



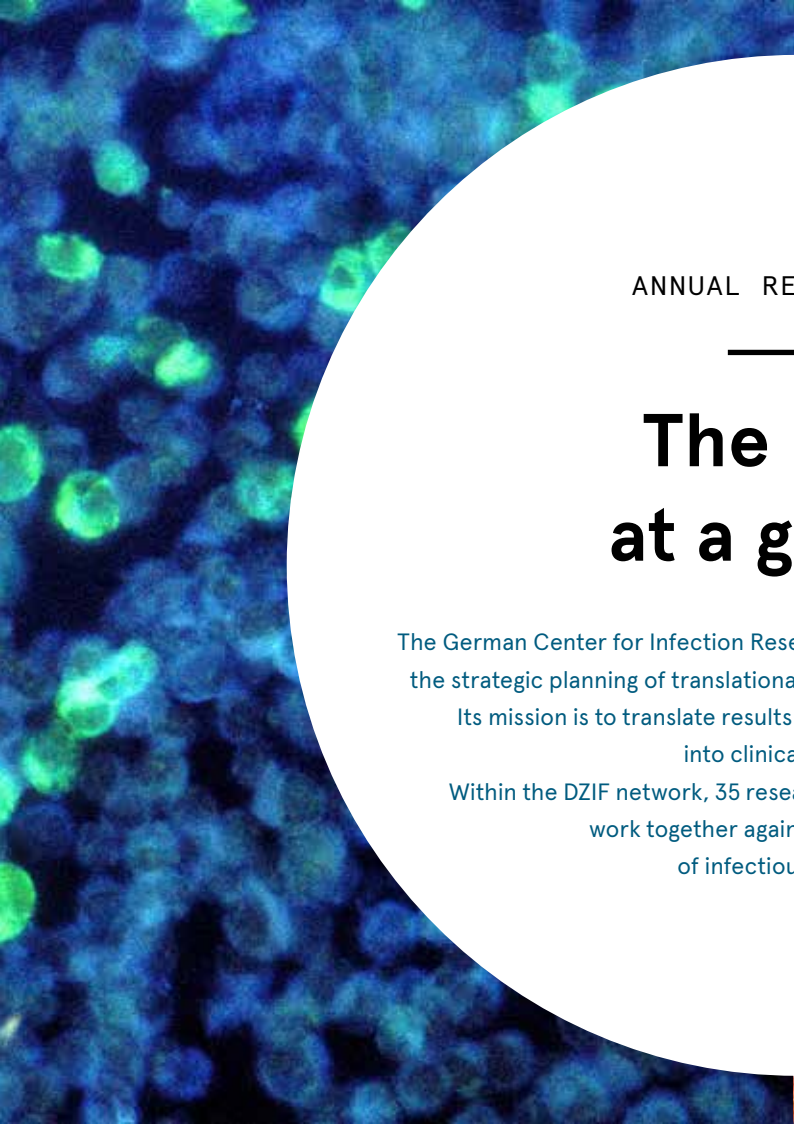
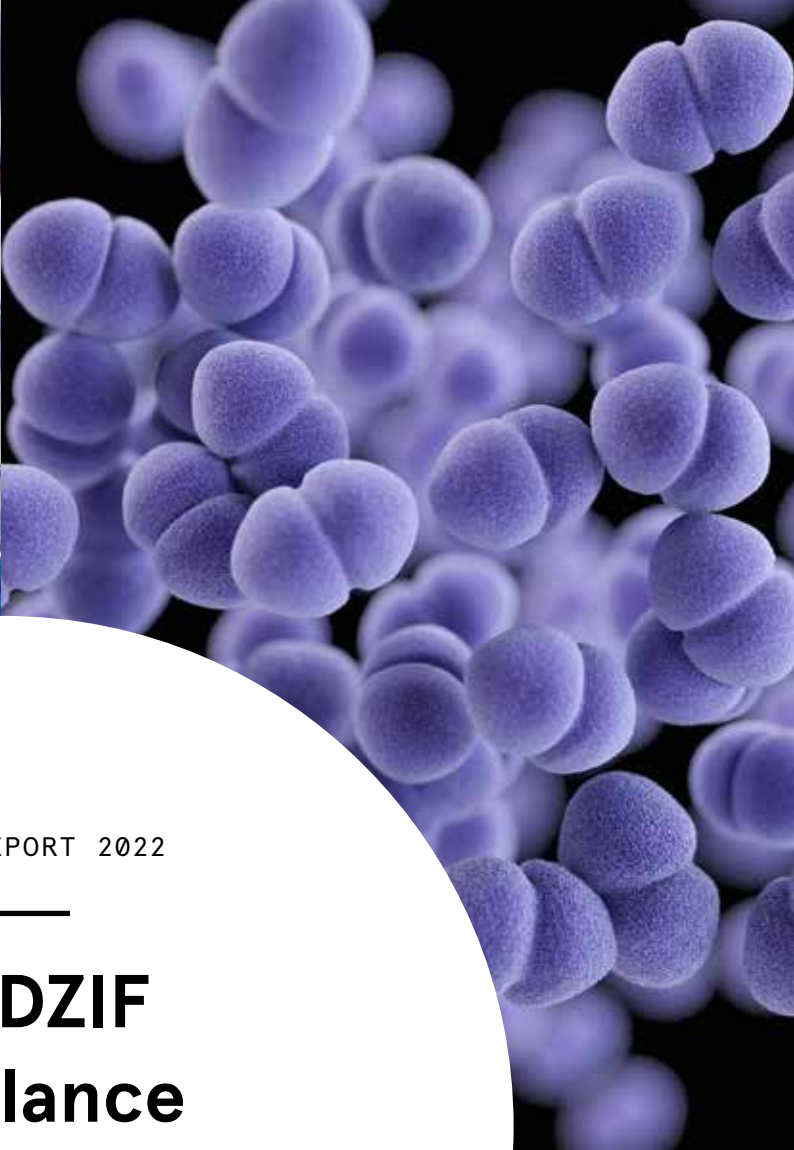
10 Years

