Tiny Lifeforms, Big Impact

By Andrew Moseman

The Center for Environmental Microbial Interactions' support of early-stage projects reaps big rewards for science and scientists.

One late summer morning, Jared Leadbetter returned to his office and found a surprise growing in the sink.

For decades, microbiologists had hunted for microbes whose growth is fueled by oxidizing manganese, an abundant element found across nature and in materials such as steel. Geochemical evidence suggests such microbes should not merely exist but abound across many environments, yet these particular metal eaters had remained frustratingly elusive. Since the search for such microbes had befuddled so many researchers before, continuing to hunt for them seemed futile. Instead, Leadbetter, an environmental microbiologist, filled some idle moments in the lab by searching for microbes that might interact with manganese in entirely different ways.

Fortunately for Leadbetter, he forgot to do the dishes. Upon returning from a 2015 summertime guest-teaching stint at the Marine Biological Laboratory in Woods Hole, Massachusetts, Leadbetter found that he had left dirty glassware containing manganese to soak in the office sink. In the intervening three months, the manganese in the glassware had turned from a light beige to a dark brown, possibly a sign that bacteria had oxidized the manganese. Now all he had to do was prove it.

Former Caltech researcher Hang Yu collaborated with Leadbetter on what would become years of hard work to confirm these really were the long-sought-after microbes. After completing his doctoral studies under Victoria Orphan, a geobiologist and director of Caltech's Center for Environmental Microbial Interactions (CEMI), Yu wanted to further investigate these manganese metabolizing bacteria. CEMI made it possible. "When Hang left my group," Orphan says, "CEMI was able to support him to do a short postdoc with Jared and take this new novel culture Jared had discovered over the finish line." Their initial study on these metal-eating microbes became a paper in the journal *Nature* and a microbiology sensation, one that could, for example, be useful for treating water containing manganese (which often discolors drinking water and has an unpleasant taste).

Formed a decade ago in recognition that researchers across the Institute's divisions study microbial life in some way, CEMI has grown to include more than 10 percent of Caltech's faculty. Thanks to philanthropic funding, the program can support several pilot projects annually and has backed 80 in its 10 years of existence. These projects may have big potential but are often in the early stages of discovery, which means they are not quite ready for the federal grant application process. The researchers doing that work probe questions that will aid in the fight against antibiotic-resistant infections, lead to better ways to clean up the environment, and illuminate the links between the human brain and the microbiome. CEMI is Caltech in microcosm, catalyzing the Institute's signature brand of interdisciplinary collaborations and bold new ideas in the field of microbial interactions.

Orphan says the center's nimble nature allows it to deliver support right when it is needed, such as with Yu's postdoctoral research or to explore new ideas that come from students rather than from principal investigators.

"We do microbiology in a very different way," Orphan says. Caltech researchers inspired by the features and talents of microbes have tried to use their unusual properties to discover new chemistries or catalysts. Others—like Orphan, Leadbetter, and biologist Dianne Newman, who was CEMI's inaugural director—focus on microorganisms themselves and how they drive other geochemical cycles, interact in natural communities, and impact environmental habitability in a way that then impacts the whole planet.

"Within CEMI, microbiology is broadly defined in a way that I think gives the students and postdocs a perspective that is unique to Caltech," Orphan says.

For more about CEMI, go to **microbiology.caltech.edu**

There could be 30,000,000,000 microbes on this page

... and a lot of them are good.

If the global pandemic taught us anything, it is that the world belongs to microorganisms. Some, like the SARS-CoV-2 virus or pathogenic bacteria, are dangerous, even seemingly malevolent. But many more are harmless or even beneficial to humans, including the species that make up a person's microbiome. To understand microorganisms is to better understand our planet ... and ourselves.

"Microbes have been driving the planet for billions of years before we ever got here," says Victoria Orphan, a geobiologist and director of the Center for Environmental Microbial Interactions. "Humans are sort of like the last blink of an eye. We evolved in a microbial soup and world, and so it's not surprising that everything about our own physiology, our ecology, our everything is connected in some way to microorganisms."

Watch a video about the research CEMI director Victoria Orphan (above) does to understand the microorganisms that play critical roles in oceanic methane oxidation:

Forging Links

Like Leadbetter's metal-eating bacteria work, CEMI itself owes something to serendipity. A decade ago, Newman says, then-provost Ed Stolper, now the Judge Shirley Hufstedler Professor of Geology, noticed that faculty investigating microbiological questions had been hired across several of Caltech's divisions. This trend was more fortuitous than it was planned, she says, but Institute leadership seized the opportunity.

"What Ed recognized was a chance to have the whole be more than the sum of the parts," she says, "to bring these people together in a way that allowed for interdisciplinary work and the creation of a community that would enrich the activity of any individual group that was interested in microbes."

Newman, who has been part of CEMI since its inception in 2012, is an exemplar of its ethos. Her lab focuses on the physiologies of bacteria that make it possible for them to survive and thrive in the absence of oxygen. Because of CEMI, Newman's techniques, strategies, and students have crossed over to help other Caltech research projects get further than they could alone.

For example, biologist Alexei Aravin studies how foreign DNA is detected and how, at a molecular level, cells know what to do to respond to this invasion. While studying this process in multicellular organisms such as fruit flies over the past decade, he recognized an analogous process that happens in bacteria. When he wondered which species might make an ideal model to investigate the question, Newman used her deep knowledge of bacteriology to point him toward a useful subject. Then, a student in Aravin's lab snagged one of the first CEMI grants to do this work.

"They wound up making a beautiful discovery of the ancestral version of this very important, fundamental pathway in eukaryotes [organisms whose cells have a nucleus] that appears to maybe have originated in bacteria," Newman says.

