SUPERBUG SUPER-WARRIOR

Professor Jian Li is on a mission: to stop the "carnage" caused by bacterial superbugs.

Story **Linda Vergnani**
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In the war that Professor Jian Li is fighting, the enemies are tiny, smart creatures that kill about 700,000 people around the world each year. They're among the so-called 'superbugs' – bacteria that have become increasingly resistant to antibiotics.

By 2050, drug-resistant infections could kill an additional 10 million people a year, according to the recent Review on Antimicrobial Resistance commissioned by former British prime minister David Cameron.

Professor Li and his team are working to optimise the use of existing antibiotics and develop new drugs to deal with this urgent global medical challenge. Professor Li, head of the Laboratory of Antimicrobial Systems Pharmacology at the Monash Biomedicine Discovery Institute (BDI) and Monash Institute of Pharmaceutical Sciences (MIPS), says antibiotic resistance is causing "global carnage". Many victims die of common and once readily treatable diseases, such as pneumonia, blood or urinary tract infections. "You can't do major surgery or chemotherapy without antibiotics, because the patient basically dies afterwards with infections."

His particular target is Gram-negative superbugs, and his weapon of choice is the class of antibiotics known as polymyxins. He says polymyxins were almost abandoned in the 1980s because they're potentially toxic to kidneys (nephrotoxic) and the nervous system. Now, two types of polymyxin, colistin and polymyxin B, are used as a last line of defence against Gram-negative pathogens that are resistant to all other antibiotics.

Professor Li explains that Gram-negative bacteria are generally harder to kill than Gram-positive bacteria because they're protected by 'double' membranes. However, polymyxins can penetrate this barrier and destroy the bacteria.

Working in collaboration with clinicians and pharmacologists in Brazil and the US, his team developed the first scientifically based dosing recommendation for polymyxin B, making it safer to use. He's also a key member of the team that developed dosing recommendations for colistin (polymyxin E).

He says many hospitals around the world use the results. "Our research has changed clinical practice worldwide." He's often asked for help by doctors who are desperate to find the right dose or combination of antibiotics to treat particular patients. "We are not a service lab, but we always endeavour to help clinicians."

What motivates him is the scope and reach of his work. "My research can potentially save millions of people's lives, and clinicians badly need the pharmacological information for their patients."

Funded by the National Institutes of Health (NIH) in the US, his team is also developing polymyxins that are much less nephrotoxic and more effective against Gram-negative superbugs.

Because pharmaceutical companies spent less than 5 per cent of venture capital on new antibiotic research between 2003 and 2013, the Review on Antimicrobial Resistance recommended 'market entry awards' of around US$1 billion each as an incentive for successful developers of new antibiotics. ➔

MASTER MIND

A prolific researcher, Professor Jian Li has been recognised internationally for his work on how bacteria develop resistance to the class of antibiotics known as polymyxins. He's a Thomson Reuters 2015 Highly Cited Researcher and is listed in its 2015 World's Most Influential Scientific Minds. Li and his team are making polymyxins more effective using modern dosing science. They're also researching how to best use polymyxins in combination with other antibiotics to combat superbugs.

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As Professor Li says: "Almost all big pharma have left antibiotic discovery because the development of new antibiotics doesn't give them a good return on investment. Even before new antibiotics become available in the clinic, resistance may have already happened."

Making the leap

Stepping into the gap, Professor Li's 25-member group recently made a breakthrough in new polymyxins. This research is funded by a five-year biodefence grant from the NIH. Under the grant, Monash University has subcontracted a US company, Rempex Pharmaceuticals, to test the new drugs in animals. This reverses the usual arrangement where pharmaceutical companies lead drug development and contract work out to academic groups.

Professor Li is proud of the discovery, saying it's arguably one of the best examples of an academic group using basic research and applying it to develop a drug.

