2026

HZI HELMHOLTZ Centre for Infection Research

InFact

The Magazine of the Helmholtz Centre for Infection Research

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DEFENSE AGAINST INFECTIONS

How modern research helps prevent diseases

DEAR READERS,

For many people, it's travel season almost all year round. Whether it‘s a trip to a city, a beach vacation, or a long-distance journey, we can now travel the world more freely than ever before. However, our mobility also makes it easier for pathogens to spread. Not only are we humans moving closer together due to ever-denser populations, but we are also getting closer to wild animals and the viruses and bacteria within them. To protect ourselves from transmission, we must first understand where specific pathogens live and how they spread. You can read about the detective work involved in this in our featured article on tracking down the monkeypox virus. Our immune system and microbiome—the community of microorganisms living in and on us—are responsible for ensuring that we do not become seriously ill. However, many pathogens have developed ways to circumvent these defenses. This is why our bodies need outside help in an emergency. In this issue, we present our approaches to preventing and treating infectious diseases at the Helmholtz Centre for Infection Research.

I hope you enjoy reading this issue!

Andreas Fischer, *Editor-in-Chief*

IMPRINT

Publisher:
Helmholtz Centre for Infection Research GmbH
Press and Communication
Inhoffenstraße 7 | D-38124 Braunschweig
presse@helmholtz-hzi.de
www.helmholtz-hzi.de/en

Photo credits: Title: Britta Freise; p. 2: Verena Meier; p. 3-5: Hamzah Shahid, HZI, Verena Meier; p. 6-9: Taï Chimpanzee Project/Constant Kaye/Carme Riutord-Fe/ HIOH/Alexander Mielke; p. 10-12: Adobe Stock/ Emiliia, Mathias Müsken, Janne Reinking; p. 13-15: Lucia Bernhardt; p. 16: Adobe Stock/PhotoArtHub (Stephan Dornbusch), TVN Corporate Media

Editorial staff: Dr. Andreas Fischer (Editor-in-Chief), Dr. Daniel Krug, Dr. Stephanie Markert, Dr. Charlotte Schwenner, Susanne Thiele (V.i.S.d.P), Dr. Magdalena Wlodarz

Design: Britta Freise

Print: Print Service Wehmeyer GmbH

MIX
Paper | Supporting responsible forestry
FSC® C106855
FSC www.fsc.org

Print product with financial climate contribution
ClimatePartner.com/11022-2607-1003

