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BACTERIAL QUORUM SENSING: THE MOST ANCIENT LANGUAGE ON EARTH

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YOUNG REVIEWERS:


ANASTASIA
AGE: 15


BRUNA
AGE: 14


HELENA
AGE: 14

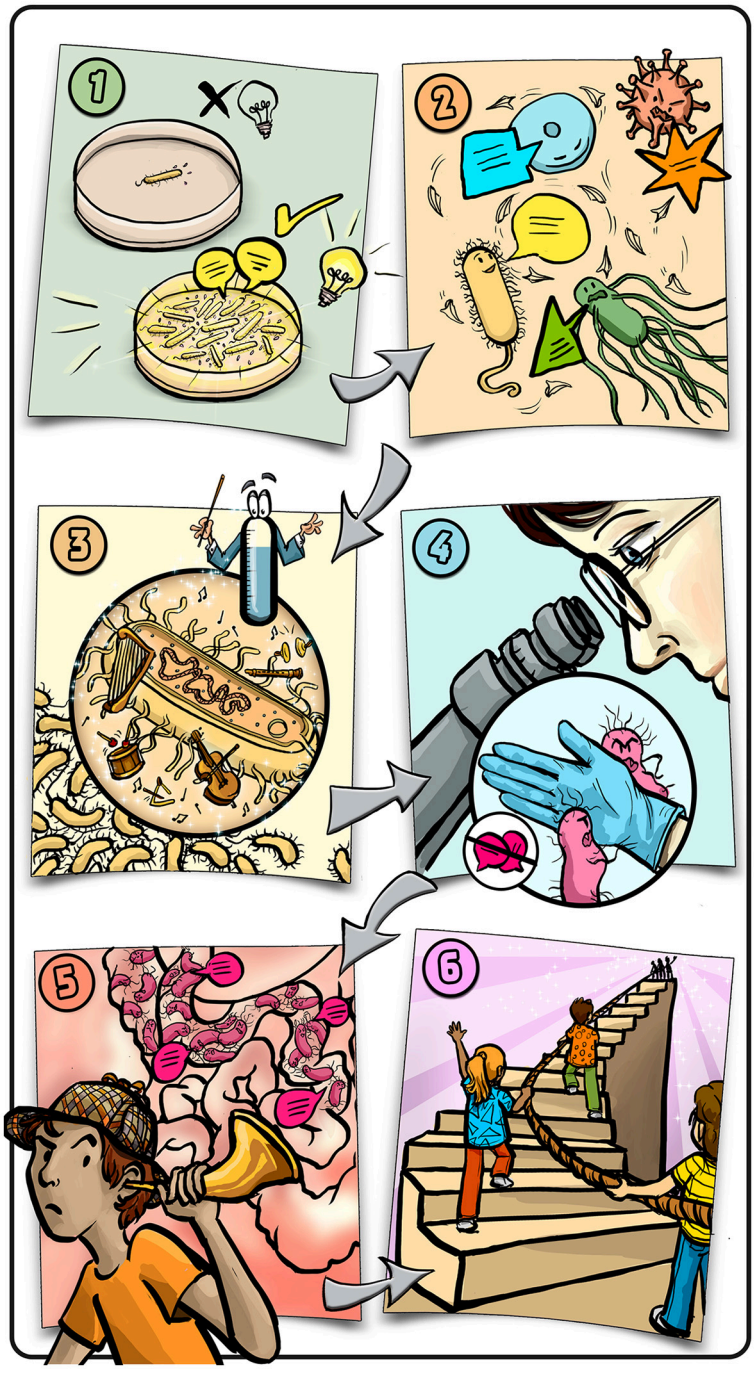

MATHILDE

A few decades ago, scientists believed that bacteria were very basic creatures that did not communicate with each other and were only good at multiplying. Recently, we have realized that this is far from the truth! Bacteria communicate with one another using a language called quorum sensing. You can think of bacterial quorum sensing as the first-ever social network! In this article, we will tell you about the discovery of quorum sensing and how it radically changed our understanding of the microbial world. We will also tell you how our new knowledge of quorum sensing might help doctors to treat dangerous bacterial infections in humans. Join us in this journey exploring the fascinating language of bacteria and how it could benefit human health.

Drs. Bonnie Bassler, Michael Silverman, and E. Peter Greenberg were awarded the 2023 Canada Gairdner International Award for their discoveries of how bacteria communicate with each other and surrounding non-bacterial cells, providing new insights on how microbes behave and opening up exciting directions for developing new drugs against infectious diseases.