GERMAN CENTER FOR INFECTION RESEARCH

Annual Report 2022



Cover image: the German Center for Infection Research (DZIF) celebrated its tenth anniversary in 2022. To mark the occasion, we arranged a few classic "birthday elements" on the cover. The three images on the front hanging above each other summarise the DZIF's mission: building bridges between basic research and clinical application. Group pictures from the annual meetings of the past ten years and the joint DZG anniversary celebration in Berlin show some of the many people who have shaped the past research years at the DZIF. The cover image has a special feature that is not obvious at first glance: it is an interplay of elements generated by an image AI and manual image processing.



ANNUAL REPORT 2022

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 practice.

Within the DZIF network, 35 research institutions across Germany work together against the global threat of infectious diseases.

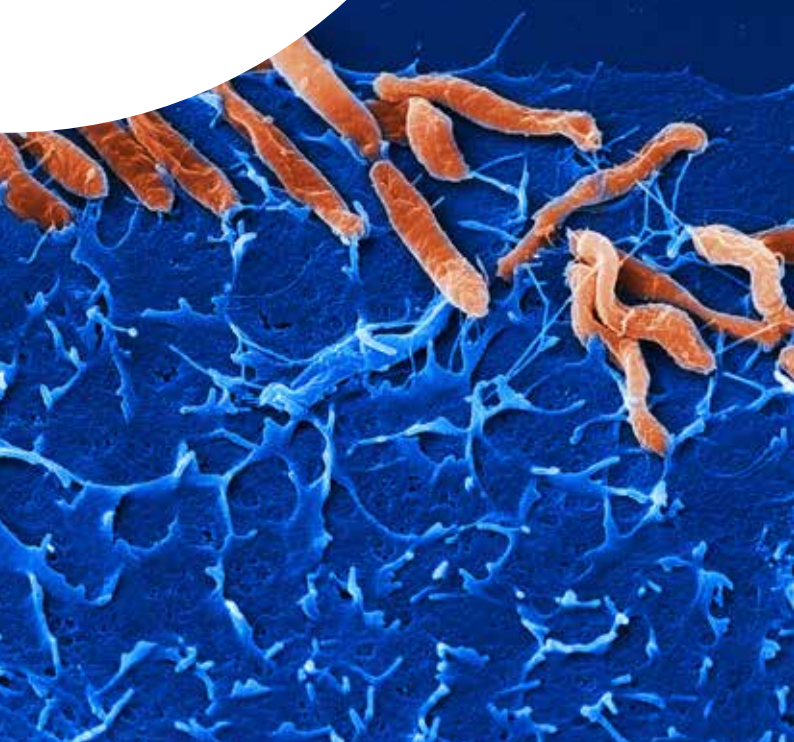


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Editorial

In 2022, we celebrated the tenth anniversary of the German Center for Infection Research (DZIF) together with three other centres—the German Center for Lung Research (DZL), the German Centre for Cardiovascular Research (DZHK) and the German Cancer Consortium (DKTK). In the presence of many prominent guests from politics and science, the success story of the German Centres in translating the results of basic research into the prevention, diagnosis and therapy of major common diseases was honoured.

