DZIF

DZG DEUTSCHE ZENTREN DER GESUNDHEITSFORSCHUNG

GERMAN CENTER FOR INFECTION RESEARCH

Annual Report 2019

Cover image: Blood meal served on a cotton swab. Mosquitoes are not only annoying, but also sometimes dangerous pests. Through their saliva they can transmit various viruses and other pathogens such as malaria parasites.

ANNUAL REPORT 2019

The DZIF at a glance

The German Center for Infection Research (DZIF) coordinates and oversees the strategic planning of translational infection research within Germany. Its mission is to translate results from basic biomedical research into clinical research.
35 DZIF research centres work concertedly against the global threat of infectious diseases.

Table of contents

Editorial

A google search for the term "COVID-19" results in 5,070,000,000 hits – an indication of how consistently high public interest has been over the past months regarding this infectious disease. This Annual Report was written during the SARS-CoV-2 pandemic, which has an enormous global impact, both on society and the economy. Today, there is a high burden of disease and there are many cases of death from COVID-19. The compulsory wearing of masks, increased hygiene measures and social distancing are shaping our daily lives. Research activities to develop new diagnostics, vaccines and treatment options for this newly emerged virus are running at full speed. Scientists and doctors at the German Center for Infection Research (DZIF) have been involved in these activities since the beginning of the pandemic and have made many important contributions.

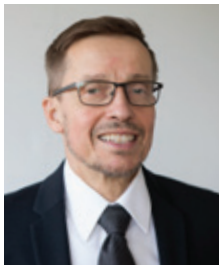
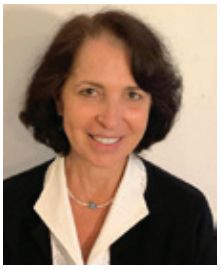
Long before the current COVID-19 crisis emerged, the scientific community has frequently warned that newly emerging pathogens could spread as rapidly as SARS-CoV-2 across the globe; for many others it was more a theoretical scenario. DZIF researchers have been dealing with newly emerging infections for years and one of DZIF's main goals has been to be sufficiently prepared for such an eventuality. DZIF researchers had been involved in developing new vaccines against MERS coronavirus and Ebola virus before. Thus, they can now build on their previous experiences in addressing the new virus.

This report focuses on the year 2019, shortly before the SARS-CoV-2 outbreak began and focuses on the multitude of other challenges in infection research that need to be overcome as well. On page eight, you can read about a clinical trial for a new antibiotic against tuberculosis that was carried out in South Africa, led by the Ludwig-Maximilians-Universität München (LMU). Other themes covered include the University of Heidelberg's research on the mechanism by which a number of HI viruses hide and survive in patient genomes, the results are being used as a basis for the further development of drugs (p. 12). In the future, hepatitis B patients will benefit from trials being carried out at the Helmholtz Zentrum München and Technical University of Munich regarding virus-specific T killer cells (p. 14). Researchers at the LMU discovered that antibiotics actually "stimulate" the bacterial pathogen *Helicobacter pylori* to develop resistance (p. 16). A team at the Technical University of Munich discovered that salt can reprogram immune cells and promote the development of neurodermatitis (p. 19). Researchers at the University of Tübingen are elucidating the mechanism of action of an endogenous substance in the human body that destroys methicillin-resistant *Staphylococcus aureus* (p. 20). These and other research projects give some insight into the many and diverse activities that are carried out at the DZIF.

The measures that have been put in place to curb new coronavirus infections have so far been quite effective in Germany. The German Federal Government has taken into consideration advice given by DZIF scientists to substantiate important political decisions. However, continuous attention is still necessary in order to stop the further spread of SARS-CoV-2, with the Robert Koch Institute stressing that the situation must be taken very seriously. DZIF researchers contribute to the large global effort to overcome the pandemic in many ways, and we will discuss these advances in detail in next year's DZIF report.
Stay healthy!

Yours sincerely
The DZIF Executive Board




Prof. H.-G. Kräusslich | Prof. D. Busch | Prof. A. Peschel | Prof. M. Dandri | Prof. D. Heinz

ABOUT THE DZIF

More than ever before, infections now call for united action

Infection research has inadvertently become one of the most scrutinised topics over the past few months. However, the sudden emergence and epidemic spread of viruses such as the current SARS-CoV-2 is not a new phenomenon and infection researchers at the German Center for Infection Research (DZIF) have been specifically working in this field ever since the organisation was founded. The organisation's "head start" and subsequent experience has contributed to it playing an important role in the current crisis. However, rapid action is also required in other areas of infection research such as chronic infections, the growing number of immunocompromised patients in increasingly aging societies and the global rise in antibiotic resistance. In order to tackle all these issues, 35 institutions have come together under the umbrella of the DZIF, and over 500 doctors and scientists are working together in the fight against infections.

TRANSLATION: DEVELOPING DRUGS MORE RAPIDLY

The DZIF has made it its objective to develop new diagnostic, preventive and therapeutic methods to treat infectious diseases. The aim is translation, i.e. the effective transfer of research results into clinical application. Scientists and doctors work together at the DZIF to transfer acquired experiences in the treatment of patients to basic research and to make laboratory results more rapidly available to patients suffering from severe diseases. In order for this procedure to function optimally, the DZIF is structured into nine research areas across various institutions. On the one hand, these research areas are dedicated to specific diseases such as "Tuberculosis", "Malaria", "HIV", "Hepatitis" and "Gastrointestinal Infections" and on the other hand, the research fields focus on specific problem areas such as "Emerging Infections", "Infections of the immunocompromised Host", "Healthcare-associated and Antibiotic-resistant bacterial Infections" and "Novel Antibiotics".

SERVICES: SHARED USE OF INFRASTRUCTURE

Eight so-called "translational infrastructures" provide the best possible services to DZIF scientists. Numerous questions arise during the development of new drugs that cannot always be easily addressed by scientists and doctors. In this case, experts in "Product Development" provide valuable advice. Once an

This was possible before corona: 2019 Joint Annual Meeting with the DGI brings DZIF scientists closer together.

agent has overcome the first obstacles in its development, the "Clinical Trial Unit" coordinates trials on trial subjects. DZIF scientists are able to obtain the necessary tissue, body fluid and cell samples from the DZIF "Biobank" for their research. Specific strains of bacteria are collected and analysed in the "Pathogen Repository". DZIF experts and establishments are also accessible at an international level. At African Partner Sites, for example, DZIF scientists conduct research on infectious diseases in locations where the diseases are more common rather than in Germany where such diseases occur less frequently. Experts in "Epidemiology", "Bioinformatics" and "Novel Antivirals" provide further expertise.

NETWORKING: MAKING NEW CONNECTIONS

A particular feature of the DZIF and all the German Centers for Health Research (DZG) is their networking structure. Universities, research institutes, hospitals, authorities and other research establishments exchange information, providing scientists and clinicians with opportunities to work together across the boundaries of their establishments and professions. Clinical practices and industrial companies also exchange extensive information, which in turn supports translational steps towards developing new drugs. In addition, the DZIF is a member of the overarching National German Centers for Health Research (DZG) alliance. Just as importantly, the DZIF continues to expand its research network in both Europe and internationally.

R&D: BRIDGING GAPS IN CLINICAL APPLICATION

Translating drugs, vaccines and diagnostics from basic research into clinical application requires a high level of investment with regard to time and financing. Research companies need partners willing to share economic risks and to make substantial scientific contributions. This is precisely where the DZIF steps in: over the past few years, the DZIF has become an important player in infection research in Germany and a reliable partner for the biotechnology and pharmaceutical industry. Currently, for example, it has laid the foundation for vaccine research on Ebola, MERS and SARS-CoV-2 viruses, starting from basic research through to the first clinical trials and is now jointly working on steps towards the approval process together with industry partners.

CAREER: PAVING THE WAY FOR INFECTION RESEARCHERS

Since the DZIF was founded, it has been committed to supporting young scientists and doctors in their infection research careers. The DZIF Academy was established with this objective and offers specific stipends that aim to provide incentives to those wanting to work in infection research. Clinical leave stipends, for example, are very popular and support young doctors in the temporary reduction of their routine clinical work in order to focus more on research. This supports the direct transfer of clinical know-how to research. Maternity leave stipends, which support young parents returning to work in research, are also very successful. The DZIF boasts several cases where this stipend has furthered the careers of parents with young children.

GLOBALISATION: THINKING AND ACTING WITHOUT BORDERS

The current pandemic has once again painfully shown that infections do not stop at borders. Encouraging infection researchers to think and act internationally has been an integral policy of the DZIF since the start. DZIF scientists and doctors work closely together with partner institutions in Africa and Europe, researching tropical and neglected diseases such as malaria and Ebola in regions where they most commonly occur. The DZIF is also involved in the CEPI (Coalition for Epidemic Preparedness Innovations) vaccine initiative. Since the beginning of 2019, the DZIF has become one of ten partners in the CARB-X accelerator network. CARB-X accelerates new drug development projects worldwide in the fight against antibiotic-resistant pathogens. The DZIF is also involved in the establishment of the new "Global Antimicrobial Resistance Research and Development Hub" with its headquarters in Berlin. Alongside researching viruses, the development of new antibiotics remains one of the key challenges for infection researchers at the DZIF.

The DZIF pools together its activities in research fields and interdisciplinary infrastructures–internally referred to as Thematic Translational Units (TTUs) and Translational Infrastructures (TIs):

Research fields

- *Emerging Infections*
- *Tuberculosis*
- *Malaria*
- *HIV*
- *Hepatitis*
- *Gastrointestinal Infections*
- *Infections of the immunocompromised Host*
- *Healthcare-associated and Antibiotic-resistant bacterial Infections*
- *Novel Antibiotics*

Infrastructures

- *African Partner Institutions*
- *Biobanking*
- *Bioinformatics*
- *Clinical Trial Unit*
- *Epidemiology*
- *Novel Antivirals*
- *Pathogen Repository*
- *Product Development Unit*
- *DZIF Academy*

Well prepared for new outbreaks

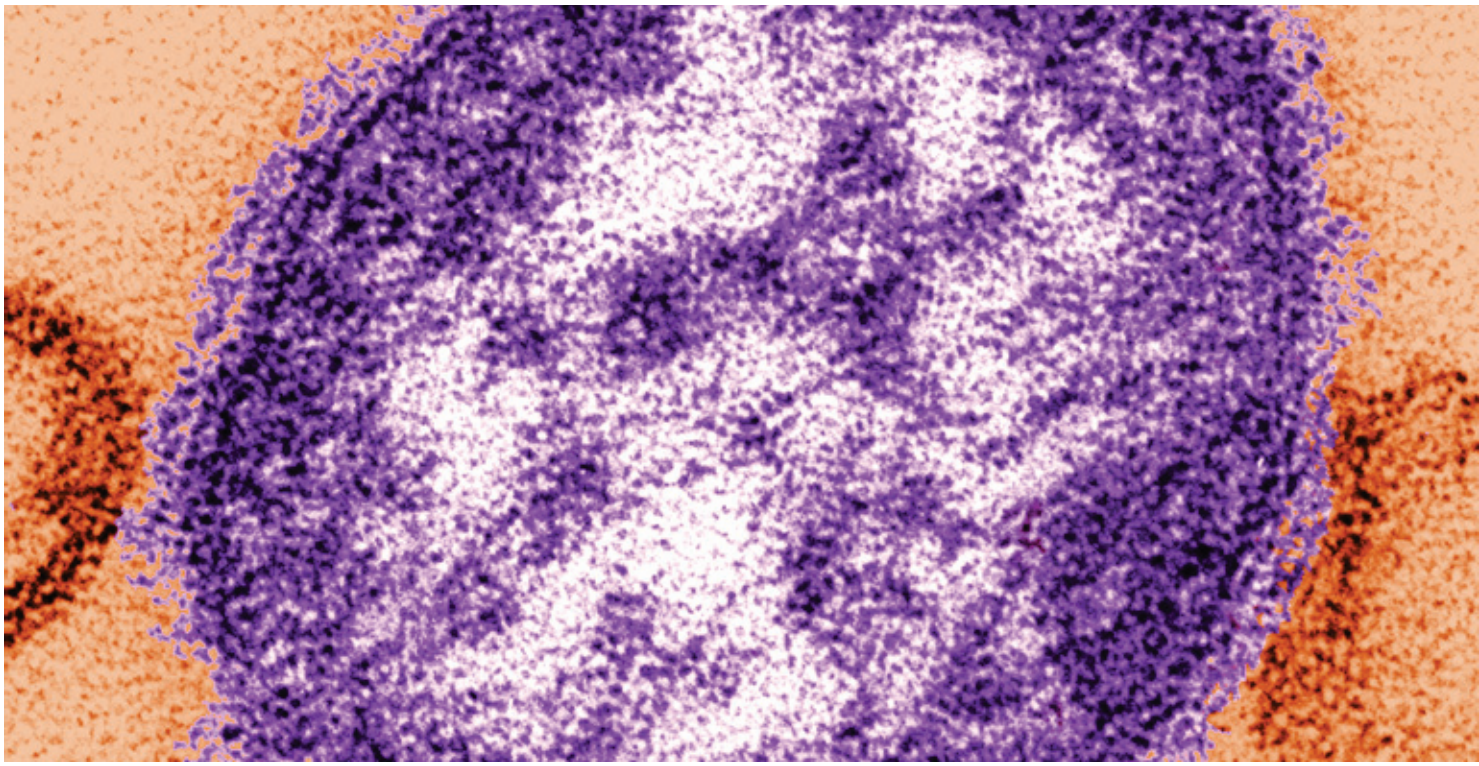
The pandemic of recent months has shown that acute infectious diseases can seriously disrupt societies around the world. The range of viruses and other pathogens with potential for new infectious diseases is large. For science it is therefore important to be prepared for a possible danger well before a new outbreak – only then can proper measures be taken in a timely and prudent manner.

Viruses influence the immune system, sometimes they trigger other diseases, sometimes they protect against them. DZIF teams are investigating the exact mechanisms. Researchers at the Paul-Ehrlich-Institut (PEI) together with British, U.S. and Dutch colleagues, showed that measles viruses gradually erase a patient's immunological memory. Scientists from the Charité – Universitätsmedizin Berlin found that immunity to dengue viruses protects the unborn fetus of pregnant women infected with Zika virus from malformations.

MEASLES VACCINATION IS MORE IMPORTANT THAN PEOPLE THOUGHT

Measles is on the rise again throughout Europe. An infection with measles virus may not only be severe and even fatal, but can also weaken the immune defences of sufferers against other pathogens for years. For example, a study conducted in the UK showed that up to 15 percent of children who had survived measles had an impaired immune system five years later. An international team linked to the DZIF investigated the

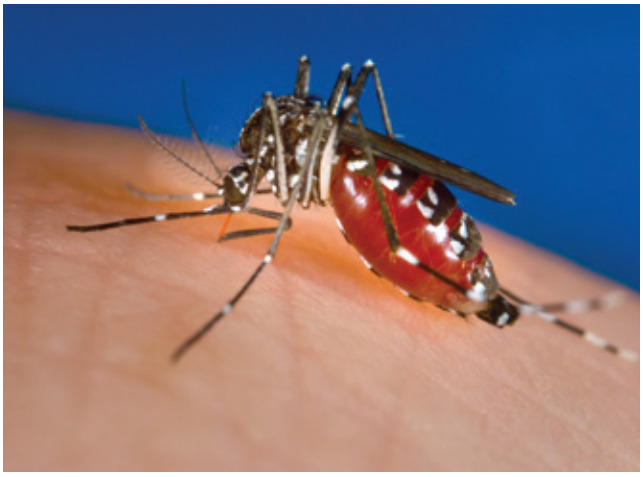
Electron microscope image of a pathogen that can cause a serious disease: the measles virus.



cause: they analysed the diversity of receptors on the immune cells, and discovered how B lymphocytes – important for the immune defences – developed. They did this in unvaccinated individuals, either with or without prior measles infection. After infection with measles, the genetic composition and diversity of immune cells were clearly reduced in most patients, and seriously impaired in every tenth patient. However, the values remained stable in people who had not yet been infected. The researchers also discovered immature B lymphocytes in measles patients – suggesting that the patients had a cell maturation disorder. The results of this genetic analysis were reproduced under controlled conditions with animal experiments on ferrets. "After an infection, measles viruses cause the immune system to forget which pathogens it had previously been exposed to," reported Dr Bevan Sawatsky from the Division of Veterinary Medicine at the PEI, who was responsible for the animal experiments. "A measles vaccination not only protects against disease, but also against damage to the immune system's memory and thus indirectly against other diseases."

WHEN DENGUE VIRUSES PROVIDE PROTECTION

The Zika virus, known since the 1940s, spread rapidly in Latin America in 2015/2016. Most of the millions of people who were infected had no or only mild symptoms such as a skin rash and headaches, as well as joint and muscle pain. However, in the northeast of Brazil, thousands of infected pregnant women later gave birth to babies with a strikingly small head, a condition known as microcephaly. Why were expectant mothers in this part of Brazil more vulnerable to Zika infection than mothers elsewhere? DZIF researchers at the Charité looked for reasons for this increased vulnerability in certain regions. Like dengue viruses, which are also widespread in Brazil, the Zika virus belongs to the flaviviruses family. Both pathogens are transmitted by mosquitoes. *In vitro* data suggested that after recovery from one or more dengue infections, antibodies have formed that cause malformations in babies with a subsequent Zika infection. The results of further studies were unclear. However, a study in Brazil then showed exactly the opposite: "Our study shows that previous dengue infections protect against Zika-associated damage," according to the Berlin virologist Prof. Felix Drexler. His team first compared the genetic material of all known dengue viruses from Brazil and analysed the serological samples of 29 mothers who had Zika infections during pregnancy and whose children showed microcephaly. Samples from 108 Zika virus-infected mothers with healthy children were used as the control. Even if the question of the cause remains unclear: "This is an all-clear signal for pregnant women with previous dengue infections," said Prof. Drexler. "They don't need to worry about contracting a severe Zika infection."



Mosquitoes transmit pathogens such as Zika and dengue viruses. This one is full of blood.

GOALS FOR 2019: OUTCOMES

◐ Launch of the DZIF Virus Test Platform and acquisition of new industrial partners.

● Development of a vaccine platform based on self-replicating RNA together with industrial partners.

● Expansion of a surveillance system to monitor known and unknown virus infections/zoonoses in rats and wild birds.

◐ *Goal partially achieved/project is still ongoing*
● *Goal achieved*

GOALS FOR 2020

○ Establishment of a mouse model for SARS-CoV-2.

○ Characterization of the cell-mediated immunity after MVA-SARS-CoV-2 S vaccination.

○ Further development of lipid metabolism inhibitors and the eIF4A-dependent translation as active agents against coronaviruses.

Coordinator:
Prof. Stephan Becker
Marburg

Different approaches, one goal

According to the WHO, around 58 million lives were saved by consistent diagnosis and treatment of tuberculosis between 2000 and 2018. This mission will continue with the help of the DZIF. Every year, around ten million people worldwide still suffer from tuberculosis. The disease could be contained even more successfully with more effective antibiotics.

Tuberculosis is regarded as the most deadly infectious disease ever. One and a half million people die of it every year. Effective antibiotics play a key role, because the tuberculosis bacteria are becoming increasingly resistant to traditional medications. DZIF researchers are working hard to improve tuberculosis treatment by looking for completely new therapeutic approaches and developing new antibiotics.

SUCCESS IN A ROUNDABOUT WAY

The tuberculosis bacterium has many ways of preventing the immune system's reactions to an infection. One way of dealing with this problem is to make antibiotics more effective with "host-oriented therapy", to shorten the duration of therapy and reduce the damage caused by tuberculosis. With active tuberculosis, it has been found that the immune system reacts in part with an "excessive" reaction to *Mycobacterium tuberculosis*, which can lead to a strong inflammatory reaction and tissue destruction. Some years ago, doctors began to use corticosteroids as well as antibiotics in the treatment of tuberculosis, and this can have a positive effect in certain stages of the disease. The mechanisms underlying this effect were not understood. However, Dr Jan Rybniker from the University Hospital Cologne, said "We were able to show that corticosteroids inhibit cell death caused by the mycobacteria and support the healing process." The researchers from Köln found that

Researchers at the University Hospital Cologne are looking for a new treatment against tuberculosis.

