Immediate Action

The development of novel antibiotics is pushing to the fore of biopharma. With political support firmly in place, the fight against drug-resistant bacteria – which are rapidly increasing in number – is under way, but further cooperation from the healthcare industry is needed

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Resistant strains of bacteria are developing at an alarming rate, rendering many antibiotics redundant. This situation has led to Professor Dame Sally Davies, the UK's Chief Medical Officer, to advocate that antibiotic resistance should be added to the National Risk Register of Civil Emergencies.

In response to this situation, the UK Prime Minister has insisted on a panel review of three key issues: the increase in drug-resistant strains of bacteria, the failure to introduce new antimicrobials, and the over-use of antibiotics globally. The panel will be headed by economist Jim O'Neill and includes experts from science, finance, industry and global health, showing the accelerated rate at which the debate into tackling antimicrobial resistance is moving.

This looming problem calls for immediate attention, including the development of new drugs with a novel mode of action that are active against resistant bacteria.

Increasing Issue

The need for new antibiotics to combat the ever-increasing issue of resistance has led to US and European health authorities launching initiatives such as Generating Antibiotic Incentives Now in the US, designed to allow novel antibiotics to enter the market in the fastest and most cost-effective manner possible. Given the introduction of these initiatives, drug development for treatment of hospital-acquired infections is likely to experience a dramatic shift. Such products could provide important and clinically meaningful benefits to a significantly growing patient population suffering from resistant bacterial infections. Historically, pharmaceutical companies have overlooked the field of antibiotics due to low revenue, but many now appear to be considering re-entry.

Novel Developments

One way to address this challenge is to develop a new class of anti-infectives: a modern class of antibacterials, with a novel mode of action. Such products are expected to provide an important treatment option in tackling the problem of infections caused by susceptible and resistant bacteria.

An example candidate is MGB-BP-3. This is an antibacterial which is active against a broad range of key multi-resistant Gram-positive pathogens, of which the oral formulation for the treatment of *Clostridium difficile* is ready to enter the clinic. In addition to this, an intravenous formulation indicated for the treatment of a range of systemic hospital-acquired, Gram-positive infections is in late-stage preclinical development.

This new drug is a minor groove binder, which binds to the minor groove of bacterial DNA by recognising specific regions. These sequences are rich in the amino acid base pairs A and T, and achieve high selectivity and efficacy by interrupting the biochemistry of bacterial cells by interfering with transcription factors and genetic regulation. Therefore, MGB-BP-3 is based on an entirely novel drug class, and is potentially an important discovery in advancing the development of new antibiotics to combat resistant pathogens. The technology platform being developed to create this product originated at the University of Strathclyde in Scotland.

Some compounds belonging to this group are already under clinical development or are commercially available, such as pentamiden and furamidine, which tackle a range of human parasitic diseases, or brostacillin – an anti-cancer agent.

Gram-Positive Infections

Gram-positive infections – including, but not limited to, *C. difficile*, *Streptococcus, Staphylococcus* and *Enterococcus* bacteria – are responsible for a large proportion of serious infections worldwide. The National Healthcare Safety Network's surveillance of antimicrobial-resistant pathogens linked with healthcare-associated infections states that Gram-positive bacteria are in the top 10 most frequently isolated organisms recorded, and are the most commonly isolated organisms in hospitals across Europe (1,2).

C. difficile infections (CDIs) are the most commonly diagnosed bacterial cause of hospital-acquired diarrhoea in developed countries. The majority

of severe CDI cases occur in the healthcare environment, such as hospitals or care homes. Older people are most at risk from infection, and those aged over 65 account for three quarters of all occurrences. The UK Office of National Statistics reported that, in England and Wales, the number of CDI cases increased from 44,107 to 51,690 between 2004 and 2005, with 2,700 deaths recorded in 2011. Recently, the US Centers for Disease Control and Prevention reported that hospital-based CDI incidence was 250,000, with 14,000 deaths (3).

Current Treatment

One of the most pathogenic strains of *C. difficile*, NAP1/027, which has emerged in recent years, tends to cause more severe infections and is becoming increasingly prevalent globally. In the US, it causes around 50% of all CDI infections; in Canada, nearly 80%; and in England, 36%. The current therapies for CDI – metronidazole, vancomycin and, recently, fidaxomicin – have very limited activity against this strain, as they have predominantly bacteriostatic activity in this strain.

The current therapeutics for CDI are associated with high recurrence rates due to their bacteriostatic activity, and have a weak effect on *C. difficile* sporulation. But the MGB-BP-3 compound has shown a strong bactericidal effect against the majority of *C. difficile* strains, including the most virulent NAP1/027 strain. In contrast to the existing CDI therapy, the product is active against vancomycin-resistant enterococci, which are found in up to 50% of CDI patients. Co-infection is often responsible for a patient's poor prognosis – vancomycin requires up to 24 hours to achieve an optimal effect, but MGB-BP-3 has been shown to act against *C. difficile* within the first hour of administration.

The economic burden of CDI is estimated at around $7 billion, or $6,000 per patient, for the cost of hospitalisation and standard treatment. The development of novel therapeutics in this area will not only substantially benefit CDI patients, but also reduce hospital stays and overall treatment costs.

On the Rise

C. difficile infections are increasing, with estimations of up to three million US cases each year, and over 3,000 in England alone, according to Public Health England's quarterly epidemiology report (4). Recurrence of this disease is observed in up to one third of patients within the first month, with recently evolved hyper-virulent strains of *C. difficile* producing inflated levels of the disease-causing toxins, spores and surface proteins, and allowing continued residence in the gut environment.

Currently, an intravenous formulation for a broader application – covering a range of Gram-positive hospital-acquired infections, such as susceptible and resistant *Streptococcus* and *Staphylococcus* (MRSA) bacteria – is in development.

New, novel anti-infectives are being created that are active against many bacteria in the Gram-positive space, including Methicillin-resistant and susceptible *Staphylococcus* species, pathogenic *Streptococcus* species, and vancomycin-resistant and susceptible *Enterococcus*, as well as *C. difficile.* Activity has also been observed against some Gram-negative bacteria, including *Neisseria meningitides* – the bacterium causing meningitis – and *Moraxella catarrhalis*, responsible for many respiratory, middle ear, eye and central nervous system infections.

With political support now in place, all that is needed is the corresponding enthusiasm and commitment from the healthcare industry. The health of the public must be the primary objective of drug development companies, regardless of size. However, the innovation required to facilitate this outcome should also be rewarded. Companies that address the major problem of antibiotic resistance using novel classes of antibacterials will be at the forefront of this sector.

References

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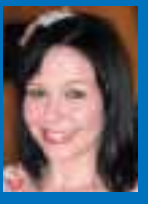
About the author



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