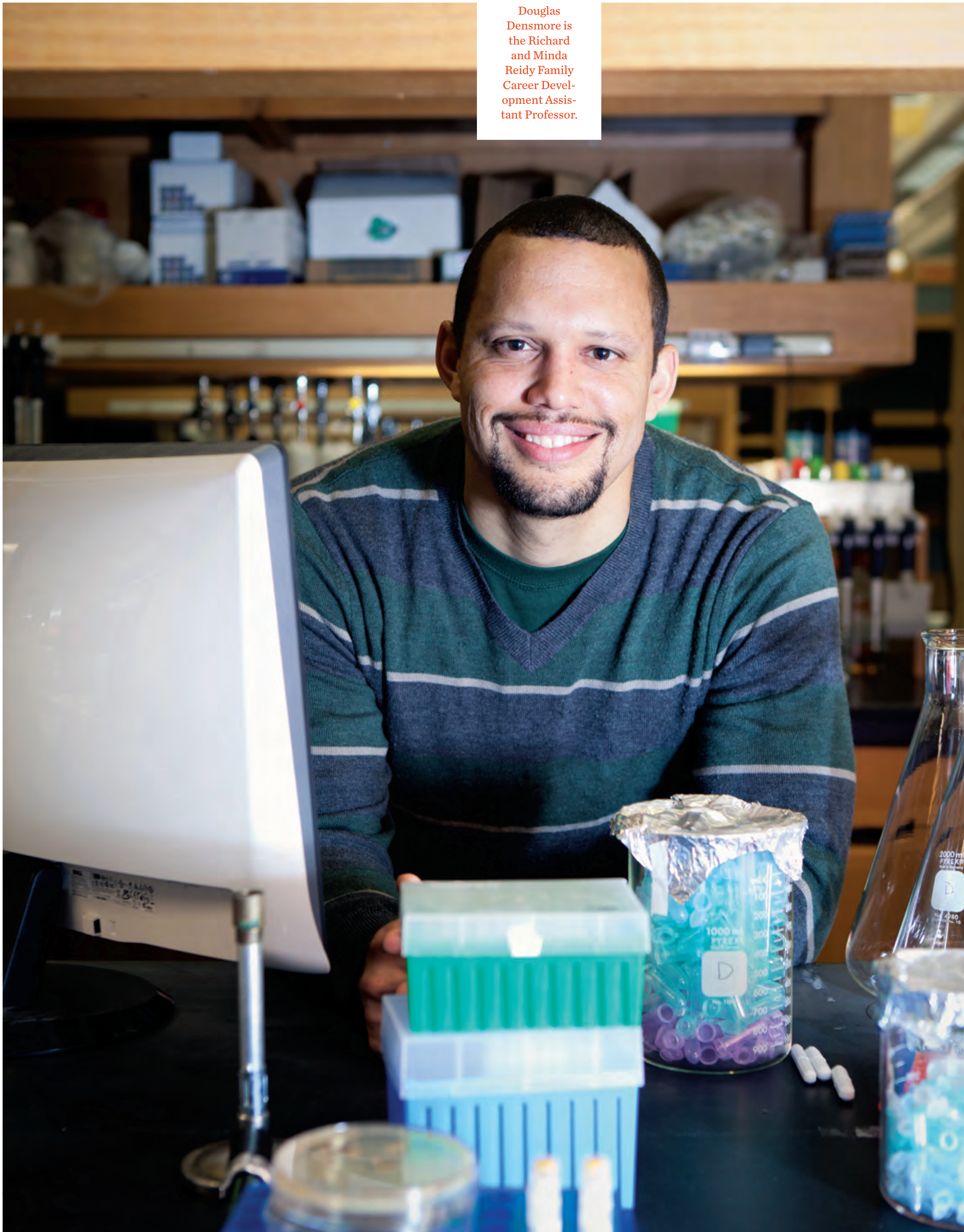

Douglas Densmore is the Richard and Minda Reidy Family Career Development Assistant Professor.

what we've done

Built a work-flow management tool that speeds the design of new organisms to create cleaner fuels and better medical treatments.

what we'll do next

Take the tool from proof of concept to commercial product.

Life Is Suite

A group of software apps helps synthetic biologists work faster and better

As biologists continue the decadeslong race to map the genomes of living things, a group of forward-thinking BU engineers is asking the kind of questions that engineers can't help but ask: what if we built a different genome?

Known as synthetic biologists, they believe that with some skillful genomic tweaks, living organisms, such as cells and microbes, can be put to work doing things that are too dangerous or not even possible for higher life-forms like ourselves.

By Art Jahnke

"There are so many possibilities," says Douglas Densmore, the Richard and Minda Reidy Family Career Development Assistant Professor in the College of Engineering electrical and computer engineering department. "Some are biotherapeutic. For example, we use chemotherapy to kill cancer cells, which is horribly damaging to the body. We may be able to noninvasively use bacteria that are already in your body to kill cancer cells. Or we can use bacteria to make clean energy."