Prof. Michael Hoelscher (back row, middle, dark blue shirt), among his team at the Department of Infectious Diseases and Tropical Medicine in München (LMU).

p38 MAP kinase (a protein in human immune defence cells) seems to cause the destructive effect of the tuberculosis bacteria. "This protein helps immune cells to release pro-inflammatory hormones. It also helps to kill infected white blood cells in the human body," said Dr Rybniker. The p38 MAP kinase also plays a role in other chronic inflammatory diseases. Several inhibitors of p38 MAP kinase are currently undergoing clinical trials regarding rheumatoid arthritis, Crohn's disease and chronic lung diseases. It is quite likely that one of these medications will also be effective against tuberculosis. With high-throughput screening in an animal model, Jan Rybniker and his colleagues in Köln plan to collaborate with the Research Center Borstel and search for further agents that block the kinase and its signalling pathways. These agents should reduce tissue destruction early and minimize permanent lung damage.

DOSE DETERMINATION FOR A NEW ANTIBIOTIC

While Jan Rybniker is pursuing a novel approach to tuberculosis treatment, Prof. Michael Hoelscher from the LMU in München is testing the brand-new antibiotic BTZ-043, which is the first of the benzothiazinones. This active substance was very effective against multidrug-resistant pathogens in preclinical tests, and the antibiotic may be able to prevent resistance permanently. BTZ-043 is currently being tested in Cape Town, South Africa, in a dose escalation study with several dose increases (multiple ascending dose study). "This helps us to assess the safety, tolerability and efficacy of BTZ-043," said Prof. Hoelscher, coordinator of the research area "Tuberculosis" at the DZIF. Each of three new research volunteers will receive a dose 250 milligrams higher than their three predecessors. "This approach helps us find the amount of the active substance that has the best positive effect with the fewest side effects," according to Prof. Hoelscher. The volunteers take a maximum of 2,000 milligrams of the active substance. "So far, they've tolerated the preparation very well," continued Prof. Hoelscher. "We're confident that we will also achieve very good efficacy data." In the next phase of the study, 80 tuberculosis patients will be treated at the Cape Town study centre with three selected drug doses to confirm safety and efficacy in a larger group. For authorisation, the right combination of medications must be found. In a large consortium of several pharmaceutical companies, BTZ-043 will be tested in various combinations with other new drugs, starting in 2021. Prof. Hoelscher hopes that in a few years, the new active substance will improve and even shorten the present treatment.

GOALS FOR 2019: OUTCOMES

- ● Molecular biology methods that confirm mutations coding for resistance in the TB pathogen's genome have been evaluated in a pilot study.
- ● Evaluation of defined biomarkers for assessing treatment success in TB patients.
- ● First TB patients have received BTZ-043, the new antibiotic for tuberculosis.

◐ *Goal partially achieved/project is still ongoing*
● *Goal achieved*

GOALS FOR 2020

- ○ Phase IIa for BTZ-043 will be started. Funding for phase IIb/c is assured.
- ○ *In vivo* validation of p38 MAPK-inhibitors for a host-directed TB therapy.
- ○ Creation of a clinical development plan to evaluate the therapy success of biomarkers in TB patients.

Coordinator:
Prof. Michael Hoelscher
München

Understanding the variants of a disease

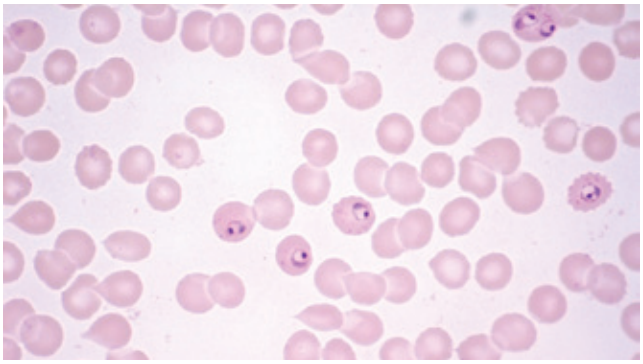
Malaria is still one of the biggest health problems in sub-Saharan Africa. Pregnant women and children fall ill and die particularly often from swamp fever. They are therefore the main focus of worldwide efforts. DZIF researchers are working hard to prevent and eradicate the disease.

Six Plasmodium species cause malaria in humans. Only if one is familiar with their behaviour can one combat them effectively. DZIF scientists are investigating whether *Plasmodium ovale* variants lead to malaria relapses. After a dormant phase of months to years, the parasites can be re-activated and cause disease again. Together with international scientists, DZIF researchers are also testing a vaccine against *Plasmodium falciparum*, which is intended to prevent a specific form of malaria in pregnant women. This Plasmodium species is responsible for 95 percent of all severe malaria cases.

HIDDEN IN THE LIVER?

Dr Mirjam Groger from the Bernhard Nocht Institute for Tropical Medicine in Hamburg is interested in two particularly rare species. In a field study in Gabon she investigated the behaviour of *Plasmodium ovale curtisi* and *Plasmodium ovale wallikeri*. "We need to learn more about these neglected pathogens if we want to eradicate malaria in endemic areas," said Dr Groger. There is evidence in the biomedical literature that these two species lead to relapsing malaria, presumably because, like *Plasmodium vivax*, they can survive in liver cells despite treatment. "However, no studies have so far been able to prove this," according to Dr Groger. And nobody knows how often recurrences occur. The researchers recruited 26 malaria patients who were infected with one of the two *Plasmodium ovale* pathogens. Their initial treatment with the combination preparation artemether-lumefantrine was successful; no pathogens were detectable after treatment. The scientists then tested at intervals of two weeks to see whether the

Adult insects develop from mosquito eggs in warm and humid regions. They transmit malaria.



The ring stage of P. falciparum (blue dots and rings) in red blood cells (in pink).

volunteers relapsed. At the end of the test, 23 percent of the volunteers had relapsed, all caused by *Plasmodium ovale curtisi*. The researchers proved that this was the original pathogen – and not a reinfection or a treatment error – with a newly developed set of criteria that included the polymerase chain reaction and gene sequencing. It is assumed that the plasmodia hide in a body tissue as 'hypnozoites', i.e. latent forms. Dr Groger has not been able to show that this is the liver. "However, this is the first study to get to the bottom of this question using molecular methods and we are starting to accept this theory," said Dr Groger.

HOPE FOR PREGNANT WOMEN AND CHILDREN

Every year, about 20,000 mothers and up to 200,000 newborns and infants die of pregnancy-associated malaria caused by *Plasmodium falciparum*. This form of malaria causes an accumulation of infected red blood cells in the placenta. In recent years, European scientists developed a vaccine called PAMVAC with the participation of the DZIF. It is based on the protein VAR2CSA, with which *Plasmodium falciparum* attaches to the placenta. Women who survive pregnancy-associated malaria produce antibodies against this protein, and these significantly reduce the risk of malaria in subsequent pregnancies. Researchers have now tested the vaccine for the first time in a randomised, double-blind study of tolerability and efficacy in healthy, malaria-naïve volunteers in Tübingen and in young women in Cotonou, Benin. "Our study shows that PAMVAC is very well tolerated. Side effects were rare and occurred equally frequently with the vaccination and the placebo," said Dr Diane Egger-Adam from the Institute of Tropical Medicine at the University of Tübingen. "The vaccine produced exactly the antibodies that protect women from pregnancy-associated malaria." In the next step, the vaccine will be tested in Africa on women of childbearing age who have not yet become pregnant. "Then we will know whether PAMVAC really prevents pregnancy-associated malaria," said Dr Egger-Adam. The need is great: according to the World Health Organization, around 50 million women in malaria-endemic areas become pregnant every year.

GOALS FOR 2019: OUTCOMES

◐ Progressing the clinical development of the malaria vaccine developed in Tübingen. Tolerability and efficacy of the vaccine are being tested in children in a phase II trial in Gabon.

◐ We would like to understand how the malaria pathogen survives the dry season and how it continues to ensure its transmission to mosquitoes during the rainy season. We plan to develop new experimental approaches for malaria vaccines.

● Development of immunity against the malaria pathogen in the first twelve months of life have been investigated. A birth cohort has been established in Ghana for this purpose.

◐ *Goal partially achieved/project is still ongoing*
● *Goal achieved*

GOALS FOR 2020

○ The clinical development of the malaria vaccine developed in Tübingen will be pursued further. The tolerability and efficacy of the vaccine in children is currently being tested in a phase-II study in Gabon.

○ We want to understand how the malaria pathogen assures its survival during the dry season and how it transfers to mosquitoes during the reinitiated rainy season. And we want to carry out the first experiments on the development of a malaria vaccine with rodent parasites that are transmissible through mosquitoes and that are in the blood stage.

○ The existing birth cohort is extended by new study participants and the recruited children will be closely attended in the first months of life in order to gain detailed information on the development of immunity to the malaria parasite.

Coordinator:
Prof. Benjamin Mordmüller
Tübingen

Unmasking the virus, developing diagnostic tests

An infection with HIV weakens the immune system. Secondary infections and some types of cancer occur more frequently in infected persons. By 2030, according to the aims of the WHO, the worldwide HIV/AIDS epidemic should be over, as well as its complications. This requires safe testing methods and medications that can cure the disease. An important prerequisite is better understanding of the virus.

Infection with HIV cannot be cured so far, because part of the virus becomes integrated into the genome of the host and survives there. Researchers at the University of Heidelberg are working hard to understand this latency mechanism. Their knowledge is decisive for the development of effective therapies. Until these are available, HIV infections must be detected early and suppressed rapidly – especially in children and mothers.

LURING THE VIRUS OUT OF HIDING

HIV-1 infects cells of the immune system, preferably CD4 T-cells. There it multiplies, the cells die and the virus spreads further. However, the virus is able to stay latent for a period during which it does not multiply. Meanwhile, it integrates itself into the genetic material of the patient's cells and remains there "invisible" to the immune system. This makes it inaccessible for current treatments. However, the quantity of virus increases by reactivation of the latent infected cells as soon as antiviral therapy is stopped. "That's why it's vital to understand which pathways the virus follows in order to either multiply or to hide in the CD4 T-cells," said Dr Marina Lusic from the University of Heidelberg. "Better understanding of how HIV-1 integrates its genetic material into the cellular DNA, which consists of chromatin, will help us to

Dr Marina Lusic's research also uncovers hidden HI viruses.

Compared to Western hospitals, conditions at the African study sites are sometimes quite simple.

develop new efficient strategies to combat it." The Heidelberg researchers were recently able to show that the virus does not integrate its genome into the host's DNA by chance. They also discovered that the individual genes of CD4 cells into which HIV-1 most often integrates form a cluster. "This makes it clear that HIV-1 is silenced by a combination of chromatin-based mechanisms," said Dr Lusic. Reactivating the virus from such a complex environment is therefore more complicated than was originally thought. In fact, all previous attempts to reactivate silent HIV-1 genomes have failed. "Our work has shown the complexity of the factors that are involved in reactivating the virus," said the Heidelberg researcher. This has important implications for the development of future therapeutic approaches.

EARLY DIAGNOSIS SAVES LIVES

Without therapy, HIV disease in newborns progresses rapidly. About every second infected child in Africa dies by the age of two. But rapid diagnosis of the disease after birth is still very difficult. Blood samples must be sent off. It then takes several weeks until the results are sent back to the infirmary – valuable time during which a child who may be HIV-positive receives no treatment. Researchers at the Ludwig-Maximilians-Universität München (LMU Munich) have therefore evaluated a point-of-care test that can be performed in the hospital itself. According to a study in Mbeya, Tanzania, the test reliably indicates positive results: it detected all 15 HIV-positive cases among the 614 children tested. In future, the mothers will also be tested like this. "This should enable us to immediately identify risk factors that make transmission from mother to child more likely," said Dr Arne Kroidl from the Division of Infectious Diseases and Tropical Medicine at the LMU University Hospital Munich. Such children would then receive prophylactic HIV therapy, even if the first test turned out to be negative. Since the end of 2019, recruitment has been underway for the LIFE study in Mozambique and Tanzania, which is investigating whether the point-of-care test and thus the rapid start of antiretroviral therapy will improve the health of these children in the long term. "We assume that early testing and antiretroviral therapy starting at birth will mean that fewer children will fall ill and die," said Kroidl. It may even be possible to achieve permanent virus suppression in some children without therapy. It is known that early therapy reduces the spread of the HI virus in the body of babies, so that the virus is permanently suppressed. The researchers expect early results of the LIFE study in 2021/2022.

GOALS FOR 2019: OUTCOMES

◐ Submit a Top HIV Cohort manuscript, which examines essential immune mechanisms for the development of a so-called HIV reservoir, as well as use cohort samples for further studies at other sites.

● Start of the clinical trial "Long Term Impact on Infant Health" (LIFE) in Tanzania and Mozambique, which investigates the impact on the health status in later life of new-borns depending on the time at which they were diagnosed with HIV-1.

● Prof. Marina Lusic's research group aims to define the role of specific elements in the host cell genome, so-called super enhancers, which are responsible for an increased integration of HIV-1.

◐ *Goal partially achieved/project is still ongoing*
● *Goal achieved*

GOALS FOR 2020

○ Investigation of the role of antioxidants and of iron metabolism in HIV-1-latency.

○ Submission of a manuscript for highly efficient genetic manipulation of dormant CD4 T-cells. This approach permits rapid functional analysis of dependency and restriction factors of HIV infection that regulate the susceptibility and latency in these important HIV reservoir cells.

○ Further characterisation of the role of non-conventional T-cells for the viral HIV reservoir in a cohort of HIV-positive stem cell transplant patients.

Coordinator:
Prof. Marcus Altfeld
Hamburg

Stop the sinister alliance

There are five different forms of hepatitis virus, known as types A, B, C, D and E. Chronic hepatitis virus infections have a high risk of developing and dying of liver cirrhosis or liver cancer. The ambitious goal of the WHO is therefore to contain or even eliminate hepatitis worldwide by 2030. To achieve this, curative therapies for chronic hepatitis B and D are urgently needed.

DZIF researchers are working on a new therapeutic approach to cure chronic hepatitis B virus (HBV) infection. They are combining their individualised immune therapies with an entry inhibitor of hepatitis B and D viruses developed in the DZIF laboratories. This is urgently needed: prolonged therapy with the currently used agent did not improve the cure rate in the world's largest therapeutic trial to date with hepatitis D patients.

SUCCESS WITH KILLER CELLS

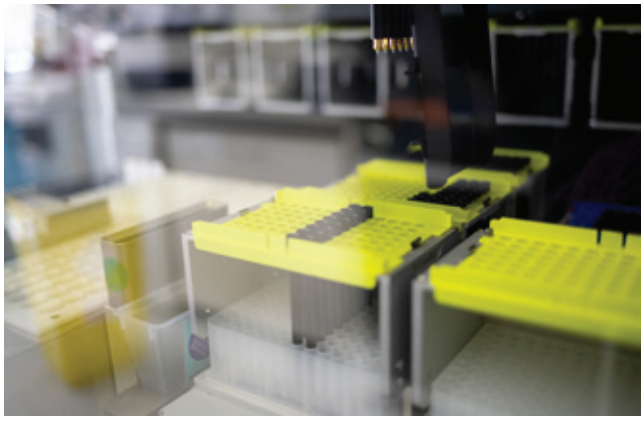
Chronic hepatitis B virus infection is still not curable. The virus hides in the nucleus of hepatocytes and can hardly be reached by therapeutic agents. DZIF researchers have now found a way to trick the hidden viruses. They knew that endogenous cytotoxic T-cells are hardly measurable in chronic HBV infections. Normally, these T-cells would eliminate the viruses. "If these cells are missing, the immune system cannot

Laboratory researchers are working to clarify the mechanisms of liver diseases.

react adequately," said Prof. Ulrike Protzer, Director of the Institute of Virology at the Helmholtz Zentrum München and at the Technical University of Munich, both member institutions of the DZIF. "Our idea is to provide patients who have HBV infection with exactly these virus-specific T-cells. The genetic information for these cells has been obtained from patients who defeated the virus and have recovered from hepatitis B. "We use the receptors on the T-cells that recognise HBV-infected cells," according to Prof. Protzer. With the help of the reprogrammed T-cells, the scientists succeeded for the first time worldwide in eliminating the virus in the humanised mouse model. "The T-cells act as living drugs, only attacking the infected liver cells, healthy tissue was spared," said Prof. Protzer. At very high viral loads, the researchers added the drug Hepcludex, which was recently approved for treatment of chronic hepatitis D. Since late 2019, the first patients suffering from HBV-associated liver cancer have been treated with the personalised T-cell therapy. In future, the therapy could also be used for hepatitis B.

PROLONGED THERAPY HAS LITTLE EFFECT

15 to 25 million people worldwide are chronically infected with the hepatitis D virus (HDV), about 30,000 of them in Germany. HDV is the smallest and most dangerous hepatitis virus. In order to multiply, it needs the envelope of the hepatitis B virus. Therefore, only people with hepatitis B can contract hepatitis D. The combined HBV/HDV infection increases the risk of liver cirrhosis and its complications. For a long time, there has been no HDV-specific antiviral therapy; patients are treated with interferon alfa, which supports the body's own immune defences. After twelve months of treatment, circulating virus components are no longer detectable in about a quarter of the patients. However, recurrence is frequent, even after many years. In an international study (The Hep-Net International Delta Hepatitis Interventional Trial, HIDIT-II), researchers at the Hannover Medical School (MHH), in cooperation with the HepNet Study-House of the German Liver Foundation, examined 120 patients to find out whether prolonged therapy for two years instead of one, or combination with tenofovir disoproxil, a drug against HBV, could reduce the recurrence rate. The DZIF supports the HepNet Study-House, and the MHH is a member institution of the DZIF. "The results show that even prolonged therapy does not improve the response rate," said DZIF Prof. Markus Cornberg, head of the Hepatitis Research Group at the MHH. Therapy with interferon alpha did improve the condition and function of the liver and inhibit disease progression, but it did not show a significantly better outcome than shorter therapy duration. New effective therapies to combat chronic HDV infection are therefore urgently needed. However, there is light at the end of the tunnel, thanks to the recently authorised Hepcludex, which was developed by DZIF researchers and is very promising for patients with HBV/HDV.



The pipetting robot can process many samples simultaneously.

GOALS FOR 2019: OUTCOMES

- ● Establishing a genotype panel for the hepatitis delta virus.
- ● Evaluation of HBV-specific T-cells that carry a chimeric antigen receptor (S-CAR T-cells) in mouse models.
- ● Clinical reassessment of the efficacy of sofosbuvir in chronic hepatitis E.

◐ *Goal partially achieved/project is still ongoing*
● *Goal achieved*

GOALS FOR 2020

- ● Market approval for Myrcludex B (trade name: Hepcludex) as the first antiviral developed by the "Hepatitis" DZIF research area.
- ○ Definition of a combination therapy to increase the efficacy of a therapeutic hepatitis B vaccine.
- ○ Preclinical investigation of the efficacy of an anti-HBV T-cell therapy against co-infection with the hepatitis D virus.

