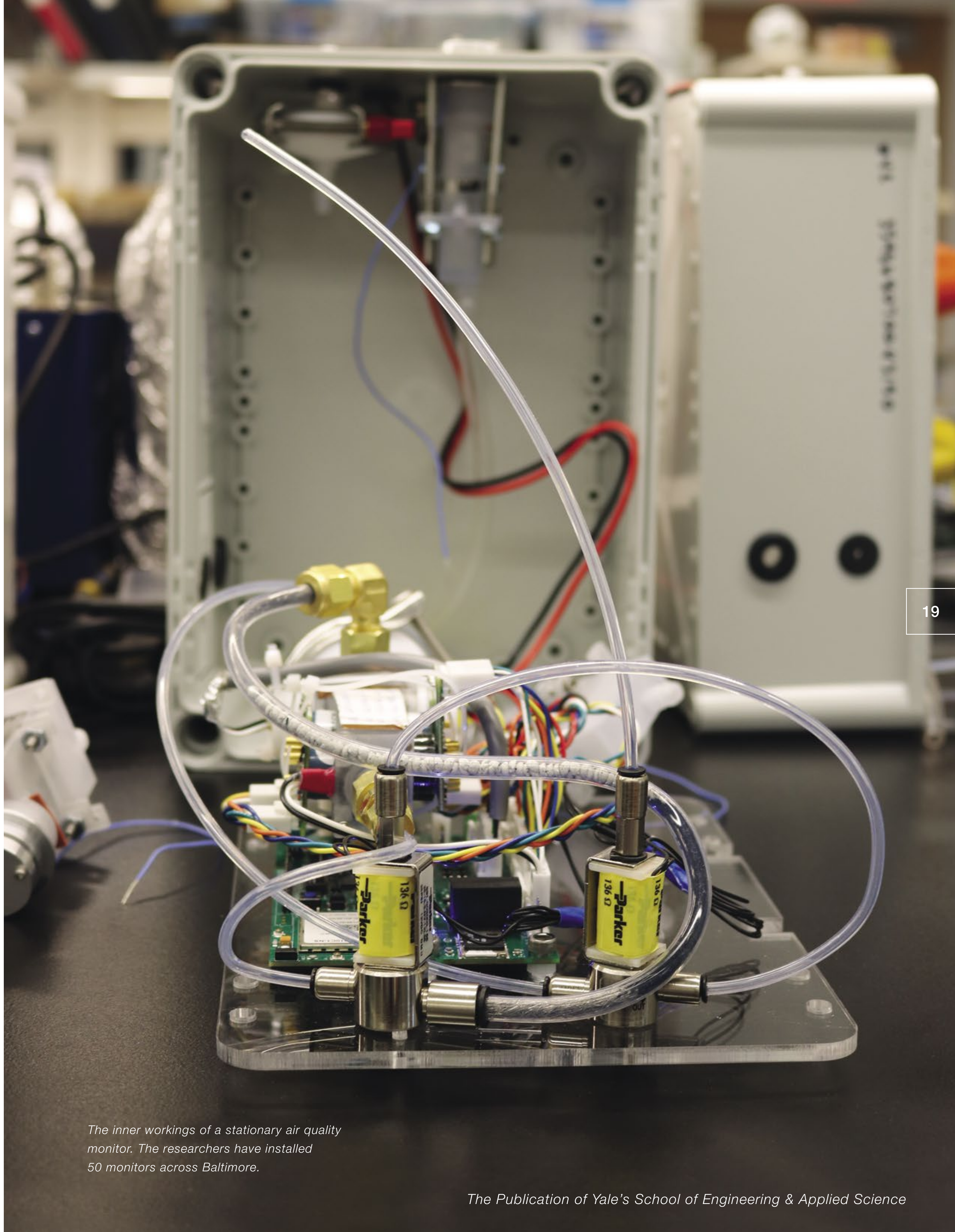








The inner workings of a stationary air quality monitor. The researchers have installed 50 monitors across Baltimore.

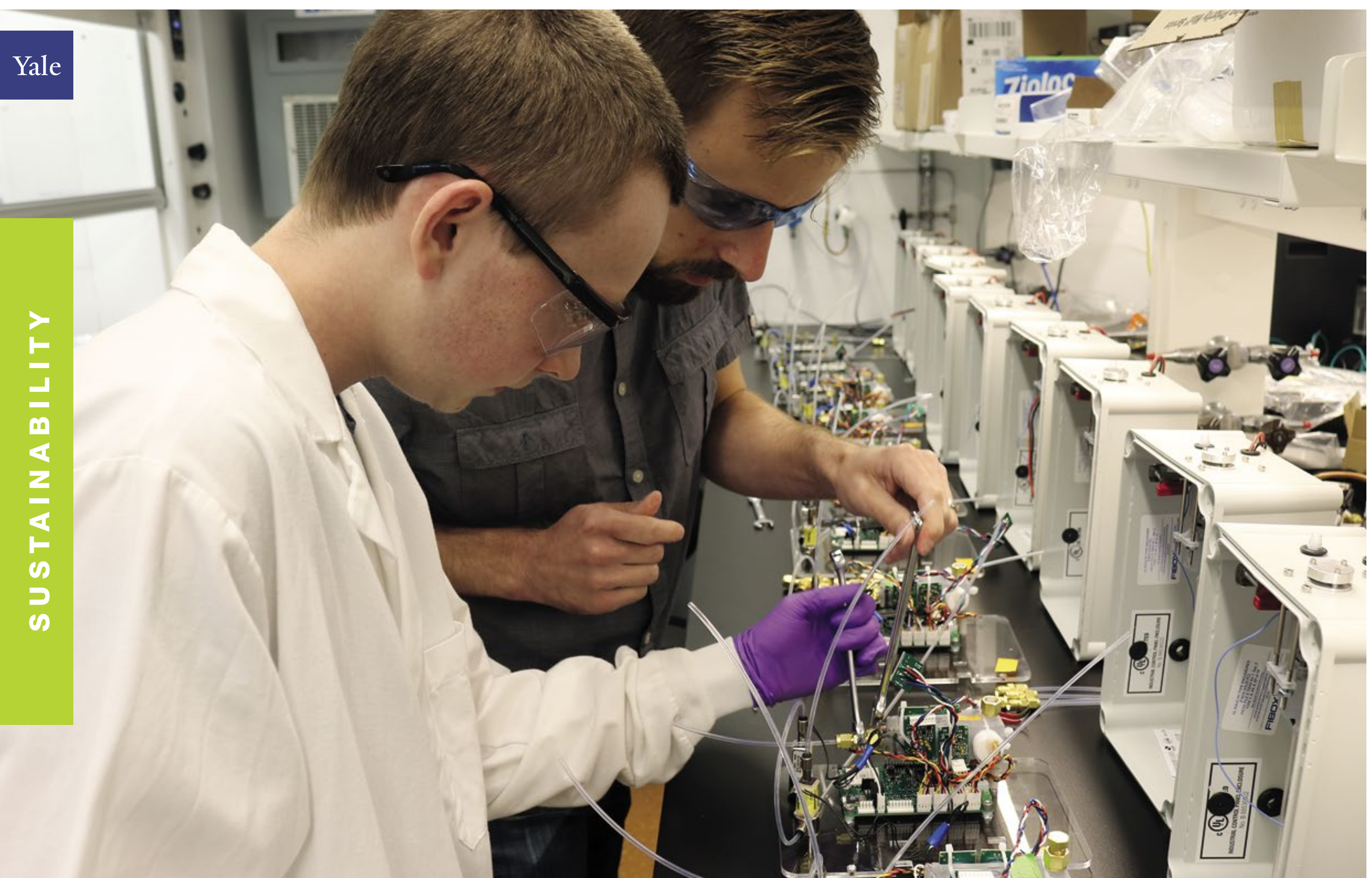
Bell, the Mary E. Pinchot Professor of Environmental Health at the Yale School of Forestry & Environmental Studies and Chemical & Environmental Engineering, serves as the director of the multidisciplinary research center. Yale, Johns Hopkins University and other institutions serve as partners.

One thing the researchers are particularly interested to see is how the data collected by the wearable air sensors differs from the stationary ones placed throughout the city. Two people could live in the same apartment building and work in the same office building, but the air they breathe could be very different depending in part on how they get to work, whether it's by car, bicycle or walking. Baltimore has a program that allows residents to share city-owned scooters; Gentner's lab hopes that some of study's volunteers will take part in it — that's one more data point.

"I think the person-to-person variations are going to be pretty fascinating," Gentner said, adding that this is especially true for indoor environments. "We've done all sorts of tests and regulations on outdoor air pollution for years, and that's brought down particle concentration outdoors. One thing that's outside these regulations has been indoor air quality. No matter how well we do things outside, concentrations indoors could be higher by orders of magnitude."

On average, people spend about 80% of their time indoors, and everything from the aerosol from cooked food to the emissions from a stove plays a role in the air quality.

Below: *Gentner and a student researcher put the finishing touches on a stationary air sensor.*



Above: *Only the finest air quality for Handsome Dan, as he models the newest air sensor prototype.*

Things as simple as being aware of how long your stove is on, or opening the windows more can make a big difference. Getting the right ventilation your home, he said, is among the most significant changes people can make to improve indoor air quality.

Gentner began working on the sensors a few years ago, when his lab and a group of undergraduate students developed the first prototypes. Developing a new technology is rarely a quick or easy process. The study requires that the monitors they developed are sensitive enough to detect such gases as carbon monoxide and nitrogen dioxide, as well as dust, soot, and any other microscopic elements that make up the atmosphere's particulate matter. Specifically, they want them to be able to detect matter as small as 2.5 micrometers in diameter — about 30 times smaller than the diameter of the average human hair, and the size that's been determined to pose particularly serious health effects.

On top of that, they also had to make the portable sensors comfortable enough for users to wear. Colby Buehler, a graduate student in Gentner's lab, has been working on the EPA project since he came to Yale a little over a year ago. He notes that it has involved building several prototypes before reaching the current solutions. One company, for instance, stopped manufacturing a sensor, so the lab had to adjust to changes in the available components.

"There's a lot of troubleshooting and testing because the sensor industry is developing so rapidly and quality control needs to be high," Buehler said, pointing to several sensors on a counter in Gentner's lab, several with notes taped to them identifying monitors at various stages in the quality control process.

The portable sensors are a little larger than a mobile phone and are attached to a battery that can be stored in a regular bag, purse, or backpack. The shoulder mounted system is fairly light, but the subjects each wear them for all their waking hours four days in a row (while sleeping, the sensors stay in the room with them), so they need to be as easy to wear as possible.

"It's gone through a couple design changes," Buehler said. "We looked at other wearable technologies as models, and we knew we wanted something that wouldn't need its own backpack" — which has been a complaint about past personal exposure monitoring studies that the Yale team sought to overcome.

They knew that it should be mounted to the shoulder to get the sensors close to the user's breathing zone and accurate data of their personal

Continued →

exposure, but designing something to comfortably fit took some careful engineering design. Eventually, they settled on a form-fitting design with a customizable attachment system, which did the trick. There were also some valuable feedback from early testers, so Buehler and the team readjusted the design to make a more user-friendly product.

Misti Zamora, a postdoctoral fellow at Johns Hopkins, has been busy finding places for the stationary sensors and volunteers for the portable ones.

"We spent a lot of time finding good sites — some at libraries, some at people's homes and some at parks and things like that," said Zamora, who works in the lab of Kirstin Koehler, an associate professor in the Johns Hopkins Bloomberg School of Public Health. "We've been working a lot with the communities because they're letting us host them in their areas — they obviously have an interest about air quality in their neighborhoods."

Zamora noted that Baltimore is a good city for this kind of study. It has a diverse population and geography, and like a lot of cities, has its share of air quality issues. She often wonders herself about the quality of her own microenvironments throughout the day.

"From where I work, it's three-quarters of a mile away, and I think about what that means as to my actual exposure,

especially since I go outside a lot," she said. "But let's say you don't go outside much — you stay inside and play computer games all day. How much outdoor air are you actually breathing? This study will give us a lot of insight into personal exposures vs. regional exposures — both of which are important for different reasons. And we can look at these and compare them side-by-side."

It's an issue that a lot of people wonder about, apparently. Not only have communities been helpful in hosting the stationary sensors in their neighborhood, the researchers even had to turn away people volunteering to wear the personal sensors due to an excess of sign-ups.

Left & Middle: *The stationary sensors are placed both indoors and outdoors to understand the quality of the diverse microenvironments people experience throughout the day.*

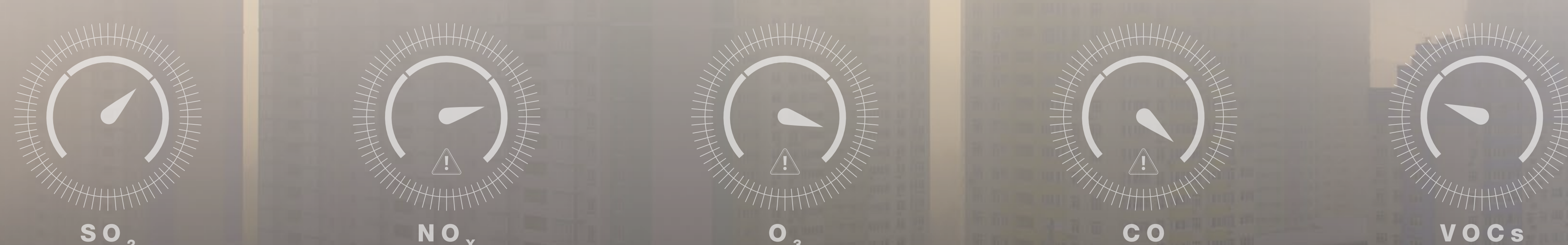
Right: *Colby Beuhler, a graduate student in Gentner's lab, prepares to install a stationary monitor.*

"I've been kind of surprised at how excited people are about this, I thought it was going to be hard to find people to host these things for us, but now we have more than we need," she said. "I sometimes think that we just do our science and people aren't as excited about it as we are, but really, they are."

Users of the technology are limited to those enlisted in the study, but it could become more widely available. Gentner's work on this air pollution monitoring technology includes a partnership with HKF Technology, a Delaware-based company developing technology for improving air quality. Ken Hu, CEO of the company, is working with Yale and Gentner on commercializing the technology – potentially allowing consumers to determine the air quality of their own microenvironments.

This, Gentner said, could empower people to take it on themselves to improve the air that they breathe each day.

"We can't regulate every microenvironment, and agencies can't regulate people's exposure to air pollution in their homes beyond certain guidelines," he said. "But people can take measures to reduce that exposure by making better choices."



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Bringing Computer Education Up to Code

With help from Code Haven, New Haven's middle schoolers catch the computing bug

Inside the gymnasium of Bishop Woods Architecture & Design Magnet School in New Haven, about 150 students are showing off the results of months of computer programming work. It's the last big event of Code Haven, an ongoing alliance between Yale undergraduate students and the New Haven Public Schools.

In addition to Bishop Woods, the students here are representing East Rock, Celentano, Lincoln Basset, Fair Haven, and Wexler Grant. Among the presenters are 6th graders Lana Almalek and Taniya Armstrong, who have developed a mobile phone app that allows them to draw over photos.

"We did this because we both like drawing and sketching," said Lana. "It was a lot harder than we thought it would be." She wants to be a doctor, while Taniya has her sights set on becoming a veterinarian. They both expect, though, to continue working with computers.

Now in its fourth year, Code Haven has helped spread an enthusiasm for computers to more than 200 students at multiple New Haven middle schools. About half of those students had no computer science experience prior to Code Haven. Every week during the school year, Yale students go to schools in the New Haven district to teach computing. Online lessons, group activities, and class-wide demonstrations are all part of the lessons.

Code Haven is driven by the philosophy that all students should have access to computer science lessons. While many middle schools in New Haven lack computer science programs, the abundance of knowledge and resources at Yale can go a long way to make up for that.