In the last few years, as computing power has multiplied and the cost of decoding and synthesizing DNA has nose-dived, synthetic biological possibilities have started to look more like probabilities. Oil spill cleanup is also high on the things-to-do list for customized microbes. So is weapons detection, which may explain why the Office of Naval Research is funding a $7.5 million project called Utilizing Synthetic Biology to Create Programmable Micro-Bio-Robots. The project, which involves Densmore and two other BU engineers as well as researchers from Harvard, MIT, Northeastern, and the University of Pennsylvania, intends to create a dynamic trio of humans, robots, and genetically engineered bacteria, all of which will work together to detect whatever the bacteria are programmed to detect. That could be explosives or toxins or heat or light. The customized bacteria will talk to one another, and they will report to miniature "chaperone robots," a mere 10 to 100 centimeters long, that will each control thousands of microbes. Finally, the chaperone robots will wirelessly report back to humans.

While all of that sounds fantastical—new life-forms reporting to robots reporting to humans—it seems perfectly doable to the BU engineers who are working on the project. They include James Collins, a William Fairfield Warren Distinguished Professor and an ENG professor of biomedical engineering, who is regarded as one of the founders of the field of synthetic biology. Collins will determine the DNA modifications required for the project. Calin Belta, an ENG associate professor of mechanical engineering, systems engineering, and bioinformatics, will help design and assemble both the microbiotic robots and the chaperone robots. Densmore will find the best way to assemble and verify the DNA used to enable the microbes to sense specific environmental signals.

"The idea," says Densmore, "is to engineer living organisms—in this case bacteria—that respond to external stimuli in the environment. They will generate a fluorescent or chemical signal that can be measured by the chap-

PHOTOGRAPH BY JESSICA SCRANTON

erone robots, which can produce signals as well that the bacteria can detect. So you have a two-way communication system. And finally, we will create chaperone robots that can also communicate with human users."

Traditionally, as much as anything can be traditional in a field that is just a few years old, finding the correct DNA sequences would be a painstakingly slow and error-prone process, but Densmore has some help in the form of a software tool suite called Clotho. He describes Clotho, named for the youngest of the Three Fates in Greek mythology and the one who spins the thread of life, as an app environment, similar to the iPhone software platform, where a variety of tools can perform specific yet interconnected tasks. In this case, however, the tools connect to repositories of biological "parts" organized in such a way that they can be used to transform descriptions readable by humans into gene networks, designing DNA assembly commands for liquid-handling robots or archiving designs to share with other labs. Densmore admits that he's a big fan of Clotho—and he should be. He built it.

A $1.1 million grant from the National Science Foundation will help Densmore take Clotho from proof of concept to viable commercial software.

The idea came to him in 2007, when he was finishing a PhD in electrical engineering at the University of California, Berkeley. He had heard about a talk given by biological engineering expert Chris Voigt, then at UC San Francisco and now at MIT, and it struck him that the genetic circuits Voigt was describing looked very much like the digital circuitry of his own studies in electrical engineering.

Densmore teamed up with friend and colleague J. Christopher Anderson, now an assistant professor at UC Berkeley, and the two of them came up with a schema of how to organize biological information. "It works like this," says Densmore. "Let's say there's this small molecule X floating around in the environment. You want to design a bacterium so that if it sees X, it glows green, and if it doesn't see X, it glows yellow. We have programming languages that let me literally write, 'If X, glow green, if no X, glow yellow.' Then we also have our database of parts connected to Clotho. Clotho apps take these programming instructions and compile them."

Finally, he says, the information goes to another Clotho app, called Puppetshow, which has "a whole bunch of instructions about what has to happen biologically to make this work. Then it sends code to a liquid-handling robot, and the robot effectively says, 'You need to go to your fridge and get sample A and put it together with sample B.'

"Basically," says Densmore, "it's fancy domain-specific data management and work-flow management, but it's one of the things that this field desperately needs."

In November 2011, Clotho apps helped a team of undergraduates from BU and Wellesley edge out teams from the United States, Europe, and Asia to win in the Best Software Tool category at the International Genetically Engineered Machine (iGEM) World Jamboree at MIT. The team had earlier won a gold medal for its overall performance at the iGEM Americas Regional Jamboree in Indianapolis.

The undergrad team designed five software apps that could speed the assembly of DNA sequences that modeled gene interactions of the bacterium that causes tuberculosis—information that could lead to more effective diagnostics and drugs for TB.

In February, Clotho and Densmore got a big vote of confidence from the National Science Foundation in the form of a three-year grant of $1.1 million. The grant, he says, paves the way for Clotho to go "from proof of concept to viable commercial software." The project includes collaborations with other researchers at BU, as well as at UC Berkeley and the University of Washington.