Coordinator:
Prof. Ulrike Protzer
München

Taking a targeted approach against gastrointestinal pathogens

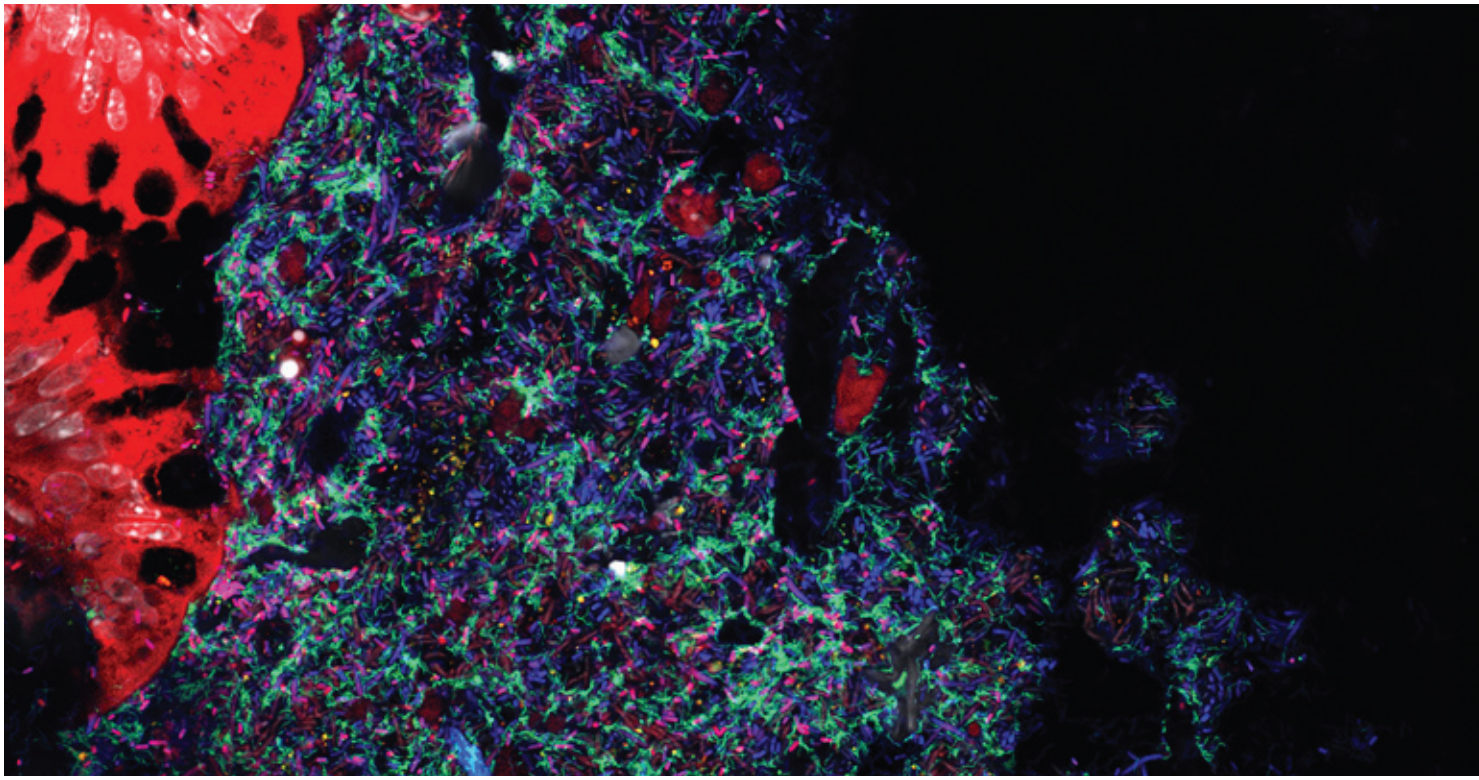
Diarrhoea, cramps and vomiting are the most common symptoms of severe gastrointestinal infections. Triggers are various bacteria, viruses and parasites. Diarrhoea is one of the top five causes of death worldwide. Infants are usually affected, often in poorer countries and malnourished. Nearly a million new cases of stomach cancer per year are caused by chronic stomach infections with the bacterium *Helicobacter pylori*.

The focus of research on gastrointestinal infections is on the most important pathogens of the gastrointestinal tract, as well as the microbiome of the intestine, which plays an important role in protecting humans against intestinal infections. DZIF scientists at the Max von Pettenkofer-Institute at the Ludwig-Maximilians-Universität München (LMU Munich) have found a bacterium in the mouse intestine that protects people against salmonella infection. Other DZIF researchers from the same institution have studied the worldwide distribution of the stomach bacterium *Helicobacter pylori* and have recently investigated its genetic diversity within the stomach.

INTESTINAL BACTERIA PROTECT AGAINST SALMONELLA INFECTION

Salmonella can lead to severe diarrhoea, especially in infants, older and immune-impaired patients. These rod-shaped bacteria are transmitted by contaminated food. However, only 10 to 20 percent of infected people get sick. What is it that protects everyone else? To find out what this is, DZIF researchers led by Prof. Bärbel Stecher from the Max von Pettenkofer-Institute in München first determined the composition of the microbiome in the intestine of mice that were protected against salmonella infection. They identified the bacterium *Mucispirillum schaedleri*,

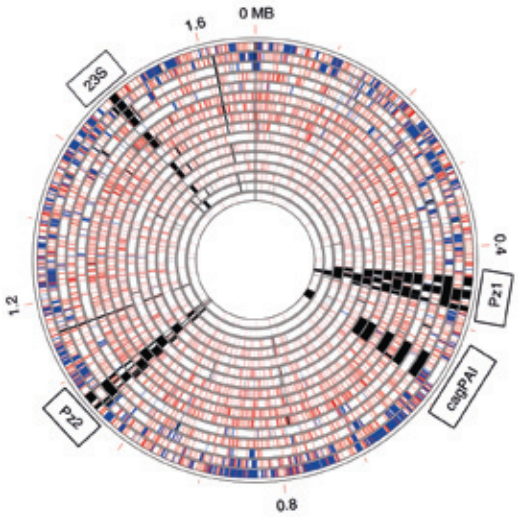
Mucispirillum (green) and Salmonella (pink) in the mouse intestine, the mucous membrane of the intestine is shown in red.



whose nearest relatives live mainly in hot springs, mud and sediments. In the subsequent study, the intestine of mice with a defined microbiome was intentionally populated with salmonella. One group of mice had Mucispirillum, another did not. Comparison showed that *Mucispirillum schaedleri* has a protective effect. It prevents the Salmonella from forming its virulence factors; in other words, its disease-making effect is reduced and it causes less inflammation. "We were able to show that the bacterium protects the microbiome of the intestine against salmonella infection," according to Prof. Stecher. Her team is planning a study for the near future with samples of the human microbiome. "It's not yet clear how often Mucispirillum occurs in humans, whether it protects them in the same way or is associated with specific diseases." The researchers also want to develop highly sensitive methods for detecting Mucispirillum in the faeces.

ANTIBIOTICS REDUCE THE GENETIC DIVERSITY OF *HELICOBACTER PYLORI*

Helicobacter pylori (H. pylori) is distributed worldwide and is genetically one of the most variable bacteria known. The bacteria can lead to inflammation of the stomach mucous membrane, stomach ulcers and stomach cancer. "The high variability is probably increased by the fact that the bacterium adapts to many hosts and various locations in a large stomach," said Prof. Sebastian Suerbaum, Board of Management of the Max von Pettenkofer-Institute at the LMU and Chair of Medical Microbiology and Hospital Epidemiology, as well as Coordinator at the DZIF. However, the extent to which diversity is present in the various parts of a single patient's stomach at a given point in time was the subject of the research carried out by Prof. Suerbaum's team. The scientists analysed tissue samples from several regions of the stomach in 16 adults with *H. pylori* – and found the genomes of ten different bacterial strains per biopsy. "Never before have so many strains per patient been isolated and characterised using Next Generation Sequencing methods," said the microbiologist. "Comprehensive genome sequencing made it possible for the first time to systematically analyse adaptation patterns in individual regions." The results show that *H. pylori* actually adapts itself to individual areas in the stomach. The researchers also found that antibiotics reduce the diversity of the *H. pylori* population and select resistant bacteria, even if the antibiotics were used in other ways than against *H. pylori*. "Antibiotics play a dominant role, because they result in loss of diversity time and again," according to Prof. Suerbaum. "For the first time, we were also able to show that systematic bacterial gene sequencing makes it possible to predict the development of resistance by bacteria."



The "stomach-wide" genome diversity of H. pylori in 16 patients.

GOALS FOR 2019: OUTCOMES

- Status analysis of all pathoblocker projects with regard to patentability and timelines for patenting, determining targets for identified "actives" and acquisition of additional funding for the development of a hit-to-lead.
- Priorisation of antigenes for prophylactic vaccines against *H. pylori*.
- Identification of microbiome biomarkers for susceptibility to EHEC infection and for the risk of developing haemolytic uraemic syndrome (HUS).

◐ *Goal partially achieved/project is still ongoing*
● *Goal achieved*

GOALS FOR 2020

○ Signing of the cooperation agreement for the HelicoPTER study by all project partners and approval by all of the ethics committees for the pilot study for HelicoPTER at the München location.

○ Submission of a patent application in at least one of the pathoblocker projects.

○ Completion of patient recruiting for the CROSSDIFF study and publication of the results of the SPECTRUM study.

Coordinator:
Prof. Sebastian Suerbaum
München

New strategies for therapies for immunocompromised patients

The immune system plays a decisive role in the fight against bacteria, viruses and other pathogens. However, if a patient's defences are weakened by immunomodulating therapies, tumours or allergies, harmless pathogens can take over and quickly become life-threatening for immunocompromised patients. Scientists are constantly researching new strategies to strengthen the immune system's defences in immunocompromised patients – and thus prevent infections.

T-cells have an important function in the immune system: they recognise antigens and initiate a corresponding immune response. DZIF scientists from the Institute for Medical Microbiology, Immunology and Hygiene at the Technical University of Munich (TUM) have generated artificial T-cells with CRISPR/Cas9 genetic scissors that have almost natural characteristics. A DZIF team from the Institute of Virology at the TUM has discovered that salt can reprogramme T helper cells – and thus promote neurodermatitis.

TARGETED MANIPULATION OF THE T-CELL RECEPTOR WITH GENETIC SCISSORS

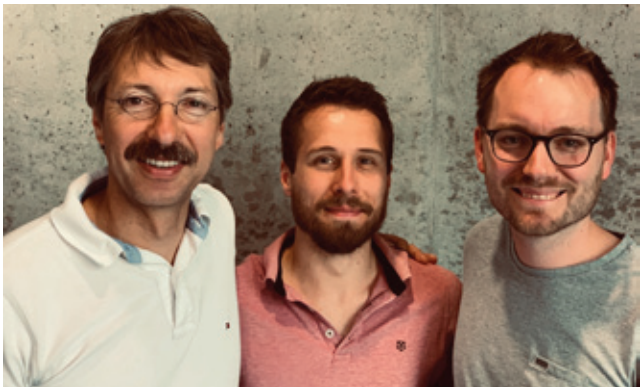
Targeting T-cells with genetic scissors will make immunotherapy more accurate in the future. Therapy involves reprogramming T-cell receptors so that they reliably recognise target cells of pathogens or tumours. The team led by Prof. Dirk Busch, Director of the Institute for Medical Microbiology, Immunology and Hygiene at the TUM, has now produced artificial T-cell receptors for the first time with CRISPR/Cas9 genetic scissors. These receptors are

DZIF Professor Christina Zielinski in her laboratory at the Technical University of Munich.

very similar to those of natural immune cells, but they are flexible and their genetic code is easily modified. The receptor on the surface of the cells consists of two interconnected molecular chains. With genetic scissors, the DNA for the chains can be exchanged precisely at a desired location in the genome. It has been possible for a long time to integrate DNA into the genome, but not at a specific location in the gene. "We have also replaced the DNA in both chains so that there are no longer any dangerous immunological side effects," explained Dr Kilian Schober, who, together with Thomas Müller, is the first author of the publication arising from this study. "Our work shows that we are now able to use artificial receptors in a way that gives the cell exactly the qualities it needs for effective therapy," added Prof. Busch. "Our targeted intervention with CRISPR/Cas9 ensures that the genetic changes are much more specific and predictable than was previously possible." In future, the team plans to investigate the new cells and their properties in preclinical mouse models.

SALT IN THE SKIN PROMOTES THE DEVELOPMENT OF NEURODERMATITIS

The number of people suffering from allergies has increased significantly over the last 60 years. Risk factors for the development of allergies are genetic predisposition, a changed environment and lifestyle. "At the same time, nutrition has also changed, people now eat more fat and salt," according to Prof. Christina Zielinski from the Institute of Virology at the TUM. It is known that salt in food leads to the conversion of T-cells into TH17 cells, which play a role in autoimmune diseases such as psoriasis and rheumatoid arthritis. Prof. Zielinski's team has now shown that salt also reprogrammes T helper cells into TH2 cells. These immune cells are active in allergies such as neurodermatitis. The triggers for malfunction of TH2 cell responses were previously unknown. "To understand them better, we first wanted to know whether patients have more salt in their skin," said first author Julia Matthias. In fact, the sodium level was up to 30 times higher than in healthy skin. "Salt in the skin has a previously overlooked effect on neurodermatitis in the skin by converting T helper cells into TH2 cells and thus promoting the skin disease," said Prof. Zielinski. The typical dysbacteriosis, the cause of which was also unclear, fits in with this. Neurodermatitis patients have a very high number of *Staphylococcus aureus* bacteria in their skin, which, in contrast to other bacteria, can survive in high salt concentrations – they are virtually salt-loving. "Why the salt content in the skin is higher and whether nutrition has an influence on this must be clarified by further studies," according to Prof. Zielinski. The same applies to the question of whether a low-salt or high-salt diet can influence the development or course of neurodermatitis or affect other allergic diseases.



The team generated artificial immune cell receptors (from left to right): Prof. Dirk Busch, Thomas Müller and Dr Kilian Schober from the TUM.

GOALS FOR 2019: OUTCOMES

◐ Development of a method for predicting graft-versus-host-disease in stem cell transplant receivers with cytomegalovirus infections.

◐ Identification of target sites for new antiviral compounds currently being developed, which demonstrate activity against the human cytomegalovirus, herpes simplex virus, Kaposi´s sarcoma-associated herpersvirus and BK virus.

◐ Proof of efficacy of a new antiviral substance developed at the DZIF.

◐ *Goal partially achieved/project is still ongoing*
● *Goal achieved*

GOALS FOR 2020

○ The "DZIF ETB database" will allow the establishment of an expert-edited database of clinically relevant, pathogen specific T-cell epitopes and T- and B-cell receptors and thereby advance the development of new treatment strategies for infections in an immunocompromised host.

○ Determine biomarkers for a CMV de novo infection in transplant patients based on spontaneous "interferon-stimulated gene expression".

○ Identification of at least three genetic defects in patients with primary immunodeficiencies.

Coordinator:
Prof. Thomas Schulz
Hannover

New approaches for avoiding resistance

Bacteria are becoming increasingly resistant to antibiotics. Based on mechanisms such as point mutations and gene transfer, bacterial resistance patterns are constantly expanding, thus limiting the use of many previously effective reserve antibiotics. Infectious diseases researchers are therefore looking for new strategies to limit development and expansion of antimicrobial resistance and to restore the clinical efficacy of antibiotics.

Can antibiotic agents that are produced by our own microbiome kill multi-resistant bacteria? In 2016, DZIF researchers from the University of Tübingen identified a substance with antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and which was synthesized by bacteria colonizing the human nose. Further research is currently under way to better understand and exploit the therapeutic potential of this newly discovered antibiotic. Which infection control measures help to prevent the spread of multidrug-resistant bacteria? Scientists at the University Hospital Cologne examined high-risk patients in several hospitals to find out whether infection control measures can contribute to reducing the carriage of cephalosporin-resistant *Escherichia coli*.

NEW ANTIBIOTIC TAKES ALL THE ENERGY OUT OF BACTERIA

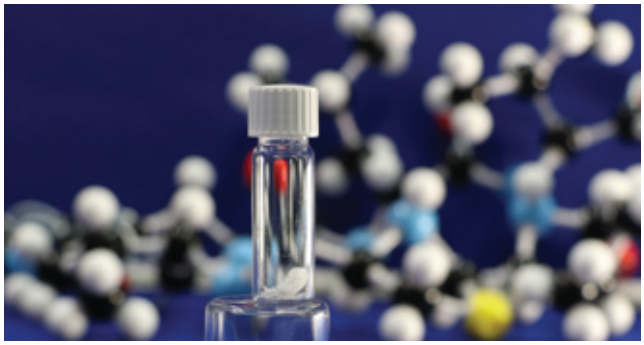
The nose of one out of three people is colonized with *Staphylococcus aureus*. While this does usually not represent a problem in healthy people, this pathogen can cause severe infections especially in immunocompromised patients, including infections with the methicillin-resistant variant MRSA. In 2015, about 670,000 people were infected in the EU, and 33,000 patients died of MRSA. In the search for agents

Professor Maria Vehreschild examining a patient at the University Hospital Cologne.

that eliminate the dangerous bacterium, Prof. Andreas Peschel from the University of Tübingen analysed the microbiome of the human nose. In 2016, his team discovered the prototype of a new class of antibiotics that inhibits MRSA. The substance (lugdunin) is formed by the bacterium *Staphylococcus lugdunensis*. The researchers have produced 50 synthetic derivatives of the basic substance – and have found clues as to how lugdunin works. "The peptide can transport protons on the cytoplasmic membrane and eliminate its vital membrane potential," according to the microbiologist. This destroys the energy supply of the cell, which then dies. This new mechanism gives scientists hope, because it is not based on any specific target structure. This makes it very unlikely that with point mutations in the bacterial target cells – a classic trick of pathogens to build resistance – the bacterium's sensitivity to antibiotics will be reduced. "However, lugdunin shuts down chemical processes on the cytoplasmic membrane in a functional way, not by protein binding." This means that its antibiotic effect is maintained, and no spontaneous resistance has occurred so far.

BASIC HYGIENE IS STILL THE BEST PROTECTION

The risk of acquiring multi-drug resistant pathogens is greatest in hospitals and preventive strategies are needed. These includes isolation measures, but their benefits are controversially discussed for many pathogens. In four German hospitals, a team led by Prof. Maria J.G.T. Vehreschild of the Clinical Microbiome Research Group at University Hospital Cologne therefore analysed the extent to which isolation of patients who were colonized with cephalosporin-resistant *Escherichia coli (E. coli)* bacteria could prevent the colonisation of non-colonized patients. At two hospitals, all patients carrying the multi-drug resistant pathogen were consistently isolated, but not at the other two hospitals. The measures included a single room and the wearing of gloves and gowns by staff. "We then documented the rate of colonized patients over twelve months and sequenced the bacterial genomes," said the first author, Lena Biehl. The result: "Patient-to-patient transmission was rare. There was no significant difference in the rate of colonisation, whether positive patients were isolated or not." Although ethical reasons prevented randomisation of the participating hospitals, the study has a great strength: analysis of the entire genome sequences of the bacteria enables an exact estimate of transmission, even across the sites. "There was no genetic relationship between the *E. coli* strains of different locations," said Dr Biehl. These results have consequences for infection control recommendations, hopes the team leader, Prof. Vehreschild. "Patients who are colonised with multidrug-resistant *E. coli* no longer need to stay in isolation afflicted with side effects. And hospitals have more scope in situations where protective measures are really necessary."



Lugdunin synthesised in the laboratory, with the structural model in the background.

GOALS FOR 2019: OUTCOMES

- ● Utilisation and expansion of previously established infrastructures (R-NET, CONTROL study, SurvCARE) to determine current dynamics and mechanisms of multidrug-resistance on a national scale with a focus on Vancomycin-resistant enterococci (VRE).
- ◐ Establishment and validation of a scoring system for rapid identification of patients with high risk of developing blood stream infections.
- ◐ Developing new eradication strategies for antibiotic-resistant pathogens infecting high-risk patients.

◐ *Goal partially achieved/project is still ongoing*
● *Goal achieved*

GOALS FOR 2020

- ○ Development and validation of prognosis models for short and long term mortality in patients with a blood stream infection.
- ○ The establishment of an *in-vitro*-intestinal model under anaerobic conditions to optimise decolonisation strategies.
- ○ Start-up of a "Fecal-Microbiota Transfer (FMT) Facility" (stool bank) in Köln to produce FMT products under GMP conditions for future application in clinical studies.

