Fighting back against TB

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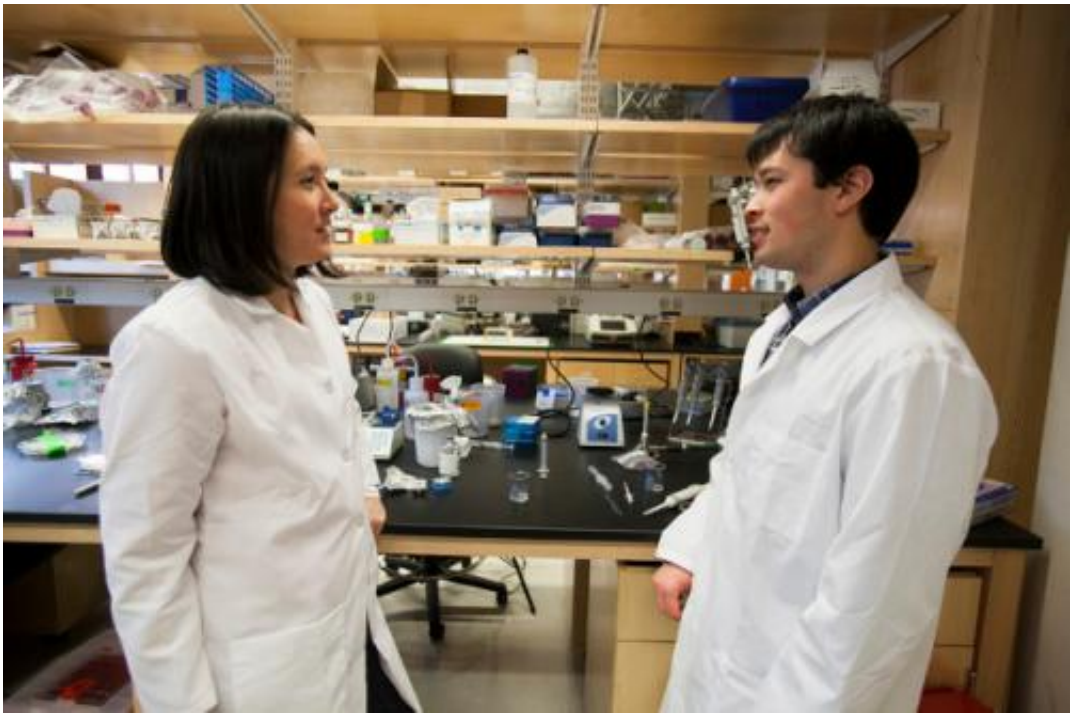

"It's kind of amazing to me that there are so many basic facts we don't understand about this bacteria," says Bree Aldridge, seen here with Owen Bennion, a research technician. Credit: Kelvin Ma

Tuberculosis is back. In 2011, almost 9 million people contracted it, and 1.4 million of them died, making TB the second deadliest infectious disease after HIV/AIDS, according to the World Health Organization.

The resurgence of TB is being fueled by antibiotic-resistant strains of the organism that causes the infection, Mycobacterium tuberculosis, and

scientists are scrambling to find new treatments.

But even before drug resistance became such a problem, Mycobacterium tuberculosis, which has killed up to one billion people over the last two centuries, was a particularly recalcitrant foe. Because it's difficult and dangerous to study in the lab, scientists didn't know much about the bug itself. Instead, they made a lot of assumptions about the tuberculosis-causing bacteria, using its more harmless relatives as models—assumptions about matters including the way it reproduces and the way it responds to drugs.

"It's kind of amazing to me that there are so many basic facts we don't understand about this bacteria," says Bree Aldridge, an assistant professor of molecular biology and microbiology at the School of Medicine. Aldridge, who also holds appointments at the Sackler School of Graduate Biomedical Sciences and the School of Engineering, is working to deepen our understanding of TB. She received an NIH Director's New Innovators Award to support her research; she is one of 41 researchers to receive the five-year, $1.5 million awards.

Already, Aldridge and her colleagues' initial findings about how the bacteria grow could open the door to new, more effective treatments for drug-resistant TB infections.

A Tough Bug to Study

Once known as consumption, because it appears to destroy its victims from the inside out, tuberculosis primarily attacks the lungs, but can do extensive damage in almost any part of the body.

Thanks to the advent of antibiotics in the 1940s and '50s, TB typically is no longer the death sentence it once was. But unlike many infections, it won't go away with a week or 10-day course of medicine. Some of the

bacteria linger for months. That's why TB patients have to take several different kinds of antibiotics for as long as two years.

"The question is, Why do we need such a long drug treatment?" asks Aldridge. "What's different between the bacteria that persist for a long time in the lungs versus the bacteria that die off right away?"

M. tuberculosis is notoriously hard to study. Mycobacteria—the family of bacteria to which it belongs—are named for the mycolic acid that coats each cell. The thick, impenetrable cell wall makes it difficult to handle in the lab.

"It is like it's covered in earwax," says Aldridge. "It makes it not only hard for drugs to get in, it also makes it hard to grow in a petri dish."

For years, scientists gleaned what they could about the TB bacteria by studying its more malleable relatives, like E. coli. When E. coli divide, one cell—known as the mother cell—splits into two identical daughter cells. They are the same size and shape; they behave the same, and—most important to Aldridge—they grow at the same rate.

"That's largely true for rod-shaped bacteria, the scientific classification into which both E. coli and mycobacteria fall," she says, "but it turns out not to be true at all for mycobacteria."

Working as a postdoctoral fellow in the lab of Sarah Fortune at the Harvard School of Public Health, Aldridge collaborated with Mehmet Toner's laboratory at Massachusetts General Hospital to design a small video device that attaches to a microscope and gives researchers an unprecedented glimpse into the daily life of mycobacteria, recording the cells' activity over several days.

The video shows mycobacteria dividing, something few scientists had

ever seen. When the mother cells split into two, the daughter cells aren't the same size or shape at all. They look like sticks and rocks strewn haphazardly on the forest floor.

"Look at how drastically different their sizes are," says Aldridge, pointing at the video on her computer monitor. "Other microbiologists thought our cells were ugly because they're not normal-looking like E. coli," says Aldridge. "After they got over that, they thought it was pretty astonishing."

The findings not only overturned a long-held assumption about mycobacteria, but also gave scientists a glimpse at the potential for new and more effective treatments for TB.

Growing Pains

When Aldridge and her colleagues took a closer look at mycobacteria daughter cells, they found they could put them into two distinct categories based on their growth rates. They named the faster growers "accelerators" and the slower ones "alternators." It turns out that accelerators and alternators respond to different classes of drugs.

Not surprisingly, accelerators succumb more quickly to antibiotics that interfere with their growth. The slower-growing alternators have a different Achilles' heel—they are susceptible to drugs that interfere with more internal cellular processes. This information alone could help refine the way TB is treated.

Aldridge's lab continues to search for other physiological differences among mycobacteria cells. Using microscopy, she and her colleagues are getting up close and personal with individual bacteria to figure out other reasons why some cells are more or less susceptible to certain antibiotic drugs than others.

The team will use mathematical models to make sense of all the information their hunt for physiological differences will generate. Aldridge, who holds bachelor's degrees in computer engineering and molecular and cellular biology and a Ph.D. in biological engineering, says applying engineering principles to a biological problem is the best approach she knows for finding ways to target drug therapies to bacteria that are harder to kill.

"We'll use mathematical models to help us resolve all those different parameters," says Aldridge. "It's too much data to make sense of without the models."

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