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# The answer to antibiotic resistance may lie in the microbiome

**Globally, increasing numbers of bacteria are becoming resistant to common antibiotics. Moreover, many reserve group antibiotics are no longer effective for infections caused by multidrug-resistant pathogens. Researchers in an excellence cluster at the University of Tübingen are investigating an alternative approach to combating bacterial infections. Their goal is to specifically influence the microbiome, the human microbial community.**

Prof. Dr. Andreas Peschel, spokesperson of the excellence cluster

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According to a recent report by the European Epidemiological Society (ECDC), around 670,000 people in the EU were infected with antibiotic-resistant pathogens in 2015; approximately 33,000 people died due to infections with antibiotic-resistant bacteria, and the numbers are increasing[1]. Bacterial infections, which many believed to be beaten a long time ago, are becoming a problem again.

"It goes without saying that huge efforts are being made to prevent the spread of antibiotic resistant pathogens, for example with better hygiene measures, and newer antibiotics that are still effective," says Prof. Dr. Andreas Peschel, head of the Department of Infection Biology at the Interfaculty Institute of Microbiology and Infection Medicine at the University of Tübingen. But since the discovery of penicillin in 1928 and the golden age of antibiotic discoveries in the 1940s to 1960s, only a few new antibiotic classes have been discovered[2].

Peschel believes that targeted intervention in the microbial ecosystem might be an effective way to tackle the problem of antibiotic resistance. Microorganisms colonise our mucous membranes, skin and intestines. These ecosystems serve as a reservoir for many potentially dangerous infectious agents. "In the case of the most serious and sometimes fatal infections, such as bloodstream infections, patients have often carried the bacteria around with them for years," says the microbiology professor.

In healthy people, the immune system usually keeps pathogens in check. However, infections can occur more easily when the immune system is weakened by an illness or when pathogens enter the body through open wounds or tube inlets, for example in patients in intensive care units - especially if the pathogens are resistant to antibiotics.

## Excellence cluster focuses on microbiome research

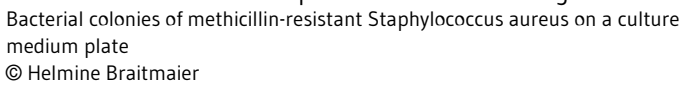
Is it possible to selectively eliminate pathogenic bacteria from the microbiome before they are able to trigger an infection? The "Control of microorganisms to combat infections" excellence cluster, set up in Tübingen in early 2019, is working on finding an answer to this question. Professor Peschel coordinates the research cluster together with Heike Brötz-Oesterhelt, his colleague and chair of the University of Tübingen Department of Microbial Bioactive Compounds, and Ruth Ley, microbiome researcher and director of the Max Planck Institute for Developmental Biology in Tübingen. In total, more than 25 research groups from Tübingen and other cooperation partners are involved in the project. The German and Baden-Württemberg governments are funding the cluster with around 37 million euros for the next seven years.

How is it possible to remove harmful bacteria from a person's microbiome without damaging the microbiome as a whole, as is usually the case with widely used broad-spectrum antibiotics? "A possible solution could be to transplant the entire microbiome of a healthy human without antibiotic-resistant bacteria to a person whose gut contains antibiotic-resistant bacteria and hope that the new bacteria will displace the unwanted bacteria," says Peschel. However, this procedure runs the risk of also transferring other infectious pathogens. Peschel believes that it would be far more sensible to introduce only benign bacteria that specifically eliminate unwanted pathogens.

## Bacteria fight back with antibiotics

Bacteria produce antimicrobial substances that help them gain an edge over other microbes in their struggle for space and food. Many of today's common antibiotics were therefore discovered in microorganisms - mostly in soil microbes. Peschel's

research group has recently shown that many bacteria that live in the human nose also produce antimicrobial agents3. The researchers wanted to find out why around a third of people carry Staphylococcus aureus, one of the most common hospital germs, as a stowaway in their noses, but why this does not affect the majority.



Bacterial colonies of methicillin-resistant Staphylococcus aureus on a culture medium plate
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The researchers discovered a novel peptide antibiotic called lugdunin in nasal swabs taken from people without antibiotic-resistant bacteria. Lugdunin is excreted by Staphylococcus lugdunensis and inhibits the colonisation of antibiotic-resistant S. aureus, i.e. methicillin-resistant S. aureus (MRSA) and other pathogens[4]. As part of the work carried out by the excellence cluster, Peschel intends to further characterise other antimicrobial substances produced by our nasal subtenants. In the meantime, the first groups of researchers have reported the discovery of antibiotics in human bacteria outside the nose. "The genes that theoretically control antibiotic synthesis are definitely present," says Peschel who believes that it is only a matter of time before the antibiotic treasure of our microbiome is uncovered.

For a long time, microbiologists have neglected the human microbiome. "Medical microbiologists are interested in infections rather than potential pathogens in the microbiome," says Peschel, explaining that in contrast, scientific microbiologists focus on specific model organisms and environmental bacteria. In addition, technological progress and the new possibilities offered by sequencing now make it possible to identify strains that could not previously be grown in the laboratory and have therefore been inaccessible.

## Manipulating the bacterial metabolism

This is the reason why little is yet known about human bacterial subtenants in humans. For example, it is not only the antibiotics produced by the bacteria that determine the order of dominance of the human gut flora, but the complete set of small-molecule metabolites found, i.e. the bacterial metabolome. “We have seen whole food chains where several bacteria symbiotically cooperate with each other: one bacterium breaks down a macromolecule and releases a substance, which is then further broken down by other bacteria and so on," says Peschel going on to highlight another benefit of microbiome manipulation: “If you know the metabolism of the human bacterial community, you can deliberately introduce nutrients to promote benign and exclude pathogenic bacteria.”

A new professorship for bacterial metabolomics will be established within the excellence cluster in order to shed light on this issue. In addition, a professorship for the imaging and simulation of microbiomes is also planned. It is also possible that another professorship will be established in the field of glycochemistry to explore how bacteria interact with their human host via sugar structures on their surface.

However, the researchers in the excellence cluster will not be limited to studying bacterial colonists of the human nose, intestines and skin. Some will also study the microbiome of wastewater and sewage treatment plants. "The mechanisms of how the bacteria of the different habitats influence each other are likely to be similar," explains Peschel.

The Tübingen excellence cluster brings together microbiologists, medical scientists, immunologists, chemists, pharmacists and bioinformaticians who can predict bacterial interactions from biomarker signatures, and ethicists who weigh the risks of microbiome manipulation. "The excellence cluster brings together exactly the right people who can make a contribution to microbiome research," says Peschel. Perhaps microbiome research can help avert the feared post-antibiotic era in which mundane infections will kill more and more people because existing antibiotics are no longer effective.

**References**


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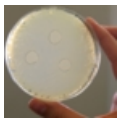
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