Coordinator:
Prof. Maria Vehreschild
Köln

Capsule and outer bacterial membrane in the focus of our researchers

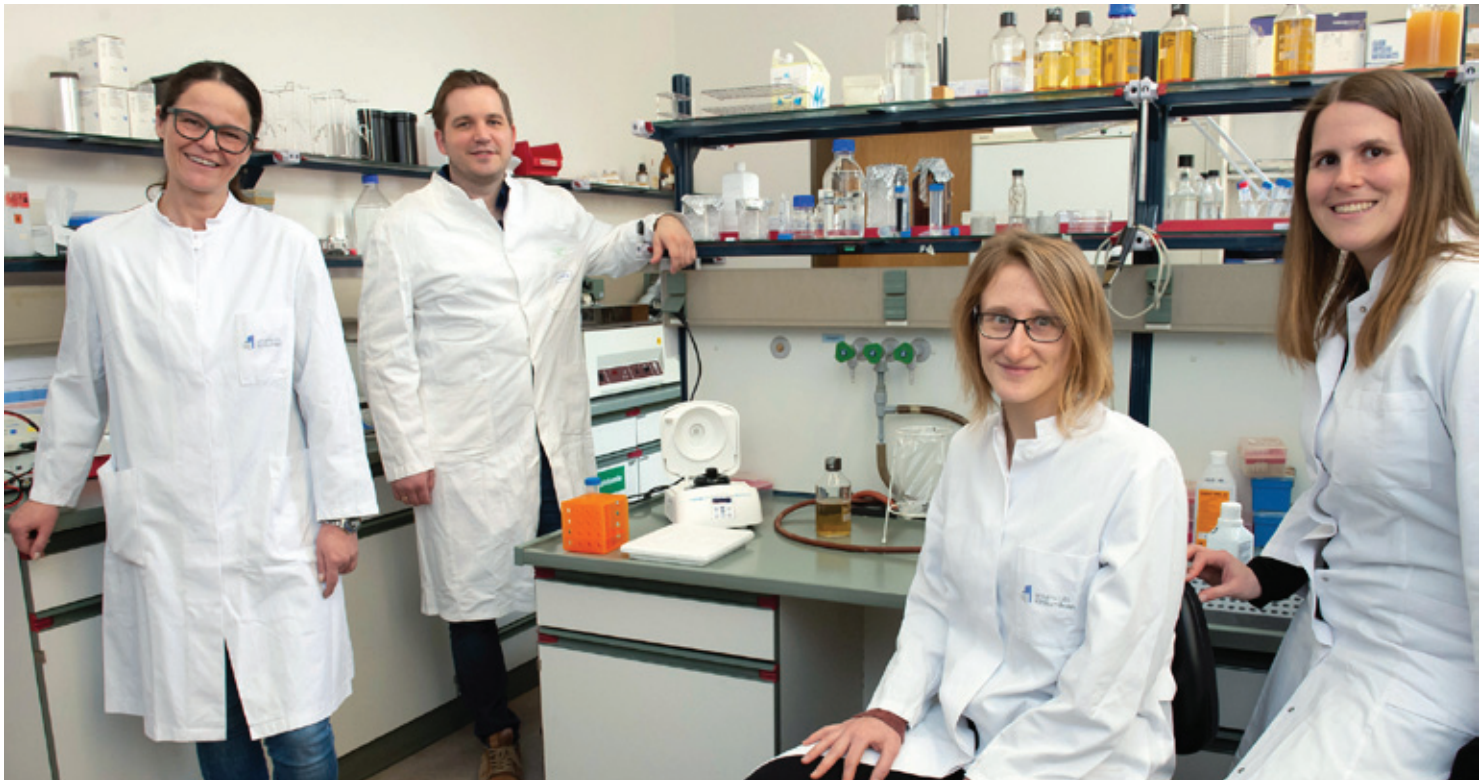
Bacteria develop resistance in order to defend themselves against antibiotics. The inappropriate use of these medications makes more and more bacteria insensitive to conventional active agents. According to the WHO, 25,000 patients in the EU die every year due to infection by resistant pathogens. In the fight against resistance, scientists are working hard to analyse the protective mechanisms of bacteria and develop appropriate drugs for the future.

In order to understand exactly how gram-positive bacteria produce a capsule for protection against medications and the human defence system, researchers at the University of Bonn have for the first time reproduced all the biosynthesis pathways of the capsule in the test tube. Researchers at Giessen University (JLU) have discovered a new peptide that attacks gram-negative bacteria at a previously unknown site.

CAPSULE SYNTHESISED IN THE TEST TUBE

Gram-positive bacteria such as *Staphylococcus aureus* build a capsule of interconnected sugar molecules that surrounds the cell, which protects them against the human immune system as well as certain antibiotics. "If formation of the capsule could be disrupted or blocked, we could make the bacterium more sensitive to an attack by the immune system. Once we understand the individual steps of biosynthesis, we can find new targets for antibiotics", said Prof. Tanja Schneider of the Institute for Pharmaceutical Microbiology at the University of Bonn. But how do the pathogens form the capsule? Sixteen enzymes are involved: what do they do? "In order to understand these mechanisms at the molecular level,

Seeking new targets in bacteria for medications (left to right): Prof. Tanja Schneider, Dr Marvin Rausch, Julia Deisinger and Dr Anna Müller.



we have reconstructed the capsule in the test tube – and published it for the first time worldwide in a journal article," said Prof. Schneider. Her research group has isolated all the necessary enzymes, purified them and put them in a test tube with artificial membranes – and then analysed the reactions. A "delivery service" is required for the biosynthesis of the capsule. This carrier molecule is anchored in the membrane and brings raw materials to the enzymes. Once the capsule's building blocks have been completed, they are transported from the inside to the outside of the cell, where they are attached to the murein wall, which is made of tightly meshed sugar-peptide fibres. This work made it possible for the first time to identify and characterise the protein that mediates this connection. In addition, certain proteins control the temporal and coordinated sequence of capsule synthesis. "We now know the role of each enzyme", according to the microbiologist. In the search for new antibiotics, this allows a targeted search for inhibitors of the enzymes with a key function. "In principle, all proteins might be target structures", said Prof. Schneider. "But until now, we had no idea how potential active agents work, or how to develop targeted systems to test unknown substances." In the next step, the scientists will search for potential active agents in huge libraries of active substances.

DAROBACTIN – A NEW PEPTIDE THAT BINDS TO THE OUTER MEMBRANE

An international team of researchers, including DZIF scientists from Giessen University, has discovered a new peptide called darobactin, which attacks gram-negative bacteria such as *E. coli* at a previously unknown site in the outer membrane. If the structure of the membrane is disrupted, the pathogens die. "Our task was to investigate the biosynthesis of darobactin," said Prof. Till Schäberle from Giessen. "Initially, extracts of bacteria living in symbiosis with nematodes were tested." One of these extracts was then used to isolate the peptide darobactin with bioactivity screening – a classic approach from natural materials research. However, darobactin binds to the BamA protein in the outer membrane. BamA has long been regarded as an interesting target, but no active ingredient that binds to the protein had been identified. "With darobactin, nature has shown us a way," said Prof. Schäberle. "What is particularly interesting is that this promising target lies on the outside of the membrane and active substances can easily reach it." Work is currently underway to increase production of this substance and generate further active agents with a comparable effect. "With detailed knowledge of its biosynthesis, we can produce new derivatives of the active substance as well as slight modifications," added Prof. Schäberle. The aim is to optimise the properties of a darobactin analogue so that it could be developed as a useful medication.

Visible with the naked eye: multidrug-resistant Escherichia coli bacteria still grow despite the administration of antibiotics.

GOALS FOR 2019: OUTCOMES

- ● Toxicological evaluation of potential kidney toxicity of chelocardin and amidochelocardin as part of the ongoing preclinical drug development.
- ● Genome-based reactivity probes for the specific identification of novel antibiotics.
- ● Establishment of a biotechnological production process for high quality Corallopyronin A, which can be transferred to an external producer.

◐ *Goal partially achieved/project is still ongoing*
● *Goal achieved*

GOALS FOR 2020

- ○ Extension of the DZIF natural compound library to > 1,000 pure substances.
- ○ Completion and publication of the ARTS 2.0 online platform for "genome mining" that extends across strains and is target-related for new antibiotics.
- ○ Transfer the established production of high-grade, pure Corallopyronin A to an industrial producer.

Coordinator:
Prof. Rolf Müller
Braunschweig/Saarbrücken

PRODUCT DEVELOPMENT UNIT

From the idea to clinical trials

Whoever wants to bring his project idea to the market needs a long breath. The PDU is always on hand to assist the scientists.

Experts of the "Product Development Unit" (PDU) support DZIF scientists from the initial project idea through to the first clinical trials of potential drugs. Without this professional support, new drug candidates would often fail to reach the first clinical trial stage. In order to identify appropriate measures in the development of new vaccines, therapeutic agents and diagnostics, the PDU works closely together with various DZIF research fields. The aim is to develop innovative agents up to the point from where the pharmaceutical industry – or other suitable third parties – can assume the following stages of drug development through to the final approval or marketing stages. The Office for Scientific and Regulatory Advice (OSRA) is part of the PDU. It is located at the Paul-Ehrlich-Institut (PEI) and at the Federal Institute for Drugs and Medical Devices (BfArM). The OSRA supports in clarifying regulatory matters and technical issues within scientific concerns and consulting procedures. The Translational Project Management Office (TPMO) at the Helmholtz Centre for Infection Research (HZI) in Braunschweig, also forms part of the PDU and provides its support in the operational and commercial aspects of drug development.

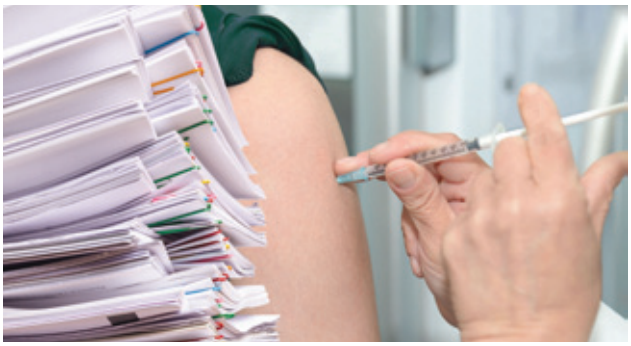
Since 2019, the PDU has also been supporting academic projects and companies as a "global accelerator" in the CARB-X network in the development of active substances against antibiotic-resistant germs. CARB-X stands for "Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator".

Coordinator:

Prof. Klaus Cichutek *Langen*

CLINICAL TRIAL UNIT

Pooled know-how for clinical trials



The CTU lends its support for the administrative work that is necessary before clinical trials can be conducted.

Clinical trials on humans must be carried out before new vaccines and medicines can be launched.

The DZIF has various clinical trial centres that specialise in infectious diseases, which fall under the "Clinical Trial Unit" (CTU) infrastructure. Twelve clinical trial centres are currently working together under the umbrella of this network. To date, the CTU has conducted 120 clinical trials. The infrastructure's central Coordinating Office is based in Köln. The CTU offers DZIF scientists consultation services for the planning of clinical trials and develops necessary recruitment strategies. As part of the DZIF FlexFunds procedure, the CTU provides advice for clinical trial applications.

The CTU has been conducting its own multicentre observational study since December 2017. The twelve clinical trial centres work together with 33 active dialysis clinics under the Dialysis and Kidney Transplant Board of Trustees e.V. A project known as "DOPPIO" is investigating the protective effects of pneumococcal vaccines in dialysis patients. For this group of patients, the current vaccination guidelines recommend a pneumococcal vaccination to be administered every six years. However, some studies question whether vaccine protection is warranted over the entire period of time. Patient recruitment ended in July 2019 with a total of 792 patients. The analysis of antibody titres and the consequent assessment of vaccine protection will take place at the end of 2021.

Coordinator:

Prof. Oliver Cornely *Köln*

AFRICAN PARTNER INSTITUTIONS

Research and networking

The DZIF supports the establishing and equipping of laboratories in Africa. In the image: Malaria researchers in Kumasi (Ghana).

The DZIF "African Partner Institutions" infrastructure strengthens longstanding partnerships between the German DZIF establishments and their African partners so as to jointly conduct research into infection. Research is being carried out in hospitals and research centres in Kumasi (Ghana), Lambaréné (Gabon), Nouna (Burkina Faso) and Mbeya (Tanzania). These countries have a high prevalence of numerous infectious diseases and demonstrate increasing antibiotic resistance.

Within the existing networks, valuable investments have been made towards personnel and laboratories. High-quality clinical, diagnostic and epidemiological studies can now be carried out at all research centres, mainly in the fields of malaria, HIV, tuberculosis, neglected tropical diseases and bacterial diseases such as salmonelloses.

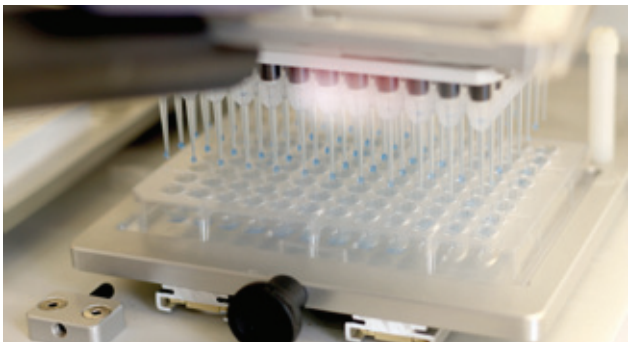
In 2019, the focus was on the setting up of an antibiotic resistance surveillance system in partner hospitals. Patient samples are analysed locally and sensitivity testing enables direct adjustments to be made to the treatment. Epidemiological, clinical and microbiological data are evaluated continuously, enabling the detection of changes in patterns of resistance, adjustments to therapies as well as the development of antibiotic stewardship programmes.

Coordinator:

Prof. Jürgen May *Hamburg*

NOVEL ANTIVIRALS

Success through screening



High-throughput processes accelerate the search for new substances with antiviral effects.

Effective drugs are lacking not only for newly emerging viruses such as SARS-CoV-2, Ebola or Zika. Also for many well-known viral diseases such as influenza or hepatitis, one looks in vain for recipes for success. Since the end of 2017, the DZIF has established a comprehensive infrastructure specifically for research into new substances with antiviral effects. In the search for new agents, focus has increasingly been on screening biobanks containing small molecular substances for use as potential drug candidates. All DZIF partner sites will have access to appropriate screening platforms as well as substance banks and, upon request, support in carrying out screening experiments. Screening platforms can be found in München, Heidelberg, Hannover and Braunschweig.

In 2019, the existing substance bank in Hannover was expanded to 60,000 substances and cooperation with medicinal chemists in particular was intensified. They advise the DZIF scientists in the infrastructure "Novel Antivirals". Even during the early stages of a project, they provide assessments as to whether active substances identified in screenings could be so-called "hits", i.e. promising candidates for drug use from a chemical perspective. In 2019, further hit derivatives were synthesized by medicinal chemists and successfully tested for their antiviral effect at the DZIF. In addition, work has begun on finding the target molecules of the identified inhibiting substances.

Coordinator:

Prof. Thomas Schulz *Hannover*

BIOBANKING

Focusing on ethical matters

No sample is stored without a patient's consent. All biosamples are made available for research projects at the DZIF.

Infection researchers often require human sample material, such as tissue or body fluids to carry out their research. The DZIF has a Biobanking infrastructure for this purpose. Patients and trial volunteers are required to be sufficiently advised on the procedures prior to giving their informed consent and before any biosamples are collected. This necessitates the creation of appropriate patient consent documents which also include information on biosample storage in the biobanks. In order to discuss and explain this and other important points concerning trial documents, the Biobanking infrastructure held a workshop entitled: "Practical aspects and success factors for clinical and epidemiological studies and biosample collection" at the 2019 DZIF Annual Meeting in Bad Nauheim. The DZIF "Epidemiology" and "Clinical Trial Unit" infrastructures were also involved in this workshop. Themes covered during the workshop included the collection of patient data, informed consent on behalf of patients, model texts, biobanking guidelines, submission to ethics committees and particular considerations with regard to the General Data Protection Regulation. Approximately 50 people participated in this workshop.

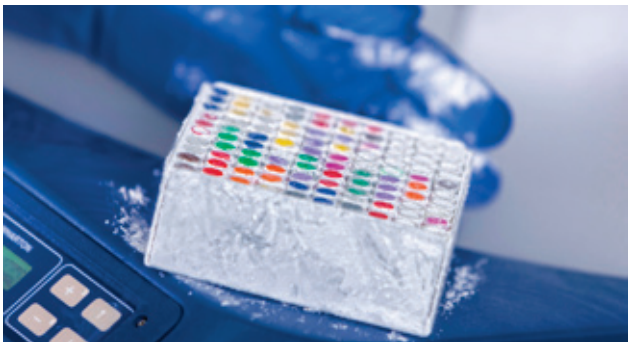
A concerted and harmonised approach which includes ethical matters is crucial for the success of multicentre trials in particular. At the DZIF, all multicentre trials that use biosamples have the possibility of drawing on the experience of the Biobanking infrastructure.

Coordinator:

Prof. Peter Schirmacher *Heidelberg*

PATHOGEN REPOSITORY

A special kind of collection



Over 2,400 pathogen strains are stored in nitrogen tanks at the German Collection of Microorganisms and Cell Cultures DSMZ.

Are newly occurring bacteria related to known common ones? How do antibiotics affect different bacterial strains? What role do microorganisms play in humans? To answer these and other questions, infection researchers require access to pathogen isolates. A broad range of pathogens is stored in the DZIF "Pathogen Repository" which is hosted by the German Collection of Microorganisms and Cell Cultures (DSMZ) in Braunschweig. Bacteria, fungi and bacteriophages, i.e. viruses that are specialised in infecting bacteria, undergo quality controls, are well documented and subsequently made available for research. Training for the professional handling of these pathogens is provided.

Over the past few years, the collection of pathogens at the DZIF has expanded to include over 2,400 microbial pathogen strains and active agent producers. Multidrug-resistant bacteria and antibiotic-sensitive "negative control strains" now also play an important role. To date, almost 250 genome sequencings have been performed in collaboration with the "Healthcare-associated and Antibiotic-resistant bacterial Infections" and "Gastrointestinal Infections" research fields. A so-called mouse microbiome, i.e. a collection of bacteria from the intestinal tract of mice, is stored in München thanks to the partnership with the "Gastrointestinal Infections" research field and others. More recently, collections of strains from the intestinal tracts of pigs have been made available.

Coordinator:

Prof. Jörg Overmann *Braunschweig*

BIOINFORMATICS

Evaluating data streams

Research quickly generates large amounts of data. Expert knowledge is required for their evaluation and interpretation.

The approaches of bioinformatics are indispensable in today's medical research. Genomes and patient samples are being sequenced in ever shorter time spans, and functional analyses (genomics, metagenomics, proteomics) generate huge amounts of data. Collecting and evaluating this data correctly requires the expertise of bioinformaticians as well as specialised soft- and hardware.

The "Bioinformatics" infrastructure supports DZIF scientists by evaluating and interpreting their infection research data. This includes developing and providing software, hardware and analysis pipelines for DZIF researchers to use independently as required. Automated and reproducible complex analyses, such as the genome-based prediction of bacterial phenotypes and antibiotic resistance, can be performed simultaneously for thousands of isolates "at the push of a button". The automated structural and functional analyses of microbial communities are also possible.

The bioinformaticians pass on their knowledge through workshops. The need for these training sessions is rising. Particularly in demand were workshops on microbiome data analysis and viral sequencing analysis, but also on the basics of Linux pipelines and statistical data analysis as well as data visualisation in free software such as "R".

Coordinator:

Prof. Alice McHardy *Braunschweig*

EPIDEMIOLOGY

Curbing the spread of disease

The digital management system SORMAS helps in the prevention and containment of infectious diseases.

Epidemiology is the study of the occurrence, spread and distribution of diseases within a given population. The prevalence of infectious diseases varies in different regions. They spread differently depending on the pathogen and the route of infection affecting some population groups more than others. Epidemiologists can recognise and curb the spread of infectious diseases more rapidly and prevent the occurrence of other diseases by taking these factors into account. The DZIF "Epidemiology" infrastructure supports the different DZIF research fields in dealing with epidemiological issues, thus bridging the methodological gap between individual research fields and infrastructures. In addition, the infrastructure offers various workshops, writes systematic reviews and develops new instruments for clinical and epidemiological research studies. These include, for example, the development of a mobile network app to record and control outbreaks in real-time (SORMAS).

In an additional project, epidemiologists are using a newly developed mobile health app (PIA) to record and monitor recurring infections in real-time in combination with self-administered nasal swabs. A DZIF infection cohort from this study has been integrated into the German National Cohort (NAKO) Health Study, the largest long-term population study on the causes of common diseases in Germany.

Coordinator:

Prof. Gérard Krause *Braunschweig*

Career opportunities for translational researchers

Promoting of young talent in translational research plays a major role at the DZIF. The DZIF Academy was established with the aim of training young doctors and scientists in infection research. It offers specific funding programmes and coordinates the selection and mentoring of stipend holders at various partner sites. The programmes' multidisciplinary approach provides good career opportunities in the fields of research covering clinical infectious diseases, microbiology, virology, immunology and molecular medicine.

In 2019, 18 young doctors benefitted from the Clinical Leave Programme. Networking opportunities during the Translational School in Lübeck.

FROM BEDSIDE TO BENCH

Many young clinicians are interested in conducting scientific research. One reason for this is the desire to get to the bottom of issues that their patients are experiencing in order to be able to help them better. However, daily routine clinical work does not allow for enough time to conduct the necessary research. A special DZIF Academy programme supports clinicians in this regard. "The Clinical Leave Stipend enabled me, as a clinician, to fully dedicate myself to scientific research for one and a half years," reported Leona Dold, who benefitted from this programme. During her clinical leave the young doctor worked on a hepatitis C vaccine project at the University Hospital Cologne. She is certain, "It would not have been possible for me to work on this translational project alongside my routine hospital work." She added, "This programme provided me with a very good foundation to further my scientific career." In 2019, 18 doctors used this stipend to work in medical research.

