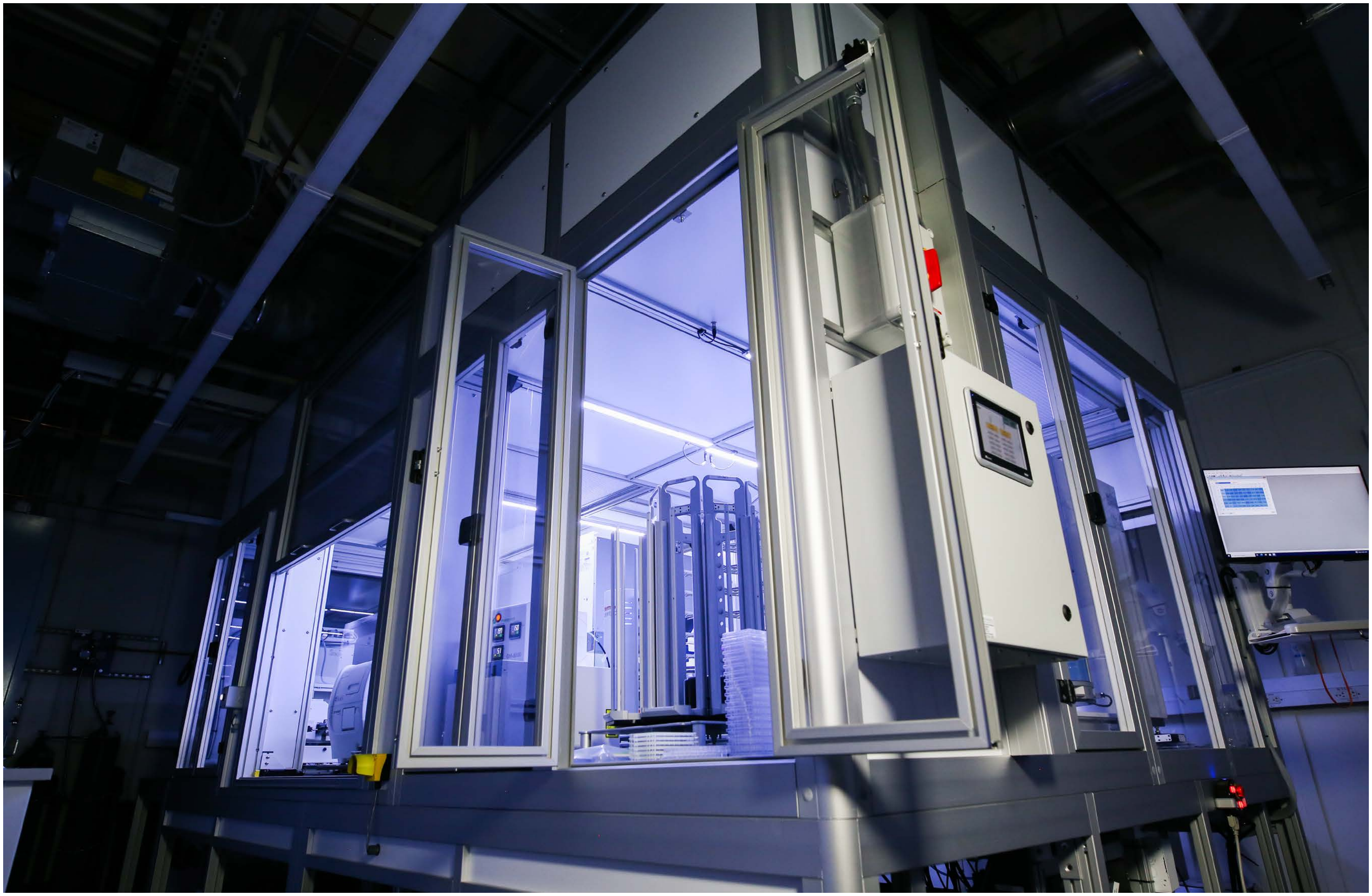


State-of-the-art instrumentation, including this automated and customized robotic assembly system, will be the centerpiece of UCSB's NSF ExFAB BioFoundry facility.

