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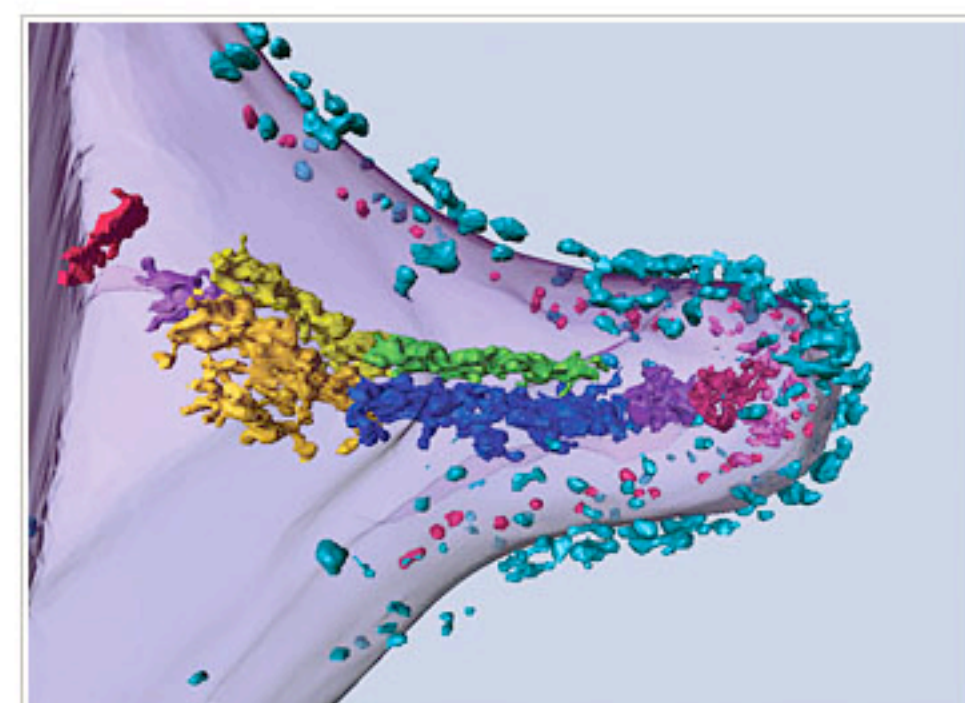
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#### WEB ONLY

## Not So Simple

by Mitch Leslie



A large complex of proteins (various colors) pulls the membrane of a bacterium outward to help propel the bacterium forward.

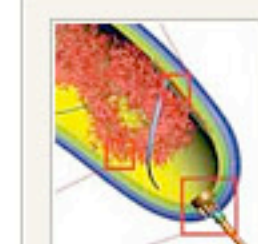
### RESEARCHERS BEGIN TO REVEAL BACTERIA'S SOPHISTICATED ARCHITECTURE; they just needed the right tools for the job.

Bacteria have not gotten the respect they deserve. For decades, scientists saw them as mere bags of enzymes that lack the internal order and complexity of eukaryotic cells like ours.

But recent findings by Christine Jacobs-Wagner of Yale University and Grant Jensen of the California Institute of Technology (Caltech)—among others—have undermined that simplistic stereotype. “Bacteria are a lot more like eukaryotic cells than we thought,” says Jensen.

He and Jacobs-Wagner, who both became HHMI investigators in 2008 and frequently collaborate, have revealed that bacteria are surprisingly sophisticated and well-organized. Their work has shown how this unanticipated order shapes cells and helps them grow, divide, and move, among other vital activities.

#### WEB EXTRA



#### Bacterial Scaffolding

See examples of bacterial structures that HHMI investigator Grant Jensen has discovered.

[SLIDESHOW](#)

“Before, it was a blur, but now we are starting to see things clearly,” says Jacobs-Wagner. What’s also clear, both scientists agree, is that the benefits of knowing bacteria better could range from medicine to efforts to curb global warming.

Earlier scientists had good reason to think that bacteria were simple, says Jacobs-Wagner. Even the most powerful electron microscopes showed little internal structure. But bacterial architecture came into focus thanks to technologies like fluorescence light microscopy and electron cryotomography (ECT). (See sidebar, “[Detailing Bacteria.](#)”)

Jacobs-Wagner first glimpsed microbial order during her postdoc work at Stanford University in the late 1990s. She was investigating a bacterial enzyme that helps control cell division. When she and her colleagues tracked the protein using a fluorescent tag, they found it was initially spread evenly around the bacterial cell membrane. But shortly before division it collected near one tip, suggesting that its location influenced the cell’s actions. “That opened our eyes that perhaps there was a lot of structural organization in [bacterial] cells that we hadn’t expected.”