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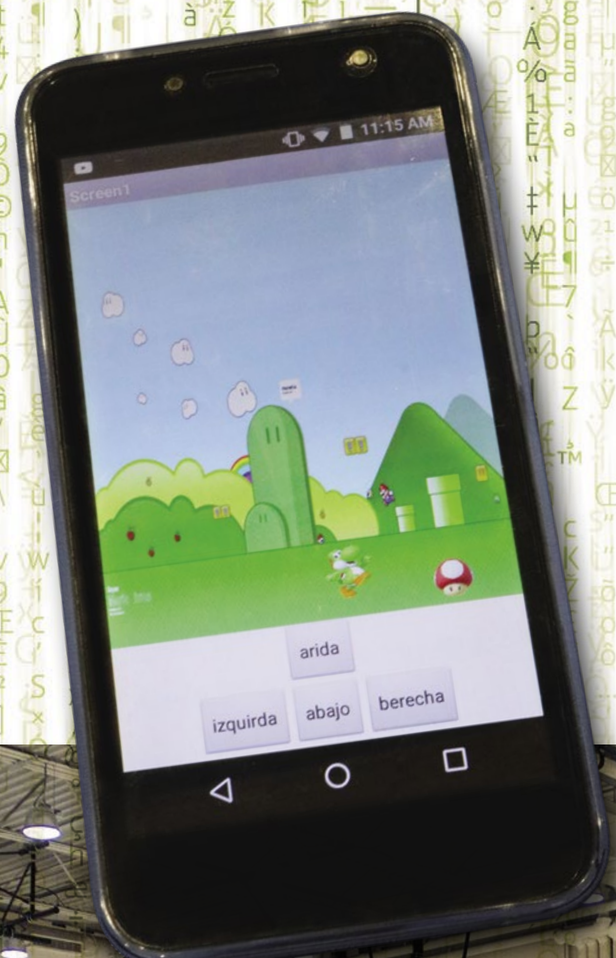

The large majority of the middle school students are from groups that are traditionally underrepresented in computer science, such as Latinos and African Americans. Code Haven is designed to correct this.

“Right now we have a system where people are not equally exposed to computer science at a young age, and that creates a lack of diversity in computer science in high school, college, and industry,” said Daniel Urke ’21, who is co-president of Code Haven with Stephanie Bang ’21.

Code Haven was founded in Fall 2016 after a conversation between Nathaniel Granor ’09 and David Weinreb, a teacher in New Haven Public Schools. They met at the Yale School of Management Education Leadership Conference. Granor attended as a representative for TEALS, an educational program of Microsoft that promotes computer science at the high school level. The two began talking about the lack of computer science education at the middle school level and saw an opportunity for a group like Code Haven. Granor talked to Computer Science Professor Dana Angluin about the idea, and she contacted Annie Chen ’19 and Dennis Duan ’19 to lead the charge as its first co-presidents.

A pilot semester was launched in Weinreb’s sixth grade classroom at Fair Haven School, with 18 students and 16 mentors. Since then, Code Haven students have made more than 120 apps in 13 classrooms.

For the first half of the year, the students learn the fundamentals of computer science. The lessons are basic enough that even undergraduate students who don’t major in Computer Science can teach them.

“One of the things we talked about when we were recruiting people to be part of Code Haven is that you don’t need to be an expert in computer science because we teach fundamental topics,” Bang said. “One thing that’s exciting about the program is that it could be anyone teaching, as long as they have the basics.”

Students enrolled in Code Haven go during the school day. Code Haven mentors say that’s critical to eliminating the self-selection bias that’s prominent in computer science — that is, students who choose not to pursue it because they don’t think they’re cut out for it.

Continued →

Yale

EDUCATION

After only four years, Code Haven has reached more than 200 students at multiple New Haven Public Schools. About half of those students had no prior computer science experience.

"Our mission is very much centered around inclusion and increasing access to computer science," Urke said. "We don't think you can do that in an extracurricular setting. It's key that it's not seen as something like an advanced math program."

For the second half of the year, the students work on building apps on Android phones (Code Haven recently received a grant from Google IgniteCS to purchase new ones for the students to use).

"We give them one of three variants and when they finish that, they're able to expand on that with their own ideas," Bang said. One app features the Mario Brothers chasing mushrooms, and the students can add more levels and more sprites to chase. A second app is illustration-based. The third is a "fortune cookie app,"—kind of like 8-ball on the iPhone, where you press a button and get a random fortune.

All of the apps are designed to give enough direction for beginning programmers, but allow enough creative freedom for the students to make it their own.

"It was easy at first, but got harder as we went along," said Brain Kelson, a sixth grader presenting his app at the Project Fair. He and his teammates chose to make a Mario app.

Beyond developing specific apps, the students learned the broader benefits of programming.

"Being in Code Haven helps me learn about technology and how it can make the future better," said fifth grader Luis Adoniz Perez.

Computer skills are only part of the lessons that are being learned. Bang and Urke noted that soft skills such as working collaboratively are emphasized. Code Haven also holds a TeachTech conference every year for teachers from kindergarten to eighth grade. There, they offer guidelines on how to implement computer science lessons into the classroom. Other events include Demo Day, in which Yale Computer Science students speak about projects they're working on and answer questions from the students. For Urke and Bang, though, working directly with the students is the heart of Code Haven.

"My favorite part of Code Haven is going into class," Urke said. "It's tiring because they're middle school students, and they're high-energy, but it's very rewarding."

Weinreb said the time his students have with Code Haven has given them a new perspective on what's possible.

"By introducing them to a group of Yale undergraduate students who become their friends over the course of a year, computer science becomes a lot more real," he said. "These people materialize as role models and the students can visualize what it would be like for them to become computer scientists in the future."

Weinreb, whose students are mostly Hispanic, said work with Code Haven counteracts many of the factors that could steer students away from considering a career in computers.

"The research substantiates that we are advertising computer science and robotics more to boys than girls, and also more to white people than to people of color," he said.

"We have to show them that this can be for them, even if they don't know people who do it, and even if they don't yet have role models in their lives who work in computer science and understand information science."

Granor noted that middle school is a great time for the students to catch the computer science bug.

"That's when you're starting to branch out into more distinct subjects but schedule-wise, there's more flexibility than in high school," he said. "Getting that first exposure in middle school means they may now be more interested and prepared to take on whatever programs that do exist at the high school level."

Sixth grade teacher Amy Binkowski said Code Haven's been a big hit with her students.

"They were excited when I told them about it," she said. "And now they enjoy working with the Yale students. At the start of the day, they'll ask me 'Do we have Code Haven today?'"

Chipping Away at Complex Diseases

Tiny devices replicate illnesses, provide hope for better treatment

As traditional methods of studying life forms reach their limits, researchers seek out new ways to observe and interact with their subjects. For many, the so-called "lab-on-a-chip" model has shown a great deal of promise. These devices draw as much from engineering as from biology as they simulate living microenvironments on a chip. They don't require the invasive methods that *in vivo* models do, and unlike animal models, the devices allow researchers to observe human physiology directly.

More than simply putting cells in a petri dish and observing them, the "lab-on-a-chip" devices recreate the living environments of these cells' homes, providing a much fuller and accurate picture for researchers. In the lab of Rong Fan, associate professor of biomedical engineering, they've recreated the environment of brain tumor cells on a chip.

In his lab, Andre Levchenko, the John C. Malone Professor of Biomedical Engineering, developed a chip that allows researchers to explore the kinds of microenvironments that can lead to asthma.

In both devices, the researchers are advancing our knowledge of these diseases — and potentially ways to treat them — in ways once unimaginable.

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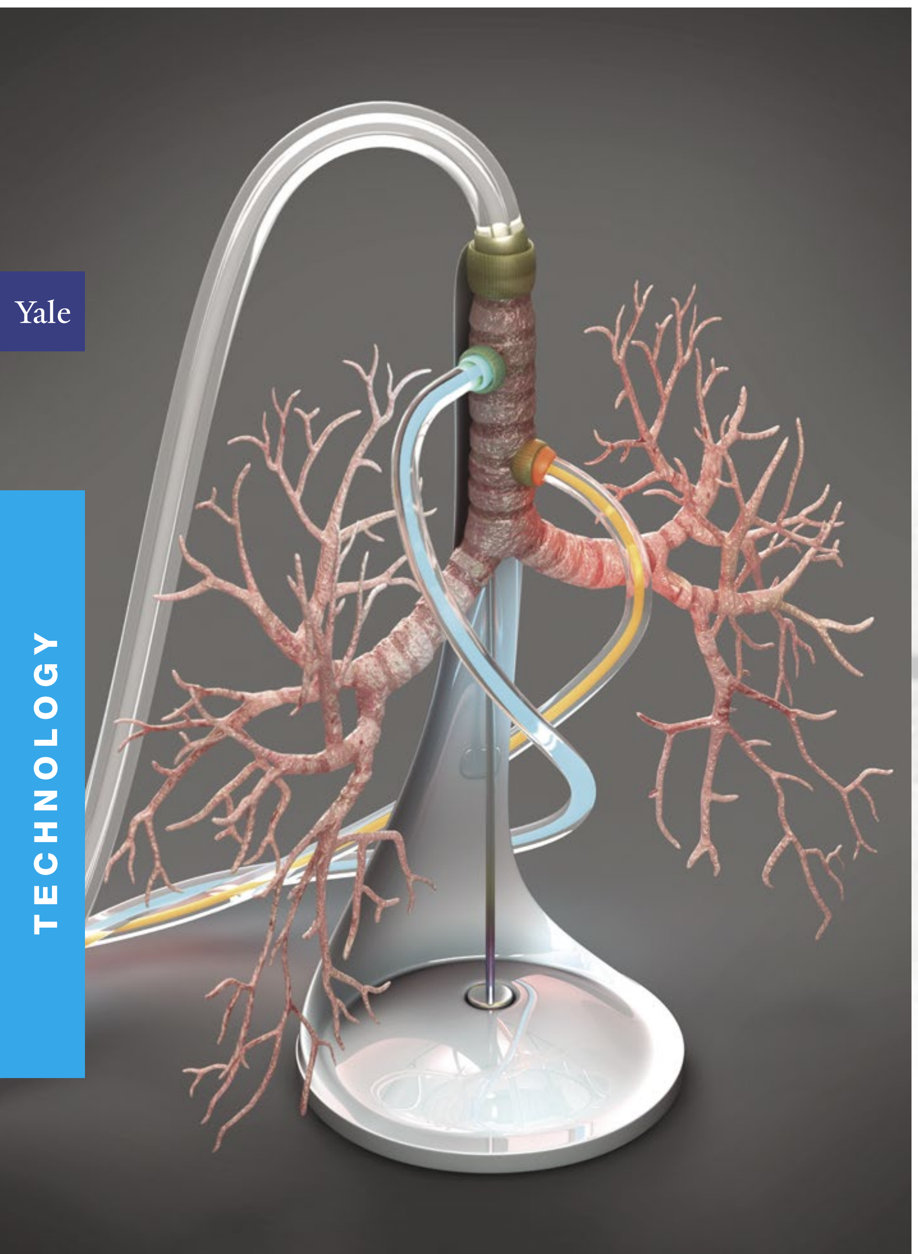
Asthma-on-a-Chip

Asthma, a condition that affects one in 13 people, can be very dangerous to those who suffer from it. But its exact causes aren't clear. Thanks to a chip-sized device that can "breathe," "cough" and otherwise mimic the human respiratory system, though, researchers have more answers about the condition.

The device, informally known as "asthma-on-a-chip," was developed in the lab of Andre Levchenko. The goal, Levchenko said, is to see what happens in the immediate event of a bronchial spasm, when the bronchi — the main passageway into the lungs — constrict. It's something that can happen to healthy people in certain cases, such as long-distance running, making it hard to breathe for a short time. When this happens over a prolonged period, an all-too-common occurrence for asthmatics, though, it can be much more severe.



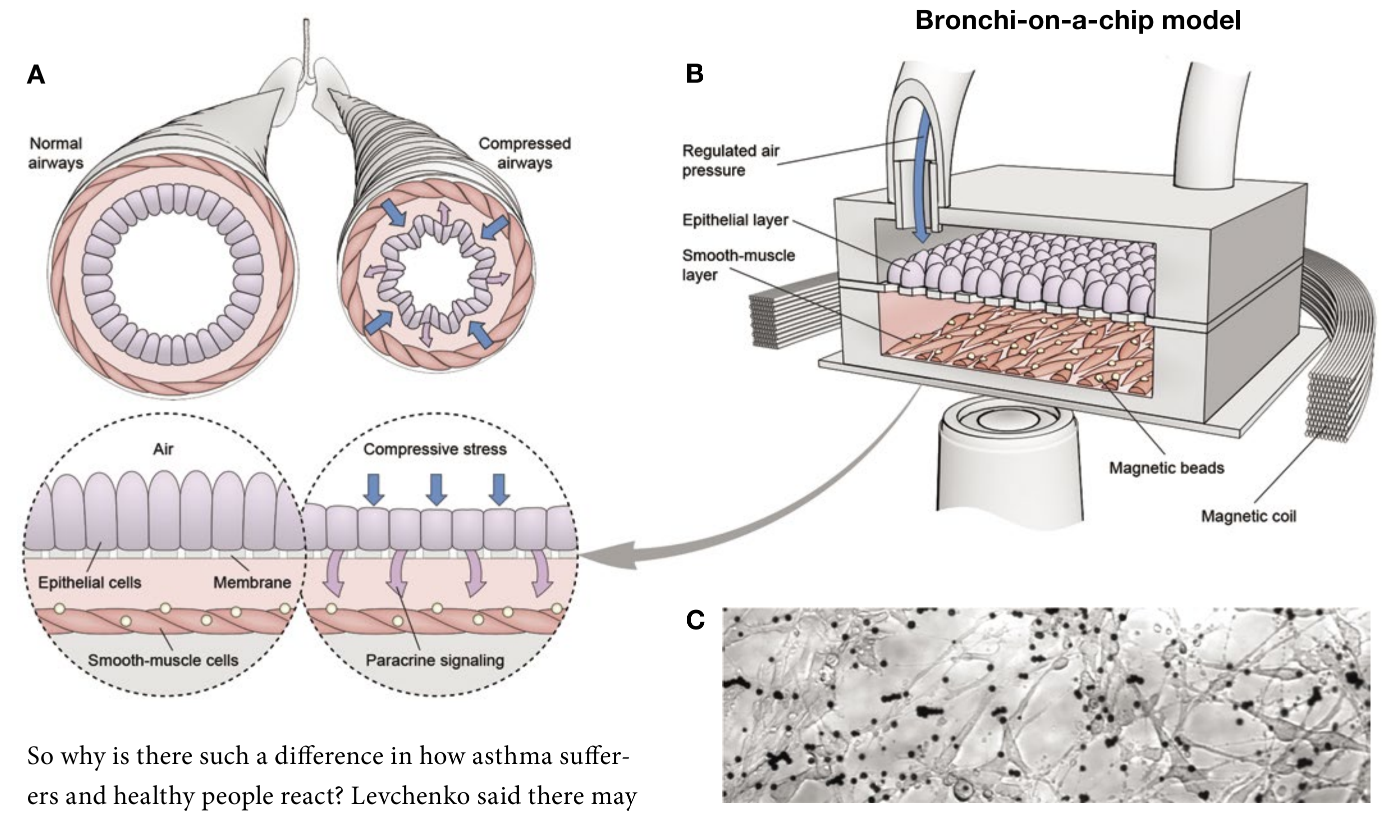
"What we did was to build the platform to investigate the interactions between the two main cell types in those airwaves," said Levchenko, who is also director of the Yale Systems Biology Institute at Yale's West Campus. "We wanted to mimic what happens in the lungs in a way that we can study."

These two types are the epithelial cells that line the outer surface of the lung, and the smooth muscle cells, which wrap in strings around the network of tubes — the bronchial airways — that deliver air into our lungs. Like any muscle in the body, smooth muscle can suddenly contract and lead to difficulties in breathing. In the worst cases, it can cause death by asphyxiation. As far as anyone can tell, the smooth muscle cells in the bronchi don't do us much good. They may have once had their purpose, but they're now considered atavistic leftovers from our evolutionary past. Because of the serious medical problems they can cause, they're sometimes referred to as "the appendix of the lungs."

A bronchial spasm can be triggered by a number of factors, including allergens such as dust, cold air, exercise, hormonal levels, infections, smoke, and aspirin. In non-asthmatic people, the airways reopen soon after the trigger has been removed. Among asthmatics, however, bronchospasm and other difficulties in breathing can last a long time, even after the triggers are removed. In fact, an attack can go on for hours and even days.

Yale

TECHNOLOGY



Above: *(A) Contraction of the smooth muscle leads to mechanical stress in the airway epithelium. (B) To analyze the interaction, researchers developed a bronchial-chip platform. The researchers apply stress and measure the resulting changes in the mechanical properties. (C) Human airway smooth-muscle cell layer with magnetic beads.*

So why is there such a difference in how asthma sufferers and healthy people react? Levchenko said there may be a genetic basis, but that researchers haven't found any mechanisms that prove this. Allergens and various environmental factors also likely play an important role, but exactly what that role is has been tough to crack.

"There's also a lot of evidence that the overactive immune response and inflammation may be all part of this," Levchenko said. "So it's a very complex disease that we don't completely understand at this point."

Part of the problem is that these interactions are both mechanical and chemical and happen between different cell types. So studying the cells in their natural environment is tricky.

"This makes it difficult to control experimental conditions in these systems, such as quantitatively evaluating mechanical responses of cells or isolating cellular secretions," says Onur Kilic, who was first author of the study while a postdoctoral fellow at Johns Hopkins.

So the researchers tried a different tack.

