

Soil bacteria to produce new antibiotics

An ever-growing number of genomes of soil bacteria of the genus *Streptomyces* are being sequenced. Using a method known as “genome mining”, researchers at the University of Tübingen are working on the identification of gene clusters that have the potential to be used in industrial biotechnology for the production of new antibiotics and other pharmaceutically active substances. To achieve this, the biosynthesis gene clusters are integrated into special production strains where they are optimized.

Antibiotics have been a medical success story ever since they were first used. However, many antibiotics have become less effective as more and more bacterial pathogens are becoming resistant to antibiotic treatment. “There is an immanent need for new antibiotics due to the large number of bacteria that have evolved resistance to antibiotics. However, far too few new antibiotics have been developed over the last decades. And this discrepancy has become one of the major problems in pharmaceutical research,” said Prof. Dr. Lutz Heide from the Pharmaceutical Institute at the University of Tübingen. Heide is one of several researchers around the world who focus intensively on the discovery and development of new antibiotic substances with the aim of closing the gap in effective antibacterial treatments.

Heide has been working with Prof. Dr. Wolfgang Wohlleben from the Interfaculty Institute for Microbiology and Infection Medicine at the University of Tübingen for many years. The two scientists share a common interest in the use of soil bacteria, the *Streptomyces* species in particular, as sources of antibiotics. In addition, they are working jointly to intensify research into anti-infective drugs in Tübingen, and to this end they are also involved in the establishment of the German Centre for Infection Research in Tübingen.



Prof. Dr. Lutz Heide from the Institute of Pharmacy at the University of Tübingen works intensively with European colleagues in the development of new drugs. © private



Streptomycetes as antibiotics producers – classics with huge potential



Streptomyces - a promising source of drugs. © Paas, Tübingen

Soil bacteria have long been potent antibiotics producers. This comes as no surprise due to their ability to live in a relatively heterogeneous environment: bacteria in soil have to withstand changing, sometimes rather extreme environmental conditions, and are also faced with a broad range of enemies and competitors. Bacteria have therefore evolved a plethora of biosynthesis pathways that enables them to produce antibiotic substances; they have developed a sophisticated regulatory system with genetic and epigenetic components to produce effective substances for fighting off enemies.

In their investigation of the biosynthesis genes and their complex regulation in Streptomyces, the Tübingen researchers benefit greatly from the progress made in DNA sequencing technologies. "Streptomyces are the most successful producers of antibiotics and have been studied in great detail. The sequenced genomes reveal that Streptomyces species are able to synthesize between 15 and 35 different antibiotics, including substances we've never seen before," said Heide. Considering the fact that a large number of soil bacteria exist and that only around 0.3 per cent of them have been subject to laboratory investigations, there is still a huge number of antibacterial substances to be discovered.

The European ERA-IB programme brings together international expertise

As part of the ERA-IB framework, which fosters innovation in industrial technology, the European Union is supporting Heide and Wohlleben over the next three years in their effort to discover new antibiotics and potentially also other drugs and make them suitable for medical applications. The Tübingen researchers are involved in two large cooperative projects dealing with drugs produced by Streptomyces bacteria. "The projects focus on different steps in the utilization scale and therefore complement each other perfectly," said Heide.

Prof. Heide is the coordinator of the "GenoDrug" project. As is a common requirement for EU

projects, the project also involves partners from several EU countries. GenoDrug brings together gene regulation experts from Poland and the Netherlands, Spanish scientists who are specialists in testing the efficacy of new substances and in developing molecular genetic strategies for optimizing bioproduction. A team from Finland, which also has a large number of medium-scale fermenters in which optimized *Streptomyces* strains can be cultured, contributes its process know-how to the project.

The major goal of the GenoDrug team is to develop a method that allows them to activate silenced gene clusters that contain the construction plans for interesting antibiotics and potentially also for other drugs to be used in the treatment of cancer, amongst other things. These gene clusters will be optimized and integrated into production strains. So in principle, the project is all about creating a new drug development technology. "We want to analyze the bioactivity and toxicity of the substances identified using the genome mining method and then produce the substances in the milligramme scale," said Heide explaining their ambitious goal.