INCREASING THE SCOPE OF ACTION

Another significant DZIF funding programme is the "Maternity Leave Stipend". It enables mothers, or fathers, to return to work in research after parental leave by funding half of their salary. In 2019, 12 women benefitted from this stipend. In addition, the Academy awards stipends to medical students and doctors who wish to complete a PhD, either to attain a German MD title or an internationally recognised PhD. In 2019, 77 MD stipends and seven MD/PhD stipends were awarded. As is standard practice in other scientific stipend programmes, the funding period for MD/PhD stipend holders was extended to three years in 2019. Besides this, the DZIF offers Summer and Autumn Schools, which not only provide training for young researchers but also gives them the opportunity to network with other infection researchers. Laboratory rotations provide for lively exchange platforms between scientists and the opportunity to work in different laboratories. Travel grants for events are also awarded. Special courses, both organised and conducted in cooperation with DZIF experts, provide basic training in different fields. Prof. Jan Rupp, Coordinator of the Academy, was pleased about the positive development: "In 2019, the Academy awarded 114 stipends through four different programmes and also enabled travel to congresses and laboratory rotations."

Coordinator:
Prof. Jan Rupp *Lübeck*

SUCCESSFUL TRANSLATION

First drug for chronic hepatitis D has been approved

Stephan Urban began his research on the hepatitis B virus 25 years ago and discovered the way in which the virus enters liver cells. Over the past few years and with support from the DZIF, he has persisted in his research and was able to develop a highly potent agent that blocks this entry process. In 2019, the final stages in the development of a drug to treat hepatitis B and D were completed. Since the end of July 2020, Hepcludex has been approved as the first drug to treat hepatitis D which also shows excellent efficacy against hepatitis B.

Prof. Stephan Urban in his Heidelberg laboratory: his research on hepatitis has led to the creation of new treatment options.

"Up to now, two billion people have contracted hepatitis B (HBV) infections at some point in their life, of which approximately 300 million have developed chronic infections. About 25 million people are in addition infected with the hepatitis D virus (HDV) and all are unable to eliminate the virus," explained Stephan Urban, DZIF Professor for Translational Virology at Heidelberg University. A vaccine against hepatitis B/D has been available since the 1980s, but this is of no use to people who have already contracted the infection. No treatment for hepatitis D and B exists to date.

FROM THE PEKING DUCK TO HUMANS

Research began with the Peking duck. Scientists discovered a hepatitis B virus in this particular duck that they used for their investigations. Initially, they wanted to find out how the virus specifically and exclusively targeted liver cells. A protein from the viral envelope which binds to a receptor of the liver cell turned out to be the "key" in this process. "We produced fragments of this protein, i.e. peptides, in the laboratory, added them to non-infected liver cells and observed if this would inhibit viral entry and it worked," explained Stephan Urban. "When we injected the duck with the peptide before we infected it with the virus, we found we could protect it from infection." Like a broken key, the protein fragment became lodged in the receptor "lock" therefore blocking it.

Stephan Urban subsequently produced peptides that corresponded to the human variant of the hepatitis B virus and conducted the same experiments on healthy human liver cells. "It worked once again and highly effectively at that!" The peptide was quickly enhanced in the laboratory so that it could completely block HBV infections in very low concentrations. The effect lasted for a surprisingly long period of time. As hepatitis B and D viruses have the same viral envelope, Urban now also had the first active agent against HDV in the world. It was called Myrcludex B.

FROM ACTIVE AGENT TO A DRUG

Following successful tests on mice, which were conducted on a mouse model developed by Prof. Maura Dandri at University Medical Center Hamburg-Eppendorf, and the identification of a receptor, the path to a new drug was paved. In 2011, Myrcludex B was administered to the first healthy volunteer. Alongside the phase I trial in Heidelberg, funded by the DZIF, phase II trials were conducted in Germany and in Russia by the licensee and DZIF's contractual partner Myr Pharmaceuticals GmbH. Since the end of July 2020, it has been approved in Europe under the name of Hepcludex, initially for HDV.

Project Coordinator:
Prof. Stephan Urban *Heidelberg*

DZIF HIGHLIGHTS 2019

News Ticker

JANUARY

Since 2013, millions of people in Latin America have contracted Zika and chikungunya virus infections. DZIF scientists at Charité – Universitätsmedizin Berlin developed extremely reliable combined testing methods. Reliable diagnostics are particularly needed for Zika-associated malformations in new-borns.

FEBRUARY

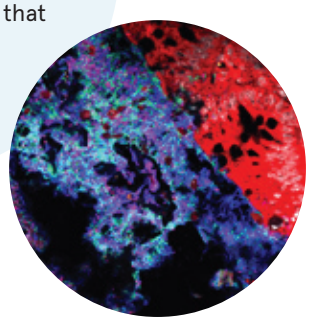
The DZIF becomes a member of the "CARB-X Accelerator Network" and accelerates the fight against antibiotic resistant bacteria. CARB-X globally funds biotechnology and pharmaceutical companies that develop new drugs.

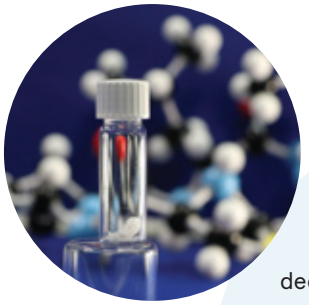
MARCH

The German Centers for Health Research (DZG) publish their first joint journal known as "SYNERGIE" which clearly illustrates the meaning of translation and how interdisciplinary research and networking help to improve people's health.

APRIL

DZIF scientists at the Max von Pettenkofer-Institute examined the gut flora of different groups of mice and identified bacteria that protect mice from salmonella infection.





MAY

DZIF scientists in Tübingen have deciphered the mechanism of action of a new class of antibiotics which is highly effective against multidrug-resistant hospital pathogens. The so-called fibupeptides impair energy supply to the bacterial cell, consequently causing their death. Scientists discovered lugdunin, the first fibupeptide of this group in the human nasal mucosa in 2016.

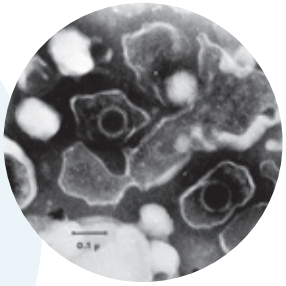
JUNE

Researchers in München, Hamburg and Heidelberg succeeded in eradicating a chronic hepatitis B virus infection in an animal model for the first time. The team demonstrated that T-cell therapy can lead to a real cure.

JULY

A team from the Technical University of Munich and the DZIF used a new pair of gene scissors, CRISPR/Cas9, to create T-cells that are very similar to natural immune cells. These could help solve issues in immunotherapy. Up to now, clinical immunotherapy against infections and tumours have only been marginally successful.

AUGUST



Transplant patients are highly susceptible to viral infections as their immune system has to be suppressed by drugs in order to prevent organ rejection. Several professional societies have developed clinical guidelines for the diagnosis, prevention and treatment in both in-patient and ambulatory settings. DZIF scientists have also been involved in this.

SEPTEMBER

Can green tea help in the fight against antibiotic resistant bacteria? DZIF scientists from the University Hospital Cologne and the University of Surrey discover a natural antioxidant in tea that makes multidrug-resistant *Pseudomonas aeruginosa* bacteria more vulnerable.

OCTOBER

Since 2018, a vaccine has been used in the fight against Ebola that was co-developed by the DZIF. However, how the vaccine worked had not been fully understood. Prof. Florian Klein's research team at the University Hospital Cologne and the DZIF were now able to decode the immune response to the vaccine in detail.

NOVEMBER

An international team of researchers, including the University of Giessen and the DZIF, discovered "Darobactin", a new agent that is effective against gram-negative bacteria. However, the site targeted by the agent is still unknown.

On 11 November 2019, ERVEBO, the first vaccine against Ebola was approved by the European Medicines Agency. The DZIF was extensively involved in the development of this vaccine.

Prof. Gülşah Gabriel and Prof. Stefan Niemann won over the jury thanks to their scientific research: the DZIF awards the Prize for Translational Infection Research worth 5,000 euro to each of them.

DECEMBER

A first clinical trial on tuberculosis patients treated with the new BTZ-043 agent is carried out in Cape Town, South Africa, led by Professor Michael Hoelscher from the Department for Infectious Diseases & Tropical Medicine at the Medical Center of the Ludwig-Maximilians-Universität (LMU) in Munich. In preclinical trials, BTZ-043 also demonstrated high efficacy against multidrug-resistant pathogens.

SCIENCE AND PUBLIC

The science communication is more important now than ever

The corona crisis has shown how much society needs scientific information. It has, in addition, underlined the importance of sound science communication, not just in times of crisis but all the time. There is a demand for fact-based information and for the honest portrayal of various uncertainties when it comes to scientific research. This is not an easy task for those responsible for communication as the main challenges involve formulating complex issues in clear and easy to understand communiqués. In 2019, the DZIF Press Office yet again pursued this aim via various media channels.

In contrast to current times, more than one research theme was of interest to the public in 2019. Information on a broad range of research themes was made available by the DZIF through numerous press releases, brochures and films. The new DZIF website, which went online in May with a completely new design and increased content, presents information on diverse research themes and provides a good overview.

DIVERSE: FROM VACCINES TO NEW THERAPIES

In 2019, the DZIF published over 30 press releases with information on research results. Alongside this, the results were also communicated via social media to make the information more accessible to other target groups besides journalists. The theme of the first press release in January focussed on "How herpesviruses shape the immune system" and the last one that year focussed on "Tuberculosis: New drug substance BTZ-043 being tested on patients for the first time". In addition to these two press releases, numerous other interesting research results were published, centred on themes ranging from multidrug-resistant bacteria and newly emerging viruses,

The DZIF Press Office team doing a test run for the next video interview.
Janna Schmidt, Karola Neubert, Martina Lienhop and Tatiana Hilger have placed Timo Jäger in front of the camera.

Top: Lively discussion during a poster session at the 2019 Joint Annual Meeting with the DGI. Bottom: The DZIF presents itself at the Conference on Life Sciences in Berlin in March 2019.

to chronic hepatitis and HIV. Only a fraction of the publications released by the DZIF are actually published as press releases. The press offices of various member establishments have been increasingly working together which has been a key success factor in communications.

UNITED: THE GERMAN CENTERS FOR HEALTH RESEARCH UNITED AGAINST WIDESPREAD DISEASES

Centres such as the DZIF are only as strong as their networks. The DZIF and five other Centers for Health Research (DZG) in Germany were established in 2010, based on the idea that fundamental research scientists and clinicians would do well to work together jointly. Currently, a total of six centres are involved in researching widespread diseases together and have made translational research their aim. This goal unites the centres which consequently developed joint communication strategies early on. The most notable result of this collaboration is the research journal known as "SYNERGIE", which published two issues in 2019. The first issue entitled "Translation" was followed by the second issue entitled "Prevention". This year, the themes "Diagnosis" and "Therapy" will be included to complete the first magazine series. The journal has been well received and features a particularly striking modern layout. In addition to this, the Centers for Health Research are also involved in jointly publishing their findings in the BMBF newsletter: "Aktuelle Ergebnisse der Gesundheitsforschung (Current Findings in Health Research)", which is directed at approximately 1,500 editorial offices and/or journalists.

MOTION: FILMS TO ENHANCE COMMUNICATION

Films, which appeal to younger audiences in particular and now podcasts once again, are becoming increasingly important in the communication of scientific information. In order to be in a position to rapidly produce the necessary films, the Press Office has established its own video department and already filmed its first interviews at the 2019 Annual Meeting. Furthermore, at the idw, a news portal for science and research, the DZIF Press Office was involved in developing a new format of video for science news. The concept was developed in 2019 and filming is now underway. The aim is to release news videos alongside important publications which will feature scientists describing their work themselves. Current research will be presented in 3-minute clips.

NETWORKING: INTERNAL AND EXTERNAL

Scientists and clinicians must work together within an interdisciplinary network across different establishments in order to conduct translational research and bring research findings to the bedside more rapidly. In order to support the consistent exchange of information, the Press Office regularly publishes a newsletter and provides information via the DZIF intranet platform which is accessible to all members of staff. At the 2019 Annual Meeting in Bad Nauheim, DZIF members from all over Germany as well as from African Partner Institutions came together to discuss their respective projects and new potential partnerships.

BEING APPROACHABLE: THE DZIF EXHIBITING AT FAIRS

Bacteria and viruses evidently do not stop at borders, which is why infection researchers act internationally. In 2019, the DZIF once again exhibited at various scientific congresses in Germany and worldwide in order to increase its national and international visibility and continue to grow its network. Once again, an important exchange of information took place at the annual GAIN meeting, a network of German scientists in North America, in which the German Centers for Health Research jointly presented their junior programmes in particular.

FIT FOR THE FUTURE: THE DZIF TAKES ON "GRAND CHALLENGES"

Research at the DZIF is in constant flow and continually faces new challenges. The DZIF has defined four "Grand Challenges" for the near future which are: immunoprevention and immune treatment, antimicrobial resistance, tropical and newly emerging infections and chronic infections. The DZIF research fields will take on these challenges and align their projects accordingly. Presenting information with regard to these in a transparent manner and supporting dialogue within society remains the responsibility of those communicating scientific information. It is not only in crisis situations that scientists are expected to communicate about courses of action and risk assessments.

Press and Public Relations:
Karola Neubert
Janna Schmidt
Braunschweig

External Partnerships

Numerous associated partnerships and other external collaborations reinforce the DZIF's position as a top-class institution in the field of infection research.

THE DZIF'S ASSOCIATED PARTNERS

Charité – Universitätsmedizin Berlin

The Charité Institute of Hygiene and Environmental Medicine is one of six partners in the DZIF network "Multidrug-resistant Bacteria" (MDRO Network: R-Net). This network is focusing on investigating the epidemiology of multidrug-resistant bacteria, bloodstream infections and *Clostridium difficile* infections.

The research group "Virus Detection and Preparedness" forms a major part of the DZIF "Emerging Infections" research field. It is led by Professor Christian Drosten at the Charité's Institute of Virology (Campus Charité Mitte) and is responsible for identifying emerging pathogens and for developing diagnotic tests for both novel and epidemic pathogens. The "Innate Immunity and Viral Evasion" research group is also located at the Institute of Virology and is part of the DZIF "HIV" research field. It is led by Professor Christine Goffinet and characterises the mechanisms of intrisic cellular immune responses and HIV-1 induced antagonising strategies. The research group "Virus Epidemiology", led by Prof Jan Felix Drexler, coordinates Zika outbreaks in Latin America projects across several DZIF partner sites and collaborates closely with the "Hepatitis" research field, conducting research on novel hepatitis viruses from animal reservoirs.

Essen University Hospital

A hepatitis C project involving scientists from the University Hospital Essen and others (see also Goethe University of Frankfurt) aims to point out individually tailored patient treatment options to the treating physician. Therapy recommendations include both hepatitis C virus genome sequences and the patient data. Scientists at the University Hospital Essen also research hepatitis delta virus (HDV) infections, the most severe form of viral hepatitis. In

For the development of cell lines or vaccine production on a larger scale, the DZIF cooperates with the company IDT Biologika, among others.

addition, the UK Essen is involved in two projects in the research field of HIV. Among other things, the efficiency of a therapeutic vaccine against HIV is being investigated, which should reduce latent viruses.

Friedrich Schiller University Jena

The Institute of Organic Chemistry and Macromolecular Chemistry at the University of Jena has been participating in a study in the research field of "Tuberculosis" since 2019. Thiopeptide derivatives and their effectiveness as antibiotics against multi-resistant tuberculosis bacteria are being investigated. Various semi-synthetically produced thiopeptides showed promising activities and are now being further developed up to preclinical studies.

German Liver Foundation/HepNet Study-House, Hannover

The HepNet Study-House has been networking study centres and is expanding nationwide networking across Germany with medical practices and physicians who are interested in taking part in hepatitis research. As a central point of contact for scientists and cooperation partners, it creates a platform for carrying out clinical trials. The DZIF can use the infrastructures and cohorts for its projects.

Goethe University Frankfurt, Frankfurt am Main

A project of the DZIF "Hepatitis" research field is currently underway at the Goethe University of Frankfurt am Main. It aims to improve the treatment of hepatitis C patients with novel drugs (directly acting antivirals, DAA). It defines treatment algorithms that maximise clinical success whilst minimising healthcare costs.

Together with the University of Cologne, the research area "Healthcare-associated and Antibiotic-resistant bacterial Infections" is running the so-called Cosima study, in which multi-resistant enterobacteria are analysed.

Hans Knöll Institute, Jena

The Hans Knöll Institute (HKI) provides the DZIF with different natural compounds. Scientists from the HKI and the Ludwig-Maximilians-Universität München (LMU) lead a project involving a clinical trial on a newly developed antibiotic against tuberculosis. The newly developed investigational agent, termed BTZ-043, is also effective against multidrug-resistant pathogens.

Julius-Maximilians-Universität Würzburg

In a clinical trial at the DZIF research area "Infections of the immunocompromised Host", leukaemia patients are administered specially purified immune cells, so-called memory T cells, after a bone marrow transplant for the first time. These special immune cells are to protect patients from infection until their own immune systems function. Some of the trial patients are being treated in Würzburg, and also at the DZIF sites in München (coordination), Tübingen and Hannover.

Medical Center – University of Freiburg

The Medical Center of the University of Freiburg is a partner of several DZIF projects which are located in the research areas "Hepatitis", "Infections of the immunocompromised Host" and "Healthcare-associated and Antibiotic-resistant bacterial Infections". Reducing hospital-associated infections is an important goal of these projects. To this end, for example, antibiotics are being used more selectively and hygiene measures improved. Freiburg is one of six partner sites at which the epidemiology of multidrug-resistant bacteria and the epidemiology of bloodstream infections and *Clostridium difficile* infections are being studied longitudinally over a period of several years. In addition, a system is being developed that is designed to indicate outbreaks of multi-resistant bacteria in the clinic in good time.

Human cytomegalovirus (HCMV) infections pose a risk for immunocompromised individuals (such as AIDS or transplant patients). The researchers are looking for new drugs against HCMV.

University Hospital – Martin Luther University Halle-Wittenberg

The University Hospital of Halle-Wittenberg is working on a DZIF project at the "Infections of the immunocompromised Host" research field. The scientists determine immune parameters in transplant patients and develop the statistical tools for analysing the data. The goal is to predict clinical outcomes from the data.

University of Bayreuth

The *Mycobacterium tuberculosis* (MTB) pathogen is in the focus of a major tuberculosis screening project in which the University of Bayreuth is involved. The goal is to create a preclinical model, based on which new drugs against tuberculosis can be identified, and both known and newly discovered drugs can undergo efficacy testing.

University of Münster

The University of Münster is partner in a project of the research area "Healthcare-associated and Antibiotic-resistant bacterial Infections", in which the lytic phage protein HY-133 is being investigated. The protein has been shown to be very effective against methicillin-resistant *Staphylococcus aureus* bacteria in the nasal cavity. The promising agent is currently being investigated in preclinical trials so as to confirm its safety for subsequent clinical trials on humans. Another project is located in the research area "Gastrointestinal Infections" and deals with new inhibitors against pathogens such as salmonella.

Scientists at the University of Münster are also involved in the development of new antibiotics against multi-resistant tuberculosis bacteria.

INDUSTRY COLLABORATIONS

BioNTech AG, Mainz

The DZIF is researching RNA-based vaccines for selected virus families with potential human pathogens in collaboration with the BioNTech Institute and the TrON Research Institute, subsequently bringing the vaccines into preclinical and early clinical development.

Coris BioConcept, Gembloux (Belgium)

DZIF scientists from the Institute of Medical Microbiology at the University of Cologne have generated antibodies against the carbapenemases OXA-23, -40 and -58, which are being used in collaboration with the Belgian company Coris BioConcept in a rapid test for the detection of carbapenem-resistant *Acinetobacter baumannii*. Dr Alexander Klimka's research group "Antibacterial Vaccine Development" is being funded by the DZIF.

HYpharm GmbH, Bernried

HYpharm GmbH and a consortium funded by the DZIF are collaborating to manufacture and preclinically develop phage lytic protein HY-133 (also see University of Münster). They are planning joint early-stage clinical development for nasal decolonisation of *Staphylococcus aureus*.

IDT Biologika GmbH, Dessau-Rosslau

Together with the company IDT Biologika, the DZIF is developing a vaccine against the MERS coronavirus in a consortium of scientists and clinicians. The company IDT Biologika developed its own cell line for the production of the vaccine on a larger scale. The company is also a partner in the current research on a vaccine against SARS-CoV-2.

