Phages could help when antibiotics fail

Bacteria-eating viruses are broadening the treatment landscape for people with drug-resistant infections. **By Elizabeth Svoboda**

After more than a decade of drug-resistant infections, Ella Balasa's options were running out. The bacterium *Pseudomonas aeruginosa* – common in people with cystic fibrosis – had taken up long-term residence in Balasa's lungs, eating away at the healthy lung tissue she had left. Balasa's lung function dipped below 20% of normal, and at age 26, she depended on supplemental oxygen. "I needed oral antibiotics inhaled constantly," Balasa says. "I knew that wasn't sustainable."

Then Balasa, who lives in Richmond, Virginia, was interviewed for a documentary about bacteriophages, or phages for short. These specialized, bacteria-killing viruses showed promise of stamping out resistant infections like hers. Fascinated, Balasa looked up biologist Benjamin Chan, who was doing experimental phage treatments at Yale University in New Haven, Connecticut, and asked him whether she could be a candidate.

Cystic fibrosis researchers have long considered phages as a last resort – a fringe treatment only offered in Eastern Europe, the long-time epicentre of phage research, and a few other places. But the growing problem of antibiotic-resistant infections has spurred fresh interest in the naturally occurring viruses. Some doctors are now using phages to treat localized bacterial infections and to promote safe wound healing, although these treatments are not yet considered mainstream. Because phages can defeat bacteria when antibiotics fail, people with late-stage cystic fibrosis are increasingly seeking the treatment on a compassionate-use basis. A dedicated network of virologists, pulmonologists, clinicians and others has stepped up to deliver, hunting down the right strains of phage to treat patients' infections.

The approach has piqued the interest of major research centres and drug companies. By the end of 2020, Armata Pharmaceuticals in Marina del Rey, California, expects to launch one of the first clinical trials of phage therapy for cystic fibrosis, funded by a US$5-million grant from the Cystic Fibrosis Foundation, a non-profit organization in Bethesda, Maryland. Similar trials are scheduled to start at other sites. In the meantime, laboratories and providers continue to deliver custom phage blends to people with cystic fibrosis-related infections. Phages are "a Hail Mary that's here right now", says Emily Kramer-Golinkoff, who has cystic fibrosis and is the founder of the research-funding non-profit organization Emily's Entourage in Merion Station, Pennsylvania. "We have to be opportunistic as a community, because people's lives are on the line."

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Ella Balasa inhales a phage treatment at Winchester Chest Clinic in New Haven, Connecticut.

Chronic infection

The hallmark of cystic fibrosis is thick mucus that severely impedes breathing. This mucus is also an ideal breeding ground for antibiotic-resistant bacteria, including strains of *Pseudomonas*, *Mycobacterium* and *Burkholderia*.

Such drug-resistant infections can linger for years and severely deplete lung function. If highly advanced, they might also disqualify patients from getting a lung transplant – one of the only treatments that significantly delays the disease's progression.

The right phages can eradicate these resident lung bacteria. Phages attach to bacterial cell surfaces and inject their genetic material, hijacking the bacterium's machinery and forcing it to churn out thousands of phages. The overstuffed bacterial cell then bursts, releasing the viruses. "Phages replicate at the site of the infection and continue to destroy bacteria," says Greg Merril, chief executive of biotechnology company Adaptive Phage Therapeutics (APT) in Gaithersburg, Maryland. Because each phage attacks a specific strain of bacteria, the treatment does not damage surrounding tissue.

Research on the use of phages in people with cystic fibrosis is promising. A study at the US Naval Medical Research Center in Silver Spring, Maryland, treated 13 people with phages, 4 of whom had cystic fibrosis[1]. In 11 of the 13, phages wiped out the targeted bacteria. And a 15-year-old with cystic fibrosis who was treated with a three-phage cocktail improved markedly: not only did their drug-resistant infection disappear, their lung and

liver function rebounded, too[2].

Although phage therapy is not a knockout punch against cystic fibrosis, it can be a way to buy time. If a course of phages can dislodge a drug-resistant infection, a patient can recover enough to become a candidate for lung transplant. Phages fit in "at the level of improving and prolonging life — taking down the bacterial players that are really causing problems", says microbiologist Jessica Sacher at the University of Alberta in Edmonton, Canada.

A 25-year-old California woman, Mallory Smith, who had struggled for years with drug-resistant *Burkholderia cepacia* infections, was among the first people with cystic fibrosis to get phage therapy in the United States. Her father, Mark Smith, reached out to a handful of phage scientists, including epidemiologist Steffanie Strathdee at the University of California, San Diego. In November 2017, Strathdee asked researchers on Twitter whether they had a phage strain that worked on *B. cepacia*.

Strathdee found a match for the bacterium, but not in time: Mallory's disease was so advanced that she died before the phages could work. Still, an autopsy showed they had already started to deplete Mallory's bacterial colonies, convincing Strathdee that phage therapy could be a huge boon for other people with cystic fibrosis. Under Strathdee's leadership, the university launched the Center for Innovative Phage Applications and Therapeutics (IPATH) in 2018, with cystic fibrosis as one of its specialities.

