Antibiotic discovery goes underground

The discovery of teixobactin could revitalise the search for new antibiotics based on the novel method the researchers used to identify the compound

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In January this year, a research article in *Nature* made headlines in the major media. It described a new antibiotic compound that efficiently kills gram-positive bacteria [1], including methicillin-resistant *Staphylococcus aureus*, *Mycobacterium tuberculosis* and *Clostridium difficile*. Given the increasing problem of antibiotic resistance among pathogenic bacteria and the fact that the new antibiotic, named teixobactin, did not seem to elicit resistance among its targets, the intense media coverage was inevitable. Yet, the real innovative breakthrough was not the discovery of teixobactin itself but how the researchers—scientists from four academic institutions and two pharmaceutical companies in the USA and Germany—discovered the compound.

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Indeed, while the initial enthusiasm about teixobactin subsided, partly because it is not efficient against gram-negative bacteria, such as *E. coli* and *Salmonella*, there has been growing interest in the detection method. The technique, based on the so-called iChip, was developed by Kim Lewis and Slava Epstein at Northeastern University in Boston, MA, USA, to overcome the prevalent problem that the vast majority of bacteria from natural environments cannot be cultivated in the laboratory [2]. The chip comprises almost 400 miniature diffusion chambers that allow the flow of nutrients and

waste products through a semi-permeable membrane while retaining bacterial cells. The researchers harvested bacteria from soil samples and sorted them into separate chambers. The intriguing step was that instead of trying to grow them on artificial medium, the device was just put back into the ground, the theory being that this gives the bacteria a more natural environment in which to develop. Using the iChip, the research team was able to grow and cultivate about 50% of the soil bacterial species investigated, compared with only 1% under laboratory conditions. This enabled the subsequent discovery of teixobactin from the previously uncultured bacterium *Eleftheria terrae* and other compounds by screening the resulting bacterial cultures.

“The benefits of teixobactin are two-fold”, said Lewis. “Firstly it’s a good validator for our discovery platform showing there’s an untapped source of metabolites. The other benefit is in the compound itself, with the most remarkable and unanticipated aspect being that no resistance has evolved to it”. Indeed, teixobactin works outside the cell by binding to several molecules of the bacterial cell wall, which makes it harder for bacteria to overcome its action by the usual antibiotic resistance mechanisms: efflux pumps that expunge toxic compounds, modification of surface molecules, chemical inactivation of the antibiotic and decreased permeability of the cell membrane to prevent toxic molecules entering the cytoplasm.

Nonetheless, many researchers remain sceptical about the prospects of teixobactin being approved for treating gram-positive bacterial infections, for several reasons. “I think that it is unlikely that it will be developed”, said Laura

Piddock, Deputy Director of the Institute of Microbiology at University of Birmingham, UK. “It does not appear to have been patented, and there was a considerable amount of information in the publication. Without protected IP (Intellectual Property), it is unlikely to be licensed or purchased by Pharma and developed as a new medicine. In addition, its activity was against gram-positive bacteria and [tuberculosis]. For the former, there are several new drugs in the pipeline”. Its main possible potential, according to Piddock, would be for treating tuberculosis, providing it showed good activity against multi-drug resistant strains. Steven Projan, Head of Infectious Disease & Vaccines at MedImmune, part of the Astra-Zeneca Group, is also cautious. “I can’t really speculate on the future of another molecule, but it bears pointing out that the key unmet need clinically is for novel, potent and safe antibiotics that are active against multi-drug resistant gram-negative bacteria, such as *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, which this molecule does not address”, he said.

Yet, both Projan and Piddock acknowledge that the iChip is a significant advance for drug discovery, which can be regarded as a comeback of the traditional approach of scouring nature for anti-bacterial metabolites rather than trying to cultivate microorganisms under laboratory conditions. “Microbiology is largely dependent upon the use of artificial media often rich in nutrients not normally accessible to many bacteria”, said Christopher Dowson, Head of The Infectious Disease Research Group at Warwick University, UK. “This paper highlights this historical flaw, which needs to be addressed by the whole microbiology community for this and all other spheres of research”.

There is also a general recognition that synthetic biology based on genomics has failed so far to come up with efficient strategies to systematically develop molecules for specific bacterial target molecules. “The world’s scientists were led astray by the Genomics revolution”, commented Anthony Coates, founder of the academic network Antibiotic Discovery UK and Professor of Medical Microbiology at St George’s, University of London, UK. “They applied genomics to antibiotic discovery and failed to get any new antibiotics to market”.

Yet, this is not the only and by far not the most important reason for the failure to come up with new effective antibiotics. “The biggest problem is that bacteria have more ways to combat antibiotics than we thought, especially the drug pumps”, said Ryland Young, Director of the Centre for Phage Technology at Texas A&M University in the USA. “It turns out that the soil bacteria were fighting antibiotic molecules from fungi and sessile bacteria for a billion years, and those genes are now finding their way into pathogenic bacteria, by our constant selection and over-use of antibiotics. We thought that antibiotics would be new magic bullets, but it turns out they are old hat. We just had a brief holiday before the genes from the soil bacteria finally started showing up in enteric and other pathogens”.

