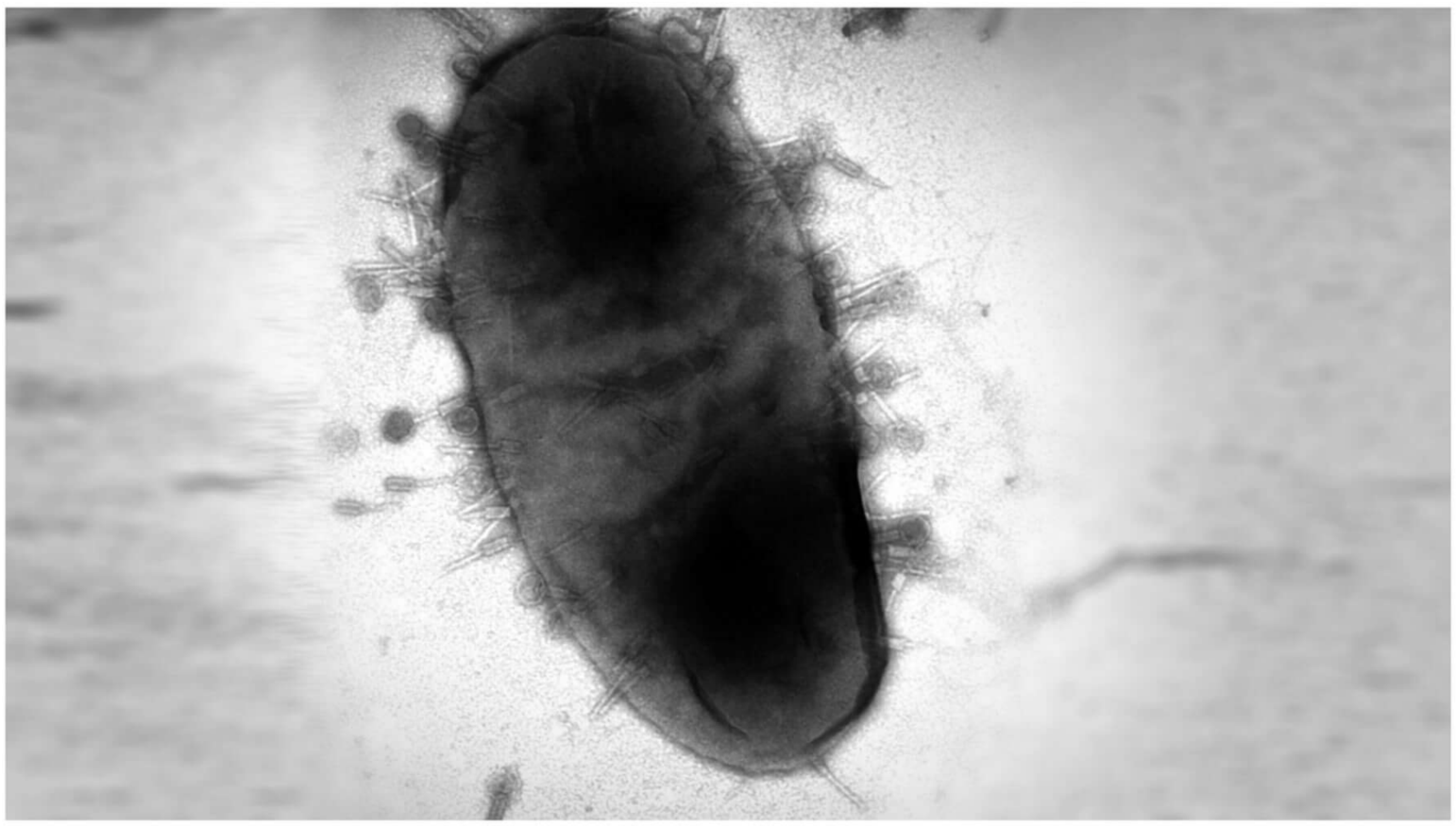
STAT

IN THE LAB

A fitting memorial: Superbug treatment named for the patient who inspired its discovery

By Eric Boodman Jan. 23, 2020



An electron microscope image of the phage BCMallory 1, which can destroy the strain of superbug that killed Mallory Smith.

RONEN HAZAN LAB AT HEBREW UNIVERSITY

Even for the most elite of bacteria-killers, these superbugs were a challenge.

They'd delayed Mallory Smith from getting a lung transplant, and when she'd finally had the surgery, the bacteria quickly migrated into her new lungs. They shrugged off cocktail after cocktail of antibiotics. Finally, Smith's father proposed an unusual last resort: finding viruses that parasitize bacteria and injecting them into his daughter. But the experimental treatment came too late. Smith died on Nov. 15, 2017, a little over a month after she'd turned 25.