The funding is among seven grants totalling about US$24.4 million that his team has received from the NIH over the past 10 years. Two of his NIH-funded projects were highlighted as an example of US–Australia innovation and science cooperation by President Barack Obama's office in 2014. Professor Li has also received grants of about A$8.6 million from Australia's National Health and Medical Research Council (NHMRC) and other funding bodies.

Professor Robert Bonomo, an expert on antibiotic resistance and professor of pharmacology at Case Western University in Ohio, says Professor Li has led the way in the understanding of the pharmacology and effectiveness of polymyxins: "His work not only provided invaluable insights into the mechanism of action and resistance, but how to administer these antibiotics to save lives.

"His most recent efforts here have shed very important light on how to use these drugs in combination to avoid resistance. The impact of these findings cannot be underestimated as clinicians struggle to wage war against these superbugs."

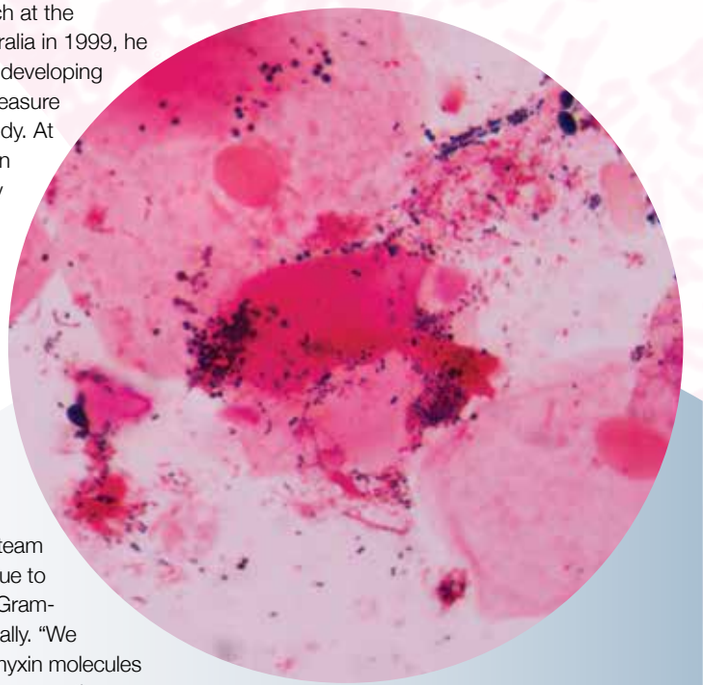
Keeping a tradition alive

It was partly Professor Li's experience of a painful gum infection while doing his postdoctoral research that kindled his interest in the power of antibiotics. "After I went to the doctor and took the right antibiotic, it cured the infection within hours." He was amazed at the speed with which the right antibiotic worked.

Born into a family of scientists in China's Shandong province, his interest in microbiology was sparked by an uncle who was a microbiologist, and through the story of penicillin's discovery by Sir Howard Florey, Sir Ernst Boris Chain and Sir Alexander Fleming.

After being awarded a scholarship to carry out PhD research at the University of South Australia in 1999, he focused on polymyxins, developing analytical methods to measure concentrations in the body. At the time, little was known about the pharmacology of these "fascinating" antibiotics. He thought: "If we still don't know how to use them, we'll lose this important class of antibiotics as resistance can develop. With my polymyxin research, we can potentially save millions of lives."

Professor Li and his team are racing against time due to the alarming increase in Gram-negative superbugs globally. "We need to modify the polymyxin molecules to make them safer and more active against drug-resistant pathogens." But this, he warns, is a "very tough job". **M**



ELIMINATE THE NEGATIVE

Bacteria is categorised as either Gram-negative or positive depending on whether it retains dye through a 'Gram staining' procedure – a technique developed by Hans Christian Gram in 1884. Gram-negative bacteria lose the colour of the stain and have an outer membrane absent in Gram-positive bacteria, are more resistant to antibiotics, and include many disease-causing species.

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Above left Professor Jian Li.
Photo Paul Philipson, Monash University
Above top Bacterium Gram staining.
Photo Chirawan Somsanuk