Website address:
https://www.gesundheitsindustrie-bw.de/en/article/news/georg-sprenger-virtuoso-of-bacterial-metabolism-manipulation

Georg Sprenger - virtuoso of bacterial metabolism manipulation

Microorganisms can be taught to do things that they are unable to do naturally. Bacterial metabolisms can be changed in order to make the bacteria produce new products and convert new substrates. In addition, existing bacterial conversion strategies can be optimised for biotechnological applications. Prof. Dr. Georg Sprenger is the head of the Institute of Microbiology at the University of Stuttgart and he is an expert in this field.

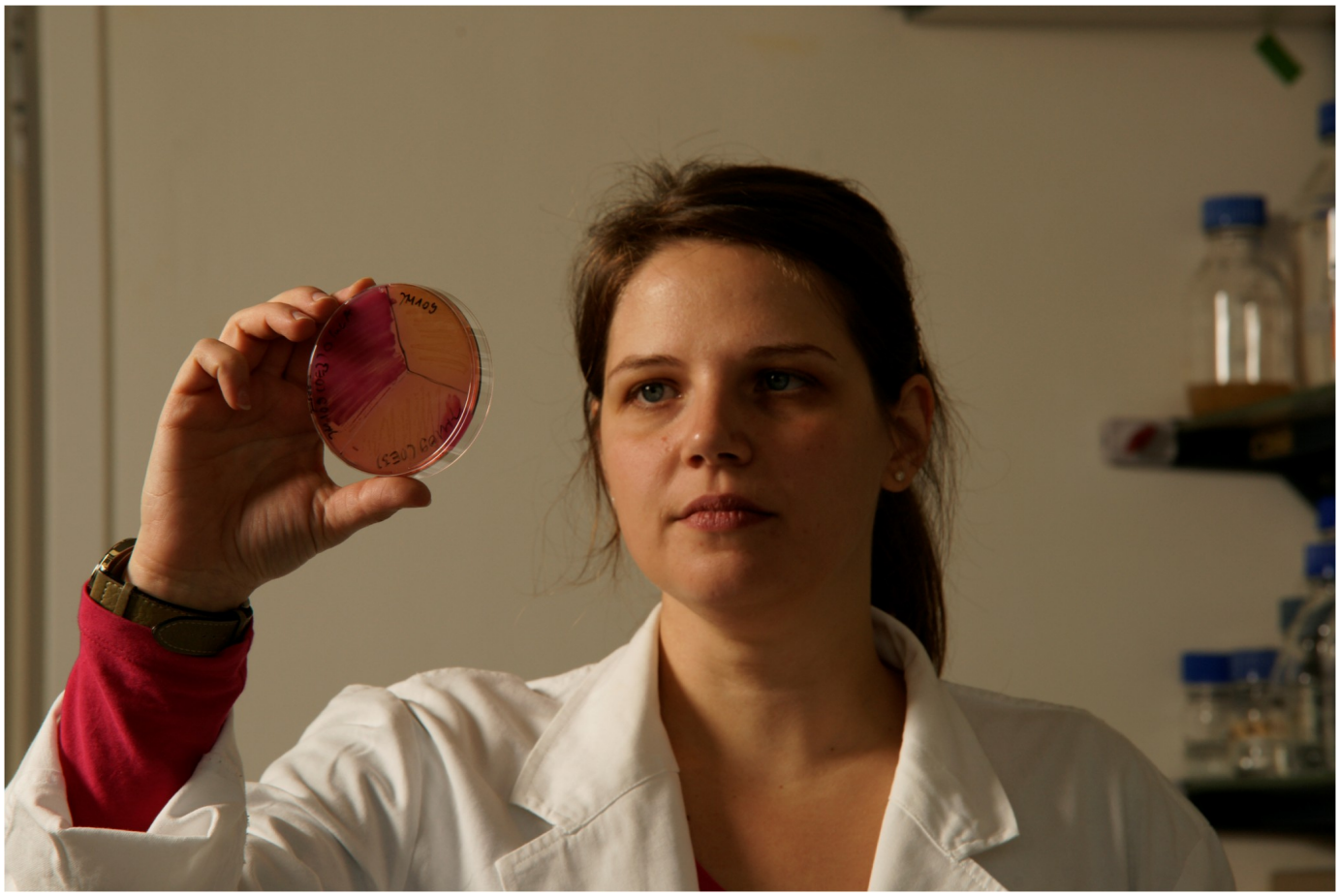
Prof. Dr. Georg Sprenger's professional career is marked by his fascination for deliberately altering biological processes, and it is this fascination that is a major source of motivation for the microbiologist. As a student, he originally wanted to become a zoologist but he changed his mind and turned instead to genetic engineering and biotechnology. "I originally chose to study biology because I wanted to become a zoologist. However, while I was still at university I decided to study the role of microorganisms in genetic engineering and biotechnology instead," Sprenger explains. He was a student at the University of Regensburg until 1981, and it was during this period that scientists discovered that biological systems had enormous potential for the production of valuable substances. Sprenger's graduate thesis focused on bacterial genetics, a topic he continued as a doctoral student at the University of Osnabrück where he obtained his PhD in 1985. "We transferred Klebsiella pneumoniae genes into E. coli, thus enabling the degradation of saccharose," said Sprenger making it clear that this was a huge methodological challenge at the time.

