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The promise of phages

Phage therapy is an exciting alternative to antibiotics. Why now?

Our world today is reliant on antibiotics to fight bacterial infections, but the way we use them has created new, drug-resistant 'superbugs' that have evolved to be resistant to most antibiotics. These killed at least 1.27 million people worldwide in 2019, according to the US Centers for Disease Control and Prevention. Furthermore, antibiotics are not specific. They target the infection-causing bacteria, but they also destroy beneficial resident microbes in our guts, leading to decreased microbial diversity, and it can take months to years to recover a more normal microbiome following antibiotic treatments. Right now, we can still treat the majority of these resistant bacteria, but this will not always be the case, so other approaches are needed. One alternative that has been around for a while is phage therapies.

While we've long known the limitations of current antibiotics, little action has been taken to find new ones or investigate alternatives. There has been a call to develop new antibiotics, but big pharma is hesitant to fund early antibiotic R&D, specifically when looking for new classes of compounds, since the return on investment in this area is generally low or even negative. Finding a new antibiotic candidate and bringing it to the market can take anywhere from 8 to 20 years.

This is where phage therapies come in. Phage therapy, which is the use of bacteriophage viruses to treat bacterial infections, has been around for over a hundred years. Phages are small viruses that can target and eliminate specific bacterial strains without compromising other microbial species within our bodies. The field has been slow to develop commercially, probably in large part due to the effectiveness of current antibiotics, but recently it seems to be having an emergence.

In a recent article, *Nature Biotechnology* discussed biotech companies that are pushing into this space. The market for phage therapies is predicted to grow 17% by 2030, to approximately $84 million annually. Big pharma companies still have not gotten on board, but this is likely to change. Why is this happening now? We've known about antibiotic-resistant bacteria for decades, and phage therapies have been around for much longer. There seems to be a combination of a few factors.

First, and most importantly, scientific research has finally been able to shed some light on phages — how to identify them and what they can do. Finding the right phages to combat a specific bacterium can take time. To find a phage that can kill a specific bacterium, you need to test libraries of phages for the ones with the strongest interactions. Traditionally, scientists have deployed several methods to match phages with bacteria: microfluidic PCR, PhageFISH, and assays such as spot tests and agar overlay assays. None of these is quick and easy, although they are highly accurate.

Computational methods can identify interactions. These include reference-based methods that work from existing databases of viral sequences. However, these suffer from low sensitivity and may identify false positives, as many viral sequences have similarities with bacterial sequences. New reference-free methods are using machine learning algorithms to make this process easier. This approach is only becoming possible now thanks to the large datasets that can be used to train and test machine learning algorithms and ultimately identify phage–bacterial matches. Of course, computational predictions still require validation, and more data will be needed to move forward, but already these methods can help by narrowing the search.

Scientists are also working hard to genetically engineer phages to target specific bacteria by modifying phage receptor-binding proteins (RBPs), avoiding the time-consuming search for naturally occurring phages that will bind bacteria. High-throughput RBP diversification strategies have been developed to screen for mutants with expanded host ranges. Synthetic biology approaches can also be used to enhance bacterial killing by using a designed phage that includes an antimicrobial gene or protein. This is another area where advances in machine learning will lead to more efficient phage design.

Phage manufacturing also needs an overhaul to ensure these therapies become accessible to the public. For now, phage therapy is still experimental, and each case needs approval from the US Food and Drug Administration (FDA) in a single-use Investigational New Drug application. To employ phage therapies, cases must be life-threatening and caused by multi-drug-resistant infections. There are established centers such as IPATH at the University of California San Diego that help get these phage treatments to patients, and several clinical trials are ongoing.

Finally, the COVID-19 pandemic has likely played a role. In one study of hospitals in the Netherlands, secondary bacterial infections were rare (1.2%), but more than 60% of patients received antibiotics. It's becoming clearer to the public that alternatives are needed to prevent the spread of bacteria resistant to these antibiotics, which emerge as a result of overuse.

Challenges remain. Manufacturing and distributing phage therapy on a larger scale isn't possible right now. Phages can multiply, and so treatment dosage needs to be carefully considered for any clinical trial. It's important to note that bacteria's job is to evolve — they have been doing this for eons, and not just in response to antibiotics. Phage resistance can occur, although we're also seeing that this can be avoided by using combinations of phages to target a bacterium, as it's unlikely that a strain will evolve to be resistant to all phages in a cocktail. In the end, phages are unapproved drugs, not just in the United States, but also in the United Kingdom and the European Union. The FDA is seemingly on board, but no guidelines are in place to bring these phages to the clinic.

It's not likely that phage therapies will take the place of general antibiotic use, but hopefully as soon as they are shown to be broadly safe and clinically useful, they will be a much needed complement to the antibiotic armamentarium.

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