MINI-ORGANS FOR THE MEDICINE OF THE FUTURE

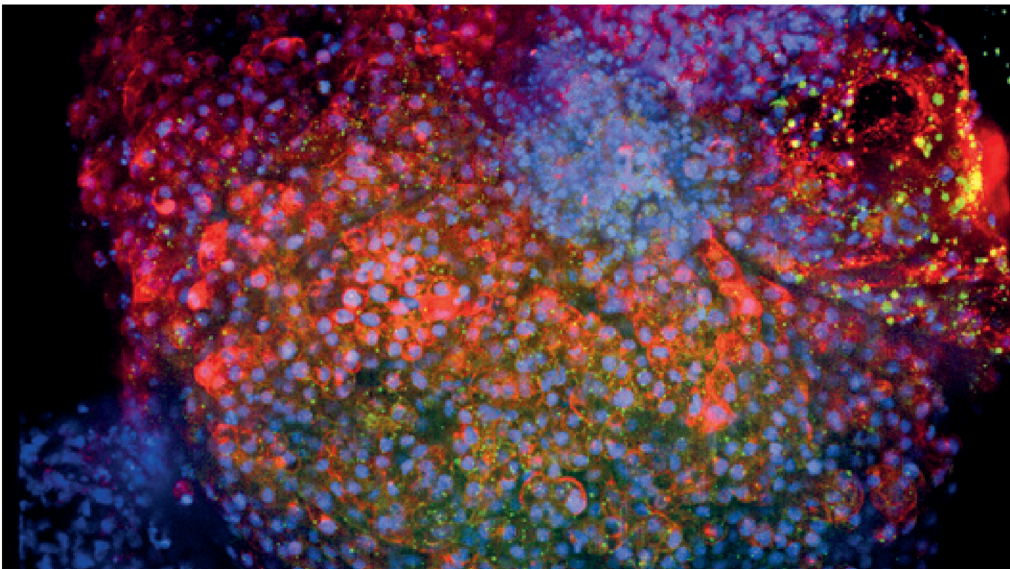
By Andreas Fischer

Organoids might sound a bit like science fiction. Yet they have firmly established themselves as a reality in research. Offering a wide range of possibilities, they enable scientists to study organ functions, diseases, and treatment options. These mini-organs are also opening up entirely new avenues for research into infections.

Molly works day and night. With just a soft humming sound, her gripper arm precisely moves cell plates from station to station. The tiny tissue structures are supplied with nutrient solutions through fine pipette tips. No action is random; every movement is accurate. Molly can produce up to 40,000 mini-organs in a month: small models of the intestine, kidney, or heart, often smaller than a pinhead.

In the laboratory at the Helmholtz Centre for Infection Research (HZI) in Braunschweig, this work has long been part of daily routine. That's because Molly isn't a scientist—she's a cell culture robot. Together with Dr. Kristin Metzdorf's team, she cultivates so-called organoids—artificially created organ-like structures that open up entirely new possibilities for medicine and infection research. Using these, researchers investi-

▼ A heart organoid with the tubulin cytoskeleton (red), cell nuclei (blue), and cardiac muscle cells (green).



gate how viruses and bacteria attack human tissue, how immune cells react, and why some people are better at fending off pathogens than others. Such investigations initially begin in classical cell culture, that is, in a Petri dish containing cells from a specific tissue. However, the limits of what is possible are quickly reached here, because in the human body, many cell types work together and are also influenced by the immune system. Since this complex interaction cannot be replicated in cell culture, the next steps previously had to be carried out in animal models—but now organoids are closing this gap.

However, Kristin Metzdorf explains that organoids should not be thought of as fully functional hearts, lungs, or brains: "Organoids are not complete organs; rather, they mimic organ-like structures. In the case of the intestine, for example, the different sections—such as the small and large intestines—have different functions, and we can grow an organoid that more closely resembles the small or large intestine, respectively."

To grow organoids, the researchers use so-called pluripotent stem cells. These are cells that still carry all the genetic blueprints in their genome and can develop into almost any type of cell. With the help of specific growth factors, the researchers guide them to develop into a specific organ structure. The cultured organoids can then be infected under high-security conditions with, for example, monkeypox viruses, SARS-CoV-2, or the tuberculosis pathogen *Mycobacterium tuberculosis*. "Organoids can be cultured for a very long time. This allows us to observe the progression of infections and treatment options in human tissue," says Metzdorf. "In these three-dimensional mini-organs, cells behave more like they do in the human body: They organize themselves spatially, send signals, and react to attacks by pathogens much more realistically than in flat cell layers."

▼ Cell culture robot Molly.

▲ Kristin Metzdorf is the deputy head of the department "Innovative Organoid Research" at the HZI.

Organoids cannot yet replicate the interaction with the immune system, but they can at least reduce the need for animal testing. Their greatest strength lies in the high reproducibility made possible by automation. "Molly carries out her work 24 hours a day and can achieve high throughput with great precision. This ensures the comparability of the organoids, which is essential for later analyses," says Kristin Metzdorf. Getting Molly to perform her routine tasks reliably didn't work right away. First, she had to be extensively trained and learn the correct procedures with the help of artificial intelligence. "We've now gotten past Molly's childhood illnesses and her puberty, so to speak," says Metzdorf. "Now she takes over many physically demanding tasks for us, such as lengthy pipetting protocols, so that we have more time for evaluations and the development of more complex organoids."