The objectives of his graduate and doctoral research were the same ones as he has today: "I wanted to gain a better understanding of metabolic pathways and find out the reasons why such a large number of diverse metabolic pathways exists, and I am still pursuing this goal today," Sprenger explained. During his postdoctoral period at the Harvard Medical School, Sprenger worked on bacterial metabolic pathways that enabled the degradation of glycerine. But only now, 25 years on, has the degradation of glycerine become a key process in biodiesel production, thus making Sprenger's work extremely important. The boom in biodiesel production generates large amounts of raw glycerine as waste product. "In rape mills, rape oil is turned into fatty acids and glycerine, which accounts for around ten per cent per weight. This means that in Germany around 500,000 t of glycerine are generated by biodiesel production every year," said Sprenger who is working on the challenging task of turning raw glycerine into useful materials using bacteria in a process that does away with expensive processing steps.

Large-scale amino acid production

Prof. Dr. Georg Sprenger has been the Director of the Institute of Microbiology at the University of Stuttgart for around seven years.

E. coli bacteria, popular all-rounders that are used for many investigations, are once again put to good use in Sprenger's work. "E. coli bacteria possess genes for the production of valuable amino acids such as L-phenylalanine, which, amongst other things, is used for the production of the sweetener aspartame. We overexpress these genes and manipulate the bacterial metabolic pathways to make the bacteria produce L-phenylalanine more efficiently," Sprenger explains. The research carried out by the Stuttgart scientists is funded by the German Environmental Foundation (DBU, Deutsche Bundesstiftung Umwelt). "The DBU is very interested in introducing closed substance cycles with no unusable by-products," said Sprenger explaining why the DBU is keen to fund this type of research. In addition, the biotech industry is also extremely interested in more efficient bioproduction.



Dr. Sarah Schneider holding one of the most important tools used at the Institute of Microbiology: an agar plate used to culture bacteria.
© Christoph Bächtle, BIOPRO

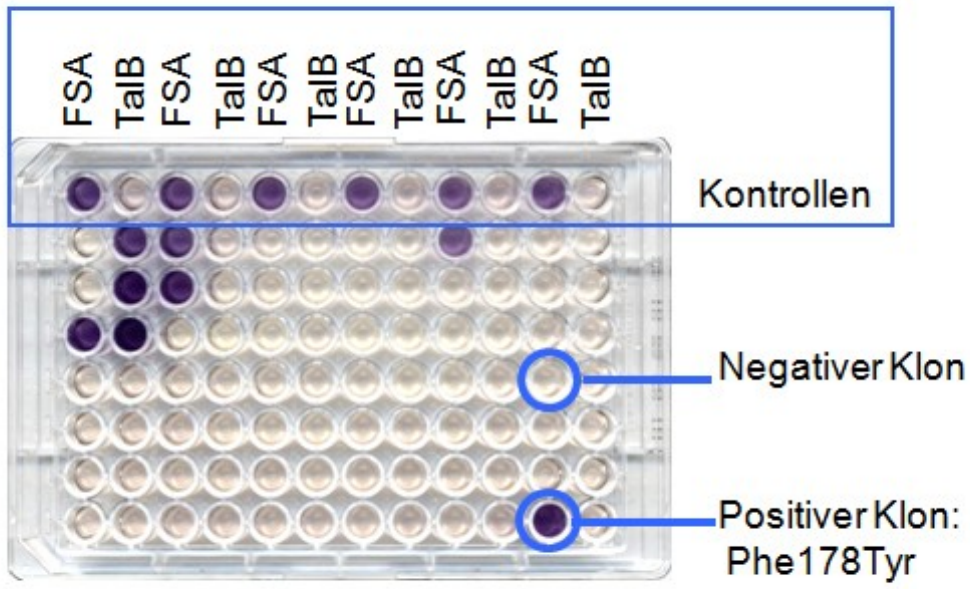
However, suitable research results are not always available at the exact moment when industry suddenly becomes interested in certain products or services. Sprenger had first-hand knowledge of this problem during the 1990s. After a research period in the USA, he returned to Germany to work as scientific assistant in the department of his former supervisor, Prof. Dr. Lengeler, at the University of Osnabrück. A year later, he moved to what is now the Jülich Research Centre where he stayed until 2003, when he accepted a chair at the University of Stuttgart. "Back then, Jülich had a well-respected biotechnology department run by Hermann Sahm," said Sprenger explaining that he shared Sahm's interest in 'teaching' bacteria new characteristics. He worked with the bacterium Zymomonas mobilis, which is also used for the production of palm wine and Mexican pulque, an alcoholic drink made from the sap of the maguey plant. Zymomonas mobilis bacteria can convert sugar into alcohol, but have the disadvantage that they can use only a handful of sugars (saccharose, glucose, fructose) as substrate. "We tried to manipulate the bacterial metabolism in order to make the bacteria use C5 sugars from hemicelluloses, large quantities of which are found in wood and straw," said Sprenger. In the mid-1990s, Sprenger and his team finally achieved their goal, but industry was not yet interested in their achievements. Nowadays, things have changed drastically and Sprenger's approach has become extremely important for the industrial use of natural resources.

