

The Australian

Vital viruses in battle against bacteria

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- From: **The Australian**
- July 24, 2010 12:00AM

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IN a laboratory in a nondescript industrial building in Sydney, Sandra Morales pulls a small tray of plastic vials from a refrigerator.

She holds the containers, capped with yellow lids, up to the light. Each is filled with a few millilitres of liquid, some clear, some tinged brown.

Swimming in the liquid, invisible to the naked eye, are hundreds of billions of remarkable viruses that Morales and her colleagues have collected from around the country. "We get them from sewage plants, from lagoons, hospitals, battery farms. They are everywhere," she says.

These viruses, unlike HIV, influenza or herpes simplex, are not harmful to humans, she explains. Just the opposite. These viruses, known as bacteriophages or simply phages, infect and kill bacteria. Scientists like Morales hope they'll soon be important allies in the global fight against antibiotic-resistant bacteria.

Antibiotics have saved countless lives since doctors first began using them in the early decades of the 20th century. But widespread use and misuse have resulted in many bacteria strains becoming resistant to their effects. Increasingly, doctors are finding patients infected with bacteria for which there are no effective treatments.

The problem has become so acute that in November last year the Infectious Disease Society of America sent a letter to the presidents of the US and the European Union, warning that antibiotic-resistance was among the world's greatest health threats.

This is where some scientists hope bacteriophages will come in. These natural predators of bacteria are among the most abundant life forms on the planet. This month, for example, US and Australian researchers reported that the 10 trillion bacteria normally inhabiting our gastrointestinal tract are accompanied by roughly 10 times more bacteriophages that affect bacterial numbers and behaviour. (Nature 2010: 466; 334-340.)

"It makes sense that nature has a way of balancing all these things," says microbiologist Tony Smithyman, founder of Special Phage Services, the small company where Morales works.

The only Australian firm working in the field, SPS plans the first Australian clinical trial using bacteriophages to treat human infections. "We have set out to produce phage therapy products for a range of bacterial infections, usually to treat antibiotic-resistant infections in humans, but also for infections in animals, plants and fish," explains Smithyman.

The clinical trial, expected to take place this year at Westmead Hospital, will involve pre-treating a group of elective surgery patients with bacteriophages targeted to methicillin-resistant *Staphylococcus aureus* (MRSA) before they're admitted.

Potentially fatal, MRSA is among the worst bacterial problems facing hospitals worldwide. But Morales and the other scientists in Smithyman's company have isolated a "panel of bacteriophages" that specifically targets and kills the bug.

Bacteriophages were first discovered in 1915 by British bacteriologist Frederick Twort, and independently two years later by Canadian Felix d'Herelle, while at the Pasteur Institute in Paris.

D'Herelle's breakthrough came while he was investigating an outbreak of dysentery in Paris. He discovered that a particular filtered fluid could kill cultures of dysentery bacteria. "In a flash I had understood: what caused my clear spots was in fact an invisible microbe . . . a virus parasitic on bacteria," he wrote. Within two years, he'd figured out how these viruses operate and applied them to human therapy, curing an 11-year-old boy of dysentery overnight. For the next 20 years, interest in phage therapy spread quickly and the approach was used with varying degrees of success to treat a range of bacterial infections, even though microscopes of the time weren't powerful enough to see them.

That ignorance about bacteriophage biology meant the approach was somewhat hit-and-miss. "They had some spectacular results, but also had some spectacular failures," says Smithyman.

Lacking any means of seeing the viruses, scientists couldn't even agree on whether bacteriophages were viruses or enzymes, a type of protein. These issues, combined with the arrival of powerful and commercially manufactured antibiotics during World War II, saw phage therapy drift into obscurity.

The phage therapy flame was kept alight only in the countries of the former Soviet Union, particularly Georgia, where an institute devoted to phage therapy had been founded in 1923 by d'Herelle and the Georgian microbiologist George Eliava.

Since then the Eliava Institute of Bacteriophage, Microbiology and Virology has produced liquid and tablet bacteriophage preparations used routinely throughout the former Soviet Union.

"We never stopped using bacteriophages as a therapy," explains Nina Chanishvili, head of the institute's Laboratory for Genetics of Micro-organisms. "At the moment, we use them for a variety of bacterial infections such as wound infections, surgery, eye infections, intestinal disorders and so on. It's an everyday therapy," says Chanishvili, a speaker at the recent Genetics of Industrial Micro-organisms symposium in Melbourne.

For many years after the formation of the Soviet Union, the institute survived on a shoe-string, Chanishvili says, getting by on annual funding of about \$10,000. Now, European Union funding has boosted this to \$200,000 a year.

Recently, as antibiotic resistance has grown, another centre has opened in the Georgian capital, Tbilisi. It offers treatment to medical tourists from other countries who want to try phage therapy for conditions such as diabetic foot ulcers, urinary infections and sinusitis.

Beyond Georgia, interest in phage therapy was reignited in the 1990s. Since then, initial scepticism about whether the technique could find a place in Western medicine has been replaced by enthusiasm as evidence from the first few clinical trials has become public.

In August last year, for instance, clinicians from the Royal National Throat, Nose and Ear Hospital in London reported that bacteriophages effectively treated drug-resistant chronic ear infections in a small study of 24 patients. (*Clin Otolaryngol* 2009;34:349-357.)

Another trial is now under way at a military hospital in Brussels, where doctors are using a cocktail of bacteriophages to treat burns patients for infections with the bacteria *Pseudomonas aeruginosa* and *Staphylococcus aureus*. (*PloS One* 2009; 4:e4944). Yet another study has begun in Poland, where doctors are using bacteriophages to treat therapy-resistant chronic bacterial infections.

This second wave of phage therapy has seen more than a dozen small companies start up around the world, seeking to commercialise bacteriophage products to treat a range of conditions, or to prevent infections in the first place.

According to Smithyman, it's a process that's already begun, with some phage products already approved by the theaustralian.com.au/.../story-e6frg8y6...

regulatory authorities in Europe and America for treating listeria contamination in food. "Some brands of cheeses and processed meats are already coming on to the market containing phages," he says.

These developments are promising, but there are still substantial regulatory hurdles to jump before companies like Special Phage Services can start selling phage products for treating human diseases in Australia. Still, Smithyman suspects the barriers could be surmounted quickly.

"You can see that the first products are going to be on the market shortly for therapy in humans and animals," he says.

One reason for Smithyman's optimism is the well-established safety of phages. Every day, each of us consumes innumerable phages without any harm, he notes. This is because each phage will only infect specific bacterial species.

Conversely, this specificity is also one of the weaknesses of bacteriophages. Because they lack the broad-spectrum effects of antibiotics, each phage is effective only against a particular bug.

That's why Smithyman envisages two main approaches to phage therapy: pre-formulated combinations of phages designed to work against several common pathogens, and specific phages targeted to a patient's particular infection.

Although bacteria can develop resistance to phages just as they do to antibiotics, Chanishvili says finding a new phage to combat that resistant strain can be done in a matter of weeks, rather than the years it might take to develop a new antibiotic.

Regardless, Smithyman and Chanishvili both take pains to explain that phage therapy isn't a panacea for all infections, nor will it replace antibiotics. "It is going to be a very powerful additional tool to antibiotics," Smithyman claims.

"What we think is going to happen is that when you go into hospital with an infection, the infection will be tested very quickly for antibiotic resistance and for susceptibility to bacteriophages, so clinicians will be able to chose the phage combination and antibiotic combination and see how they go."

And things could go very quickly, Smithyman predicts: "I'd say that we will see the first phage therapy treatment products on the market within two to three years".

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