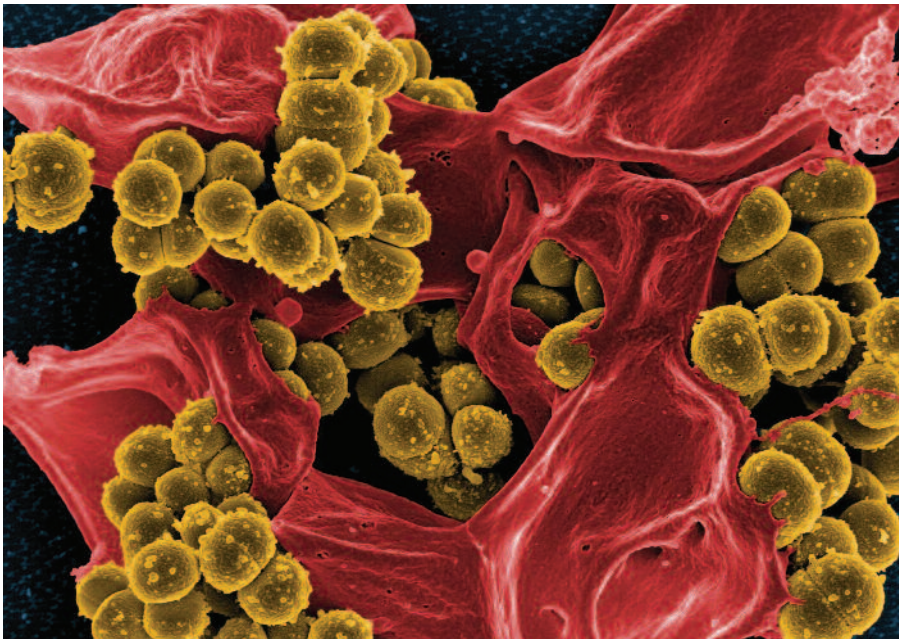
Endolysins: finding the answers to the problem of antibiotic resistance

In the wake of the problems associated with increasing antimicrobial resistance, scientists have now developed the first effective alternative to antibiotics in a significant advance in the fight against drug-resistant infection. Here, Bjorn Herpers looks at the promise of endolysins.

It is easy to become numb to stories we frequently hear in the media. Cancer, dementia and obesity are all health-related stories we read about every day. Antimicrobial resistance also falls into this category; however, the wider public do not give it the recognition it deserves as a major health threat. The only time most of us consider antibiotics is when we are ill, and focused firmly on our personal health, rather than public health. It is unfortunate that our main contact point with antibiotic usage is here, when we are in exactly the wrong mindset to protect the viability of these drugs.

The danger of antimicrobial resistance is clear and present. According to a UK government-commissioned report, the total number of deaths as a result of antimicrobial resistance is projected to rise to 10 million per year globally by 2050,[1] more than the number currently dying from cancer. This threat of antibiotic resistance is not new; the first reports of *Staphylococcus* spp. resistance to penicillin occurred in 1947, just four years after the antibiotic was first mass-produced, and methicillin-resistant *Staphylococcus aureus* (MRSA; Fig 1) was discovered over 50 years ago.



National Institute of Allergy and Infectious Diseases (NIAID)

Fig 1. Methicillin-resistant *Staphylococcus aureus* was identified over 50 years ago.

Despite the size and age of the problem, investment in research and development is limited; the unpredictable nature of bacterial infection makes trial design complex, and the short treatment courses, coupled with conservative usage, mean antibiotics are not particularly lucrative compared with treatments for longer-term conditions. Most importantly, history has taught us that bacteria are strong survivors and, ultimately, they will develop resistance against every new traditional-type of antibiotic. So, if antibiotics are not coming along as quickly as we would like, what is going to save us from so-called superbugs like MRSA?

The need for antibiotic alternatives

While much of the discussion around antimicrobial resistance focuses on the development of new antibiotics, it is important to take a broad view on antimicrobial resistance; we need antibiotic alternatives – treatments that change the antimicrobial playing field, and work both separately from, and in conjunction with, antibiotics to stop resistant organisms spreading.

So, where are we looking for these alternatives? A lot of exciting research is going on in vaccination, the use of laboratory-generated antibodies, phage therapy (Fig 2) and antimicrobial molecules from the immune systems of other animals.

