A New Future for Antibiotics?
Article by IPI Editor Cecilia Stroe

A future without antibiotics is deemed to be bleak, if bacteria continue to develop new resistance mechanisms and the pharmaceutical industry have to produce novel classes of antibiotics at the existing rate. Things may change, though. Recently, a UK-based company announced a major collaboration in the fight against resistance with the discovery of patented ‘resistance breaker’ compounds, a new series of potent, fast-acting antibiotic resistance breakers that can ‘rejuvenate’ old antibiotics. Cecilia Stroe reports.

On 14th November, a small UK drug company, Helperby, announced its first licensing deal with the major Indian pharma company Cadila Pharmaceuticals, which will take the lead compound HT61 through further clinical trials and approvals, and into commercialisation. Helperby will supply Cadila with so-called ‘Antibiotic Resistance Breakers’, whilst Cadila will develop the combinations with old antibiotics. The agreement was signed at the British High Commission in Delhi, but the deal value was undisclosed.

Cadila Pharmaceuticals is one of the largest privately held pharmaceuticals in India, and was the first Indian company to receive Investigational New Drug approval by the FDA. It is now actively considering a presence in the UK with a corresponding programme for UK microbiologists as part of the collaboration. According to Helperby’s Chief Scientific Officer, Professor Anthony Coates, this exciting and timely partnership offers us all hope. ‘A future without antibiotics is unthinkable but it could happen – imagine a time when a cut finger could leave you fighting for your life. The emergence and spread of drug-resistant pathogens has accelerated whilst the pipeline for new anti-microbial drugs has all but run dry.’

At Helperby Therapeutics, the scientists have been investigating ways to combat antibiotic resistance for the past 12 years. These new drugs were tested specifically on non-multiplying dormant bacteria - something that had never been done before, according to the researchers.

The researchers focused on one compound in particular, called HT61. In a Phase II trial, this drug was successful in improving the effect of an old antibiotic. Professor Coates began his scientific career in the laboratory of Professor Denis Mitchison, the father of modern treatments against tuberculosis. The current standard therapy is still based on Professor Mitchison’s research and the numerous clinical trials he conducted in this area. Understanding the ability of the causative agent – Mycobacterium tuberculosis – to enter a dormant state was an important breakthrough in the fight against this dangerous disease. While studying the factors associated with dormancy, Professor Coates realised this phenomenon was not confined to the tubercle bacillus, but is a normal occurrence with all bacterial species. Professor Coates began looking for antibiotics that would specifically target this dormant subpopulation of bacteria, and this led to the development, with Dr Yanmin Hu, of a proprietary antibiotic screening approach that in turn led to the discovery of antibiotics that are active against dormant bacteria.

The ‘Make-over’
What the scientists have discovered is a new series of potent, fast-acting antibiotic resistance breakers that can ‘rejuvenate’ old antibiotics. Instead of targeting multiplying bacteria, their approach focuses on non-multiplying, dormant bacteria. Professor Coates sees the multiplying bacteria like the leaves of a weed, while non-multiplying bacteria are like its root. ‘Developing antibiotics that specifically target these root-like bacteria has never been done before; indeed, conventional methods of screening have consistently missed these promising candidate drugs. The result of Helperby’s innovation is a unique, patented approach that we have found to be extraordinarily effective.’

Using this approach, the scientists found that they could break resistance when combining the new compounds with old antibiotics. ‘This is perhaps the most important innovation in the discovery of new antibiotics since Alexander Fleming’s original breakthrough over 80 years ago. Our work is all the more important because increased resistance means existing antibiotics are becoming less effective at a faster rate than new antibiotics are being discovered.’

‘Antibiotic Resistance Breaker’ Set for Phase III Trials
Helperby’s lead compound, HT61, which is a topical antibiotic resistance breaker, has been shown to boost the anti-Staphylococcal effect of an old antibiotic in a Phase II clinical trial in humans for the decolonisation of the nose prior to hospitalisation. According to the researchers, this shows, in principle, that it is feasible to boost the effect of old antibiotics in humans.

As Hu et al., explained in a paper published in the open-access journal PLoS One, in a clinical infection, multiplying and non-multiplying bacteria co-exist. Antibiotics kill multiplying bacteria, but they are very inefficient at killing non-multipliers, which leads to slow or partial death of the total target population of microbes in an infected tissue. This prolongs the duration of therapy, increases the emergence of resistance, and so contributes to the short lifespan of antibiotics after they reach the market. Targeting non-multiplying bacteria from the onset of an antibiotic development programme is a new concept. The antibiotic, called HT61, is a small quinolone-derived compound with a molecular mass of about 400 Daltons, and is active against non-multiplying bacteria, including methicillin sensitive and resistant, as well as Panton-Valentine leukocidin-carrying Staphylococcus aureus. It also kills mupirocin resistant MRSA.

The mechanism of action of the drug is depolarisation of the cell membrane and destruction of the cell wall.