"We built this rather interesting, unique device that turns out to be very easy to use but quite sophisticated," Levchenko said. "We wanted to mimic what happens in the bronchi and lungs in a way that we can study. The advantage to using this is we can see how the cell types interact and how stimulating the epithelial cells and the smooth muscle cells could trigger some interesting interactions between them."

The silicone-polymer microdevice is lined with bronchial airway cells from asthmatic and non-asthmatic lung donors. The device is able to "breathe" air in and out, even simulate a cough, and undergo a process similar to a bronchial spasm. With the chip, the researchers can measure the liquid between the smooth muscle and the epithelial lining cells, allowing them to discover new things that lead to inflammation.

"It's very, very close to what you have in an actual human airway," Levchenko said. "We have a way to measure very precisely how soft or stiff the cells may become as a result of the muscle contraction. And we can analyze what chemicals are secreted by the epithelial cells so we have a very good handle on the chemical and mechanical aspects of it."

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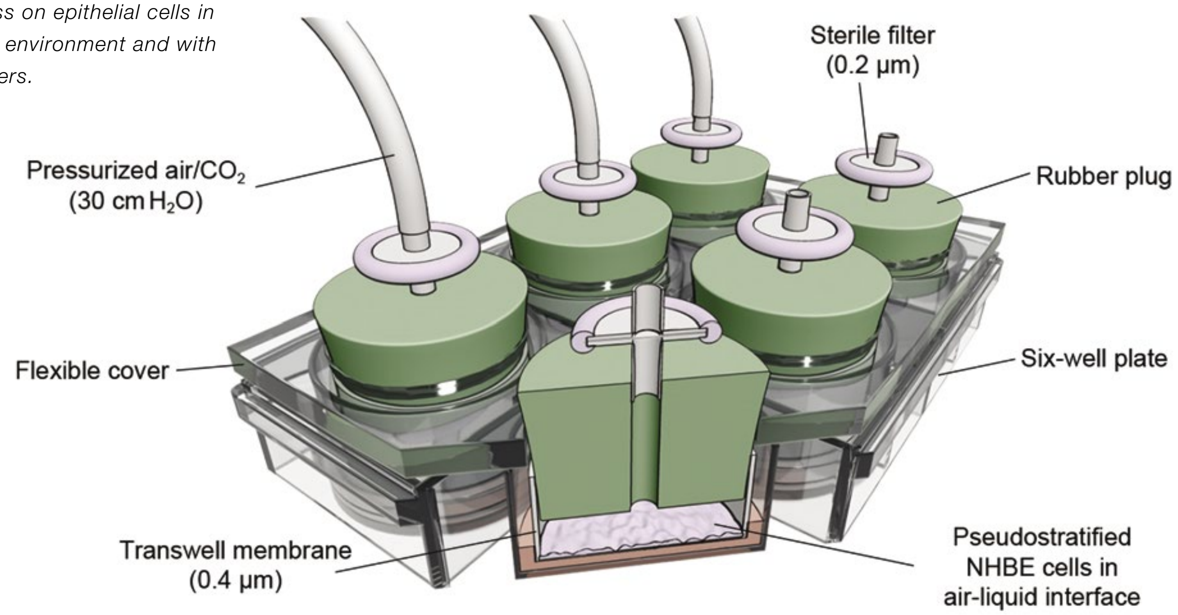
Compressive stress application

The novel device analyzes the effects of compressive stress on epithelial cells in a more controlled environment and with greater cell numbers.



It took little time for the device to upend some long-standing ideas about asthma.

"We saw dramatic differences from traditional concepts," said co-author Reynold A. Panettieri Jr, MD, director of the Rutgers Institute for Translational Medicine and Science. "For example, we thought calcium was so important to the shortening of the muscle, but you can actually get shortening without calcium going up. That's a paradigm shift, and it could lead to a new approach for therapy."

Co-author Stephen Liggett at the University of South Florida has been studying asthma for 30 years, and noted that the field has a long way to go in terms of developing new drugs.

"My feeling is that one reason we've had a lot of trouble is we don't have a lot of models to work with," said Liggett, professor of internal medicine, molecular pharmacology & physiology. "A lot of the animal models turned out not to be predictive — because mice aren't humans. Our device has human airway epithelial cells and human airway muscle cells, so that gets us into the human realm. We can apply pressure to the synthetic airway, which is what normally happens when you breathe while there's an airway obstruction, so that adds even more physiological components to it."

The tiny device yielded a number of surprising insights. When smoke or other triggers cause the smooth muscle cells to constrict, that mechanical stress can lead to the secretion of hormone-like compounds known as prostaglandins. The researchers found that prostaglandins eventually reached the smooth muscle cells and chemically stimulated them to cause further contraction — all of which creates a mechanical-chemical feedback loop between the two types of cells. Furthermore, there was another, delayed negative feedback driving the ultimate smooth muscle cell relation.

Among the cells from healthy people, the constriction is short-lived, as the positive feedback is not very strong and negative feedback can quickly take over, so the contracted smooth muscle quickly relaxes. The synthetic airways with asthmatic cells, though, told a very different story. Here, the smooth muscle is hyperresponsive, so it responds quicker and more severely to triggers, leading to a much stronger positive feedback. In moderate cases, this just means that it takes longer for the negative feedback to relax the airways. In severe cases, however, the smooth muscle contracts so strongly that the initial positive feedback loop is enough to keep it obstructed even when the negative feedback loop is activated. So when smoke, allergens or other triggers are cleared, severe asthma sufferers often still can't find relief.

"For healthy people, there might be shortness of breath, but it usually passes without long-term effects," Levchenko said. "But for asthma patients, what we see is that the same stimulation can lead to the closing of this feedback and a strong mutual attraction between the cells, and ultimately, a very strong constriction."

The researchers say their next step is to use the device to discover new drugs for asthma.

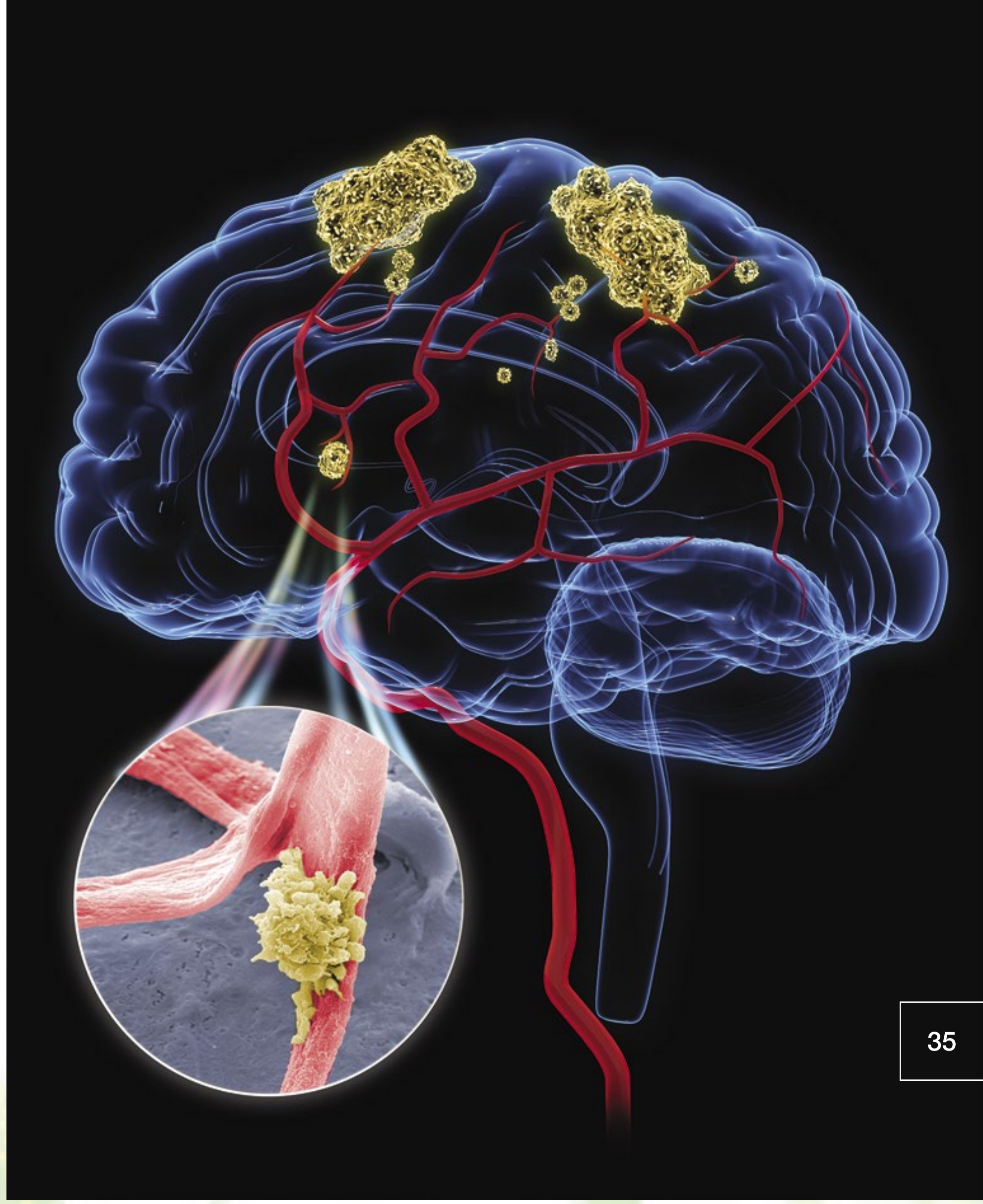
"Here we have basically limitless opportunities since these studies are done in a model less than a hair's thickness, so we can do lots of screenings with compounds to find the ones that could be the newest therapies," Panettieri said.

Liggett, who has mild asthma and understands what it's like to wake up in the middle of the night with an asthma attack, believes this work could lead to a much-needed breakthrough for asthma sufferers.

"I think we're right at the cusp of the whole field moving forward," he said. "And we need some ways to examine our hypotheses in ways that we haven't really had before. I have a lot of optimism that there will be new treatments that we had never considered before that can come from this."

Tumor-on-a-Chip

The ability to study in living patients the behavior of brain tumor cells in their natural environment would give valuable insight into the nature of glioblastoma, one of the most common types of brain cancers and among the biggest challenges for researchers to study.



Above: *Rong Fan has replicated brain tumor cells on a chip, the first of its kind.*

"But obviously, you can't open a patient's brain to see what the live tumor cells are doing to understand the mechanism of disease," said Rong Fan. What Fan's laboratory has done instead, though, is to model the cells' environment on a chip so that they can study them *ex vivo* — that is, outside the body but still operating in the surroundings similar as the *in vivo* environments in patients. Fan and his research team published their findings (and made the cover of the issue) in *Advanced Science.*

"This is really the first demonstration of *ex vivo* tumor cell behavior interrogation on an organ-on-a-chip device," Fan said. "This means we can do an *ex vivo* interrogation of tumor cell behaviors and see it in this kind of microenvironment which is what makes the patient's brain tumors."

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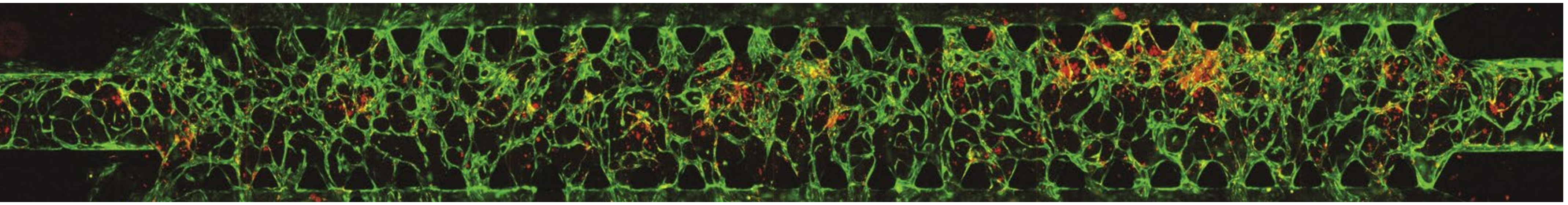
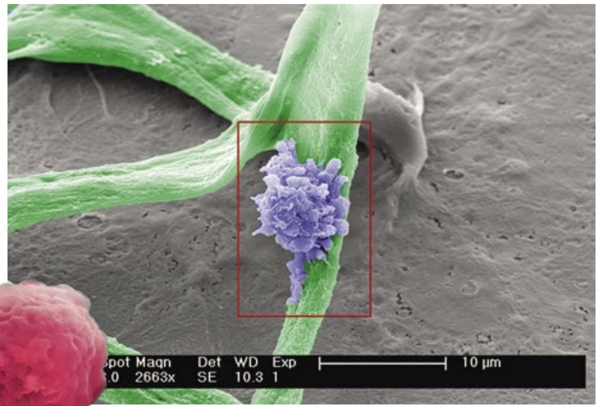
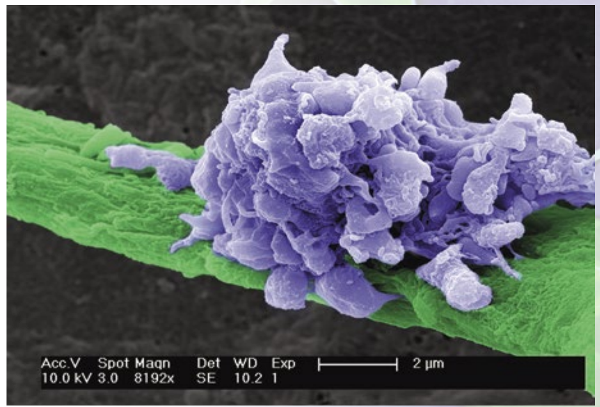


Left: *Chip scan showing microvascular formation and loading of a single stem-like cell from a brain tumor.*

Below: *SEM images of a stem-like cell from a patient-derived brain tumor attached to the vessel wall.*





This device provides the cells a miniature microvasculature, the environment of small vessels where blood is distributed within tissue. A major takeaway from this is that the cells on the chip behave as they did in the patients' brains. "We can watch them in real time, and we see that even though we've taken them out of the brain that they still remember their native homes. Once we put them in our microvasculature chip device, they try to find a place that looks like their native home."

Researchers have previously developed organ-on-a-chip systems from different immortalized tumor cell lines. However, these models can't provide clinical information about specific patients. With his organ-on-a-chip, Fan is able to study the cells of specific patients — in this case, 10 patients with glioblastoma. Each cell in a patient's brain tumor is different, and those differences shape the nature of a particular cancer.

"Now we have this platform to really look at what these differences are," Fan said. "The device allows us to track the patients' own brain tumor cells and see what every cell is doing and we can see how the behavior of every single cell differs from one cell to the other in real time."

One thing they found, and were very surprised by, is that the perivascular region — an area very close to a blood vessel — plays a significant role in the behaviors of brain tumor cells. It's potentially a key to knowing how certain cells will respond to cancer treatments. By conducting a real-time tracking of the cells, Fan and his team discovered that the cells in the perivascular region tended to fall into two categories: those that remained within a specific location, and those that traveled a very long distance along the microvessels.

"We looked at it and said 'Wow they really know where to go,'" Fan said. "One subtype has a stem cell-like behavior where they just keep to themselves and continue to produce tumor cells, and the other can move over long distances to invade the entire brain. That's something people have speculated for a long time, but now we see this in real time under a microscope."

This difference in cell behavior is a critical part of understanding glioblastoma. Unlike in other solid tumors, glioblastoma cells rarely metastasize to other organs. However, they can invade the entire brain by moving along blood vessels and other brain tissue structures. This leads to high rates of relapse. That's why knowing which cells are moving and which remain in place is so important.

Specifically, the brain tumor stem-like cells are the ones that tend to stay in the perivascular niche, while those known as "mesenchymal" cells are the ones that go traveling along the microvascular tracks and invade other parts of the brain. For further validation, the researchers relied on the Fan laboratory's expertise in single-cell sequencing and did a transcriptional analysis of 21,750 single cells from the 10 patients to identify tumor cell subtypes.

"By sequencing them, we're targeting them by each single cell, not at the population level, but individually — we looked at 4,000 different genes of a single cell," said Yang Xiao, a graduate student in Fan's lab and the first author of the study.

By doing so, the researchers were able to confirm the correlation between the cell types and their behaviors.

"We can compare these two sets of data — one is the transcriptional sequencing in the single cells and the second is live cell behavior in the organ-on-a-chip," Fan said. "We also quantify every single cell and when we compare this to a set of data, it actually gives you a pretty interesting correlation."

This could potentially answer big questions about cancer treatment. While fully differentiated tumor cells have shown to be responsive to drug treatment, tumor stem-like cells have proven resistant. Being able to observe the behaviors of the cells and discern their subtypes could help steer the approach to a particular patient's care. That's one of the ways that Fan and his team plan to build on their work toward patient stratification and personalized medicine.

