



A conversation with Bonnie Bassler

Bonnie Bassler of Princeton University and the Howard Hughes Medical Institute has revolutionized the way that we think about microbiology. She elucidated the chemical language that bacteria use to communicate through a process called quorum sensing that allows bacteria to count their numbers, determine when they've reached a critical mass, and then change their behavior in unison to result in virulence or even bioluminescence. Called everything from a [MacArthur] genius to the bacteria whisperer, Bassler (Figure 1) also excels at the art of scientific communication, has dabbled in theater, and many mornings a week leads an aerobics class in Princeton. The full interview with many more stories can be seen on the JCI website, <http://www.jci.org/kiosk/cgm>.

JCI: What you were like as a child?

Bassler: I had a regular childhood, sort of middle class family, no scientists, but I had enlightened parents and they tried to give me opportunities. I am the middle kid with a older sister and a younger brother, growing up in the '60s and '70s. I loved nature. I loved animals. I loved being outside. I loved doing puzzles. I loved figuring things out. I was the assistant to the veterinarian at the zoo and I came home overjoyed everyday. I ended up loving biology. I went to UC Davis, which has a famous vet school, with the idea that I was going to be a veterinarian, because in my generation, if girls showed inkling for science, you became a nurse or you became a veterinarian. That lasted about two weeks because when I got into the anatomy classes, I realized instantly that what I really love are live animals. But what was wonderful for me was the program ensured that I was taking biology, biochemistry, and molecular biology; and I just loved those classes, so I stayed in that track. For me, when I was just memorizing the answers — terrible. But in biochemistry or genetics class, I actually figured it out, like a puzzle; those classes absolutely appealed to me.

JCI: You did some work during college on *E. coli*.

Bassler: Back then there was a little piece of paper circulated with different possibilities for lab work. A professor named Frederic Troy in the medical school had

two projects: one was on Epstein-Barr virus and cancer, and one was on *E. coli*. I was a junior in college and my mother had died the summer before, and I was committed to curing cancer for very personal reasons. I saw this little blurb, and I volunteered. He took me in, but he put me on the *E. coli* project. I didn't have any skills, and so I thought to myself, I would try really hard and I would prove to him that I was good enough to be put on the cancer project. But, I fell in love with these little critters and how one could find out so much about them in such a short time.

With bacteria, you could have a surprise in the incubator every single morning — that fit for me. The simplicity of the systems was something my brain could manage. I loved the morass, that confusion where you don't understand what the results are for a long time and they're kind of rattling around in your head, and then at some point it comes together, and you get understanding. I still love that. I never looked back, and I've never worked on anything except bacteria since I was 19 years old.

JCI: You moved on to Hopkins for your graduate work.

Bassler: Dr. Troy had done a sabbatical at Johns Hopkins with Saul Roseman. I had this handful of letters from grad programs and I got a yes from Johns Hopkins and I remember Dr. Troy said, "Throw the other envelopes away." It was not a sophisticated decision but I think that's going to be a theme of this interview, that I do things impulsively.

And so I went and worked for Saul Roseman. My project, which was how sugars got metabolized and processed in bacteria, wasn't going anywhere. At a certain point, Roseman brought me this little vial of a marine bacterium called *Vibrio furnissii*, and said, "Here, this is your thesis project." I found that the bacteria chemotacted to a particular sugar, GlcNAc, which is the most abundant sugar in the ocean and made from a polymer called chitin. Chemotaxis leads them to the chitin surface, where they attach and they start to metabolize the sugars. What I got fascinated by was how these bacteria were perceiving their environment — they didn't swim past the chitin, they swam there directly. I started to appreciate that

bacteria have these amazing sensory perception systems.

JCI: It then was at an Office of Naval Research conference where you...

Bassler: Now we fast forward. I was in my fifth year of graduate school. And the ONR held a conference in Baltimore for the researchers it funded. One of the speakers, Mike Silverman of the Agouron Institute was working on bioluminescence. Silverman gave this talk about this bioluminescent bacterium, *Vibrio fischeri*, that he had been working on, expanding on earlier findings from Woody Hastings that showed when bacteria were dilute, they didn't bioluminesce, but when they grew to a certain cell number, all the bacteria turned on light together. Silverman was a geneticist — before GFP, before genomes, before microarrays. He realized that he could exploit bioluminescence to identify the genes that told that bacterium when they had a group present and to turn on light simultaneously.

JCI: It was an awakening for you.

Bassler: It was the great epiphany of my life. Silverman told this story that the bacteria don't glow but then they do glow when they're in a group, and then he knew about the molecules [autoinducers] that caused it. I'm just sitting there, and I had never heard anything like that in my life. We all, meaning scientists including microbiologists, thought that bacteria were asocial reclusives. They divided in half and each cell did its own thing. I remembered thinking, "That is either the coolest thing I've ever heard or this guy's a nut case."

When his talk ended, I ran up to the podium and I said, "You just have to let me be your post-doc or I'll kill myself." Not the best interview strategy, but eventually he did. He was the most amazing mentor. Most of the time I was the only one in the lab, together with his technician of 20 years, Miriam Wright. For four years, it was this utopian postdoc. Remember, when I got there I didn't know what a gene was, what a restriction enzyme was, and he'd say things like, "Let's do a transposon mutagenesis." And I'm like, "Transposon?" He taught me everything about genetics.

