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Editorial overview: Antimicrobials: Tackling AMR in the 21st century

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Matt Hutchings is Professor of Molecular Microbiology at UEA in Norwich. His work focusses on antibiotic producing actinomycete bacteria like *Streptomyces* species and their interactions with plants and insects and other microbes in their soil environment. He is interested in identifying the environmental signals which activate the production of antibiotics and other secondary metabolites and also understanding their functions in nature.

Andrew W Truman

Andy Truman is a Group Leader at the John Innes Centre (JIC) in Norwich, where he began his independent research career in 2013. He uses genomics to guide the discovery of new natural products from Actinobacteria, with a major focus on ribosomally synthesised and post-translationally modified peptides. His group aim to understand the biosynthesis, engineering and natural function of these natural products.

In just over 100 years, the introduction and use of antibiotics is estimated to have increased average human life expectancy by around 23 years and made possible previously unthinkable medical procedures, including organ transplantation. Unfortunately, these medical advances are put at risk by the inexorable rise of antimicrobial resistance (AMR), whereby pathogenic bacteria and fungi become resistant to the drugs normally used to eradicate them or prevent them infecting a patient undergoing surgery. This issue of *Current Opinion in Microbiology* provides an overview of AMR and the strategies that scientists and clinicians are using to combat this dire threat to modern medicine. These include the development and use of rapid diagnostics to more accurately treat infectious disease, alternatives to antibiotics such as bacteriophage therapy, computational and structure-led synthetic approaches, as well as new strategies to discover natural product antimicrobials from microbes that encode many more bioactive natural products than they make when cultured in the laboratory.

Our own article in this issue gives a brief overview of the history of antibiotics, a summary of the current state of play with regards to the development of new therapeutics and our personal perspective on the prospects for future antimicrobial drug discovery. Lucy Foulston explains the field of genome mining, which uses bioinformatic methods to predict biosynthetic gene clusters (BGCs) that encode the biosynthesis of novel bioactive metabolites in bacterial and fungal genomes. Many of these BGCs are not expressed under standard laboratory growth conditions and the signals and signalling pathways that induce their expression are not known. Marie Elliot *et al.* explain how co-culture, elicitor screening and the use of genetics to rewire the regulation of BGCs can activate these pathways and lead to the discovery of new chemical scaffolds. The latter approach, which is also known as refactoring, has been accelerated by synthetic biology and the development of CRISPR/Cas-mediated genome editing for antibiotic-producing strains. Olga Genilloud describes the highly integrated approach that industry is taking to the discovery of new natural product antibiotics including the power of targeted whole cell and phenotypic screening approaches. She also highlights the importance of advances made in analytical and computational chemistry, and in our understanding of natural products biosynthesis, for the discovery process.

Lorena Fernández-Martínez and Paul Hoskisson hypothesise that limitations in primary metabolism might explain why bacteria and fungi can only make around 10% of their encoded specialised metabolites at any given time, and why the remainder of their BGCs are cryptic. It is possible that

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reprogramming or expanding primary metabolic capabilities of individual strains could increase the numbers of specialised metabolites they make. Paul Straight and Chengxi Zhang focus on a more naturalist approach for the activation of cryptic BGCs, which is to understand and exploit the ecology of the producing microorganisms to activate these pathways and unlock their chemistry. They discuss work carried out on microbial interactions which, arguably, is why these natural product antimicrobials have evolved. Studying these interactions not only reveals fascinating biology and chemical ecology but can also lead to the discovery of new and useful natural products. Fungi are also prolific producers of specialised metabolites. In their review, Claudio Greco, Nancy Keller and Antonis Rokas describe how genome mining combined with heterologous expression can be used to discover new and useful molecules from these microbes.

Although there are hundreds of thousands of cryptic specialised metabolite BGCs in sequenced microbial genomes, it is possible that the antibiotic scaffolds we have discovered thus far could represent the majority of scaffolds that exist. In other words, even if we successfully mine genomes and activate cryptic BGCs, there may be an inherent lack of chemical diversity left to discover. This would mean switching to synthetic biology to generate new-to-nature scaffolds. Marcelo Der Torossian Torres and Cesar de la Fuente-Nunez describe how computational-led synthetic biology can be used to generate semi-synthetic scaffolds that could be used to target specific drug-resistant bacterial pathogens. Barrie Wilkinson and Kenan Bozhüyük postulate that insights gained from structural biology combined with synthetic biology also has great promise for the engineering of the mega enzyme complexes (polyketide synthases and non-ribosomal peptide synthetases) that produce known scaffolds, and that this could generate new chemical diversity and lead to new anti-infectives.

Despite all these technological advances to enable drug discovery, the fact remains that resistance is inevitable. Gerry Wright outlines the concept of the antibiotic resistome, which is the collection of all antimicrobial resistance genes (ARGs) in a given environment. He highlights that ARGs are as ancient as antibiotics, and that antibiotic-producing bacteria must carry ARGs to protect themselves against their neighbours and their own antibiotics. These ARGs spread from producers to pathogens under the selective pressure provided by antibiotic therapy. Although, as he points out in his article, not all ARGs are equal when it comes to mobilisation. Steven Dunn, Christopher Connor and Alan McNally write about the spread of multidrug resistant (MDR) *Escherichia coli* and *Klebsiella pneumoniae* around the globe, with most clinical isolates now carrying MDR genes on plasmids that are spread and acquired without significant fitness costs.

These articles tell us that however carefully we use the next generation of antibiotics, there will always be a need to develop new drugs and come up with new anti-infective strategies that do not just rely on targeting a single essential process in a bacteria cell. Such strategies may include phage therapy, which involves targeting a bacterial infection with a bacterial-specific virus (bacteriophage) that infects and kills a very narrow spectrum of related bacterial strains. This therapy has been used in Georgia for more than 100 years. Anca Segall, Dwayne Roach and Steffanie Strathdee provide a brief history of phage therapy and an overview of recent efforts to use phage therapy to treat disease, sometimes in combination with traditional antibiotics. Strathdee herself used a phage cocktail to save the life of her husband who had a systemic MDR infection in what appears to be a first in US healthcare.

Phage treatment relies on identifying the infectious agent and to do this in a short appointment with a physician requires rapid diagnostics. This issue is completed by a description of recent research in this area is covered by Alexander Trotter, Alp Aydin, Michael Strinden and Justin O'Grady, who review the latest technologies and advances. One major advantage of knowing the exact cause of an infection is the ability to prescribe a narrow-spectrum antibiotic or phage that will not damage the patient's natural microbiota.