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Alexander Titz: molecular design to combat antibiotic-resistant bacteria

Pseudomonas aeruginosa has become an important cause of infection, and is often picked up in hospitals, especially by patients with weakened immune systems. It can cause respiratory and urinary tract infections, as well as lead to infections on implants and wounds. P. aeruginosa lives in a gel-like matrix, a so-called biofilm that is highly resistant to antibiotics, making it very difficult to eradicate. Dr. Alexander Titz and his team at the University of Konstanz are aiming to use the structure-based rational design of carbohydrate conjugates to render the pathogen harmless.

Dr. Alexander Titz, chemist at the University of Konstanz
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Antibiotics have long been the most effective weapon against bacteria and the infections they cause. However, bacteria's resistance to antibiotics has been growing at a ferocious rate due to their very short generation time, which enables mutations that confer antibiotic resistance to accumulate very fast. In addition, bacteria are being exposed to increasing selection pressure as a result of antibiotics frequently being overused or used incorrectly. Bacteria thus become resistant and are more likely to survive. "Antibiotics are only effective against bacterial infections. However, they are often used for the treatment of viral infections, which renders them ineffective. In addition, an unfinished course of antibiotics enables bacteria to survive and develop resistance," said Dr. Alexander Titz, biochemist at the University of Konstanz. Only a small number of new antibiotics is being developed and the number of bacteria that are resistant to common antibiotics is set to increase.

Carbohydrate-protein interactions

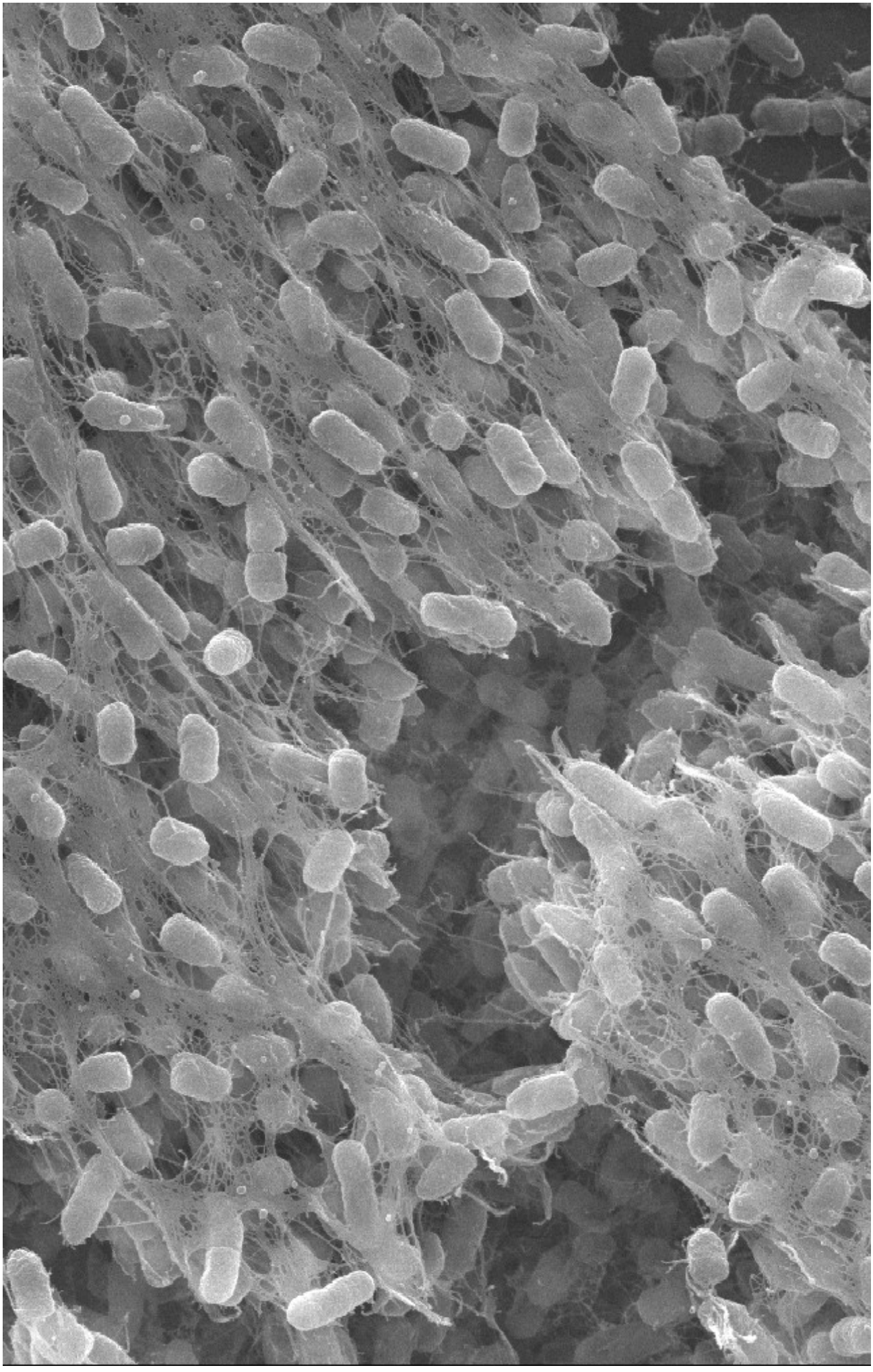
Dr. Alexander Titz and his team of researchers are very interested in Pseudomonas aeruginosa, an opportunistic pathogen that has become resistant to many antibiotics. It is the fourth most frequent cause of hospital-acquired infections. "The bacteria are known to form biofilms on implants, open wounds or in the respiratory organs of artificially respirated patients. Biofilms effectively protect bacteria against antibiotics, thus leading to chronic infections and high mortality," said Titz. The disadvantage of artificial respiration is that bacteria and other germs can enter a patient's lungs with the air that is inhaled. Patients with respiratory disorders who need artificial respiration are usually unable to clear foreign material from their lungs, therefore causing mucus to aggregate and become a breeding ground for bacteria, which can lead to lung infections such as pneumonia. Bacteria can grow on the surface of the lungs as well as on the surface of respirator tubes. Pseudomonas aeruginosa infection is also a serious problem in cystic fibrosis patients. The mortality rate in such patients is very high as the bacterial biofilm causes chronic lung infections.