Aravin appreciated the chance to work with a microbiologist after making the leap into the field from biology. "Sometimes you need help," he says.

Similarly, Priya Chittur, a graduate student working with chemical engineer Julia Kornfield (BS '83), the Elizabeth W. Gilloon Professor of Chemical Engineering, became interested in biofilms, which are communities of microbes that form on a surface. In particular, she wanted to look for exotic properties in biofilms whose cells are oriented in a specific direction, which can create a gorgeous iridescence. "Their unique optical properties are much like what you see with peacock feathers or butterfly wings," she says.

Chittur and Kornfield sought the expertise of Leadbetter, who suggested searching in Southern California. And, in fact, it was on kelp in the Malibu wetlands where Chittur found samples of the biofilms that became the subject of her CEMI research.

Southern California was likewise an inspiration for graduate student Shivansh Mahajan, who wanted to explore the arsenic contamination that is a concern for the region's groundwater. Mahajan received CEMI funding in 2021 for an ongoing study of the mechanisms bacteria use to pump dangerous arsenic out of a cell, a project that unites the expertise of Newman; Doug Rees, the Roscoe Gilkey Dickinson Professor of Chemistry; and Bil Clemons, the Arthur and Marian Hanisch Memorial Professor of Biochemistry.

In addition to such collaborations, CEMI has also launched careers. Elaine Hsiao (PhD '13), now a faculty member at UCLA, received CEMI support to become a senior research fellow at Caltech between graduation and when she secured a full-time faculty position.

"The pilot fund from CEMI was the first grant I received as I was transitioning into my independent scientist position," she says. "It helped to support a new research project that forms the basis of my lab's current research on how microbes in the gut can affect the brain, and it helped me gain confidence and visibility as I began my professorship role."

Scott Saunders (PhD '20) took his CEMI research in a surprising direction. His doctoral work under Newman studied *Pseudomonas aeruginosa*, an important opportunistic pathogen. An understanding of how it survives in the absence of oxygen, he knew, could lead to new ways to fight infections. In the course of earning his PhD, however, Saunders became fascinated with finding better ways to manipulate bacterial genes.

"Now I'm at a medical center, UT Southwestern," he says. "The important, long-term goal is to extend these approaches into a variety of pathogenic bacteria that are related to *E. coli* and *Pseudomonas*. These are important pathogens that cause antibiotic-resistant infections that kill lots of people every year. It is very important to understand their basic biology and develop tools to help us understand them more quickly and more deeply."

A Microbiology Culture

Integral to CEMI's success, Leadbetter says, is that the center taps into the bedrock strengths that define Caltech, namely its intimate size, tradition of collaboration across disciplines, and boldness to move into new research areas. "These interdisciplinary pilot projects seem to emerge out of nowhere because of the tradition we have at Caltech where faculty and students talk to each other across disciplines," he says. "CEMI is about microbial interactions, but it's also about the interactions among members of our community."

Over the past decade, the center built its own unique culture of collaboration and inspiration. Saunders remembers helping set up food and drink for "MicroMornings," a tradition of serving bagels while someone within the microbiology sphere at Caltech described their research. This grew into what are now called "CEMInars," a lecture series that Saunders credits with making him feel like part of a community and giving him the opportunity to connect with Caltech microbiologists who might have far-flung research interests.

Those informal interactions spark further collaborations. Years ago, one of those talks was given by then-postdoctoral scholar Martin Pilhofer, now a professor at ETH Zurich. In attendance was Newman lab postdoc Nicholas Shikuma, now an associate professor at San Diego State University. Shikuma saw in Pilhofer's cryo-electron microscopy work a direct connection to his own research in bacteriology. Together, they discovered a new class of molecular syringes, which are natural structures released by bacteria. These molecular syringes then interface with an animal and inject a protein into it that triggers its metamorphosis.

"One of the most thrilling scientific moments in my life actually came one afternoon when Grant Jensen [professor of biophysics and biology], Martin Pilhofer, Nick Shikuma, and I were sitting in my office looking in real time at the data they'd collected," Newman says. "The things we started seeing visually just blew our minds. They were structures no one had ever seen before, and this discovery resulted directly from the creativity of these two postdocs and their meeting through CEMI."

The omnipresence of microbes creates an unlimited array of possibilities for CEMI's second decade. In addition to continuing to promote collaborations among the center-affiliated researchers, Orphan also hopes to forge new partnerships with similar centers around campus, including the Resnick Sustainability Institute, the Tianqiao and Chrissy Chen Institute for Neuroscience at Caltech, and the Merkin Institute for Translational Research, due to microbiology's deep and powerful connections to those burgeoning fields of study. Growing CEMI's endowment would also help to build its educational program by offering fellowship support for students and postdoctoral scholars alongside the pilot-project funding the center has supplied for 10 years.

"The main currency of success is really the people," Orphan says. "We have the ability to bring people in and support them and teach them the novel ways we think about microbiology here at Caltech, and then send them off so they can share that with their future universities and careers. If we could expand that bubble out even further, that would be wonderful."

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Dianne Newman is the Gordon M. Binder/Amgen Professor of Biology and Geobiology and executive officer of Biology and Biological Engineering. Her work is funded by the National Institutes of Health, the National Science Foundation, the Schwartz-Reisman Collaborative Science Program, the Doren Family Foundation, the Simons Foundation, the Jane Coffin Childs Foundation, and the Damon Runyon Cancer Research Foundation.

Victoria Orphan is the James Irvine Professor of Environmental Science and Geobiology and the Allen V. C. Davis and Lenabelle Davis Leadership Chair for CEMI. Her work is funded by the Department of Energy, the National Science Foundation, NASA, the Gordon and Betty Moore Foundation, the Simons Foundation, and the Nomis Foundation.

Nearly 50,000 microbes could sit on the tip of this needle.