Graphical Abstract

Article summary. **(1)** Researchers found that a light-producing bacterium made light only when surrounded by others of its species. They hypothesized that these bacteria produce "chemical words" called "autoinducers" that build up in the environment and trigger light production. **(2)** Further research showed that bacteria use autoinducers to communicate—with themselves, with other species of bacteria, with viruses, and with eukaryotic cells. **(3)** This bacterial communication, called quorum sensing, orchestrates which genes are turned on or off within the bacteria. **(4)** Scientists are developing new treatments for bacterial infections that disrupt the communication of harmful bacteria. **(5)** Knowledge of quorum sensing could help us to "eavesdrop" on the bacterial communication in our bodies. **(6)** It took some decades and many steps to get to where we are, and you can do it, too! Illustration by: Iris Gat.



Graphical Abstract

GLOWING BACTERIA REVEAL AN ANCIENT LANGUAGE

BIOLUMINESCENT

A word that describes a living organism that produces and emits light.

AUTOINDUCER

A chemical that is used in bacterial communication that helps bacteria count other bacteria and other organisms in the environment.

Our story begins with a tiny glowing bacterium. In the 1970s, Ken Nealson and Woody Hastings found that a **bioluminescent** marine bacterium called *Vibrio fischeri* made light only when many bacteria of the same species were close together [1]. These scientists also noticed that, when a large enough group of *V. fischeri* were present, they all started making light at the same time. The scientists hypothesized that the bacteria were producing a chemical called an **autoinducer**, and when there were enough bacteria close to each other, the concentration of the autoinducer got high enough to switch the light on. This was a radical new idea because it meant that bacteria were communicating with each other—these organisms were previously thought to be simplistic "loners" that had no way of communicating.

Then, the three of us (Peter, Mike, and Bonnie) worked for a few decades to uncover the secrets behind this bacterial communication and proved that Ken Nealson and Woody Hastings were right (Box 1). Bacteria constantly communicate and share surprisingly complex information about themselves and their environments—not only with one another, but also with other cells and organisms.

Box 1 | Our main discoveries on bacterial communication.

In the early 1980s, Mike et al. found the genes that were responsible for bioluminescence in *Vibrio fischeri* (Figure 1A) [2]. They showed that when the genes were inserted into other types of bacteria, those bacteria become bioluminescent as well! Later on, Peter took the genes that Mike et al. found and inserted them into a type of bacteria commonly used in research, called *Escherichia coli*, to study the process of bacterial communication [3]. He then showed that other types of bacteria communicate the same way. He also showed that bacterial communication is responsible for **virulence** in a bacterium called *Pseudomonas aeruginosa*, which causes dangerous lung infections in people with diseases like cystic fibrosis (Figure 1B). In 1994, Peter et al. coined the term **quorum sensing** to describe bacterial communication *via* chemical signals, inspired by the legal term quorum, which means the minimal number of people required to attend certain important meetings. Bonnie, who joined Mike's lab in 1990, studied another bioluminescent bacterium called *Vibrio harveyi* and found that it used one autoinducer to communicate with other *V. harveyi* bacteria, and a second autoinducer that turned out to be a "universal" language, shared by many kinds of bacteria [4, 5] (Figure 1C). Bonnie later discovered more types of autoinducers, and that bacteria use these substances to communicate not only with other bacteria but with other organisms, including viruses [6]. She then showed that interfering with quorum sensing could treat certain bacterial infections in animals [7].

VIRULENCE

The ability of bacteria (and other microorganisms) to damage the organisms they infect.

QUORUM SENSING

A type of bacterial communication using chemicals called autoinducers. Quorum sensing is responsible for group behaviors of bacteria, such as bioluminescence and virulence.

