

INTERVIEW

Endolysins: redefining antibacterial therapy



Bjorn Lars Herpers* speaks to Natasha Leeson, Commissioning Editor:

Bjorn Lars Herpers was born on 16 February 1974 in Schaesberg. In 1992 he graduated summa cum laude at Gymnasium Rolduc in Kerkrade (The Netherlands) and started to study medical biology at the University of Utrecht. After 3 years, he started to study medicine as well. He graduated cum laude in medical biology in 1999 and obtained his medical degree in 2001. After 1 year of residency in internal medicine at Gooi-Noord Hospital under supervision of DW Erkelens and P Niermeier, he switched to a residency in medical

microbiology at the University Medical Center Utrecht and the St Antonius Hospital Nieuwegein under supervision of J Verhoef and B M de Jongh. During his residency, he started to work on his thesis on genetic polymorphisms in MBL and L-ficolin, two complement-activating pattern recognition receptors. In 2009 he became a medical microbiologist and joined the staff at the Regional Public Health Laboratory Kennemerland in Haarlem. Since 2012, he has been involved in clinical research on endolysin therapy in collaboration with Microcos in Bilthoven.

Q Why is it so important that we find new alternatives to antibiotics?

As a clinical microbiologist, in daily practice I see patients with infections. One of the greatest steps forward in medicine was the invention of antibiotics, as a result of which we saw the mortality rate of patients with infectious diseases dropped dramatically. However, antibiotics have two major disadvantages: first, they do not only kill the unwanted bacteria, but also the beneficial bacteria; second, the more you use them, the quicker you lose them; therefore, resistance has become widespread. This is where we are, at the moment, on the verge of antimicrobial resistance making antibiotics ineffective in the future. Although we do not currently have a lot of methicillin-resistant *Staphylococcus aureus* (MRSA) in Holland (The Netherlands), we do see a lot of Gram-negative bacteria that are resistant to antibiotics. In other parts of the world, however, MRSA is a big problem. Consequently, the emergence of untreatable superbugs threatens the basis of modern medicine and, therefore, new strategies to combat these infections are of paramount importance.

Q What are the potential alternatives to antibiotics?

I have just been to the 'Antibiotic alternatives for the new millennium' conference in London (UK) and there were many people who are trying to find alternative treatments, through a variety of methods. However, there is very little in the research pipeline at this moment. There is a low rate of emergence of new, clinically useful antibiotics and when a new antibiotic does appear on the market, it is always a variation of an antibiotic that has already been there before, for example, the next antibiotic of the same class.

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- resistance

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I think that with the discovery of phages as the natural enemy of bacteria 100 years ago, phage therapy could be a promising strategy against bacterial infections. The only problem was that technologically; it was hard to reach that goal. In the last few years, however, a special part of phage therapy, endolysin therapy, has gained much more attention. This is because endolysins have two characteristics that make them a suitable alternative; they can be directed specifically against the unwanted bacteria, leaving the other bacteria unharmed, and it is very unlikely that bacteria will develop resistance against them.

Q What can you tell me about your research on endolysins?

Staphylococcus aureus is one of the major culprits of infectious diseases in humans. Therefore, we have developed the Staphitekt™ SA.100™ (Microos, Bilthoven, The Netherlands), which is a ‘designer’ endolysin constructed by Fritz Eicheseher and Martin Loessner at ETH Zurich (Switzerland) that is only targeted against *S. aureus*. First, we tested *in vitro* to see whether *S. aureus* strains, which had been isolated from patients, are susceptible to Staphitekt SA.100 and they all were. We also showed that it is lysis specific. We then checked whether there was a difference between methicillin-susceptible *S. aureus* and MRSA; however, it was exactly the same – they were equally susceptible to Staphitekt. Within 4 h we saw a reduction of 100- to 1000-times in colony-formed units per milliliter in the lab. In addition, we looked at the distribution of minimum inhibitory concentration, namely, the susceptibility of the strains and there was no difference between MRSA and methicillin-susceptible *S. aureus*.

I think what is most important is that we tried to make strains resistant to endolysins. We did this by exposing the strains repeatedly to sub-optimal concentrations of Staphitekt SA.100 and we did not see resistance induction against Staphitekt SA.100. However, in the same experiments we did see resistance induction against lysostaphin and mupirocin, a frequently used antibiotic. Consequently, resistance induction is not happening *in vitro*, which is consistent with the promise of this endolysin technology.

The next step is looking at whether resistance induction could happen in patients and whether *S. aureus* is removed from the region where Staphitekt SA.100 is applied. In the meantime, the Staphitekt SA.100 is registered as a medical

device and in the formulation code of Gladskin it has already been sold over the counter to over 10,000 individuals with eczema, rosacea and acne. And in this formulation it has a customer satisfaction rating of over 80% from customer questionnaires.