Juno Therapeutics GmbH, Göttingen

Juno Therapeutics, formerly Stage Cell Therapeutics, is collaborating and exploitation partner of a research group led by Prof. Dirk Busch, Technical University of Munich, working in the field of GMP quality-assured manufacture of central memory T cells for the treatment of infections and cancer. The DZIF is funding Prof. Busch's group.

MYR GmbH, Burgwedel

Together with the University of Heidelberg, an active agent which inhibits hepatitis B viruses from penetrating cells is being developed and could potentially be used to prevent hepatitis B and D infections. MYR GmbH is coordinating the entire project and overseeing the clinical trial. At the end of July 2020, the European Commission approved the active ingredient under the name Hepcludex – initially for hepatitis D.

ABOUT DZG

German Centers for Health Research

The main objective of the German government's health research programme is to develop more effective ways to combat widespread diseases. The foundation for this was laid at both federal and state levels through the establishment of the German Centers for Health Research (DZG) with long-term, equal partnerships between non-university research institutes, such as the Max Planck, Helmholtz and Leibniz Institutes, and universities with their medical centres.

The jointly produced magazine "SYNERGIE" of the German Centers for Health Research will soon appear in its fourth issue.

The German Centers for Health Research pool all of their existing expertise, thereby greatly helping to close knowledge gaps and improve prevention, diagnosis and therapy of common diseases. Research policies aim to ensure close collaboration between basic research and clinical research, always in line with the indications and needs of the patients. Close networking and the expansion of existing research structures will enable for the quicker transfer of research results into clinical practice (translation). This is the mission of all German Centers for Health Research.

Strategic collaborations between leading scientists in the German Centers for Health Research reinforces Germany's international position as a high-ranking science location and substantially increases its attractiveness to young scientists in Germany and worldwide. Pooling different disciplines and expertise has already markedly increased the international visibility of translational, clinical and application-oriented research in Germany.

2009 already saw the foundation of the "German Centre for Neurodegenerative Diseases" and the "German Centre for Diabetes Research". In 2012, the "German Centre for Cardiovascular Research", the "German Consortium for Translational Cancer Research" and the "German Center for Lung Research" were launched in addition to the DZIF. Two more centres, one for child and adolescent health and one for mental health are currently being created.

From the outset, the six German Centers for Health Research have worked closely together in order to share their findings taking advantage of this cooperation. As a result, SYNERGIE, a jointly produced health magazine was published for the first time in early 2019. The magazine is available in high-quality print and online. It has attracted much interest and the fourth issue is currently in progress.

The DZIF's structure

GENERAL ASSEMBLY

The General Assembly is the central decision-making organ of the DZIF and comprises representatives of the DZIF member establishments. The General Assembly elects the Executive Board members and the Executive Director, and decides on the allocation of funds to the research fields and infrastructures (TTUs and TIs).

COMMISSION OF FUNDING AUTHORITIES

The Commission of Funding Authorities is made up of the Federal Government and respective states (Länder) and decides on important matters of finance, organisation and personnel. The Executive Board and the Managing Director report to the Commission on all funding measures.

EXECUTIVE BOARD

The Executive Board represents the DZIF externally. It implements the resolutions and tasks assigned by the General Assembly and is responsible for routine administrative affairs.

SCIENTIFIC ADVISORY BOARD

The association is supported by the Scientific Advisory Board, consisting of internationally renowned experts from the field of infection research. The Scientific Advisory Board advises the Executive Board and General Assembly on all scientific and programme-related matters.

MAIN OFFICE

The Main Office is located in Brunswick and supports the Executive Board in its work. Its duties include organising research initiatives and coordinating the DZIF's press and public relations activities.

INTERNAL ADVISORY BOARD

The members of the Internal Advisory Board are DZIF scientists representing all research fields and locations of the centre. The council advises the Executive Board on all scientific, programme-related and technical matters and performs representative duties.

THEMATIC TRANSLATIONAL UNITS (TTUS)

The Thematic Translational Units (Research Areas) pool the DZIF's research activities. Each unit is dedicated to one pathogen or to one specific problem in infection research.

- Emerging Infections
- Tuberculosis
- Malaria
- HIV
- Hepatitis
- Gastrointestinal Infections
- Infections of the immunocompromised Host
- Healthcare-associated and Antibiotic-resistant bacterial Infections
- Novel Antibiotics

TRANSLATIONAL INFRASTRUCTURES (TIS)

Strategically aligned translational infection research requires modern infrastructures. These are provided in the form of the Translational Infrastructures, and can be used by all DZIF members.

- Product Development Unit
- African Partner Institutions
- Biobanking
- Pathogen Repository
- Bioinformatics
- Novel Antivirals
- Epidemiology
- Clinical Trial Unit
- DZIF Academy

PARTNER SITES

The DZIF conducts its research in 35 research establishments at seven locations across Germany. At each site, two scientists are appointed to coordinate the collaboration and to advise the Main Office. Various external research partners are also involved in DZIF projects.

Bonn-Köln	Gießen-Marburg-Langen	Hamburg-Lübeck-Borstel-Riems	Hannover-Braunschweig
Heidelberg	München	Tübingen	Associated Partners

Central bodies

EXECUTIVE BOARD

- Prof. H.-G. Kräusslich
  (Chair)
  Heidelberg University and University Hospital
- Prof. D. Busch
  (Vice Chair)
  Technical University of Munich
- Prof. M. Dandri,
  University Medical Center Hamburg-Eppendorf
- Prof. D. Heinz,
  Helmholtz Centre for Infection Research, Braunschweig
- Prof. A. Peschel,
  University and University Hospital Tübingen

MANAGING DIRECTOR

- Dr T. Jäger, DZIF e.V.

as at July 2020

SCIENTIFIC ADVISORY BOARD

- Prof. R. Burger
  (Chair)
  former President of the Robert Koch Institute, Germany
- Dr A. Ammon,
  European Centre for Disease Prevention and Control, Sweden
- Dr H. Feldmann,
  National Institute of Allergy and Infectious Diseases, USA
- Dr K. Klumpp,
  Riboscience LLC, USA
- Prof. R. Laxminarayan,
  Center for Disease Dynamics, Economics & Policy, USA
- Prof. C. Mgone,
  former Executive Director of the European & Developing Countries Clinical Trials Partnership, Tanzania
- Prof. D. Moradpour,
  Lausanne University Hospital, Schweiz
- Prof. C. Rooney,
  Baylor College of Medicine, USA
- Prof. R. Wallis,
  The Aurum Institute, South Africa
- Prof. S. Ward,
  Liverpool School of Tropical Medicine, Great Britain

INTERNAL ADVISORY BOARD

- Prof. G. Sutter
  (Chair)
  Ludwig-Maximilians-Universität München
- Prof. H. Brötz-Oesterhelt
  (Vice Chair)
  University of Tübingen
- Dr S. Castell,
  Helmholtz Centre for Infection Research, Braunschweig
- Prof. K. Cichutek,
  Paul-Ehrlich-Institut, Langen
- Prof. O. Cornely,
  University Hospital Cologne
- Prof. K. Heeg,
  Heidelberg University Hospital
- Prof. C. Meier,
  Universität Hamburg
- Prof. T. Pietschmann,
  TWINCORE, Centre for Experimental and Clinical Infection Research, Hannover

Partner sites and member establishments

Germany-wide infection research

BADEN-WÜRTTEMBERG

The DZIF partner site in **Heidelberg** co-coordinates the *Hepatitis, Malaria* and *Infections of the immunocompromised Host* research fields. Alongside this, scientists in Heidelberg also co-ordinate the DZIF translational *Biobanking* infrastructure with a focus on establishing tissue banks. One focus of the research activities is on imaging methods in order to render infections visible in various complex systems ranging from clonal cells to mixed cell populations through to organs and animal models. Research on HIV is also conducted here.

HEIDELBERG

Spokesperson: Prof. Klaus Heeg (Heidelberg University Hospital)
Establishments: German Cancer Research Center in the Helmholtz Association, Heidelberg University, Heidelberg University Hospital
TTU coordination:

- Hepatitis (co-coordination)
- Infections of the immunocompromised Host (co-coordination)
- Malaria (co-coordination)

TI coordination:

- Biobanking (coordination)

The DZIF partner site in **Tübingen** coordinates the Malaria research field. It also co-coordinates *Gastrointestinal Infections*, *Healthcare-associated and Antibiotic-resistant bacterial Infections* and *Novel Antibiotics*. Scientists in Tübingen focus on translating research results into drug and vaccine development as well as on infection models and epidemiology. For infections caused by bacterial pathogens that are resistant to antibiotics, scientists in Tübingen focus on multidrug-resistant pathogens such as methicillin-resistant staphylococci (MRSA) and gram-negative pathogens (e.g. so-called ESBLs).

TÜBINGEN

Spokesperson: Prof. Peter Kremsner (University of Tübingen)
Establishments: University of Tübingen, Max Planck Institute for Developmental Biology, University Hospital Tübingen
TTU coordination:

- Malaria (coordination)
- Gastrointestinal Infections (co-coordination)
- Healthcare-associated and Antibiotic-resistant bacterial Infections (co-coordination)
- Novel Antibiotics (co-coordination)

BAVARIA

The DZIF partner site in **München** coordinates the *Gastrointestinal Infections, Hepatitis and Tuberculosis* research fields. Scientists at the DZIF site in München are also involved in researching the immune control of infections and the development of new treatment methods. Pathogen-specific immunotherapies (e.g. vaccinations or (adoptive) T-cell transfer) aim to strengthen the body's immune system in order to better control or completely cure specific infectious diseases. The München partner site further focuses on HIV and Biobanking.

MÜNCHEN

Spokesperson: Prof. Michael Hoelscher (LMU Munich and Klinikum der Universität München)

Establishments: Helmholtz Zentrum München – German Research Center for Environmental Health, Bundeswehr Institute of Microbiology, Klinikum der Universität München, Klinikum rechts der Isar of the Technical University of Munich, Ludwig-Maximilians-Universität München, Technical University of Munich

TTU coordination:

- Gastrointestinal Infections (coordination and co-coordination)
- Hepatitis (coordination)
- Infections of the immunocompromised Host (co-coordination)
- Tuberculosis (coordination)

TI coordination:

- DZIF Academy (coordination till May 2020)
- Biobanking (co-coordination)

HAMBURG/ SCHLESWIG-HOLSTEIN

The **Hamburg - Lübeck - Borstel - Riems** site has a unique concentration of expertise and infrastructure for research on national and globally relevant emerging pathogens and for the development of strategies to combat them. Scientists at the site are involved in clinical, entomological and virological studies. It is also the DZIF base for medical chemistry, active ingredient discovery, the epidemiology of malaria and translational research studies on tuberculosis, viral haemorrhagic fever and hepatitis. The site coordinates the *HIV* research field and the TI *African Partner Institutions*.

HAMBURG - LÜBECK - BORSTEL - RIEMS

Spokesperson: Prof. Marylyn Addo (University Medical Center Hamburg-Eppendorf)

Establishments: Bernhard Nocht Institute for Tropical Diseases, Research Center Borstel - Leibniz Lung Center, Friedrich-Loeffler-Institute, Heinrich Pette Institute – Leibniz Institute for Experimental Virology, University of Hamburg, University Medical Center Hamburg-Eppendorf, University of Lübeck

TTU coordination:

- HIV (coordination)
- Tuberculosis (co-coordination)
- Emerging Infections (co-coordination)
- Healthcare-associated and Antibiotic-resistant bacterial Infections (co-coordination)
- Malaria (co-coordination)

TI coordination:

- African Partner Institutions (coordination)
- DZIF Academy since May 2020

HESSE

In **Gießen - Marburg - Langen**, DZIF researchers identify emerging pathogens, develop new agents and vaccines and use quality-assured production processes to produce them for scientific industrial partners. Research activities focus on developing strategies which enable quick, effective action to combat outbreaks of new or re-emerging infectious diseases, for example, through vaccine development. Scientists in Marburg concentrate on viral pathogens while the main focus in Giessen is on bacteria and antibiotic resistance. The institutions involved provide infrastructures such as the BSL-4 laboratory in Marburg and the BSL-3 laboratory at the Paul-Ehrlich-Institut (PEI) in Langen. The PEI contributes towards the rapid translation of research results into clinical practice by providing expertise with regard to drug approval and development.

GIESSEN - MARBURG - LANGEN

Spokesperson: Prof. Trinad Chakraborty (Giessen University)

Establishments: Giessen University, Paul-Ehrlich-Institut Langen, Philipps-Universität Marburg, Mittelhessen University of Applied Sciences

TTU coordination:

- Emerging Infections (coordination)
- Healthcare-associated and Antibiotic-resistant bacterial Infections (co-coordination)

TI coordination:

- Product Development (coordination)

LOWER SAXONY

Seven partner institutes work together within the DZIF **Hannover – Braunschweig** site. The *Infections of the immunocompromised Host* and *Novel Antibiotics* research fields are coordinated from here. Scientists are involved in the establishment of a national transplant cohort and their research projects make considerable contributions towards developing new methods for the treatment and diagnosis of herpesvirus and hepatitis virus infections as well as for the vaccine development for hepatitis C virus. They also focus on developing new approaches for the effective treatment and control of multidrug-resistant bacteria and examine different molecular target sites for active agents. Another key aspect of this site is the identification and development of agent candidates as potential antibiotics.

HANNOVER – BRAUNSCHWEIG

Spokesperson: Prof. Thomas Pietschmann (TWINCORE)

Establishments: Helmholtz Centre for Infection Research, Brunswick, Leibniz Institute DSMZ – German Collection of Microorganisms and Cell Cultures, Hannover Medical School, Robert Koch Institute, University of Veterinary Medicine Hannover, Foundation, Technische Universität Braunschweig, TWINCORE – Centre for Experimental and Clinical Infection Research.

TTU coordination:

- Infections of the immunocompromised Host (coordination)
- Novel Antibiotics (coordination)
- Gastrointestinal Infections (co-coordination)
- Hepatitis (co-coordination)
- HIV (co-coordination)

TI coordination:

- Bioinformatics (coordination)
- Epidemiology (coordination)
- Novel Antivirals (coordination)
- Pathogen Repository (coordination)

NORTH RHINE-WESTPHALIA

DZIF activities at the **Bonn – Köln** site concentrate on the research and development of new antibiotics. In cooperation with the TPMO and BfArM, the preclinical development of corallopyronin A, a new antibiotic, continues to be a top priority for the Bonn-Köln site. In vaccine research, vaccines against bacterial pathogens such as *S.aureus* and *A. baumannii* are developed up to the clinical application stage. Scientists at the TTU *Healthcare-associated and Antibiotic-resistant bacterial Infections* research bacterial colonisation and infections with multidrug-resistant pathogens with regard to both their type and prevalence. They also examine treatment options and the effectiveness of infection control measures. With regard to HIV research, scientists bring new antibody mediated treatment approaches into translational research. This site also coordinates the DZIF Clinical Trial Unit.

BONN – KÖLN

Spokesperson: Prof. Achim Hörauf (University of Bonn)

Establishments: Federal Institute for Drugs and Medical Devices, University of Bonn, University Hospital Bonn, University of Cologne, University Hospital Cologne

TTU coordination:

- Healthcare-associated and Antibiotic-resistant bacterial Infections (coordination)
- HIV (co-coordination)
- Novel Antibiotics (co-coordination)

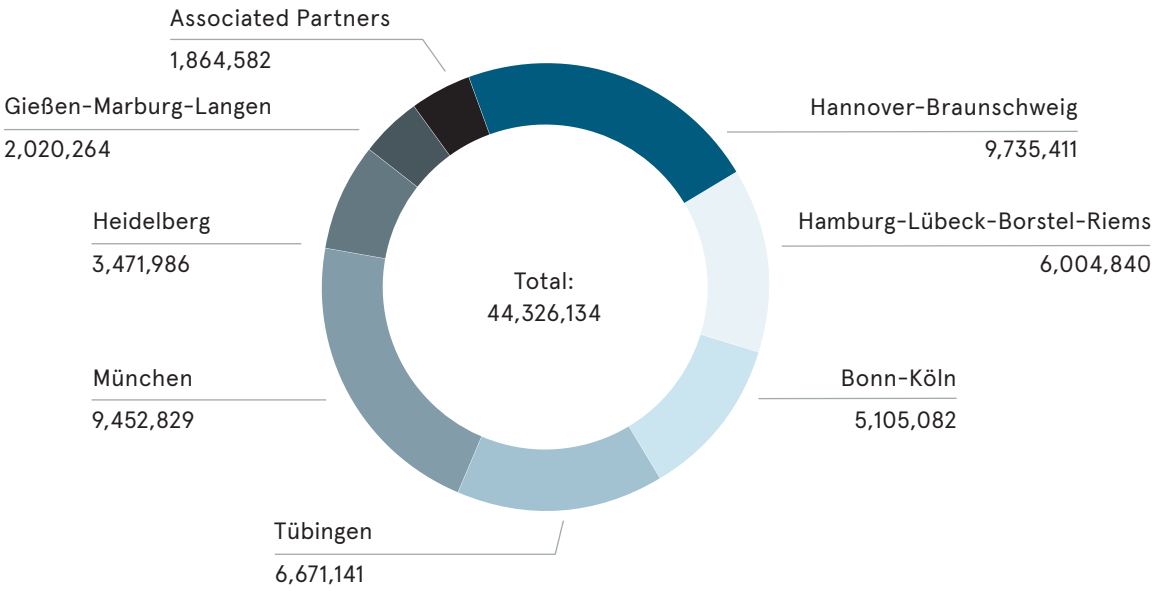
TI coordination:

- Clinical Trial Unit (coordination)

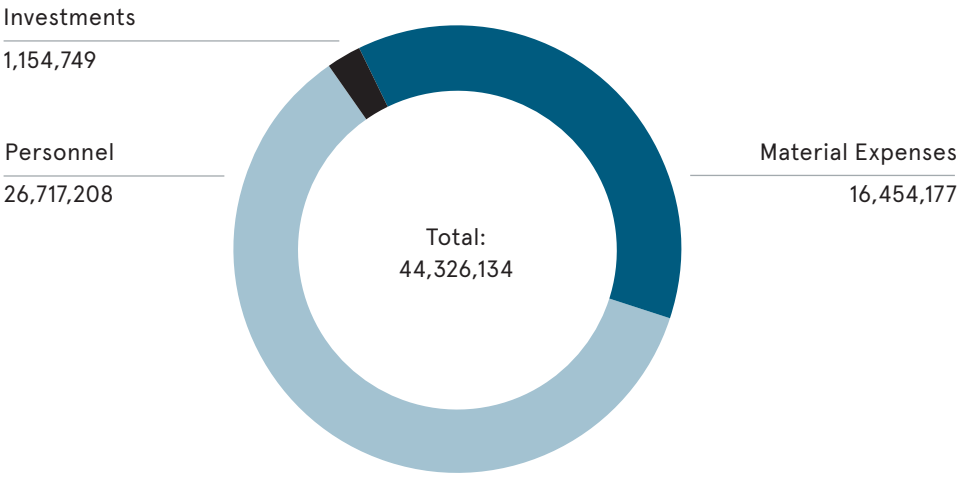
DZIF financial data 2019

REPORTED EXPENDITURE IN EUROS

BY PARTNER SITE



BY TYPE OF EXPENDITURE



BY FIELD OF WORK

FIELD OF WORK	Euro
Emerging Infections	2,941,166
Tuberculosis	2,273,501
Malaria	2,342,606
HIV	2,688,234
Hepatitis	4,677,423
Gastrointestinal Infections	1,891,325
Infections of the immunocompromised Host	7,009,098
Healthcare-associated and Antibiotic-resistant bacterial Infections	5,087,311
Novel Antibiotics	3,806,191
Product Development Unit	987,685
Clinical Trial Unit	768,418
African Partner Institutions	1,035,582
Biobanking	444,895
Bioinformatics	345,163
DZIF Academy	2,964,500
Pathogen Repository	237,211
Epidemiology	389,688
Novel Antivirals	418,058
Administration	4,018,077
Total	**44,326,134**

BY FUNDERS

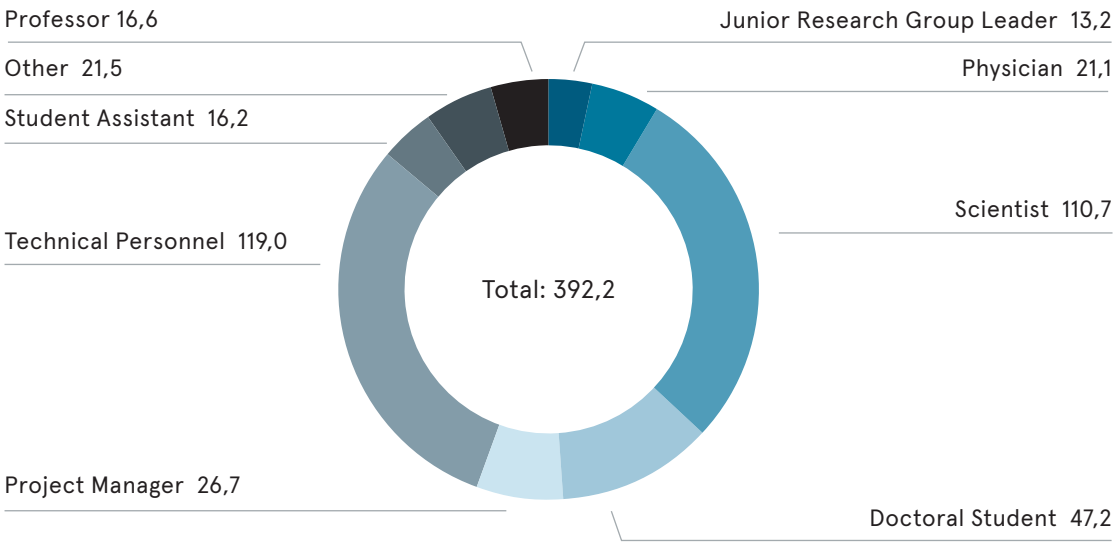
FUNDER	Euro
Baden-Württemberg	1,053,220
Bavaria	969,030
Hamburg	418,242
Hesse	163,345
Lower Saxony	911,427
North Rhine-Westphalia	521,609
Schleswig-Holstein	191,787
Financial contributions from associated partners	186,458
Federal Government	39,911,015
Total	**44,326,134**

In 2019, the German Center for Infection Research's reported expenditure amounted to approximately 44,3 million Euros. 214 projects and 114 stipends were funded within DZIF in 2019. The majority of funding came from the Federal Government (90 %) and from Länder funds (10 %). Only departmental research projects of the federal R&D institutions were fully funded by Germany's Federal Ministries. Funding management at the Helmholtz Centre for Infection Research in Braunschweig transfers the federal funds to the DZIF partner institutes for their projects.