UCSB to Lead NSF-Funded Center on Exceptional Microorganisms

A SIX-YEAR, $22-MILLION GRANT INCLUDES PARTNERS UC RIVERSIDE AND CAL POLY POMONA. TOGETHER THEY WILL ESTABLISH A FIRST-OF-ITS-KIND BIOFOUNDRY.

Synthetic biology involves engineering the genetic material of organisms such as viruses, bacteria, plants, and yeast to have new desirable characteristics. The multidisciplinary field employs biological technology (*biotech*) techniques, such as DNA sequencing and genome editing, to modify or engineer new organisms with the aim of addressing challenges in medicine, agriculture, manufacturing, and the environment. For example, scientists are using synthetic biology to develop next-generation vaccines, to engineer organisms that capture carbon, and to create nutrients for crops to minimize the need for industrial fertilizers.

New robotic workflows and technology powered by machine learning have emerged to accelerate and prototype designs of microorganisms for applications in biotechnology. This infrastructure is housed in facilities, called *biofoundries,* most of which are privately owned and operated by pharmaceutical and biotech firms. In an effort to broaden access to state-of-the-art technology, workflows, processes, and knowledge, the National Science Foundation (NSF) created the BioFoundries Program. In August, NSF announced a six-year, $22-million award to UC Santa Barbara to establish the BioFoundry for Extreme and Exceptional Fungi, Archaea and Bacteria (ExFAB), a collaboration led by UCSB, together with UC Riverside (UCR) and Cal Poly Pomona (CPP). The NSF ExFAB BioFoundry establishes the nation's first biofoundry focused on largely untapped and unexplored microbes that live in extreme and unusual environments.

"We are extremely excited, because this funding provides access to instrumentation and infrastructure that nobody, especially in academia, has had access to before," says ExFAB director, **Michelle O'Malley,** a professor of chemical engineering and bioengineering at UCSB. "The facility will allow us to unlock the promise of a new generation of synthetic biology focused on extreme and unusual microorganisms isolated from nature."

"UCSB is a world leader in promoting multidisciplinary, center-level science," says **Umesh Mishra,** dean of the UCSB College of Engineering and a professor of electrical and computer engineering. "We are extremely proud to host the NSF ExFAB BioFoundry, because it unites several strengths across our campus for the first time — from marine science to chemical engineering and bioengineering. This sizable NSF award raises the profile of our campus and serves as a focus point for continued investment in biotechnology and bioengineering at UCSB."

Foundry researchers will focus on developing techniques to learn from nature's more unusual microorganisms, referred to as "extreme," because they do not conform to standard growth habits and culture conditions in a lab. They may have unusual nutritional requirements or grow at extremely high or low temperatures — or even without oxygen — all of which makes them difficult to study with existing infrastructure.

"These extreme microorganisms defy our current understanding of biology, yet they still host traits and components that we want to harness for biotechnology, such as enzymes that chew up waste, or pathways that could be used to make valuable products and new medicines," says O'Malley, who is pioneering a new research field by engineering anaerobes to turn plant waste into more sustainable fuels, chemicals, or bio-based materials.

> "The facility will allow us to unlock the promise of a new generation of synthetic biology focused on extreme and unusual microorganisms isolated from nature."

ExFAB director, Michelle O'Malley

RESEARCH THEMES

By focusing on extreme microbes, ExFAB researchers are pushing the boundaries of biotechnology discovery and innovation within three central research themes: bioremediation, biosynthesis, and using extreme microbes to better understand the rules of life.

Bioremediation refers to the process of using microorganisms to break down hazardous materials and substances into less toxic or nontoxic products. Such ubiquitous microbes, including algae, fungi, and bacteria, are found in nature and thrive in their harsh environments by using the contaminants as a source of food and energy. ExFAB researchers will collect, identify, and categorize microbes that thrive in various extreme environments to unlock their secrets and engineer microorganisms that are able to degrade waste. In one project under the bioremediation pillar, researchers seek to address environmental contamination caused by per- and polyfluoroalkyl substances (PFAS), also known as "forever chemicals," because they are nearly indestructible and resist breakdown in the environment and in our bodies. Another interdisciplinary team will study marine bacteria that host unique genes enabling them to remove chlorine molecules, via a process called *dehalogenation,* when a remaining amount of an insecticide, such as long-banned DDT, is discovered in soil.

