



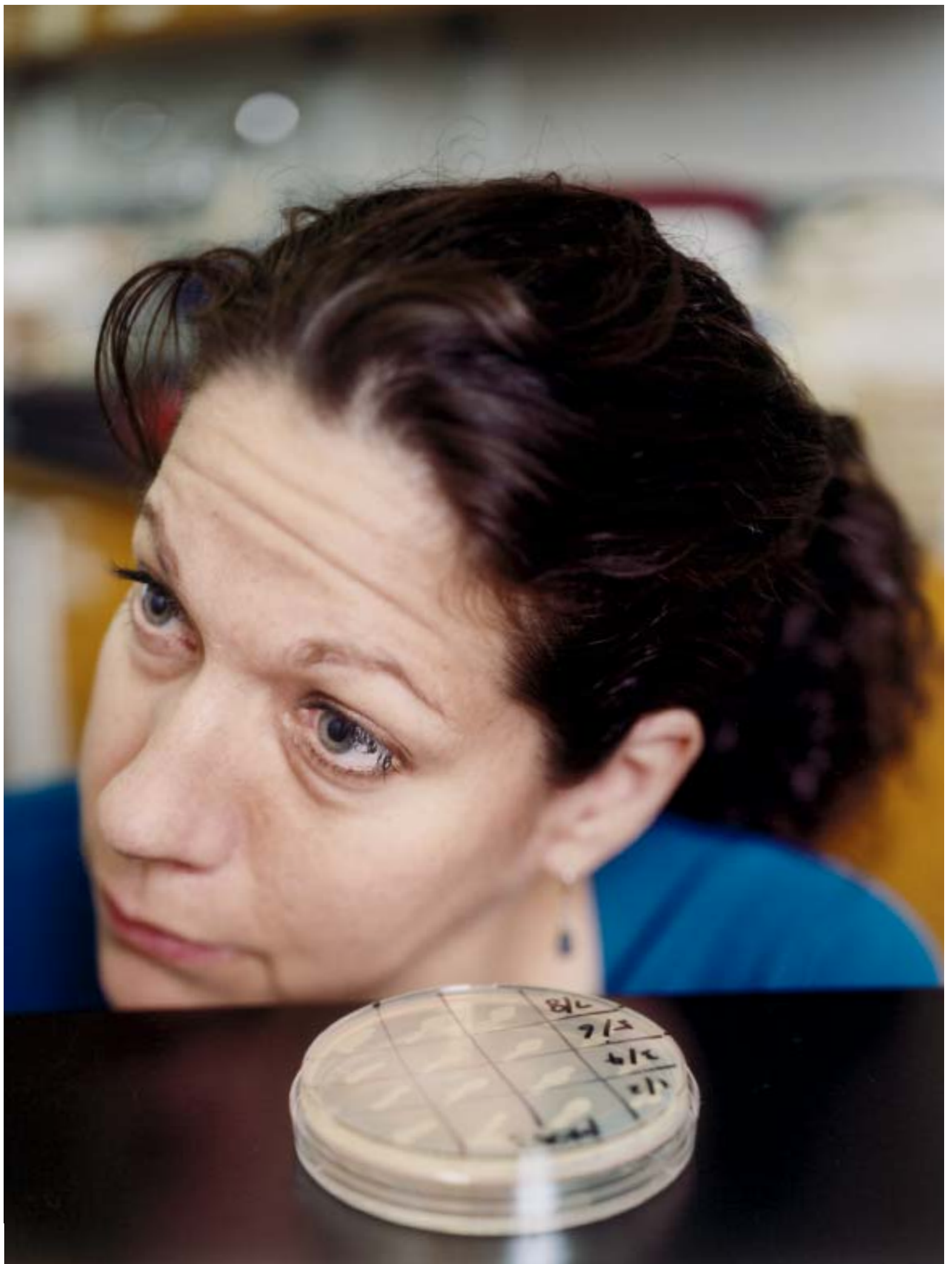
## SMALL TALK

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Studying how marine bacteria light up when ready, a scientist known for her communication skills revealed the purposeful chitchat used by these tiny organisms.

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*by Paul Raeburn*  
*photographs by Greg Miller*



KNOWN FOR  
HER FULL-  
STEAM-AHEAD  
APPROACH  
TO LIFE AND  
WORK, HHMI  
INVESTIGATOR  
BONNIE L.  
BASSLER BEGAN  
HER CAREER  
PONDERING  
OCEAN-  
DWELLING  
BARNACLES  
THAT FOUL  
SHIPS AND  
SLOW THEM  
DOWN.

Her graduate adviser had funding from the U.S. Navy to study how certain bacteria provide footing for the barnacles, which cling to hulls and rudders with epoxy-like strength, causing an enormous drag on a ship's progress.

