## Innovation Incubation

SEAS fosters entrepreneurial ventures that innovate beyond the classroom and the lab

## Creating as a Community

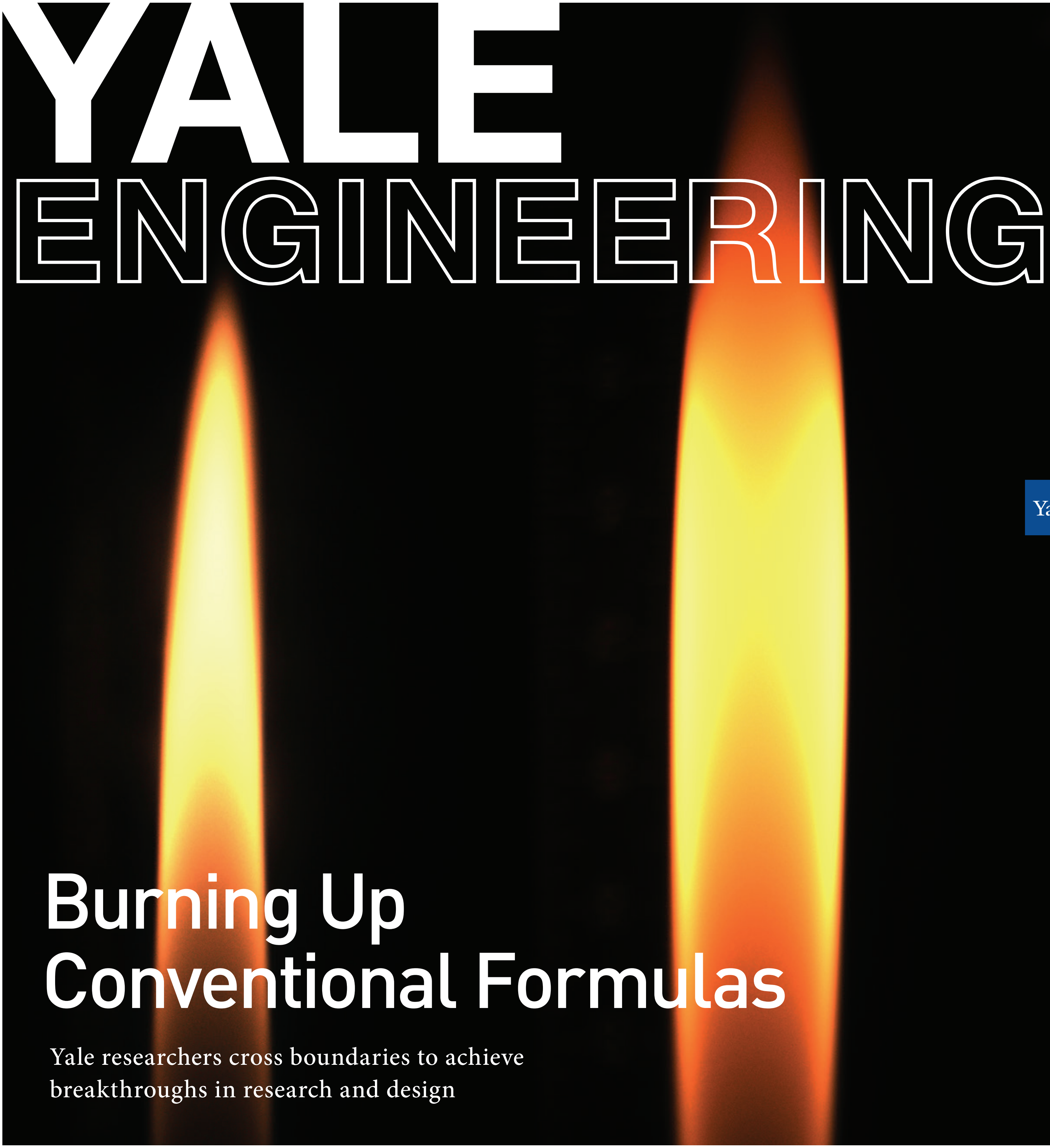
Yale's Center for Engineering Innovation & Design opens its doors

## Special Delivery

Novel nanoparticles offer advances in cancer treatment, stem cell cultures, and more

2012

# YALE ENGINEERING



# Burning Up Conventional Formulas

Yale researchers cross boundaries to achieve breakthroughs in research and design

Yale

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

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EDUCATION · ENTREPRENEURSHIP · INTERDISCIPLINARY · MEDICAL INNOVATION · TECHNOLOGY

**YALE ENGINEERING** 2012

**YALE UNIVERSITY**
**School of Engineering & Applied Science**

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# Message From the Dean

Here at Yale, interdisciplinary collaboration is a hallmark of many academic programs, and a principle we fully embrace at the School of Engineering & Applied Science. Our students and faculty are encouraged to connect with their peers both across engineering departments and across campus, and the fruits of such efforts are evident in the pages of this year's magazine, which highlights the value of such collaborations.

Solutions to the global problems of the 21st century can only be achieved when engineers join their colleagues from the sciences and humanities to apply engineering principles within the context of the human experience. Whether the challenge is sustainable energy, climate change, clean water, security, transportation, or disease, a truly collaborative effort across all disciplines is required — exactly the kind of effort we hope to encourage on an even larger scale with the opening of the new Center for Engineering Innovation & Design, which debuted at the start of the 2012-2013 school year.

Yale Engineering is at the cutting edge of research that addresses global societal problems. The faculty, researchers, and students in our laboratories are developing new materials, engineering tissues, building photon-powered machinery, and much more — each with the end goal of leading collaborative efforts toward solutions to improve the human condition. I am proud to be able to share their achievements with you in the 2012 edition of *Yale Engineering*.

T. K. Vanderlick

T. Kyle Vanderlick
Dean, School of Engineering & Applied Science

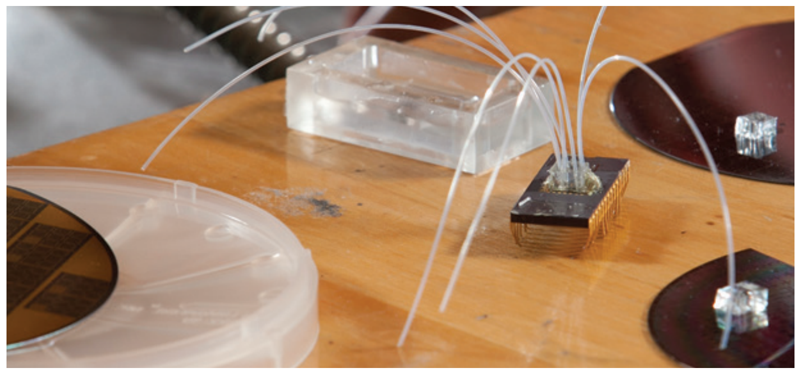
# Year in Review

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

2011 : September

## New Materials Research Center

A $13 million grant from the National Science Foundation established a Center of Excellence for Materials Research and Innovation, doubling the capacity of Yale's existing Center for Research on Interface Structures and Phenomena (CRISP). This new center became part of the NSF's Materials Research Science and Engineering Centers (MRSECs).



2011 : October ^

## Screening for Food Safety

A team of Yale Engineering students led by graduate student Monika Weber won the grand prize in *NASA Tech Briefs* magazine's national "Create the Future" design contest. Weber and her team came up with a design for a device to screen food for bacterial infection, and also allow medical personnel to identify bacteria from blood samples. For winning the contest, which drew more than 7,000 entries, the team was awarded $20,000.

*Kathryn Miller-Jensen*

< 2011 : November

## Gates Foundation Funding

SEAS received funding through the Bill & Melinda Gates Foundation's Grand Challenges Explorations for work by biomedical engineering assistant professor Kathryn Miller-Jensen. The program awarded 110 grants including Miller-Jensen's, which focuses on distinguishing HIV-infected cells from healthy cells using their phosphorylation signatures. Grand Challenges Explorations provides funding for projects that show promise in addressing global health issues where solutions are currently lacking.

Yale

INTERDISCIPLINARY

W. Mark Saltzman

< 2011 : December

## Novel Nanoparticles

Chair of biomedical engineering W. Mark Saltzman and collaborators developed a novel nanoparticle with applications in gene therapy. The group's particle mimics the behavior of a virus by introducing a specific gene into cells; but their approach avoids the potential for immune reactions that comes with viral gene therapy methods. The researchers tested the new nanoparticles both in cell culture and in mouse models, and hope to eventually adapt the technology for use in the treatment of brain tumors.

2012 : January

## Intelligent Buildings

Led by associate professor of electrical engineering & computer science Andreas Savvides and Michelle Addington of the School of Architecture, Yale's Intelligent Buildings Project received a $200,000 grant from the Wells Fargo Foundation. The project aims to develop new methods for evaluating energy consumption in large buildings. An early effort found potential savings of 30% in power costs at Yale's Rosenkranz Hall, home to the Department of Political Science and the Jackson Institute for Global Affairs, with the use of a novel system that would manage air-handling in zones of the building based on real-time occupancy data.



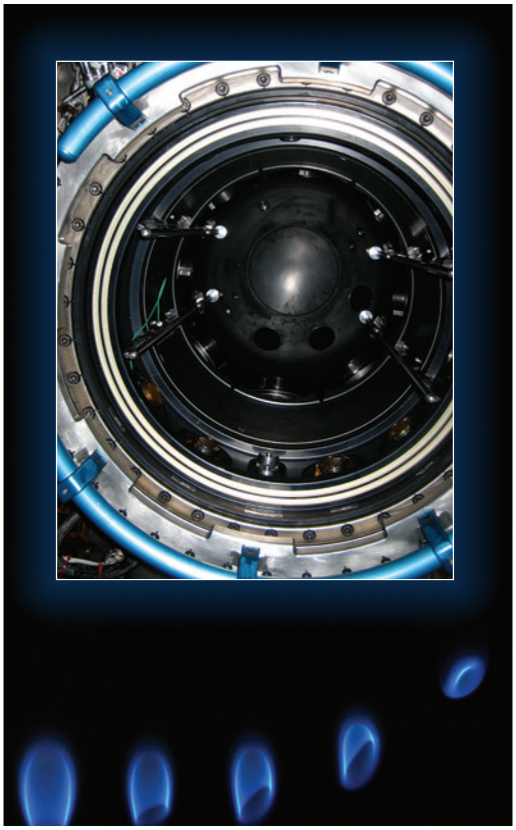
2012 : February >

## Engineers Week

SEAS hosted its first ever "Engineers Week," with events planned primarily by graduate students Enping Hong of biomedical engineering and Ying Zheng of mechanical engineering & materials science. The week ran simultaneously with National Engineers Week, which was established by the National Society of Professional Engineers in 1951. Yale's Engineers Week included an academic fair featuring engineering student groups, a catapult design competition, and a panel with Yale Engineering faculty members.

Continued on next page →

## Year in Review



< 2012 : March

# Modeling in Microgravity

The last of a set of microgravity combustion experiments, termed the Structure and Liftoff in Combustion Experiment (SLICE), was completed on the International Space Station by astronaut Don Pettit. The experiments were performed as part of combustion modeling efforts by mechanical engineering professors Marshall Long and Mitchell Smooke, with the end goal of allowing engineers to design improved combustion systems. A future set of space station experiments is planned, and may begin in the next three to four years.

2012 : April

# Supplying $CO_2$-Free Electricity

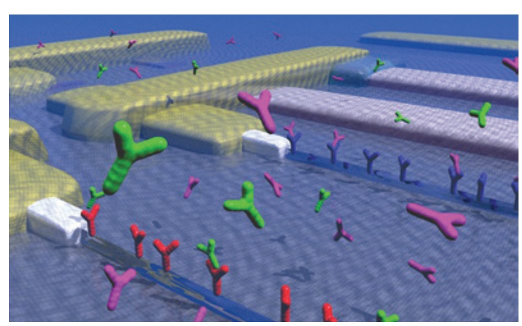
Menachem Elimelech, professor of chemical & environmental engineering, reported that pressure-retarded osmosis could supply electricity for more than 500 million people. Elimelech and a colleague calculated that the process, which exploits the difference in salt content between freshwater and seawater as rivers flow into oceans, could supply that much power using only a tenth of the global river water flow into oceans, and do so without generating carbon dioxide. By comparison, they calculated, electricity generated by a coal-based power plant would release more than one billion tons of greenhouse gases in a year.



2012 : May >

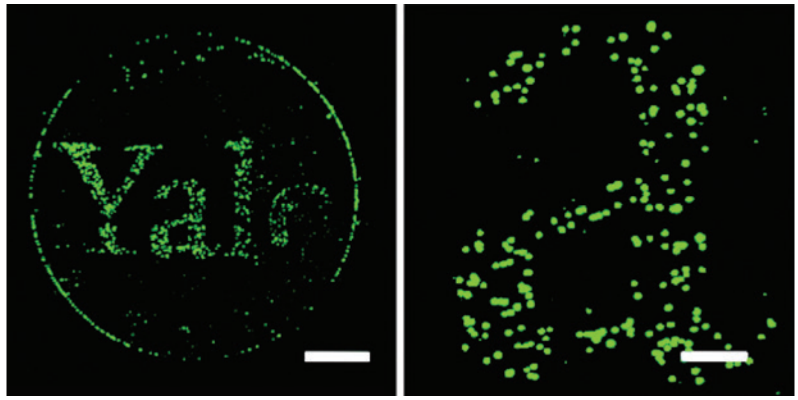
# Protein Interactions in Real Time

Electrical engineering professor Mark A. Reed led a group who demonstrated that silicon nanowires can be used as sensors in a system to study interactions between proteins. Previous methods were limited by low sensitivity and speed, but the researchers' approach provides real-time results with higher sensitivity. Eventually, this approach has the potential to be applied to "lab on a chip" technologies that are of great value in remote regions, where lab testing for disease diagnosis or genetic testing may not be readily available.

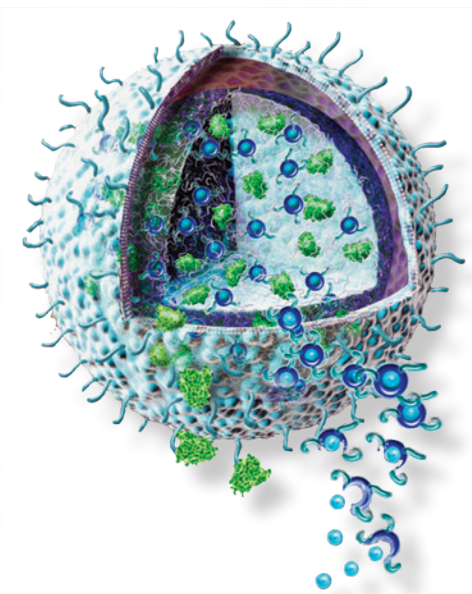


2012 : June >

# Nanowires Count Tumor Cells




Working with colleagues from Yale and elsewhere, Rong Fan, assistant professor of biomedical engineering, developed a nanowire-based system to separate and count circulating tumor cells from blood samples. These cells are shed by both primary and metastatic tumors and are of interest in the study of how cancer metastasizes and spreads, and more importantly are early-stage biomarkers for diagnosis of metastatic diseases. Fan and colleagues noted that their laser scanning technique could be fully automated for use in a clinical setting.



< 2012 : July

# Disrupting Tumors' Defenses

Tarek Fahmy, associate professor of biomedical engineering and chemical & environmental engineering, reported a new technique for the treatment of cancerous tumors. Working with colleagues at the Yale School of Medicine and elsewhere, Fahmy developed biodegradable nanoparticles that can deliver therapeutic agents directly to the site of a tumor, both disrupting the tumor's ability to defend itself from the immune system and encouraging a stronger immune response. Tests in mice showed a significant delay in tumor growth and increased survival time, with additional tests planned.

2012 : August

# Building Better Biomaterials

Paul Van Tassel, professor and chair of chemical & environmental engineering, reported an approach to address a key challenge in biomaterials design. Applications in this field often require materials to be both mechanically rigid (to promote strong cell adhesion) and bioactive (able to communicate specific cues to contacting cells). To date, achieving one of these features usually required sacrificing the other. Van Tassel and colleagues presented an approach that forms a thin polymer film biomaterial in the presence of sacrificial nanoparticle templates. The film is rigidified using chemical cross-linking before the template species are slowly dissolved, leaving "pores" that can be filled with proteins to render the film bioactive.

# Building Bridges

## Engineering's campus footprint grows with two new facilities in 2012


Yale

INTERDISCIPLINARY

Engineering is an intellectual bridge between the sciences and the humanities: engineers apply scientific principles to advance the human condition, relying as much on an understanding of physics and mathematics as they do on an appreciation of history and philosophy. Engineering bridges the physical laws dictated by science with the limitless nature of human talents and passions found in the humanities.