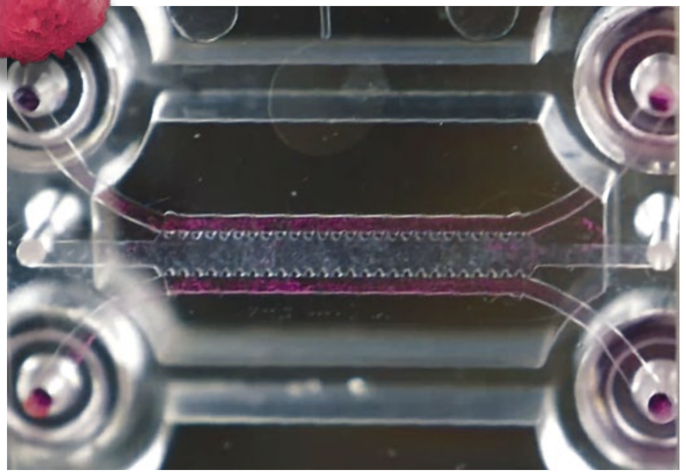
"We can place one patient's tumor on our device and see how the tumor cells move around in a 3-dimensional space and then see how many cells are localized in the perivascular niche, and that can probably predict a patient's response to a standard chemotherapy."

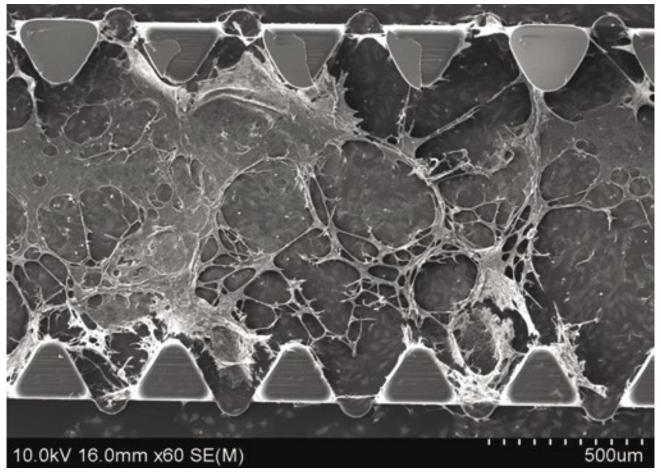
And this is just the start of where the work can go. The combination of single-cell transcriptomics and the organ-on-a-chip device gives the researchers unprecedented insight into the nature of the brain tumor cells.

"We've provided a window for how brain tumor cells are migrating and invading, and we identified them so we know who the bad guys are," Xiao said. "For the first time, we see their behavior and we've sequenced them, so we know who's doing what."

Below Left: *Microfluidic device (250 µm in height) containing a cell/gel loading microchamber (8000 µm × 1300 µm) flanked by two medium flow channels (500 µm in width).*

Below Right: *A large-scale scanning electron microscope (SEM) image of the chip.*





A School for Dreamers

A Yale-Afghanistan collaboration creates a "symbol of hope"

When a team of high school girls from Afghanistan was initially denied visas to enter the U.S. for FIRST Global, the international robotics competition in 2017, the setback proved only temporary.

The story of the team's plight made international news and gained support from U.S. legislators and the president. And it set in motion a collaboration between Yale and the team's coach, entrepreneur Roya Mahboob, to design a technology school for high school students in Afghanistan. The school, to be called The Dreamer Institute, is particularly remarkable because it will be attended by both boys and girls. In a country that has only recently started to accept women in science, such a school would have been impossible just a few years ago.

The collaboration brings together Yale's School of Engineering & Applied Science (SEAS), the School of Architecture, and the Whitney and Betty MacMillan Center for International and Area Studies at Yale.

The Dreamer Institute, to be built in Kabul, will focus on robotics, artificial intelligence and blockchain, and will consist of two interlocking buildings on the campus of Kabul University. One building is the high school, to be attended by girls for one half of the day and by boys the other half. The other is an innovation center based partly on Yale's Center for Engineering Innovation & Design (CEID), which would be shared by the high school students and students from Kabul University.

Continued →

Above and Below Left: *Mahboob meets and discusses the needs of the project with the Yale School of Architecture team at the Center for Engineering Innovation & Design.*

Below Right: *Mahboob and Wilczynski discuss the Dreamer Institute at the Yale-hosted International Symposium on Academic Makerspaces (ISAM).*

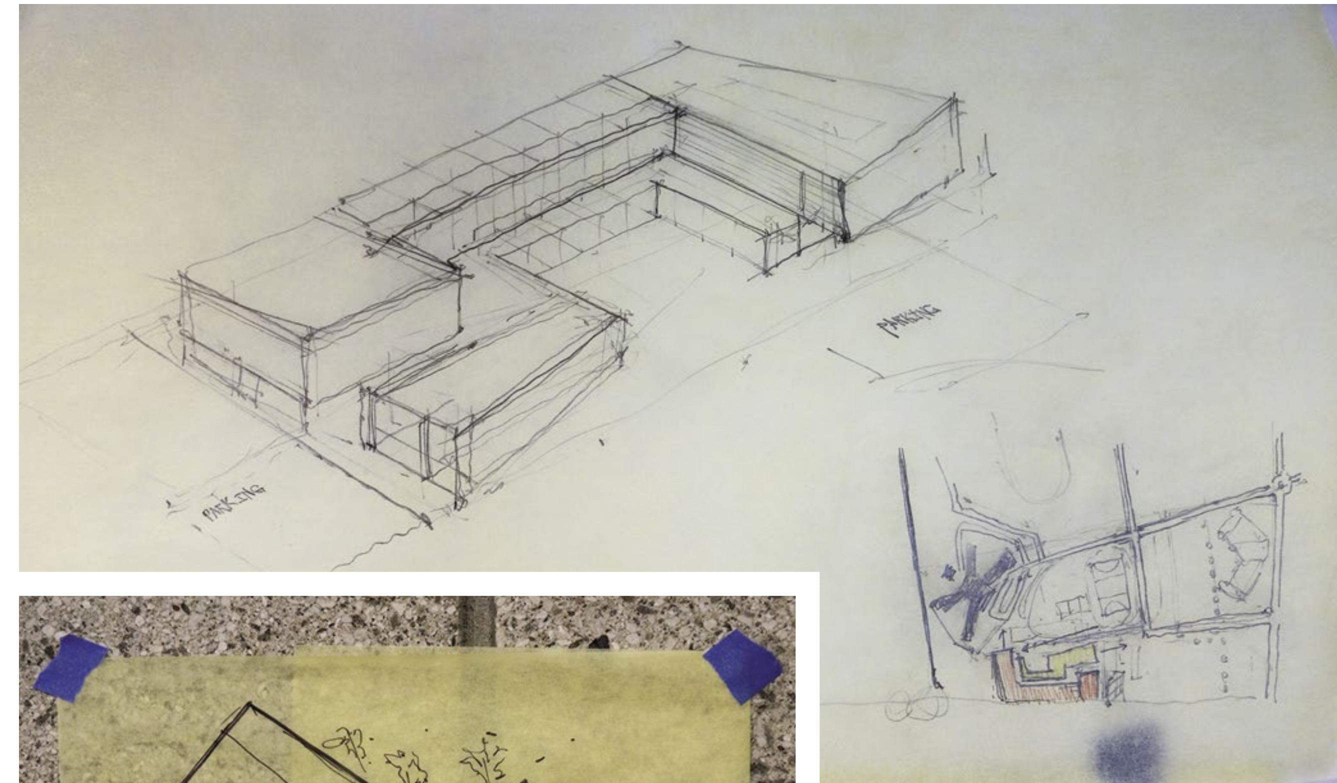
Mahboob, an entrepreneur from Afghanistan and a founder of numerous startups, said the idea for the school was sparked by the team's tour of North America. Their visits to numerous tech-based high schools fascinated the team members, who had little exposure to technology training until joining the robotics team.

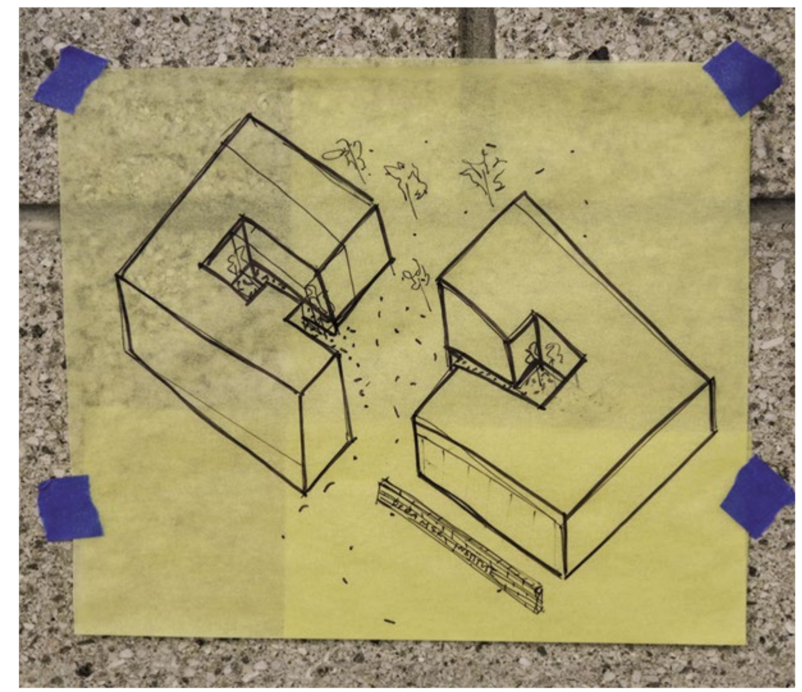
"We went to these schools and saw how the students worked together — all the girls wanted this back home," Mahboob said. "We did some research about STEM schools and figured out what we needed to bring one to Afghanistan."

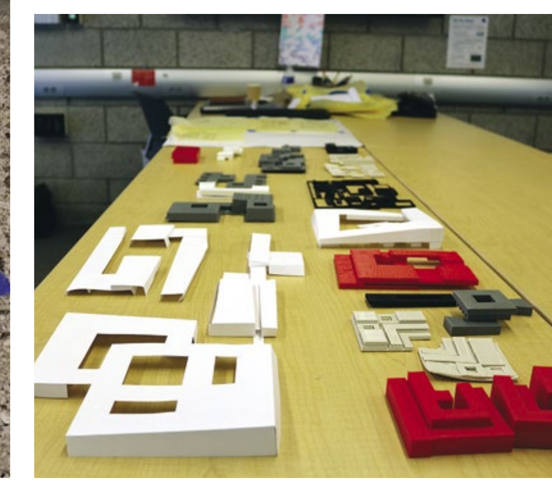
Through Yale's work with FIRST Global, Mahboob mentioned the idea to Vincent Wilczynski, deputy dean of SEAS and director of the CEID.

"When I heard Roya's idea, I thought 'Yale could do this, and Yale should do this,'" Wilczynski said. "There was a need, and we have the resources, we have the people, and we have the talent. All of us coming together to do this is reflective of what's possible at Yale."

He sent out a few emails and a collaboration was soon struck between SEAS, Architecture and the MacMillan Center. From there, things moved fast. Sunil Bald, associate dean for curriculum and admissions for the architecture school, led a team of five architecture students, working out of the CEID for four weeks over the summer to draw up the plans for the 150,000 square feet of building space. The project presented unique challenges to the student team of Michelle Badr, Camille Chabrol, Deo Deiparine, Alexandra Pineda, and Jerome Tryon. Among







Above: *The Yale School of Architecture team sketched and created numerous prototypes that feature two interlocking buildings.*

them was figuring out how to combine traditional aspects of Afghan architecture with more modern elements, creating a secure space while maintaining a sense of openness, and how to make the building adaptable to a country with a quickly changing cultural environment.

"This is a pretty unique endeavor in terms of having a group of students working with a faculty member to design something that we hope will see the light of day in another part of the world," Bald said. "To see these kinds of tangible results in such a short amount of time has been really encouraging."

Bald and the students presented the final designs to Mahboob at the School of Architecture Gallery.

"It was amazing," Mahboob said after the presentation. "I had envisioned it with a totally different design, and then I come here and they bring this very innovative scheme for the buildings. Thank you for making the dream come true. I hope you can one day come to Afghanistan and see the school. It is a symbol of the future of Afghanistan and especially the young people."

Through Yale's work with FIRST Global, Mahboob, the first female CEO for a tech company from Afghanistan, said this kind of

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plan would have been a non-starter in her country a few years ago.

"But now, you see a lot of women as owners of companies or forming technology groups robotics, animations or coding. The perceptions of women's ability in science and technology and engineering have changed."

A lot of that has to do with the robotics team that toured the world.

"It just changed the whole country," she said. "It became a symbol of hope and unity and courage for many young generations, especially women. Even more conservative people saw this and said, 'OK women can be mentors or designers or scientists.' That was a huge shift."

George Joseph, executive director of the MacMillan Center, said the project is a "perfect opportunity to bring together a number of entities across Yale." He noted that much of the center's financial support that goes to faculty and students is for "more standard academic modes of communication."

"To see a real-world application of our effort, it's very inspiring," Joseph said. "The potential for impact that this could have, not only on these girls in Afghanistan, but on Afghanistan as a whole — that motivates us for why we do what we do at MacMillan."

Architecture student Michelle Badr said she jumped at the chance to be part of the team. Being of Afghan descent, she felt especially connected to the project's goals.

"It was incredibly meaningful to be able to do a project based in Afghanistan," she said. "My parents fled during the Soviet invasion, so for me, this was very much my chance to give back to the homeland that I've been part of only in terms of a diaspora relationship."

Above: *(l to r) Jerome Tryon, associate dean of architecture Sunil Bald, Deo Deiparine, Camille Chabrol, Roya Mahboob, dean of architecture Deborah Berke, Alexandra Pineda, and Michelle Badr.*

Below: *Mahboob holds a final prototype of the Dreamer Institute which could be built as early as 2021.*

The team consulted with Mahboob numerous times while putting together the design.

"Roya is always giving us such visionary words and talking about a society that's moving forward and not tied to the past," said Alexandra Pineda. "One of the things that came up in discussion was 'What does this building mean for Afghanistan, and what is this doing for the identity of Afghanistan?"

"It's also really exciting interacting with Roya because she sees the building as a sign of optimism for how the political context can improve in Afghanistan," added Deo Deiparine. "So the building becomes a symbol of hope, or of a more progressive society."

But there were also some practical matters that the architects had to consider. For one, a high school teaching technology to girls could still stir controversy in Afghanistan despite the progress that's been made there. To that end, the architects consulted with a civil engineer familiar with Afghan architecture who suggested that they add some complexity to the interior. That would make it difficult for someone unfamiliar with the building to make their way around.

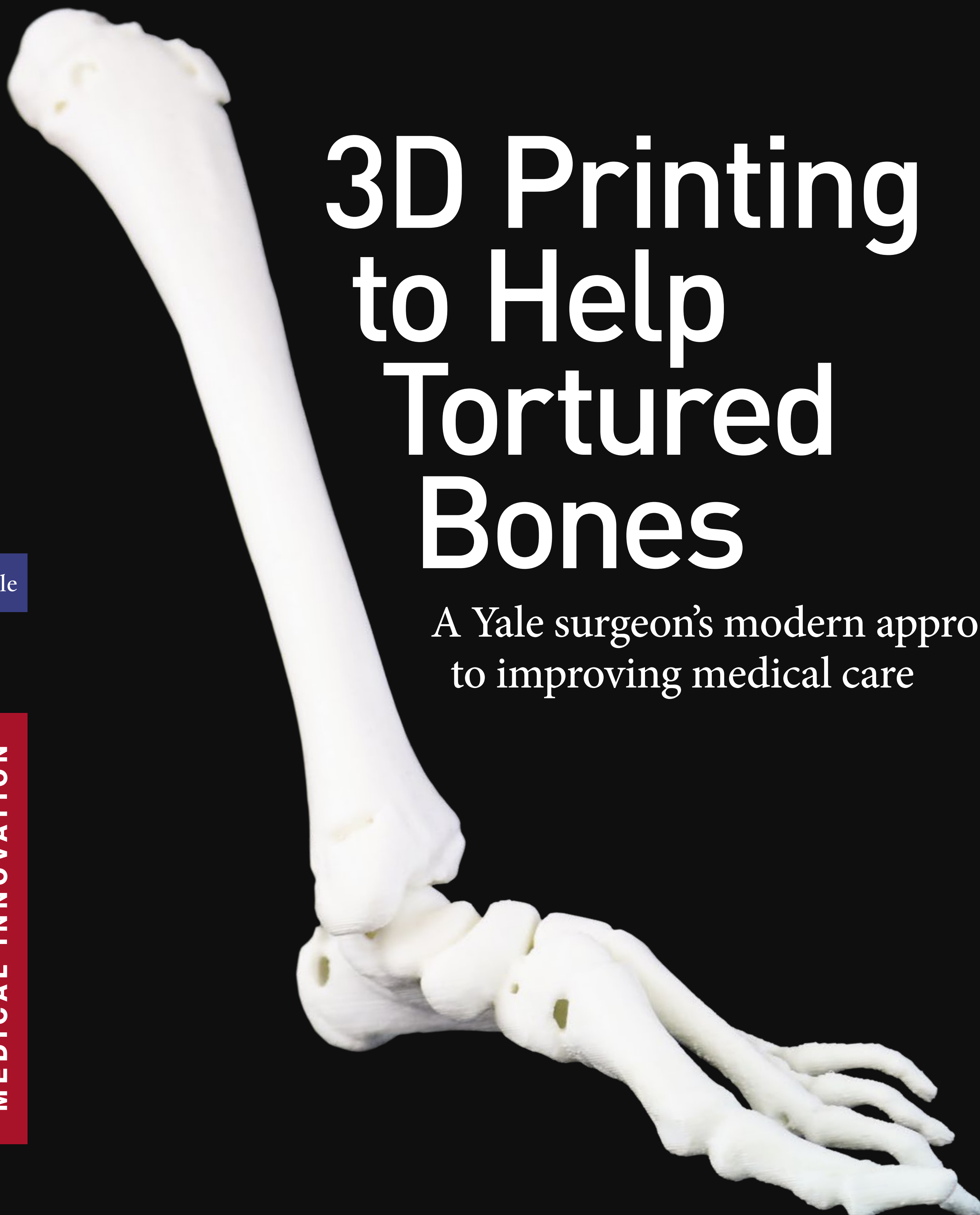
"It was interesting working with Roya because it's a project about investing in youth and it has some radical ideas about education, but then we also talked about the functional things like security and maintenance," said Camille Chabrol.