Biosynthesis is a multi-step enzyme-driven process accomplished by the action of microorganisms and by which simple compounds are converted or combined to form more complex products that are valuable to society. Engineers already use biosynthesis to produce fuels, chemicals, medicines, and cosmetics. Examples of biosynthetic-themed research within ExFAB include work by O'Malley's group to exploit the power of anaerobic gut fungi to secrete enzymes that degrade dry plant matter, as well as a collaboration aimed at harnessing the basidiomycete yeast Rhodotorula as a way to produce chemical precursors.

In pursuing both the biosynthesis and bioremediation themes, the ExFAB team will also uncover new *rules of life*, which the NSF defines as "elucidating the sets of rules that predict an organism's observable characteristics; its phenotype." Inspired by NSF's ten "Big Ideas," extreme and exceptional microbes offer clues into the surprising inner workings of microorganisms. Many of the microbes that will be studied in ExFAB have not been cultured or described previously, and they host highly unusual cellular traits and compartments. For example, ExFAB research led by **Jean-Marie Volland,** an assistant professor of molecular, cellular, and developmental biology (MCDB) at UCSB, is aimed at characterizing new nuclear compartments in exceptionally large sulfur bacteria, which could redefine textbook knowledge of bacteria. Finding and characterizing these surprising structures will help scientists predict how biology works, and also guide them in engineering desirable traits into microorganisms.

Researchers believe that the new high-throughput experimental workflows made possible by ExFAB will change how biology is discovered and engineered in microbes. Gene-to-gene function studies of extreme microbes in both anaerobic and aerobic environments will now be possible. As a result, researchers will be able to capture unique rules of life by performing genome editing from every type of extreme microorganism, ranging from gut fungi and bacteria found deep in the oceans, to large sulfur bacteria and microbes existing in outer space.

"The facility provides an exciting opportunity to open synthetic biology to the vast diversity of microbes that nature provides," explains ExFAB co-director Ian Wheeldon, a chemical environmental engineering professor at UCR and an expert in synthetic biology and engineering non-conventional microbes. "Until now, the focus of synthetic biology has been to develop new approaches to engineering a small number of commonly used microbes. This facility will dramatically broaden this approach by enabling synthetic biology in any microbe."

Research in the areas identified above will be aimed at achieving three major goals for the center that have been established by the interdisciplinary team: to enable basic science discoveries from extreme organisms, to pioneer new strategies using microbes to capture and convert carbon, and to fabricate novel workflows and infrastructure to advance biotechnology and translate it into the real world.

THE GROUNDWORK

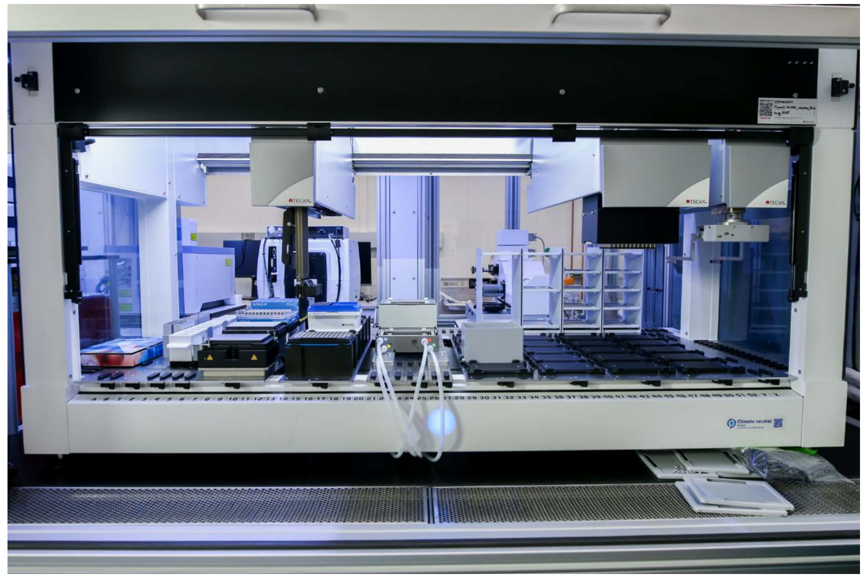
UCSB laid the foundation for the ExFAB months before applying to the NSF's BioFoundries Program when O'Malley received a $9.85-million grant through the Department of Defense's Defense University Research Instrumentation Program (DURIP). The grant, which followed twenty years of sustained funding from the U.S. Army Research Office for the Institute for Collaborative Biotechnologies (ICB), a large interdisciplinary research alliance led by UCSB, allowed the university to purchase a pair of workflow systems comprising robotic assembly and analytical tools to enable automated synthetic biology. The systems are major components of the NSF ExFab BioFoundry, complementing and extending each other for researchers embarking on this frontier of biological investigation.

