NEWS IN FOCUS

ELIAVA INST.

Bacteriophages could be a resource for fighting drug-resistant bacterial infections.

MICROBIOLOGY

Phage therapy gets revitalized

The rise of antibiotic resistance rekindles interest in a century-old virus treatment.

BY SARA REARDON

For decades, patients behind the Iron Curtain were denied access to some of the best antibiotics developed in the West. To make do, the Soviet Union invested heavily in the use of bacteriophages — viruses that kill bacteria — to treat infections. Phage therapy is still widely used in Russia, Georgia and Poland, but never took off elsewhere. "This is a virus, and people are afraid of viruses," says Mzia Kutateladze, who is the head of the scientific council at the Eliava Institute in Tbilisi, which has been studying phages and using them to treat patients for nearly a century.

Now, faced with the looming spectre of antibiotic resistance, Western researchers and governments are giving phages a serious look. In March, the US National Institute of Allergy and Infectious Diseases listed phage therapy as one of seven prongs in its plan to combat antibiotic resistance. And at the American Society for Microbiology (ASM) meeting in Boston last month, Grégory Resch of the University of Lausanne in Switzerland presented plans for Phagoburn: the first large, multi-centre clinical trial of phage therapy for human infections, funded by the European Commission.

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For more on antibiotics and phage therapy, see: go.nature.com/pykv3d

Ryland Young, a virologist at Texas A&M University in College Station, attributes the previous lack of Western interest to clinicians' preference for treating unknown infections with broad-spectrum antibiotics that kill many types of bacterium. Phages, by contrast, kill just one species or strain. But researchers now realize that they need more precise ways to target pathogenic bacteria, says microbiologist Michael Schmidt of the Medical University of South Carolina in Charleston. Along with the rising tide of strains resistant to last-resort antibiotics, there is growing appreciation that wiping out the human body's beneficial microbes along with disease-causing ones can create a niche in which antibiotic-resistant bacteria can thrive. "Antibiotics are a big hammer," Schmidt says. "You want a guided missile."

Finding a phage for a bacterial target is relatively easy, Young says. Nature provides an almost inexhaustible supply: no two identical phages have ever been found. As a bacterium becomes resistant to one phage — by shedding the receptor on the cell surface that the virus uses to enter — the Eliava Institute researchers simply add more phages to the viral cocktails that patients receive. Kutateladze says that they update their products every eight months or so, and do not always know the exact combination of phages that make up the cocktail.

Resch, who is one of the leaders of the Phagoburn study, says that regulatory agencies would need to figure out how to oversee such a rapidly evolving product before the therapy could progress beyond clinical trials. He hopes that phage therapy will be treated in a similar way to the seasonal influenza vaccine, for instance, which is updated every year as new flu strains emerge.

The fact that the European Union (EU) is contributing €3.8 million (US$5.2 million) to the Phagoburn study shows that it is willing to consider the approach, Resch says. Beginning in September, researchers in France, Belgium and the Netherlands plan to recruit 220 burn victims whose wounds have become infected with the common bacteria *Escherichia coli* or *Pseudomonas aeruginosa*. The patients will be given phage preparations from a company in Romainville, France, called Pherecydes Pharma, which has isolated more than 1,000 viruses from sources such as sewage or river water and screened them for the ability to kill ▶

pathogenic bacteria. To lower the chance that resistance will develop, the patients will receive a cocktail of more than a dozen phages that enter bacterial cells in different ways. If the phage treatment fails, patients will then receive standard antibiotics.

Although governments are starting to pay attention to phage therapy, pharmaceutical companies remain reluctant to get on board, Young says. Because phage therapy is nearly a century old, it would be difficult for a company to claim a treatment as intellectual property, and therefore recoup its costs. Young says it is likely that a 2013 ruling by the US Supreme Court against the patenting of natural genes would also apply to phages isolated from nature. Jérôme Gabard, chief executive of Pherecydes, says that the company is banking on hopes that developing and characterizing precise combinations of natural phages to target particular bacteria will be patentable.

An engineered phage could, in theory, be patented. At the ASM meeting last month, researchers led by synthetic biologist Timothy Lu at the Massachusetts Institute of Technology in Cambridge presented work on a phage engineered to use a DNA-editing system called CRISPR to kill only antibiotic-resistant bacteria. The phage injects the bacterium with DNA, which the microbe transcribes into RNA. If part of the bacterium's antibiotic-resistance gene matches that RNA sequence, an enzyme called Cas9 cuts up the cell's DNA, killing it.

In initial trials, the researchers found that their phage could kill more than 99% of the *E. coli* cells that contained specific antibiotic-resistance gene sequences, whereas it left susceptible cells alone. Giving the phage to waxworm larvae infected with resistant *E. coli* increased the worms' chance of survival. The researchers are now starting to test the system in mice (human trials are a long way off).

Gabard does not expect that phage therapy will ever replace antibiotics. But he says that he can envisage regulatory agencies approving it for patients in whom drug treatments have failed. And some people with antibiotic-resistant infections are taking matters into their own hands. Kutateladze says that an increasing number of EU patients are travelling to Georgia for phage treatment. She adds that doctors in some EU countries send patients' samples to the Eliava Institute, which then sends back a phage cocktail specific to the bacterium causing the infection. "When there's no hope, you'll do anything," Schmidt says.

Meanwhile, researchers are watching the Phagoburn study with interest, hoping that it will lay the groundwork for moving the technology into the clinic. "We just need one really great success for the field to really open up," says Lu. ■

Sections of Mongolian grassland will undergo climate-manipulation analysis at the Duolun research centre.

SHIQIANG WAN

GLOBAL WARMING

Land models put to climate test

Study under way on Mongolian steppes aims to improve knowledge of warming effects on vegetation.

BY JANE QIU

Shiqiang Wan remembers his first experience of a major sandstorm more than a decade ago in Inner Mongolia. "It was like sands being dumped on me by a gigantic dustbin," he says. "I couldn't see anything just a few metres away." Decades of overgrazing were turning the region into desert.

Grassland is now developing there again after strict grazing limits were imposed on the autonomous region by China in 2000. But Wan, an ecologist at Henan University in Kaifeng, worries that another, more challenging, menace will eat away at vegetation there and elsewhere: climate change. And if grasslands wither on a global scale, "it would not only cause widespread desertification, but accelerate climate warming by increasing carbon dioxide levels in the air", he says.

Yet scientists know little about the effects of climate change on land ecosystems, or how they will affect atmospheric CO_2.

Wan and his colleagues have an ambitious plan for filling that information vacuum. In a US$260,000 operation, they have cut 54 6-tonne chunks of soil — 2.2 metres by 1.5 metres, by 1.2 metres deep — from three types of grassland in the Mongolian Plateau, and are now growing them at the