A school that looks toward the future while maintaining its Afghan identity can be a delicate balance to strike, but everyone involved agreed that they had succeeded.

"The building is aspirational, it's hopeful, but at the same time, it's very grounded," said Jerome Tryon, also of the student team.

Mahboob said the building, if all goes according to plan, would be up and running in 2021. She's currently seeking funding for the construction from various sources, including the Afghanistan government, and plans to present the design to the president. Further down the road, she said, more Dreamer Institutes could be built around the globe.

"All countries need to focus on student development, and they have to start investing in them today," she said. "The idea of the Dreamer Institute is to give students access to emerging technologies, where there's a much bigger gap between the richest and poorest countries. Countries and governments are responsible for making sure that this knowledge is in the hands of the young generations."



3D Printing to Help Tortured Bones

A Yale surgeon's modern approach to improving medical care

Yale

MEDICAL INNOVATION

For one recent case, Dr. David Frumberg had to figure out how he was going to fix the left leg of his patient, a 14-year-old girl.

"She has an abnormal connection between these two bones, and she's missing half of her tibia," said Frumberg, assistant professor of orthopaedics and rehabilitation. "Have you ever had pain on the outside of your foot? It's awful, and she experiences that with every step."

It's a tricky case, and X-rays and CT scans weren't giving him enough information to go on. To better understand what was going on, Frumberg went to the Center for Engineering Innovation & Design (CEID) to get a 3D-printed model of the joints. Having the model allowed him to hold the problem in his hand, turn it around, and help him see things he couldn't before.

"For me, the model helps in so many ways," he said. "It helps me come up with a plan, it helps me figure out the relationships between all the different complex deformities, and what needs to be repaired and what doesn't."

It's one of several bone models that Frumberg has had printed at the CEID in the last year. They're especially useful for the more complicated cases, and go a long way to reduce a lot of guesswork. And now, when he opens up a patient, there aren't so many surprises to work out on the fly. "Every time I get a model, it changes my plan 100%," he said.

That's because his procedures involve not just a lot of parts, but parts that often don't look like anything he's seen in previous cases. Many cases in the field of orthopedics fall under the "routine" category — that is, they require textbook-style knowledge of standard treatments. Frumberg specializes in the other kind.

"I never see the same patient and I rarely do the same operation," he said. "My work is this: How do I take this uniquely abnormal limb and what can I do that's best for the patient? It's that kind of critical thinking that makes it interesting to me."

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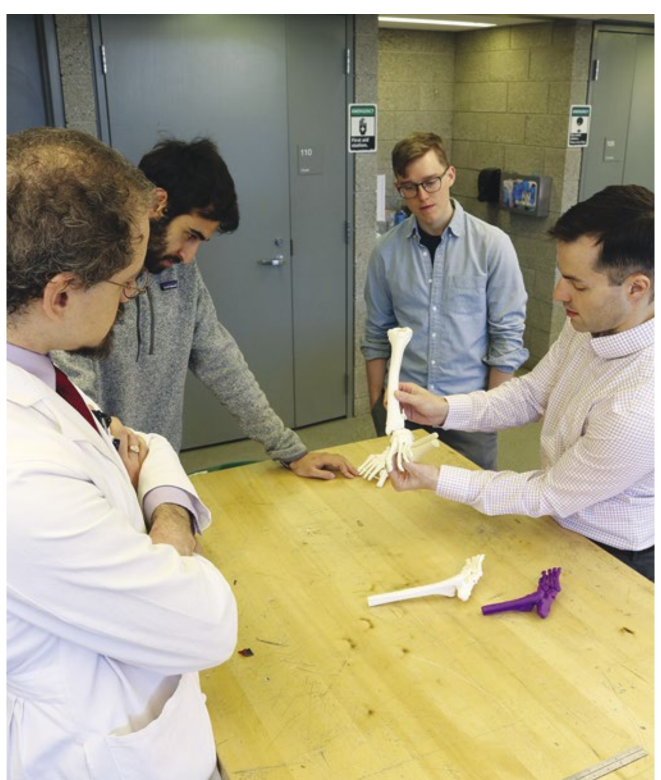
Preparing for an upcoming surgery, Dr. Frumberg and the team observe and discuss a recently printed 3D model.



His focus on the unusual cases is how he came to take on the case of an 11-year-old girl from the Middle East. Her family moved to the U.S. last year and was steered toward Frumberg because of the complexity of her condition.

“The outside half of her leg doesn’t grow well, and as a result, she has a significant deformity. You can see her tibia, ankle, and foot are all misaligned and the leg is much shorter.”

The first part of the treatment entailed a complicated reconstruction of the foot and ankle. A few months later, he brought her back to lengthen her leg. The first part was like “nine procedures in one,” he said and could take many hours. The 3D model helped a lot with his planning. “Without the model I had a list of treatment options, but once I held the model in my hand I knew exactly what I was going to do,” Frumberg said.

The way Frumberg discovered the value of the 3D models is typical of how a lot of things happen at the CEID. He first came to the makerspace looking to use its laser cutter to devise a grid that would better ensure the proper alignment of bones. He took a look around the room and got some new ideas. “There were students there doing the most amazing things.”

He asked about the 3D printers, and former CEID Fellow Dante Archangeli ’17 brought out some samples made for other doctors and told Frumberg to come by again if he ever had a case that could use one.

“A few weeks later, he came back and said, ‘I have one for you,’” Archangeli said.

Archangeli then spoke to Sean Lisse, a resident in Radiology, who had been spending a lot of time at the CEID working on his own project [see sidebar on right]. Lisse converted the scans into formats that can be used with the 3D printers. He then handed them to Archangeli, who did the printing.

Archangeli said the CEID’s printers have helped out a lot of doctors — some

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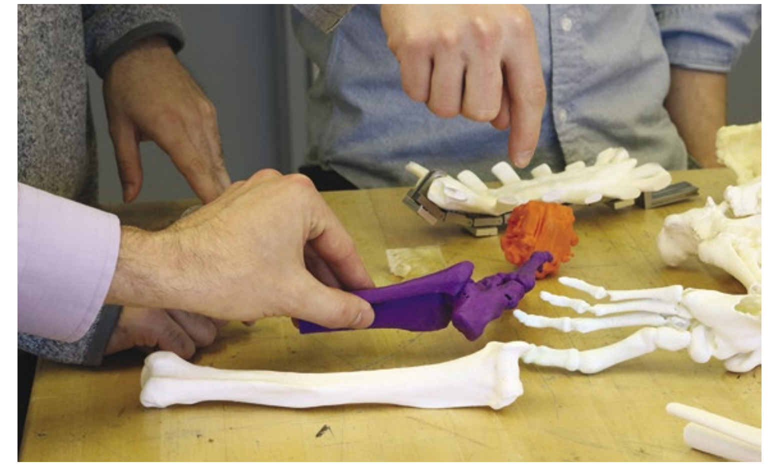


Augmenting the Ultrasound

Dr. Sean Lisse became involved in using the 3D printer to make bone models with Dr. David Frumberg through a separate project of his, also being worked on at the CEID.

Along with Fabian Laage Gaupp and Jitendra Bhawnani, both also in Radiology, Lisse has been working on a medical device that uses augmented reality (AR) to help physicians perform certain procedures that require ultrasound.

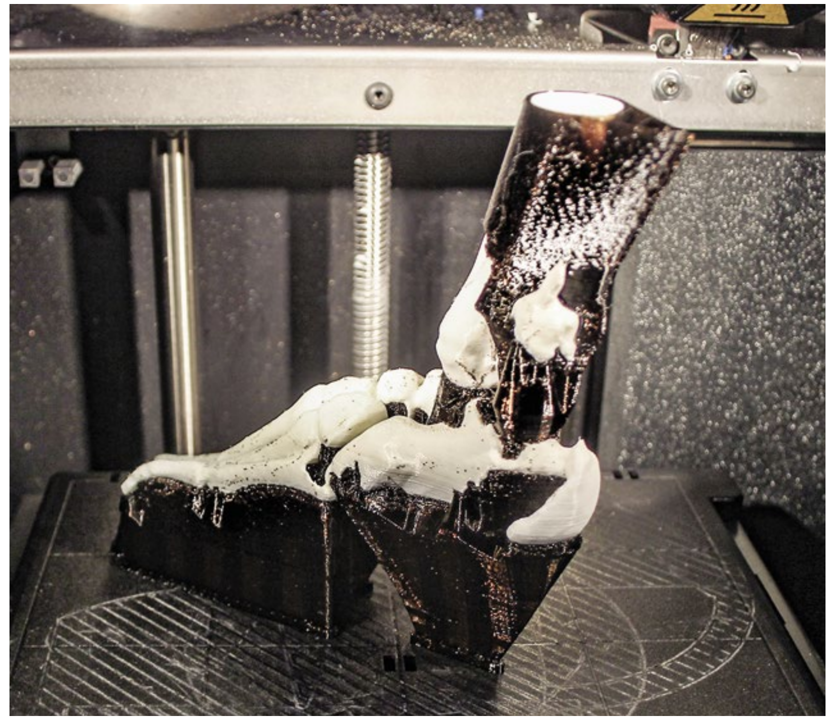
Currently, a doctor using ultrasound has to look at the image on the monitor, which could be a good distance from where he’s supposed to stick a needle, insert a tube, or whatever other procedure is being performed.

“It can get very, very awkward,” Lisse said. “It’s like trying to manipulate a Rubik’s Cube but you’re not allowed to look at the Rubik’s Cube — you’re only allowed to look at your hands on a video monitor to your left, while your hands are actually off to your right.”

Using AR, which displays graphics relative to the user’s field of view, the device would project the patient’s anatomy in the right place.

Lisse had been at the CEID, printing out pieces for the device, which is when CEID Fellow Dante Archangeli connected him with Brian Beitler *(see page 49)* and Frumberg.

A few years into the project, Lisse and his team have made an impression. The project won at the Radiology Healthcare Hackathon hosted by the Yale University Center for Biomedical Innovation and Technology, and they are currently talking with the Philips company about collaborating.



Left: *A scan of the foot and leg of one of Frumberg's patients prior to surgical intervention.*

Right: *The 3D model in the process of printing. The models can take a few hours to print but costs only a few dollars to make.*

for bones, but others have asked for models of neurons and various organs. It can take a few hours to print out the models but only about 15 minutes of prep time. And each model only costs a few dollars.

"I think there's no other technology that would be able to make the things that he wants made," Archangeli said.

Another CEID regular, Brian Beitler '19, a Yale medical student who recently graduated with a degree in mechanical engineering and molecular biophysical & biochemistry, has since taken over for Lisse in formatting the scans for the 3D printer. He has accompanied Frumberg in the operating room, and even there, the 3D models come in handy. "He'll often refer to the model in the operating room itself," he said. "Someone on the outskirts of the room will essentially hold up the model so he can look at it."

Indeed, Frumberg has become something of an advocate for the 3D models, talking them up with other orthopedists.

"Now that I've had all these cases, I've been telling my colleagues that it's available," he said. "I've gone to the OR in every single room to show everyone. 'Look at this! This is what we can do at Yale!' And everyone's like 'Really? Where? How?'"

Unorthodox cases require unorthodox methods — and a lot of thinking and studying. One of the ways Frumberg prepares for surgeries is by staring at images of the limbs he's working on. Not just in his office — crammed with bone models and frames — but everywhere. He'll hang X-rays in random places in his house as a way to keep his mind on the problem. But 2-dimensional images have limitations.

"For complicated deformity corrections it is challenging to plan the surgery," he said. "When I use external fixaters, I must plan where to mount them and where to make bone cuts, which tendons and ligaments to reconstruct, which growth centers to modulate — it can get really complicated. And there are a lot of ifs."

For instance, he brings out a model of the bones of a man in his 30s born with a clubfoot, a condition in which the feet turn inward. He had lived with it until the pain and difficulty of walking became too much. A groundskeeper, he found it increasingly difficult to work. A look at the 2D images gave Frumberg an idea of what to do. The 3D model, though, significantly changed his approach.

"Among a few other things, I didn't fully appreciate how much of his foot was skewed this way up in the air," he said, pointing to the bone of the big toe, which heads skyward. "I can't really picture from x-rays exactly what I'm looking at, or even

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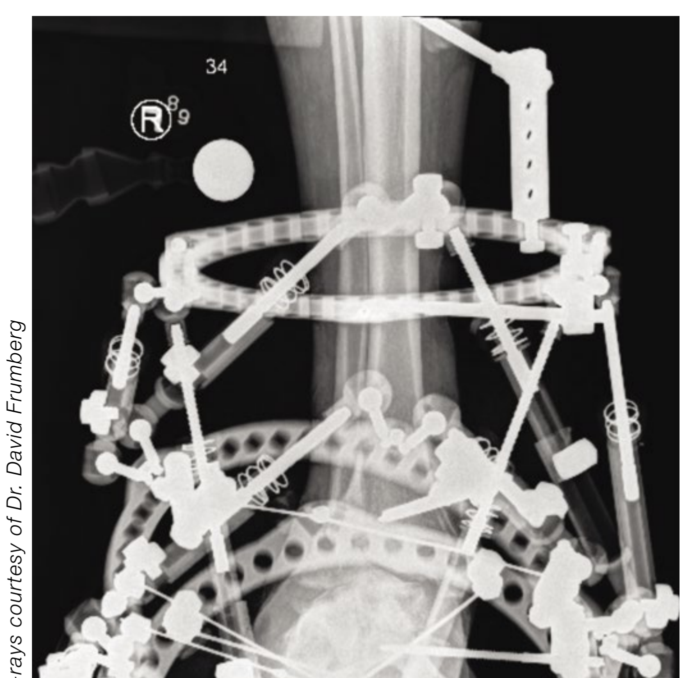
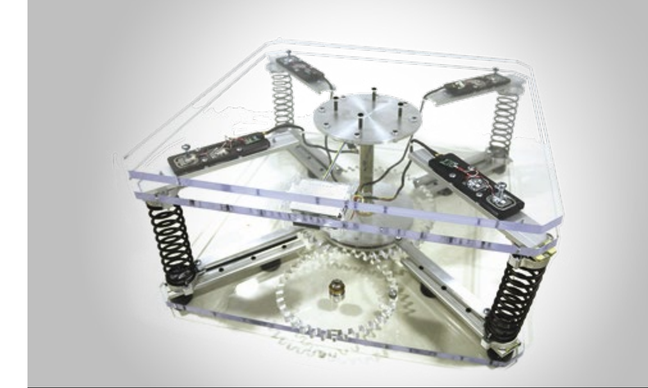
While X-Rays and CT scans help Frumberg comprehend a patient's problem, he says 3D printing is key for a more complete understanding.



X-rays courtesy of Dr. David Frumberg



The (Virtual) Reality of Concussions

Brian Beitler '18 got involved in printing bone models also through the CEID. Both as an undergraduate Mechanical Engineering major and currently as a medical student at Yale, Beitler's been working at the CEID developing OnTrack Rehab, designed to help doctors better diagnose and rehabilitate patients with concussions.