Bassler has picked up speed since then, becoming what one colleague calls a “rock star” of microbiology and earning a 2002 MacArthur Foundation Fellowship, popularly known as a “genius” award. “Bonnie stuck to her guns and knew what she was doing,” says Richard M. Losick, an HHMI professor at Harvard University with whom Bassler has collaborated and published. “She is quite extraordinary in her energy and breadth of interests.”

It comes as no surprise to people who've worked with her that Bassler's unglamorous experiments with barnacle-involved bacteria led to the puzzle of how and when a little-known ocean-dwelling bacterium becomes luminescent. And in solving that puzzle, she moved from an obscure area of research to a central unsolved problem in microbiology: How do bacteria communicate with each other?

The answers she found have transformed thinking about bacterial communities. She has shown that bacteria, far from being opportunistic loners, are highly social creatures that incessantly chatter among themselves, with the hosts they infect, and even with other species of bacteria by means of a common “language” that no one thought existed. That signaling system has been dubbed “quorum sensing” and Bassler is poised to devise a radically new

type of antibiotic based on interrupting bacterial communication—one that might work against all kinds of bacteria, not just one or a few species.

#### THE COMMUNICATOR

Bassler, often described as a force of nature, is known not only for her research achievements. She is a distinguished speaker, a gifted teacher, and having a conversation with her is like taking a drink of water from a fire hose. Ask her why she became a scientist, for example. “I had this wonderful experience in graduate school, where I loved doing experiments. I really liked being at the bench, and I really wanted to keep being in school, because Heaven forbid I should actually have to get a real job, I mean, I wasn't going to do that ... and so anyway ...”

Or ask her about teaching an introductory biology class to non-science majors. “We use the word ‘evolution’ in every lecture. We use it to explain how every protein folds to make its binding site, how the cell membrane and the proteins in it function. We don't use the word to imply anything about monkeys but, rather, to explain every single reaction in one's body that has been optimized to make us alive, or how things have gone wrong to, say, give you cancer. We try to convey to the students that evolution underpins every single, beautiful, magical biological thing that happens.” Where she finds time to take a breath is itself a kind of magical biological thing.

Five days a week, Bassler begins her day with a 5:42 alarm, giving her just

enough time to get to the YMCA to teach a 6:15 a.m. aerobics class. She met her husband, actor/dancer Todd Reichart, shortly after she moved to Princeton, when she signed up for a swing dance class; he was the teacher. They still dance off and on. “We look really good at weddings, but that’s it,” she jokes. Her dual interests in dance and biology led to a friendship with choreographer Liz Lerman, who received a MacArthur Fellowship the same year that Bassler did. Bassler participated with other researchers in the development of a Lerman dance piece called *Ferocious Beauty: Genome*.

Bassler and Reichart (who refers to his wife as “hyperkinetic”) also canoe and hike whenever they get the opportunity, often taking an extra week after one of Bassler’s far-flung scientific meetings to climb the nearest 14,000-foot peak. “I don’t do anything where I have to be attached to a rope and could fall off and die,” she says. “But I will walk forever.”

With all that exercise, Bassler is athlete trim. She curls her legs up under her on the chair when she talks, and when she wants to make an important point she leans in and whispers, as if confiding a secret. Or she stands up and shouts, if that’s what it takes.

Her communication skills serve Bassler well in her teaching, something she considers an essential part of her work. She is director of graduate studies in the molecular biology department at Princeton and also teaches the molecular biology course for non-science majors.



**Bonnie Bassler** SENSED THAT A TINY, LIGHT-EMITTING ORGANISM COULD REVEAL BIG THINGS ABOUT BACTERIAL COMMUNICATIONS.

“For many of these kids, it’s the first class they’ve taken that isn’t subjective,” she says. Unlike literature classes or creative writing workshops, in science—she teaches them—“there’s a right answer and a wrong answer.” Without a class like hers, she says, many of them may graduate from college without understanding that or anything about science. And that, in turn, will make it more difficult for them to address scientific debates as adults, and as citizens.



#### FOLLOW THE LIGHT

Back when Bassler was working on barnacles, while at Johns Hopkins University, she attended a meeting of Navy-sponsored researchers where Mike Silverman, a

geneticist at the Agouron Institute, a nonprofit research organization in La Jolla, California, presented his research.

Silverman’s focus was a marine bacterium called *Vibrio fischeri*, which has the ability to light up, or bioluminesce. It is found, among other places, in the “light organ” on the underside of the bobtail squid, with which the bacteria live symbiotically. The squid hunts at night in shallow water, and when moonlight threatens to make it visible to predators by virtue of its shadow on the sand below, the bacteria bioluminesce and the light organ glows. Goodbye shadow.