The DZIF was particularly challenged during the SARS-CoV-2 pandemic and, by joining forces, was able to contribute important results to research and control of COVID-19 from the very beginning. After the coronavirus infection situation in Europe subsided in spring 2022 and legal measures to contain the spread of infection expired, many DZIF researchers were able to devote more time to their previous core research areas: urgent topics such as increasing antibiotic resistance, gastrointestinal infectious agents, tuberculosis, malaria and other widespread infectious diseases came back into focus. On pages 6-7, for example, you can learn which new viral pathogens are spreading via migratory birds and global trade.

Important progress was also made in the early detection of active tuberculosis in HIV-infected patients (page 9) and in hepatitis C vaccine development (pages 14-15). A vaccine

against the Epstein-Barr virus developed at Helmholtz Munich is in the starting blocks for first clinical trials in humans (pages 18-19).

A number of positive translational impulses were also set in the DZIF infrastructures in 2022: the *Bioresources, Biodata and Digital Health* infrastructure launched the “DZIF Data & Tools Hub” in 2022, a beta version of an IT platform designed to facilitate access to research data and improve the quality of research projects (pages 24-25). With the recruitment of Dr Klaus Schwamborn as the new industry-experienced Head of Vaccine Development in the “Translational Project Management Office”, the DZIF *Product Development Unit* has been strengthened as of October 2022 (page 27). The promotion of senior clinical scientists continued to be successful: the *DZIF Academy’s* “Advanced Clinician Scientist Programme”, launched in 2021, successfully funded four researchers in the reporting year (page 28). Good networking with DZIF scientists led to the successful funding of three innovative projects on antimicrobial resistance by INCATE (INCubator for Antibacterial Therapies in Europe), which the DZIF helped to found (page 29).

As every year, you will find all important information on facts and figures at a glance in the 2022 report. We wish you an informative read!

Yours sincerely,

The Executive Board of the German Center for Infection Research



Prof. Dr D. Busch



Prof. Dr H.-G. Kräusslich



Prof. Dr M. Dandri



Prof. Dr D. Heinz



Prof. Dr A. Peschel

ABOUT THE DZIF

Learning from each other— the DZG and DZIF ten years on

Exchange among each other, joint research and learning from each other—this has been important for cooperation between the German Centers for Health Research (DZG) from the very beginning, but of course also within the German Center for Infection Research (DZIF) itself. The COVID-19 pandemic once again highlighted the importance of transnational and interdisciplinary cooperation (not only) in research. Together with the DZIF, three other DZG Centers celebrated their tenth anniversary in 2022: the German Center for Lung Research, the German Centre for Cardiovascular Research and the German Cancer Consortium. The fact that we were able to celebrate together on site in Berlin was not a given after the pandemic years.

FOUR GRAND CHALLENGES

More than 500 scientists and medical specialists within the DZIF work in 35 member institutions at seven partner sites in Germany. In addition, there are researchers from associated partner institutions as well as from transnational collaborations and alliances. This synergistic DZIF network of universities, clinics and research institutes has created an infrastructure that is unique worldwide, bringing together expertise from a wide range of fields, including medicine, biology, epidemiology, chemistry and bioinformatics.

Research results are to be rapidly translated into practice through close integration of research and clinical practice, so that patients can benefit as quickly as possible from promising preventive measures, diagnostics and therapeutics. All DZG Centers are committed to this translational approach in order

to fight the major widespread diseases, such as diabetes or cancer.

In infectiology, researchers and practitioners are facing four major challenges in particular. These include antimicrobial resistance, chronic infections, immune prevention and therapy as well as tropical and emerging infections. The DZIF's activities are strategically aligned to address these major challenges.

RESEARCH AREAS AND INFRASTRUCTURES

Driven by these grand challenges, the DZIF bundles its projects in nine research areas, each dedicated to a pathogen, a specific disease or a common topic in infection research. The four „Translational Infrastructures“ are available to all DZIF researchers with their expertise and services (see box on the next page).

For the first time since the outbreak of the COVID-19 pandemic, the DZIF was able to hold its joint annual conference with the German Society of Infectiology.



BRIDGING TOPICS

Since 2022, interdisciplinary groups have also been set up within the DZIF to address and coordinate important current developments in DZIF research areas in the form of “bridging topics”. So far, the DZIF has established bridging topics on antibody-based therapies, cell and gene therapies and the microbiome. The themes vaccines and diagnostics are also planned as bridging topics.