Yet her bacterial infection lived on, passed from scientist to scientist, from freezer to freezer, traveling from Smith's hospital room in Pittsburgh, Pa., to a lab in Ann Arbor, Mich., eventually landing in a Petri dish in Jerusalem, some 6,000 miles away. Now, microbiologists at Israel's Hebrew University have described a new virus that's especially good at combating Smith's superbug.

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It isn't the first bacteriophage — as such bacteria-fighting viruses are known — that can work against this sort of intractable infection. After all, there are trillions of phages out there, feasting on the bugs that fill our sewage and hunting for hosts in puddles after rain. Even if they're extreme specialists, attacking only specific strains of a specific species of bacteria, there's usually more than one that infects a particular superbug. Smith's doctors had tried out a few that may have done the trick if injected earlier.

Yet the mere fact that researchers are looking for phages to try as therapies is a sign of how much has changed since — and because of — Smith's death. The hope is that next time there's a case like hers, a potentially lifesaving treatment will be ready sooner.

The recent surge of phage therapy enthusiasm is a revival of sorts. In the 1930s, you could get phage concoctions to treat everything from dysentery to urinary tract infections to outbreaks of the skin. But then, in the 1940s, penicillin hit the market, and antibiotics became the rage. Eastern European researchers continued to use phages as treatment, but such Soviet science was viewed with suspicion back in the United States.

It was only with the rise of antibiotic-resistant bacteria that Western interest in these viruses-as-treatments began to brew again. Even so, in 2017, many still considered the idea esoteric at best. That was part of the holdup for Smith. There was no established method for finding, purifying, and delivering the viruses her doctors hoped might save her life. When her father reached out to scientists who had a bit of experience with phage therapy, all they could do was send out a frantic flurry of emails and tweets.

Mallory Smith

COURTESY

Smith's story helped change that. She'd been born with cystic fibrosis, a genetic illness that fills the lungs with a particularly gluey sort of mucus. Not only does that make it hard to breathe — it also acts as a cushy home for bacteria. When two friends who'd met through swing dancing — one a grad student, the other a tech consultant — read about Smith's desperate attempt to find a virus that would beat back the bacteria within her, they created an online phage directory to help speed things up. Then, in 2018, the University of California, San Diego, established the first phage therapy center in the U.S.

Yet for a patient with Burkholderia cepacia — the kind of bacterial infection that Smith had — finding the right phage in time is hardly a shoo-in. Partially that's because it's not the most common superbug infection, even among cystic fibrosis patients, so not all that many researchers are working on treating it with phage therapy. But it's also because B. cepacia is an especially tricky type of bacteria to phage-hunt for. Some phages — the ones that are easiest to use as therapies — enter a superbug, replicate like crazy, and cause the host to explode. Others, though, simply integrate peaceably into the bacterial genome. And the phages discovered for B. cepacia often fall in the peaceful-coexistence camp. Plus, for other kinds of bacteria — Pseudomonas, say, or Klebsiella — a phage might be active against a large swathe of strains; for Burkholderia, Hazan explained, the viruses are choosier.

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That's where his lab comes in. The team's hope is to build up a library of B. cecpacia-killing phages that can be used in cocktails whenever a case like Smith's pops up. To do that, the scientists have collected all sorts of substances most people would rather not deal with. They take the used saliva, urine, and fecal samples from hospitals. "Instead of discarding them, we take them and search for phages," Hazan explained. "We're looking in water bodies, small lakes. After the rain, in puddles. Whenever a student goes on vacation we ask him, 'Bring some samples of soil or water or whatever!'"

They also regularly take wastewater from West Jerusalem's sewage treatment plant, which is where the phage active against Smith's bacteria came from. "Everybody complains about the smell, but we are finding gold in that sewage," Hazan added.

Three Hebrew University students — Chani Rakov, Ortal Yerushalmy, and Leron Khalifa — first isolated the phage in question this past December. When they put it into a Petri dish covered in the kind of bacteria that had been collected from Smith's lungs, it began to create clear spots where the superbug was dying off. The decision was unanimous that it should be named BCMallory1, for the initials of the bacteria it's active against, and the name of the person who helped inspire the search.

When she heard the news, Smith's mother began to cry. To her, it meant that other families might not have to live through what she did. "It's a very bittersweet feeling," said Diane Shader Smith. "You know the suffering, and you don't want anyone to suffer, but also you think, Mallory could have lived."

Because bacteria often develop resistance to phages as well, many researchers think it's best to deliver a cocktail of phages alongside antibiotics, and Hazan plans to keep searching. He's also thinking about the possibility of genetically engineering some of the phages his team finds, to make them safer or more efficient bacteria-killers.

"We don't want to have another Mallory Smith," said Steffanie Strathdee, co-director of the Center for Innovative Phage Applications and Therapeutics, at University of California, San Diego, and co-author of "The Perfect Predator," a book about how she saved her husband's life through a similar phage hunt in 2016. Smith's case still haunts her, she said: "I think about her every day. We came so close to saving her life."