BY KATIANNE WILLIAMS

Emulating Human Biology on a Chip

KARALIS RECREATING THE HUMAN BODY ENVIRONMENT

When the human body senses injury or infection, its response is to inflame. This inflammation serves as a barrier, isolating the infected or injured area from the rest of the body. There are dozens of inflammatory disorders, though, that occur when the human body goes overboard in response to a trauma or when this inflammation occurs for no reason. Rheumatoid arthritis and diabetes are two examples. Asthma, too, is an inflammatory disease, as inflammation of the air passages narrows the airways that carry oxygen.

Clinical molecular geneticist Katia Karalis has spent her career performing research in pathophysiology that is paving the way for new therapeutic approaches to inflammatory diseases in humans. If you take the studies she performs in her laboratory and lay them alongside the great advances scientists have made in physiology, genetics, and therapeutics, you could potentially have all you need to develop new personalized treatment plans for people suffering from a number of different diseases affected by stress.

Katia received her M.D. degree from Athens University Medical School in 1986. She wanted to be a pediatrician from the time she was very little, when she used to visit one herself, but over the years she learned that she prefers the research side. Still, Karalis has remained a large part of that pediatric community, even if she did not follow the clinical path.

As vice president of research at Emulate, clinical molecular geneticist Karalis is part of a team developing an organs-on-chips technology that could revolutionize medicine.

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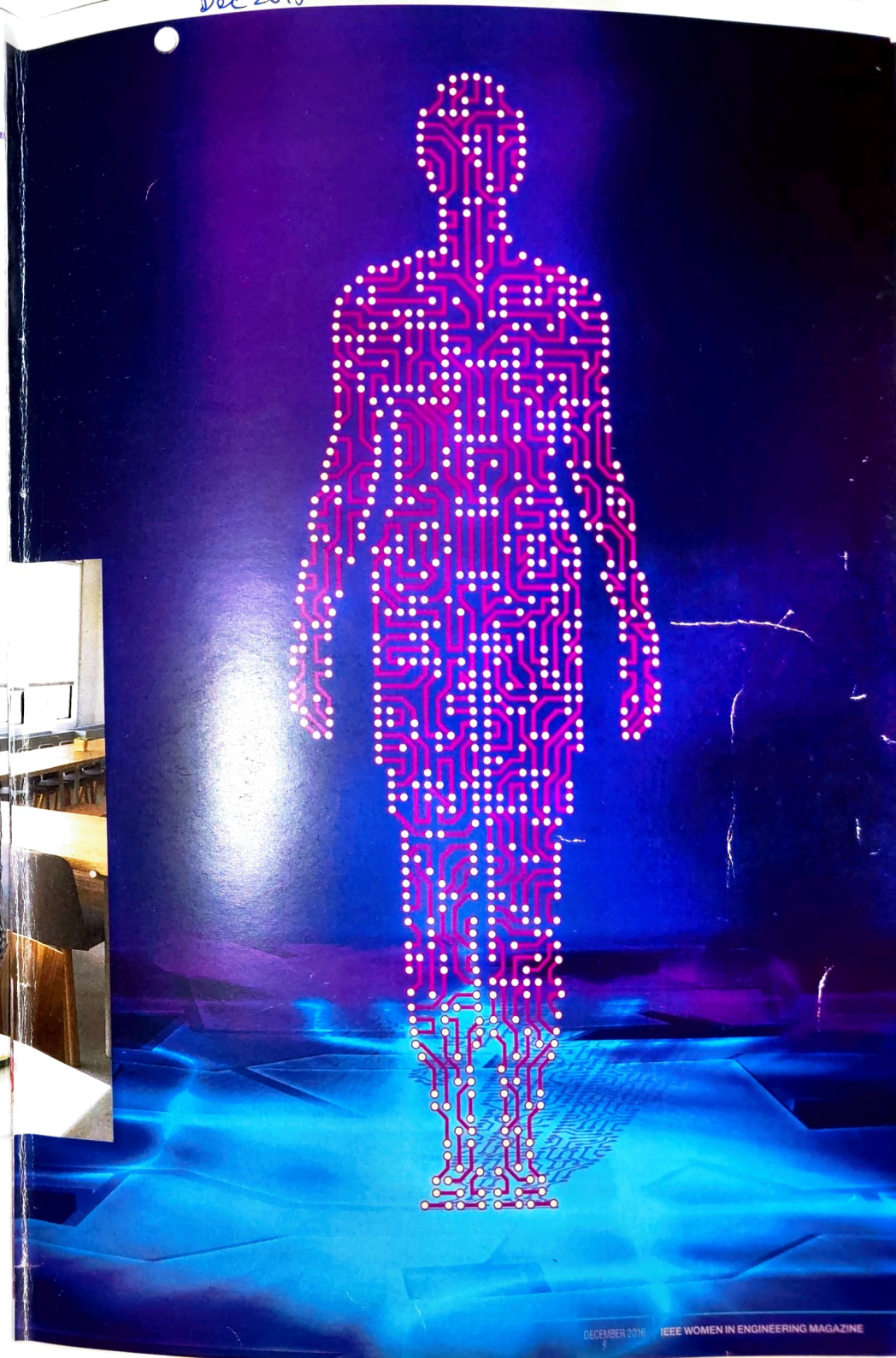