QUORUM SENSING—THE WORLD'S EARLIEST COMMUNICATION

Bacteria are the oldest organisms living on Earth. They have about 5,000 genes, and up to 600 of those genes are controlled by quorum sensing. This means that up to one *fourth* of the bacterial genome is like an orchestra that is conducted by quorum sensing. In an orchestra, the conductor does not want all the instruments to play at once—at

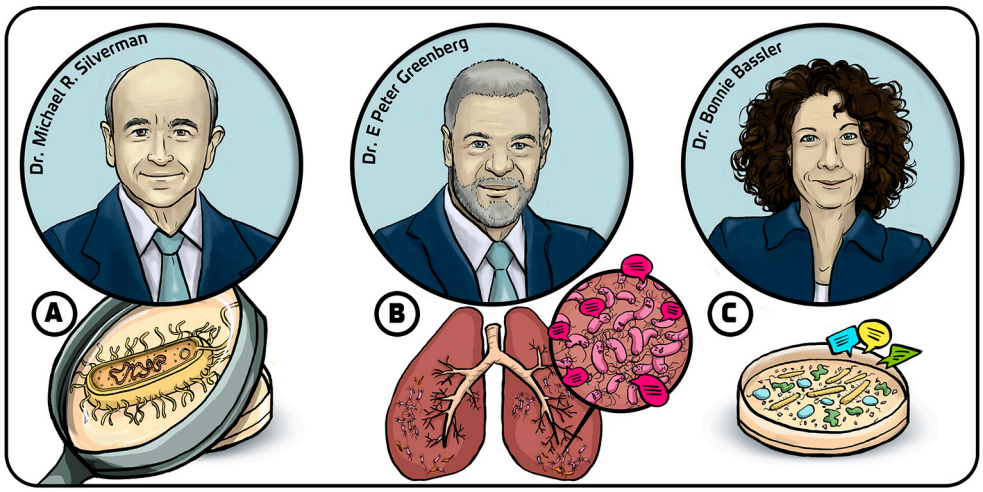


Figure 1

Key discoveries of Drs. Silverman, Greenberg, and Bassler. **(A)** Dr. Silverman found the genes responsible for bioluminescence in *Vibrio fischeri*. **(B)** Dr. Greenberg identified and studied quorum sensing in *Pseudomonas aeruginosa*, which often causes lung infections. **(C)** Dr. Bassler discovered that bacteria communicate using various autoinducers—not only with their own species, but also with other species of bacteria and with viruses. Illustration by: Iris Gat.

a certain moment, she might want the violins to start playing, and at another moment she might want to add the brass instruments. In the bacterial orchestra, the same thing applies: certain gene "instruments" are activated at different autoinducer concentrations. At other times, when autoinducer concentrations are different, some genes might "stop playing" and be switched off.

Quorum sensing was the first communication method to develop on Earth. It is also the earliest social behavior seen on Earth. Bacteria are so tiny that they cannot do much by themselves. But when they use quorum sensing to send and receive information about how many bacteria are around them and about how related they are to each other, they are acting more like a multicellular organism.

We now know that there are at least four types of autoinducers, or "chemical words," in the quorum sensing language (Figure 2). One type is unique in every species of bacteria, and it allows bacteria to communicate with members of their own species. Using this autoinducer, one bacterium can tell another, "you are my twin." Another type of autoinducer is made only by genetically close (but not identical) bacteria, and it says, "you are my relative." A third type is made by many types of bacteria, and basically says, "I am a bacterium." This autoinducer is used to communicate with other species of bacteria. We think that bacteria count the total number of bacteria that are present in their environment. They can even use this third type of autoinducer along with the first type to compute whether their species is the majority or minority in the environment, by dividing the number of "twin" autoinducer molecules by the number of "bacteria" autoinducer molecules. The most recent type of autoinducer discovered is made of two molecules that say, "you are a eukaryote" and "you are a virus." Using these four different "words," bacteria can recognize others of their own species, know

when there are other species of bacteria around, and identify other types of organisms.