More of that organization came to light when, after she joined the faculty at Yale in 2001, Jacobs-Wagner and colleagues uncovered a key part of the bacterial cytoskeleton. In eukaryotes, this mesh of protein filaments supports a cell somewhat like bones support our bodies. Eukaryotic cells continually rebuild and reorganize their cytoskeleton, so they can crawl, capture food, and divide. For years, experts thought that bacteria didn’t have one. But in the 1990s and early 2000s, researchers identified bacterial versions of two of the three main types of proteins that form cytoskeleton filaments—actin and tubulin. Then in 2003, Jacobs-Wagner and colleagues discovered that some bacteria carried a protein they called crescentin that was equivalent to building blocks that form the third filament type, known as an intermediate filament.

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#### HHMI INVESTIGATOR



**Christine Jacobs-Wagner**

#### HHMI INVESTIGATOR



**Grant J. Jensen**

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"The fact that we found this cytoskeletal element in bacteria was really exciting," says Jacobs-Wagner. It meant that eukaryotes and bacteria constructed their cytoskeletons from the same parts, hinting that structure performs similar functions in both kinds of cells.

One of those functions, Jacobs-Wagner's team demonstrated in the same study, is shaping the cell. After tagging crescentin, they found that it was in the right position to help bend cells of the water-dwelling bacterium *Caulobacter*. The protein forms a spiral structure along the inner surface of the curved cell. When the researchers removed the protein, the cell straightened out. In a paper published in *EMBO Journal* in 2009, Jacobs-Wagner and colleagues clarified how crescentin works—it spurs some parts of the bacterial cell wall to grow faster than others.

### ANOTHER VIEW INSIDE

Jensen's lab is one of the few in the world using ECT to scrutinize bacteria. He's trained the microscope on everything from the chemical receptors that allow a bacterium to sense food—in essence, the cell's nose—to the base of the flagellum, the bacterial propeller. His work has linked structural subtleties of bacteria to cellular functions such as movement and division.

In a 2006 study published in *Science*, for example, his group teamed with HHMI investigator Dianne Newman, also of Caltech at the time, to take a close look at how bacteria arrange their organelles. Bacteria lack most of the organelles found in eukaryotes, such as mitochondria and chloroplasts, but some species harbor organelles called magnetosomes. These bags of iron-containing crystals serve as a compass and usually line up in chains along the length of the cell.

ECT revealed that one type of cytoskeletal filament made up of a protein called MamK, an equivalent of actin in eukaryotic cells, flanks the magnetosome chains and helps shepherd them into formation. If the protein is absent, magnetosomes scatter, and the bacteria lose their sense of direction. "It's one of the first cases in which we visualized a filament in a bacterial cell and saw that it was being used to position an organelle," says Jensen. Cytoskeletal filaments perform the same job in eukaryotes.

Jensen's results have also suggested a new explanation for how a cell cuts itself in two during division. The researchers homed in on the protein FtsZ, the bacterial equivalent of the eukaryotic cytoskeletal protein tubulin. Previous studies suggested that FtsZ proteins wrapped around the midsection of the cell. When a bacterium was ready to divide, researchers assumed that the protein ring tightened like a belt and eventually pinched the cell in half. But ECT images showed that the filaments were too short and too disorganized to form the continuous loops necessary for belt tightening. In a 2007 paper, Jensen and colleagues proposed that the filaments gradually constrict the cell wall by repeatedly straightening and bending, an alternative they call iterative pinching.

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The emerging picture from these and other studies is that, although bacteria aren't as orderly and sophisticated as eukaryotes, they are far from the simple containers that researchers once thought, Jensen says. The discoveries about bacterial structure might help researchers crack some of the deepest questions about the organisms, he says. "We still don't know why they have a certain shape, how they divide, how they establish polarity, and in many cases how they move."

In turn, answering these questions could have a practical payoff, revealing ways to nurture beneficial bacteria and combat the killers. "If you want to control your enemies, you'd better know them very well," says Jacobs-Wagner.

#### DETAILING BACTERIA

The precedent of studying bacterial architecture dates back to the late 1600s, when the Dutch draper Antonie van Leeuwenhoek first observed the cells through his simple microscope.

"Every time you have a big imaging advance, you have an increase in understanding," says Caltech's Grant Jensen. Today's researchers have profited from two technological leaps forward. The first, Jensen says, is green fluorescent protein and other tags that can reveal cell structure through fluorescence microscopy. They allow researchers to locate molecules and follow their movements.

The second technique is electron cryotomography, or ECT, a method that researchers have been using to probe bacteria for only a few years. Unlike the two-dimensional projections provided by traditional electron microscopy, ECT can capture three-dimensional images of a whole bacterium to reveal internal nuances.

ECT has another big advantage. Preparation of specimens for conventional electron microscopy includes steps such as dehydration and chemical treatment that obliterate much of the internal detail, Jensen says. In ECT, instead of going through this harsh process, the cells are "fixed" by dunking them in liquid ethane at around minus 190 degrees Celsius.

"You get a sample that is stopped in time," says Jensen. All the molecules and water in the cell stop moving instantly without forming ice crystals that would destroy everything around them. Even fine details are preserved, allowing scientists to see the nuances of individual large molecules. —M.L.

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