At Yale, however, engineering is not only an intellectual bridge, but also a geographical one. Engineering spaces act as the bridge between the sciences and the humanities on Yale's campus — and that bridge continues to grow stronger each year. In addition to launching the new Center for Engineering Innovation & Design in Becton Center (see feature story, page 18), SEAS also opened new facilities at the former site of the Yale Health Plan this fall, expanding engineering's footprint along Hillhouse Avenue. Four floors of the building at 17 Hillhouse were fully renovated as part of a $17.5 million project. The first floor and basement offer six classrooms as well as academic support offices, while the second and third floors include lab space, conference rooms, and offices for 12 professors and their research teams.

Library services for the Engineering & Applied Science Library are also available at 17 Hillhouse, with an engineering librarian and a science data librarian in residence for students and faculty within SEAS.

Yale

ENTREPRENEURSHIP

# Innovation Incubation

## 3Derm ▪ Chairigami ▪ Red Ox Systems

Yale's unique culture of engineering fosters innovation, and there's no better evidence of that innovative spirit than the entrepreneurial ventures that have emerged from the School of Engineering & Applied Science. From remote dermatology to cardboard furniture, SEAS students and faculty are bringing their ideas out of the classroom and laboratory to solve real-world problems.


Left: *3Derm's initial design*

Right: *rendering shows updates to scanning device. Property of 3Derm Systems, LLC.*

# 3Derm

3Derm Systems, LLC, founded by biomedical engineering student Liz Asai and electrical engineering and computer science student Elliot Swart, develops biomedical technologies and low-cost medical devices. The venture began when Asai and Swart, along with mechanical engineering student Nickolas Demas, developed a device that captures three-dimensional images of skin abnormalities, which are then uploaded to a web-based database. The technology allows dermatologists to remotely analyze and monitor patients' skin conditions, with patients being able to upload new images over time. The potential impact is substantial; a study conducted by the students found that dermatologists were able to diagnose as many as 40% of skin lesions as benign based on images alone.

The students built an initial prototype of their device, the "Stereoscopic Plug-and-Play Dermatoscope and Web Interface," for just $400 using the School's 3D printing facilities. Their design won $100,000 in the Center for Integration of Medicine & Innovative Technology's Primary Healthcare Prize competition in 2011, and an additional $12,500 as the first place undergraduate winner in the Collegiate Inventors Competition. Demas has since departed to start a small business providing design and engineering consulting for medical professionals and inventors in the greater New Haven area; Asai and Swart incorporated earlier this year and are continuing to work on a patent-pending version of their device, consulting with a design lab in Palo Alto to make the tool more patient-friendly.

They've also been exploring new funding opportunities. At press time, the two were applying for a federal small business grant; they plan to produce a run of a few hundred devices and perform a clinical trial to study their tool's home monitoring capabilities. (A previous clinical trial focused on how well the tool worked for physicians; in this trial, they'll give the tool to patients to take home and generate scans every few weeks for remote monitoring.)

Asai credits SEAS and the Yale Entrepreneurial Institute for helping their group find its business footing.

"Engineering has been behind us every step of the way," says Asai. "From negotiations with lawyers to funding support, we got all that through the engineering department, and through YEI. We've basically gotten an entire business team together through them."

Continued on next page →

Innovation Incubation


*Zachary Rotholz at the Chairigami storefront*

# Chairigami

Mechanical engineering graduate Zachary Rotholz did his senior project on the material properties of corrugated board, after years spent teaching kids to engineer with cardboard, working as a cardboard apprentice, and designing cardboard furniture for dorm rooms during his time as a Yale undergrad. In 2011, Rotholz launched Chairigami, which sells "temporary yet durable" furniture made entirely from cardboard.

The idea, explains Rotholz, is to rethink contemporary furniture. Instead of buying cheap and flimsy pieces that can only end up in a dumpster when they wear down or break, his customers take home inexpensive but sturdy tables, chairs, and even beds that are easy to transport and assemble without tools or glue, and can be recycled when it's time for something new. He's filed for patents on most of his products and his manufacturing process, and recently completed his first manufacturing run to keep pieces in stock (previously, they were all made-to-order).

Although Chairigami has a storefront location, Rotholz is beginning to expand his focus on online sales. He also has ideas for marketing his products to new audiences, including theater companies who want them as props, startup companies that might need quick, cheap, and moveable furniture, and of course, college students. Separately, he's collaborating with the Yale Center for British Art to create modular toys out of cardboard, providing inexpensive kits that teach engineering principles and structural design to kids.

None of this, says Rotholz, would have been possible without the support he received from SEAS.

"It would have been impossible to take all these designs and make them full-scale without having access to the tools and machinery the School provided," he says. "That was just an incredible asset, but so was having an engineering community to test my product, and ask for advice — it was great to get initial feedback from all of the engineers. Even after I graduated, I feel like I received so much support from the engineering school."

# Red Ox Systems

In the United States, oil and gas companies spend billions of dollars each year to treat and dispose of wastewater that's produced during oil and gas extraction. But to the Yale students and faculty behind Red Ox Systems, one industry's waste stream is their revenue stream.

Oil and gas wastewater has an extremely high salt content, in addition to various other chemicals collected while extracting fuels from the earth. Traditional disposal methods require the wastewater to be treated and transported to a suitable deep well and re-injected into the earth, or prepped for disposal in a surface evaporation pond. Both methods have significant time and financial costs, and don't take advantage of the recoverable materials within the wastewater.

The group uses an electrochemical desalination cell to not only remove up to 90% of salt from wastewater, but also recover coproducts such as hydrochloric acid that can be resold, all while generating electricity.

"We're commercializing a technology that changes the paradigm for wastewater treatment from waste minimization to value creation," says CEO David Kohn (engineering sciences '11), who co-founded the company with fellow SEAS graduate Claire Henly (environmental engineering '12) and advisors André Taylor and Menachem Elimelech of the chemical & environmental engineering faculty.

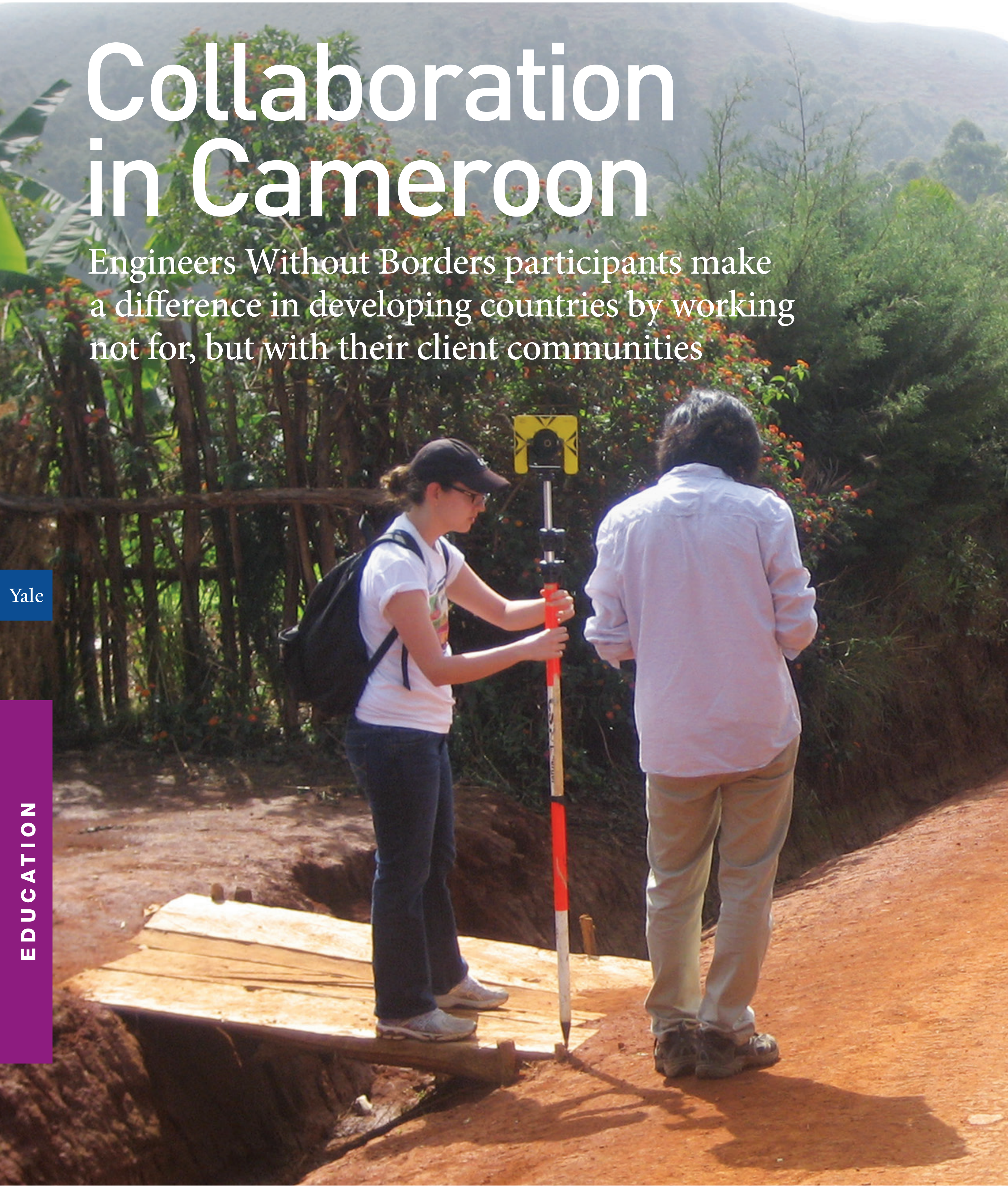
The team received the 2012 Sabin Sustainable Prize this April, awarded to "the best Yale student and/or faculty ideas for a product, service, project or program that advances a more sustainable way of life." The contest, established by the Andrew Sabin Family Foundation and managed by the Yale Center for Business and the Environment, awards a $25,000 cash prize.

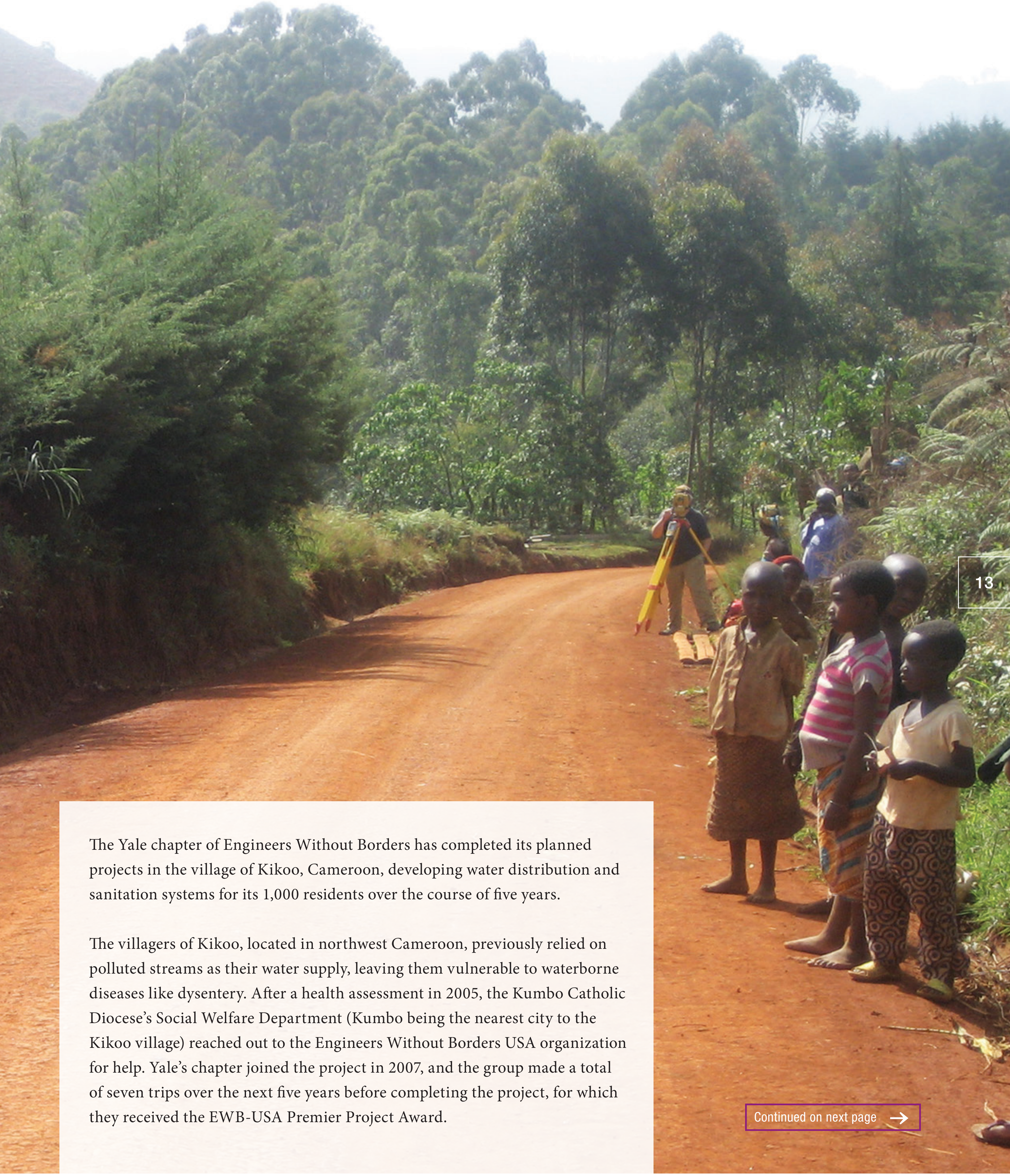


*David Kohn and Claire Henly show their prototype*

# Collaboration in Cameroon

Engineers Without Borders participants make a difference in developing countries by working not for, but with their client communities





The Yale chapter of Engineers Without Borders has completed its planned projects in the village of Kikoo, Cameroon, developing water distribution and sanitation systems for its 1,000 residents over the course of five years.

The villagers of Kikoo, located in northwest Cameroon, previously relied on polluted streams as their water supply, leaving them vulnerable to waterborne diseases like dysentery. After a health assessment in 2005, the Kumbo Catholic Diocese's Social Welfare Department (Kumbo being the nearest city to the Kikoo village) reached out to the Engineers Without Borders USA organization for help. Yale's chapter joined the project in 2007, and the group made a total of seven trips over the next five years before completing the project, for which they received the EWB-USA Premier Project Award.

Continued on next page →


*Yale EWB chapter members conduct health surveys as part of their water supply and sanitation projects*

Yale

EDUCATION

The efforts in Kikoo mark the second completed project for EWB-Yale, which was founded in 2004 by associate professor of environmental engineering, chemical engineering and forestry & environmental studies Bill Mitch. The group's first efforts were in Honduras, where they implemented repairs to an existing water system for the town of El Rosario before being given the Kikoo project.