Three months later, the Office of Naval Research gave Densmore more than $400,000 to buy machinery that will give him a better understanding of the behavior of DNA and proteins in biological systems.

And while Clotho has yet to be widely adopted by synthetic biologists, Densmore says it has at least 10 power users and several groups that use it collaboratively. Collins, who also is codirector of the BU Center for Biodynamics and a core founding faculty member of the Wyss Institute for Biologically Inspired Engineering at Harvard, says Clotho "is a novel computer-aided design platform for the field, one that will help fast-track efforts to reprogram organisms."

Avi Robinson-Mosher, a Wyss Institute researcher who is reengineering caffeine production in *E. coli*, agrees. Clotho reduces the likelihood of errors, he says, and allows him to work much faster.

"I heard that Doug was developing this," he says, "and I contacted him. He said, 'Come on over.'" Densmore's graciousness is typical in the field of synthetic biology. "In general," he says, "we like to share."

Which doesn't mean that synthetic biologists are welcome everywhere. "There is a group of biologists out there who say, 'Biology is way too complicated to engineer,'" Densmore says. "Biology is complicated, but that doesn't mean you shouldn't try to push the boundaries. We are saying, 'Let's not wait. We are going to learn things and we are going to predict things and we are going to build things.'"

In the Beginning, Man Created…

BU is poised to become a synthetic biology powerhouse

James Collins

KALMAN ZABARSKY

The age of synthetic biology was turned on, literally, with a switch built by two BU researchers 13 years ago. James Collins, now a William Fairfield Warren Distinguished Professor and a College of Engineering professor of biomedical engineering, and his graduate student Timothy Gardner (ENG'00) altered the genes of *E. coli* bacteria so that they could be made to produce proteins or not produce proteins, essentially creating a two-gene on/off switch for a biological circuit. The researchers described the achievement in a paper published in *Nature* in January 2000, an issue that also described a three-gene oscillating circuit built with the same genetic components by two Princeton physicists. Exactly 10 years later, *Nature* described the work done at BU and Princeton as the "defining pair of experiments" that mark the start of synthetic biology.

In those days, says Collins, who is also a Howard Hughes Medical Institute investigator, the Human Genome Project had captured the attention of cutting-edge biologists, as well as of the press. It would be years before the appellation "synthetic biology" entered the vernacular, and more important, before the science was distinguished from genetic engineering. Today, he says, the difference between the two fields is almost as clear as on and off.

"What genetic engineers were doing was cutting and pasting," says Collins. "They were introducing genes to enable organisms to be production organisms—they were essentially swapping a red lightbulb for a green lightbulb." By contrast, he says, synthetic biologists design and build the circuits that power the bulb. "Introducing the lightbulb is not engineering. That's home design. Designing the circuit is engineering. Synthetic biology is genetic engineering on steroids."

Collins' standard definition of the field goes like this: "Synthetic engineering is a new field that is bringing together engineers and biologists who design and construct biomolecular components and synthetic gene networks to reprogram cells, endowing them with novel functions."

The novel functions he refers to include the production of new fuels and medical treatments. Collins was recently awarded a Bill & Melinda Gates Foundation grant to engineer a yogurt bacterium that will respond to, and kill, cholera bacteria in the human intestine.

Synthetic biology has intrigued scientists at dozens of research institutions, but the field's alpha schools are generally considered to be the University of California, Berkeley, and the University of California, San Francisco, on the West Coast, and Harvard and MIT on the East. Recently, however, with encouragement from President Robert A. Brown, as well as Jean Morrison, University provost and chief academic officer, and Kenneth Lutchen, ENG dean, Collins has been strengthening the ranks of synthetic biology expertise at BU.

Douglas Densmore, the Richard and Minda Reidy Family Career Development Assistant Professor in the ENG electrical and computer engineering department, came to BU two years ago from UC Berkeley. Ahmad "Mo" Khalil, an ENG assistant professor of biomedical engineering and a former postdoctoral fellow under Collins, joined BU last fall. Also last fall, Collins helped to recruit Wilson W. Wong, an ENG assistant professor of biomedical engineering and previously a postdoctoral scholar in cellular and molecular pharmacology at UC San Francisco. The recruits, who like Collins work in a large, new state-of-the-art lab at 36 Cummington Mall, belong to a happily incestuous community: Khalil earned a PhD at MIT, which is a member of SynBERC, the Synthetic Biology Engineering Research Center, where Densmore was a postdoc. Collins is also affiliated with Harvard through that university's Wyss Institute for Biologically Inspired Engineering.

"You could build it around the four of us," Collins says. "And I don't think there's much doubt that BU is a major player in this exciting new field." AJ

WEB EXTRA ENG's James Collins talks about Boston University's powerful new team of synthetic biologists at bu.edu/bostonia.