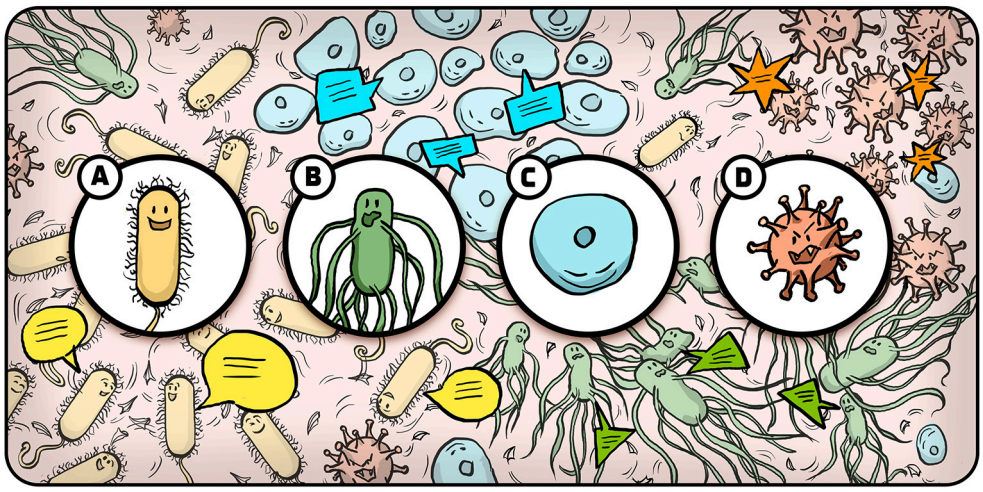


Figure 2

Four types of bacterial communication. Through quorum sensing, bacteria **(A)** talk with other members of their own species, **(B)** communicate with other types of bacteria, **(C)** communicate with eukaryotic cells and **(D)** communicate with viruses. Illustration by: Iris Gat.

NEW ANTIBIOTICS?

Quorum sensing can play an important role in human health, as it is used by harmful, disease-causing bacteria. Disease-causing bacteria have specific genes that make them virulent, and these genes are controlled by quorum sensing. For example, some bacterial genes help bacteria create hard-to-kill communities called **biofilms**, and others help them release their toxins at the right time, to most effectively attack their host. Normally, bacterial infections are treated with antibiotics designed to kill the bacteria or stop them from multiplying. But there are always a few bacteria that are not affected by the antibiotic, and these **antibiotic resistance** bacteria remain alive and keep multiplying within the body (to read more about antibiotic resistance, see this Frontiers for Young Minds article). Might there be another way to neutralize harmful bacteria? Maybe there is a way to disrupt their communication so that they become less harmful?

BIOFILMS

Groups of bacteria that stick to each other and to various surfaces, such as the insides of the intestines.

ANTIBIOTIC RESISTANCE

The trait of bacteria that are insensitive to certain antibiotics and can still multiply in the presence of those drugs.

Scientists are currently working on new antibiotics that prevent bacteria from detecting or producing autoinducers, thereby blocking their communication (Figure 3). When quorum sensing is blocked, bacteria are much less harmful because they can no longer coordinate their harming activities. Unlike "regular" antibiotics, drugs that disrupt quorum sensing do not interfere with bacterial growth and do not kill bacteria, so scientists hope that it will take bacteria much longer to become resistant to antibiotics that target quorum sensing.

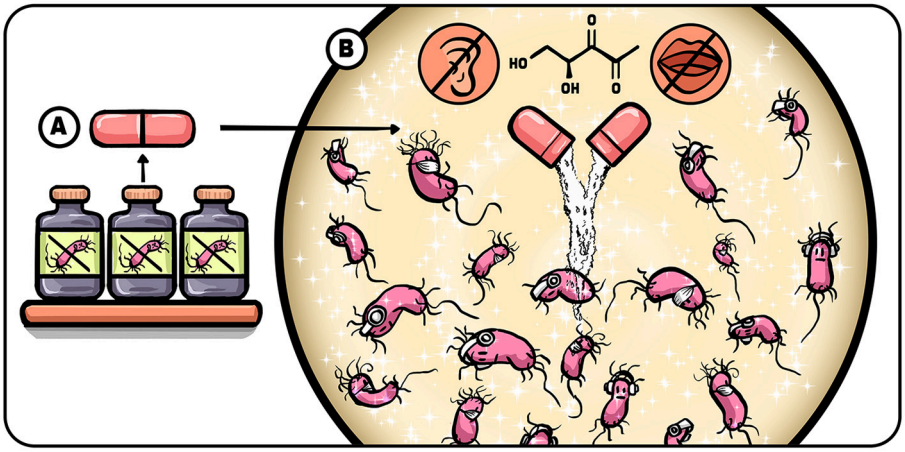


Figure 3

Figure 3

New antibiotics based on quorum sensing. **(A)** Researchers are developing new types of antibiotics based on quorum sensing. **(B)** These antibiotics interfere with the ability of bacteria to communicate, either by making them unable to "talk" to other bacteria (meaning, produce autoinducers), or by making them unable to "hear" what other bacteria are saying (meaning, sense autoinducers in their environment). Illustration by: Iris Gat.

WHAT ELSE CAN WE DO WITH QUORUM SENSING?

