Rapid Identification of Superbugs and New Drugs to Combat Them

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Synthetic biology is playing a key role in creating new tools for rapid detection of potentially fatal bacterial infections such as E. coli and allowing scientists to create novel molecules that may provide new antibiotics to tackle the problems of multiply-resistant strains.

Prof Chris Thomas and Dr Tim Dafforn from the University of Birmingham are part of a growing number of scientists worldwide searching for effective ways to deal with increasingly problematic superbugs. A critical stage in dealing with infection is identifying what the bacterium is that is causing the problem.

Tim Dafforn is an expert on biophysical spectroscopy and, more specifically, a spectroscopic technique that detects molecules when they line up in solution if you stir it – just like when you stir a bowl of spaghetti.

“We realised that we could detect long, thin virus particles easily with this method, but that when they attach to a bacterium, that signal disappears,” explains Tim, Director of Knowledge Transfer in the College of Life and Environmental Sciences.

The group went on to engineer the viruses to attach to specific sorts of bacteria and then showed that their machine could detect those bacteria more rapidly than any other procedure on the market.

“This provides the basis for creating almost instantaneous diagnosis of what is causing an infection and what will be the best way to treat it,” continues Tim. “However, a lot of work is still needed to turn it into a routine procedure that will be found in every doctor’s surgery.”
Once diagnosis is clear, there will still be the need to combat resistant bacteria. Chris Thomas’s work aims to create new hybrid antibiotics from mutant molecules that are significantly more potent than the drugs currently available.

“We have made progress on MRSA – having discovered how marine bacteria join together two antibiotics they make independently to produce a potent chemical that can kill drug-resistant strains of MRSA,” explains Chris, Professor of Molecular Genetics.
“One high priority now is to use this principle to generate families of new hybrids that can be tested against MRSA but also things like E.coli and Klebsiella pneumoniae, because that’s where there is currently the greatest need.”

“We mustn’t be complacent about MRSA, as it might become a really worrying problem again, but we need always to be developing new antibiotics – the time to be developing them isn’t when there’s a crisis.”

Using synthetic biology, Chris is working alongside chemists from Bristol University and pharmaceutical scientists in Japan to understand the assembly lines that build up micro-organisms such as fungi and bacteria that are used to make antibiotics.

“If we can understand the assembly line, which is quite complex, then we can manipulate it,” says Chris. “If we know what the rules are, we can control it and change it to ensure it’s doing what we want it to do rather than what the bugs want it to do.”

One way to exploit this understanding is “mutasynthesis”, which means taking a mutant bug that is defective in making part of the antibiotic – making it less effective in treating infections – and giving it altered versions of that part.

In conjunction with this, the scientists have discovered how two antibiotics – individually ineffective against certain resistant strains of MRSA – can be joined together to produce a potent chemical that can combat some strains of the superbug.

The research started with studies on the pathway that leads to the antibiotic mupirocin, to which MRSA is becoming resistant. But by extending the research to a marine bacterium that makes the antibiotic thiomarinol, they discovered they could also make mupirocin more potent by joining it to another antibiotic, holomycin.

Now the teams in Birmingham and Bristol have found that mupirocin can be manipulated by using mutant strains that were unable to make either the mupirocin part or the holomycin part, but when fed alternative, lookalike compounds made a successful hybrid.

“We’re working on how to exploit that idea to generate families of new hybrids that will be screened for novel antibiotic activity,” explains Chris. “It’s synthetic because we’re creating the blueprint: we’re reprogramming the genes so that they make a new factory. We’re creating new pathways and assembly lines to make new molecules.”

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• Detection of Pathogenic Bacteria Using a Homogeneous Immunoassay Based on Shear Alignment of Virus Particles and Linear Dichroism (2012) Raul Pacheco-Gomez, Julia Kraemer, Susan Stokoe, Hannah J. England, Charles W. Penn, Emma Stanley, Alison Rodger, John Ward, Matthew R. Hicks and Timothy R. Dafforn. Analytical Chemistry 84, 91–97.
• Murphy, A.C., Fukuda, D., Song, Z., Hothersall, J., Cox, R.J., Willis, C.L., Thomas. C.M. and Simpson, T.J. (2011) Novel Thiomarinol antibiotics active against MRSA are generated by mutagenesis and mutasynthesis of Pseudoalteromonas SANK73390. Angewandte Chemie International Edition 50, 3271–3274.
• Fukuda, D., Haines, A.S., Song, Z., Murphy, A., Hothersall, J., Stephens, E.R., Cox, R., Crosby, J., Willis, C., Simpson, T.J., Thomas, C.M. (2011) A natural plasmid uniquely encodes two antibiotic pathways creating a potent hybrid. PLoS ONE 6, e0018031.

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