The translational research of Professor Young Jik Kwon at the University of California, Irvine aims to fill a formidable void created by the lack of available effective antibiotics. Combining naturally-occurring antimicrobial substances with conventional antibiotics, Professor Kwon’s nanoantibiotics are a novel generation of compounds molecularly engineered to safely and effectively target drug-resistant bacteria. One of his current projects aims to tackle the particularly persistent Pseudomonas aeruginosa infection in cystic fibrosis patients. He also explores therapeutic delivery of stimuli-transforming polymers directly to sites of bacterial infection.

Bacterial infections that are resistant to antibiotics are predicted to be the major global cause of death by 2050. Indeed, infectious diseases cause around a quarter of deaths globally, with approximately 23,000 deaths attributable to drug-resistant infectious diseases in the US in 2014.

While pharmaceutical companies strive to develop novel antibiotics, only two new classes of drug have been discovered since 1962, highlighting the desperate need for alternative approaches to tackling drug-resistant infections. Current treatments include the use of high doses of broad-spectrum antibiotics, drugs which target a large class of bacteria, rather than focusing on the specific strain responsible for the infection (when it can be identified). This approach often results in significant side-effects, most of which affect the digestive system and may be the result of antibiotics disrupting the resident, ‘good’ bacterial community in the gut, and in fact, drives antibiotic resistance further as the bacteria continually evolve to avoid them and transfer resistance mechanisms to one another if faced with environmental pressure. Furthermore, even if new antimicrobials are effective, it is likely to only be a short-term fix, taking anywhere from a few months to around ten years for a resistant gene to develop.

THE NEED FOR INNOVATIVE THERAPEUTICS

Professor Young Jik Kwon, University of California, Irvine, spearheads a translational research project that is set to change this. He investigates novel pharmaceutical materials for emerging therapies and is currently involved in the development of nanoantibiotics. Nanoantibiotics are nanomaterials, or particles of 100 nanometres (nm) or less (a sheet of paper is about 100,000 nm thick), that have their own antimicrobial activity, or are able to improve the efficacy and safety of administering existing antibiotics. They include an efficient delivery vehicle to deliver cargo into bacteria, with the cargo being RNA to cause gene editing (CRISPR-Cas9 guide RNA) or gene silencing (siRNA) which can be specifically targeted to drug-resistant bacteria. The delivery vehicle is based on a form of chitosan, a sugar normally found in the hard-outer skeleton of shellfish, and which already provides a broad spectrum of antimicrobial mechanisms. Using gene editing and RNA interference (RNAi) allows sensitisation of the bacteria to antimicrobials, by silencing the resistance gene that they contain. Professor Kwon’s novel approach combines gene editing or RNAi with nancobiotics. Using this synergistic strategy allows him to combat multi-drug resistant bacteria. Whilst evolutionarily used by bacteria to develop resistance, the process can be turned back onto the bacteria, to edit or silence their resistance mechanisms.

The advantages of antimicrobial nanoparticles over conventional antibiotics include production, storage, durability and versatility. For example, because they are often composed of existing antibacterial materials, metals or carbon-based nanomaterials, preparation costs are significantly lower, the process is faster and the resulting nanoantibiotics have a longer shelf life. The therapies designed by Professor Kwon also offer much more control over drug administration once inside the body, as they can be engineered to have a site-specific, sustained release which can be given in a single dose. Most conventional antibiotics require multiple doses in order to achieve this. The mechanism of action of a nanoantibiotic may also be more sophisticated than that of its conventional relative, harnessing pathways such as premature aging of bacterial components through reactive oxygen species, interrupting energy pathways and inhibiting enzyme activity and DNA synthesis.

TARGETING THE RIGHT ENVIRONMENT

Research evidence suggests that the environment of the microbe may be linked to its virulence, meaning that environment-specific activation of a drug is highly beneficial. Professor Kwon has therefore incorporated a unique characteristic into his product, the ability to use stimuli-responsive components to tune the nanoantibiotics to certain infections or sites, based on environmental cues such as temperature, pH, oxygen and carbon dioxide levels, and iron levels. This means that, in the same way that bacteria can tailor their attack depending on whereabouts in the body they are, now drugs can too. Leading on from this, multi-stimulus responses are also a possibility, for example by including components that respond to temperature and pH, to create a polymeric antibiotic.

One of the challenges of nanoantibiotics is the potential toxicity of the nanomaterial. However, incorporating naturally occurring materials, such as chitosan, bestows high levels of biocompatibility on these stimuli-transforming polymers, meaning they are compatible with living tissues, will not cause an adverse reaction, and are able to accumulate in sites of infection before transforming to an active antimicrobial state.

THE FUTURE OF NANOANTIBIOTICS

The possibilities for this new technology...
Nanoantibiotics are delivered using a form of chitosan, a sugar found in the hard outer skeleton of shellfish.

The possibilities for this new technology are endless and include the combination of nanoantibiotic treatment alongside conventional antibiotics. Ultimately, the research of Professor Young Jik Kwon and colleagues will fill the void left by the lack of new antibiotic discoveries by using novel materials which are molecularly engineered for safe and effective use against bacterial infections, particularly drug-resistant bacteria. The versatile delivery vehicle can be personalised to expand this to the treatment of pneumonia, a frequent cause of death amongst stroke and cancer patients in hospital, as well as a significant threat of community-acquired pneumonia in vulnerable populations. Professor Kwon is also involved in a project using a similar technology, which explores the possibility of using vehicles to deliver chemotherapy drugs to the site of action in rodent models of cancer. His work also explores gene therapies for cancer and drug delivery vehicles for treating diabetes, suggesting that these nanoscale biomaterials are going to underpin multi-modal therapeutic strategies in the future. With the increasing interest in using bacterial viruses (phages) to treat bacterial infections, non-phage antibiotics offer a safer alternative as the risk of using a virus is that it has the potential to self-replicate and evolve.