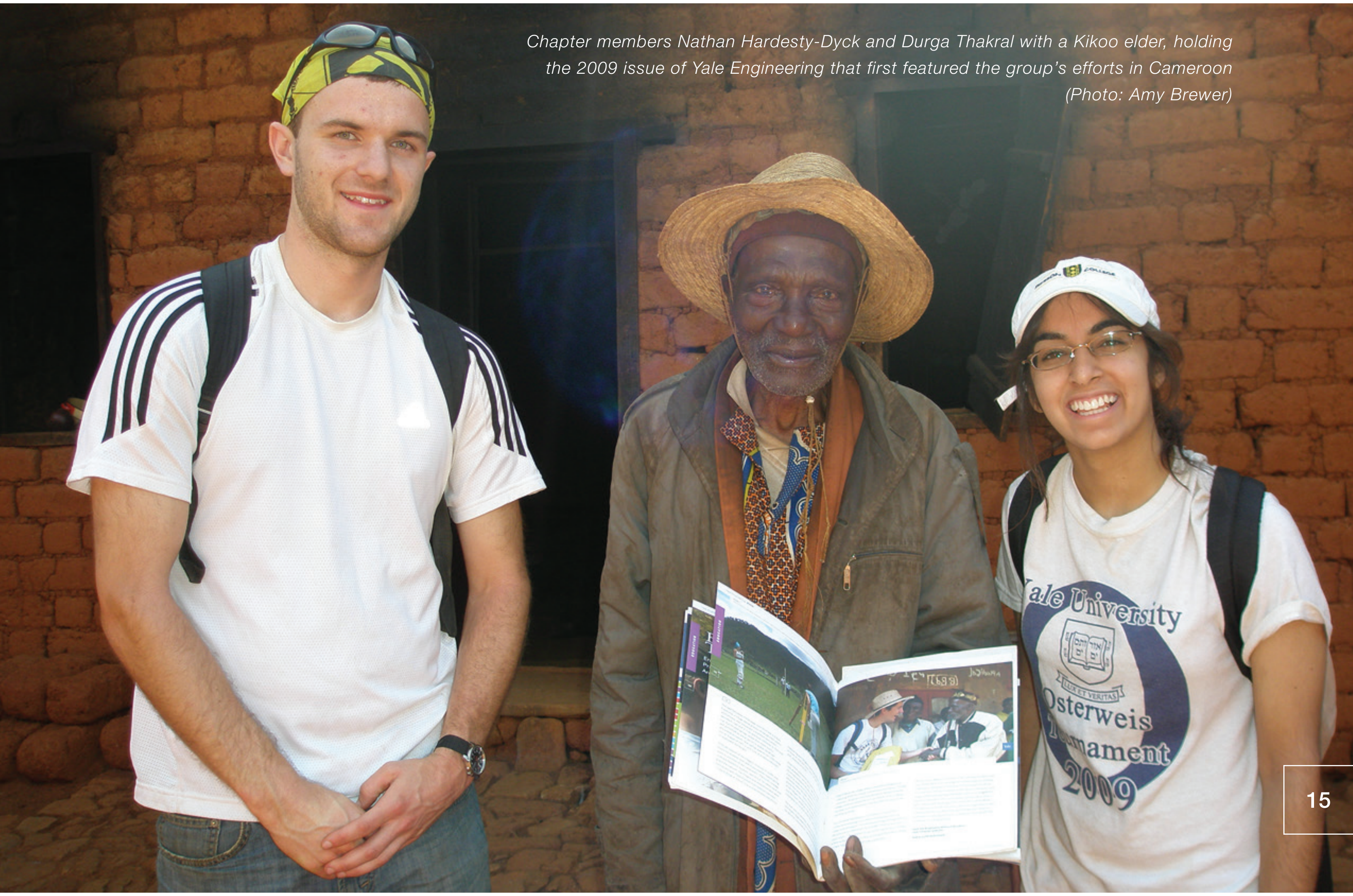
For Mitch, founding the group was an opportunity to let students apply some of the theoretical constructs they get in classes and see how they actually play out in practice.

"EWB is a good way to introduce people to practical applications of engineering, and also combine that with the obvious interest in helping developing countries," says Mitch.

Dave Sacco, a civil engineer and Yale architecture graduate who works with the group as a professional mentor and joined the students on all but two of the trips to Kikoo, agrees.

"EWB-USA projects offer an opportunity to interact with 'clients' and tailor a solution to their needs and resources," says Sacco. "I think of engineering as the place where science encounters people's needs; an EWB project is a tangible way to see that there are design considerations that cannot be expressed numerically, like culture or experience or motivation."

Sacco has also been honored by the national EWB organization — earlier this year he received the EWB-USA Professional Founders Award, which recognizes individuals who "exhibit outstanding leadership in their regions, chapters and/or project teams by fostering responsible leadership with other members, chapters and partnering communities and helping partner communities meet their




*Chapter members Nathan Hardesty-Dyck and Durga Thakral with a Kikoo elder, holding the 2009 issue of Yale Engineering that first featured the group's efforts in Cameroon (Photo: Amy Brewer)*



basic human needs." The award comes as no surprise to the student members of the group or to Mitch.

"Dave is a great mentor to the students," says Mitch. "His involvement is a big part of the reason our chapter was able to win the premier project award."

Sacco, for his part, places the credit for the group's successes firmly back in the hands of the students.

"The Yale students I've worked with over the past seven years have come to EWB-USA for a variety of reasons and from a lot of different directions," says Sacco. "The best of them have been extraordinarily dedicated to the organization but even more devoted to our partner communities. Their enthusiasm and energy have been essential to our successes."

Chapter co-presidents Natalie Pancer (Silliman '14) and Parker Collins (Trumbull '13) were enthusiastic about the idea of joining EWB even before they were accepted to Yale.

"When I was applying to colleges, this was one of the things that stood out for me," says Pancer. "Once I was here, I joined because I think it's amazing the way that we impact communities, and I wanted to do something outside of New Haven." Pancer, a biomedical engineering major, is particularly interested in the public health aspect of the project, including the health surveys that the students do in communities before and after the completion of their projects.

Collins, an environmental engineering major, is particularly proud of the group's efforts to design solutions

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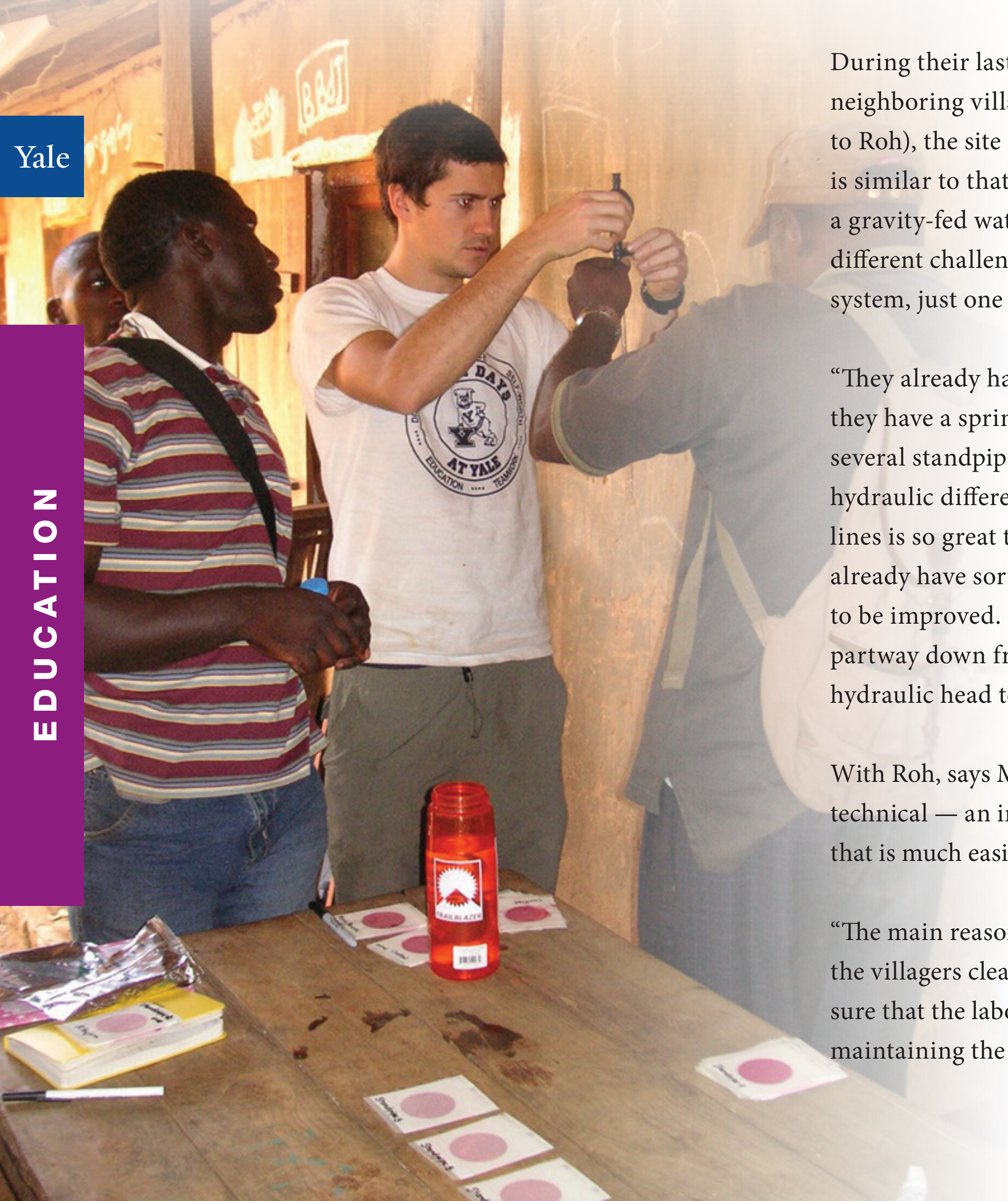
that can be maintained by community members after the students have returned to Yale.

"I was excited about EWB before college too, but I've stuck with it because of the sustainability issue," he says. "I think a lot of people go abroad and do something amazing and very well-intentioned, but after they leave, it kind of stops. And I don't think that's the case with us. We're always working to improve that, and I like that that's a consideration with our group.

*Testing water cleanliness early in the Kikoo project*



"I like working *with* the communities," he continues. "They obviously know a lot more than we do about the local topology and what's going on with the ground, what will work and what won't, even socially. It really is a collaboration, which I don't know that a lot of other projects are. The communities deserve as much credit, if not more, than we do."

Sacco echoes Collins's sentiment.

"The technology we are applying is not cutting edge, but very purposefully chosen to reflect locally available materials as well as the skill level and work experience of the community, in order to maximize village participation and ensure ongoing maintenance," he says.

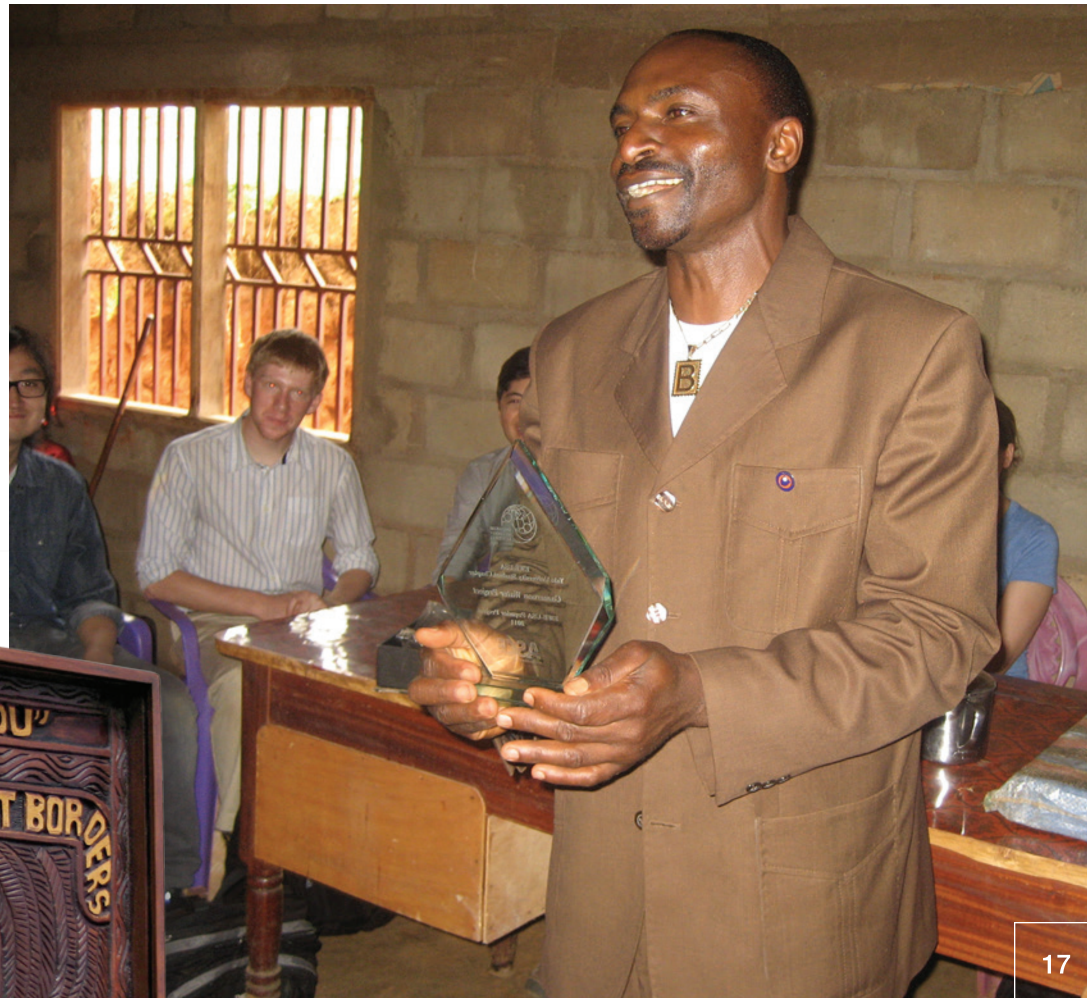
During their last trip to Kikoo, the group also visited the neighboring village of Rohvitangitaa (usually shortened to Roh), the site of their next project. While the basic goal is similar to that of their initial goal in Kikoo — develop a gravity-fed water distribution system — Roh offers a different challenge in that it already has the makings of a system, just one that needs improvement.

"They already have a portion of a system. Essentially they have a springbox and a pipeline that comes down to several standpipes in Roh village," says Mitch. "But the hydraulic difference between the spring and these pipelines is so great that they can't turn the faucet off. So we already have sort of the makings of a system, it just needs to be improved. Basically we'll be building a storage tank partway down from the springbox so that we can reset the hydraulic head to something that will not burst fittings."

With Roh, says Mitch, the challenges are more societal than technical — an important aspect of engineering problems that is much easier to see in practice, outside the classroom.

"The main reason why Kikoo was successful was because the villagers clearly had organized themselves to make sure that the labor was there, as well as the commitment to maintaining the system. It wasn't entirely clear with Roh

*Kikoo water secretary Wilfred holds a replica of the EWB-USA Premier Project award, presented to the community by EWB-Yale to recognize the joint efforts of both groups. The community presented the Yale chapter with a hand-carved wooden clock as a thank you gift.*




whether the same thing was going to go on," says Mitch. "So over the past couple of years, as we've been going to Kikoo, the group has been going over to talk to Roh and make sure that that same commitment applied, and put in some conditions that they would have to follow to make sure that that commitment was demonstrated."

The group has already collected initial data for the system in Roh, and they plan to begin design work this fall in preparation for an initial implementation trip in 2013. The full build-out of the system will be another multi-year project.

In the meantime, the EWB-Yale members have plenty to do back on campus as well.

"Although our primary function is to go to Cameroon and do our projects, there are so many things to do around here," says Pancer. "Fundraising, campus relations, education work that we do with New Haven schools, even concrete-pouring workshops, since that's what we do on the ground in Cameroon. There's always room for more people, even if they're not necessarily going on a trip the first time one comes up."

> Students interested in joining the group can visit the EWB-Yale chapter website at www.yale.edu/ewb. Alumni and industry partners are also encouraged to share their knowledge and expertise as well as donations of equipment — the group is especially interested in portable GPS units, AutoCAD software, and survey equipment. Finally, financial contributions to the chapter are accepted through the EWB-USA organization and are tax deductible; more information is available on the group's website.

EDUCATION

# Creating as a Community

Engineering's new innovation & design center is poised to connect groups throughout and beyond Yale's campus in open-ended problem solving



Yale's Center for Engineering Innovation & Design opened its doors this fall for the start of the 2012-2013 school year. First announced by Dean of Engineering T. Kyle Vanderlick in 2011, the $6.5 million Center offers 8,500 square feet of space, all part of a goal to encourage collaborative idea generation not just among engineers, but with students from the many schools and programs on Yale's campus.

"Innovation develops by connecting ideas from seemingly unconnected areas," says Vanderlick. "Just as engineering acts as a bridge between the sciences and the humanities, the CEID will bring together Yale's most important assets, its wide-ranging students and faculty, in an intellectually stimulating environment."

"The Center will empower Yale students to realize their creative vision," agrees CEID Director Eric Dufresne, associate professor of mechanical engineering and materials science. "It will help students bridge the gap between formal coursework and the real challenges that face society."

More than just being a space to gather and generate ideas, the Center gives students the ability to realize their ideas with the resources it offers: its affiliated faculty and staff, available training (both in higher-level design and the basic skills required to work with tools), and the physical tools themselves. Beyond the traditional wood and machine shops found in design spaces, the CEID work areas offer two high-end 3D printers, computer-controlled

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milling machines, and a large bed laser cutter to enable rapid prototyping. In a unique and progressive move for a design space, the facility also includes a wet lab that can be used to support design efforts in medical devices or research in microfluidics, which is particularly well suited for undergraduate research efforts.

Situated on the first floor and mezzanine of Becton Center, the CEID's working space includes a reconfigurable classroom that seats 50, as well as five reconfigurable, reservable meeting rooms on the second floor. The meeting rooms, which offer whiteboard space as well as computer monitors, have movable walls and can be combined to accommodate larger groups when necessary.

Finally, the CEID's largest area is an open studio space on the ground floor, fully visible to passers-by on Prospect Street via its wall of floor-to-ceiling windows and outward-facing projectors displaying current center activities. This public face of the CEID serves as an inviting reminder that the space is open to the entire Yale community.