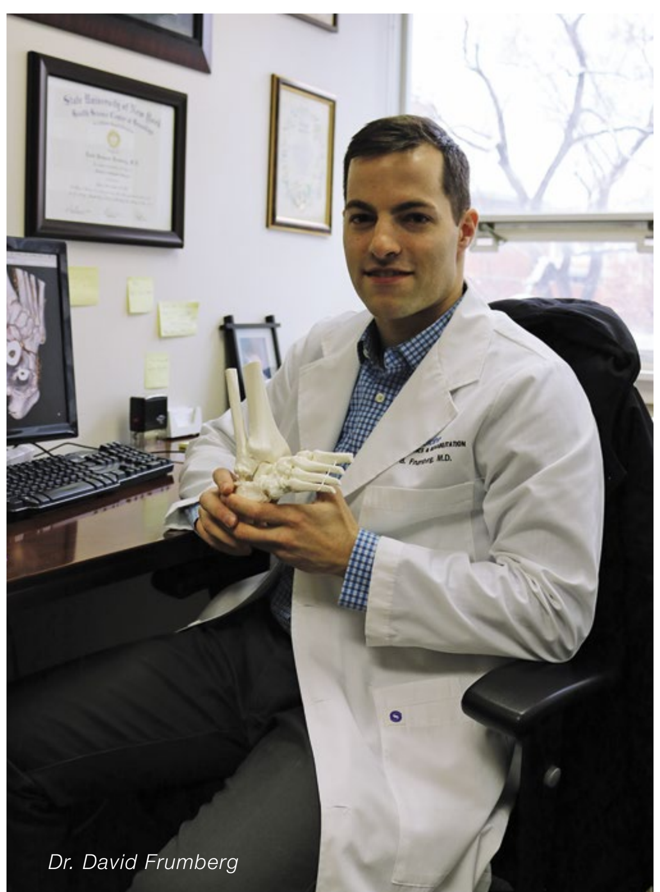
The device, which grew out of Medical Device Design and Innovation (MENG/BENG 404), features a virtual reality headset with eye tracking and motion detection, a physical balance board with adjustable stability that tracks the center of gravity, and a cloud platform that collects and synthesizes the data. He developed it with fellow students Holly Zhou '18, Mrinal Kumar '18, and Pong Trairatvorakul '18.

To use it, a traumatic brain injury patient outfitted with a VR headset tries to balance on the platform, which measures the patient's center of gravity. While balancing, the patient interacts with a virtual environment through the VR system. Physicians evaluate the patient's recovery progress by analyzing the data collected by the balance board and assessing the patient's own descriptions of symptoms.

This year, it won the $15,000 Rothberg Catalyzer Prize at StartUp Yale, a three-day event sponsored in part by the Tsai Center for Innovative Thinking at Yale (CITY).

For all its success, though Beitler said there's still work to be done on it.

"We're improving the functionality of it and getting to a form where we'd be happy giving it to researchers or selling it to physicians," he said.



Dr. David Frumberg

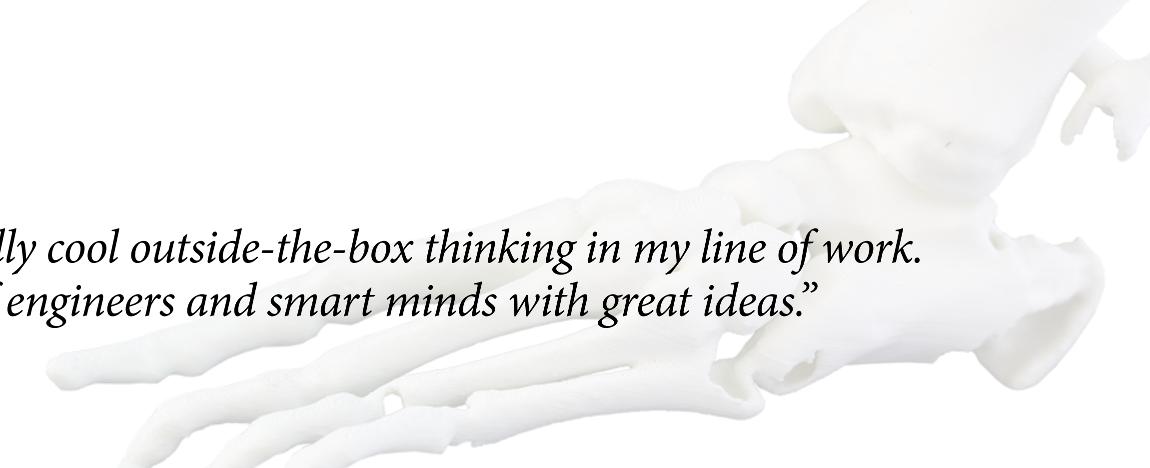
looking at the CT scan. Some people are really good at studying 3D imaging and figuring out in their head where everything is. For me, though, 3D printing is the key."

The models also go a long way in getting his patients on board with whatever approach Frumberg is planning. "It helps parents and the patients themselves understand what I'm proposing and why I am proposing it."

He showed the printed bones to the groundskeeper with the clubfoot.

"He had no idea what I was talking about. He asked, 'What do you mean I have abnormal contact between my fibula and my calcaneus?' And then I showed him the model and he understood: 'OK, I get it now.'"

It's especially helpful with his younger patients. Some of them think the models are really cool and want to keep them. More importantly, it helps them see how a certain procedure may change their body appearance.



"There's a lot of really cool outside-the-box thinking in my line of work. The CEID is full of engineers and smart minds with great ideas."

› Dr. David Frumberg

"It's hard enough to tell a kid that he or she has to wear a brace for scoliosis, but imagine how hard it is for a child to hear me say 'I'm going to cut your foot open,'" he said. "With the model, though, I can show them, 'This is your foot, this is what makes it different — I can correct this, and this is how I'll do it, and this is what I think it would look like when I'm done' — then it goes a lot easier."

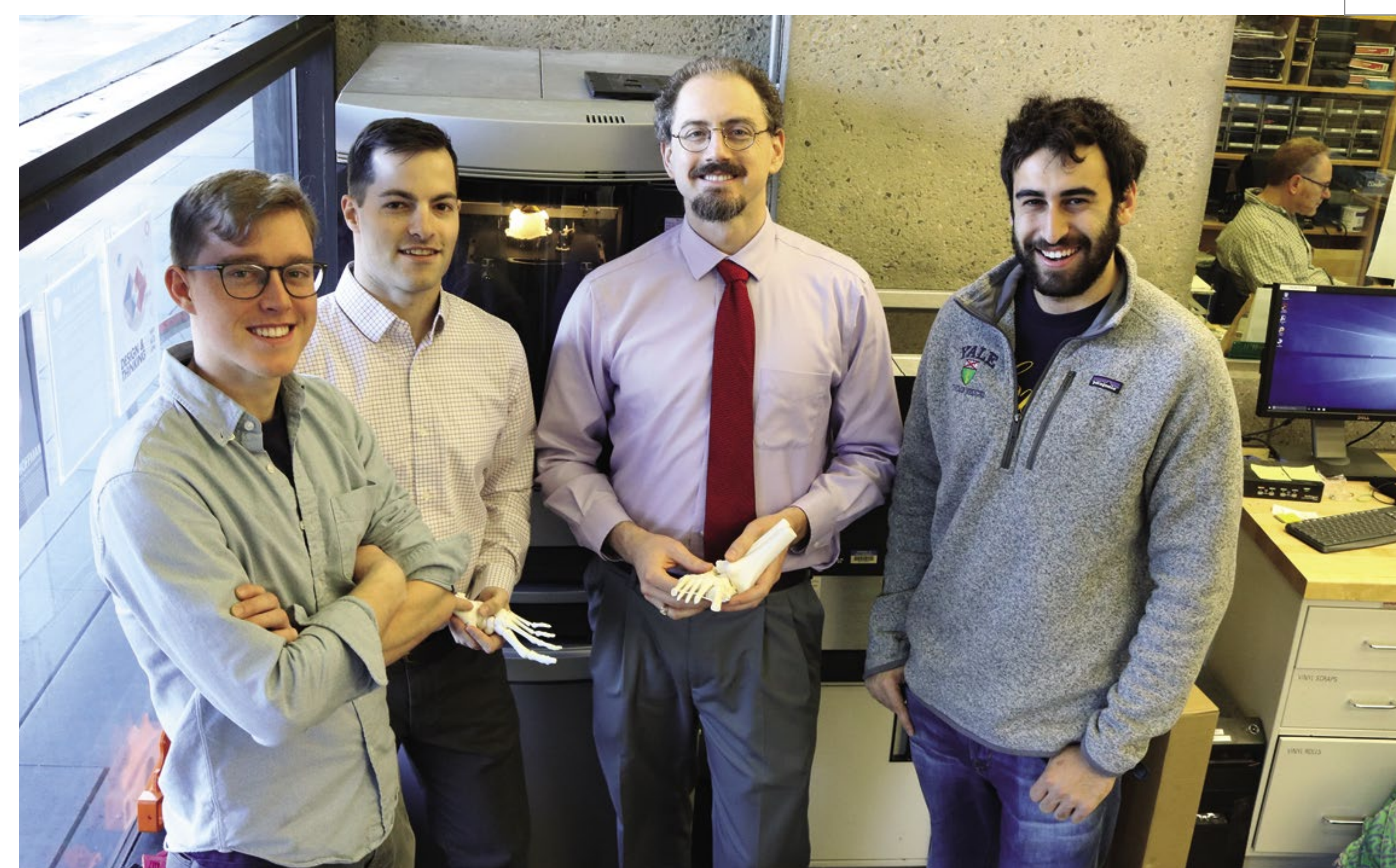
Archangeli said he's heard similar experiences from other doctors who have come to the CEID for assistance.

"For them, they see this stuff all the time in and textbooks and in patients so for them, it's just another case, but for the patients, this is the first they've ever seen this, so definitely having something in front of them that's physical is probably really helpful," he said.

Frumberg grew up wanting to be an architect, and said he gravitated toward orthopedics partly because it's closely related to engineering and construction. He plans to continue working with the CEID on future projects.

"There's a lot of really cool outside-the-box thinking in my line of work. The CEID is full of engineers and smart minds with great ideas. I appreciate most how much room there is for growth and collaboration."

Below: *(l to r) Dante Archangeli '17, Dr. David Frumberg, Dr. Sean Lisse, and Brian Beitler '19.*



The Beauty of Engineering

L’Oréal and Yale students use rheology, surface tension, and other science to innovate personal care

The world is so filled with engineering problems and their solutions, it’s easy to overlook some of them. Walk down the beauty products aisle next time you’re out shopping. All those shampoos and conditioners, for instance, involve complex fluids and soft solids. Optimizing these materials to turn frizzy hair into shiny, springy curls requires a mastery of things like rheology, surface tension and microscopy.

Seyma Aslan has these skills, and even she hadn’t considered how they might apply to the cosmetics industry until a few years ago, near the completion of her Ph.D. in Chemical Engineering here at Yale a few years ago.

“I never thought that I would work for a cosmetics company,” said Dr. Aslan, now a manager of innovation at L’Oréal — the largest cosmetics company in the world. “I never knew this field even existed or that they were hiring people working in colloid systems.”

When she started her job search, though, she found a lot of openings in the field. She applied to L’Oréal, got the job, and has been there since. Aslan recently returned to Yale to lead a nine-week program created through a partnership between L’Oréal, the School of Engineering & Applied Science (SEAS) and the Tsai Center for Innovative Thinking at Yale (CITY). The program, known as an “intensive,” welcomed students from all disciplines to learn the process of identifying a problem, finding a solution, turning it into a product and creating a marketing plan. It proved a productive endeavor, and two of the projects are now in the process of patent approval.

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"It is a win-win-win approach, where students get a certificate of completion signed by L'Oréal," Aslan said. "Yale gets a great model for students to strengthen their innovation and soft skills, and L'Oréal wins by engaging with the students to identify talent and getting a lot of inspiration for innovation"

The program began to take shape when Aslan and her colleagues were brainstorming about personal care problems and their potential solutions. Perhaps, they decided, it would help to bring in some new ideas.

"We wanted to chat with university students and identify technical challenges and build strong collaborations," Aslan said. "And I remembered my good old days at Yale where we used to have a lot of hackathons in the Center for Engineering Innovation & Design (CEID)."

Aslan contacted Deputy Dean Vincent Wilczynski, director of the CEID, who had been her advisor while she was in the SEAS Advanced Graduate Leadership Program (AGLP), a program designed to give students work experience beyond the research lab. Wilczynski contacted Tsai CITY, and three parties hashed out some ideas, and the plan for the nine-week program was hatched. Thirty students were selected for the program (more than twice as many had applied).

Molly Grun, a graduate student in the lab of Mark Saltzman in biomedical engineering, heard about the program through her participation in AGLP. It sounded like a great opportunity.

"I hadn't had a lot of experience as a graduate student that involved anything like product design," she said. "And it was part of the reason I joined AGLP, because I had been wanting to work with Tsai CITY and learn about design process."

Below: *The L'Oréal Intensive was so popular that only half of the individuals who applied were selected.*

The students were broken up into seven four-person teams. Each team had a technical expert to advise them, some from L'Oréal, some from Yale. The student teams submitted their milestones every other week so the advisors could help keep them on track. That's an important part of the process; Aslan noted that industry timelines and methods can differ greatly from those in academia.

"Sometimes students are very ambitious, very innovative, very out of the box — but with only nine weeks it's impossible to create something like a moonshot," she said. "We didn't want to constrict their innovation in any way, but they needed to be aware of the obstacles."

Most of the work was done either at the Greenberg Engineering Teaching Concourse (GETC) or in the John Klingenstein Lab at the CEID. In both venues, the students learned to use various tools, like a Rayneri Turbotest benchtop mixer to make cosmetic formulations, and a rotary evaporator to remove solvents. Sara Hashmi, then a SEAS associate research scientist, was recruited to help with lab work.

"A lot of science goes into it," said Hashmi, now an associate professor of chemical engineering at Northeastern University. "The students were given pretty free reign — they were basically told 'We want you to go and make a product.' Some made actual hardware like hair rollers, and others made products from chemicals to add to your hair."

Above: *Students were able to hear from L'Oréal representatives on such topics as innovation, operations, and business management. They also had a chance to learn how to use various tools, like a rotary evaporator, or rotovap, used to remove solvents.*

In addition to working on their projects, the students also attended inspirational talks from L'Oréal representatives, each with a different take on how industry works — innovation, operations and business management.

Continued →

Top to Bottom: *The four-person teams — seven in all — were designed for background diversity, so engineers worked with students from completely different disciplines. The first- and second-place teams' products so impressed L'Oréal that the company has filed patents for each.*

"The students enjoyed hearing about the real-world problems — some failures, sometimes success stories," Aslan said. "They got to hear about what it actually means to work in industry and the kinds of things you encounter."

Rodrigo Ojeda, a graduate student in the lab of Jan Schroers in Mechanical Engineering, said it was that real-world experience that appealed to him about the program. His team ended up developing a product to help consumers' hair dry faster, using super-absorbent polymers.

"For me, it was about getting more industry experience," he said. "You're doing research, but you still have to come up with results in some way. You might have these great ideas, but can you actually deliver them in this time frame? We had to take into account the time and the budget needed to produce the project. So you get the industry experience — but you're not exposed, like 'Oh I'm going to get fired!'"

The teams were pre-assigned and designed for background diversity. So engineers might work with someone from the School of Management or a history major. Both Grun and Ojeda noted that working with non-engineers on a project like this was a new experience. "It's challenging to work in interdisciplinary teams, but everyone does have something to contribute — you just have to work at it," Grun said.

Another lesson Grun learned early on in the process: "Coming up with new ideas is really hard. The consumer product field is a very crowded space — if you think of an idea, it's probably been done before." Nonetheless, her team came up with an original idea and marketing plan. Combining chemistry and smartphone technology, the product tested for hair health. It took third place at the pitch-off that was held at the end of the nine weeks.

The pitch-off was judged by L'Oréal USA's Mohamed Kanji, Senior Vice President and head of research & innovation, the company's human resources director, Omer Imtiaz, and head of Hair Care Development labs, Anthony Potin. From Yale the judges were Katherine Schilling, associate research scientist and Paul Anastas, the Teresa and H. John Heinz III Professor in the Practice of Chemistry for the Environment.

"When the seven groups presented, everyone in the room was amazed by the quality of the work," Aslan said. "The approaches and solutions were all very pragmatic, and all the teams brought a prototype, which is astonishing for a nine-week, non-credit certification program."

The first- and second-place teams' products so impressed L'Oréal that the company has filed for patents for each. The first-place team presented a product that allowed users to change their hair colors within seconds.

"The students did a demonstration, and the audience was shocked that they could come up with a solution with such a dramatic effect on the hair in such a short amount of time," she said. Besides the product's technological innovation, she said, it also meets consumer demand for ever-faster products. "Consumers desire different things, depending on the time they live in. This is the time of 'I want it now, at this moment!'"

