Synthetic anti-infectives: The new approach the world needs

Antimicrobial resistance is a ticking time bomb, argues Recce CEO James Graham, and a genuinely novel anti-infective approach is needed to truly make progress in an area that poses one of the greatest threats to the future of public health

With a historic lack of innovation in antibiotic drug development, the need for new anti-infectives has never been greater. Antimicrobial resistance (AMR) or superbugs are on the rise and exist as an urgent global health threat that has outpaced the development of effective antibiotics. Successful surgeries, chemotherapy treatment, and low maternal and neonatal mortality all depend on our ability to effectively treat infections. Each year, multidrug-resistant bacterial infections cause hundreds of thousands of deaths worldwide, and this number is projected to reach millions over the next three decades.

Now a major concern of governments and the World Health Organization (WHO), antibiotic resistance is not only one of the world's most urgent medical issues but also poses as a global threat to public health and a potential economic burden to individuals and societies. If no action is taken, WHO estimates that, by 2050, antibiotic resistance associated deaths may begin overtaking deaths projected from cancer, diabetes, or car accidents.

A new class of promising anti-infectives

The global antibiotic pipeline remains deficient as most drugs advancing through the clinic are predominantly derivatives of well-established antibiotic classes and do not include any new class of molecules or new mechanisms of action. Traditional antibiotics generally operate similarly to a 'lock and key' mechanism of action; when a traditional antibiotic is used against a bacterium, it often works until the bacteria mutates, and the 'key' no longer functions. Rather than inhibiting a specific bacterial protein or process, Recce Pharmaceuticals is pioneering the development of new classes of synthetic anti-infectives – a 'master key' – designed to overcome limitations of conventional antibiotics and address the urgent global health problems of superbugs and emerging viral pathogens.

Current antibiotics are developing resistance fast and the consequences are recognised globally, with bacterial infections becoming more aggressive and harder to treat. With a universal mechanism of action that allows its compounds to continuously kill pathogens, including multidrug-resistant superbugs, Recce's lead compound, RECCE 327, represents one of the first new classes of antibiotics in over 30 years. Initially developed for the treatment of sepsis, a life-threatening blood infection for which no specific treatments exist, RECCE 327, has demonstrated in preclinical studies to be a fast acting, broad-spectrum antibiotic effective against Gram-positive and Gram-negative bacteria, including antibiotic resistant superbugs.

Tackling superbugs with a 'master key' synthetic antibiotic

Preclinical studies have shown the potential efficacy of Recce's lead candidate against Methicillin-resistant *Staphylococcus aureus* (MRSA superbug). In rats with topical burns, RECCE 327 demonstrated compelling *in vivo* antibacterial activity. The results showed that RECCE 327 was effective in reducing bacterial load within a wound and showed enhanced wound contraction compared to

the best in class, Soframycin. RECCE 327 showed repeated efficacy at different dosing levels on topical skin conditions even at low doses.

In another recent study in mice, RECCE 327 demonstrated significant *in vivo* antibacterial activity against *Neisseria gonorrhoeae (N. gonorrhoeae*), a species of Gram-negative bacteria the second most common sexually transmitted infection (STI) globally. The data revealed a promising dose-dependent decrease in bacterial load in infection as compared to the vehicle control and approved therapy.

Furthermore, previous *in vitro* studies of RECCE 327 against *S aureus, E coli, and P aeruginosa* bacteria showed no resistance, even after over 25 repeated exposures. RECCE 327 continued to demonstrate the same clinically relevant kill-rates for standard bacteria and their superbugs forms. This data suggests that RECCE 327 may be more effective against a wider range of bacteria and may come without the toxicity concerns associated with current antibiotics. It also supports RECCE 327's hypothesised universal mechanism of action representing new class of antibiotics in more than three decades.

