Commentary: Dawn Firmin

Getting traction against antimicrobial resistance

Antimicrobial drug resistance is finally being recognised as a serious global public health concern that could make common infections hard to treat unless adequate new drugs are developed. It is clear that there is an urgent need for new drug classes that are more effective than existing treatments if this nightmarish scenario is to be averted. Governments are starting to grasp the scale of the problem. For example, health authorities in the US and Europe have introduced initiatives such as the GAIN (Generating Antibiotic Incentives Now) Act in the US which is expected to facilitate a faster and less expensive process in bringing novel antibacterial agents to the market.

The biopharmaceutical industry, after years of scaling back research into new antibiotics owing to low returns, has seen some moves towards re-entering the field. In particular, recent development has focused on Gram-positive infections. These infections are responsible for a large proportion of serious infections worldwide.

In this vein, given the huge medical need, our privately owned biotechnology company has been working on a new agent for Gram-positive infections based on technology from the University of Strathclyde in Scotland, UK. We recently received authorisation from the UK Medicines and Healthcare products Regulatory Agency to conduct a Phase I study of our most advanced programme, MGB-BP-3, which is a synthetic polyamide directed against Gram-positive infections. The Phase I trial, which is expected to start in 2015, will be investigating an oral formulation of MGB-BP-3 for treating *Clostridium difficile* infections, one of the most common, yet resistant and difficult-to-treat, Gram-positive infections.

MGB-BP-3 was developed by Professor Colin Suckling at the University of Strathclyde. It binds to the minor groove of bacterial DNA; these are the grooves created from the close proximity of DNA strand backbones. Research into minor groove binders, an entirely novel drug class, including its failures, has proved to be an important event in advancing the development of new antibiotics that could be resistant to potentially increasingly fatal pathogens. Consequently, this is the first time that minor groove binders are being investigated as an antibacterial agent, creating an entirely new class of antibacterials with a new mechanism of action.

Minor groove binders as a class are chemically very heterogeneous, with their respective antibacterial, antifungal, antiviral, antiparasitic and anticancer activity. The common feature of these compounds, including MGB-BP-3, is that they recognise specific regions of DNA and appear to be able to achieve high selectivity and efficacy by interrupting the biochemistry of a cell at a fundamental level. The activity of minor groove binders is determined by their ability to bind to sequences that are rich in the amino acid base pairs A and T within the minor groove of DNA in a sequence and conformation-specific fashion. As a result, this process interferes with transcription factors and alters genetic regulation. Some compounds belonging to this group are already under clinical development or are even commercially available, such as pentamiden and furamidine against a range of human parasitic diseases and brostacillin as an anticancer agent.

MGP-BP-3 has been tested preclinically, *in vitro* and *in vivo*, and has shown activity against a number of pathogens. In the Gram positive space, this includes Methicillin-resistant and susceptible *Staphylococcus* species, pathogenic *Streptococcus* species, and Vancomycin-resistant and susceptible *Enterococcus*, as well as *Clostridium 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.

We are currently advancing MGB-BP-3 against Gram-positive infections, given their prevalence in hospital and community settings. *C. diff*. infections are on the rise, for example, with recent estimates suggesting that up to three million cases occur in the US each year. Public Health England's most recent quarterly epidemiology report (Q1, 2014) stated that in England alone, the number of cases of *C. diff*. is over 3,000. A third or more of patients experience recurrence of this disease within the first month. Furthermore, recently evolved hyper-virulent strains of *C. diff*. produce robust amounts of the disease-causing toxins, more spores and additional surface proteins that help it to persist in the gut environment.

In parallel, the company is developing an intravenous formulation of MGB-BP-3. This formulation is in late preclinical development and is expected to be IND-ready in the second half of 2015. While the oral formulation is being investigated specifically for *C.diff*., the intravenous formulation could have far broader application across a range of Gram positive hospital-acquired infections. MGB-BP-3 has shown activity against Methicillin-resistant *Staphylococcus aureus* (MRSA) in mouse models and good acute tolerability.

Our company believes that the hospital antibiotic market has changed dramatically, following the introduction of major public health initiatives to promote the development of new antibacterials, such as the GAIN Act. Other initiatives are also underway elsewhere in Europe.

Bringing together experts from various disciplines shows how far and how quickly the debate into tackling antimicrobial resistance is moving. The political support now exists and this needs to be matched with commitment from the industry. It is encouraging to note that drug development companies are realising that, while innovation needs to be rewarded, public health also has to be safeguarded at all costs.

This commentary was written by Dr Dawn Firmin, Head of Project Management, MGB Biopharma Ltd in Glasgow, Scotland, UK.