New guidelines for phage preparation can accelerate lifesaving treatment

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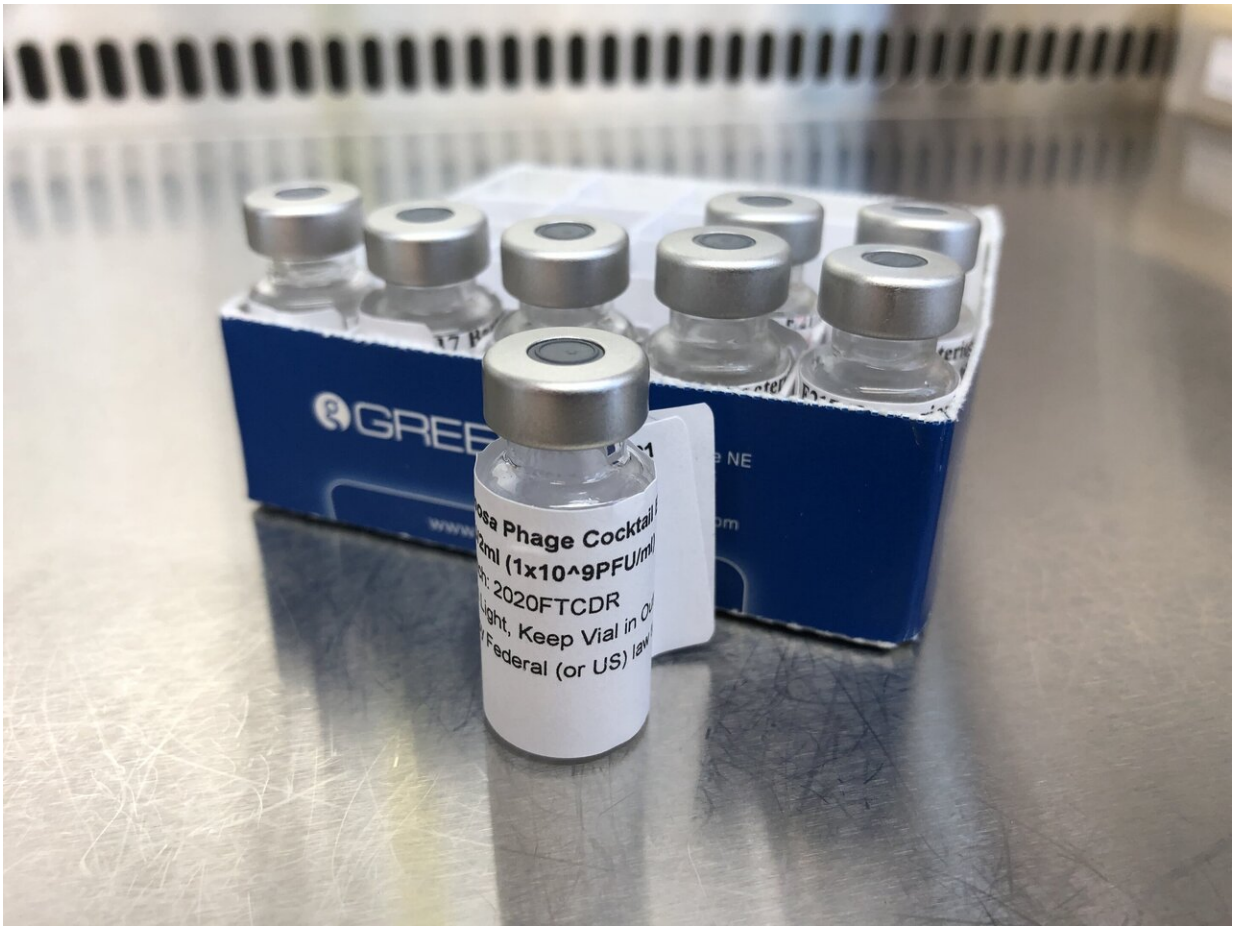

San Diego State University microbiologist Dwayne Roach's phage lab has developed new guidelines to prepare phage that will accelerate the time to therapy while streamlining the process. Credit: SDSU Roach Lab

When clinicians resort to phage therapy for patients who don't respond to antibiotics, the patients are usually very ill and time is of the essence. But the average time for labs to produce therapeutic phages is more than a month.

The main reason for this is the lack of a standardized phage purification process for research labs, despite the fact that phage therapy—which uses viruses to destroy disease causing bacteria—has been around for over a century.