The expenditures amounting to the BMBF funding were reported by the DZIF partners in the interim and final financial report 2019 and will be investigated by the DZIF Funding Management. The amounts of state and associated partner funding were calculated on the basis of these interim and final financial reports.

DZIF staff

FULL-TIME EQUIVALENT BY PROFESSIONAL GROUP



NUMBER OF EMPLOYEES BY PROFESSIONAL GROUP AND GENDER

PROFESSIONAL GROUPS	MEN	WOMEN	TOTAL
Professor	14	5	19
Junior Research Group Leader	9	7	16
Physician	22	33	55
Scientist	80	140	220
Doctoral Student	38	62	100
Project Manager	11	46	57
Technical Personnel	49	209	258
Student Assistant	17	36	53
Other	6	36	42
Total	**246**	**574**	**820**

In 2019, the DZIF recruited six employees from abroad and assisted twelve mothers and fathers respectively on their return from maternity leave.

AWARDS AND COMMENDATIONS

AWARD RECIPIENT	AWARD
Prof. Dr Christina Zielinski *Technical University of Munich*	Paul Langerhans Award German Neurodermatitis Award Ingrid zu Solms Award for Medicine
Dr Stephan Glöckner *Helmholtz Centre for Infection Research*	First place at the "Clinical Artificial Intelligence Conference & Datathon" in Munich
Melanie Stecher *University Hospital Cologne*	Young Researcher Award of the German AIDS Society
Dr Sven Pischke *University Medical Center Hamburg-Eppendorf*	Dr. Martini Award Else Kröner Excellence Scholarship
Prof. Dr Ralf Bartenschlager *Heidelberg University*	Heinrich-Pette-Lecture (honorary lecture) McGuigan Prize for Distinguished Work in Drug Discovery Prince Mahidol Award
Dr Monika Schütz *University of Tübingen*	DGHM Award
Julia Matthias *Technical University of Munich*	Egon Macher Award
Dr Ute Klarmann-Schulz *University of Bonn*	Research Award "BONFOR" of the Medical Faculty of the University of Bonn
Dr Anna Müller *University of Bonn*	Post-doctoral Award – Robert Koch Foundation
Prof. Dr Gülşah Gabriel *Heinrich Pette Institute, Leibniz Institute for Experimental Virology*	DZIF Prize for Translational Infection Research
Prof. Dr Stefan Niemann *Research Center Borstel, Leibniz Lung Center*	DZIF Prize for Translational Infection Research

The DZIF in figures

FLEXFUNDS*

28 Number of new FlexFunds projects approved in 2019

2.560.749 total budget in euros. Corresponding to

6 % of the annual DZIF budget

*funds available at short notice for translational projects

DZIF ACADEMY PROGRAMMES

18 Clinical Leave Stipends

07 MD/PhD Stipends

12 Maternity Leave Stipends

77 MD Stipends

06 Lab Rotations

18 Travel Grants

WORKSHOPS AND SYMPOSIA

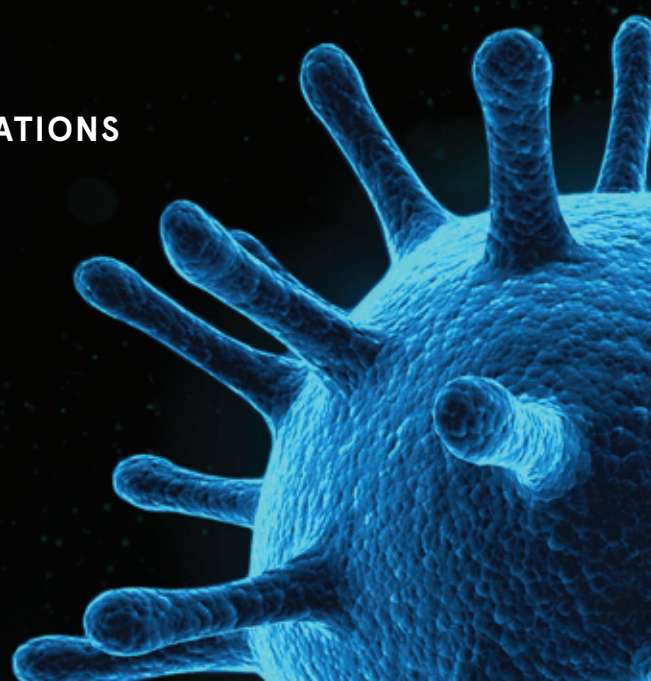
26

PUBLICATIONS WITH DZIF AFFILIATIONS

567

PUBLICATIONS WITH IMPACT FACTOR >10

58



CONFERENCE CONTRIBUTIONS
464

PATENTS AND PROPERTY RIGHTS
46

INDUSTRY COLLABORATIONS
6

PRESS RELEASES
30

DATA- AND BIOBANKS
42

CLINICAL STUDIES
45

CONFIRMATORY PRECLINICAL STUDIES
15

COHORTS
47

WEBSITE VISITORS*
88.235
*In the period from 01.05. to 31.12.2019 (after the website relaunch)

PUBLICATIONS

Scientific achievements 2019

The following shows a list of selected 2019 publications
(impact factor greater than ten*).
Please see our website for a complete list of DZIF publications.

BASIC RESEARCH

1. Alanjary M, Steinke K, Ziemert N (2019) *AutoMLST: an automated web server for generating multi-locus species trees highlighting natural product potential.* **Nucleic Acids Res**, 47(W1): W276-W282

2. Bacher P, Hohnstein T, Beerbaum E, Rocker M, Blango MG, Kaufmann S, Rohmel J, Eschenhagen P, Grehn C, Seidel K, Rickerts V, Lozza L, Stervbo U, Nienen M, Babel N, Milleck J, Assenmacher M, Cornely OA, Ziegler M, Wisplinghoff H, Heine G, Worm M, Siegmund B, Maul J, Creutz P, Tabeling C, Ruwwe-Glosenkamp C, Sander LE, Knosalla C, Brunke S, Hube B, Kniemeyer O, Brakhage AA, Schwarz C, Scheffold A (2019) *Human Anti-fungal Th17 Immunity and Pathology Rely on Cross-Reactivity against Candida albicans.* **Cell,** 176(6): 1340-1355.e15

3. Blin K, Shaw S, Steinke K, Villebro R, Ziemert N, Lee SY, Medema MH, Weber T (2019) *antiSMASH 5.0: updates to the secondary metabolite genome mining pipeline.* **Nucleic Acids Res,** 47(W1): W81-W87

4. Deng L, Jiang W, Wang X, Merz A, Hiet MS, Chen Y, Pan X, Jiu Y, Yang Y, Yu B, He Y, Tu Z, Niu J, Bartenschlager R, Long G (2019) *Syntenin regulates hepatitis C virus sensitivity to neutralizing antibody by promoting E2 secretion through exosomes.* **J Hepatol,** 71(1): 52-61

5. Estibariz I, Overmann A, Ailloud F, Krebes J, Josenhans C, Suerbaum S (2019) *The core genome m5C methyltransferase JHP1050 (M.Hpy99III) plays an important role in orchestrating gene expression in Helicobacter pylori.* **Nucleic Acids Res,** 47(5): 2336-2348

6. Fritz A, Hofmann P, Majda S, Dahms E, Droge J, Fiedler J, Lesker TR, Belmann P, DeMaere MZ, Darling AE, Sczyrba A, Bremges A, McHardy AC (2019) *CAMISIM: simulating metagenomes and microbial communities.* **Microbiome,** 7(1): 17

7. Gassen NC, Niemeyer D, Muth D, Corman VM, Martinelli S, Gassen A, Hafner K, Papies J, Mösbauer K, Zellner A, Zannas AS, Herrmann A, Holsboer F, Brack-Werner R, Boshart M, Müller-Myhsok B, Drosten C, Müller MA, Rein T (2019) *SKP2 attenuates autophagy through Beclin1-ubiquitination and its inhibition reduces MERS-Coronavirus infection.* **Nat Commun,** 10(1): 5770

8. Giersch K, Bhadra OD, Volz T, Allweiss L, Riecken K, Fehse B, Lohse AW, Petersen J, Sureau C, Urban S, Dandri M, Lütgehetmann M (2019) *Hepatitis delta virus persists during liver regeneration and is amplified through cell division both in vitro and in vivo.* **Gut,** 68(1): 150-157

9. Gräb J, Suárez I, van Gumpel E, Winter S, Schreiber F, Esser A, Hölscher C, Fritsch M, Herb M, Schramm M, Wachsmuth L, Pallasch C, Pasparakis M, Kashkar H, Rybniker J (2019) *Corticosteroids inhibit Mycobacterium tuberculosis-induced necrotic host cell death by abrogating mitochondrial membrane permeability transition.* **Nat Commun,** 10(1): 688

10. Greule A, Izoré T, Iftime D, Tailhades J, Schoppet M, Zhao Y, Peschke M, Ahmed I, Kulik A, Adamek M, Goode RJA, Schittenhelm RB, Kaczmarski JA, Jackson CJ, Ziemert N, Krenske EH, De Voss JJ, Stegmann E, Cryle MJ (2019) *Kistamicin biosynthesis reveals the biosynthetic requirements for production of highly crosslinked glycopeptide antibiotics.* **Nat Commun,** 10(1): 2613

11. Hentzschel F, Mitesser V, Fraschka SA, Krzikalla D, Carrillo EH, Berkhout B, Bártfai R, Mueller AK, Grimm D (2019) *Gene knockdown in malaria parasites via non-canonical RNAi.* **Nucleic Acids Res,** 48(1): e2

12. Herp S, Brugiroux S, Garzetti D, Ring D, Jochum LM, Beutler M, Eberl C, Hussain S, Walter S, Gerlach RG, Ruscheweyh HJ, Huson D, Sellin ME, Slack E, Hanson B, Loy A, Baines JF, Rausch P, Basic M, Bleich A, Berry D, Stecher B (2019) *Mucispirillum schaedleri Antagonizes Salmonella Virulence to Protect Mice against Colitis.* **Cell Host Microbe,** 25(5): 681-694.e8

13. Hoffmann MD, Aschenbrenner S, Grosse S, Rapti K, Domenger C, Fakhiri J, Mastel M, Börner K, Eils R, Grimm D, Niopek D (2019) *Cell-specific CRISPR-Cas9 activation by microRNA-dependent expression of anti-CRISPR proteins.* **Nucleic Acids Res,** 47(13): e75

14. Hubel P, Urban C, Bergant V, Schneider WM, Knauer B, Stukalov A, Scaturro P, Mann A, Brunotte L, Hoffmann HH, Schoggins JW, Schwemmle M, Mann M, Rice CM, Pichlmair A (2019) *A protein-interaction network of interferon-stimulated genes extends the innate immune system landscape.* **Nat Immunol,** 20(4): 493-502

15. Imle A, Kumberger P, Schnellbächer ND, Fehr J, Carrillo-Bustamante P, Ales J, Schmidt P, Ritter C, Godinez WJ, Müller B, Rohr K, Hamprecht FA, Schwarz US, Graw F, Fackler OT (2019) *Experimental and computational analyses reveal that environmental restrictions shape HIV-1 spread in 3D cultures.* **Nat Commun,** 10(1): 2144

*Impact Factor Stand 2019

16. Kaur P, Rausch M, Malakar B, Watson U, Damle NP, Chawla Y, Srinivasan S, Sharma K, Schneider T, Jhingan GD, Saini D, Mohanty D, Grein F, Nandicoori VK (2019) *LipidII interaction with specific residues of Mycobacterium tuberculosis PknB extracytoplasmic domain governs its optimal activation*. **Nat Commun,** 10(1): 1231

17. Lagkouvardos I, Lesker TR, Hitch TCA, Gálvez EJC, Smit N, Neuhaus K, Wang J, Baines JF, Abt B, Stecher B, Overmann J, Strowig T, Clavel T (2019) *Sequence and cultivation study of Muribaculaceae reveals novel species, host preference, and functional potential of this yet undescribed family*. **Microbiome,** 7(1): 28

18. Lucic B, Chen HC, Kuzman M, Zorita E, Wegner J, Minneker V, Wang W, Fronza R, Laufs S, Schmidt M, Stadhouders R, Roukos V, Vlahovicek K, Filion GJ, Lusic M (2019) *Spatially clustered loci with multiple enhancers are frequent targets of HIV-1 integration*. **Nat Commun,** 10(1): 4059

19. Matthias J, Maul J, Noster R, Meinl H, Chao YY, Gerstenberg H, Jeschke F, Gasparoni G, Welle A, Walter J, Nordström K, Eberhardt K, Renisch D, Donakonda S, Knolle P, Soll D, Grabbe S, Garzorz-Stark N, Eyerich K, Biedermann T, Baumjohann D, Zielinski CE (2019) *Sodium chloride is an ionic checkpoint for human TH2 cells and shapes the atopic skin microenvironment*. **Sci Transl Med,** 11(480): eaau0683

20. Meyer F, Bremges A, Belmann P, Janssen S, McHardy AC, Koslicki D (2019) *Assessing taxonomic metagenome profilers with OPAL*. **Genome Biol,** 20(1): 51

21. Neufeldt CJ, Cortese M, Scaturro P, Cerikan B, Wideman JG, Tabata K, Moraes T, Oleksiuk O, Pichlmair A, Bartenschlager R (2019) *ER-shaping atlastin proteins act as central hubs to promote flavivirus replication and virion assembly*. **Nat Microbiol,** 4(12): 2416-2429

22. Niehrs A, Garcia-Beltran WF, Norman PJ, Watson GM, Hölzemer A, Chapel A, Richert L, Pommerening-Röser A, Körner C, Ozawa M, Martrus G, Rossjohn J, Lee JH, Berry R, Carrington M, Altfeld M (2019) *A subset of HLA-DP molecules serve as ligands for the natural cytotoxicity receptor NKp44*. **Nat Immunol,** 20(9): 1129-1137

23. Norsigian CJ, Pusarla N, McConn JL, Yurkovich JT, Dräger A, Palsson BO, King Z (2019) *BiGG Models 2020: multi-strain genome-scale models and expansion across the phylogenetic tree*. **Nucleic Acids Res,** 48(D1): D402-D406

24. Petrova VN, Sawatsky B, Han AX, Laksono BM, Walz L, Parker E, Pieper K, Anderson CA, de Vries RD, Lanzavecchia A, Kellam P, von Messling V, de Swart RL, Russell CA (2019) *Incomplete genetic reconstitution of B cell pools contributes to prolonged immunosuppression after measles*. **Sci Immunol,** 4(41): eaay6125

25. Rausch M, Deisinger JP, Ulm H, Müller A, Li W, Hardt P, Wang X, Li X, Sylvester M, Engeser M, Vollmer W, Müller CE, Sahl HG, Lee JC, Schneider T (2019) *Coordination of capsule assembly and cell wall biosynthesis in Staphylococcus aureus*. **Nat Commun,** 10(1): 1404

26. Rosenbaum M, Gewies A, Pechloff K, Heuser C, Engleitner T, Gehring T, Hartjes L, Krebs S, Krappmann D, Kriegsmann M, Weichert W, Rad R, Kurts C, Ruland J (2019) *Bcl10-controlled Malt1 paracaspase activity is key for the immune suppressive function of regulatory T cells*. **Nat Commun,** 10(1): 2352

27. Schober K, Müller TR, Gökmen F, Grassmann S, Effenberger M, Poltorak M, Stemberger C, Schumann K, Roth TL, Marson A, Busch DH (2019) *Orthotopic replacement of T-cell receptor alpha- and beta-chains with preservation of near-physiological T-cell function*. **Nat Biomed Eng,** 3(12): 974-984

28. Tett A, Huang KD, Asnicar F, Fehlner-Peach H, Pasolli E, Karcher N, Armanini F, Manghi P, Bonham K, Zolfo M, De Filippis F, Magnabosco C, Bonneau R, Lusingu J, Amuasi J, Reinhard K, Rattei T, Boulund F, Engstrand L, Zink A, Collado MC, Littman DR, Eibach D, Ercolini D, Rota-Stabelli O, Huttenhower C, Maixner F, Segata N (2019) *The Prevotella copri Complex Comprises Four Distinct Clades Underrepresented in Westernized Populations*. **Cell Host Microbe,** 26(5): 666-679.e7

29. Tsopoulidis N, Kaw S, Laketa V, Kutscheidt S, Baarlink C, Stolp B, Grosse R, Fackler OT (2019) *T cell receptor-triggered nuclear actin network formation drives CD4(+) T cell effector functions*. **Sci Immunol,** 4(31): eaav1987

30. Wotzka SY, Kreuzer M, Maier L, Arnoldini M, Nguyen BD, Brachmann AO, Berthold DL, Zünd M, Hausmann A, Bakkeren E, Hoces D, Gul E, Beutler M, Dolowschiak T, Zimmermann M, Fuhrer T, Moor K, Sauer U, Typas A, Piel J, Diard M, Macpherson AJ, Stecher B, Sunagawa S, Slack E, Hardt WD (2019) *Escherichia coli limits Salmonella Typhimurium infections after diet shifts and fat-mediated microbiota perturbation in mice*. **Nat Microbiol,** 4(12): 2164-2174

31. Yin Y, Yao H, Doijad S, Kong S, Shen Y, Cai X, Tan W, Wang Y, Feng Y, Ling Z, Wang G, Hu Y, Lian K, Sun X, Liu Y, Wang C, Jiao K, Liu G, Song R, Chen X, Pan Z, Loessner MJ, Chakraborty T, Jiao X (2019) *A hybrid sub-lineage of Listeria monocytogenes comprising hypervirulent isolates*. **Nat Commun,** 10(1): 4283

PRECLINICAL RESEARCH

1. Banda DH, Perin PM, Brown RJP, Todt D, Solodenko W, Hoffmeyer P, Sahu KK, Houghton M, Meuleman P, Müller R, Kirschning A, Pietschmann T (2019) *A central hydrophobic E1 region controls the pH range of hepatitis C virus mem-brane fusion and susceptibility to fusion inhibitors*. **J Hepatol,** 70(6): 1082-1092