A key focus at the HZI is personalized medicine, as cells isolated from patient samples can also be stimulated to form organoids. One such project is MARITH, short for "Mapping Recall Immunity in Human Tonsil Organoids Across Viral Histories", which the HZI team is undertaking in collaboration with the MRC–University of Glasgow Centre for Virus Research and Hannover Medical School (MHH). The researchers aim to generate organoids from cell samples of the pharyngeal tonsils of donors and use them to investigate the development of immune memory in humans. It has long been known that our immune system remembers characteristic components of pathogens when they enter the body and then forms memory cells for future encounters. However, why this immune memory triggers a much stronger defense in some people than in others remains a mystery. Due to their location at the foremost part of the respiratory tract, the tonsils are particularly frequently exposed to viruses transmitted via the air and droplets. Thus, they are an ideal tissue for studying immune memory. "We can grow organoids from tonsil tissue that reflect the key characteristics of their natural environment and contain functional immune cell populations," says Kristin Metzdorf. In this way, these mini-organs help uncover the next secrets of our immune system.

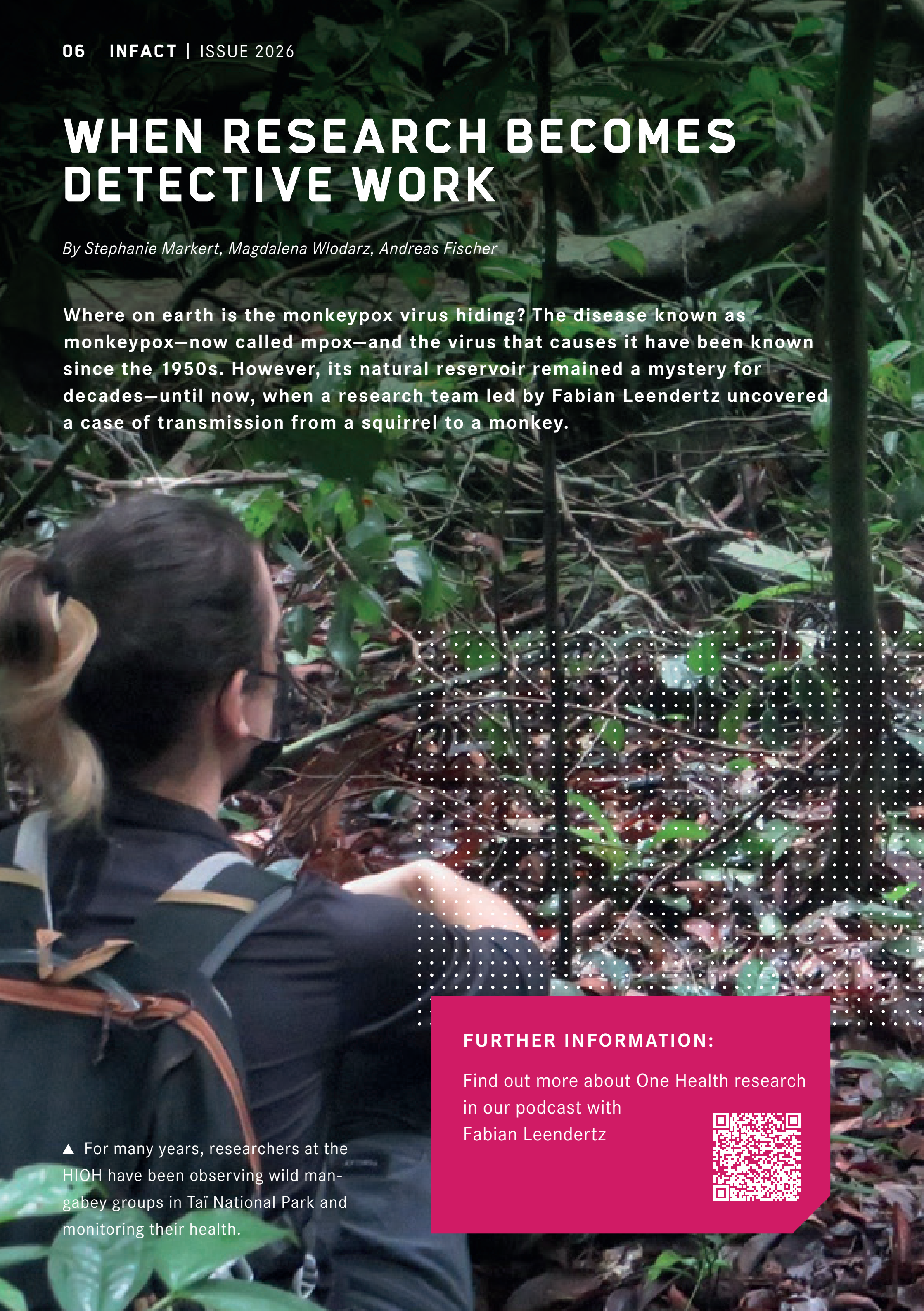
FURTHER INFORMATION:

