A scientist's quest to eradicate one of the most common—and potentially deadly—infections

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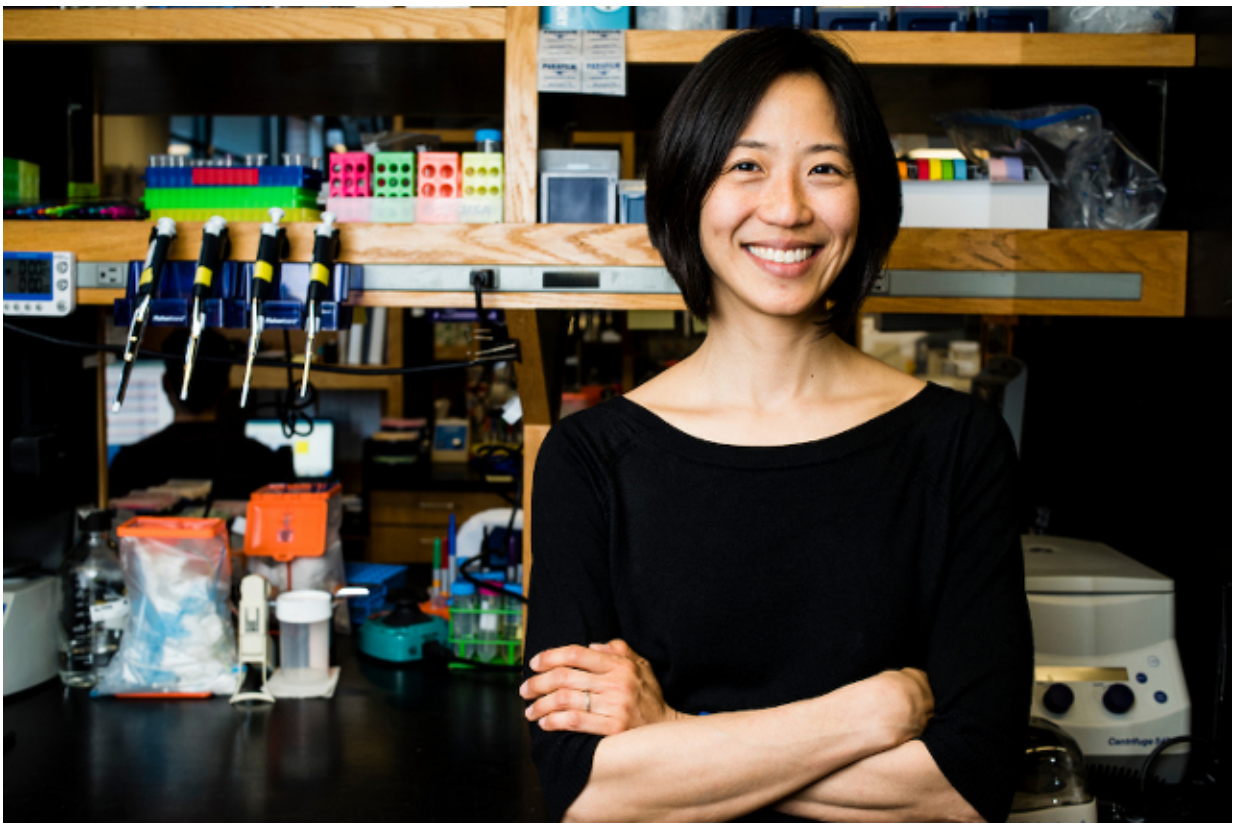

“When I started studying C. diff, we didn’t know anything about how its spores worked,” Aimee Shen said. “What drives me is the thrill of uncovering something new, and figuring out how it works.” . Credit: Alonso Nichols

When a patient visits a doctor's office or a hospital, they're usually seeking relief for an ailment. But many will leave with more than just a prescription. Seven to 10 percent of all patients receiving medical care come down with preventable infections—from pneumonia to sepsis to colitis—while inside a health-care facility, according to the World Health Organization.

