Chasing resistant microbes.

In Europe, an estimated 25 000 deaths per year can be attributed to resistant pathogens. Classic antibiotic therapies are increasingly ineffective. Time to think about completely new concepts. This is what Martin Fussenegger from the D-BSSE does. He wants to tackle the pathogens with designer cells.

Prof. Martin Fussenegger heads the research group Biotechnology and Bioengineering at the Department of Biosystems Science and Engineering (D-BSSE) of the ETH Zurich in Basel. He studied molecular biology at the Biozentrum and completed his diploma thesis under supervision of Werner Arber. He continued his studies at the Max Planck Institute for Infection Biology in Tübingen, where he received his doctorate in 1994. In 2002, he received an SNSF Professorship followed by a professorship at the ETH Zurich two years later. In 2009, he moved to Basel to establish the D-BSSE here.

For years, infection biologists have been warning about the rapid spread of antibiotic resistance. The WHO even speaks of an era of deadly infections. Increasingly more bacteria are losing their sensitivity to antibiotics. Especially in the hospitals, physicians observe this development with great concern. Drugs that have been used successfully to fight infections for many years are suddenly ineffective. And the situation is becoming worse.

One of the most feared pathogens is the bacterium *Staphylococcus aureus*. Although referred to as a hospital bug, it is usually a harmless colonizer of the skin. However, should it enter the body through wounds or implants, it can lead to life threatening infections. Multi-resistant staphylococci (MRSA) in particular, present a deadly threat. Equipped with an arsenal of defensive strategies they can evade antibiotics. Moreover, staphylococci produce a mucous layer that protects them from antibiotics and immune cells. They also form this dangerous biofilm on the surface of implants such as a hip prosthesis, cardiac pacemakers or artificial heart valves.

Martin Fussenegger's research group at the D-BSSE of the ETH Zurich in Basel is fighting the hospital bug in a very innovative way. Like a hunting dog trained to track a hare, he has set human cells onto staphylococcus. "We have equipped designer cells with various sensors. These are specific receptors found on human immune cells which detect bacterial components, such as cell wall fragments," says Martin Fussenegger. "This information is transmitted via a synthetic signaling cascade and stimulates the production of the antibacterial peptide lysostaphin, which kills the staphylococci. This substance is not produced by human cells."

In order to test their system in a mouse model, they first had to embed the designer cells into tiny alginate gel capsules. They are about half a millimeter in diameter and resemble caviar in their appearance and consistency. Packed in this way, the human cells are protected from the mouse's immune system. "We already started working with these alginate capsules more than ten years ago and we are not the only ones," says Martin Fussenegger. "The capsules have been clinically tested and are already being used for the transplantation of pancreatic Langerhans islets into patients with type 1 diabetes."

The capsules have tiny pores through which the bacterial fragments can reach the embedded cells. Lysostaphin can easily diffuse out. Because the capsules are so small, they can conveniently be injected via a cannula to be deposited under the skin or in the abdomen. The encapsulated cells then automatically connect to the blood circulation enabling them to interact continuously.

From the start, Martin Fussenegger and his team were aware that they had to test their system in an animal model. However, without experience in infection biology procedures, not being able to handle MRSA at this safety level and requiring a suitable infection model, they approached the infectious diseases specialist Nina Khanna at the University Hospital Basel. They knew that she had established the so-called "tissue cage model" in the mouse, in which a plastic body, simulating an implant, is implanted. "With our designer cells we were able to dissolve the staphylococcal biofilm formed on the implant. Even newly beginning infections can be contained with the help of these cells."

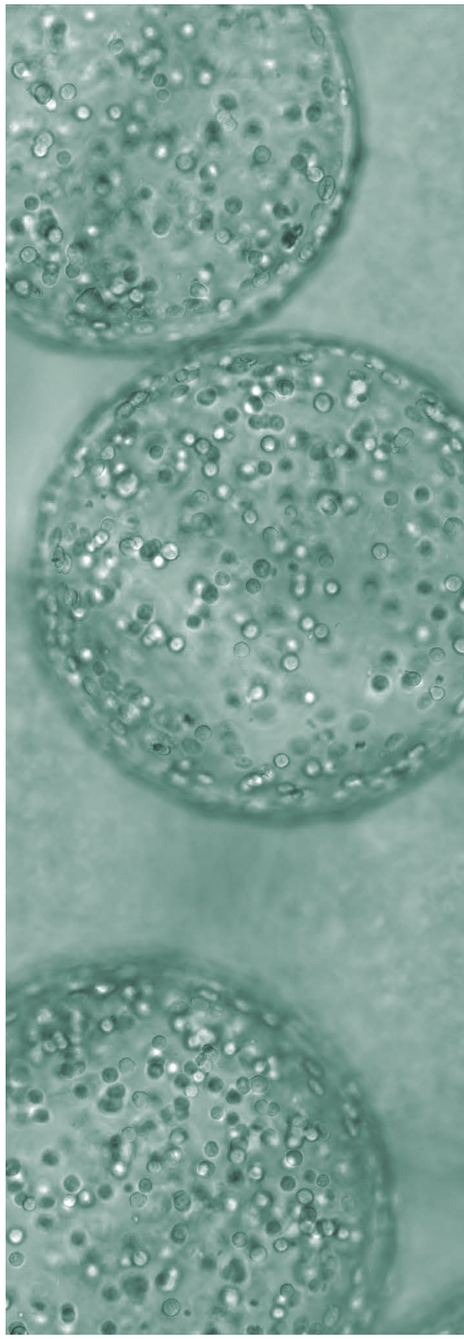
According to Martin Fussenegger, the advantage over conventional antibiotics lies in the idea of the molecular switch. "Our systems are not permanently switched on. Lysostaphin is therefore not being constantly released, but only if staphylococci are present. Once the bacteria are eliminated, the system turns off again. Hence, the level of lysostaphin is not permanently elevated." In contrast to the classical treatment, in which high doses of antibiotics are administered for almost two weeks, favoring the selection of resistant bacteria, the molecular switch prevents a rapid development of resistance.

The range of applications for the designer cell is extremely broad. Theoretically, they could also be reprogrammed. For example, by exchanging the receptors for the input signal or changing the output therapeutic peptide, other pathogens can be specifically combated. The system is very flexible and can be adjusted and expanded accordingly.

Martin Fussenegger works in various fields. His approach, however, is always based on the concept of the "molecular prosthesis". He equips designer cells with a sensor, whether for blood lipids, blood glucose levels or now, for the first time, for bacteria, and deposits the cells in the body like prosthesis. "We combine this sensor technology with the release of therapeutic proteins. This could be an appetite suppressing hormone to reduce elevated blood lipids; insulin when the blood glucose level is too high or, as in this case, antibacterial peptides when pathogens appear in the blood. The concept of a molecular prosthesis, to repair defects in the body, underlies all of our projects."

Although the project has a great potential for application, the step to industry is not so easy. "There is a yawning gap in the path from academic proof-of-concept research to the clinic. Translational research is still too early to get industry on board. Therefore, we are always looking for partners in industry and with BioVersys we have founded our own spin-off. It is important in the long-term to strengthen the financial support of academic translational research but this must be solved at the political level." ☒

Y. Liu, P. Bai, A. Woischnig, G. Charpin-El Hamri, H. Ye, M. Folcher, M. Xie, N. Khanna, M. Fussenegger «Immunomimetic Designer Cells Protect Mice from MRSA Infection» Cell (2018).



Fighting infections: alginate gel capsules packed with designer cells.