AN ALTERNATIVE APPROACH TO ANTIBIOTICS
by Bjorn Herpers and Johan Frielings

Often in medicine, treatment is shaped by the characteristics of the treatment options available, and not purely by the nature of the disease. Bacterial diseases are a prime example of this, with the inherent strengths and weaknesses of antibiotics moulding treatment. So what would we do differently if our treatment of bacterial diseases was released from the confines of antibiotic therapy? What if we stepped away from the status quo to explore innovative new approaches?

Dr Bjorn Herpers and Dr Johan Frielings of Dutch biotech Micreos shed some light on the companys newest offering to the antibiotic-alternative field, Staphefekt™.

Introduction
The discovery of antibiotics and their widespread availability revolutionised healthcare after the Second World War. They are medicines that underpin some of the 20th century's greatest medical advances, and, yet, they now seem to be on the losing side. The tables have turned with bacteria on top again.

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, 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 4 years after penicillin was first mass-produced, and Methicillin-resistant Staphylococcus aureus (MRSA), was first recognised over 50 years ago.

Despite the size and age of the problem, investment in research and development is limited; the unpredictable nature of bacterial infections 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. There is also no guarantee new antibiotics will be used straight away in practice, with the likelihood being that they are stored away to be used as a last resort antibiotic.

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 aren’t coming along as quickly as we would like, what is going to save us from superbugs like MRSA?

The need for alternatives
As our existing stock of antibiotics becomes increasingly ineffective due to the development of resistance, we need to change our prescribing behaviours for both humans and animals and feed the antibiotic pipeline. However, even with an increase of investment into this field, there is no guarantee that we are able to prevent the issue of antibiotic resistance in the long term. This means we need to look elsewhere for alternative solutions to either replace or complement our current antibiotic armamentarium.

Biotechnology companies are leading the search for alternatives. Some exciting alternative research areas include: antibodies which bind and inhibit specific bacteria; immune stimulation that boosts the patient’s natural immune system; and endolysin technology which uses enzymes to target and kill bacteria through lysis of the cell wall.

This endolysin technology is particularly exciting for biotech Micreos Human Health, which has managed, for the first time, to harness and use it as a therapeutic agent.

Endolysin technology – an alternative to antibiotics
Micreos' antibiotic alternative uses an endolysin known as Staphefekt™ (SA.100) to selectively kill the gram-positive bacteria S. aureus, including the antibiotic-resistant strain MRSA.

Staphefekt™ is a chimeric enzyme that works by specifically targeting highly conserved regions in the cell wall of S. aureus which are unlikely to evolve, meaning the bacterium is unlikely to develop resistance to Staphefekt™. So far, resistance has not been observed nor is it expected (see Figure 1).
Figure 1. Graph indicates the absence of induction of resistance to Staphefekt™ in contrast to the antibiotic mupirocin and the endopeptidase lysostaphin².

Figure 2. 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. Because antibiotics are not selective and induce resistance, their use is limited in time and indication. Unlike antibiotics, Staphefekt™ is very selective and does not induce resistance. Therefore, it can be used to suppress S. aureus colonisation and intervene at the early stages of the continuum, before colonisation leads to infection³.
One of the main advantages of Staphefekt™ is that it only targets *S. aureus* – regardless whether it is resistant to antibiotics or not – while leaving beneficial bacteria unharmed, therefore, reducing the chance of related side effects and opportunistic infection following treatment. These characteristics make Staphefekt™ a great candidate for treating conditions which require long-term therapy.

### Colonisation Infection Continuum

The Colonisation Infection Continuum is the spectrum of stages across which bacteria interact with the human body (see Figure 21). The different stages of the continuum are interrelated. Every influence exerted on bacteria during the colonisation stage – such as emerging antimicrobial resistance or eradication of pathogens – has its ‘downstream’ effect on the later stages of the continuum. The use of antibiotics induces resistance and antibiotics are not selective in the bacterial species they target. This makes them unsuitable for longer-term treatment. As a result, they are mainly used for infections at the later stages of the continuum.

Staphefekt™ is able to intervene at the earlier stages of the continuum when *S. aureus* is colonising the skin, thereby preventing later and more serious infection. This is particularly advantageous when we transfer the applicability to treating inflammatory conditions, such as eczema, known to be associated with *S. aureus* colonisation, and other inflammatory skin conditions where *S. aureus* can give rise to secondary infections, such as rosacea, acne and folliculitis.

A recent systematic review published in the British Journal of Dermatology found that, on average, 70% of atopic dermatitis (AD) patients are colonised with *S. aureus* on their skin lesions4. The study also confirmed a strong correlation between *S. aureus* colonisation and the severity of AD, underscoring the importance of colonisation as a potential causal factor in the pathogenesis of AD.

### Laboratory to market

Micreos has targeted this potentially causal relationship of a disturbed microbiome due to overgrowth of *S. aureus* and AD by engineering Staphefekt™ into gels and creams. The product line known as Gladskin in about 80% of patient organisations. All of the studies pointed towards the positive effect of Gladskin in about 80% of eczema patients, by reducing the typical eczema symptoms, such as redness, itching and scratching, and reduced the need for corticosteroids in 53% of corticosteroid users.

Micreos will take a new generation of Staphefekt™ through clinical development, Staphefekt™ XZ.700. This modified protein is slightly shorter than its predecessor and has demonstrated improved bioactivity. Micreos is currently establishing the production methods required for XZ.700 as a pharmaceutical product before proceeding to preclinical and clinical studies. Near future developments will focus on local therapy of *S. aureus* colonisation often found in diabetic wounds, burns and vascular ulcers, to prevent progression to invasive infection and sepsis.

### Summary

Endolysin technology is emerging as a real alternative to antibiotics. Although, in the short term, Micreos’ Staphefekt™ may not replace antibiotics for systemic infections, Gladskin is already now an alternative to antibiotics for patients with chronic inflammatory skin conditions, where *S. aureus* is a culprit. For the near future, Micreos is developing Staphefekt XZ.700 as a pharmaceutical product, for conditions like atopic dermatitis and superficial wound infections. Micreos intends to continue to use its innovative approach to alleviate the mounting pressure on antibiotics.

### References