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New drugs from mutant bugs

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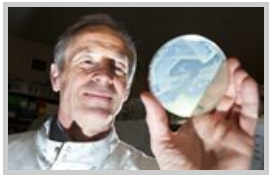

Professor Chris Thomas

Scientists from the Universities of Birmingham and Bristol have discovered how marine bacteria join together two antibiotics they make independently to produce a potent chemical that can kill drug-resistant strains of the MRSA superbug.

Working with Japanese pharmaceutical company Daiichi-Sankyo, and funded by the UK Biotechnology and Biological Sciences Research Council (BBSRC), the researchers' work paves the way for the creation of new hybrid antibiotics that may help to solve the growing problem of bacterial infections that are resistant to essentially all antibiotics.

The research is published online in the journal PLoS ONE.

The team, comprising microbial geneticists from Birmingham and chemists from Bristol, determined the sequence of the complete DNA content of the marine bacterium that produces the new antibiotic, thiomarinol, owned by Daiichi-Sankyo. They then identified the genes responsible for making the antibiotic on the basis of their similarity to genes that make the related but less potent antibiotic, mupirocin, which is currently used to combat MRSA (methicillin resistant Staphylococcus aureus).

They found the genes are on a relatively small, separate DNA molecule called a plasmid, which is just big enough to carry the genes for making the antibiotic plus genes to allow the plasmid to replicate autonomously in the bacterium. The plasmid thus carries genes that make both the mupirocin-like antibiotic as well a second antibiotic, holomycin, and a gene responsible for joining both antibiotics together, forming a more potent molecule.

Tests showed that by joining the antibiotics together the resulting chemical is able to inhibit the growth of MRSA strains that have become resistant to mupirocin. 'This shows how mupirocin can be modified to make it more potent and suggests that related molecules could be used against the increasingly problematic Enterobacteriacae like Escherichia coli and Klebsiella pneumoniae,' says University of Birmingham research lead Professor Chris Thomas.

By using mutant strains that were unable to make either the mupirocin part or the holomycin part the team was able to feed alternative compounds to the bacteria – so-called mutasynthesis - so that a family of novel molecules was created, and tests showed some of these had biological activity. 'This provides hope that the system will allow the production of new antibiotics that may help to combat the growing problem of antibiotic resistance in pathogenic bacteria,' adds University of Bristol research lead Professor Tom Simpson.

For more information or to arrange an interview with Professor Chris Thomas, please contact Jenni Ameghino, Press Office, University of Birmingham, 0121 415 8134.

Notes to Editors

- A Natural Plasmid Uniquely Encodes Two Biosynthetic Pathways Creating a Potent Anti-MRSA Antibiotic is published in PLoS ONE. It is available online at **http://dx.plos.org/10.1371/journal.pone.0018031 (http://dx.plos.org/10.1371/journal.pone.0018031)** . The detailed chemical analysis was recently published in Angewandte Chemie International Edition at **http://dx.doi.org/10.1002/anie.201007029 (http://dx.doi.org/10.1002/anie.201007029)** (Novel Thiomarinol Antibiotics Active Against MRSA are Generated by Mutagenesis and Mutasynthesis of Pseudoalteromonas SANK73390, by Professor Thomas Simpson, Dr Annabel Murphy, Dr Daisuke Fukuda, Dr Zhonshu Song, Dr Joanne Hothersall, Professor Russell J Cox, Professor Christine L Willis and Professor Christopher M Thomas.
- For comments on the genetics aspect of this research please contact Professor Chris Thomas (**c.m.thomas@bham.ac.uk (mailto:c.m.thomas@bham.ac.uk)**). For comments on the chemistry aspect of this research please contact Professor Tom Simpson FRS (**tom.simpson@bristol.ac.uk (mailto:tom.simpson@bristol.ac.uk)**).
- The BBSRC grants that funded this work included a contribution from the Engineering and Physical Sciences Research Council (EPSRC) and this support has recently been renewed with a joint grant of £1 million to cover the next three years.

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