Unearthing novel antibiotics to deal with the rise of superbugs

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As doctors globally are warned that overconsumption of antibiotics has led to resistance to the drug – medical researchers are equally focussed on finding alternatives to treatments for bacterial infections, particularly with the rise of 'superbugs' such as multi-drug resistant Staphylococcus aureus (MRSA), which are resistant to current drugs.

Associate Professor Max Cryle, from the Monash Biomedicine Discovery Institute, is one such researcher. However his approach to finding new antibiotics is not so much about discovering new drugs – but rather by studying antibiotics already existing in nature and working out how to recreate their chemistry in the lab.

Professor Cryle uses as a starting point harmless bacteria that are common in soil and are already exploited to produce the vancomycin-type antibiotics commercially. By altering the natural production line that produces these antibiotics novel forms of these drugs can be created. Importantly he and his team have worked out how enzymes within these bacteria manufacture vancomycin-type antibiotics, allowing for the process to be done on a large scale in the laboratory. His research was published today in the *Journal of the American Chemical Society*.

"Once we know how these enzymes work, we can re-engineer these helpful 'safe' bacteria to create antibiotics that we can then use against harmful bacteria such as MRSA," Professor Cryle said.

He adds that it is important to know how these enzymes work – in

creating new antibiotics – so that the process can be mimicked in the lab.

"In an efficient way – we need to be able to make these compounds at scale so we can eventually use them in the clinic," he said.

A crucial part of the puzzle is to create novel antibiotics from the ground up in the way that the vancomycin-type antibiotics are formed naturally. "These antibiotics are made of a peptide backbone that starts out as something very floppy. We have – by understanding how the natural systems work - developed a way to take these peptides and internally crosslink them so that they become very rigid," he said.

"It is this rigidity that is crucial when creating a drug that needs to bind to bacterial cell walls in order to kill them."

Professor Cryle and his team from both the Monash Biomedicine Discovery Institute and the European Molecular Biology Laboratory Australia (EMBL Australia) in Melbourne now have an ongoing program to decipher the enzyme processes involved in creating the vancomycin-type antibiotics, recreate these antibiotics in a chemical form that can actively kill dangerous bacteria and do it in such as way that the whole process – when it identifies good drug candidates – can be repeated and used to make the novel drugs at scale.

"Our system allows us to develop a very focused pipeline of relevant compounds and turn them into novel antibiotics for clinical use," he said.

More information: Madeleine Peschke et al. Regulation of the P450 Oxygenation Cascade Involved in Glycopeptide Antibiotic Biosynthesis, *Journal of the American Chemical Society* (2016). DOI: 10.1021/jacs.6b00307

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