Colitis can be especially pernicious. Caused by a bacteria named Clostridium difficile (C. diff, for short), it leads to painful swelling of the colon, diarrhea, fever, dehydration and even death. In 2011 alone, an estimated 453,000 patients in the U.S. contracted C. diff infections—more than 293,000 of them in health-care settings—according to a 2015 study in the *New England Journal of Medicine*. At least 29,000 of those infected patients died, some 15,000 as a direct result of the disease.

"C. diff is everywhere," said Aimee Shen, an associate professor of molecular biology and microbiology at Tufts who studies the microbe. Luckily for most, the infection is rare in healthy people. A functioning immune system, combined with communities of "good" bacteria already living in the gut, can fight off the microbes once they enter the body. But for people with weak immune systems or compromised gut bacteria, such as the elderly and some patients in hospitals, C. diff is much more dangerous.

Part of the microbes' ability to wreak havoc in health-care settings is because it is naturally resistant to antibiotics, but that's only part of the story, Shen said. C. difficile is an anaerobic bacteria, meaning it can only live in low-oxygen environments like the human gut. In order to spread to new hosts, however, it needs to leave the body somehow, which means braving oxygen-rich air that will quickly kill it.

To get around this problem, the bacteria creates spores—seed-like

capsules that keep their offspring in a dormant state—and send those into the world within a patient's fecal material. Once outside the body, the spores can stick around for weeks, even years, until they get onto human hands and somehow make their way back into a new host, where they'll sprout again into thriving bacteria.

Spores, Shen said, are tough little buggers—much of the reason why the name C. difficile is so apt. "They're resistant to commonly used disinfectants. The ethanol-based hand sanitizers you see everywhere in hospital settings don't have any effect on spores," she noted. "You can get rid of them with bleach, but you can't necessarily use that in all settings—so it really takes special containment measures to stop them from spreading,"

Aimee Shen holds a pair of Petri dishes with germinated C. diff spores in her lab. Credit: Alonso Nichols

Rock Solid Defenses

A spore's tenacity, she explains, is provided by a multi-layer defense system. At the center is the "core," made up of a nascent C. difficile cell. A thick, tough structure called the cortex forms around it and expands, helping to squeeze water from the core and placing the cell into a sort of suspended animation. A third and final layer, a thin sheet of proteins called the coat, forms a kind of protective shell.

The exact mechanism that lets these capsule-like spores produce living bacteria remains a bit of a mystery, but Shen is gathering plenty of clues. She's already discovered that the spores's germination process may rely on a trio of proteins in the cortex called CspA, CspB and CspC. When a C. difficile spore reaches your gut, she says, bile salts in your digestive fluids are thought to bind to CspC, which activates CspB; CspA helps incorporate CspC into the spore. Once there, the proteins trigger an enzyme called SleC, which degrades the cortex, lets water inside and revives the microbe.

Shen's past studies hinted that Csp proteins play a major role in spore germination. Most recently, however, she found a protein called GerG that's unique to C. diff bacteria, and seems to control how much Csp makes it into a spore. When Shen's team removed that gene in the lab, many of her C. diff spores failed to open. If the mother cell doesn't have that gene, it'll still make same amount of Csp in cells making the spores—"but we think far less of the molecule makes it into the spore cortex itself," Shen said. "Whatever process allows the Csp proteins to become part of the spore may be defective."

Her lab is currently doing basic research to understand the mechanisms that let spores germinate, but she's hoping her work will eventually lead to treatments. By manipulating Csp proteins, for instance, it might be possible to trick spores into opening up and germinating when they're outside of the body. Without the protection of a tough cortex, the bacteria could be killed on hospital surfaces by traditional antiseptic sprays.

Shen's prowess with C. diff hasn't been lost on her funders at the U.S. Department of Health and Human Services. Late last year, they recommended her for the prestigious Presidential Early Career Award for Scientists and Engineers, which she received in January. "At first, I thought the email from the White House was very well-targeted spam," she said with a laugh. "I couldn't believe it was real."

Awards are exciting—especially since Shen got an extra year of funding on her grant from this one—but she really gets a rush from unraveling biological mysteries piece by piece. "When I started studying C. diff, we didn't know anything about how its spores worked," she said. "What drives me is the thrill of uncovering something new, and figuring out how it works. Right now, we're uncovering layers we didn't even know existed."

Provided by Tufts University

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