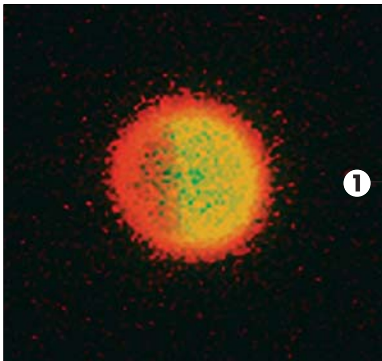

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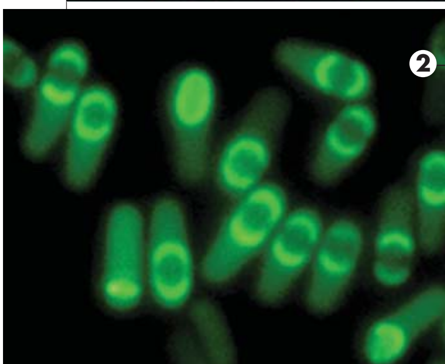

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1: The double membranes of *Gemmata obscuriglobus* may be durable enough to produce "molecular fossils": traces of early life on Earth that have been preserved for billions of years. 2: *Bacillus subtilis* forms spores (in green) with lipid membranes that help protect the spore from oxygen damage. These tough cellular membranes appear in the fossil record at about same time Earth's atmosphere became enriched with oxygen, and may help trace changes in the planet's early atmosphere.

fessor of biological chemistry and molecular pharmacology at HMS. Unfortunately, he says, due to the spread of antibiotic resistance, "we are running out of effective antibiotics." For economic reasons, pharmaceutical companies are not investing as much as they used to in the development of new ones, which has left physicians looking for an antibiotic of last resort to be held in reserve for the one patient once a year who has a resistant strain of tuberculosis or pneumonia, explains Kolter. "That drug would be the billion-dollar blockbuster that nobody buys, because doctors shouldn't be prescribing it widely. Nobody in the corporate world will develop it." He believes that "there may be a role for the University in research that is not going to be as profitable for corporations to pursue: the development of targeted, ecologically sound antibiotics."

Whole-genome studies of microbes suggest that only a small fraction of the natural products that come from even well-known bacteria have been discovered. A prime example is *Streptomyces avermitilis*, the bacterium from which researchers derived a drug called Ivermectin. "Ivermectin," says Clardy, "is grown on the ton scale because it is used against river blindness in Africa, for treating almond trees in California, and for getting rid of all kinds of parasites" (equine worms, for example). "Here you have a 'bug' that is producing a useful molecule grown on a huge scale, and intensively so." Once the genome was sequenced, he says, "Just looking at it casually, you could see where Ivermectin is made, but you could also see [other gene sequences]—over 30 of these clusters—that it seems should each make a small molecule. We know only *three* molecules that come from that bug," he adds—one of them the source of Ivermectin. "That means we know only 10 percent of what it can potentially make."

But probing those secrets is far from easy. When grown in a lab in pure culture, microbes apparently don't need to activate all their genetic machinery to survive. In their natural setting, by contrast, microbes live in a complex ecology: they interact with their environment and with other microbes by using a vast array of virtually unknown small-molecule products. These organic compounds often play multiple roles: a small molecule used for signaling among bacteria engaged in mutually beneficial metabolite exchange (one microbe's metabolic waste is another's meal) might also be used to kill competitors trying to gain a foothold in the same ecological niche. Such compounds, if researchers could identify them, produce them, and figure out how they work, might form the next generation of medical antibiotics.

At Harvard, an MSI-facilitated collaboration between Kolter and Clardy uses creative methods for prompting even unculturable microbes to yield such genetic secrets. Clardy was among the earliest researchers to use "metagenomics," which involves sampling the environment—your gut, a lake, or in his case, the soil—and collecting the "metagenome," or composite genome, of all the individual organisms dwelling there. After extracting the many strands of DNA, Clardy screens for sequences that make compounds. He can isolate these sequences and transfer them

Glossary for an Invisible World

Archaea: One of three major domains, or classifications, of life, archaea are morphologically similar to bacteria, but have a different molecular transcription machinery, indicating an ancient evolutionary divergence.

Bacteria: One of three major domains of life. Bacteria are single-celled microorganisms with neither a nucleus nor organelles (specialized intracellular structures; see below).

Cyanobacteria: A division of bacteria that produce their energy through photosynthesis. Formerly called blue-green algae (hence the name "cyano," or blue, bacteria), they are not "true" algae. Algae are eukaryotes, while the cyanobacteria are prokaryotes.

Eukarya: One of three major domains of life, the eukarya include all single and multicellular organisms in which the cells have a distinct nucleus. Examples are plants, animals, and fungi. The classification includes everything that is not a bacterium or an archaean.

Microbe: Generally considered to include all life that cannot be seen with the unaided eye, microbes are found in all three major divisions of life and include all the bacteria, all the archaea, and some of the eukarya. Some scientists say that only prokaryotes (see below) should be considered microbes, thereby excluding even single-celled fungi. Others argue that even multicellular organisms can be considered microbes. Mushrooms, for example, are the multicellular fruiting bodies of fungi that may start as unicellular organisms in the soil. Furthermore, both unicellular bacteria and archaea form aggregates ("colonies") on surfaces, often referred to as biofilms, that exhibit distinctive multicellular patterning.

Organelles: Structures within a cell that perform specialized functions, such as energy production. Mitochondria and chloroplasts are examples of energy-producing organelles that are thought to have evolved from autonomous bacteria. Eventually they became dependent on their hosts—and vice versa.

Primary production: Production is the creation of new organic matter. Primary production refers to the creation of new organic matter by photosynthetic microbes.

Prokaryotes: An inclusive term that refers to the bacteria and archaea, single-celled organisms that, as distinct from eukaryotes, lack a nucleus.