One customized system was designed to handle mammalian cells — the type of cells that researchers use as platforms for drug discovery or to learn how human cell biology works. A second set allows for rapid screening and engineering of microbial cells and microbial communities.

"Automation eliminates the bottleneck and allows us to develop and analyze incredibly large datasets to find true breakthroughs," says O'Malley.

"This technology provides the kind of experimental firepower of a mid-size biotechnology or pharmaceutical company, but in such a way that we can be flexible in pursuing answers to many different problems," says **Max Wilson,** an assistant professor in UCSB's MCDB Department. "When you have robots that don't sleep and don't make mistakes, you can do extremely precise research at unprecedented scales."

"The exciting new investment from the NSF recognizes UCSB's growing research prominence in the field of synthetic biology and builds upon the recent investment from the Army Research Office," says chemical engineering professor **Brad Chmelka,** co-director of ICB. "This NSF award exponentially expands UCSB's interdisciplinary research culture in biology, materials science, physics, chemistry, and engineering, which will benefit from, and can be expected to catalyze, new innovations and applications in biotechnology."



A view of one of two Tecan Fluent 780 liquid handlers — this one is for the Mammalian system — that will be customized so that the filtration unit can be swapped out for a colony-picking robot, called the Pickolo. O'Malley lab project scientist Elaine Kirschke, who worked on customizing the liquid handler, which is just over seven feet wide and a yard deep, describes it as "a pretty serious piece of automation," complete with its own robotic gripper arm. Incredibly versatile, it can carry out complex liquid-handling tasks, such as magnetic bead separation and vacuum filtration. "It is the closest thing you can get to robotically mimicking human hands at the bench, but it is capable of throughputs that would break the human wrist," she says.

NEW FACILITIES

The transformative nature of the NSF award is especially evident when it comes to infrastructure and access to experimental facilities. All three campuses will house state-of-the-art equipment suites, and research activities will be supported by a team of project scientists, process engineers, and specialists.

Researchers are especially thrilled about the NSF's BioFoundry award, because it will enable them to leverage and expand the already-funded DURIP equipment, most of which has been installed, while the facilities at UCR and CPP make it possible for more researchers and students to access the technology there.

The funding allows CPP to establish its first shared-use facility that is open to outside industry and academics. CPP will lead ExFAB's efforts to identify and perform metagenomic analysis of microbes newly collected from the environment. The space will feature a high-throughput sequencer and additional equipment to support sequencing projects. Prior to such equipment becoming available on the three campuses, faculty had to send their sequences to be analyzed at third-party facilities.

"This is an amazing opportunity for our students, and I can't wait to get started," says ExFAB co-principal investigator Jamie Snyder, an associate professor of biological sciences at CPP who specializes in archaea and archaeal viruses. "Our students will be working on projects directly related to the research mission of ExFAB, and they will know that they are part of something that is unfolding on a grand scale."

UCR will build a new facility dedicated to high-throughput microbial phenotyping. The automated platform, which will feature liquid handlers and robots, will be able to process thousands of aerobic microbes at high-speed, characterizing how well various species grow in different environments, at different temperatures, and on different carbon sources.

"The UCR team brings expertise in engineering microbes, genomics, environmental microbiology, and synthetic biology," explains Wheeldon.