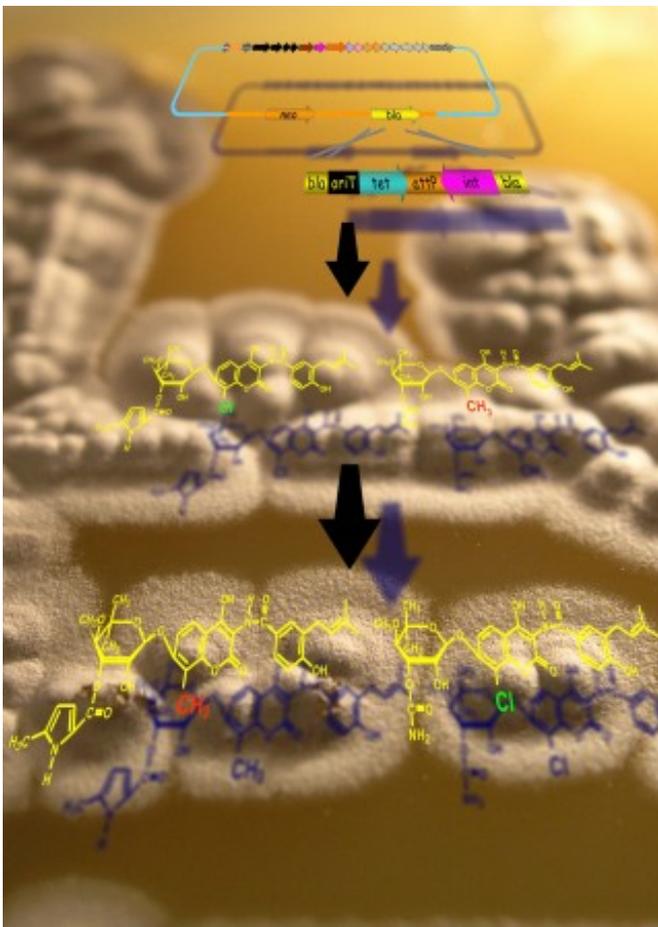
Bioproduction of anti-infectives and anti-tumour drugs will be optimized

The second collaborative project, IMMUNOTEC, is being coordinated by Prof. Dr. Juan-Francisco Martin from INBIOTEC, a biotechnology institute in the Spanish city of Leon. In addition to the teams led by Heide and Wohlleben, the project also involves a Spanish SME that produces antibiotics. The project focuses on known drugs that can be produced with *Streptomyces* species – tacrolimus and ascomycin. These two substances are effective immunosuppressants and are used, amongst other things, to prevent rejection of organ transplants. Further developments of these substances also have huge potential for tumour treatment. "The patent relating to the production of tacrolimus has recently expired, which is one of several reasons why we have included this substance in our research programme," said Heide. The project partners plan to develop *Streptomyces* production strains that enable the production of larger quantities of pharmaceutically active substances at a considerably lower price.

"In order to achieve such goals, "random mutagenesis" is the method of choice for changing the genetic information of an organism in a stable manner, resulting in mutations. We hope that our methods, which target the regulation of gene expression, will enable us to achieve our objectives more quickly. We also intend to optimize the methods for our specific purposes. In order to do this, we will integrate the gene clusters of interest into other bacteria. We will use the same genus of bacteria, but another species, for example *Streptomyces griseus*, as production strain," said Heide.

Sophisticated molecular biology and genetic engineering are key

Something that appears to be relatively easy thanks to the availability of innovative genetic engineering methods is nevertheless associated with quite a few pitfalls. Heide explains, "The gene clusters we are dealing with are around 100 kb in size, which makes them difficult to clone. We need to produce clones that contain the inserts of several plasmids. And we also work with artificial bacterial chromosomes, which are far from easy to handle. Another challenge is to integrate the huge clusters stably into the production strain. This is why we want to optimize the rest of the bacterial metabolism for our purposes, for example the



The DNA of Streptomyces bacteria will be recombined in order to produce new antibiotics with biotechnological means. © Paas, Tübingen

nitrogen- and phosphate-dependent regulatory pathways,” said Heide.

Such sophisticated and complex relationships can only be achieved using bioinformatic methods. Both projects rely on bioinformatic methods in order to deal with and interpret the huge amount of data produced. In the medium term, the research will use metabolism models and simulations to help them advance their laboratory work.

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