For Sprenger himself, these investigations were the starting point of a research topic that has since become his second major scientific interest. Sprenger started working with bacterial metabolic enzymes, particularly E. coli transaldolases and transketolases, by expressing and characterising these genes in Zymomonas bacteria. Sprenger and his team are currently looking for new reactions that can be triggered by these enzymes. Although the approach is relatively new, it nevertheless opens up a plethora of new applications. "One of our goals is to produce sugar analogues into which we introduce chemical groups using bacterial transaldolases. Chemists can produce such chemical

groups, for example sulfo-, amino-, or deoxy groups," said Sprenger.

Optically pure building blocks for the pharmaceutical industry

The production of stereospecific substances for use in the pharmaceutical industry is a highly interesting option. Using bacterial enzymes, the researchers are able to produce one single optical isomer of a certain compound. “Chemical production often leads to mixtures, i.e. racemates with a 50:50 ratio of (R) and (S) isomers. Racemic mixtures can have severe consequences, as was shown by thalidomide. Thalidomide is a sedative drug introduced in the 1950s. Several thousands of children were born with deformities after thalidomide was given to pregnant women. The production of thalidomide resulted in a racemic mixture of “safe” and teratogenic thalidomide, which turned out to be the cause of deformities. Since then, regulations have been put in place that require racemic mixtures to be tested, the effect of left- and right-handed isomers to be established and allow only the effective and safe enantiomer to be used for medical treatment,” Sprenger explains. This example highlights how important and useful it is to be able to produce one single stereomer.



Sprenger has developed a system for screening mutant enzymes that is based on a colour reaction.

Sprenger uses a process known as mutagenesis to alter metabolic pathways and the associated enzymes. This process is followed by the screening and selection of useful and beneficial mutants. However, mutagenesis does not always lead to the desired effects. "The bacteria have adapted to their specific environment during evolution and often we come up with a metabolic pathway that leads to exactly the opposite of what we expected."

However, we have access to efficient screening methods that help us identify enzymes with interesting altered properties in terms of substrate affinity, activity or substrate specificity. In biological production, it is often more effective if the altered enzyme can convert more than just one

substrate," said Sprenger who, in cooperation with his team, has developed a screening method based on colour reactions. "We are able to screen several thousand clones in a couple of days," said Sprenger. The researchers have already found an enzyme that is now being applied in practice. This altered enzyme is a glucosidase inhibitor which delays the processing of glucose in the human gastrointestinal tract, something that is a desired effect in diabetes type II patients. A spin-off company of a Spanish research partner is planning to market the enzymatic product as a dietary supplement.

Optimisation of bacterial production following the building block principle

There are occasions when Sprenger needs to combine a particular metabolic production pathway with a bacterial strain that best suits his plans. In a BMBF project, also involving BASF and another big company as partners, the researchers plan to optimise the Pseudomonas putida metabolism for the production of certain substances. Sprenger and his team will once again transfer the required E. coli genes into Pseudomonas. “E. coli is far more sensitive to solvents used in biological production,” said Sprenger explaining the reasons for using E. coli genes.

Considering the broad range of projects that Sprenger and his team are working on, it comes as no surprise that the team has a large number of collaboration partners. The team works closely with groups at the University of Stuttgart, external research groups and companies. In general, Sprenger always tries to pursue a well-balanced mixture of theoretical and applied projects. “I would like to continue focusing on basic and applied science in the future because I know from experience that applied research projects will at some stage reach a point where inspirations from basic science are needed,” said Sprenger who also makes a point of communicating the benefits of basic and applied science to his students.

Sprenger wants his students to understand that many principles are common to different biological systems. He hopes that this understanding will help the students to discover things and principles that are typical for a specific biological system. “My team and I are seeking to communicate a comprehensive picture and we attach great importance to comparative observations. We then explain to the students how the microbial metabolism works, provide them with information about the enzymes and substrates involved, which products can be produced by the bacteria and how they are produced,” said Sprenger.

Further information:
University of Stuttgart
Institute of Microbiology
Allmandring 31
70569 Stuttgart
Tel.: +49 (0)711 6856-5487
E-mail: georg.sprenger(at)imb.uni-stuttgart.de

Article

11-Oct-2010
leh
BioRegio STERN