Talking Bacteria

Microbes seem to talk, listen and collaborate with one another—fodder for the truly paranoid. Bonnie L. Bassler has been eavesdropping and translating By MARGUERITE HOLLOWAY

It is far too early in the morning, and Bonnie L. Bassler is charging across the Princeton University campus, incandescent purple coat flying, brown curls bouncing, big laugh booming. She has come directly from the aerobics class she teaches every morning at 6:15—"I get up at exactly 5:42, not a minute earlier, not a minute later," she says emphatically. She says most things with similar energy, and when the conversation turns to her work, she becomes, impossibly, even more dynamic. "I am not meant to be stopped in time," she laughs. "I am supposed to be a blur."

ABIGAIL POPE

BONNIE L. BASSLER: EARS TO BACTERIA

- **Discoverer of potential "bacterial Esperanto": the compound AI-2, which may present a target for a new class of antibacterial drugs.**
- **Hoped to be a veterinarian but became queasy during dissections.**
- **Nonbacterial passions: drama, song and dance, with occasional performances. Married her dance instructor, Todd Reichart.**
- **On achieving scientific success: "I am just really a person for whom nothing is ever good enough. I always think everything is wrong. And my little gift to my students is that they think everything is wrong, too."**

The 41-year-old Bassler—a professor of molecular biology, winner of a 2002 MacArthur Foundation genius award, and occasional actress, dancer and singer—studies bacteria and how they communicate among their own kind and with other species. Quorum sensing, as this phenomenon is called, is a young science. Until recently, no one thought bacteria talked to one another, let alone in ways that changed their behavior, and Bassler has been instrumental in the field's rapid ascension. She has figured out some of the dialects—the genetic and molecular mechanisms different species use—but is best known for identifying what might be a universal language all species share, something she has jokingly referred to as "bacterial Esperanto."

As its moniker suggests, quorum sensing describes the ways in which bacteria determine how many of them there are in the vicinity. If enough are present (a quorum), they can get down to business or up to mischief. For instance, millions of bioluminescent bacteria might decide to emit light simultaneously so that their host, a squid, can glow—perhaps to distract predators and escape. Or salmonella bacteria might wait until their hordes have amassed before releasing a toxin to sicken their host; if the bacteria had acted as independent assassins rather than as an army, the immune system most likely would have wiped them out. Researchers have shown that bacteria also use quorum sensing to form the slimy biofilms that cover your teeth and eat through ship hulls and to regulate reproduction and the formation of spores.

If it all holds up, the implications are enormous. Quorum sensing offers a way to think about evolution.

COPYRIGHT 2004 SCIENTIFIC AMERICAN, INC.

Perhaps early bacteria communicated, then organized themselves according to different functions and, ultimately, into complex organisms. More practically, quorum sensing provides a strategy for medicine: muck up the communication system of dangerous bacteria, such as antibiotic-resistant enterococcus, and perhaps the bugs can't so effectively orchestrate their assault. As Bassler puts it, "You can either make them deaf or you can make them mute."

The study of quorum sensing has its roots in the late 1960s. Two scientists—J. Woodland Hastings and Kenneth H. Nealson—discovered that a marine bacterium, *Vibrio fischeri,* produced light when its population reached a critical size. When fewer were present, the bacteria didn't bioluminesce. The two researchers speculated that the bacteria released a signal—something they called an autoinducer—that cried out, like Horton the elephant's dust speck in the Dr. Seuss book, "We are here! We are here! We are here! We are here!" When the cacophony became loud enough, the assemblage glowed. In 1983 Michael R. Silverman, then at the Agouron Institute in La Jolla, Calif., and a colleague identified the genes for *V. fischeri*'s autoinducer and its receptor.

COLONIES of the glowing bacterium *Vibrio harveyi* provided clues about quorum sensing to bacteriologist Bonnie Bassler.

Bassler came to work with Silverman in 1990, after finishing her doctorate at Johns Hopkins University. She decided to focus on another glowing marine bacterium, *V. harveyi,* to determine whether its signaling system was similar. She got to work making mutant bacteria—disabling a gene here, a gene there, to see if she could impair the one that triggered the bug to bioluminesce when it was in like company. "You turn off the lights in the room and just look for the ones that are dark when they should be bright or bright when they should be dark. It is genetics for morons," she quips. Bassler found the genes for *V. harveyi*'s autoinducer and its receptor.

She also discovered something surprising. If she knocked out those two genes and put the altered *V. harveyi* in mixed company—that is, around masses of different species of bacteria—it glowed. "So I knew there was a second system," Bassler remarks. Bacteria "don't have enough room in their genome to be stupid, so there had to be a separate purpose for this system." The foreign bacteria were emitting something that *V. harveyi* responded to. Bassler called that something autoinducer two (AI-2). In 1994, as the field of quorum sensing was coming alive, Bassler moved to Princeton. Over time, she and others showed that quorum sensing initiates the release of toxins by bacteria such as *V. cholerae*. And they found that every bacterium they tested has its own personal autoinducer, the one it uses to communicate with its own kind. Gram-negative bacteria such as *Pseudomonas aeruginosa* use different versions of AHL molecules (acylated homoserine lactones); gram-positive bacteria such as *Staphylococcus aureus* use peptides.

But most bacteria Bassler looked at also used AI-2. By 1997 "we could see that all these bacteria made this molecule and that it was not just weird, crazy bacteria from the ocean," Bassler recalls. "So we got the idea that the bacteria must have a way of knowing self from other." For Bassler, the idea that different bacteria chat makes perfect sense. "There are 600 species of bacteria on your teeth every morning, and they are in exactly the same structure every single time: this guy is next to that one, is next to that one," she says. "It just seemed to us that you can't do that if the only thing you can detect is yourself. You have to know 'other.' "

Bassler and her students set out to purify and characterize AI-2. Finally, through the efforts of postdoctoral student Stephan Schauder and the crystallography of Frederick M. Hughson and Xin Chen, they got it. AI-2 is an unusual package—a sugar with a boron sitting in the middle of it. "What is amazing about that molecule is that it is the first *ever* to have a biological function for boron. *Ever!*" Bassler exclaims.

Now Bassler and her colleagues are trying to determine whether AI-2 is, indeed, one molecule that works alone as a signal and does not combine with other molecules to give rise to slightly different "languages." If it is the latter, no more Esperanto. "Her work has been truly superb," comments microbiologist Richard P. Novick of New York University. "But there is argument about where [AI-2] comes from and why. And what role it plays in different systems is unclear."

Some scientists are also concerned that aspects of quorum sensing—but not Bassler's findings—have been slightly overinterpreted. "Do bacteria want to communicate with each other, or is it just by accident?" asks Stephen C. Winans, a microbiologist at Cornell University. "This idea has taken hold that these bacteria want to communicate with each other. It may be just too good to be true."

Bassler's drive—her friend and former mentor Silverman describes her as "intensely motivated," "on a quest" and "just fierce"—suggests that she will hear bacteria's every last word. For the time being, she remains focused on understanding AI-2. "I want it all to be one thing, so I am sure that is wrong," she says. "I want it to be one thing because that is better if you want to make a drug, right?" Bassler is one of several quorum-sensing researchers working with companies to develop drugs. In 1999 she formed a company called Quorex with a former colleague from Agouron. Although her involvement is limited at the moment, she is hopeful that the start-up will find new antibacterials. "This was really considered fringe science," Bassler says. "Now it is this amazing field that didn't even exist 10 years ago." SA

BONNIE L. BASSLER

COPYRIGHT 2004 SCIENTIFIC AMERICAN, INC.