2. Bitschar K, Sauer B, Focken J, Dehmer H, Moos S, Konnerth M, Schilling NA, Grond S, Kalbacher H, Kurschus FC, Götz F, Krismer B, Peschel A, Schittek B (2019) *Lugdunin amplifies innate immune responses in the skin in synergy with host- and microbiotaderived factors*. **Nat Commun,** 10(1): 2730

3. Gärtner K, Luckner M, Wanner G, Zeidler R (2019) *Engineering extracellular vesicles as novel treatment options: exploiting herpesviral immunity in CLL*. **J Extracell Vesicles,** 8(1): 1573051

4. Imai Y, Meyer KJ, Iinishi A, Favre-Godal Q, Green R, Manuse S, Caboni M, Mori M, Niles S, Ghiglieri M, Honrao C, Ma X, Guo JJ, Makriyannis A, Linares-Otoya L, Böhringer N, Wuisan ZG, Kaur H, Wu R, Mateus A, Typas A, Savitski MM, Espinoza JL, O'Rourke A, Nelson KE, Hiller S, Noinaj N, Schäberle TF, D'Onofrio A, Lewis K (2019) *A new antibiotic selectively kills Gram-negative pathogens.* **Nature,** 576(7787): 459-464

5. Le P, Kunold E, Macsics R, Rox K, Jennings MC, Ugur I, Reinecke M, Chaves-Moreno D, Hackl MW, Fetzer C, Mandl FAM, Lehmann J, Korotkov VS, Hacker SM, Kuster B, Antes I, Pieper DH, Rohde M, Wuest WM, Medina E, Sieber SA (2019) *Repurposing human kinase inhibitors to create an antibiotic active against drug-resistant Staphylococcus aureus, persisters and biofilms.* **Nat Chem,** 12(2): 145-158

6. Lempp FA, Schlund F, Rieble L, Nussbaum L, Link C, Zhang Z, Ni Y, Urban S (2019) *Recapitulation of HDV infection in a fully permissive hepatoma cell line allows efficient drug evaluation.* **Nat Commun,** 10(1): 2265

7. Schilling NA, Berscheid A, Schumacher J, Saur JS, Konnerth MC, Wirtz SN, Beltrán-Beleña JM, Zipperer A, Krismer B, Peschel A, Kalbacher H, Brötz-Oesterhelt H, Steinem C, Grond S (2019) *Synthetic Lugdunin Analogues Reveal Essential Structural Motifs for Antimicrobial Action and Proton Translocation Capability.* **Angew Chem Int Ed Engl,** 58(27): 9234-9238

8. Wisskirchen K, Kah J, Malo A, Asen T, Volz T, Allweiss L, Wettengel JM, Lutgehetmann M, Urban S, Bauer T, Dandri M and Protzer U (2019) T *cell receptor grafting allows virological control of Hepatitis B virus infection.* **J Clin Invest,** 129(7): 2932-2945

CLINICAL RESEARCH

1. Ailloud F, Didelot X, Woltemate S, Pfaffinger G, Overmann J, Bader RC, Schulz C, Malfertheiner P, Suerbaum S (2019) *Within-host evolution of Helicobacter pylori shaped by niche-specific adaptation, intragastric migrations and selective sweeps.* **Nat Commun,** 10(1): 2273

2. Aregay A, Sekyere SO, Deterding K, Port K, Dietz J, Berkowski C, Sarrazin C, Manns MP, Cornberg M, Wedemeyer H (2019) *Elimination of Hepatitis C Virus has limited impact on the functional and mitochondrial impairment of HCV-specific CD8+ T cell responses.* **J Hepatol,** 71(5): 889-899

3. Diel R, Kohl TA, Maurer FP, Merker M, Meywald Walter K, Hannemann J, Nienhaus A, Supply P, Niemann S (2019) *Accuracy of whole genome sequencing to determine recent tuberculosis transmission: an 11-year population-based study in Hamburg, Germany.* **Eur Respir J,** 54(5): 1901154

4. Dobaño C, Sanz H, Sorgho H, Dosoo D, Mpina M, Ubillos I, Aguilar R, Ford T, Díez-Padrisa N, Williams NA, Ayestaran A, Traore O, Nhabomba AJ, Jairoce C, Waitumbi C, Agnandji ST, Kariuki S, Abdulla S, Aponte JJ, Mordmüller B, Poku Asante K, Owusu-Agyei S, Tinto H, Campo JJ, Moncunill G, Gyan B, Valim C, Daubenberger C (2019) *Concentration and avidity of antibodies to different circumsporozoite epitopes correlate with RTS,S/AS01E malaria vaccine efficacy.* **Nat Commun**, 10(1): 2174

5. Ehrhardt SA, Zehner M, Krähling V, Cohen-Dvashi H, Kreer C, Elad N, Gruell H, Ercanoglu MS, Schommers P, Gieselmann L, Eggeling R, Dahlke C, Wolf T, Pfeifer N, Addo MM, Diskin R, Becker S, Klein F (2019) *Polyclonal and convergent antibody response to Ebola virus vaccine rVSV-ZEBOV.* **Nat Med,** 25(10): 1589-1600

6. Guo Y, Zhang Y, Gerhard M, Gao JJ, Mejias-Luque R, Zhang L, Vieth M, Ma JL, Bajbouj M, Suchanek S, Liu WD, Ulm K, Quante M, Li ZX, Zhou T, Schmid R, Classen M, Li WQ, You WC, Pan KF (2019) *Effect of Helicobacter pylori on gastrointestinal microbiota: a population-based study in Linqu, a high-risk area of gastric cancer.* **Gut,** gutjnl-2019-319696

7. Jakob CEM, Stecher M, Classen AY, Hamprecht A, Cornely OA, Vehreschild JJ (2019) *Association Between Prescribed Opioids and Infections in Patients Neutropenia and Cancer.* **JAMA Intern Med,** 180(2): 320-322

8. Jandus P, Boligan KF, Smith DF, de Graauw E, Grimbacher B, Jandus C, Abdelhafez MM, Despont A, Bovin N, Simon D, Rieben R, Simon HU, Cummings RD, von Gunten S (2019) *The architecture of the IgG anti-carbohydrate repertoire in primary antibody deficiencies.* **Blood,** 134(22): 1941-1950

9. Jensen SB, Fahnøe U, Pham LV, Serre SBN, Tang Q, Ghanem L, Pedersen MS, Ramirez S, Humes D, Pihl AF, Filskov J, Sølund CS, Dietz J, Fourati S, Pawlotsky JM, Sarrazin C, Weis N, Schønning K, Krarup H, Bukh J, Gottwein JM (2019) *Evolutionary Pathways to Persistence of Highly Fit and Resistant Hepatitis C Virus Protease Inhibitor Escape Variants.* **Hepatology,** 70(3): 771-787

10. Kafetzopoulou LE, Pullan ST, Lemey P, Suchard MA, Ehichioya DU, Pahlmann M, Thielebein A, Hinzmann J, Oestereich L, Wozniak DM, Efthymiadis K, Schachten D, Koenig F, Matjeschk J, Lorenzen S, Lumley S, Ighodalo Y, Adomeh DI, Olokor T, Omomoh E, Omiunu R, Agbukor J, Ebo B, Aiyepada J, Ebhodaghe P, Osiemi B, Ehikhametalor S, Akhilomen P, Airende M, Esumeh R, Muoebonam E, Giwa R, Ekanem A, Igenegbale G, Odigie G, Okonofua G, Enigbe R, Oyakhilome J, Yerumoh EO, Odia I, Aire C, Okonofua M, Atafo R, Tobin E, Asogun D, Akpede N, Okokhere PO, Rafiu MO, Iraoyah KO, Iruolagbe CO, Akhideno P, Erameh C, Akpede G, Isibor E, Naidoo D, Hewson R, Hiscox JA, Vipond R, Carroll MW, Ihekweazu C, Formenty P, Okogbenin S, Ogbaini-Emovon E, Günther S, Duraffour S (2019) *Metagenomic sequencing at the epicenter of the Nigeria 2018 Lassa fever outbreak.* **Science,** 363(6422): 74-77

11. Karimzadeh H, Kiraithe MM, Oberhardt V, Alizei ES, Bockmann J, Schulze zur Wiesch J, Budeus B, Hoffmann D, Wedemeyer H, Cornberg M, Krawczyk A, Rashidi-Alavijeh J, Rodríguez-Frías F, Casillas R, Buti M, Smedile A, Alavian SM, Heinold A, Emmerich F, Panning M, Gostick E, Price DA, Timm J, Hofmann M, Raziorrouh B, Thimme R, Protzer U, Roggendorf M,

Neumann-Haefelin C (2019) *Mutations in Hepatitis D Virus Allow it to Escape Detection by CD8+ T Cells and Evolve at the Population Level.* **Gastroenterology,** 156(6): 1820-1833

12. Lückel C, Picard F, Raifer H, Campos Carrascosa L, Guralnik A, Zhang Y, Klein M, Bittner S, Steffen F, Moos S, Marini F, Gloury R, Kurschus FC, Chao YY, Bertrams W, Sexl V, Schmeck B, Bonetti L, Grusdat M, Lohoff M, Zielinski CE, Zipp F, Kallies A, Brenner D, Berger M, Bopp T, Tackenberg B, Huber M (2019) *IL-17(+) CD8(+) T cell suppression by dimethyl fumarate associates with clinical response in multiple sclerosis.* **Nat Commun,** 10(1): 5722

13. Schuch A, Salimi Alizei E, Heim K, Wieland D, Kiraithe MM, Kemming J, Llewellyn-Lacey S, Sogukpinar O, Ni Y, Urban S, Zimmermann P, Nassal M, Emmerich F, Price DA, Bengsch B, Luxenburger H, Neumann-Haefelin C, Hofmann M, Thimme R (2019) *Phenotypic and functional differences of HBV core-specific versus HBV polymerase-specific CD8+ T cells in chronically HBV-infected patients with low viral load.* **Gut,** 68(5): 905-915

14. Soon CF, Behrendt P, Todt D, Manns MP, Wedemeyer H, Sällberg Chen M, Cornberg M (2019) *Defining Virus-specific CD8+ TCR Repertoires for Therapeutic Regeneration of T Cells against Chronic Hepatitis E.* **J Hepatol,** 71(4): 673-684

15. Stein-Thoeringer CK, Nichols KB, Lazrak A, Docampo MD, Slingerland AE, Slingerland JB, Clurman AG, Armijo G, Gomes ALC, Shono Y, Staffas A, Burgos da Silva M, Devlin SM, Markey KA, Bajic D, Pinedo R, Tsakmaklis A, Littmann ER, Pastore A, Taur Y, Monette S, Arcila ME, Pickard AJ, Maloy M, Wright RJ, Amoretti LA, Fontana E, Pham D, Jamal MA, Weber D, Sung AD, Hashimoto D, Scheid C, Xavier JB, Messina JA, Romero K, Lew M, Bush A, Bohannon L, Hayasaka K, Hasegawa Y, Vehreschild M, Cross JR, Ponce DM, Perales MA, Giralt SA, Jenq RR, Teshima T, Holler E, Chao NJ, Pamer EG, Peled JU, van den Brink MRM (2019) *Lactose drives Enterococcus expansion to promote graft-versus-host disease.* **Science,** 366(6469): 1143-1149

16. Tesch VK, Abolhassani H, Shadur B, Zobel J, Mareika Y, Sharapova S, Karakoc-Aydiner E, Rivière JG, Garcia-Prat M, Moes N, Haerynck F, Gonzales-Granado LI, Santos Pérez JL, Mukhina A, Shcherbina A, Aghamohammadi A, Hammarström L, Dogu F, Haskologlu S, İkincioğullari AI, Bal SK, Baris S, Kilic SS, Karaca NE, Kutukculer N, Girschick H, Kolios A, Keles S, Uygun V, Stepensky P, Worth A, van Montfrans JM, Peters AMJ, Meyts I, Adeli M, Marzollo A, Padem N, Khojah AM, Chavoshzadeh Z, Stefanija MA, Bakhtiar S, Florkin B, Meeths M, Gamez L, Grimbacher B, Seppänen MR, Lankester A, Gennery AR, Seidel MG (2019) *Long-term outcome of LRBA deficiency in 76 patients after various treatment modalities as evaluated by the immune deficiency and dysregulation activity (IDDA) score.* **J Allergy Clin Immunol,** 145(5): 1452-1463

17. Vieira Braga FA, Kar G, Berg M, Carpaij OA, Polanski K, Simon LM, Brouwer S, Gomes T, Hesse L, Jiang J, Fasouli ES, Efremova M, Vento-Tormo R, Talavera-López C, Jonker MR, Affleck K, Palit S, Strzelecka PM, Firth HV, Mahbubani KT, Cvejic A, Meyer KB, Saeb-Parsy K, Luinge M, Brandsma CA, Timens W, Angelidis I, Strunz M, Koppelman GH, van Oosterhout AJ, Schiller HB, Theis FJ, van den Berge M, Nawijn MC, Teichmann SA (2019) *A cellular census of human lungs identifies novel cell states in health and in asthma.* **Nat Med,** 25(7): 1153-1163

18. von Felden J, Alric L, Pischke S, Aitken C, Schlabe S, Spengler U, Giordani MT, Schnitzler P, Bettinger D, Thimme R, Xhaard A, Binder M, Ayuk F, Lohse AW, Cornelissen JJ, de Man RA, Mallet V (2019) *The burden of hepatitis E among patients with haematological malignancies: A retrospective European cohort study.* **J Hepatol,** 71(3): 465-472

19. Wedemeyer H, Yurdaydin C, Hardtke S, Caruntu FA, Curescu MG, Yalcin K, Akarca US, Gurel S, Zeuzem S, Erhardt A, Luth S, Papatheodoridis GV, Keskin O, Port K, Radu M, Celen MK, Idilman R, Weber K, Stift J, Wittkop U, Heidrich B, Mederacke I, von der Leyen H, Dienes HP, Cornberg M, Koch A, Manns MP (2019) *Peginterferon alfa-2a plus tenofovir disoproxil fumarate for hepatitis D (HIDIT-II): a randomised, placebo controlled, phase 2 trial.* **Lancet Infect Dis,** 19(3): 275-286

MEMBER ESTABLISHMENTS

Member establishments of the German Center for Infection Research

Bernhard Nocht Institute for Tropical Medicine
Bundeswehr Institute of Microbiology
Federal Institute for Drugs and Medical Devices
Friedrich-Loeffler-Institut
German Cancer Research Center
Giessen University
Hannover Medical School
Heidelberg University
Heidelberg University Hospital
Heinrich Pette Institute–Leibniz Institute for Experimental Virology
Helmholtz Centre for Infection Research
Helmholtz Zentrum München–German Research Center for Environmental Health
Klinikum der Universität München
Klinikum rechts der Isar der Technischen Universität München
Leibniz Institute DSMZ–German Collection of Microorganisms and Cell Cultures
Ludwig-Maximilians-Universität München
Max Planck Institute for Developmental Biology
Mittelhessen University of Applied Sciences
Paul-Ehrlich-Institut
Philipps-Universität Marburg
Research Center Borstel Leibniz Lung Center
Robert Koch Institute
Technische Universität Braunschweig
Technical University of Munich
TWINCORE–Centre for Experimental and Clinical Infection Research
Universität Hamburg
Universität zu Lübeck
University of Bonn
University of Cologne
University of Tübingen
University of Veterinary Medicine Hannover, Foundation
University Hospital Bonn
University Hospital Cologne
University Hospital Tübingen
University Medical Center Hamburg-Eppendorf

IMPRINT

GERMAN CENTER FOR INFECTION RESEARCH (DZIF E.V.)
Main Office
Inhoffenstraße 7
D-38124 Braunschweig

T +49 (0)531-61 81-11 52
info@dzif.de
www.dzif.de

Project coordination: DZIF Press Office
Text: Beate Wagner & Constanze Löffler (medizintexte) and
Karola Neubert & Janna Schmidt (DZIF Press Office)
Picture editorship: Janna Schmidt & Martina Lienhop (DZIF Press Office)
English translation: David Tracey, Julia Kyambi
Layout: www.freisedesign.de

Image credits: Title: BNITM I p. 3 (from left to right): DZIF, TU München/Astrid Eckert; Andreas Heddergott, Universität Tübingen, DZIF, HZI/Verena Meier I p. 4: DZIF/Gerhard Kopatz I p. 6: CDC/Cynthia S. Goldsmith; William Bellini I p. 7 (top): CDC/James Gathany I p. 7 (bottom): Justus-Liebig-Universität Gießen/Rolf K. Wegst I p. 8: Medizinische Fakultät der Universität zu Köln I p. 9 (top): Tropeninstitut München I p. 9 (bottom): DZIF I p. 10: BNITM/Miriam Groger I p. 11 (top): Universitätsklinikum Tübingen/Jana Held I p. 11 (bottom): Universitätsklinikum Tübingen I p. 12: Universitätsklinikum Heidelberg I S. 13 (top): Universität München/Arne Kroidl I S. 13 (bottom): Universitätsklinikum Hamburg-Eppendorf/Axel Kirchhof I p. 14: Deutsche Leberstiftung I p. 15 (top): TU München/Moritz Knolle I p. 15 (bottom): TU München/Astrid Eckert I p. 16: Bärbel Stecher I p. 17 (top): from Ailloud et al. (2019): p. 3 I p. 17 (bottom): DZIF/scienceRELATIONS I p. 18: TU München/Andreas Heddergott I p. 19 (top): TU München/Kilian Schober I p. 19 (bottom): Medizinische Hochschule Hannover/Karin Kaiser I p. 20: DZIF/scienceRELATIONS I p. 21 (top): Universität Tübingen/Sebastian N. Wirtz I p. 21 (bottom): Universitätsklinikum Frankfurt I p. 22: Universität Bonn/Barbara Frommann I p. 23 (top): Universität Gießen/Katrina Friese I p. 23 (bottom): HIPS I p. 24 (top left): background: DZIF; foreground: This is Engineering RAEng I p. 24 (top right): background: Hyttalo Souza; foreground: iStock.com/Jaruek Chairak I p. 24 (bottom left): Paul-Ehrlich-Institut I p. 24 (bottom right): MedizinFotoKöln I p. 25 (top left): DZIF/Johanna Brinkel I p. 25 (top right): DZIF/Fabian Grein I p. 25 (bottom left): BNITM I p. 25 (bottom right): Medizinische Hochschule Hannover/Karin Kaiser I p. 26 (top left): Benjamin Stottmeier I p. 26 (top right): DSMZ I p. 26 (bottom left): Universitätsklinikum Heidelberg I p. 26 (bottom right): DSMZ/Jörg Overmann I p. 27 (top left): www.istock.com/gorodenkoff I p. 27 (top right): HZI/Verena Meier I p. 27 (bottom left): Yamel photographie I p. 27 (bottom right): Gérard Krause I p. 28: DZIF/Nadja Käding I p. 29: Dominik Buschardt I p. 30 (March): DZG/wirDesign I p. 30 (April): Bärbel Stecher I p. 30 (May): Universität Tübingen/Sebastian N. Wirtz I p. 31 (August): Helmholtz Zentrum München/Georg Bornkamm I p. 31 (September): CDC/James Archer I p. 31 (November): DZIF/Gerhard Kopatz I p. 32: DZIF I p. 33 (top 1): DZIF/Gerhard Kopatz I p. 33 (top 2): BIOCOM AG I p. 33 (bottom right): DZIF/Sascha Gramann I p. 34: IDT Biologika/Hartmut Bösener I p. 37: DZG/wirDesign

Paper: FSC®-certified, made of 100 % recycled paper

FSC
www.fsc.org
RECYCLED
Paper made from recycled material
FSC® C106855

Climate neutral
Print product
ClimatePartner.com/11022-2007-1002

Funded by:

Bundesministerium
für Bildung
und Forschung

Hamburg | Behörde für Wissenschaft, Forschung und Gleichstellung

Bayerisches Staatsministerium für Wissenschaft und Kunst

HESSEN

Hessisches Ministerium
für Wissenschaft und Kunst

Ministerium für Innovation,
Wissenschaft und Forschung
des Landes Nordrhein-Westfalen

Niedersächsisches Ministerium
für Wissenschaft und Kultur

SH

Schleswig-Holstein
Ministerium für Soziales,
Gesundheit, Wissenschaft
und Gleichstellung

Baden-Württemberg
MINISTERIUM FÜR WISSENSCHAFT, FORSCHUNG UND KUNST

German Center for Infection Research (DZIF e.V.)
Main Office
Inhoffenstraße 7
D-38124 Braunschweig

T +49 (0)531-61 81-11 52
F +49 (0)531-61 81-11 53
info@dzif.de
www.dzif.de

Follow us on