This clever masquerade depends on an unusual property of *V. fischeri*, discovered in the 1970s. When grown in the laboratory,

### A Different Approach for Cholera

Most bacteria want to get into the body, reproduce, and stay forever. They multiply until they have reached sufficient numbers to attack, and then, sensing that they have a quorum, launch the attack. **○ But *Vibrio cholerae*,** the cause of the devastating infection known as cholera, is different. It lives in contaminated drinking water, which is how it typically enters the body. Once there, it attaches itself to the intestine and begins to manufacture the toxins that cause the illness, even before its numbers have significantly risen. It is virulent from the start. And when it reaches a particular population threshold—which it measures through quorum sensing—it switches off its virulence genes. **○ Then *V. cholerae* produces** an enzyme that clips many of its number off the intestinal walls. By that time, enough toxin has been produced to cause diarrhea, which washes the newly freed bacteria out of the body. Some of them wind up in puddles and rivers, and eventually in drinking water. *V. cholerae*'s behavior clearly differs from that of most other pathogenic bacteria. It wants to stay in the body for only a short time—to reproduce far faster and more efficiently than it could in a pool of standing water—and then escape in large numbers to infect more hosts. **○ Although with other infections** the idea is to develop a drug that disrupts quorum sensing—so that the bacteria don't initiate virulence—with *V. cholerae* the opposite strategy applies, says Bassler. "Here, the drug is the autoinducer itself, or a similar molecule that would hasten quorum sensing—and terminate virulence prematurely. We want the *Vibrio cholerae* to let go before they've increased their numbers and produced a lot of toxin." **○ In some of their most recent** research efforts, Bassler and her colleagues have purified, identified, and synthesized the *V. cholerae* autoinducer. And they've shown that if they add the synthetic molecule to *V. cholerae* it turns off virulence. The next step is to try that experiment in mice. If the scientists can curtail virulence in mice, they could have the makings of a powerful new cholera drug. —P.R.

the bacteria don't glow until their population passes a critical threshold. Then they light up simultaneously.

But if bacteria are loners, seeking nothing more than nutrients and an opportunity to reproduce, how do they know their population has exceeded the threshold to light up and then do so in concert?

Silverman figured out that this light-emitting behavior represents an amazing feat of self-recognition on the part of the bacteria. He discovered the mechanism underlying how the bacteria produce and release a chemical signal that their fellows can detect. As the population grows, this chemical accumulates, and the bacteria detect it when it reaches a

certain peak. When the level gets high enough, the lights go on.

The general reaction at that Navy research meeting, Bassler recalls, was "So what?" His findings were seen as an oddity in an odd organism, nothing more. But Bassler was fascinated. "I was a biochemist, Silverman was a geneticist. I didn't know any molecular biology or genetics. I didn't really know what a gene or a transcription factor was—nothing! But I knew I wanted to work on these *Vibrios*. I ran up to him—literally ran—after his talk, and said, 'You have to take me on as your postdoc.'" Despite her lack of experience, he did take her on. "I still don't understand that," she says, laughing.

### DO WE HAVE A QUORUM?

Silverman, now retired in Jackson Hole, Wyoming, remembers it differently. "She came from a good lab, and I ran a small operation and I needed her," he says. "From the time she arrived, she worked hard. I would come into the lab at night, and there she was. And she would be there again in the morning." She soon asked for more responsibility, and he gave it to her. "In Wyoming, they say give a horse its head—let it run," he says.

In Silverman's lab, she began working on *Vibrio harveyi*, a species closely related to *V. fischeri* and also bioluminescent—again, as long as its population is large enough. Bassler's job was to learn how the bacteria produce and monitor the population-indicating chemical signal.

She started making mutants of the bacteria—to try to knock out the signal so that they wouldn't illuminate. But she couldn't get them to go dark. Sometimes they were dim, but they always lit up. That led to the first of a series of discoveries that, she says, were then difficult to imagine—but seem perfectly obvious in hindsight. *V. harveyi*, it turned out, has not one chemical signal but two. "You knock one out and the other one works, and they still light up," she says.

Another surprise was that the two *Vibrio* species use different molecules for signaling and different mechanisms for detecting those signals. Because they are so closely related, Bassler and everyone else had guessed they would use the same signaling



machinery. It was interesting work but still considered at that time to be an anomaly of these two bizarre bacteria.

“Everybody kept asking me ‘Why do you want to study bioluminescence?’ and I kept trying to explain that I wasn’t studying bioluminescence,” says Bassler. “I was trying to study cell-to-cell communication. Bioluminescence was the thing we could see in the lab—a remarkably easy way to detect when cells ‘talked to each other’ with the aid of these chemical words.”