You can also listen to Kristin Metzdorf in our podcast episode "Mini-Organs, Big Impact: How Organoids Are Revolutionizing Infection Research"

WHEN RESEARCH BECOMES DETECTIVE WORK

By Stephanie Markert, Magdalena Wlodarz, Andreas Fischer

Where on earth is the monkeypox virus hiding? The disease known as monkeypox—now called mpox—and the virus that causes it have been known since the 1950s. However, its natural reservoir remained a mystery for decades—until now, when a research team led by Fabian Leendertz uncovered a case of transmission from a squirrel to a monkey.



▲ For many years, researchers at the HIOH have been observing wild mangabey groups in Taï National Park and monitoring their health.

FURTHER INFORMATION:

Find out more about One Health research in our podcast with Fabian Leendertz

For decades, researchers at what is now the Helmholtz Institute for One Health (HIOH) have been working closely with the Taï Chimpanzee Project to monitor the health of wild chimpanzees, sooty mangabeys, and other animal species in Taï National Park in Côte d'Ivoire. This involves, among other things, collecting non-invasive samples such as feces and thoroughly examining all animals found dead in the forest. Their goal, in line with the One Health approach, is to gain a better understanding of the interactions between human, animal, and environmental health and, for example, to identify risks of disease outbreaks. One of the diseases the research team is focusing on is mpox—a zoonotic infectious disease caused by the monkeypox virus (MPXV) that can lead to severe illness in humans. In West and Central Africa, transmission from wild animals to humans occurs regularly. Some of these spillover events most recently triggered major global outbreaks in 2022 and 2024, which were subsequently sustained by human-to-human transmission. To effectively prevent such outbreaks, it is essential to understand how the virus circulates in wildlife populations and which factors facilitate spillover events. However, it has not yet been determined in which animal species the monkeypox virus has its natural reservoir—that is, where it lurks without causing disease in its host animals.

When Prof. Fabian Leendertz's research team observed an mpox outbreak in a well-studied group of sooty mangabeys in early 2023, months of true detective work followed, during which the researchers ultimately benefited from their decades of monitoring in Taï National Park. During that mpox outbreak, about one-third of the animals showed clinical signs of the disease, including, for example, the typical skin lesions; four baby mangabeys died.

Sequencing of tissue and fecal samples from the infected monkeys revealed that the detected virus was nearly identical to a viral strain that had been detected twelve weeks earlier in a fire-footed rope squirrel—a small rodent species—found dead nearby. To link these two observations, the team analyzed fecal samples from the mangabeys for signs of MPXV circulation prior to the outbreak, as well as for contact between the host species. A sample collected eight weeks before the outbreak began contained DNA from both the virus and the fire-footed rope squirrel—strong evidence of transmission between the two species at that time. Furthermore, behavioral data supported the findings: Sooty mangabeys from this group had already been observed catching and eating fire-footed rope squirrels, which opens up a direct route for viral transmission.

Squirrels have long been suspected of being potential reservoirs for MPXV. The virus was first isolated from a wild animal in 1985—at that time, it was a rope squirrel captured in the Democratic Republic of the Congo. In 2003, imported squirrels infected with MPXV were also suspected of triggering an mpox outbreak among prairie dog owners in the United States. However, direct evidence that these animals in the wild can actually cause an outbreak in another animal species has been lacking until now. The new findings therefore represent an important breakthrough and provide insights into the circulation of the pathogen in nature.