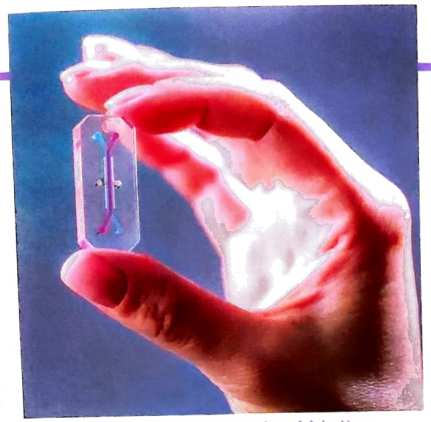

The clear chip, about the size of an AA battery, recreates human physiology.

As a postdoc in endocrinology, she spent years at Cedars-Sinai Medical Center in California and at the National Institutes of Health in Bethesda, Maryland. She moved to Boston for a postdoctoral fellowship in pediatrics and medicine at the Division of Endocrinology at Harvard University and then went on to study clinical molecular genetics and cytogenetics at Harvard's Department of Genetics. She returned to Greece and worked in the newly established Institute for Biomedical Research at the Academy of Athens, researching and training young scientists.

Karalis kept "one leg in Boston," and three years ago, she began looking for a sabbatical opportunity there that would allow her to spend time researching subjects related to new technologies for understanding how human diseases develop and progress. Her husband and her two children accompanied her.

She says it was serendipity that led to her to talk to Donald Ingber, director of the Wyss Institute for Biologically Inspired Engineering at Harvard University. He offered her a position as a visiting scholar working on a Defense Advanced Research Projects Agency-funded initiative to engineer a virtual body-on-chip by linking ten different organ-chips. Karalis was focused on the human intestine-on-chip, and her work also focused on the development of the intestine-chip to simulate inflammatory bowel disease and other diseases of the gastrointestinal tract.

Karalis came for one year but ended up staying for two. When the second year was up, she returned with her family to Greece. It was then that Wyss spun off a new company called Emulate, Inc. This move was expected—a large part of the Wyss Institute's mission is to bridge the gap between academia and industry, making it easier for technologies like organs-on-chips to actually make it to market. Many leaders of her project took positions at Emulate, and Karalis was offered the position of vice president of research, which meant she would oversee the development of biology-related research.

"That is how I am here," she says, gesturing around the Emulate office, "after a lot of years in academia."

Emulate This

Emulate's new office sits at the far end of Boston's historic Innovation and Design Building, a long, narrow structure that once served as a waterside storehouse for the South Boston Army Base. The building's north side stretches along Drydock Avenue, home to one of the country's largest dry docks, while the south side runs along the Black Falcon Cruise Terminal. If you look out of one of Emulate's many windows, you are bound to see water. Beyond the water, you may also see the Boston skyline, the Tobin Bridge, Logan Airport, or a low-flying 747.

It's an area full of technology start-ups, architecture firms, manufacturing businesses, and research and development companies. The tenants have moved into this area while it is still very much up-and-coming—the building sits in the midst of a bustling construction site. Much of its Drydock Avenue frontage is behind temporary fencing. Construction trucks are omnipresent, as are pigeons, sea gulls, the dings of elevators, the groans of delivery trucks being unloaded, and the high-pitched beeps of trucks that are backing up.

Up on the fifth floor, Emulate occupies a large warehouse-like space that combines design, engineering, and biology into one integrated space. High ceilings, slab floors, glass walls, a shabby chic piano in the kitchen—it's an open, industrial area decorated with fuchsia and teal bucket seats. Inside a glass-walled lab that stretches along the width of the main office space, engineers and scientists work side-by-side developing the organs-on-chips technology. The 46 (and growing) team members skew on the millennial side. In ball caps, jeans, and Converse sneakers, they carry laptops and white take-out boxes from the shipping containers-turned-eateries that line the walkway outside. Some wear tee shirts that read *EMULATE THIS*.

Here, they have expanded greatly on the initial lung-chip system, emulating a wider range of human biology by using the organs-on-chips technology to recreate various organs—such as the brain, liver, and kidney—inside their microengineered chip environments. Better than in vitro and less invasive than in vivo, this organs-on-chips technology is being designed to help revolutionize medicine. It is already proving it can provide greater precision than cell cultures or animal testing, and it has the potential to open the door to a wide range of personalized health applications.