Any bacteria present in the bloodstream is bad bacteria and can often lead to sepsis. Doctors treating sepsis patients are in a race against time – each hour sepsis goes untreated the likelihood of patient mortality increases by 6%. RECCE 327 is an efficacious broad-spectrum antibiotic delivered through intravenous (IV) infusion, to treat bacterial sepsis, including strains caused by multidrug-resistant bacteria. Once RECCE 327 enters the bloodstream, it is attracted to the plasma membranes of bacteria via hydrophobic interaction. RECCE 327 binds to the plasma membrane proteins, subsequently weakening the bacterial cell walls.

Data from the company's recent study, along with other previous studies, continue to highlight the potential of RECCE 327 to not only become a potent broad-spectrum antibiotic but, most critically, to continue working against antibiotic resistant bacteria or superbugs, even with repeated use. These data also suggest that RECCE 327 is more effective against a wider range of bacteria and may come without the toxicity concerns associated with current antibiotics.

A new approach to antiviral drug development

As a new class, synthetic polymer drugs may be effective against other deadly superbugs, beyond those that are bacterial in origin, including viruses. In particular, Recce's 'master key' synthetic anti-infectives have exhibited efficacy against the Influenza A virus in mice and are currently being investigated for efficacy against other viruses. RECCE 327 showed a significant dose-dependent decrease in the viral growth rate and viral load in lungs for mice infected with Influenza A following treatment with RECCE 327 compared to the control group and the group treated with an approved antiviral drug.

The ongoing global pandemic highlights the critical need and importance of new anti-infective treatments to help reduce the spread and mortality rate of patients infected by SARS-CoV-2. In response to the pandemic, Recce is currently investigating the potential therapeutic effect of two synthetic compounds against SARS-CoV-2, the virus that causes COVID-19. As noted with past viral pandemics, a substantial number of deaths are caused by secondary bacterial infections, often starting as pneumonia, and progressing to sepsis. The broad-spectrum capabilities of RECCE anti-infectives show potential as an initial treatment before diagnosis has been made.

Wholly owned and manufactured in Australia, Recce's anti-infectives have the potential to address the increasing global threat posed by antibiotic resistance and emerging viral pathogens. Conventional methods that derive anti-infectives from natural sources rely on lengthy and large-scale manufacturing processes, which can involve the cultivation of bacterial or viral cultures followed by several time-intensive purification stages. In contrast, Recce has an automated manufacturing process, producing 500 doses per automated manufacture output in less than one hour with a 99.9% product yield.

Recce's anti-infectives are synthetic and based on a patented polymeric structure that is 100% soluble in water at all pH levels. The versatility of these anti-infectives, which can be easily formulated for IV, topical, nasal, oral, or inhaled use, are beneficial in Recce's development of anti-infectives for indications beyond sepsis. Recce has demonstrated its manufacturing quality and volume capabilities with RECCE 327 as it enters first-in-human Phase I clinical trial.

Addressing AMR before it casts us back into the dark ages of medicine

Without effective anti-infectives to treat bacterial and viral infections, lifesaving medical procedures such as surgeries may become risky to perform because of the potential of difficult-to-treat surgical site infections.

Those infections that are especially challenging, are a group of deadly bacteria known as the ESKAPE pathogens, which are comprised of: *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter*. Approximately 700,000 people die every year from antibiotic-resistant infections globally, many of these deaths are due to ESKAPE pathogens. Due to their rate of mutation, the ESKAPE pathogens not only pose a significant risk to all patients but a heightened threat to those developing antibiotic resistance.

If the current trends continue, superbugs will be the leading global cause of death by 2050. RECCE anti-infectives represent one of the first new classes of synthetic antibiotics in over three decades that have the potential to address this global threat by continuously killing these pathogens. RECCE anti-infectives will be further investigated for efficacy and safety in animal model studies against common and emerging viral pathogens.

James Graham, CEO of Recce Pharmaceuticals.

James Graham now serves as Chief Executive Officer of Recce Pharmaceuticals having been an early investor and supporter of Recce. He has extensive experience in marketing, business development, and commercialisation of early stage technologies with global potential.