The second-place team devised a product to broaden hair-curling possibilities — again filling a consumer need, Aslan said. "This area has been neglected for so long and curly hair is very hard to manage. It's a complex routine and there are certain challenges to be addressed."

Aslan said much of her job is aimed at reaching out to neglected consumers. On example is a paper that she and her colleagues recently published in the International Journal of Cosmetic Science on the physical characteristics of the hair of Mexican women.

Above: *A team poses with Aslan (far-right) after successfully presenting their product, which uses super-absorbent polymers to make hair dry faster.*

After four years in the cosmetics industry, Aslan said she's still glad she took the job. Unlike the pharmaceutical or refinery industries — the two fields she had expected to enter while a student — you see results fast.

"Seeing a product you worked on when you're passing through the supermarket, it's such an amazing feeling," she said. "Having an impact on consumers and actually being able to explain your innovation and your work to your grandmother – it feels great!"

Reinventing Brain Care for the 21st Century

Engineering and Neuroscience team up to better treat brain injuries

Monitoring a traumatic brain injury (TBI) is no easy task. The brain's electrical activity, oxygen, blood flow, pressure and temperature all need to be measured over a period of days. Each of these indicators is monitored directly from the brain, and the data is continuously streamed and tracked. Doing so requires creating multiple access points and inserting probes a few centimeters into the brain.

"The real problem is not just the individual probes but that each has their own proprietary electronic systems," said Mark Reed, the Harold Hodgkinson Professor of Electrical Engineering. "So you have a nurse trying to take care of this with multiple monitors, and all the data's incompatible between them."

As systems go, it's expensive, unwieldy and confusing. At Yale, Reed is working to change that with Dr. Dennis Spencer, the Harvey and Kate Cushing Professor of Neurosurgery and the chief of epilepsy surgery, and Hitten Zaveri, assistant professor of Neurology.

"Our idea was to create something that does all these things together," Reed said. "This is an attempt to cut through all of that and simplify it."

The Engineering-Medicine collaboration is an ambitious project that, in the researchers' words, aims for nothing less than "reinventing brain care for the 21st century."

The three-part system uses one device (the NeuroProbe) to measure and track the five modalities — EEG, oxygen, blood flow, pressure and temperature. The data from the sensors are digitized and transmitted by a device known as the NeuroLink to the NeuroMonitor, which displays the data in real time. The NeuroMonitor comes with the option of connecting to cloud-based processing and machine-learning algorithms.

The idea for the NeuroProbe arose from conversations between Reed and Spencer. Reed's lab specializes in developing biosensors, including those capable of detecting cancers and tuberculosis. Spencer invented an earlier probe for the human brain about 20 years ago known as the Spencer Depth Electrode. But as medical researchers learned more about brain injuries, monitoring them became more complicated.

"There's more awareness now that it isn't just the primary injury that hurts the patient," Reed said. "There's secondary injuries, due to a contused brain causing increased pressure, seizures, lack of oxygen, changes in cerebral blood flow and things like

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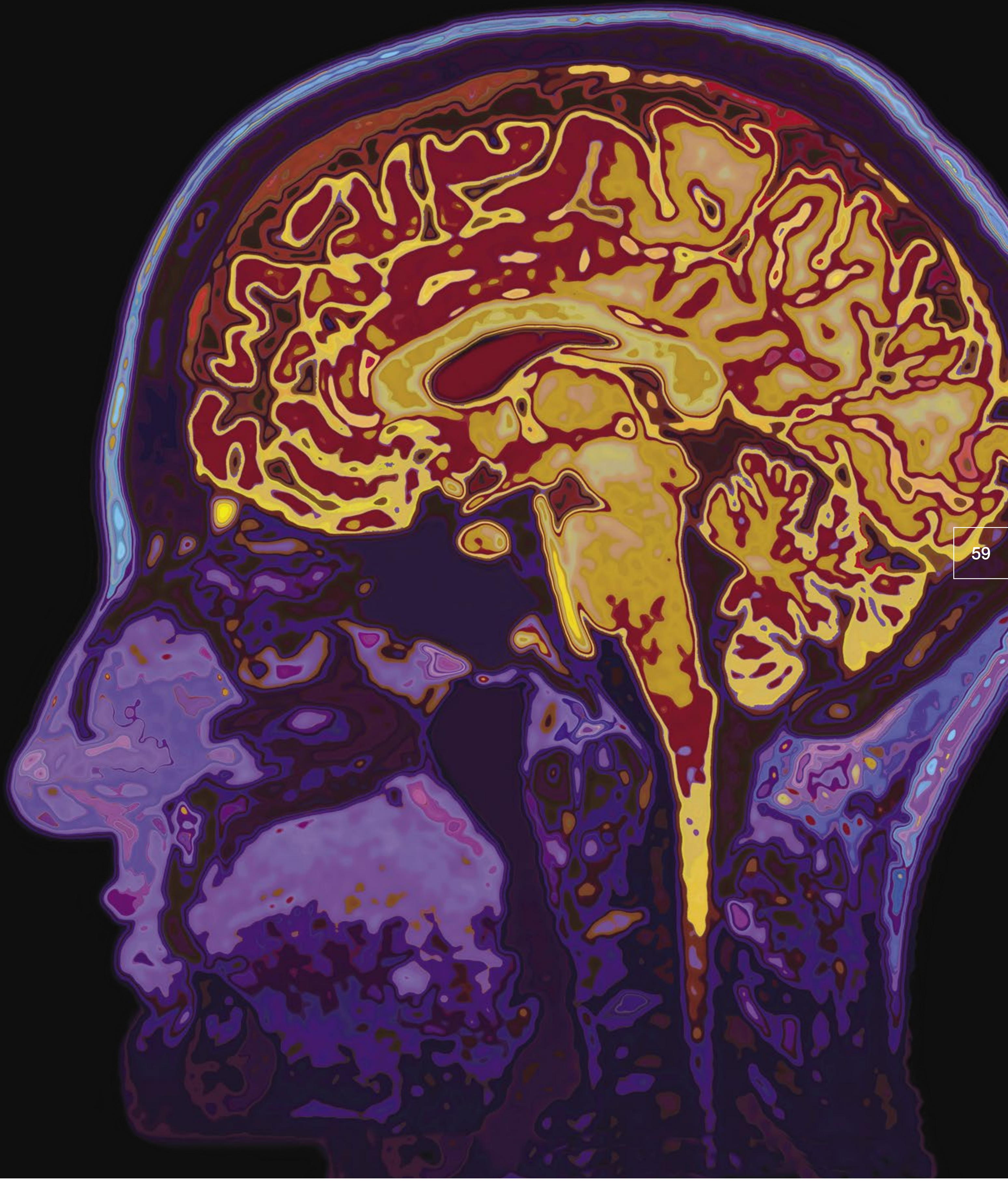


that, which really cause problems for TBI patients. It used to be that surgeons mainly cared about pressure and temperature. But now we need to watch all of these other modalities — oxygen, blood flow and EEG."

The technology for doing so, though, has had trouble staying on pace. Zaveri points to a photo of a TBI patient's hospital bed, outfitted with conventional technology. Multiple wires are hooked up to multiple machines. It's complicated and moving around the area looks very precarious.

"It's Grand Central with all the electronics and wiring — you have to have people with expertise on each of those instruments, maintaining them, and making sure that they link together," Zaveri said. "We also need to have these external devices. That means purchasing, maintaining, and training the staff to use them."

Emily Gilmore, director of the Yale-New Haven Hospital Neurointensive Care Unit, has worked closely with the team and looks forward to when comprehensively monitoring TBIs doesn't require such a cluster of technologies.

"You have a mechanical ventilator, and the patient's bedside monitor, and you've got all these other monitors tethered in places or on bed posts — it gets very… there's just a lot of stuff!" Gilmore said. "And if you actually have to transport the patient to a procedure or to a scan, you have to de-tether all of this stuff."

Not only is the current standard cluttered and expensive, it's also pretty limited as to where it can be used. The simpler and more portable NeuroProbe, however, would allow caregivers to monitor the brain in remote areas and by a much wider array of health professionals.

"We're designing it in such a way that you don't necessarily need the operating room for placement," Zaveri said. "With this re-design, the placement could be performed at the bedside at 3 a.m. by a resident." He also noted that their system may be of interest to the military, since the NeuroProbe could easily be taken to remote facilities and even the battlefield.

Zaveri, who has degrees in electrical engineering, computer engineering and bioengineering, will develop algorithms for the system based on those created by Ronald Coifman, the Phillips Professor of Mathematics and Computer Science. Doing so will make it easier to interpret the continuously streaming multimodal data.

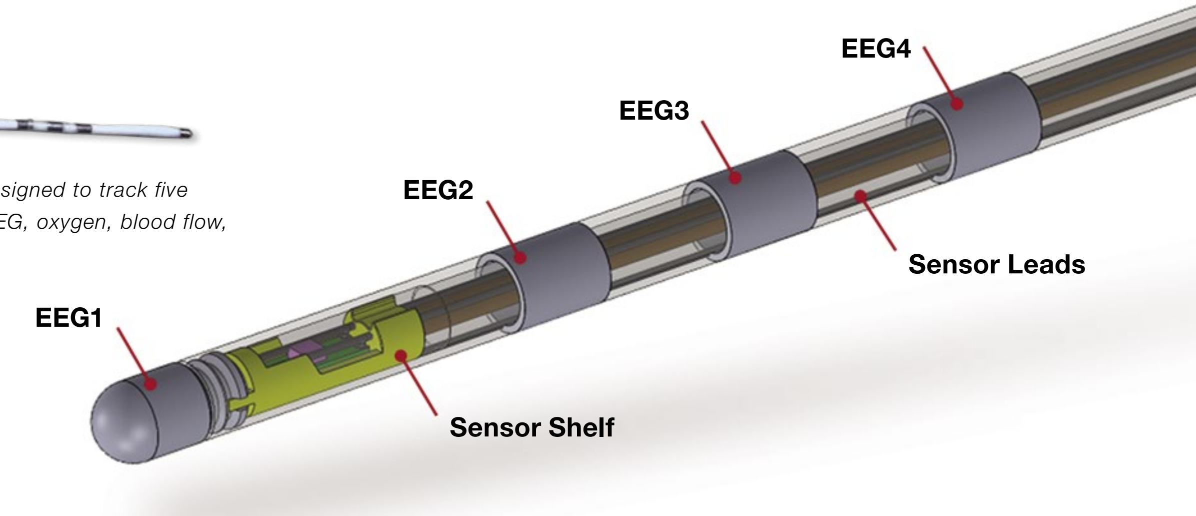
"Because we're currently looking at five different modalities, you need expertise to understand it, but we're hoping to automate a lot of that and bring in machine-learning algorithms that will help users understand all of those different measurements."

The algorithms could also give physicians a more accurate profile of each specific patient and serve as a guide toward treatment. It's part of a larger trend in medicine of tailoring treatment to each individual patient.

Left: *Conventional technology clutters a hospital room with multiple wires hooked up to several external devices. With its numerous capabilities and portable design, the NeuroProbe aims to eliminate the dangerous and unwieldy clutter.*

Yale

TECHNOLOGY



Above: *The NeuroProbe is designed to track five indicators of brain health — EEG, oxygen, blood flow, pressure, and temperature.*

"A patient's condition may be different for each parameter, so you develop an algorithm that says that if blood flow is this, and temperature is this, and oxygen is that — then you do the following," Spencer said. "Now, you have therapeutic ways of managing each individual patient."

Gilmore said treatment of brain injury needs to get away from large studies that may not accurately reflect individual patients — especially considering that a patient's physiology can change by the hour.

"I think the NeuroProbe has the potential to allow us to do that," she said. "If we focus more on the individuals' intrinsic physiology and personalize their care, we have the potential to change the prognosis in many of these severely injured patients, and advance the field in ways we haven't previously been able to."

The project is being funded by Connecticut Innovations, the state's primary investment organization focusing on medical and bioscience startups. From a business perspective, the researchers are aiming initially for the market dealing with TBI cases. Soon, though, they expect to add more sensors and also market it for broader use, including vascular disorders and epilepsy. Currently, Spencer said, there's no way to have a precise, real-time look at what's happening inside the brains of patients who have an aneurysm — a common vascular problem.

"The probe provides an understanding of blood flow and oxygen and pressure while the patients are being treated," Spencer said. "At the present time, it's unwieldy for TBI patients to have all of these different monitors and such. For the vascular patients, it's even more of a problem because they're moving back and forth and going to angiograms and so on. I think our system is going to be a major corrective to this."

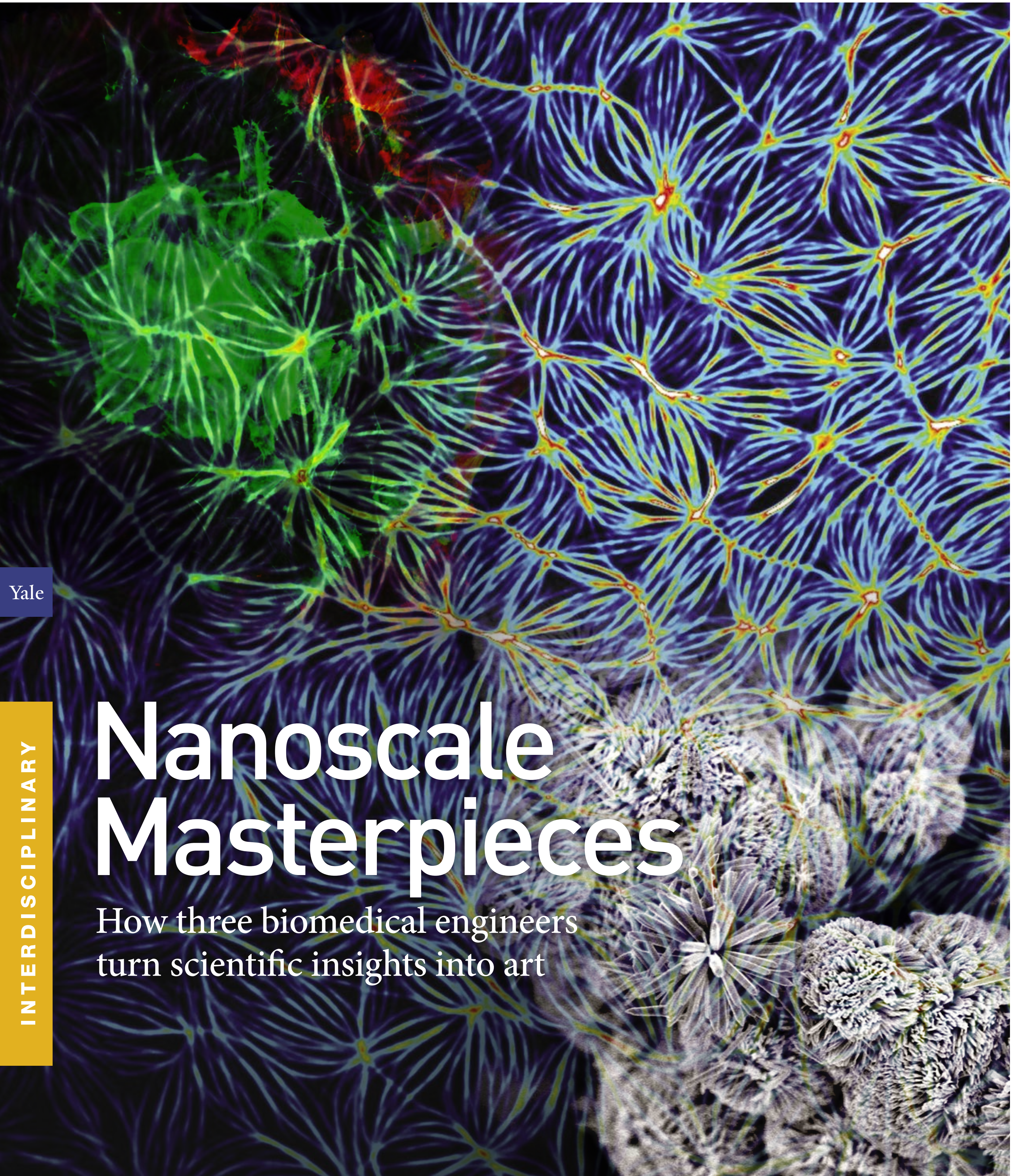
After Reed's lab tested sensors for the five modalities, the team decided to use commercially available sensors for blood pressure and EEG. Others are custom-made. "Over the past year, we've made some of our own individual sensor components," Reed said. "For example, we've developed a certain type of heater and thermometer to measure blood flow."

The team has a prototype of the NeuroProbe device, which was manufactured by the medical device company Archimedic. With Kevin Ryan, Yale research support specialist in Electronics and Electrical Engineering Systems, the team will shortly have the accompanying electronics in place.

Because the fundamental science behind all the sensors has already gone through the rigors of FDA testing, this saves a huge amount of time getting the device ready for market. The researchers still want to do some additional testing, but believe that they could have a market-ready product within a few years.