The Holy Grail is a treatment that can sidestep bacterial resistance, and is therefore viable for long-term or prophylactic (preventative) therapy. The use of endolysins is one innovation that has this potential.

Endolysins are an essential part of the reproduction process of phages. Phages are common microorganisms that can replicate only through a bacterial host. When a

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bacterial cell is infected, the phage takes over its machinery and starts to produce new phages. The phage uses enzymes called endolysins to destroy the bacterial cell wall, releasing the new phages and killing the host bacterium. Endolysins have three characteristics that make them good candidates for fighting resistant bacteria such as MRSA, and these are:

- a working mechanism unrelated to that of antibiotics, meaning even antibiotic-resistant strains of bacteria, such as MRSA, are susceptible
- phages have co-evolved with bacteria over billions of years, so endolysins target areas of the bacterial cell wall that the bacterium cannot change during reproduction, which means that bacterial resistance is not observed, nor expected
- endolysins target specific bacterial species, meaning beneficial bacteria are not killed, reducing the chance of related side-effects and opportunistic infection following treatment (as is often seen after courses of antibiotics).

These characteristics are certainly useful in fighting infection, but they also open up treatment options in other areas of medicine that we wouldn't normally consider under the umbrella of antibiotics.

Treating more than just infection

When the threat of resistance is removed, and treatment is specific to a certain bacterial species, this unlocks antibacterial treatment options that previously wouldn't have been possible.

Bacteria interact with the human body across a spectrum of stages, which we call the colonisation-infection continuum. Antibiotics are not selective in the bacterial species they kill, and overuse of these agents has driven the emergence of resistance. Therefore, antibiotic use historically has been limited to the infection stage of this continuum.

New data presented at the Royal Society of Medicine Spring Innovation Summit showed that Staphefekt (an endolysin) selectively kills only *S. aureus*, including MRSA, without inducing bacterial resistance, leaving the good bacteria unharmed.[2,3] This is very exciting as it opens up the possibility that endolysins such as Staphefekt could be used as a measure to prevent infection. It also

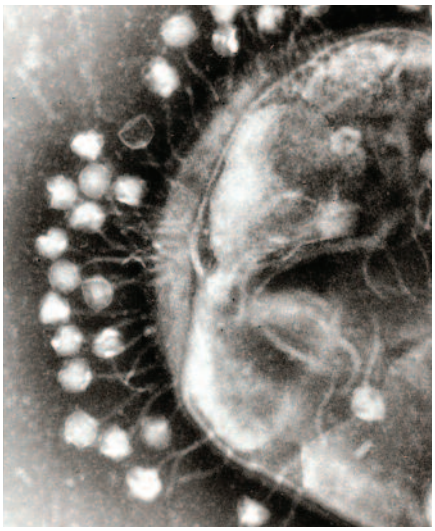

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Fig 2. Phage therapy has been seen as a possible therapy against multidrug-resistant strains of many bacteria.

means that endolysins could play a big role in the maintenance treatment of chronic skin conditions where bacteria are thought to cause inflammatory symptoms, such as eczema, acne and rosacea, where the first endolysin products on the market are already in use. Continuous suppression of *S. aureus* on the skin means that progression to inflammation and infection can be halted in these dermatological conditions (Fig 3).

For the further development of endolysin therapy, the first logical step is to develop

strategies for wound care. Diabetic ulcers, burn wounds and pressure ulcers are infected frequently with *S. aureus*, often MRSA. Not only could current endolysins be used therapeutically to address these issues, but also as a preventative measure, halting the progression from the colonisation stage to local wound infection. Recently, the development of second-generation Staphefekt endolysins has been achieved; these new endolysins target the major microorganisms responsible for prosthetic joint infections.

The natural reservoir of endolysins able to target other bacterial species is vast and thus we are likely to see more come into use in years to come.

Protecting beneficial species

The average human is home to over 100 trillion bacteria – 10 times as many bacterial cells as there are humans cells – and we are just at the beginning of understanding the interactions between humans and bacteria, and the implications of these interactions on human health. As we understand more, medicines which are targeted to individual bacterial species will become increasingly effective.

Just as we get to grips with all of the negative effects bacteria can have on humans, it is only now that we have started to understand all of the benefits bacteria convey. In the digestive system, they help break down food that is hard to digest (eg the polysaccharides present in plant cell walls), increasing the amount of nutrition available from our food. Intestinal microflora synthesise large quantities of menaquinones, which are a source of vitamin K, and most species also produce biotin.