Therefore, we wanted to see if Staphitekt SA.100 could be used in a medical setting. Of course, in a medical setting satisfaction is not enough; you need proof that *S. aureus* is removed from the skin. Therefore, skin cultures were taken from seven patients with rosacea to study the effect of Staphitekt SA.100 on *S. aureus*. Three were lesional *S. aureus* carriers. Within 30 min of therapy, the *S. aureus* was gone and did not reappear during the therapy. This research was expanded to include a case series of eight patients with recurring dermatitis who were being treated by physicians that incorporated Staphitekt SA.100 in their treatment. In these eight patients, we looked at relief of symptoms and corticosteroid use. Overall, six had *S. aureus* and of these six *S. aureus* carriers, five of them showed a decrease in *S. aureus* burden and they reported relief of symptoms and less corticosteroid use. However, the other patient did not report relief of symptoms and the *S. aureus* did not disappear. So, unfortunately, one of them failed but in the other five patients we saw a positive effect. This was the first time that endolysin therapy has been observed in humans.

We already have people contacting us to see if Staphitekt SA.100 can be used as a salvage therapy for patients who cannot be operated on and have a *S. aureus*-related prosthetic problem, for instance. To be able to help these patients, Staphitekt SA.100 is now available in an aseptic formulation, without preservatives, which is necessary for doing research on systemic use. The route now is from the over-the-counter product to make it available for medical studies and clinical trials to investigate which patients may benefit from endolysin therapy and what the possibilities and limitations are. Of course, these are fragile enzymes, so it is the technological aspect that makes this now possible. With Staphitekt SA.100, the promise of endolysin therapy has finally landed.

Q What are the next steps for this research? Are there any upcoming clinical trials?

Next year we will be conducting a randomized control trial on eczema using the endolysin. We are also collaborating with the Association

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of Dutch Burn Centers to conduct studies in burn wounds, first in an *ex vivo* model and, if that succeeds, we will trial it on patients. In addition, we hope that doctors will contact us in case they have any ideas. For example, many physicians contacted us regarding particular patients with MRSA-related problems, ranging from simple topical problems to an infection of a vascular prosthesis in the aorta. The latter patient cannot be operated on but the MRSA infection needs to be treated. The physician asked the medical committee of his hospital if he could produce his own phages, because he thought that could be the best treatment option, when he heard about Staphfekt SA.100. He contacted us to see whether it was possible to use the endolysin as a salvage therapy in this patient. We are currently in contact to see whether this new aseptic product could be used in a trial setting in this case.

I think it is very important to stress at this point that this is not the complete answer to all the bacterial infections in the world. However, if we can work together with doctors in the field, to see what problems they encounter and how we can solve them, we can really define the place of endolysins in modern medicine.

Q What challenges do you face with this treatment option? Where do you see this field of research going in the future?

For topical use, this treatment is already being used in patients and we hope to include it in an eczema trial, so there should not be any real challenges. What could be possible in the near future is to treat local infections, for example, *S. aureus* prosthesis infections, because knee and hip prosthesis infections are very difficult to treat and the morbidity of these infections is very high. In the next 5 years, it would be interesting to see whether this could be an application.

Treatment of systemic infections is more challenging. As an example, endolysins are very large molecules; therefore, they do not enter the cells and they cannot be used in the case of intracellular infections. Consequently, I think a combination of antibiotics and endolysins could be a very good one. Currently, other research groups are studying different compounds and bacteria

in animal models and have shown that this combination is appealing and effective. Endolysin technology has been around for a few years now and this is the first time it has been successfully brought to patients.

Furthermore, what I really like about this aseptic formulation is that it will be made available freely to researchers or clinicians who want to use it in research, for example, animal models of a prosthesis infection. We get a lot of questions from physicians who want to use Staphfekt systemically with their patients suffering from invasive MRSA infections and do not react to therapy. The possibilities of this kind of salvage therapy in a research setting need to be addressed by the physician and the local medical ethical committee, as the product has not been registered for this kind of use. Of course, we want to pursue this in the future.

We very much want to interact with other experts about this. I think that this is very appealing and is the way we should share this knowledge and technology and hopefully make many scientific advances. I remember that first heard about endolysins in 2006 at a congress in Munich (Germany). I saw the same speaker a while later at a congress in Switzerland and I asked him if he had succeeded in making an endolysin in *S. aureus* and he shook his head, saying that it was too hard. Therefore, it was the technology that was holding us back, but now the technological challenge has been overcome – at least in one area – there is a lot of potential for the future.

Disclaimer

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