The speed of kill is within two hours. In comparison to conventional antibiotics, HT61 kills non-multiplying cells more effectively: six logs versus less than one log for major marketed antibiotics. HT61 kills methicillin sensitive and resistant S. aureus in murine skin bacterial
colonisation and infection models. No resistant phenotype was produced during 50 serial cultures over a one-year period. The antibiotic caused no adverse affects after application to the skin of mini-pigs. Targeting non-multiplying bacteria using this method should be able to yield many new classes of antibiotic. These antibiotics may be able to reduce the rate of emergence of resistance, shorten the duration of therapy, and reduce relapse rates. And there is more. The UK-based company has developed seven further compounds which are all at the preclinical stage of development and all have the potential to break antibiotic resistance in combination with old antibiotics. These antibiotic resistance breakers, when used in combination with old antibiotics, are targeted at both systemic and topical infections. The spectrum of antibacterial activity includes both Gram-positive and Gram-negative resistant bacteria. Several of the compounds are also active against fungal infections. The clinical indications are urinary tract infection (systemic), genito-urinary infection (anti-gonococcal systemic), cystic fibrosis infections (inhaled), skin and mucosal bacterial infections (topical), skin and mucosal fungal infections (topical), eye infections (topical) and ear infections (topical).

Facts on Antimicrobial Resistance
According to the World Health Organization (WHO), in 2011 there were an estimated 630,000 cases of MDR-TB among the world’s 12 million cases of TB. Globally, 3.7% of new cases and 20% of previously treated cases are estimated to have MDR-TB, with substantial differences in the frequency of MDR-TB between countries. Extensively drug-resistant TB (XDR-TB, defined as MDR-TB plus resistance to any fluoroquinolone and any second-line injectable drug) has been identified in 84 countries globally.

A high percentage of hospital-acquired infections are caused by highly resistant bacteria such as methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant enterococci Gram-negative bacteria. Ciprofloxacin is the only antibiotic currently recommended by WHO for the management of bloody diarrhea due to Shigella organisms, now that widespread resistance has developed to other previously effective antibiotics. But the rapidly increasing prevalence of resistance to ciprofloxacin is reducing the options for safe and effective treatment of shigellosis, particularly for children. Antimicrobial resistance (AMR) has become a serious problem for treatment of gonorrhoea (caused by Neisseria gonorrhoeae), involving even “last-line” oral cephalosporins, and is increasing in prevalence worldwide. Untreatable gonococcal infections would result in increased rates of illness and death, thus reversing the gains made in the control of this sexually transmitted infection.

New resistance mechanisms, such as enzymes produced by the bacteria that destroy last-generation antibiotics, have emerged among several Gram-negative bacilli and have rapidly spread to many countries. This can render ineffective powerful antibiotics, which are often the last defence against multi-resistant strains of bacteria. This new resistant mechanism is encountered in ordinary human pathogens (e.g. Escherichia coli) that cause common infections such as urinary tract infection.

Resistance to earlier generation antimalarial medicines such as chloroquine and sulfadoxine-pyrimethamine is widespread in most malaria-endemic countries. Falciparum malaria parasites resistant to artemisinins are emerging in South-East Asia; infections show delayed clearance (meaning that the parasite remains in the blood for longer) after the start of treatment, and increased morbidity and mortality. Resistance is an emerging concern for treatment of HIV infection, after the rapid expansion in access to antiretroviral medicines in recent years; national surveys are underway to detect and monitor resistance.

Because of the constantly evolving nature of influenza, resistance to antiviral drugs is continuously emerging. By 2012, virtually all circulating A viruses in humans were resistant to amantadine and rimantadine, while the frequency of resistance to the neuraminidase inhibitor oseltamivir remains low (1-2%) and no resistance to zanamivir has been detected. Antiviral susceptibility is monitored through the WHO Global Surveillance and Response System.

Novel Classes of Antibiotics Urgently Needed for the Future
According to an article published in May 2011 in the British Journal of Pharmacology by Anthony Coates, Gerry Halls and Yanmin Hu, novel classes of antibiotics are urgently needed for the future. The two new classes of antibiotics which have been introduced into the market, oxazolidinone (linezolid by Pfizer) and cyclic lipopeptide (daptomycin by Cubist) are active against Gram-positive bacteria, such as MRSA, but there are no new classes in Phase II or III clinical trials, and none in the pre-registration stage.

Of the antibiotics in clinical development, two belong to new classes. There are no antibiotics against the major Gram-negative pathogens K. pneumoniae, P. aeruginosa and A. baumannii in Phase IIb and III. Furthermore, there are only a few compounds against these pathogens in earlier stages of development. Most of these compounds are analogues of existing marketed antibiotics. Because there are no new classes in the later stages of development, Phase II, III and pre-registration, there may be no new classes in the market in the short term.

Although there are two potential new class compounds in early clinical Phase I development, the high attrition rate, particularly for new classes, means that the odds are against these compounds reaching the market, and it is possible that no new classes will reach the market within 10 years. In the longer term, during the next 20 years, the likelihood of discovering 20 novel classes including many broad spectrum antibiotics, similar to the achievements in the 1940s-1960s, seems to be remote, particularly for multi-drug-resistant Gram-negatives.

Not to be overlooked, there is also the issue of the risk and cost of developing a new class of compounds, one that is considerably greater than that of an analogue, according to the scientists. For example, the starting point for an analogue is likely to give rise to compounds which are soluble and are not toxic, on the grounds that the parent molecule has these characteristics. Toxic side-effects are a common cause of failure of a compound to proceed past Phase I clinical trials. In contrast, a new class of compound has unknown toxic potential, and may have chemico-physical features which make them unsuitable for drug development.