In the early 1990s, other scientists began to investigate chemical signaling in terrestrial bacteria as well, finding that it was not limited to marine oddities. “Now we understand that probably *all* bacteria use chemical

communication, likely with multiple signals,” Bassler says. “They have incredibly complicated chemical lives, of which we so far understand almost nothing.”

Bacterial chemical communication is now referred to as “quorum sensing.” That is, the bacteria determine when their population has attained a quorum, so to speak, and that tells them they can go into action in unison—doing whatever they need to do. Not only do they converse with one another and then act simultaneously, they also divide up chores and specialize.

“They’re recognizing that if they have the right number—and they synchronize their behavior—they can carry out tasks that they could never accomplish if they

acted as individuals,” explains Bassler. Thus, long before the appearance of multicellular organisms, bacteria had devised a way to act together, as if they *were* a multicellular organism.

Bassler’s work gave bacteria a central role in the development of higher forms of life on earth. They have survived for billions of years not only because they are tough but also because they are far more sophisticated than anyone had realized.

These big-picture observations attracted other scientists’ attention. Princeton professor Thomas J. Silhavy, who helped bring Bassler to Princeton, says he saw that her work on *Vibrio* “could lead to some

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very interesting biology.” His instinct was right. “She is the leader in quorum sensing,” he says. “Which is a pretty big deal.” Yet again it wasn’t just Bassler’s research that attracted the attention. “We were very, very impressed with her obvious enthusiasm,” Silhavy says.

### A Universal Language

That second chemical signal she had discovered in *V. harveyi* revealed what Bassler calls a bacterial Esperanto—a universal language that bacteria use to talk to other species. The first signal, called AI-1 (AI stands for autoinducer, because it induces the bacteria to act), was unique to *V. harveyi*; it didn’t exist in any other species of bacteria. But Bassler found that all kinds of bacteria produced the second molecule, AI-2, suggesting that it had an entirely different role. While the bacteria used AI-1 to talk among themselves, AI-2 was a common language among different species. And, critically, it helps them distinguish between like and unlike bacteria—self and other.

“This is the basis for cells specializing,” Bassler explains. “If you have a mix of species, different groups can do different things.” Bacteria, in other words, not only invented multicellularity, they also invented the kind of division of labor seen in multicellular organisms.

For example, biofilms—like the sticky glaze that collects on teeth overnight—are composed of hundreds of species of bacteria, each performing a specialized job to keep the “organism” alive. “You brush them off, and

then the next morning they come back and they’re in exactly the same organization,” Bassler says. “Only a couple of species are the primary colonizers, then the next guys depend on them to stick.” Others provide nutrients, and so on. All in all, it’s a mutually advantageous architecture that allows all the species to flourish.

This level of complexity is another example, Bassler says, of something she and her colleagues could not have imagined a decade ago. “How could I have been so slow?” she says. “Now it seems obvious to me that it had to work like this.”

Bassler decoded the structure of the AI-2 molecule and has shown what happens inside bacteria when they detect these chemical signals—how their communication changes the bacteria’s behavior. “She’s shown that bacteria have much more sophisticated information-processing systems than we imagined,” says Harvard’s Losick.

Researchers elsewhere have now found Bassler’s second signal in hundreds of other bacterial species. But there is an unsolved problem regarding the determination of “other.” The molecules they’ve been studying identify an organism as self or other but do not tell who that other organism is or whether it’s an ally or a threat. Bacteria must have additional signals—other molecules—to distinguish between species. “There are probably a lot of them,” says Bassler. Nobody yet knows how many.

### Better Than Poison

One potential application of Bassler’s work is an entirely new kind of antibiotic. At

present, most antibiotics are poisons of one sort or another—they kill bacteria. But here, she says, “the idea is that instead of killing bacteria, you make molecules that lead to behavior modification.”

When infectious bacteria invade human beings, they generally do not start to make toxins right away. That would only draw the attention of the immune system, which would blast them out of existence. They wait until their numbers have increased, and, using quorum sensing, when they detect the appropriate threshold population, they act together to launch a major attack, making it far more likely they can overpower the immune system’s defenses. An anti-quorum-sensing drug, by preventing this process from occurring, should avert or even cure infections. It might also be possible to make molecules that enhance quorum sensing in the commensal bacteria, described by Bassler as “those harmless gobs of everyday bacteria that live in and on us,” thereby allowing them to keep out invading infectious microbes.

And then comes the next leap, as Bassler sees it. Over billions of years of evolution, bacteria have undoubtedly learned to modify quorum sensing in competing bacteria. Therefore, the drugs that researchers seek probably already exist in nature. It’s just a question of finding them. She’s interested in basic research—not drug development—but her work could point drug makers to these naturally occurring medicines. ■

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