We are also protected from infection by the beneficial bacteria that colonise our skin. These friendly bacteria occupy the ecological niche that pathogenic species could opportunistically make their home. This protects us from serious infection in the event of skin breakage.

Experiments have shown that animals raised in a sterile environment without any bacteria are more susceptible to infection, require more calories to survive and die young.[4] The importance of targeted antimicrobials in protecting beneficial bacteria cannot be overestimated.

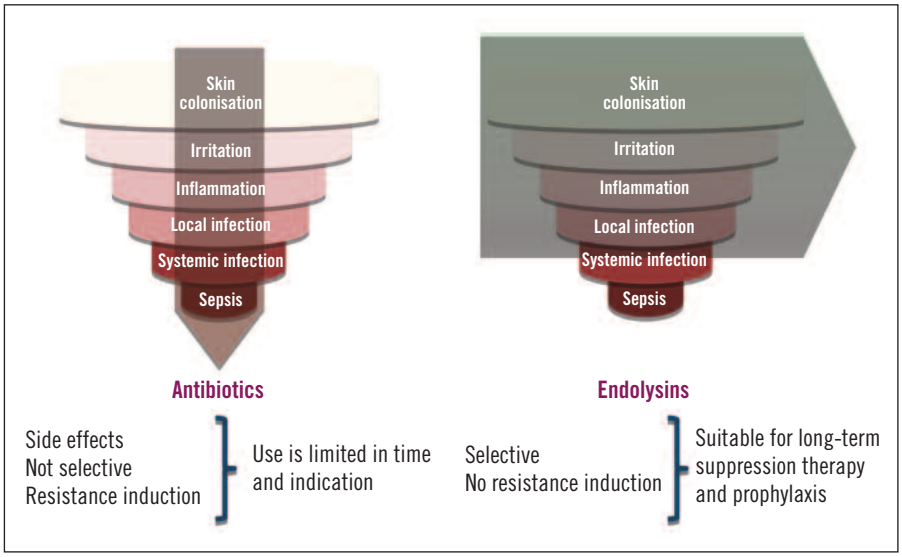

Fig 3. Bacteria interact with the human body across a spectrum of stages, the colonisation-infection continuum. Every infection is preceded by colonisation, after which progression to severe systemic infection and sepsis eventually can occur. As antibiotics are not selective and induce resistance, their use is limited in time and indication. Unlike antibiotics, endolysins are very selective and do not induce resistance. Therefore, they can be used to suppress *S. aureus* colonisation and intervene at the early stages of the continuum, before colonisation leads to infection.

New developments

While it is antibiotics that currently receive most of the media attention, some of the most exciting developments that may save us from superbugs are not antibiotics but those that work through new mechanisms. The threat of resistance arising can never be ruled out with any new treatment – bacteria have proved themselves to be extremely adaptable – but by approaching the threat of resistance through as many different mechanisms as possible, we protect ourselves against the 'apocalyptic scenario' described by Professor Dame Sally Davies as best we can. The government's five-year plan calls for investment in the problem-solvers, the innovative minds of today and tomorrow. It is reassuring to know that antibiotic alternatives, such as endolysin technology, are emerging, as they could prove vital in years to come when our supply of effective antibiotics runs out.

LONGITUDE PRIZE 2014

While the goal of reducing antibiotic resistance is clear, challenge prizes such as the Longitude Prize 2014 do not make assumptions about the source of a solution or what it will look like, because successful innovation often stems from unexpected places.

Just as the original Longitude Prize saw the success of John Harrison, a craftsman whose contribution was not foreseen, and of the establishment figures of John Hadley and Tobias Meyer, so the Longitude Prize 2014 hopes to encourage innovative submissions both from centres of research excellence and non-traditional origins.

You could be the innovator who wins the prize and helps society tackle one of the greatest challenges of our era. Submissions are welcomed from anyone, and they can be at any stage of development. Support will be offered to advance the development of early-stage ideas into potential winners. The Longitude Prize 2014 was launched last autumn and the competition will remain open until 2019 before the prize is awarded in 2020.

Time is ticking: antimicrobial resistance requires the 21st-century equivalent of John Harrison's beautiful and practical H4 marine timepiece, the winner of the original Longitude Prize.

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