A Living Environment on a Chip

"The idea is that we create a living environment ex vivo, where we put human cells, but in contrast with traditional ways of cell culturing—such as in a dish or in a flask, on a flat surface, that may be coated with a material to keep the cells 'more happy'—we provide a very dynamic environment that is like a home away from home for the cells," Karalis explains. "We try to incorporate what is very vital for a cell, tissue, or organ in vivo—that it is to be fed in a constant, dynamic way…and also that it is exposed to the mechanical forces that cells would experience inside the human body, such as stretching and pressure."

Karalis continues by explaining how these mechanical forces are so very relevant for the function of the organs. A lung needs to expand and contract and then come back to its original position for us to breathe efficiently. Muscles attached to bone provide a component that can be stretched.

"We recreate this human body environment," Karalis says. "We emulate it. That is where the name of the company comes from."

Emulate does this through a combination of microengineering, biological research, medicine, materials science, design, programming, and data science. In one lab, scientists in clean-room suits huddle at incubators performing tissue culture work. Adjoined to this is the microfabrication lab, where engineers also in white clean-room suits work to design and create new chip models.

In the engineering lab, Associate Director of Discovery Chris Hinojosa gives a demonstration of Emulate's new Human Emulation System. The system contains instrumentation, chips, and software apps, and it is designed to make the technology plug-and-play and "lab-ready" for use by a wide range of research and commercial organizations. For this technology to find a home in the labs of research institutions and pharmaceutical companies around the world, it must be easy to use—so automated and precise—that it provides standardization around product design, development, and testing.

Currently, there are chips for the lung, intestine, kidney, skin, and even a chip for thrombosis. The chip itself is clear and about the size of an AA battery. Hold the chip the long way and you see two different microchannels criss-crossing it, piggybacking each other for a while along the center line before ending in the opposite corners from which they began. The cells must be fed in a constant way, and these two channels supply the goods. This is where the microengineering comes in. Where the channels meet in the center, they are separated by a porous membrane coated with extracellular matrix proteins from an actual organ. This provides the physical surface upon which the cells—be they lung, kidney, or skin—attach and perform their role. This is the materials science. This, in effect, recreates a human physiology that can be used for safety testing new chemicals, the safer design of new consumer products, developing new organ models, and studying disease development or even treatment.

Researchers alter parameters to affect the tissue in a way that will provide an environment susceptible to the development of disease. If you're testing a lung cell, for example, you might introduce a bacteria as one input, and blood in the circulatory system provided by endothelial cells as the other. When the bacteria meet the blood cells along the porous membrane, the white blood cells react and create an inflammation response. Karalis uses hypoxia as another example. "Say that a person has lowered oxygen supply somewhere because of a blood clot," she explains. "This hypoxia that the tissue senses is something that we can emulate."

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Progress All Around

Walking around the Emulate space, one can only think that there must be many more people hiding somewhere to get all of this work done. There aren't—but they do have major plans for growth. Emulate is looking to almost double its size, from 40 to 85, by the end of 2016. It also secured US$28 million in Series B funding in March 2016 to develop its automated "lab-ready" product platform.

As it looks now, organs-on-chips could be the disruptive technology that changes the way we identify, design, and test new drugs. Since the chips create an environment similar to the in vivo conditions, researchers can predict what effect drugs may have before they go to humans. Emulate can develop chips with rat cells, dog cells, or any organisms used in the clinical evaluation of drugs, and it can use this test to replace part of the clinical studies that currently use animal test subjects. "It can give us a hint of how different drugs work in the different species," Karalis says. "Something may be fine for a rat but toxic for a human. We can do a comparative analysis of the behavior, the response of the cells of different species, and move safely to patients."

Karalis, who has spent years researching inflammatory diseases, has found her years at the Wyss Institute and Emulate to be fruitful. Together, Emulate and Merck have already published data showing that Emulate's lung-chip has achieved accurate modeling of the human lung small airways. They have also made progress into understanding the mechanics of airway changes that occur as a result of the respiratory distress caused by asthma or chronic obstructive pulmonary disease and have taken steps toward developing an improved model for predicting responses to therapeutic interventions.

Emulate will continue working on adding new organs and disease models to chips, concentrating on more complex organs like the heart and brain. The idea is to scale up. Eventually, the organs-on-chips technology will be produced on such a scale that they will be available to develop targeted, therapeutic treatments through precision medicine. If we can one day take a person's stem cells and create their own personal chip, we may be able to develop combinatory therapies that not only are highly effective for a particular patient, but also eliminate harsh side effects elsewhere within the body.

—Katianne Williams is a freelance writer specializing in the technology field.