Spencer said that the standard technology being used now for TBI isn't fundamentally different from when he started in the mid-1970s. Things are now aligned for that to change.

"Technology has a way of moving in paradigm shifts and I think we're at that transition period," he said. "You go for a long period without taking advantage of the technology that's there, and I think we're at that moment when we're capable of doing this."



Yale

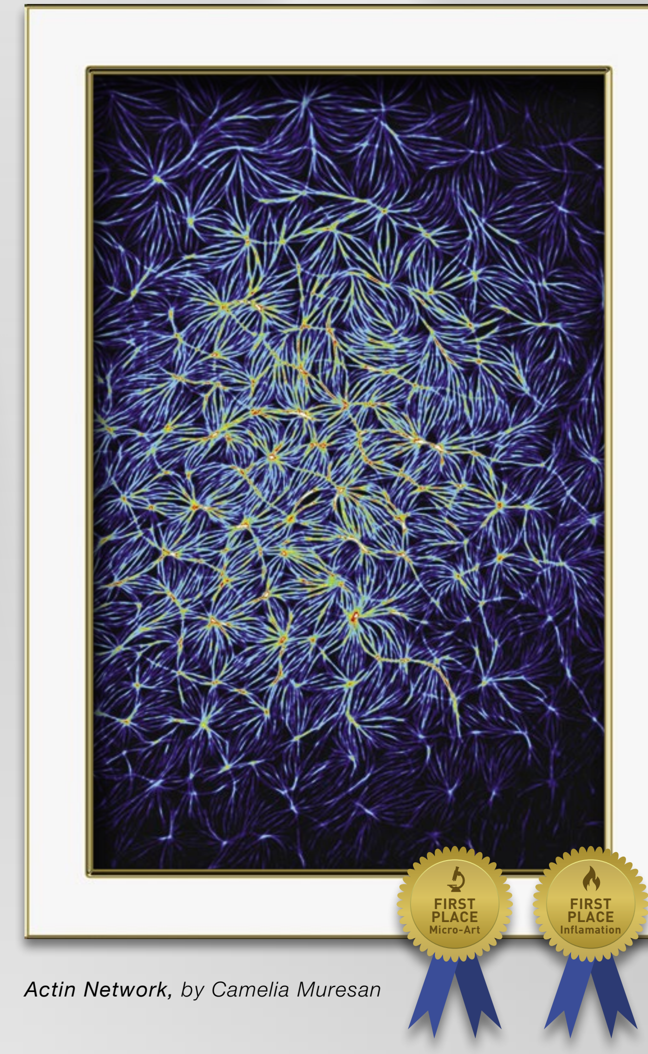
INTERDISCIPLINARY

Nanoscale Masterpieces

How three biomedical engineers turn scientific insights into art

At the Yale School of Engineering & Applied Science, there's been a good deal of exploration into the science of art, including courses and workshops on the methods and materials that go into creating artwork. Equally fascinating, though, is the art of science — images developed in the service of research, often of the mysterious and visually breathtaking world that exists at a scale well below the perception of the naked eye. Here we focus on three images, all from biomedical engineering researchers, which took first, second and third in this year's inaugural Art in Research Competition hosted by the Yale Postdoctoral Association and the Office of the Provost

We spoke about these images with the researchers who made them as well as with our in-house art expert, Katherine Schilling, who teaches The Materials Science of Art and is a research scientist at the Institute for the Preservation of Cultural Heritage and in Chemical & Environmental Engineering.



Actin Network, by Camelia Muresan

"Actin Network"

Camelia Muresan, a postdoctoral associate in the lab of Michael Murrell, assistant professor of biomedical engineering, won first place in the micro-art category and first place in the inflammation category. It gives us a close-up look at actin, a protein that regulates such fundamental processes as cell division and intracellular interactions.

What's happening here?
The yellow and red indicate the difference in fluorescent intensity, Muresan says. "You have regions that are brighter than others. All of this is just actin, which is a protein that's polymerized and forms this network."

"Our group is interested in how cells produce mechanical force and how they translate force. We have this biomimetic system, which is like an *in vitro* model for a cell. So this is a nice and simple model to study the physics of cells."

How did you make the image?
The image, which shows the structure of an F-actin network, was acquired with a confocal fluorescent microscope. "It has a camera and you just shine some light and the camera detects the emitted light. We can see the fibers, because they are fluorescent-labeled. Later on, during image processing, you can change the colors, so I just played with the colors and tried to make it as beautiful as I can.

"From the first time I saw this, I thought it was beautiful, and I wanted to share it with other people," she says. "I was not thinking about winning the competition because it's something so common for me to generate."

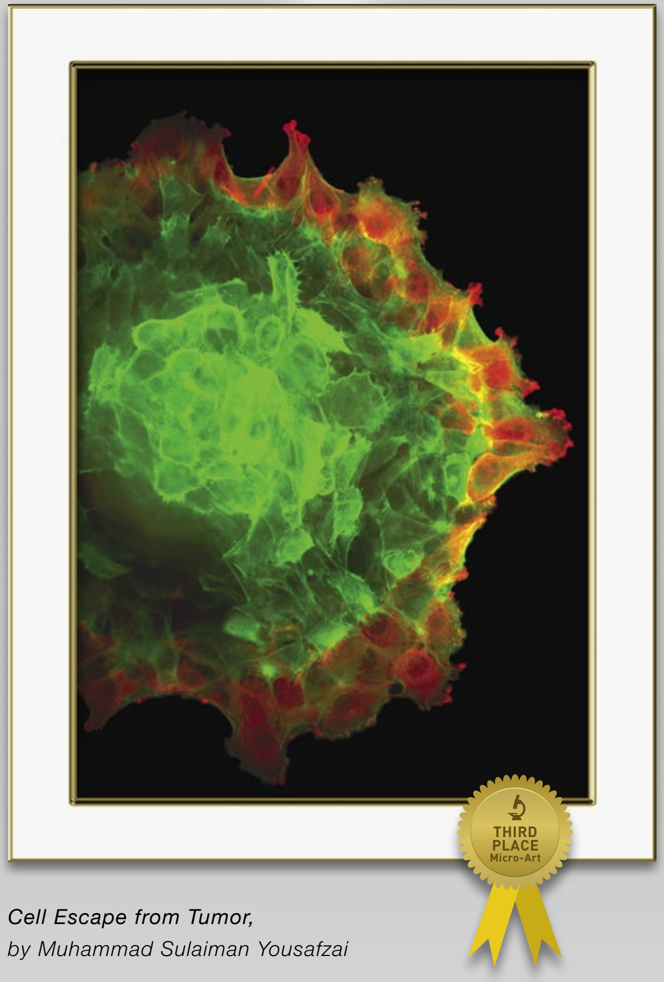
On what a good research image can do:
"I definitely think it can draw people to science, especially for teenagers and kids who are interested in research. I think there's a great need for outreach and saying to them, 'Look how beautiful science can be, and we can simulate the cytoskeleton of a cell, and look at how these filaments can behave."

Continued →

How do you get a good image?
"One thing is good preparation, good microscopes and good equipment, good skills — but also your penchant for science."

What the critics say:
"For me, this image is reminiscent of impressionist paintings, specifically "Starry Night" by Vincent van Gogh," says Schilling. "The F-actin network looks woven together like clouds in a van Gogh sky."

"Cell Escape from Tumor"



Cell Escape from Tumor,
by Muhammad Sulaiman Yousafzai

Muhammad Sulaiman Yousafzai, a postdoctoral associate in Michael Murrell's lab, won third place in the micro art category. This work is an example of a research image that's visually captivating, while depicting something scary. It captures the moment that cancer cells escape from the tumor and metastasize. Created with a confocal microscope, the actin cytoskeleton is seen in green, and focal adhesions are magenta.

"We are interested in exploring these things for breast cancer cells and also brain tumors, and we want to find a mechanistic way — an engineered way — to stop the migration of these cells."

What's happening here?
"These are unique images never before taken like this," Yousafzai says. "These are cancer cells and they were stained for transfiction to make them glow bright when you image them in different colors. Here we see the cytoskeleton of cells. [The bright green images] are the stress fibers that give the structure to cells. The red ones are focal adhesions, so they're like the feet of the cells which give them the ability to crawl along surfaces.

"They mature and get strong enough to drag themselves. Just as we push and move along the ground, it's the same with cells. They push against the ground and move forward. What we are actually modeling are these tumors."

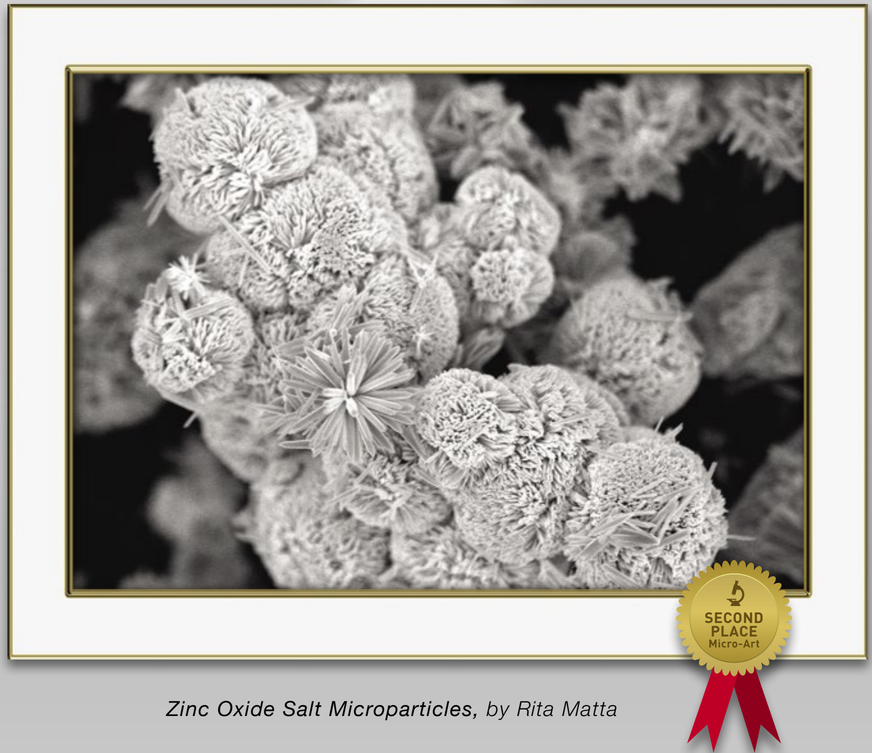
Why did you pick this image?
"All biologists work with these colors, and these are interesting things. Things become very fascinating when you look into the really minute. We see really tall buildings and architectures, but when you go deep into the micro- and nano-levels, you see all of these other things happening and it's really fascinating."

Do you do any artwork outside of research?
"I love to draw things. I did my Ph.D. in Italy, which I think was one of inspirations that you look to for beautiful architecture and sculptures."

What's the importance of a good research image?
"If everyone sees them, they will generate new ideas and new thinking for how to look into different things and get different perspectives. And they're helpful to present to people who are not in this field and to be able to show them what is happening."

What the critics say:
"This image of cell escape from a tumor looks like a big, bold action painting," Schilling says. "The splashes of color suggest chaotic motion through the shapes of the focal adhesions and the actin cytoskeleton."

"Zinc Oxide Salt Microparticles Imaged Using Scanning Electron Microscopy"



Zinc Oxide Salt Microparticles, by Rita Matta

Rita Matta, a Ph.D. candidate in the lab of Anjelica Gonzalez, an associate professor of biomedical engineering, won second place in the micro art category.

The image is from work that aims to better understand the signaling clues that promote neural stem cell migration. Doing so could help tissue engineers and neurologists develop therapies that enhance cellular response to brain tissue damage.

What's happening here?
"These are called zinc oxide particles, which we use to porate our hydrogels," Matta says. "We're aiming to produce gels that look like human tissue. For my research, I'm trying to mimic brain tissue, and we can use the gels to observe cell migration.

Why did you choose this image?
"I liked the focus, how we have this one particle in the center and some irregular particles around where you can actually see the fibers in good detail. I liked the contrast as well as the clarity of the different particles around the main one in the focus. These images come out really beautiful — it was really difficult to pick just one! These images I took using a scanning electron microscope (SEM), but most are taken using a fluorescent microscope. Those images are also very beautiful.

"SEM images are also in grayscale so that has its own perks. I think the beauty of SEM is that you get these images raw with no color, and they shine in their own way."

Do you ever frame your pictures?
"Oh yeah, this one has been my laptop background for about a year and I've had it framed at my desk for about a year. When I present at conferences, I hear a lot of 'Wow!' and 'Amazing!'"

Why does biomedical engineering produce such striking images?
"As engineers, we think very critically and systemically, so that when we're thinking of an image it's not as simple as taking a picture. It's optimizing, designing, characterizing. So as an engineer, there's a lot more that goes into capturing a beautiful image."

What the critics say:
"This SEM image could be a ringer for an Ansel Adams close-up photograph of leaves," Schilling says. "Adams showed the fine structure of leaves, declaring them to be a beautiful thing worthy of attention and meditation. These microparticles also ask for similar attention, when you stop and consider them in this context."

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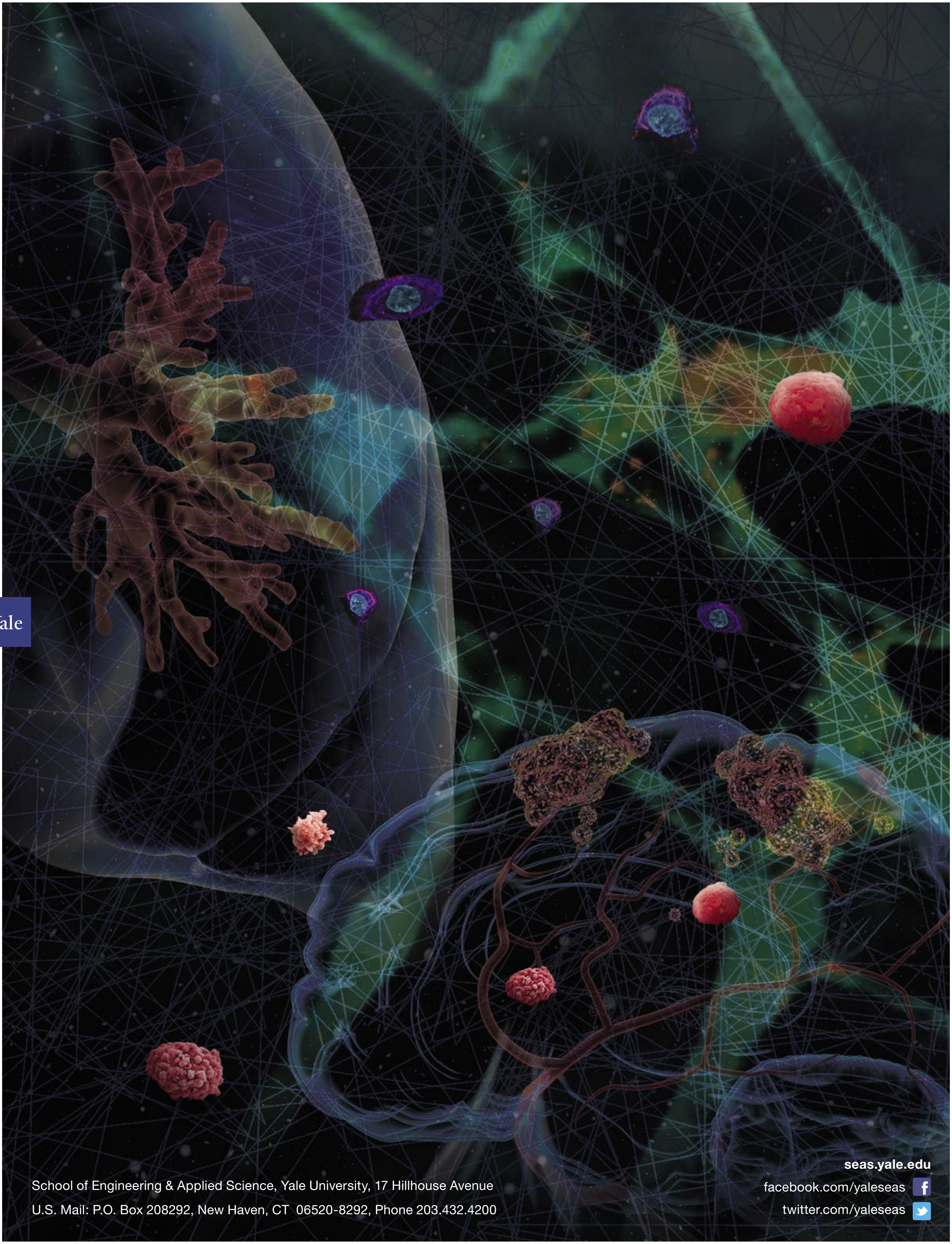

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