"One of Yale's greatest strengths is its diverse collection of leading academic programs and disciplines," says Richard Levin, Yale University President. "The new Center for Engineering Innovation & Design gives students throughout all of these disciplines the opportunity to leverage their different backgrounds and experiences and collaborate in open-ended problem solving."




As a natural progression of such collaborations, the CEID can also serve as an incubator for commercial product design, continuing the engineering school's tradition of entrepreneurial spirit (see "Innovation Incubation," page 8). The CEID also offers the potential for increased collaboration with the Yale Office of Cooperative Research and the Yale Entrepreneurial Institute, which already work with many engineering students and faculty on ventures ranging from cardboard furniture design to a remote dermatology device — both developed by Yale engineering students using equipment that the CEID now offers for use by students throughout the Yale community.

Academically, the CEID will support both existing and new classes, from capstone design courses, to new product development, to the popular ME491, "Appropriate Technology for the Developing World." The course (co-developed and co-taught by CEID Assistant Director Joseph Zinter) is open to students from across Yale, pooling their varied talents and backgrounds to address the multifaceted problems of the developing world.

Past groups of ME491 students have developed a mechanical intervention to promote economic growth among farmers and a system to increase the availability and

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Yale

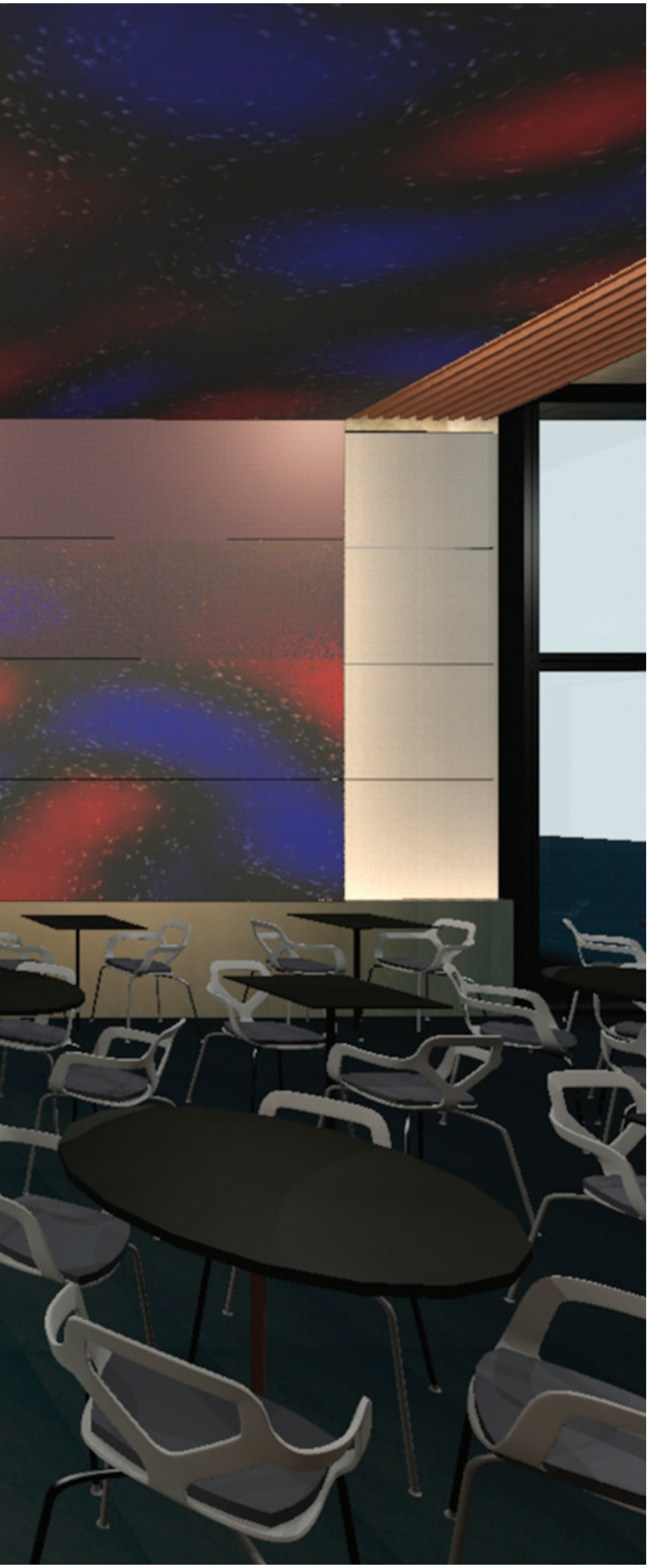
EDUCATION

# Caffeine and Creativity

Adjacent to the new Center for Engineering Innovation & Design space in Becton Center, a new engineering café will serve as a meeting spot for students and faculty from across campus, uniting many different disciplines within an engineering space — over a cup of coffee and under a sea of LED art.

The café features a signature 356 square foot installation of programmable art. Climbing to cover nearly a full wall and wrapping across the ceiling, the piece includes more than 23,000 individual LEDs, each individually programmable to display custom images and video visible throughout the space and to passersby on the street via new windows on the south side of the café space. (In the rendering shown, the installation is displaying images from the research of Nicholas Ouellette, assistant professor of mechanical engineering & materials science, who studies fluid dynamics.)

Students will have access to the blank canvas of the LED installation, so that not just engineering majors but all students can produce content to be viewed by the entire Yale community. As with the café itself and the neighboring CEID, the feature wall can draw a wide spectrum of students and faculty, enabling Yale community members who might not otherwise interact to do so in a space designed to promote creativity and the exchange of information.



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reliability of electricity in both rural and urban settings in Ghana. Last year's class included 15 graduate and undergraduate students from eight different disciplines: mechanical, chemical and environmental engineers worked alongside students from physics, global affairs, economics, management, and anthropology. ME491 aims to do what the CEID looks to achieve on a larger scale: actively engage students from different backgrounds in collaborative learning by focusing on real problems and, potentially, designing novel solutions.

Beyond integrating design into coursework, however, Dufresne is enthusiastic about extracurricular design opportunities as well.

"Yale students are creative, energetic and smart. They are not satisfied with challenging coursework," says Dufresne. "They are passionate about extracurricular activities that allow them to express themselves creatively while working on real projects that have the potential to change lives."

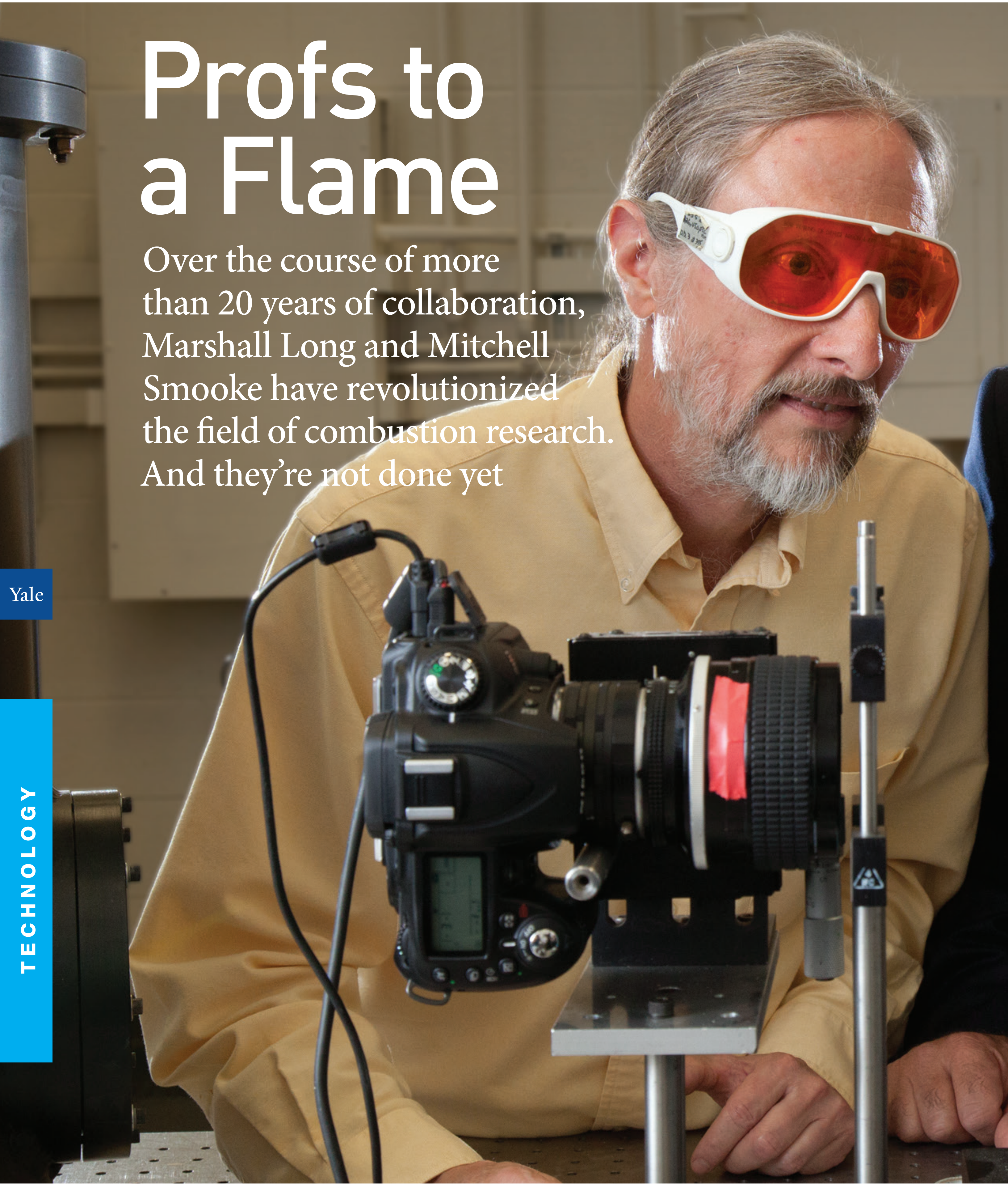
There are a number of student groups whose efforts could be well-served by the interdisciplinary capabilities and resources of the CEID, Dufresne notes, highlighting Yale's iGEM (International Genetically Engineered Machine) group as one such organization. Their efforts are particularly well suited to take advantage of the CEID's wet lab facilities, for example.

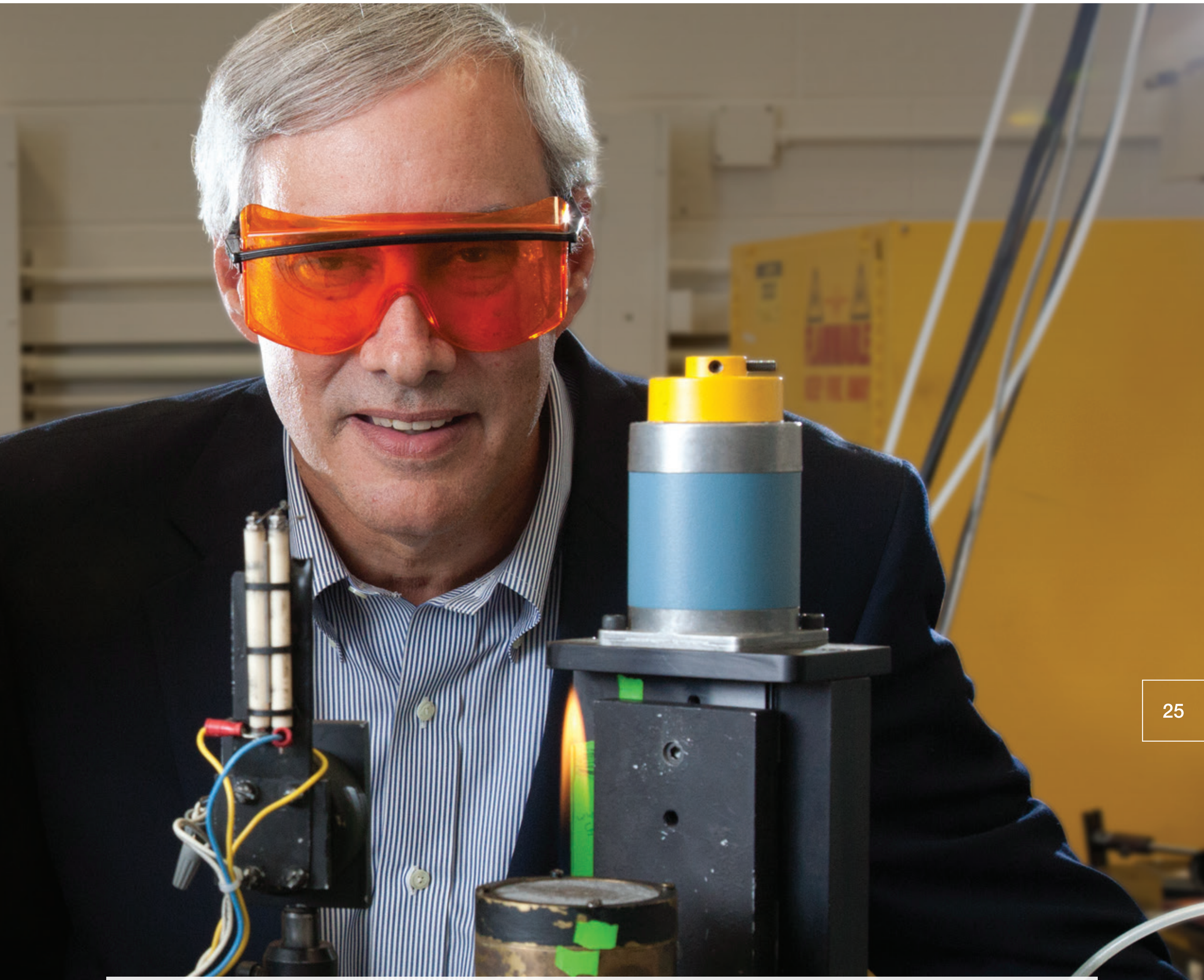
And of course, beyond organized student groups, the CEID will be open to the curious individual student as well — with hopes that he or she will end up collaborating with others.

"As we do within SEAS itself, we want to encourage collaboration between many different groups at Yale, and engage both engineering students and those from other disciplines in creative problem solving," says Vanderlick. "Ultimately, the CEID will be a community of people creating."

# Profs to a Flame

Over the course of more than 20 years of collaboration, Marshall Long and Mitchell Smooke have revolutionized the field of combustion research. And they're not done yet







In 1984, Mitchell Smooke was a newly appointed assistant professor of mechanical engineering, with a background in combustion research honed over six years as a staff scientist at Sandia National Labs. Down the hall another combustion researcher, Marshall Long, had been appointed an assistant professor of mechanical engineering just a few years earlier after completing his PhD at Yale.

The two had seen each other at Department of Energy contractor meetings, but had never met before Smooke joined the mechanical engineering department. On the recommendation of a colleague from Sandia, Smooke invited Long to lunch to discuss the possibility of working together; they met at Naples Pizza on Wall Street. More than two decades later, Long and Smooke have combined to receive more than $8M in grants on the way to publishing dozens of papers together and graduating more than 20 students. They have both been elected fellows of numerous research societies while receiving awards for teaching and research — Smooke was honored in August with

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the Combustion Institute's Ya B. Zeldovich Gold Medal for outstanding contributions to the theory of combustion — and have both served as chair of the mechanical engineering department. (And Naples Pizza is still standing.)

Although both researchers are focused on combustion and hold the same position — professor of mechanical engineering & materials science & applied physics — they go about things very differently. Long approaches combustion research from the experimental side. In particular, he uses laser diagnostics to study flames in multiple dimensions. Smooke studies combustion from the computational side, using numerical methods to model flames using parallel computing systems. Their end goal, however, is the same.

Even with a growing focus on alternative energy sources, combustion still accounts for most of the world's energy, whether it's powering a passenger car or a cargo plane. Improving combustion-based systems remains a critical engineering problem, both to increase efficiency and to reduce the pollution that results from combustion exhaust. Long and Smooke work together to develop better models of combustion that can lead to improvements in the design of combustion systems.

"Experiments and computations are really complementary ways of looking at the same thing," says Long. "Ideally what you want to end up with is computations that get the right answer—but without experiments to verify that, it's not so clear. And experiments have benefited from computations, which include some things that we would like to know about that are hard to measure."

Despite the complementary nature of experimentation and computation, however, the idea of coupling Long's laser diagnostics with Smooke's adaptive numerical methods to study combustion was not the norm when Long and Smooke first began working together.

"Up until that point, most of it was really qualitative research—making nice color pictures," recalls Smooke. "We really tried to put an emphasis on getting quantitative data."

The build-up to doing that successfully took a few years. "Multi-dimensional experiments are very difficult, but they were especially difficult at the time, in the late 1980s," says Smooke. "This was an opportunity to use an experimental technique that was fairly new, and a computational technique that was fairly new, and try to get quantitative information.