"Patients really want this, and they want it now."

Along with Phage Directory, a non-profit organization in Atlanta, Georgia, that Sacher co-founded, IPATH helps to match people who have late-stage cystic fibrosis with phages that target their infections. When a patient needs phages for an antibiotic-resistant infection, an e-mail or social-media request goes out to dozens of research labs. These labs scan their phage collections to see whether they have the right phage to destroy the person's bacterium. Once a lab finds the ideal phage, technicians grow billions of the viruses and ship them out. So far, Phage Directory has coordinated phage sourcing for seven or eight patients. Others have secured phages through independent arrangements with labs elsewhere.

After hearing from Balasa, Chan told her he would take on her case. He had phages at Yale that would combat the *P. aeruginosa* in her lungs, and Balasa scheduled a trip to New Haven to begin her treatment. But as the date drew closer, her condition declined. "I had this really bad infection flare-up. I was really nervous," she recalls. Worst-case scenarios flitted through her mind: what if the phage treatment caused her airways to swell and tighten? But she decided to go through with it anyway. She knew that the status quo — mega-doses of antibiotics — would be ineffective.

Finding the right phage

Despite her fears, Balasa knew she was lucky to find a researcher who could treat her. Hunting down the right phage can take months of painstaking, unpaid detective work, even when Phage Directory is on hand to move things along. Of 260 patients requesting phage therapy at a Belgian hospital between 2013 and 2018, about half had to be turned down because the hospital did not have the right phages[3]. "Cystic fibrosis patients really want this, and they want it now," Strathdee says. "Sometimes patients and their loved ones are angry that we can't help them."

To streamline the process of patient–phage matching, some researchers are building standardized phage libraries. Phage Directory is compiling an open-access database that indexes collections around the world, and in 2019, researchers at the Baylor College of Medicine in Houston, Texas, reported that they had created libraries that work against three common pathogens[4]. In March, the US Food and Drug Administration approved APT's application to create a comprehensive phage library called PhageBank. Sourcing phages in random labs or in nature "takes time", Strathdee says. "If you have a phage library, it's like a giant walk-in cooler."

Another obstacle is that phage therapy doesn't always fit into a standard clinical-trial framework. In most drug trials, each participant in the test group gets exactly the same medication at the same dose. But that approach can be impractical with phages. In cystic fibrosis, many people's drug-resistant infections are highly unusual, requiring physicians to create custom phage preparations.

Armata Pharmaceuticals' upcoming phage trial sidesteps this issue by using a cocktail of phages that target only *P. aeruginosa*. Other researchers are pursuing less-conventional routes. At the behest of molecular biologist Jean-Paul Pirnay at the Queen Astrid Military Hospital in Brussels, Belgian regulatory authorities now allow phages to be used in what Pirnay calls "magistral preparations". This means pharmacists can legally create custom phage blends for individual patients, drawing from a commercialized bank of phages that have been pre-approved by the Belgian government. "You take the ones that work, you can mix them," says Pirnay. "You can make a suspension for intravenous use, or a nasal spray."

APT is taking a similar tack in its clinical trial, which is scheduled to start before the end of the year. The company will draw on its own library to create personalized phage cocktails for participants, and the trial will evaluate the effectiveness of this approach.

Safety must remain paramount along the way, says Elizabeth Burgener, who studies microbial interactions in people with cystic fibrosis at Stanford University in California. Before approval, researchers will continue to assess phages' long-term effects in early recipients — monitoring whether the viruses shift the overall bacterial balance in the lungs, for instance, and whether they cause swelling in infected airways.

Life-changing

On 17 January 2019, Ella Balasa inhaled her first dose of phages through a nebulizer in a Yale clinic room. Seven days later, she hadn't noticed any improvement in her symptoms. Her regular physician issued a discouraging assessment of the treatment when she returned to Richmond. "He said, 'Obviously it's not doing much for you. You're probably going to need a transplant'," remembers Balasa.

A few days later, when Balasa was at Duke University in Durham, North Carolina, for a lung-transplant assessment, things started to turn around. "I started coughing out all this dark, old mucus," Balasa says. "It just started coming out." From past experience, she knew that meant her infection was clearing. She also began to recover her strength — before the treatment, she had felt too weak even to wash her hair. Chan soon confirmed through bacterial cultures that her drug-resistant bacterium was indeed diminishing.

Although the phages helped to vanquish Balasa's infection, they could not repair her tissue damage. Her lung function now hovers at about 25% of normal. Still, Chan's treatment helped to stabilize her condition enough that she postponed her lung transplant and began Trikafta drug therapy instead (see page S2). "Cutting out those severe infections," Balasa says, "has changed my life." As phage research and trials proceed, she hopes others with cystic fibrosis will be able to say the same.

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1. Duplessis, C. A. *et al. J. Intens. Crit. Care* **5**, 11 (2019).
2. Dedrick, R. M. *et al. Nature Med.* **25**, 730–733 (2019).
3. Djebara, S. *et al. Viruses* **11**, 265 (2019).
4. Gibson, S. B. *et al. Front. Microbiol.* **10**, 2537 (2019).