Eventually, the bacteria die and their cell walls burst open, freeing the phage progeny to start the cycle anew. If scientists can find a way to use this natural process to their advantage—or, better yet, engineer phages that are more effective predators—they could bolster their arsenal in the war against bacterial resistance.

The idea is gaining in popularity. “There’s a renaissance going on with phages,” says Timothy Lu, a synthetic biologist who studies phages at the Massachusetts Institute of Technology (MIT) in Cambridge. “And what people are doing is trying to engineer them.”

In many ways, bacteriophages are an old solution to an even older problem. They were discovered almost a century ago, first in 1915 by British microbiologist Frederick Twort and then again by the French-Canadian microbiologist Félix d’Hérelle in 1917. It was d’Hérelle who gave them the name “bacteria-
“This is not phage therapy. It’s a twist on phage therapy.”

Regulatory clearance remains another hurdle. In addition to the inherent safety concerns surrounding a live biological agent, neither the US Food and Drug Administration (FDA) nor the European Medicines Agency has an approval process in place that can easily accommodate the ever-changing combinations of phages that companies need to develop to stay one step ahead of evolving pathogens. To put it bluntly, “phage cocktails aren’t compatible with how the FDA approves drugs,” says Lu.

To circumnavigate these hurdles, Lu and others are modifying phages to try and create something that can be tightly controlled and more effective than natural viruses, with a potential patentability that could tempt pharmaceutical investment. In a landmark 2009 paper, Lu, together with Boston University bioengineer James Collins, took a phage that infects quinolone-resistant Escherichia coli and engineered it to insert a gene into the bacterium that prevents the repair of quinolone-induced chromosomal damage. Delivered in conjunction with the antibiotic, the phage increased the drug’s effectiveness by up to 10,000-fold, the researchers showed.

In a similar vein, Udi Qimron and his colleagues at Tel Aviv University in Israel published a study earlier this year in which, using modified phages, they caused drug-resistant E. coli to become susceptible again to two antibiotics: streptomycin and nalidixic acid. But rather than administering the phage alongside the drugs, as Lu and Collins had done, Qimron’s team applied its phage to the bugs days before the drug therapy.

In light of these findings, Qimron now hopes to develop a phage-containing spray that can be routinely applied to the surfaces of medical wards to prevent the spread of hospital-acquired infections, opening the

Breaking bad biofilms: Scanning electron micrographs of E. coli biofilms without treatment (left), with unmodified T7 phage (center) and with phage engineered to express an enzyme that degrades biofilms (right).
possibility for reversing drug resistance even before superbugs have infected people. “This is not phage therapy; it’s a twist on phage therapy,” he says. “Using this phage product every day, you will eventually replace all the resistant pathogens in a hospital with susceptible ones.” Importantly, notes Qimron, because these phages aren’t intended for human consumption, such a spray could be considered by regulators as an industrial product and, thus, have an easier path to FDA approval than phages formulated as ingestible or topical medicines.

In the last year, the Bill & Melinda Gates Foundation has even gotten behind phage engineering. In a recent Grand Challenges Explorations round devoted to synthetic biological solutions to global health problems, the Seattle-based organization, the largest nongovernmental funder of biomedical research in the world, awarded its first such $100,000 grants to investigate new ways of using bacteriophages for antibacterial purposes. MIT synthetic neuroscientist Feng Zhang is using his money to engineer phages capable of delivering DNA sequences encoding enzymes that prompt the bacteria to start cutting up their own genomes. Argentinean microbiologist Héctor Morbidoni of the National University of Rosario is hoping to develop a phage-based biosensor for pathogen detection. And Spain’s van Raaij wants to create libraries of randomly mutated phages that can act against a wide range of different bacteria.

According to venture capitalist David Berry, a partner at Flagship Ventures, a Cambridge, Massachusetts–based firm that does not currently fund any phage-based companies, there’s plenty of market opportunity to go around. Engineered phages “could very easily become a billion-plus-dollar opportunity,” he says.

Yet, despite many of the advantages of engineered phages, Graham Hatfull, cofounder of the Pittsburgh Bacteriophage Institute in Pennsylvania, foresees a future in which all sorts of phage-based approaches will be needed. “I think bacteriophages, whether natural or engineered, are likely to play a role,” he says. “I like the idea of having as broad an arsenal as possible, which will include all these different types of strategies.”

The sum of its parts

One of those new strategies involves extracting the bacteria-killing components of phages without having to rely on the living viruses themselves. As a graduate student in the late 1960s, Fischetti discovered that he could kill group C Streptococcus bacteria by applying a type of protein called a lysin isolated from phages. He purified the enzyme and found that it stripped away the mesh-like layer from the surface of the bacterial cell wall, punching holes right through the barrier and resulting in a kill that was specific and immediate. Thirty years later, Fischetti returned to his doctoral work and tested the same lysin on mice with strep throat. Within two hours of oral treatment, the bacteria had completely disappeared. Since then, Fischetti has uncovered phage-derived lysins that act against a range of pathogenic bacteria, including Enterococcus faecalis, methicillin-resistant Staphylococcus aureus and even Bacillus anthracis, to name a few.

So far, Fischetti has tested his lysins only in rodent models. But through a Yonkers, New York–based startup called ContraFect, which has licensed nine of Fischetti’s lysins and counts the Rockefeller scientist as one of its scientific advisors, he expects the first human trials to begin within the next year.

Meanwhile, the Indian company GangaGen Therapeutics is advancing a related approach. By combining a truncated phage lytic enzyme with part of a small molecule directed against S. aureus, the company has created a chimeric protein, called P128, that can kill various staph strains, including those recovered from the nostrils of human volunteers. Notably, both GangaGen’s and ContraFect’s protein-based products will not be subject to the same difficult approval process that their parent phages would be.

Fischetti is confident that one of these many phage-based therapies will ultimately pay off. “Every two days, half the bacteria on Earth are killed by bacteriophages,” he says. “It’s a hugely dynamic process that’s going on constantly.” Thus, no matter how menacing a bacterial infection might seem, some phage somewhere has the ability to knock it down to size. Scientists now just have to find those phages—and tweak them accordingly.

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