"It took a while to just get things right to get the experiment so that we could compare against it," he continues. "We wanted to eliminate many of the variables like heat transfer to the burner — we wanted the flame lifted, we didn't want a lot of ancillary information that had to be provided, and we wanted to have a very clean experiment and clean calculation."

In 1988, they got their first funding for the research — a Department of Energy grant that's been renewed each time it's come up for review over the last 24 years. The fact that they have a grant that's older than some of their students makes Long and Smooke laugh, but they're very serious when they talk about the impact that the grant has had on their work.

"It really is quite amazing," says Smooke. "A lot of this wouldn't have been possible without it."

"This" is a paradigm shift in the field of combustion research — a growing acceptance of their particular "experimentation plus computation" approach until it eventually became the de facto way of doing things. And while they were leading that change as it spread through the field, Long

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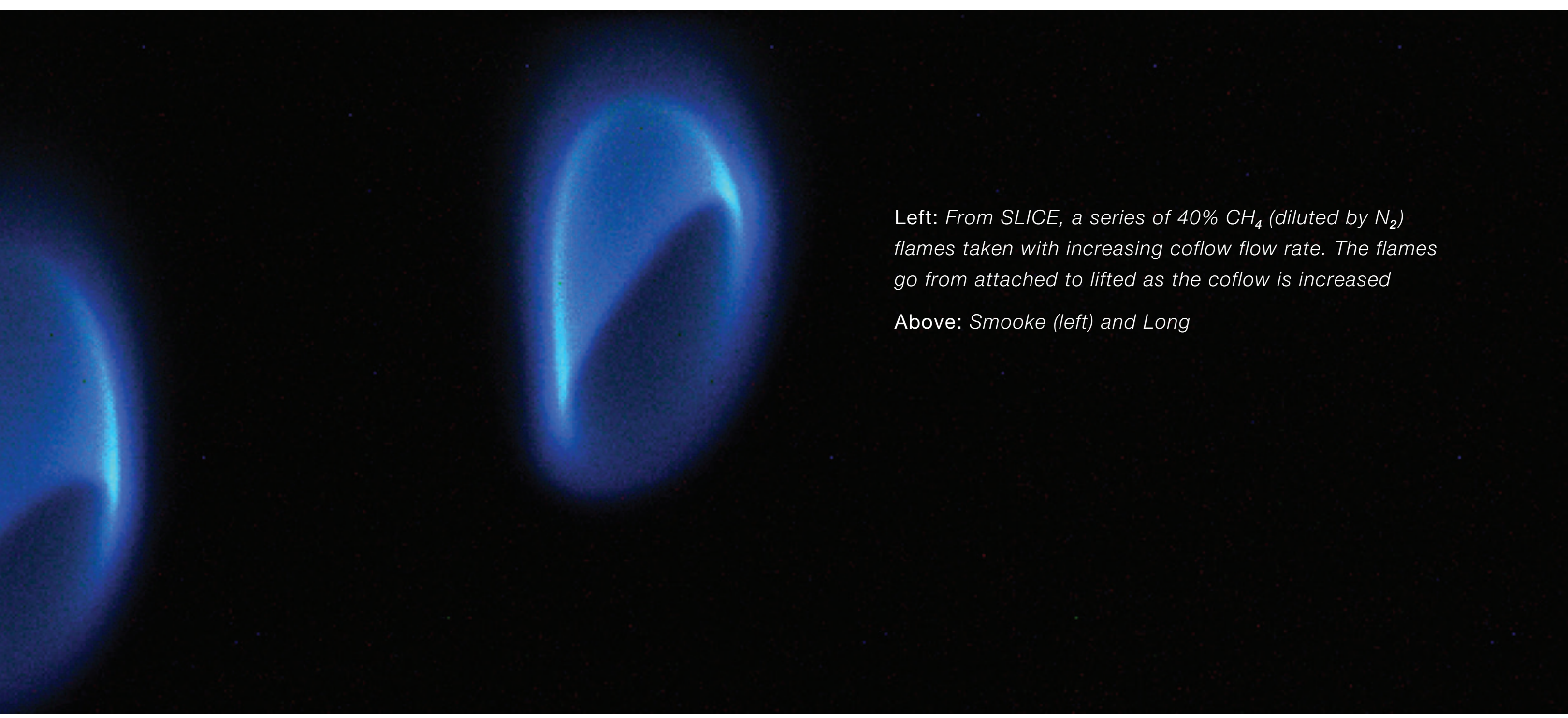


**Left:** *From SLICE, a series of 40% $CH_4$ (diluted by $N_2$) flames taken with increasing coflow flow rate. The flames go from attached to lifted as the coflow is increased*

**Above:** *Smooke (left) and Long*

and Smooke got first-hand experience with another change: the explosion of high-performance computing power.

"The first flame [we studied] had 16 chemical species and 46 reactions," recalls Smooke. "The one that my latest student computed and did some experiments on with Marshall had close to 250 chemical species and 5,000 chemical reactions. And instead of being done on a single workstation-type computer, it was done in parallel on several hundred processors.

"With the required computer time scaling as the square of the numbers of [chemical] species, these calculations never would have been able to be done in 1990," he continues. "Even if the memory was available, it would have been years."

Being able to see those changes happening is something both Long and Smooke list as one of the great benefits of working together for such a length of time.

"To have such a long-running collaboration — it's not only the papers that you do, but all the things that you tried that *didn't* work," says Long. "And then things change, and things that didn't work before will work now. There have been huge changes in what computers can do, and also huge changes in what lasers and imaging systems can do, and in turn, that changes the kinds of things that you can measure and the kinds of things that you can compute."

While major changes have been happening across the field over the last few decades, one aspect of Long and Smooke's individual research has also been subject to change: where it takes place. The two mechanical engineers still do combustion research in their own labs at Yale, but additional experiments have moved into the microgravity environment — first on NASA's KC-135 "Vomit Comet" in the 1990s, and more recently on the International Space Station.

Setting up combustion experiments on the space station isn't easy. Aside from the logistics involved with preparing for experiments that won't be carried out for a year or more, the cost of delivering the necessary equipment to the ISS comes to $10,000/kg. The space station's microgravity environment, though, offers an important advantage to flame research carried out on earth.






*Astronaut Don Pettit ignited more than 100 flames on the International Space Station for Long and Smooke's Structure and Liftoff In Combustion Experiment (SLICE).*

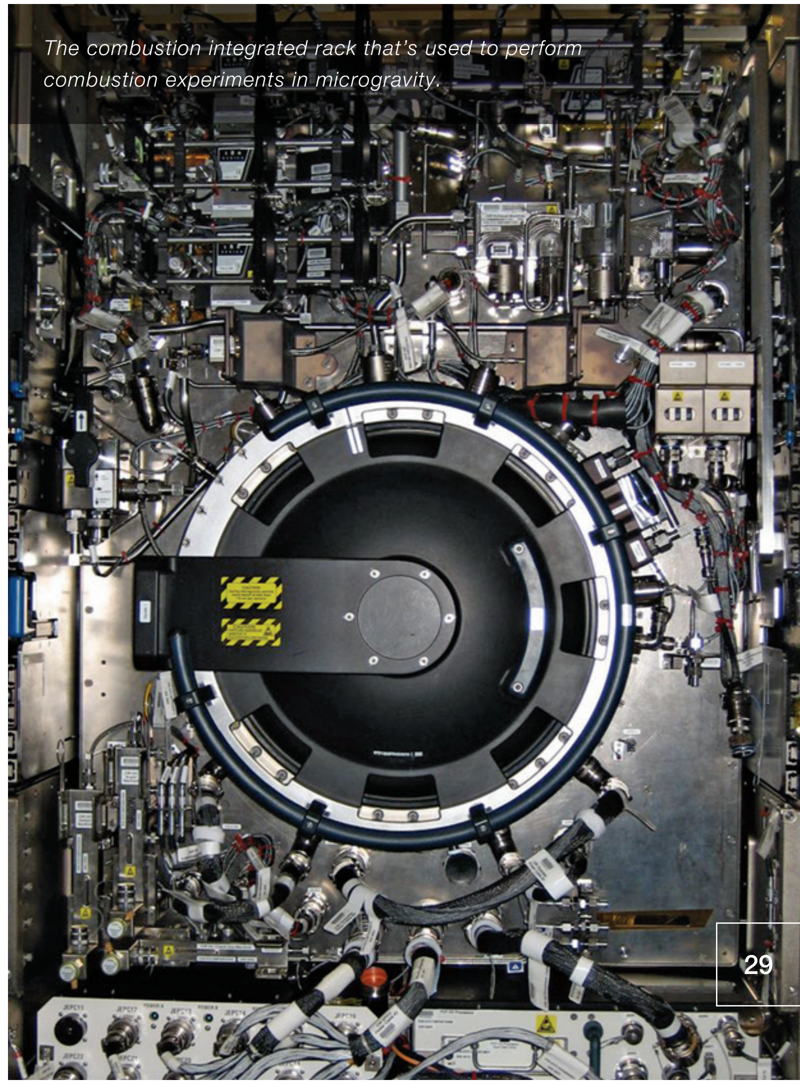
"Without buoyancy it's a simpler problem, in terms of things you have to take into account," explains Long. On earth, gravity causes hot air to rise; in the microgravity environment of the space station, buoyancy is no longer an issue, and is one less thing that has to be considered in the computations.

Microgravity also offers access to a wider range of experimental conditions. For example: without gravity, the chemical processes that form soot in flames take much longer than on earth. That gives the researchers a chance to develop models for a larger range of conditions than usual.

Long and Smooke aren't performing these experiments on the space station themselves, although Long has spent some time on the Vomit Comet. For their latest ISS effort, the Structure and Liftoff In Combustion Experiment (SLICE), NASA astronaut Don Pettit ignited more than 100 flames using various concentrations of methane or ethylene. Long and Smooke watched live feeds from Long's office "at the very small hours of the morning," as Long puts it — the space station runs on Greenwich Mean Time — relaying instructions and feedback to Pettit through NASA personnel.

A camera captured high-resolution images of all the flames for study; by carefully calibrating the camera, Long and Smooke can calculate the number density of CH [one carbon, one hydrogen] radicals in a particular flame. With this data, Smooke will work to determine how accurately models can reproduce the experimental results. They'll also be repeating every flame experiment performed on the ISS in earth's 1g environment, using a copy of the SLICE rig that's still on the space station. And of course, they're already looking toward their next big project.

"This set of experiments that we just completed was a run-up to things that will be done with much cleaner boundary conditions, which are important for the computations," says Long. "[They'll] have different cameras and better diagnostic capabilities. It's not the same, but similar enough that the results from this experiment will help us to improve the next set of experiments."

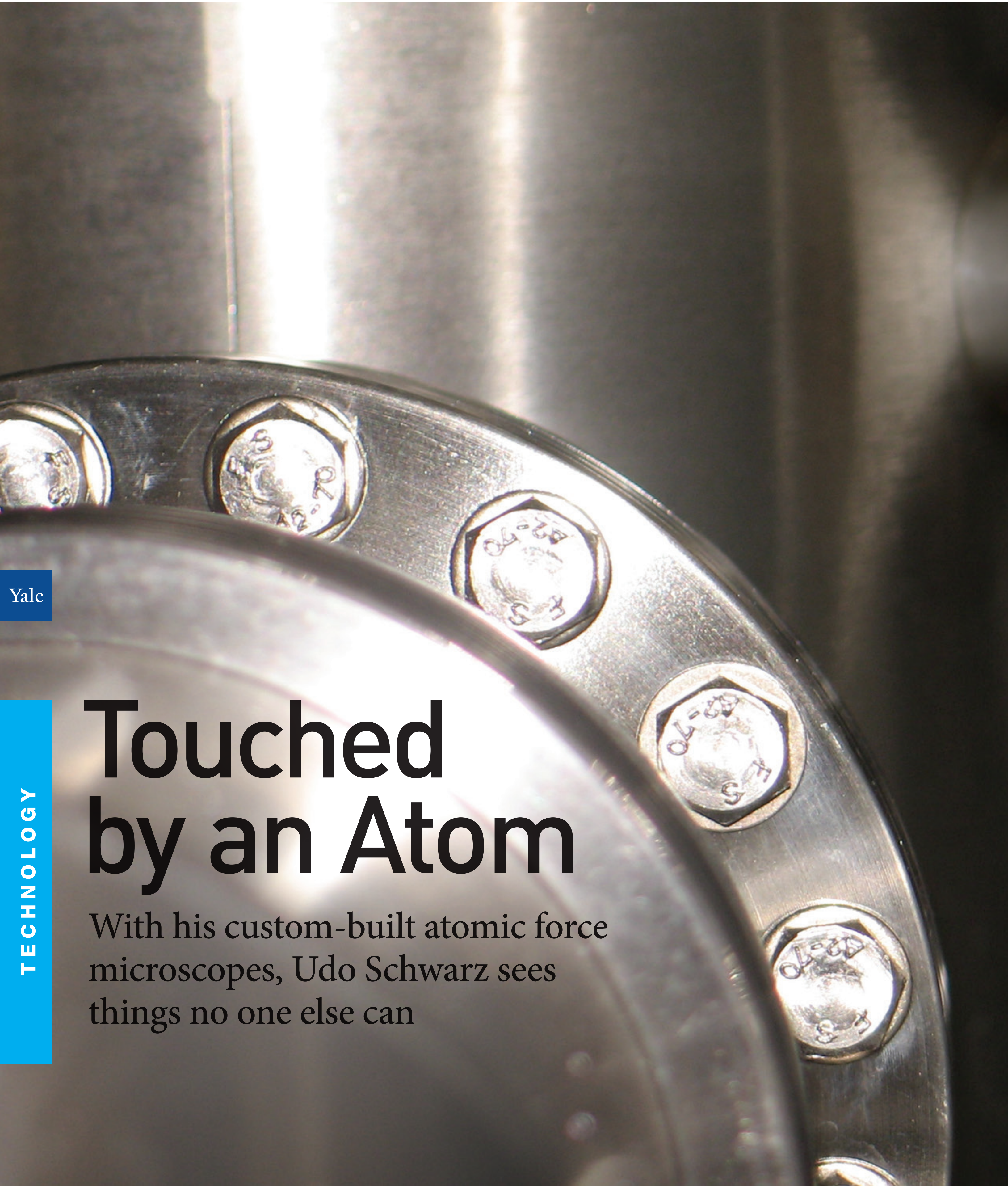

The combustion integrated rack that's used to perform combustion experiments in microgravity.

By the time the next round of NASA experiments is completed, Long and Smooke will have been working together for almost 30 years, with those decades of successful partnership growing steadily from that very first revolutionary effort.

"There's a lot of parts to this and it's still ongoing," says Smooke, "But in the early days, we took a problem that had not really been computed or measured with this level of accuracy and these techniques and got real quantitative information."