JCI: It was during this time you came upon the second set of autoinducers.



Bassler: We decided to work on a free-living bacterium, *Vibrio harveyi*, which clearly would have quorum sensing. Our idea, initially, was that there would be more sensory inputs controlling bioluminescence than Silverman had found controlled bioluminescence in *Vibrio fischeri*, which lives as a symbiont in a rather controlled environment.

I started doing transposon mutageneses, but I could never find the genes we were hunting for. What I did find were two communication circuits that worked in parallel. There was a molecule and a receptor, and if you knocked them out, there was another molecule and another receptor. What I found was this completely new kind of cell-cell communication circuit that was much more sophisticated.

JCI: I read that you applied for 20 jobs, got two interviews, and landed at Princeton. And you've never left.

Bassler: You write the same application 20 times — so what did Princeton see that the others didn't see? Princeton does very basic science and everybody in my department works on how sensory information from the outside gets in, whether you work on a neuron, whether you work on an embryo in development, whether you work on a cancer cell. They took a chance on me. It took me 13 years to get an NIH grant. After 5 years Princeton risked the fact that I might not ever be able to get traction and they still gave me tenure. In that decision they said, "This is a brand new way to think about bacteria." That's why I'm still there, because I still feel I'm repaying that debt. But I don't want to act like I'm Mother Teresa here. The science has also gone great. The other part of why it is a joy to be at Princeton is, with no medical school, everyone works on basic fundamental problems, no matter whether you're in biology or physics or chemistry or engineering. We all make knowledge.

JCI: You've said before that you think the next generation antibiotic is maybe 5 to 10 years down the road.

Bassler: That is my hope. We are screening for molecules that shut down quorum sensing, and at this point, if you are a worm, we could save you. If you are a cell in a tissue culture dish, we can save you with our molecules. We have some molecules that are starting to work in mice models. We know we can shut down biofilm formation in *Pseudomonas* and in cholera. And so those experiments give me confidence

to pursue this line of reasoning. Every antibiotic we've had until now slows the growth of a bacterium or kills it. Our strategy doesn't do that. It would make bacteria so they can't count, and don't launch their virulence cascades, and then buy time for your immune system to mop them up. I think somebody should ask the question, is behavior modification a workable strategy for therapeutics? Maybe quorum sensing won't be the behavior, but maybe



Figure 1
Bonnie Bassler on October 24, 2013. Image credit: Alena Soboleva.

flagellar formation, or swarming, or some other behavior will be the modification to manipulate. My gang is trying, in our academic way, to step toward that. The molecules we have are neither potent enough nor drug-like enough yet, but they're starting to work.

JCI: How do you feel about the popularity of antibacterial gels?

Bassler: It's very clear: you need to wash your hands when you're preparing food and after you go to the bathroom. Soap is fine. I wish people would realize that most of the bacteria that they encounter are keeping them alive. If you live in a developed country, your chances of dying of a bacterial infection are really, really low. I just find it amazing and sad that there's this incredible paranoia about germs when that has nothing to do with

our lives because we have clean water and clean food.

JCI: You were dubbed the "bacteria whisperer" when you were interviewed by Neil deGrasse Tyson. You got a standing ovation at your 2009 Ted Talk, and you clearly excel at making complicated scientific concepts easy to digest.

Bassler: I work on communication; it would be bad if I couldn't talk about it.

JCI: Well, would you ever consider a second career as a pundit?

Bassler: I have this passion for science and I worry so much: why do people hate science? Why do they think it's too hard to learn? Why do they think it's boring? And why do they think it's dangerous? I think a lot about going into politics. Could I actually work in politics and in education to change how people learn science, and to change their appreciation of what it does and what it will do for the future of this country? I've also thought about who are the scientific heroes. I think Neil deGrasse Tyson is this country's right now. I think Carl Sagan was. But who's the next one? Is it me? I don't know. I don't have any training for it. I don't know how to make a leap into either of those professions. What I will say is whenever I go do any of those outreach or political events, I enjoy them, but I find myself running back to my lab because the thing I love the best is when some young student says, "Look what I found." Bad or good, I am the second person to know that finding. At least for now, that still gives me the same rush as when I was doing the experiments with my own hands, and the same feeling of why I went into science in the first place.

JCI: Well then a different question, if not science and science communication, what else do you think you could have done in your life? Would you have gone on to be a veterinarian, if you had the right teachers?

Bassler: No, I think I did have the right teachers at that moment. Because learning what you don't like is as important as learning what you do like. What would I be if I weren't a scientist? I'd like to be a movie star. I'm a ham, right? The real truth is I like giving seminars, I like talking about things, I like people, and so I guess I would pick some other career like that, like a stand-up comic or something where you're in front of an audience. But the truth is, whenever I'm in front of an audience, if I don't have a picture of *Vibrio harveyi* behind me, I'm frozen.

Ushma S. Neill