"A biofilm is a complex aggregation of bacteria growing on solid substrates, implants or tissue, for example, and embedded in what is known as an extracellular matrix. This matrix consists of carbohydrates and proteins. We are therefore focusing specifically on carbohydrate-protein interactions," said Dr. Titz. Biofilms physically protect bacteria against antibiotics as well as against the human immune system. "Standard antibiotic treatment of bacterial infections lasts 5 to 10 days during which time cells known as persister (dormant) cells can survive the antimicrobial treatment, therefore allowing acute infection to recur," explains the chemist. Although it is also frequently caused by other pathogens, this phenomenon is a common cause of chronic urinary tract infections, particularly in women.

Blocking lectins and dissolving biofilms

Dr. Titz and his team are specifically interested in Pseudomonas aeruginosa biofilm. This extracellular matrix has a very complex composition and acts like molecular glue. Approaches aimed at dissolving this glue are based on the enzymatic destruction of extracellular DNA, which is one of the components of biofilm. "This approach is associated with several problems. Amongst other things, it is rather difficult to bring big molecules such as enzymes to the site of infection, implants for example," said Dr. Titz who, together with his team, is therefore specifically focusing on other components of "molecular glue", lectins for example. Lectins mediate the maturation of the biofilm by combining the different carbohydrate structures on the host cell, the bacterial cell and in the extracellular matrix. "Our approach focuses on the selective blocking of these lectins with molecules that can also be transported to surface-exposed sites such as implants. We hope that this will prevent the formation of biofilm as well as dissolve already existing biofilm," said the researcher explaining that bacteria that are not embedded in the extracellular matrix can be more effectively treated with antibiotics and cure chronic infections.

These molecules are derived from the three-dimensional structure of Pseudomonas aeruginosa lectins. They are produced by way of organic synthesis and then tested in a biochemical assay for their ability to inhibit lectins. "This leads to a structure-activity relationship that forms the basis for the development of a new generation of inhibitors," said Dr. Alexander Titz. In the laboratory, the molecules are also tested directly in Pseudomonas aeruginosa biofilms which helps the researchers develop effective inhibitors.



Microscopic image of Pseudomonas aeruginosa biofilm with rod-shaped bacteria embedded in the extracellular matrix

This principle also works for other bacteria, including uropathogenic Escherichia coli, which are the major cause of chronic urinary tract infections. “Pharmacies sell cranberry extract that has been found to prevent the lectin-mediated adhesion of bacteria. However, the practical outcome is rather limited,” said Titz going on to explain that “recent studies have shown that specific lectin inhibitors have the potential to diminish the occurrence of urinary tract infections in mice”. These synthesised inhibitors are defined individual substances with a precisely known range of effects tailored to the selective inhibition of the lectins.

Alexander Titz and his team are looking for industrial partners who are interested in the molecules’ ability to inhibit Pseudomonas lectins and would like to work with his team on the development of anti-infective drugs.

About:

During his university studies, Dr. Titz worked on the organic synthesis of natural compounds. He gained a great deal of valuable experience during his one-year ERASMUS exchange in Bordeaux, France in the laboratory of Prof. Stéphane Quideau. In 2004, Titz did his degree thesis under the supervision of Dr. Marcel Blommers from Novartis Pharma AG and Prof. Boris Schmidt from the TU Darmstadt. He went on to do his doctorate on the medical chemistry of carbohydrate-protein interactions in the laboratory of Prof. Beat Ernst at the University of Basle in 2008 and his post-doctoral studies with Prof. Markus Aebi at the ETH Zurich on the molecular and microbiology of carbohydrate-protein interactions. He has been head of a group of researchers in the Department of Chemistry at the University of Konstanz and member of the Future College since 2010.

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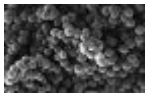

Multiresistant pathogens – a self-inflicted threat?

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