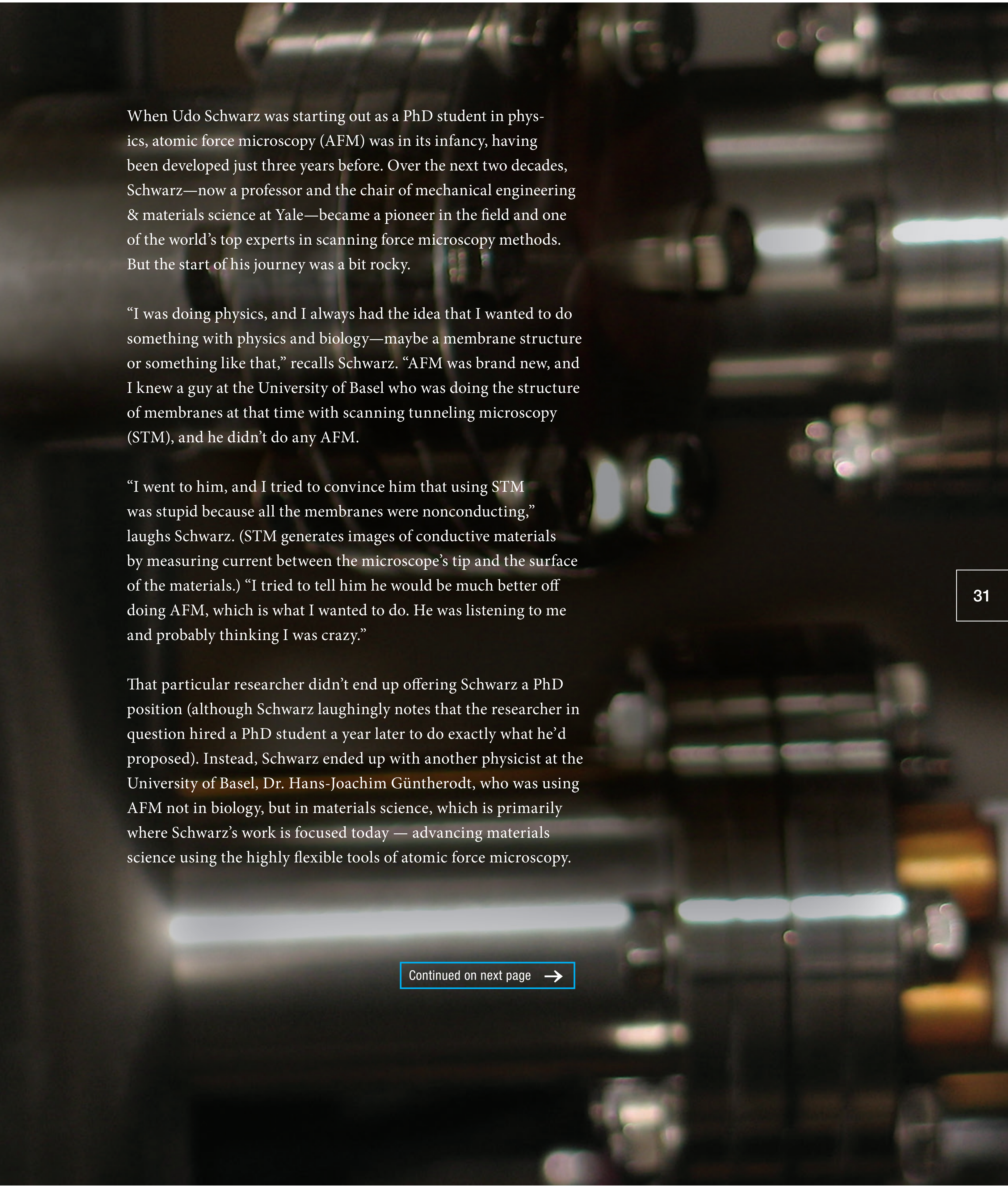
And that, they both agree, would not have been possible without their fairly unique partnership.

"This isn't something that would have happened if we had tried to do it without a real coauthor kind of collaboration," says Long. "It just wouldn't have happened the same way."




# Touched by an Atom

With his custom-built atomic force microscopes, Udo Schwarz sees things no one else can



When Udo Schwarz was starting out as a PhD student in physics, atomic force microscopy (AFM) was in its infancy, having been developed just three years before. Over the next two decades, Schwarz—now a professor and the chair of mechanical engineering & materials science at Yale—became a pioneer in the field and one of the world's top experts in scanning force microscopy methods. But the start of his journey was a bit rocky.

"I was doing physics, and I always had the idea that I wanted to do something with physics and biology—maybe a membrane structure or something like that," recalls Schwarz. "AFM was brand new, and I knew a guy at the University of Basel who was doing the structure of membranes at that time with scanning tunneling microscopy (STM), and he didn't do any AFM.

"I went to him, and I tried to convince him that using STM was stupid because all the membranes were nonconducting," laughs Schwarz. (STM generates images of conductive materials by measuring current between the microscope's tip and the surface of the materials.) "I tried to tell him he would be much better off doing AFM, which is what I wanted to do. He was listening to me and probably thinking I was crazy."

That particular researcher didn't end up offering Schwarz a PhD position (although Schwarz laughingly notes that the researcher in question hired a PhD student a year later to do exactly what he'd proposed). Instead, Schwarz ended up with another physicist at the University of Basel, Dr. Hans-Joachim Güntherodt, who was using AFM not in biology, but in materials science, which is primarily where Schwarz's work is focused today — advancing materials science using the highly flexible tools of atomic force microscopy.

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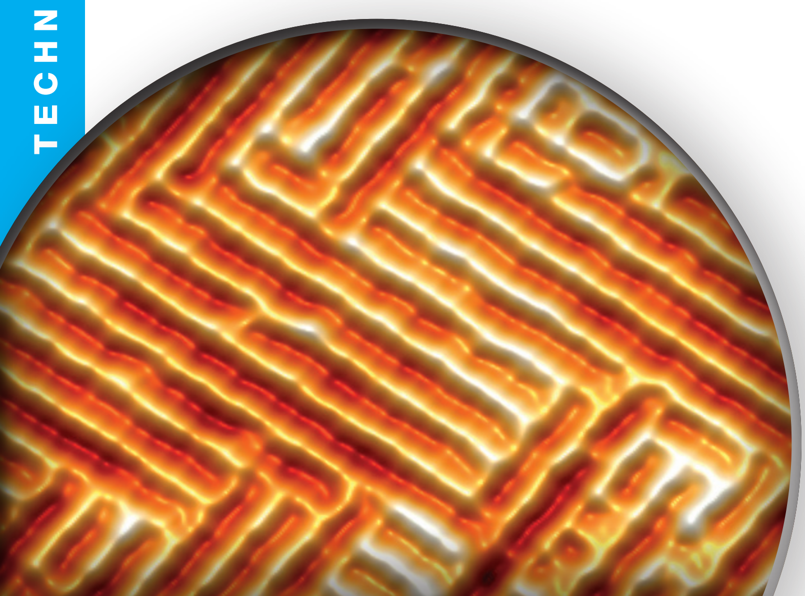
AFM, as Schwarz describes it, is like looking for the light switch in a pitch-black basement.

"You know there must be a light switch somewhere," says Schwarz. "So you start moving your hand over the wall, and even though you can't see anything, you can feel. You know the texture of the wall, and you know, 'Okay, that's not where the light switch is,' until you find the switch. Then you feel the switch and you know, 'Okay, the switch looks like this, so I have to flip it' — and in your brain, there's an image formed of something that you can't see, simply because of touching. And atomic force microscopy is exactly the same way."

Microscopes don't have fingers, of course. Scopes designed to simply magnify visual images of specimens for human eyes have lenses; but when you're studying *very* small things—things smaller than light's wavelength—an optical lens won't do you any good. Atomic force microscopes have sharp tips that run over the surface of a material, just as you'd run your fingers over the wall in the dark basement. The tip is attached to a soft spring allowing it to move up and down; by moving the tip back and forth over a surface and measuring how *much* the tip moves up and down at each location, you can generate a visual representation of the surface.

"Ideally," explains Schwarz, "Your tip end is just one atom, and that's when you can achieve atomic resolution. You see every individual atom in the surface."





Schwarz does more than just *use* atomic force microscopes, though — he builds his own, which he began doing about ten years ago. Yale is home to two of his custom-built machines, both of which do things no other microscopes do.

The first, designed for super high-resolution low-temperature applications, is in a soundproof room, on a specially-built concrete foundation of its building.

"Basically the building is built around that microscope," says Schwarz.

Measurements at low temperatures provide for higher stability, which leads to better resolution. All thermal vibrations are frozen, and any elasticity in the microscope's tip is frozen as well. Basically, everything stops moving long enough to generate a very accurate visual representation of the surface.

Schwarz's second microscope can generate measurements at any given temperature between 10 kelvin (about -441°F) and room temperature. Built to see both magnetic and electrostatic effects, it has a large scan range of several microns at low temperatures. And perhaps most notably in comparison with other devices, the entire microscope is cooled.

"We were interested in having the entire microscope cooled as a whole because if your tip is hot, and your sample is cold, you think 'How does the warm tip influence the measurements?'" explains Schwarz. "So you want everything to be the same temperature, so there is no doubt what you're doing."

Because the entire microscope is cooled and can be used in a wide range of temperatures, Schwarz and his colleagues can take measurements both below and above transition temperatures, where materials change from one state to another, as when a material goes from a normal to a superconductive state. This gives researchers a clear view of the effects that happen during those transitions — an important area of study in materials science.

Continued on page 34

# In Eric Altman's lab, the macroscopic meets the microscopic.

"Broadly, we look at what happens at solid surfaces in terms of their interactions with the environment," says Altman, a professor of chemical & environmental engineering. "We look at these things on a fundamental basis — try to understand what happens molecule by molecule, atom by atom. That involves scanning tunneling microscopy as well as traditional surface science measurements, which are more macroscopic: surface-sensitive spectroscopies, mass spectrometry, and electron diffraction, which tells you something about order at atomic scale distances, but now averaged over a span of about a millimeter. That gives us a connection between the more macroscopic and the microscopic."

Altman's research has applications in multiple fields of study, from chemical sensing to the growth of thin films to catalysis, where there are multiple relevant sub-fields.

One such sub-field, explains Altman, involves the fundamentals of how molecules interact with surfaces.

"You want to understand not only the strength of the interaction, but also how the molecules are altered by interactions with these surfaces, how the nature of the surface affects these changes, and so on," explains Altman. Ideally, researchers would use single-molecule catalysis techniques, which is one of the goals of Altman and Schwarz's collaboration.

"This is the idea of interrogating the surface not by the normal way of watching where molecules go and then trying to figure out what they've done, relating the microscopic to the macroscopic," says Altman, "But to rather take the molecule by the scruff of the neck, so to speak, and drag it over the surface and see how strongly it interacts at different surface sites. And if you did this with complementary molecules, you could map out the interactions that actually govern how things react."

Single-molecule catalysis remains a primary goal for the researchers' collaboration. In the meantime, Altman is pleased to see the more complete picture of surface interactions that's made available by their combined use of both atomic force microscopy and scanning tunneling microscopy.

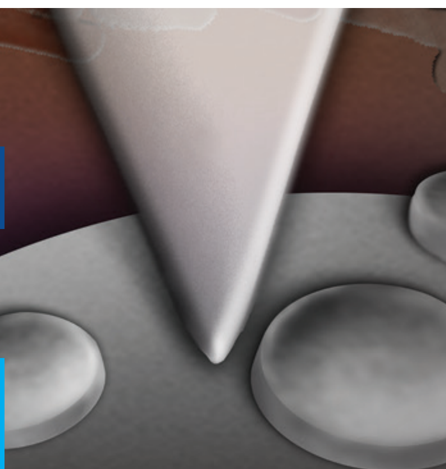
"AFM and STM are obviously sensitive to different things," says Altman. "Once you get past this idea of trying to see how things interact [using force measurements], you ask the question — well, why? That's where the electrons come into play. So if you could simultaneously map out the [force and] electronic properties, then you have the 'how much' and the 'why' all put together."

Still, atomic force microscopy isn't the only way to study surfaces down to the level of single atoms. Before AFM was created in 1986, scanning tunneling microscopes were the state-of-the-art for studying materials at the atomic scale, and they're still used today. These microscopes are similar to AFM in that they use a tip just one atom wide, but instead of putting the tip in contact with the material to be studied, the STM hovers its tip just above the surface while a small electric current flows between them. The resulting current at each location on the surface provides a measurement of the distance between the tip and the atoms on the surface; after a scan is complete, the measurements can be used to generate an image.

Because this method relies on electric current, however, it is only useful on conductive surfaces. AFM, which was developed five years after STM, offers functionality on all surfaces. Schwarz, however, sees additional possibilities in using both AFM and STM together.

"One application we're shooting for is what we like to call three-dimensional atomic force microscopy combined with scanning tunneling microscopy for local functionalized imaging or chemical imaging," says Schwarz. "We're measuring the entire three-dimensional space over the surface with atomic resolution, and at each of data points we quantify the tip-sample interaction and we measure in parallel the tunneling content.





# How to Build an Atomic Force Microscope: First, Start with the Tip

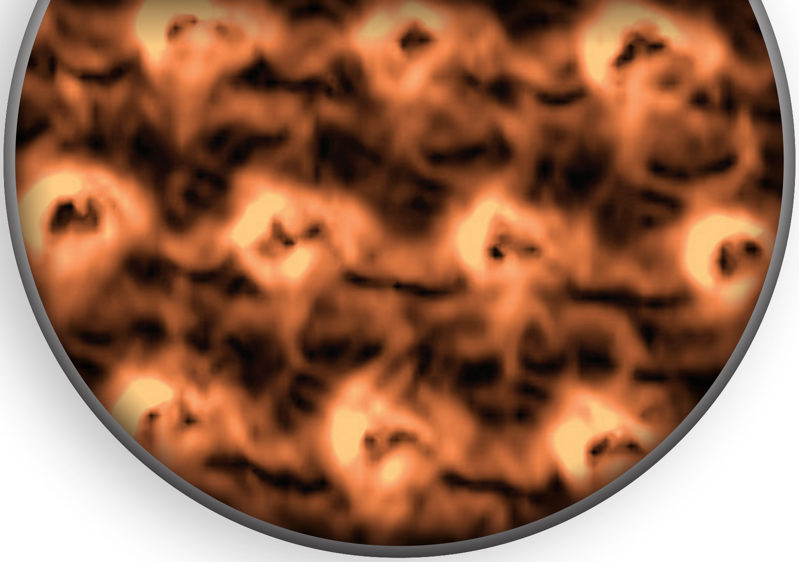
While the measurements that can be made with atomic force microscopy are incredibly precise — down to the atom — that precision depends on having a very good tip. To get true atomic resolution, the tip being used must be only a single atom wide at its point. Surprisingly, methods to reliably produce good tips still involve a lot of trial and error — another aspect of AFM research that Schwarz is trying to improve.

While he was doing his PhD in Switzerland, Schwarz notes, they could make pretty good AFM tips through trial and error simply by putting platinum, tungsten or whichever other metal wire they wanted to use on a hard surface, cutting it on a diagonal, and pulling a bit. ("Because it was Switzerland," says Schwarz, "We used our Swiss army knives.") You can try a similar technique yourself with a paperclip and a pair of scissors (but note that a stainless steel paper clip is a very poor choice for an AFM tip).

Now, researchers use more advanced techniques like etching: setting up a very small loop with a specific voltage, grounding the tip, and using a pipette to drop the etch solution into the loop, where surface tension holds it in place. If you then move the tip through the loop, you can achieve different shapes by adjusting the AC voltage, although there is still a lot of trial and error involved.

Another option is even more difficult to do in a reproducible fashion: you simply crash a metal tip into a metal surface, then pull it back out. Because metals flow, the tip will end up with a "neck formation": a deformation in a small region of the tip from crashing it into the surface. At some point, the neck ruptures, and in substrates that flow nicely like gold, copper, or platinum, it ruptures so that only a single atom is left at the end. In each of these techniques, there's still a large element of luck.

"That's why we're putting a lot of work into how to reproducibly produce good tips," says Schwarz. "So far, nobody has a good answer for that."



"What that gives you is, first, the tip-sample interaction is directly the chemical interaction of the surface with whatever you have at the tip apex — at your last atom," he continues. "You can quantify and characterize locally changing chemical interactions."

The tip-sample interaction aspect of that approach is particularly interesting for catalysis research — studying the acceleration of chemical reactions. Scanning tunneling microscopy provides the second element of the new application.

"If you have the tunneling content at the same time, now you can correlate the chemical interaction that you did [with the force microscopy] with the electronic properties," Schwarz explains. "Tunneling current gives you something about the electronic properties: Where are electrons that you can suck out of a surface to get your current, for example."

Schwarz gives the example of a transition metal oxide as a type of material that is ripe for study using this technique. These materials have both metal and oxygen atoms in their surfaces; the oxygen atoms will interact with a metal tip used in an AFM, so you would get strong chemical interactions and good contrast in the resulting AFM imaging. The metal atoms, however, are where electrons would tend to be, making them easier to see with STM.

So, combining both AFM and STM, "You have two channels that run in parallel. In one channel you see where all the oxygen atoms are. In the other channel you see where all the transition metal atoms are, and you can put that information together and you get complete information," says Schwarz. "You get chemical-sensitive imaging, so depending on what you want to see, you see it in different channels, but at the same time. This gives you full information, for instance, on what defects look like. That's brand new."

Schwarz, who also has a joint appointment in chemical & environmental engineering and works closely with C&E professor Eric Altman on these efforts (see sidebar, page 33), hopes to develop this combined AFM and STM method for catalysis, and eventually facilitate studying single-molecule catalysis: putting a single molecule on a surface and scanning it to see which end of the molecule is active and which is inactive. These efforts are also integrated into his work at CRISP (Center for Research on Interface Structures and Phenomena), Yale's NSF-sponsored materials science research center, where he is a co-leader of one of the center's two main tracks and a member of the second. Altman is also a CRISP member, and co-leader of the second track.

Schwarz would also like to add additional data channels to the combined scan, possibly using classical STM spectroscopy, which provides the entire energy level landscaped per point as opposed to a single snapshot at a particular voltage. In the end, it comes down to three goals: more reliable, more stable, and faster.