Quorum sensing research is developing rapidly, and we keep finding new quorum sensing molecules with very different properties. These molecules may contain more complex information than we initially thought! One fascinating area to study is the communication between bacteria within the human **microbiome**, which is the entire collection of bacteria and other microorganisms in the human body [6]. The human microbiome can communicate with the body, and it is so crucial to the body's healthy functioning that it is now thought of as another organ—even though it is made of non-human cells. For example, the gut microbiome interacts with the immune system and other bodily systems and may even influence mental health. We would like to be able to "eavesdrop" on the interactions between bacteria, and between bacteria and other microbes in the gut microbiome—like investigators listening in on suspects' phone calls. Mapping the communications between organisms in the microbiome might lead to important insights about human health.

MICROBIOME

All the microorganisms that are living in a particular environment, such as the human gut.

We also want to use quorum sensing to study how communities of bacteria cooperate with each other and how they deal with "cheaters" that do not play by the "rules." These cheaters do not help produce necessary substances which the whole community uses, but they still consume them. This makes cheaters more fit than cooperators, because they enjoy these necessary substances without having to invest energy into their production. If being a cheater is so profitable, why do the cheaters not take over the population? It turns out that cheaters do not activate the genes controlled by quorum sensing—which makes them not produce necessary substances, but also makes them vulnerable to a toxin that is released in the population. Cooperators that do activate quorum sensing genes activate a gene that makes them more resistant to this toxin, so they are significantly less affected by it. This is how populations of bacteria maintain

cooperation, and we think we can use this molecular-level knowledge to understand other types of cooperation seen in nature.

LOVING NATURE

The three of us share a great love for nature, and we chose to express this love through science—but there are many other ways to study or work with nature that are also very fulfilling and gratifying. Some of you might want to be doctors; others might enjoy traveling into the jungle and watching exotic animals. Whichever choice connects you with the beauty and wonder of nature is a great path to follow.

If you choose the scientific path, you can view it like a treasure hunt. The "treasures," or big eureka moments that we experience and scientific discoveries that we make, are extremely important and exciting, but they may not happen very often. To find them, we usually work for long periods of time with no positive results. During these times, we must find ways to stay curious and enthusiastic as we "hunt" for the next treasure. Even after we find a treasure, it often takes time for other scientists—or even the scientists who made the discovery—to appreciate what was found. This certainly happened with quorum sensing, and it is frequently the case with any brand new science—it takes time for enough data to accumulate to make an impact. Luckily, we had great colleagues and students that love nature as much as we do, and this made our entire journey fun.

Young people often think that they can never be as successful as we are. The truth is that we were just like you when we were students a few decades ago! It takes time to become a good scientist. We think that any student can become like us, if they stay dedicated to their work for as long as we have been. While it can be useful to have scientific idols that you want to become like 1 day, we also think that, at each stage in your career, you should also choose role models who are closer to where you currently are—these people could serve as steppingstones toward your end goal.

ADDITIONAL MATERIALS

1. How Bacteria "Talk"—Bonnie Bassler (TED)
2. Canada Gairdner International Award Laureates: Drs. Bassler, Greenberg and Silverman

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YOUNG REVIEWERS

ANASTASIA, AGE: 15

I am Anastasia, a student captivated by science! I am very passionate about learning and discovering new opportunities. My dream is to study medicine as I am very interested in how our body works and how it can be affected. Outside of my studies, I love painting, drawing, crafting as well as participating in many other extracurricular clubs. But most of all, I love cooking deserts (I have a sweet tooth ☺).

BRUNA, AGE: 14

I love to play volleyball and basketball, besides watching soccer games. I love to go out with my friends and spend time with my family too. I like to talk and have fun with my little sister, it is good for our relationship. My favorite school subject is math and physics. I really want to have a good health, for example have a healthy eating and do a lot of exercises, I think it is important for young people like us.

HELENA, AGE: 14

I like to do so many things, but there are some activities that I like most. Some of them are playing volleyball, traveling and watching TV shows/concerts. One of the most important things in my life is my family. Also, my dogs. They always make me happy. My life in school is really good. My friends and teachers are so much fun.

MATHILDE

Hi my name is Mathilde and I am going into my senior year of high school in a French school. In my free time I read but can never stick to a book. I also play rugby/ capoeira and wonder where I should study economics and marketing.

