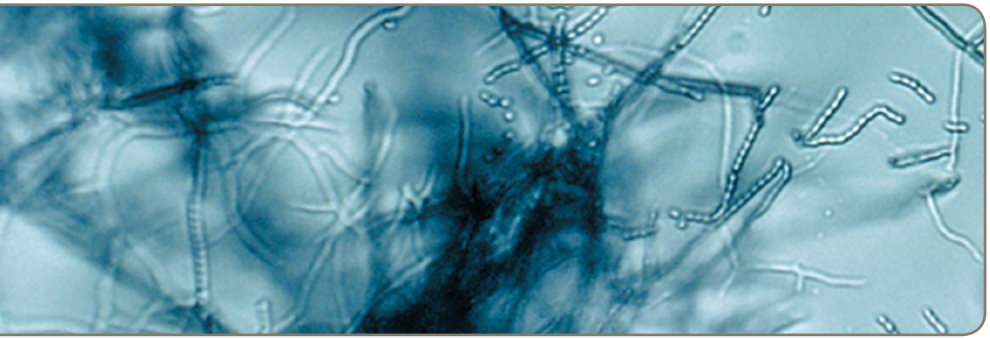
New antibiotics from bacterial bioscience



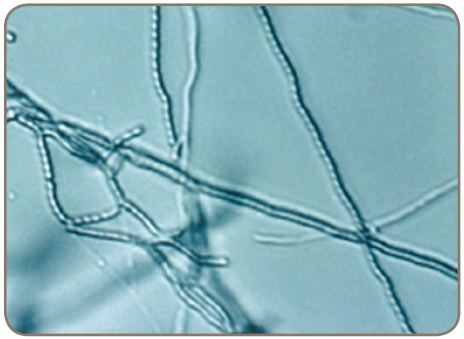


Image: Slide culture of *Streptomyces sp.*
Credit: US Centers for Disease Control and Prevention

Natural products from certain bacteria are forming the basis of promising new antimicrobials being developed to tackle drug-resistant infections. Researchers led by Professor Mervyn Bibb at the John Innes Centre[1], which receives strategic funding from BBSRC, are studying a group of bacteria called actinomycetes, that produce unique 'specialised metabolites'. These compounds are not vital to the bacteria's immediate survival, but can give them a long-term advantage in their natural environment. Many of these specialised metabolites inhibit the growth of rival microbes, and so could potentially be used to develop new human or animal antimicrobials.

Professor Bibb and his group have been studying a specialised metabolite, which acts as a potent antimicrobial compound, called NAI-107 (also known as microbisporicin). It is from a class of antimicrobials called 'lantibiotics' that are not currently used clinically, and is produced by the actinomycete *Microbispora*. In 2010, the researchers cloned the gene cluster that makes NAI-107 and developed a comprehensive understanding of how the bacteria synthesise the compound and control the amount that is produced[2,3].

Around the same time, Italian company NAICONS began developing NAI-107 commercially. An EU-funded project then brought the company, the JIC researchers, and scientists from Germany, Denmark, Italy and Switzerland together to develop it further[4]. The JIC researchers are helping to increase the amount of the lantibiotic produced by the bacteria. "A big issue for pharma companies, when they proceed towards clinical trials, is getting enough of the natural product, because often these compounds are made in very small amounts," says Professor Bibb.

"By understanding how the gene cluster is regulated we've been able to manipulate the natural producer and make significantly more."

NAI-107 is now on the verge of entering phase I clinical trials to treat MRSA. The market for MRSA therapeutics was estimated to be worth around $2.7Bn in 2012, growing to $3.4Bn in 2019[5].

Fundamental bacterial biology

The researchers at JIC are interested in the fundamental biology of actinomycetes – how natural products such as NAI-107 are made and regulated by the bacteria. However, Professor Bibb is also keen to ensure his work is of use to industry, and collaborates with researchers from pharmaceutical companies. "We develop a lot of technology, and fundamental understanding which we feed in to pharma and to small biotech companies. Additionally, two start-up companies have resulted from work carried out in our group," he explains.

One of those companies, Novacta Biosystems[6], was established in 2003 based on intellectual property developed by JC researchers studying the lantibiotic cinnamycin, from *Streptomyces cinnamoneus* bacteria. The group, in collaboration with Novacta,

developed a method using synthetic biology to construct 'artificial' genes to generate variants of cinnamycin[7], based on their understanding of how the bacteria produce and regulate the compound[8]. Novacta adopted this technology to develop and screen around 170 variants of cinnamycin for their antimicrobial properties.

The same technology was later used by Novacta during their in-house programme to develop an antibiotic based on the lantibiotic actagardine, which can be used to treat *Clostridium difficile* infections. A semi-synthetic variant of actagardine called NVB302 has successfully passed phase I clinical trials and is now waiting to enter phase II[9].

A potent antibiotic

Professor Bibb is also using synthetic biology to develop improved variants of the antibiotic tunicamycin, produced by the actinomycete *Streptomyces chartreusis*[10]. Working with Professor Ben Davis' group at Oxford, Professor Bibb and colleagues are investigating whether it is possible to use synthetic biology to modify tunicamycin to make it more suitable for use as a human antimicrobial.

"It's a very potent antibiotic," says Professor Bibb. "The attractive thing from an antimicrobial perspective is that it has a clinically unexploited target. It targets the production of lipid I, which is used in the production of the bacterial cell wall. No one else has used that as a target, so there is no resistance out there in the clinic at the moment."

"The bad thing is that it also inhibits [a vital biological process called] protein glycosylation in people, so it is toxic."

The aim of the latest project is to use synthetic biology to modify tunicamycin so that is loses its toxic effects in people while retaining its antimicrobial properties[11].

BBSRC and its predecessors have funded research into the biology of the actinomycetes, and in particular a species called *Streptomyces coelicolor*, since the 1960s[12]. Much of this research was conducted at JIC, and in 2002 resulted in the first sequence of an actinomycete genome; that of *S. coelicolor*.

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