“This discovery was only possible thanks to many years of ecological research, continuous health monitoring, and systematic sampling in Taï National Park,” says Fabian Leendertz, co-director of the Taï Chimpanzee Project and director of the HIOH, which was founded in Greifswald as a site of the Helmholtz Centre for Infection Research (HZI) in Braunschweig. “We must continue and expand these efforts to better understand the risks posed by emerging infectious diseases—including mpox—and to address them preventively,” Leendertz adds.

The circulation of MPXV in the wild plays a significant role in human health: Particularly in sub-Saharan Africa, bush-meat—that is, meat from wild animals—is an important part of the local population’s diet. However, since hunting activity has drastically reduced the populations of larger wild animals, people are now increasingly hunting and consuming smaller species

▼ Severe mpox-associated skin lesions in a sooty mangabey baby.

▲ The proof: Although mangabeys feed mainly on fruits, seeds, and nuts, they occasionally hunt small rodents such as squirrels—a potential route of transmission for pathogens.

such as squirrels and other rodents. This increases the likelihood that humans will come into contact with MPXV—and with it, the risk of zoonotic transmission also rises. The now-confirmed direct involvement of fire-footed rope squirrels in interspecies transmission therefore has significant implications for public health.

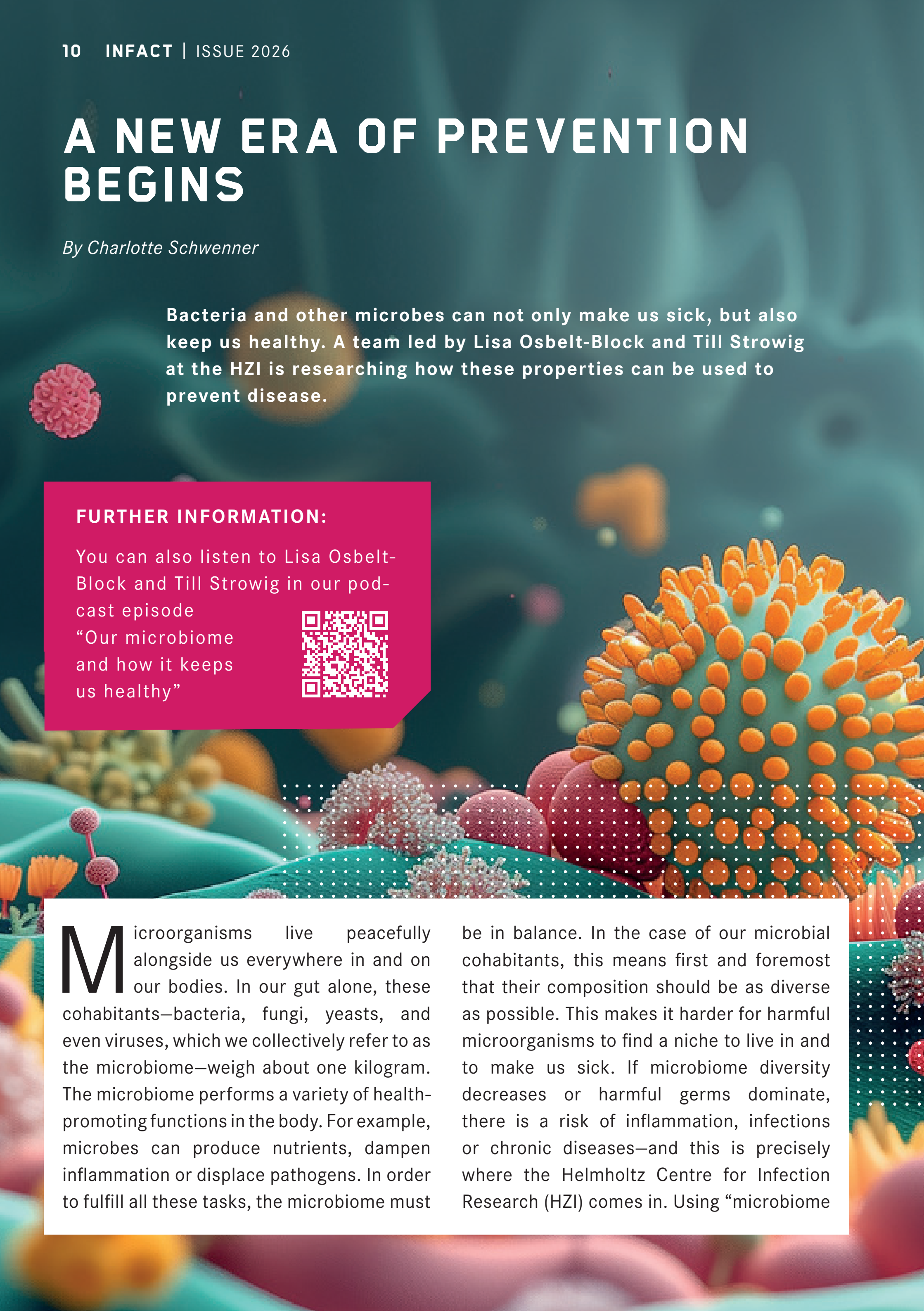
"Identifying the animal sources of the virus and the exposure routes that lead to inter-species transmission are key steps towards understanding spillover mechanisms and developing effective prevention measures to mitigate the risk of transmission to humans," says Dr. Livia V. Patrono, a researcher at HIOH. Together with her co-authors, she recommends raising awareness among population groups that come into contact with squirrels and other wild animals, such as children. To strengthen evidence-based prevention strategies, the research team also advocates for a deeper understanding of the ecology of the monkeypox virus in reservoir species—particularly squirrels—as well as in intermediate hosts such as non-human primates in regions where the virus is endemic.