AUTHORS

BONNIE L. BASSLER

Bonnie Bassler is a Howard Hughes Medical Institute Investigator and the Squibb Professor and Chair of the Department of Molecular Biology at Princeton University. She grew up in northern California. As a young person, she adored nature and animals and hoped to be a veterinarian when she grew up. However, she became fascinated with biochemistry and molecular biology when she went to college, so she switched direction. Bonnie received a BS in Biochemistry from the University of California at Davis and a PhD in Biochemistry from the Johns Hopkins University. She performed postdoctoral work with Michael Silverman in Genetics at the Agouron Institute. Bonnie joined the Princeton faculty in 1994. Her research focuses on molecular mechanisms that bacteria use for intercellular communication; a process called quorum sensing. Bonnie's discoveries are paving the way to novel therapies to combat disease-causing bacteria. She received prizes including a MacArthur Foundation Fellowship, the Shaw Prize in Life Sciences and Medicine, the Dickson Prize in Medicine, the Gruber Genetics Prize, and the Wolf Prize in Chemistry. Bonnie received Princeton's President's Award for Distinguished Teaching. She is devoted to diversity in the sciences and educating lay people about the thrill and relevance of scientific research. Bonnie was President of the American Society for

Microbiology, and she served on the National Science Board. She was nominated to the Board by President Barack Obama. The Board oversees the NSF and prioritizes the nation's research and educational activities in science, math, and engineering. *bbassler@princeton.edu

E. PETER GREENBERG

Born November 7, 1948, Hempstead, New York. Education: BA in Biology Western Washington University, 1970; MS Microbiology, University of Iowa, 1972; PhD Microbiology, 1977, University of Massachusetts; Postdoctoral, Harvard University 1977–1978. Academic Positions: Cornell University Assistant Professor Microbiology 1978–1984, Associate Professor Microbiology 1984–1988, University of Iowa Professor of Microbiology 1988–2005 (Shepperd Professor of Microbiology 2000–2005). University of Washington 2005–2008 Professor and Chairman Microbiology, Current position, Nester Professor of Microbiology. Co-Director Microbial Diversity Summer Program, Marine Biological Laboratories, Woods Hole MA, 1985–1990. Major editorial responsibilities: Associate Editor, Annual Reviews of Microbiology, 1987–2001; Editor, Journal of Bacteriology, 1991–2001, Founding Reviewing Editor eLife, 2013–2022; Editorial Board PNAS 2005-present. Selected Honors and Awards: 1984-Elected Member, American Academy of Microbiology, ASM Minority Student Career Support Program, Lecturer: 1989, Elected Fellow, AAAS 1991, Associate Director, University of Iowa Cystic Fibrosis Research Center: 1998-ASM Foundation Lecturer: 2002 Elected Member, American Academy of Arts and Sciences; 2004 Elected Fellow, National Academy of Sciences; 2008, ASM DC White Award 2013, Awarded Honorary Doctorate, University of Guelph; 2015-Shaw Prize in Life Science and Medicine 2017, Honorary Chair North American Cystic Fibrosis Foundation Conference 2022, Clarivate Citation Laureate in Chemistry. Greenberg is widely considered the father of the field of microbial quorum sensing. He has studied quorum sensing since the late 1970s and in fact the term quorum sensing originates in a 1994 *Journal of Bacteriology* article on which he was senior author.

MICHAEL R. SILVERMAN

Mike was born October 7, 1943 in Fort Collins Colorado. He was the son of a rural veterinarian who practiced in western Nebraska, USA. In high school, Mike studied vocational agriculture and later worked on an experimental farm where he developed an interest in plant diseases and bacteriology. He received a BS (1966) and an MS (1968) degree in Bacteriology from the University of Nebraska. In 1972, Mike completed a PhD from the University of California, San Diego studying the molecular genetics of motility and chemotaxis in *Escherichia coli*. This work required the application of classical and modern genetic methods such as DNA cloning and sequencing, gene product programming and transposon mutagenesis. He continued research as an independent scientist at the Agouron Institute and as an Adjunct Professor of marine biology at Scripps Institute of Oceanography in La Jolla California. There, he investigated motility and bioluminescence in marine bacteria. In particular, work with JoAnne Engebrecht and Bonnie Bassler resulted in the discovery of fundamental genetic mechanisms that control bioluminescence. These mechanisms were later found to control many different functions in many species of bacteria. Mike retired to the mountains of Wyoming in 2000.