Unpacking the future of biotech: UCSB ExFAB BioFoundry staff and senior participants with a shipment of newly arrived equipment (from left): Oliver Vining, Elaine Kirschke, Jean-Marie Volland, Nathalie Elisabeth, Sherylle Mills Englander, Max Wilson, Michelle O'Malley, Joel Rothman, Niels Volkmann, Carolyn Mills.

> "The unique suite of cutting-edge instrumentation will enable technologies to address some of the nation's biggest challenges, and a workforce that is ready and able to put these innovations to use."

"These skill sets are critical to helping solve important biotechnology challenges, develop new biotechnologies, and discover new biology."

The state-of-the-art instrumentation will be the centerpiece of the UCSB facility, which will also be the first and only one of its kind in the United States. "The signature piece of UCSB's biofoundry will be the environmentally controlled preparation-and-analysis chamber, which can be completely anaerobic," says O'Malley. "The user community from industry and academia will finally have access to an anaerobic biofoundry dedicated to the study of exceptional microbes, one that can carry out genetic engineering and prototyping, and use imaging, sorting, and rapid chemical profiling to link that directly to microbe function."

The anaerobic workflows provided by the foundry will also allow researchers, such as UCSB bioengineering professors **Dorit Hanein** and **Niels Volkman,** to apply cryogenic electron microscopy and cryo-electron tomography to visualize the structure of the microorganisms with nearly atomic resolution. Those additional insights will allow scientists to better understand natural processes, knowledge that can inspire future applications in such areas as renewable energy and environmental remediation.

The California NanoSystems Institute (CNSI) at UCSB, which was established by the Governor's Office in 2002, will manage and coordinate ExFAB operations at all three campuses. CNSI is currently home to two $20-million-plus NSF-funded centers — the Quantum Foundry (see article on page 18) and the BioPACIFIC MIP (dedicated to scalable production of bio-derived building blocks and polymers), as well as the campus's only deep-computing center and seven specialized shared-instrumentation facilities dedicated to fields ranging from quantum to biotech.

"CNSI is proud to be the home of ExFAB and to provide foundational support that will increase the impact of ExFAB innovations," says CNSI co-director **Craig Hawker,** a professor of materials and of chemistry and biochemistry. "The unique suite of cutting-edge instrumentation will enable technologies to address some of the nation's biggest challenges, and a workforce that is ready and able to put these innovations to use."

External users from industry and academia can access the ExFAB Bio-Foundry in two ways: by directly shipping samples for complete handling by staff, and via on-site training and co-use of equipment with staff. Leadership aims to complete at least one hundred total user projects over the first six years of operation, estimating that more than half will be external projects.

TRAINING A DIVERSE WORKFORCE

The ExFAB will establish an educational program to train and attract the future biotechnology workforce by establishing a solid partnership between two UC campuses and a third university that is part of the California State University (CSU) System. All three are Hispanic-Serving Institutions (HSI) and Asian American Native American Pacific Islander Serving Institutions (AANAPISI). By creating shared-use facilities on three campuses, ExFAB will offer unprecedented access to cutting-edge instrumentation to members of industry and academia, including students and faculty from the 23 CSU campuses.

ExFAB will recruit CSU master's students to participate in a ten-week research internship at UCSB or UCR, during which they will receive professional development and work in a scientific community at an R1 (research-intensive) university. ExFAB will also offer one-quarter fellowships to PhD students at UCSB and UCR and host a summer school to train and recruit new users.

"Many CSU students want to enter industry or PhD programs but lack experience at an R1 university setting," says Snyder. "This opportunity will allow them to be trained on automated equipment they will likely find in industry, and to interact with PhD students, postdocs, lab technicians, and senior scientists in R1 labs. The facility will enable us to create more pathways into the biotechnology workforce for people who, currently, may not feel represented in the field."

Between the unique rapid-throughput equipment that can leverage machine learning to predict outcomes and perform hundreds of experiments in the time humans could do only a few, the singular focus on radical organisms, the interdisciplinary reach and multi-university involvement, and the opportunity to bring a wide range of students into this exciting area of research, the NSF ExFAB BioFoundry is set to dramatically expand the frontiers of biological understanding.

More information about the ExFAB BioFoundry can be found at exfab.org.