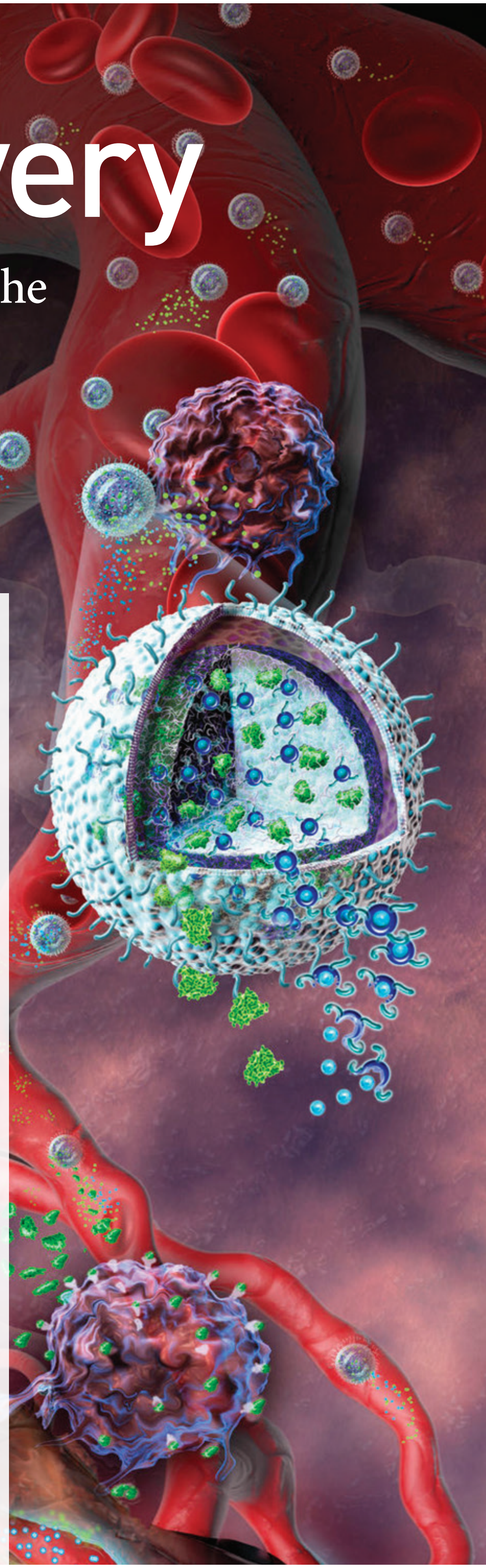
"The longest measurements we do are 40 hours, so if one set could be done in hours instead of tens of hours, or maybe even in minutes, that would be great," says Schwarz. "Getting the technique more practicable, more easy to apply, that's one big goal.

"The other thing is, of course you're particularly interested in molecule interactions at surfaces. We're starting to put molecules on surfaces, which is the easier part, and the more difficult part is to have really defined tips and then have specific molecules attached on your tip and image with that," he continues. "That's really challenging. Nobody's been able to do that in a good, reliable way at this point, but we're trying."

In the meantime, Schwarz and his microscopes still see things no one else can.

# Special Delivery

## Targeted nanoparticles are changing the standard approaches to maintaining stem cell cultures, modulating the human immune system, and more



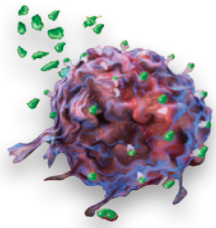
Tarek Fahmy, an associate professor of biomedical engineering & chemical & environmental engineering, has long been focused on biomaterials: substances engineered to interact in a therapeutic or diagnostic manner with living systems. One of Fahmy's primary interests has been in using biology to drive the design of such materials, and then using them as package carriers in biological systems.

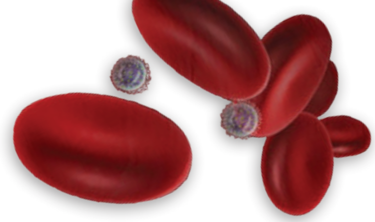
Fahmy has developed nanomaterials that deliver growth factors to stem cells in culture, vaccine antigens directly to T cells, and therapeutic agents to tumor sites for the treatment of cancer, while suggesting additional uses for such nanomaterials in drug delivery and immunotherapy. His recent work with stem cell cultures suggested a novel and superior method for maintaining the cells in culture, demonstrating equivalent growth among the cells as in traditional methods, while using much less biological material than previously required.

Fahmy and his colleagues packed Leukemia Inhibitory Factor (LIF) into biodegradable nanoparticles for slow-release delivery to the stem cells. LIF can be a key growth factor for stem cells, and is ordinarily introduced to stem cell cultures via a liquid medium that must be exchanged by hand every day. Using Fahmy's new method, researchers can sustain the same level of growth among stem cells in culture with just one ten thousandth the amount of LIF — and because it's introduced via the nanoparticles and slowly released over time, there's no need to exchange the growth medium every day.

Separate from his work with stem cell cultures, Fahmy has also demonstrated that nanoparticles could be useful in developing treatments for

*Illustration depicts a nanolipogel administering its immunotherapy cargo. The light-blue spheres within the blood vessels and the cutaway sphere in the foreground are the nanolipogels. (Illustration by Nicolle Rager Fuller, NSF)*





autoimmune diseases, as well as in the case of immune system modulation after organ or tissue transplants.

Within the human immune system, T lymphocytes are generally born as "naïve" cells. They can develop into either regulatory cells that prevent the immune system from attacking the body itself, or into effector cells that attack and destroy foreign invaders like viruses or bacteria. Leukemia Inhibitory Factor also plays a role here: LIF encourages T lymphocytes to mature into regulatory cells, and keeps them from developing into a specific type of effector cell that's been implicated in a number of autoimmune diseases, including multiple sclerosis and rheumatoid arthritis.

Fahmy and colleagues packaged LIF into nanoparticles, this time for targeted delivery to T lymphocytes. The technique not only kept the cells from developing into the autoimmune-associated effector cells, but also prolonged the survival of grafted heart tissue in mice by producing more regulatory cells. As in the case of nanoparticle delivery of LIF to stem cell cultures, a much smaller dose of LIF was required when delivered via the nanoparticles than when delivering the LIF via solution in soluble form.

Fahmy's results suggest that nanoparticles could be used to release materials like LIF on a stable schedule, regulating immune tolerance without exposing other cells in the body to the encapsulated materials.

"The implication of this is that it is possible, using such systems, to tune the immune response for therapeutic applications," says Fahmy. "Tuning immunity to be either tolerant or aggressive within specific areas in the body is a highly sought after goal for autoimmune disease, organ transplantation and even cancer."

His most recent work, in collaboration with Richard Flavell, chair of immunobiology at Yale, highlighted the potential role that nanoparticles can play in cancer treatment. Cancerous tumors defy the human immune system by releasing agents that interfere with its function; Fahmy developed a novel nanoparticle formulation to deliver two therapeutic agents directly to tumor sites. One agent, interleukin-2, encourages a stronger immune response; the other, transforming growth factor-β inhibitor, counteracts the agent released by the tumor — disrupting the attempted disruption so that the immune system can do its job. On tests in mice with melanoma tumors, the particles (called nanogels) increased survival times and slowed tumor growth while increasing the activity of the immune system's natural killer T cells.

The tumor, Fahmy explains, can be thought of as an alien spaceship with advanced technology. The tumor's cells and network of blood vessels make up the ship; its defense system, a force field that protects it from attack, is powered by transforming growth factor β (TGF-β). When the nanogels release TGF-β inhibitor, the force field comes down, leaving the ship—the tumor—open to attack by the immune system.

In conjunction with the inhibitor, the nanogels also release interleukin-2 (IL2), which increases the immune system's response in the area surrounding the tumor.

"Interleukin-2, a cytokine, calls for the body's T-cells to attack the tumor," explains Fahmy. "The nanogels deliver a primary assault in the form of TGF-β that defeats the force field, and a secondary call for reinforcements with IL2 that encourages the immune system to attack the ship—the tumor—directly."

Fahmy and his colleagues used only components that have already been approved by the United States Food and Drug Administration—paving the way for future experiments in humans, both with additional components and on other types of cancer, to be expedited.

Most importantly, Fahmy notes, the nanoparticles have been designed to work with many different drug types and sizes, creating a wide range of potential applications in medicine.

"Ultimately, such systems could prove powerful for many different diseases," says Fahmy, "In any situation where therapy is hampered by a lack of means to deliver powerful drugs directly to where they need to be acting, instead of the whole body."

Yale

# Measure Twice, Aim Once

## Probabilistic methods offer improved patient data for cancer and epilepsy treatments

MEDICAL INNOVATION

Jim Duncan's research reflects his roots in electrical engineering. The professor of biomedical engineering, electrical engineering & diagnostic radiology started out in aerospace research, working on imaging systems for communications satellites; a growing interest in applying signals and imaging processing techniques to biomedical problems brought him to Yale in 1983. Since then, he's grown especially interested in using mathematical models to analyze biomedical images.

One recent effort targets improving treatment approaches for cervical cancer, which affects 12,000 women in the United States each year and is usually treated with radiation.

"The typical treatment is that they do five weeks of radiation, and when they can see that the tumor is regressing, they put radioactive seeds right in the [tumor] area to help. That seems to be the successful approach," says Duncan. Throughout these treatments, cone beam computed tomographic (x-ray) scans can be taken each week to track the tumor's response. In the future, magnetic resonance scans may also be acquired.

The problem is, patients can't place themselves in the exact same position for a new scan each week, so the raw images don't line up.

"Both the patient and the anatomy move over time," says Duncan. People shift within the imaging machine, and if the radiation is working, the tumor itself also shrinks and can shift. "So the idea is to simultaneously warp the baseline

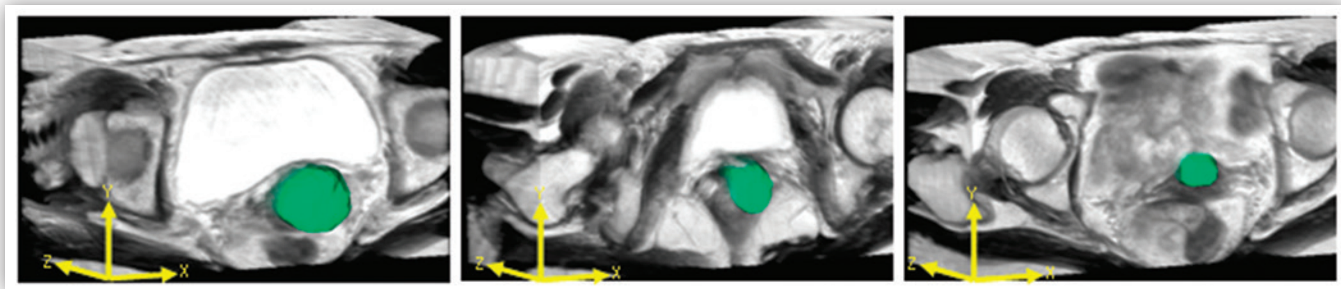


image to the future time points — or better yet, the future time points all back to the baseline. And while you're doing that, simultaneously find the anatomy, like the bladder and uterus, that can help with the process, because the anatomical features can help you put things in the right place."

Working with Drs. Sue Higgins and Zhe Chen of therapeutic radiology, graduate student Chao Lu and others, Duncan is investigating the use of automated computational mathematical methods to match features between the set of images and provide more accurate views of the tumor's current location and size. In the short term, this imaging may help guide radiation treatments to accurately target the tumor.

"We're talking about megavolt beams that are trying to blast and destroy cancer," says Duncan. "With improved image analysis, you can adjust the treatment to where the tumor currently is."

In the long term, analyzing collections of images from multiple patients may allow the researchers to characterize different tumors and find trends.

"The ultimate idea is that this sort of segmented tumor tissue from these images could be a predictor of what finally happens due to radiation," Duncan explains. "So if you could see a tumor at two weeks in and say, 'It's doing this at two weeks, so we can predict that it's not going to be responsive at five weeks,' you can get in there earlier and make some change: more radiation, switch to chemotherapy, and so on."

Duncan also applies similar imaging techniques to improve the pre-operative information for surgical treatment of epilepsy, working with Dr. Dennis Spencer, chair of neurosurgery at Yale. In extreme cases of epilepsy that don't respond to medical therapy, the only remaining option is to cut the problematic tissue out of the brain. Obviously, surgeons want to limit the removed section of brain as much as possible. A battery of imaging is done to determine the brain's structure; functional MRI tests map out which areas are responsible for language, memory, and so on. Finally, a craniotomy is done to remove 10cm of the skull and lay electrodes on the surface of the brain. These provide additional information to help estimate seizure sites; unfortunately, the craniotomy that allows the placement of electrodes creates a separate challenge.

"When they do this craniotomy, cerebrospinal fluid leaks out," Duncan explains. "There are changes in swelling and gravity, so the brain actually shifts or deforms inside the skull." As a result, all of the pre-operative imaging may show the brain in a different shape or position than it is after the craniotomy — in fact, it can be off by as much as a centimeter.

Duncan and his colleagues, including Chrissy Delorenzo (now an assistant professor at Stony Brook) and biomedical engineering associate professors Larry Staib and Xenophon Papademetris, use image-based methods to find the skull's anatomy beforehand, creating a baseline. Then, using stereo cameras mounted in the operating room, they can reconstruct the surface of the brain at the opening.

"From there, you can model the brain and its deformation properties from the pre-operative images, use the cameras to get a surface, and then basically push on the brain in the model and update how the brain shifted during surgery," says Duncan. This updated location information can then be provided to the surgeons. As with the efforts to focus cancer treatments specifically on tumor tissue, the goal here is to remove only the necessary sections of the brain, without harming healthy areas.

"It's all about cutting in the right region," says Duncan, "And not eliminating things you don't want to."





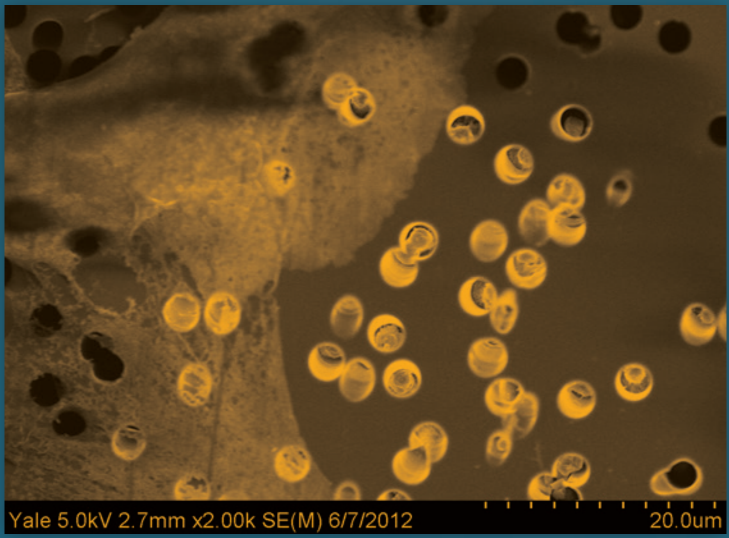
# Innovating Across Disciplines

Through a generous gift from Donna Dubinsky (Yale College ’77), the School of Engineering & Applied Science created the Dubinsky New Initiative Grants. Designed to foster new research initiatives aligned with the School’s Interdisciplinary Research Priorities (IRPs), these grants provided funding for two major projects in the program’s introductory year. The School has four IRPs; this year’s grant recipients are pursuing research within two of them — Biomolecular Engineering & Biodesign, and Energy & Sustainability.

## Modeling the Microvessel

A team consisting of primary investigator Anjelica Gonzalez and collaborators Rong Fan from biomedical engineering and Paul Van Tassel from chemical & environmental engineering, as well as colleagues from immunobiology, anesthesiology and pulmonary medicine, will develop techniques to advance the understanding of pulmonary inflammation. The team plans to develop a "microvessel-on-a-chip": a device to provide biomedical researchers with a comprehensive model of the microvessel.

This type of modeling capability will give researchers new insights into how microvessels contribute to the regulation of lung tissue inflammation, with widespread applications in the study of pulmonary fibrosis, lung damage that leads to multiple organ failure in septic patients, and breast cancer metastasis into the lung.




"Due to the overwhelming prevalence of adult and pediatric lung disease in our country, the impact of an easy-to use device for understanding of chemical signals that lead to tissue damage will be far-reaching," says Gonzalez. "Here, we will develop a true model of microvasculature for analyzing lung inflammation, but in the future this approach may also be extended to the analysis of acute and chronic inflammatory diseases of the skin, eye and heart."

