IMPROVING 'LAST RESORT' ANTIBIOTICS

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Antibiotic resistance has been identified by the World Health Organization (WHO) as one of the greatest threats facing human health globally. In a world without effective antibiotics, modern medical procedures that we take for granted, such as chemotherapy or simple surgery, will become too dangerous or simply impossible to undertake, due to the threat of untreatable bacterial infections.

Then there is the economic burden on society. In the United States alone, it is estimated that antimicrobial resistance costs the economy $20–35 billion annually in excess direct healthcare costs, and an additional $35 billion per year due to lost productivity. This issue has been further compounded by the lack of development of new antibiotic drugs by the pharmaceutical industry.

This situation is particularly dire for multi-drug-resistant (MDR) gram-negative pathogens such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Klebsiella pneumoniae*, which are spread worldwide in virtually all environments that support life. These opportunistic pathogens have a range of serious consequences for infected patients, including secondary meningitis, respiratory problems and ventilator-associated pneumonia.

There are currently very limited options available for the treatment of infections caused by MDR gram-negative 'superbugs'. This has forced clinicians to revive 'old' antibiotics, such as the polymyxins. These peptide-based antibiotics were first discovered in 1946 in soil samples from a market garden in Surry, England. Despite their fantastic activity against gram-negative bacteria, effective use of these antibiotics is limited by their potential to cause kidney toxicity in patients. For many years, they were not used in the clinic due to the availability of safer antibiotics. This situation changed in the 1990s with the emergence of MDR gram-negative superbugs.

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The polymyxins (polymyxin B and colistin) are now increasingly used as a 'last resort' treatment for these MDR gram-negative pathogens. Their toxicity issues still remain, and delivering a smaller, suboptimal dosage does not present a viable solution, as this will decrease efficacy and potentially promote resistance to the polymyxins. There is an urgent need to develop new polymyxins that have improved safety and efficacy.

Today, academic research groups and small biotechs, with the help of government financial support, are leading the way in the race to discover and develop new antibiotic drugs. To this end, our research group at Monash University is currently leading a US National Institutes of Health–funded drug discovery program, which aims to produce novel, safer polymyxins over the currently available polymyxin antibiotics. This program is based on intellectual property developed by Monash University, and is being carried out in collaboration with an American biotech company.

The progress of our drug discovery program is quite exciting. Our team has identified novel structure-toxicity relationships, which has allowed us to design some really promising novel polymyxins that have significantly improved safety in animal models, while maintaining efficacy. Over the next 12 months, our lead compound and a back-up compound will undergo IND-enabling evaluation. If successful, it will then move into phase I clinical trials. When the polymyxins were first discovered in the 1940s, they were not subjected to contemporary drug development procedures. If they had been, they would not have made it past the pre-clinical stage of development.

Kade Roberts will be speaking at the 17th International Biotechnology Symposium (IBS 2016).