



The rise of bacteria that are resistant to several different antimicrobial agents is a major challenge to healthcare systems around the world. Part of the solution may be the development of novel agents such as plectasin, an antimicrobial peptide discovered by Novozymes that is currently under development.

*The Pseudoplectania nigrella fungus.*



## Plectasin, a potential new weapon against antimicrobial resistance

The discovery of antimicrobials (antibiotics and other drugs) in the 20th century was one of the greatest scientific achievements of that era. Many diseases that were previously widespread, untreatable and often fatal became manageable. The lives of millions of people were saved and many scientists and doctors believed that dozens of infectious diseases had been conquered.

Sadly, the development of antibiotics went hand in hand with the development of bacterial resistance to these same drugs; nowadays, many bacteria are sensitive to just one or two agents. Some notable examples include methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae*, vancomycin-resistant *Enterococci* and multi-resistant *Mycobacterium tuberculosis*.

### Selective pressure

The mechanism by which bacteria become resistant to antibiotics is called selective pressure. When a population of bacteria is exposed to an antibiotic, there may be a lucky few that are carrying mutated genes that give them resistance to that agent

(this happens frequently among bacterial populations because they reproduce exponentially and produce billions of 'offspring' with altered genes). Of course, these survivors quickly replicate and become the dominant strain. Furthermore, they can pass on their resistance genes to other microbes. Thus, resistance to a single agent can spread rapidly through a bacterial population.

Hans-Henrik Kristensen, manager of anti-infective discovery at Novozymes, says that societal mistakes have exacerbated the problems of antimicrobial resistance. "The inappropriate use of antibiotics and poor patient compliance, where patients forget to take their medication or stop when they begin to feel well, create the ideal conditions for microbes to flourish and develop resistance rather than being killed off. That said, probably the biggest contributor to the development of antibiotic resistance is their overuse in agriculture.

"Multi-resistant bacteria are now a major problem among vulnerable patient populations such as those in hospital, the immunocompromised and the elderly."

### Renewed urgency

The world has belatedly woken up to the problems of antimicrobial resistance, and new efforts are being made to educate people about the dangers of the misuse of these agents. In 2001, the World Health Organization launched the first global strategy for combating the problem. Known as the WHO Global Strategy for Containment of Antimicrobial Resistance, the strategy recommends a series of actions that various groups can take, including patients, prescribers, hospital managers and national governments.

### Antimicrobial peptides

The pharmaceutical industry has also begun to speed up the development of new compounds that show different and, hopefully, better resistance profiles than early antibiotics. One such group of compounds is called antimicrobial peptides (AMPs) and one of the most promising candidates, plectasin, is under development by Novozymes.

AMPs are a unique class of antimicrobials with novel modes of action. These ancient molecules are widely distributed in animals, plants and fungi, and they are one of the



earliest defensive mechanisms to be discovered. Surprisingly, the molecules are rather small, ranging in size from just six to 60 amino acids.

According to Hans-Henrik Kristensen, AMPs have several properties that make them a very exciting prospect for clinical development. These include:

- Rapid onset of action
- Low toxicity to mammalian cells
- Synergistic effect when used in combination with other antibiotics.

“One of the most exciting things about AMPs, however, is that they show few of the resistance mechanisms seen with other antibiotics. This means that they have the potential to treat conditions caused by organisms such as MRSA, e.g. sepsis and pneumonia, where traditional antibiotics are much less effective,” says Hans-Henrik Kristensen.

### Plectasin

Plectasin itself was discovered by Novozymes in 2002. It comes from a fungus, *Pseudoplectania nigrella*, that grows on the shady floors of north-European pine forests. It was isolated from other proteins secreted by the fungus using the screening and selection procedures refined by Novozymes for use in its more traditional business areas such as the detergent and brewing industries.

“One of the reasons why Novozymes has been able to make such strides with its AMP programme is that many of the

core skills that we have here in-house were transferable to this area,” says Søren Kjærulff, director of antimicrobial peptides at Novozymes.

“These skills include protein design, strain development and improvement, and ultimately will include our ability to produce proteins on a large scale, which will be critical to producing these compounds commercially,” he adds.

### Unique properties

In comparison with many other AMPs, plectasin has some unique properties that make it particularly exciting. Preclinical testing has shown that plectasin has a good safety profile and high specificity and does not adversely affect other cells such as red blood cells. This means that it can be given in large doses with little or no adverse reaction. Furthermore, early testing has shown that it has no cross-resistance with other antibiotics such as penicillin, erythromycin and chloramphenicol.

Indeed, results from animal testing have been so compelling that they were recently published in the prestigious scientific journal *Nature*, an achievement of which the scientists working on the programme are justly proud.

The data presented in the *Nature* article shows the activity of plectasin against *Streptococcus pneumoniae*, a bacterium responsible for a host of diseases, including community-acquired pneumonia, sepsis and otitis media. The results show that plectasin kills *S. pneumoniae* at rates

comparable to penicillin and vancomycin. Importantly, however, the mechanism of action, which is still being unravelled, appears to be different to that of these older antibiotics. This means that the mechanisms by which bacteria develop resistance to these antibiotics will not work against plectasin.

### Next steps

According to Søren Kjærulff, the product is still in the preclinical phase and it will be for many years before a finished product reaches the market.

“It is expected that most of the future research and potential commercialisation will take place in liaison with a partner,” he says.

Nevertheless, the development of AMPs, and plectasin in particular, is an exciting prospect when increasing resistance threatens the use of many conventional antibiotics. As the authors of the *Nature* article put it so eloquently in their conclusion to the paper: “The ‘Antibiotic Era’ was born almost 80 years ago when an uninvited *Penicillium* spore landed on a Petri dish and eliminated nearby staphylococcal colonies. Perhaps its duration can be extended by antimicrobial peptides such as plectasin produced by other fungi.” ●

### FOR MORE INFORMATION

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