"This study also highlights the value of close cooperation with our African partners. Only through strong, trust-based collaborations with local authorities and research institutions can we effectively tackle zoonotic diseases and make an impact, not just regionally, but globally," says HZI Scientific Director Prof. Josef Penninger, emphasizing the great significance of this discovery. The interdisciplinary research team published the results of this study in the journal *Nature*—thereby solving a long-standing mystery in the field of infectious disease research.

A NEW ERA OF PREVENTION BEGINS

By Charlotte Schwenner

Bacteria and other microbes can not only make us sick, but also keep us healthy. A team led by Lisa Osbelt-Block and Till Strowig at the HZI is researching how these properties can be used to prevent disease.



FURTHER INFORMATION:

You can also listen to Lisa Osbelt-Block and Till Strowig in our podcast episode "Our microbiome and how it keeps us healthy"

Microorganisms live peacefully alongside us everywhere in and on our bodies. In our gut alone, these cohabitants—bacteria, fungi, yeasts, and even viruses, which we collectively refer to as the microbiome—weigh about one kilogram. The microbiome performs a variety of health-promoting functions in the body. For example, microbes can produce nutrients, dampen inflammation or displace pathogens. In order to fulfill all these tasks, the microbiome must be in balance. In the case of our microbial cohabitants, this means first and foremost that their composition should be as diverse as possible. This makes it harder for harmful microorganisms to find a niche to live in and to make us sick. If microbiome diversity decreases or harmful germs dominate, there is a risk of inflammation, infections or chronic diseases—and this is precisely where the Helmholtz Centre for Infection Research (HZI) comes in. Using "microbiome engineering", Dr. Lisa Osbelt-Block and Prof. Till Strowig are specifically editing the gut microbiome to prevent disease.

While probiotic foods or supplements usually provide only transient and harmless bacteria, and a fecal microbiota transplantation (FMT), also known as stool transplantation, can replace the entire microbiome, microbiome engineering aims at precise interventions: Researchers remove individual pathogens from the community, replace lost functions or redesign the ecosystem so that it repairs itself. At the HZI, the main question is: How can we prevent infections before they occur?