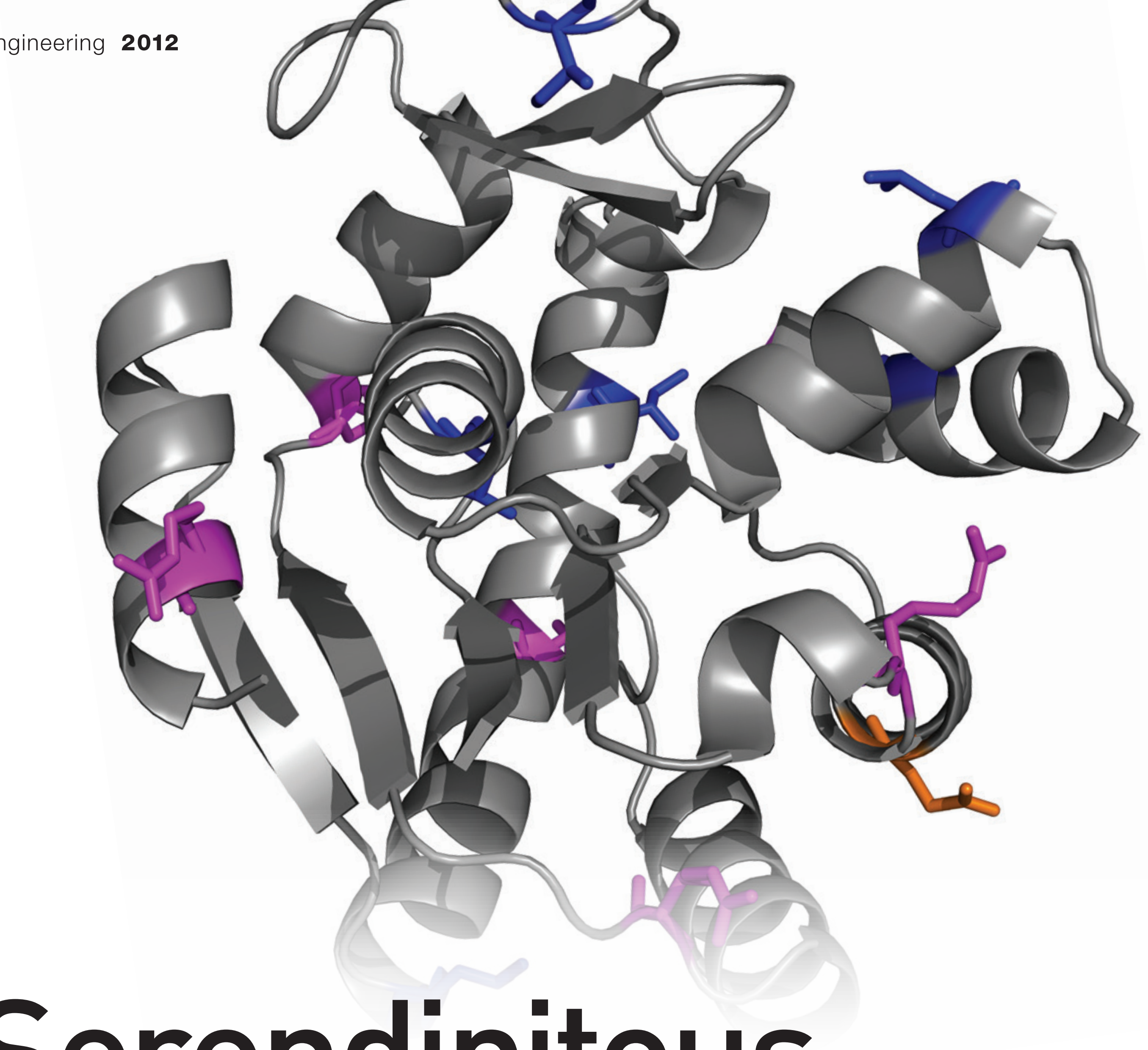


## Addressing Clean Energy Challenges

A group consisting of Chinedum Osuji from chemical & environmental engineering, Charles Ahn from applied physics and mechanical & materials engineering, and Hui Cao and Frederick Walker from applied physics will study clean energy generation by pyroelectric conversion of solar radiation. Pyroelectric materials generate a voltage when their temperature changes, which has led to efforts to develop materials and engineer systems to harvest energy from waste heat and solar sources.

A critical limitation of pyroelectric energy generation, however, is the need for a continually changing temperature, or continually varying heat flow: the more often and more drastically the temperature changes, the more power the system generates. The SEAS group is working to surmount this obstacle by using thermochromic materials that can self-regulate the heating of pyroelectric films due to absorption of sunlight in a photothermal layer. Their goal is to demonstrate self-sustained periodic temperature variations driven by sunlight absorption, using this as a basis for pyroelectric energy generation. This would achieve an important advance toward the use of pyroelectrics in solar energy conversion.

"The idea of self-sustained thermal cycles is pretty interesting in and of itself, from an engineering perspective," says Osuji. "Combining that with novel thermochromic and pyroelectric materials to generate clean energy makes for a truly exciting endeavor."



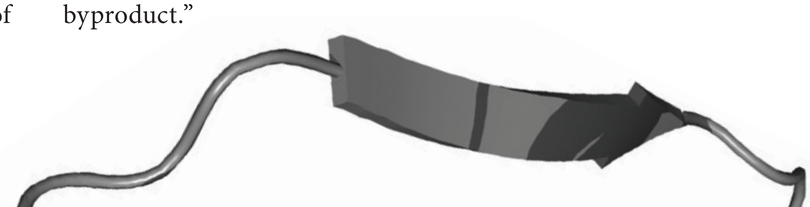


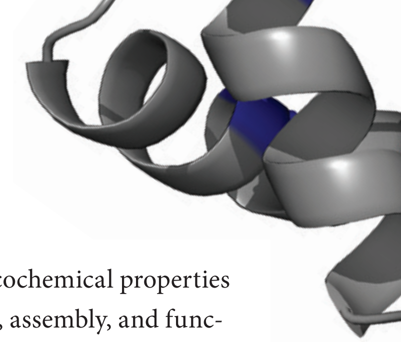
# Serendipitous Collaboration

## Environmental and protein engineering efforts combine to optimize water treatment methods

Bill Mitch's research sits at the intersection of engineering, public health, and sustainability. The associate professor of chemical & environmental engineering and forestry & environmental studies works on everything from carbon sequestration to sustainable wastewater recycling; one of his latest efforts focuses on the carcinogenic byproducts of disinfecting water supplies.

"The main purpose of treating water is to remove pathogens," says Mitch — things like E. coli and cholera. "But there's always a trade-off with everything. No matter what you do to disinfect water, whether you use chlorine, or ozone, or ultraviolet treatment, you're going to make some byproduct."





The resulting byproducts develop because of the treatment reacting with organic matter in the water, like rotting leaves. Some of the resulting byproducts can be carcinogenic.

"In that case, you trade off the acute risk of getting sick versus the chronic risk of cancer," says Mitch. "We're trying to understand what the tradeoffs are and optimize them, and that starts with what sorts of transformations occur in the organic matter and what sort of byproducts there are."

In a strange twist, the fact that clean water supplies are dwindling makes this research somewhat easier.

"In the old days this research was pretty difficult because the precursor materials you get in a clean water supply, called humic substances, are from leaves degrading — and nobody knows what they look like," says Mitch. "You rely on analytical chemists to identify byproduct peaks coming off a chromatogram, and you don't know whether the products are important or not.

"What's changing now is that we're running out of clean water. So more often than not, people are using water supplies that are contaminated with wastewater effluents upstream, or algae blooms," explains Mitch. "Now you have fresh biomolecules, and we have a better concept of what those look like. So now we can apply organic chemistry and predict what sorts of byproducts should form."

Mitch and his colleagues have focused particularly on the protein elements of these byproducts.

"Carcinogenic byproducts that are nitrogen-based tend to be a lot more toxic than carbon-based byproducts," explains Mitch, so it makes sense to look closely at those. And in those products, most of the nitrogen is in protein.

"Luckily enough," continues Mitch, "Here at Yale we have a protein engineer."

Enter Corey Wilson, assistant professor of chemical & environmental engineering, biomedical engineering and molecular biophysics & biochemistry. Wilson's research focuses on understanding the physicochemical properties that dictate protein folding, stability, assembly, and function — critically important in the case of byproducts from water disinfection, even if at first glance Mitch and Wilson are an unexpected research pair.

"It's just one of those collaborations that you don't see coming," says Wilson. "But the more we talked, the more I realized that you couldn't ask for a better complement in collaborating. I think it is serendipitous, but at the same time, some of the most exciting stuff happens just out of luck."

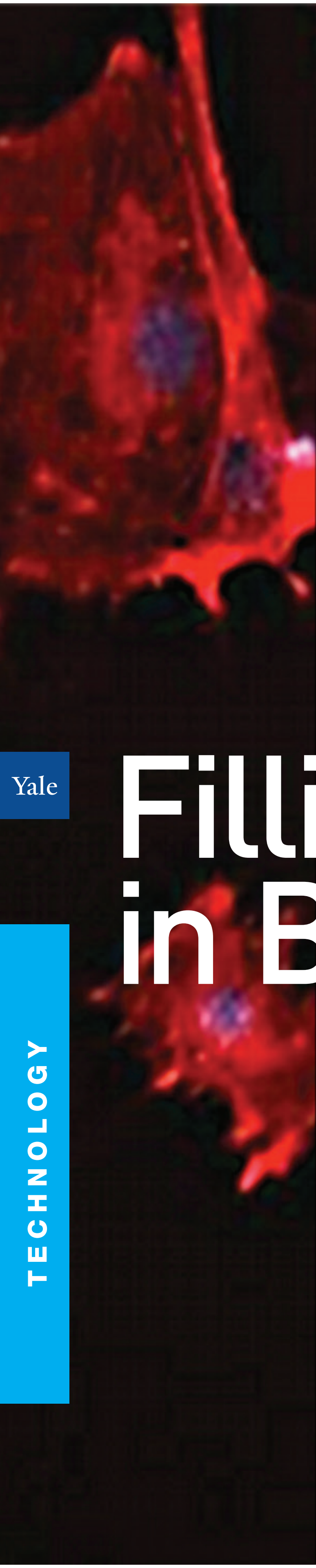
Wilson's team applies its expertise in protein engineering to study exactly what happens when disinfectants are applied to the organic materials in water supplies.

"When we started talking about oxidative damage, the going theory is that particular residues, amino acids in the proteins, play a crucial role in how oxidative damage happens throughout the system," explains Wilson. "We test those hypotheses by generating variants of proteins that are devoid or include these key factors that people claim are important in oxidative damage. We can do this systematically using our rational design software to improve the likelihood that we get a system that is stable and functions, and from here we can generate the protein variants and experimentally test the model."

"We focus on determining what is the covalent modification happening to the amino acid residue," says Mitch, "and [Wilson] can see how it translates into 3D structural changes."

Beyond focusing on the byproducts of water treatment, Mitch points out that despite disinfection being the major reason we treat water supplies, no one really understands exactly how it happens.

"Maybe if we understand the mechanistic aspects of how you modify the amino acids, which denatures the protein, or deactivates enzyme sites, we'll understand how that actually kills a bug," says Mitch. "And if you understand the mechanism, you can fine-tune the treatment approach."



Paul Van Tassel, professor and chair of chemical & environmental engineering, and his research team are seeking to create new materials for next generation biomedical applications, such as tissue engineering and cell-based therapies. One area of particular interest is thin "nanofilm" biomaterials. Biomaterials must interface with living cells and tissues, but at the same time meet other stringent mechanical and structural criteria. Addressing all these demands is challenging, but nanofilm coatings allow for surface and bulk material properties to be decoupled: film design may be based solely on optimizing the cell response.

Early research in biomaterials aimed for inertness — minimizing the cell response as much as possible. Current work in the field, however, follows more of a "biological engagement" paradigm, where initial cell adhesion is sought, together with transmission of cues toward specific cellular activities, referred to as bioactivity. This offers another biomaterials challenge: increasing a material's cell adhesiveness often suppresses its bioactivity, and vice versa.

Van Tassel's team is investigating methods toward creating nanofilm biomaterials that are both cell adhesive and bioactive. Increasing material rigidity through chemical cross-linking of a polymer network — much like the hardening of glue — generally increases cell adhesion, and the team is seeking new ways to cross-link without sacrificing bioactivity. They first experimented with limiting the cross-linking to the surface of their films, creating a rigid supporting "skin" while maintaining film bioactivity.



# Filling the Holes in Biomaterials



More recently, chemical engineering undergraduate student Connie Wu, graduate student Seyma Aslan, and Van Tassel collaborated with Emmanuel Pauthe's lab at the University of Cergy-Pontoise (France) to develop a novel approach combining cross-linking with templating. The initial film is formed in the presence of "sacrificial" nanoparticle templates, which essentially act as placeholders. The film is then exposed to tetrahydrofuran, a solvent that dissolves the nanoparticles. This leaves the film looking something like Swiss cheese, with holes where the nanoparticles used to be. The open space may be filled with proteins, thus rendering the film bioactive, while maintaining mechanical rigidity, and thus also cell adhesiveness.

"Porous nanofilm biomaterials would be ideal for applications in regenerative medicine, where materials of optimal rigidity and tailored bioactivity are needed to support tissue healing or re-growth," Van Tassel states. "Our work thus far establishes feasibility — we now move on to testing on medically relevant cell systems, the first being human bone cells, with an eye on ultimately regenerating lost or damaged bone tissue."

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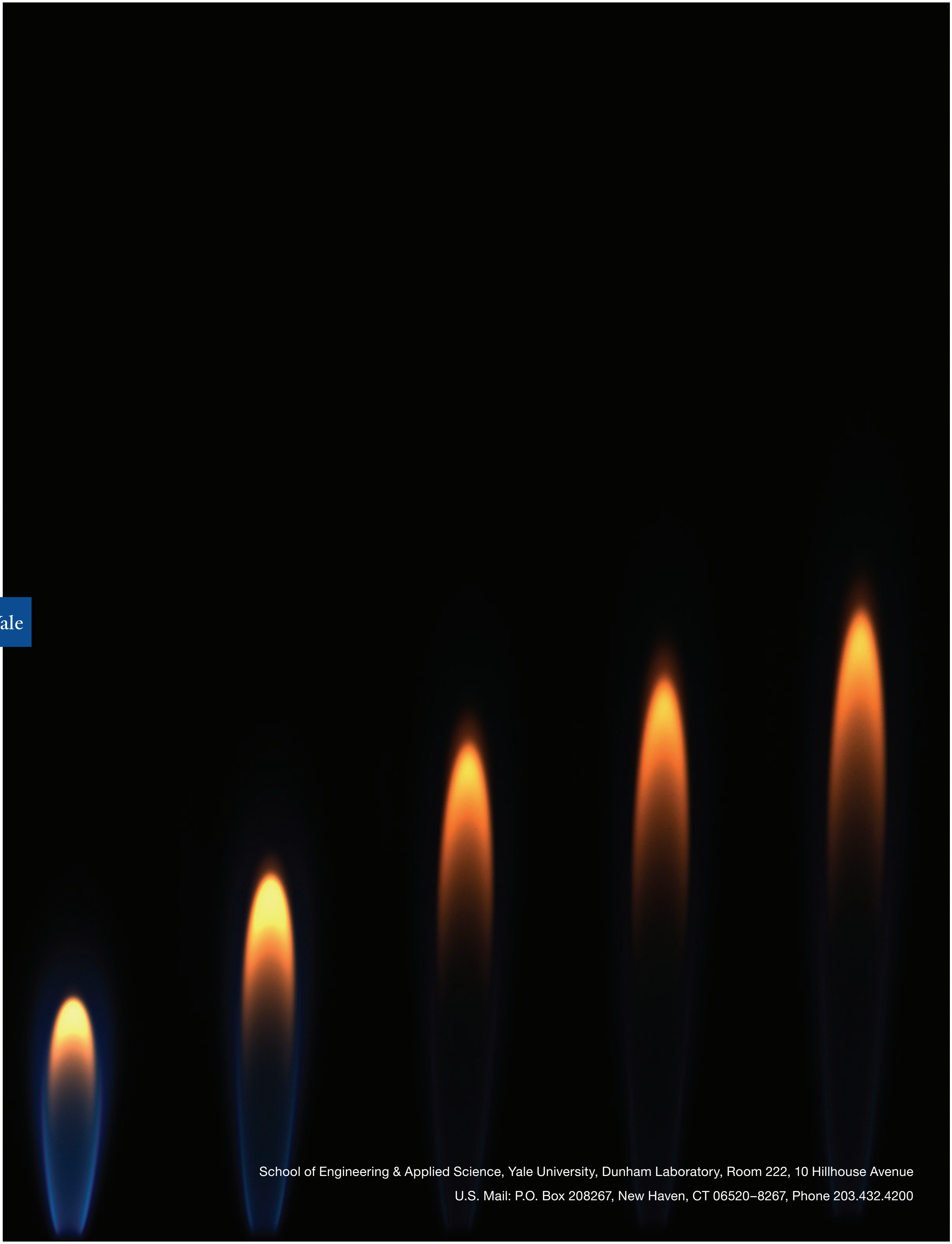

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