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Another major factor is economics as the market for antibiotics fragments into a larger number of drugs each with a smaller target, including people suffering from a specific strain resistant to existing drugs. “Certainly marketing and commercial decisions have driven many companies away from antibacterials”, said Karen Bush, Professor of Practice in Biotechnology at Indiana University in the USA. “Companies don’t like to develop drugs that treat only a small percentage of patients, those who don’t respond to some pretty effective antibiotics

that we are already using for the rest”. One irony, as Bush noted, is that antivirals, which on balance are less successful than antibiotics since they only alleviate symptoms and sometimes reduce duration of an infection rather than effect a complete cure, are now more in favour with the pharmaceutical industry. Many antivirals were developed to treat common diseases, such as flu, the common cold and shingles, which present a big target market. This means they have a higher so-called Net Present Value, which is an economic measure of a drug’s success; with antivirals, the larger target group outweighs the relatively limited efficacy.

Another factor has been a lack of consensus over not just individual drug candidates but also which platforms are worth pursuing for future drug discovery. This has been especially evident in the case of bacteriophages, which have a sizeable constituency but also a large number of critics who consider it a blind alley. Research into phage therapy actually predates the use of antibiotics. This interest evaporated quickly in the West after the discovery of penicillin, but phage research was kept alive in the old Soviet Union and continued after its collapse in the 1990s. The long history of phage research has been used as evidence against it on the grounds that, despite all this time, it has still failed to deliver. “Phages are not the answer”, Coates said. “They have been around as a potential human medicine for as long as antibiotics but not one has become a marketed medicine in the West”.

But others believe that the potential advantages of phage therapy, notably its specificity against pathogens without affecting commensal bacteria, make it still worth pursuing. In March 2014, the US National Institute of Allergy and Infectious Diseases listed phage therapy as one of seven prongs in its plan to combat antibiotic resistance [3]. Then, in May 2014, Grégory Resch of the University of Lausanne in Switzerland presented plans for Phagoburn, the first large, multi-centre clinical trial of phage therapy for human infections, funded by the European Commission. Resch conceded that phage therapy faced challenges, primarily the need for effective diagnostic tests and a suitable protocol for clinical trials, but he argues that the specificity of phages had become a compelling advantage. “This specificity was certainly a disadvantage in

the past when it was more interesting to develop antibiotics that efficiently killed several pathogenic bacterial species without distinction”, Resch commented. “Now that we increasingly realise the importance of the commensal microbiomes and in a time where personalised medicine is growing, this aspect of specificity might be crucial”.

Yet, others believe that the biggest need is for new broad-spectrum antibiotics to treat acute, life-threatening infections when diagnostic tests cannot readily be performed in time and where the temporary impact on commensal bacteria is a minor consideration. For this reason, Coates argued that the greatest need is to revive existing antibiotics through the use of secondary drugs that target the bacterial resistance mechanisms and thus restore the original toxicity against resistant bacteria. “In my view, the only promising long-term approach is to rejuvenate life-saving antibiotics with Antibiotic Resistance Breakers”, said Coates. “These have a long and distinguished track record, starting with clavulanic acid, a beta-lactamase inhibitor which rejuvenates amoxicillin when combined into a medicine called Augmentin”. Beta-lactamases are enzymes produced by some bacteria that confer resistance against the so-called β -lactam antibiotics, such as penicillins, cephamycins and carbapenems. Coates conceded that some bacteria already produce some beta-lactamases that are resistant to clavulanic acid, “[b]ut there are Antibiotic Resistance Breakers which rejuvenate non-penicillin classes such as the aminoglycosides” [4].

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There is also some progress towards developing more specific antibiotics, particularly to treat chronic infections of longer duration where the impact on commensal microflora can have a significant impact on the patient’s health. Projan commented that this requires greater collaboration between

academia and pharmaceutical companies to develop new ways of enabling clinical trials. “I cannot speak for the pharmaceutical industry in aggregate, but I can say that MedImmune, which is the global biologics research and development arm of AstraZeneca, is committed to this area”, he said. “We are actually looking at innovative ways to advance clinical trial development in the anti-infectives field through initiatives like the Innovative Medicines Initiative (IMI)-funded New Drugs 4 Bad Bugs (ND4BB) program”. The IMI, a joint venture between the European Union and the pharmaceutical industry association EFPIA, is Europe’s largest public/private initiative with the aim of accelerating development of new therapies. “Within the ND4BB program is the COMBACTE (Combating Bacterial Resistance in Europe) consortium, which represents a unique European public/private partnership set up to promote the clinical development of new drugs in the anti-infectives field”, Projan said.

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This and other research and development programmes are addressing the increasingly urgent need to deal with antibiotic-resistant pathogens. Indeed, the problem has gained much more attention from public health experts, politicians and the media, along with activities to curtail the abuse of antibiotics and to extend the usefulness of existing ones. Notwithstanding, the identification of new antibacterials remains the first step for managing the impact of infectious diseases in the future. In this regard, the iChip by Epstein and Lewis could become an important new tool

for microbiologists and drug researchers to find new chemical weapons against bacteria in nature.

References

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