The tools of microbiome engineering are not measuring tapes and dial gauges, but microorganisms, bacteriophages and the CRISPR gene scissors. "In a way, we are all engineers of our microbiome. What we eat and who we surround ourselves with influences our microbiome. However, our approach to microbiome engineering is more targeted," says Till Strowig, head of the HZI department "Microbial Immune Regulation". "Our aim is to prevent serious infections that may originate in the gut. We want to remove these bacteria from the intestine before they breach the intestinal barrier and complications can arise."

Helping microbes as a shield against infections

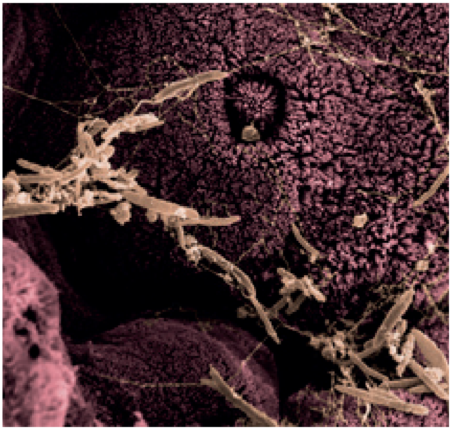
To this end, Strowig's team is relying on the power of other gut-inhabiting bacteria, as the researchers have made an important discovery: The reservoir of pathogenic bacteria in the gut can be eliminated if it is colonized with certain antagonists. "Our research is most advanced on the species *Klebsiella oxytoca*, which can displace other Klebsiella and Salmonella from the gut," says Lisa Osbelt-Block, a scientist in Strowig's department. "We were able to show that *K. oxytoca* competes with pathogenic Klebsiella for the same nutrients and also changes the conditions in the gut so that the community of beneficial bacteria can recover. *K. oxytoca* acts like a mini-engineer that repairs the microbiome." The team is also testing the effect of microbial antagonists against enterobacteria such as pathogenic *Escherichia coli*.

With the support of the German Center for Infection Research (DZIF), the team is developing its bacterial strains as living biotherapeutics (LBP) and aims to launch a startup. Such a preparation with freeze-dried but living microorganisms is considered a drug and must be clinically tested and approved. This also distinguishes the researchers' approach from conventional probiotics, which are marketed as dietary supplements. Although they are said to have health-promoting effects, the clinical effect is usually not proven.

"Our approach is intended to be used in cases of miscolonization, when we want to displace individual potentially pathogenic bacterial strains from the microbiome," says Osbelt-Block. However, if the microbiome has been completely disrupted by repeated administration of broad-spectrum antibiotics or the persistent germ *Clostridioides difficile* has spread in the intestine, a different approach such as stool transplantation is necessary. This involves transferring healthy intestinal bacteria from a donor to a recipient in order to restore the dysfunctional microbiome. ▶

A scalpel for the microbiome

"If stool transplantation is a sledgehammer, our microbiome engineering technology is a chisel: powerful, yet still fine enough to work precisely," says Osbelt-Block, comparing the tools. Research groups around the world, including at the HZI, are testing complementary tools to manipulate the microbiome with a "scalpel". They want to achieve microbiome changes with as few side effects as possible. To this end, they are researching how they can use programmable antibiotics or the CRISPR gene scissors to switch individual genes of bacteria on or off directly in the intestine. Other projects are dedicated to bacteriophages, which also act directly in the intestine. These viruses can specifically infect unwanted bacterial strains and thus remove them from the community. With these tools—from the chisel to the scalpel—the researchers at the HZI not only want to repair the microbiome, but also shape it in a targeted and sustainable way—for a new era of prevention.



▲ A detailed electron micrograph of a mouse's small intestine showing various bacterial species of the microbiome.

▼ Lisa Osbelt-Block and Till Strowig aim to specifically modulate the gut microbiome to prevent infections.