Now, a San Diego State University lab that produces phage therapeutics for clinicians across the country for compassionate use has developed standardized guidelines intended to not only streamline the process using existing lab equipment, but also shorten it to two to three weeks, cutting the typical processing time by half.

"Many of our patients have so little time, so speed is of the essence and this protocol would really make a difference, since one run can produce enough doses to treat a patient for months," said Dwayne Roach, the Conrad Prebys chair of virology and assistant professor at SDSU.

The protocol, he said, combines traditional techniques with modern filtration technology to produce higher phage yields and reduce endotoxin levels compared to previously developed methods.

The open source guidelines were published in a paper in *Nature Protocols* in July.

Bacteriophages and phage therapy

Typical candidates for phage therapy are patients who have multi-drug resistant bacteria, a more and more common fallout of overusing antibiotics. Phage is short for bacteriophage, which literally means

"bacteria eater." They are viruses that only attack bacteria, not people, and are found in soil, water and sewage, requiring them to be purified before use.

Phage therapy is not approved yet in the United States and Europe, except on a case-by-case basis under compassionate use. The military is also interested in phage therapy for the battlefield, where it could be used as a sterilizing wash to remove bacteria from wounds.

Since this is still an emerging field, labs take varying approaches to phage purification. The protocols developed by the SDSU researchers are straightforward, and use simple, standard microbiology lab equipment to remain affordable. They are suitable even for labs in countries with limited resources that wish to ramp up phage production.

Lack of protocols a key bottleneck

Since Roach's lab has a library of phages on hand, much of the back-end work of collecting and cultivating them has already been completed. The protocols allow his team to supply clinicians with the best-fit phages in as little as a week.

"Our protocol provides a standard of production for medicinal phages that consistently provides potentially thousands of phage treatment doses," said Tiffany Luong, first author and a doctoral student in Roach's lab. "We provide instruction and rationale for each step in our process which allows the user to tailor the procedure to their specific equipment and bacterial species."

Identifying groups of phages that are effective against multi-drug resistant bacteria has become easier over the years.

But Dr. Robert 'Chip' Schooley, director of the Center for Innovative

Phage Applications and Therapeutics at the University of California San Diego, said however that the absence of rigorous, scalable approaches for producing therapeutic phages in academic laboratories and delivering them to the patient's bedside is a major bottleneck.

"Dr. Roach's protocol guidelines are an outstanding example of the rigor required to safely take phages into the clinic," Schooley said. "These guidelines will be of great interest to other academic laboratories and to regulatory agencies as we move into the next phases of phage therapeutics."

Reducing endotoxins

When Roach's team began working with physicians in spring 2019, they had to figure out how to streamline the process. By scrutinizing each step and comparing different methods, the team identified cross-flow filtration—when the flow travels across the surface of the filter instead of into it—as the most efficient and effective purification method, and Roach presented the results and accelerated timeline at a conference later in the year.

While Roach and Luong looked at process optimization, Ann-Charlott Salabarria, a postdoctoral researcher, worked on setting parameters for ensuring safety of the end product with multiple tests, including confirming that endotoxin levels met U.S. Food and Drug Administration (FDA) guidelines.

One of the FDA's major concerns with phage products is its endotoxin levels, which can harm patients and need to be removed as part of the purification process. The published protocol will help ensure the phage products are safe above and beyond the FDA minimum requirements, Roach explained.

"Our tests do validate that this process removes almost all endotoxins and exotoxins," Roach said. "We wanted to publish our protocol as a resource for other labs because purification has been very time consuming, taking away time from research."

Phage strain selection is another important aspect to developing phage therapeutics. To screen out unwanted genes in phage genomes, Roach enlisted the help of SDSU microbial geneticist and bioinformatics expert Robert Edwards.

"Phage genomes contain so many different components and may mobilize other toxins or antibiotic resistance genes," Edwards said. "It is absolutely imperative that we understand these viruses at the molecular level to ensure that we are not introducing anything potentially harmful into already ill patients."

The researchers will continue to focus on improving safety in phage therapy, by testing it on tissue and mice cell cultures.

"We hope this protocol will allow more research labs to participate in re-introducing phages to Western medicine," Luong said.

More information: Tiffany Luong et al, Standardized bacteriophage purification for personalized phage therapy, *Nature Protocols* (2020). DOI: 10.1038/s41596-020-0346-0

Provided by San Diego State University

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