MICROBELIX: THE SOIL AS A MICROBIAL TREASURE TROVE

By Daniel Krug

There is an urgent need for novel drugs in the fight against infectious diseases, and natural compounds derived from soil bacteria are a promising source for their development. Researchers at HIPS, the HZI site in Saarland, are counting on the public's help: The citizen science project MICROBELIX aims to harness the biodiversity of soil bacteria for drug discovery.

The increasing resistance of pathogenic bacteria to known antibiotics is an urgent problem—there are increasingly frequent reports of multidrug-resistant pathogens against which even reserve antibiotics are ineffective. At the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), an HZI site in cooperation with Saarland University, scientists are using myxobacteria as a source of new active compounds. These soil-dwelling bacteria have, so to speak, a long history at the HZI, as it was the two Braunschweig-based scientists Prof. Hans Reichenbach and Prof. Gerhard Höfle who, through their decades of work, laid the foundation for an extensive global collection of myxobacteria. This collection is still used today as a rich source of new active compounds with interesting chemical structures and often extremely potent biological activities. This microbial treasure trove has since grown to more than 14,000 myxobacterial strains, and in the HIPS department "Microbial Natural Products", led by Prof. Rolf Müller, researchers are working intensively to unlock as many of the myxobacteria's chemical secrets as possible. After all, every newly discovered substance brings with it the hope of having found a molecule that might be suitable for further development into a pharmaceutical active compound.

Anyone taking a walk in Saarbrücken's primeval forest just outside the city at the start of summer will come across a surprising scene: Children and adults are intently working at microscopes and handling freshly collected soil samples, which they spread onto agar plates—along with a dab of yeast to lure the ever-hungry myxobacteria out of the soil sample. Here, at the MICROBELIX Wilderness Camp, microbiologist Dr. Ronald Garcia from HIPS supports the citizen scientists' search for new bacterial species and explains: "The soil samples collected by the citizen scientists are of great value for the discovery of new myxobacteria, because we are convinced that virtually every habitat harbors a microbial community with considerable diversity." Some of the methods used at the Wilderness Camp are applied in much the same way by researchers

▼ Collecting soil samples at the MICROBELIX Wilderness Camp.

in the HIPS laboratory, supplemented by modern genetic and mass spectrometric analyses to ensure that no interesting novel soil bacterium is overlooked. “Ultimately, the key to success lies in the isolation methods,” says Garcia. “We use a highly selective approach to isolate natural product-producing myxobacteria, and they’re quite good at defending themselves against other bacteria. Occasional contamination with common germs therefore doesn’t affect our chances of success.”

From the MICROBELIX soil samples—some of which were even sent in by mail—Ronald Garcia and his colleagues have already isolated over 1,100 new myxobacteria, including strains that, due to their low degree of relatedness to known species, belong to a new genus or even a new family. “That is exactly what matters: finding new and rare taxonomic groups of myxobacteria. These are more likely to produce an active compound with a chemical structure that is still unknown,” explains Garcia.

Soil samples are being collected not only in the forests of Saarland; citizen scientists participating in the MICROBELIX project are now active across the country. To facilitate this, HIPS researchers have created sample collection kits, with blue plastic spoons in sterile plastic bags as the key component, and printed codes that allow the samples to be registered on the website. The kit also includes a return envelope, an informational flyer on sampling, and a mini magnifying glass. So far, HIPS has distributed several thousand of these sample kits; interested persons can request them on the website. There, a map shows in real time where samples have already been collected.

In the summer of 2026, MICROBELIX is also traveling across Germany aboard the “MS Wissenschaft”. In the “Medicine of the Future” exhibition, guests can use the “Myx-o-Mat 3000” to playfully try their hand at finding myxobacteria that produce a new active ingredient against selected pathogens—and then set out as citizen scientists with the sample collection kit to actually support the search for new active compounds at HIPS and HZI with a soil sample.

▲ The sample collection kit is sent back to HIPS by mail along with the collected soil samples.

Would you like to collect and send in soil samples? You can order a sample collection kit here:


Did you know?
About 80 million bacteria are transmitted during a kiss.
We offer fascinating insights from infection research.
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