Four to seven experts from the DZIF are represented in each of the interdisciplinary groups, and one member of the Executive Board accompanies each group. External experts can also be invited if necessary. In regular workshops, the research needs for the respective bridging topic are defined and coordinated.

SUCCESSFUL TRANSLATION AT THE DZIF

The development of new drugs, vaccines or diagnostics is usually a lengthy process that can take many years from the initial idea to a finished product. The fact that the DZIF can already look back on a number of translational successes after its first ten years of existence underlines the great potential of the research network. With Hepcludex (bulevirtide), for example, the world’s first drug against hepatitis D was brought from basic research to approval; TherVacB—a promising novel therapeutic vaccine—could help cure chronic hepatitis B; and another vaccine candidate against the cancer-causing Epstein-Barr virus has also been co-developed in the DZIF. With corallopyronin A and BTZ-043, two promising new antibiotics are in development at the DZIF. While BTZ-043 offers hope for the treatment of multidrug-resistant tuberculosis, corallopyronin A is proving successful in combating filarial diseases, among other things. Diagnostics such as rapid tests to detect certain diseases or antibiotic resistance have also been developed by DZIF researchers. Of course, the DZIF continues to take measures to ensure that we are as well prepared as possible for any further pandemic.

The translational idea has also played an important role in the successful promotion of young researchers within the framework of the *DZIF Academy* from the very beginning: the various sponsorship programmes are designed to inspire young medical professionals and scientists for infection research. At the same time, the *DZIF Academy* fosters long-term research perspectives: many successful careers have been launched with the help of the *DZIF Academy*. In particular, the path from the clinic to science and back again is supported by programmes such as Clinical Leave or Advanced Clinician Scientist.

INFECTIONS DO NOT RECOGNISE NATIONAL BORDERS

Joint research across national borders is of great significance within the DZIF because infectious diseases do not stop at borders. From the beginning, the DZIF has sought and

strengthened cooperation with partner institutions in Eastern Europe or Africa in order to study diseases such as tuberculosis or malaria where they occur most frequently.

As co-initiator of the UNITE4TB consortium, the DZIF is spearheading research into the development of new treatment solutions for tuberculosis. The DZIF helped to set up INCATE, a European initiative to fight increasing antibiotic resistance: innovative approaches are promoted here at an early stage. To develop drugs against antibiotic-resistant bacteria, the DZIF has similarly been involved as a partner in the CARB-X Global Accelerator Network. Likewise, the DZIF is participating in the CEPI vaccine initiative for the development of protective measures against emerging infectious diseases. Furthermore, the DZIF is involved in numerous other industrial and academic collaborations to meet the major infectious disease challenges of our time.

The DZIF bundles its activities in research areas and cross-disciplinary infrastructures—internally referred to as Thematic Translational Units (TTU) and Translational Infrastructures (TI) (as of 2022):

Research areas

- *Emerging Infections*
- *Tuberculosis*
- *Malaria and Neglected Tropical Diseases*
- *HIV*
- *Hepatitis*
- *Gastrointestinal Infections*
- *Infections of the Immunocompromised Host*
- *Healthcare-Associated and Antibiotic-Resistant Bacterial Infections*
- *Novel Antibiotics*

Infrastructures

- *Bioresources, Biodata and Digital Health*
- *Clinical Trial Unit*
- *Product Development Unit*
- *DZIF Academy*

EMERGING INFECTIONS

Viral zoonotic pathogens: monitoring and treatment

Climate change is already enabling pathogens from the tropics and subtropics to penetrate previously cooler regions of the earth. Other zoonotic pathogens are already here in Central Europe, but are neglected. It is good to know the distribution of both types of pathogens in order to be prepared for infection-related events. Drug research also makes it possible to reduce mortality from certain zoonotic infectious diseases in the global South.

DZIF researchers in Greifswald and on the island of Riems are investigating emerging or re-emerging zoonotic pathogens. Hamburg colleagues are researching where within the human body Lassa viruses still hide once infection has resolved.

Examples from research

VIRAL CONQUEST OF THE GLOBE

West Nile virus (WNV), which is transmitted to humans and other vertebrates by blood-sucking mosquitos, is found today on all inhabited continents and reached Germany too in 2018. The virus's reservoir and propagation hosts are birds, including highly susceptible passerine birds, raptors and owls, which become ill more frequently and usually die from the infection. Since 2011,

the Friedrich-Loeffler-Institut (FLI) has coordinated a nationwide wild bird network for the monitoring of flaviviruses, including WNV and Usutu virus. "From universities, wildlife sanctuaries, veterinary practices as well as zoos and animal parks, we receive blood samples from live birds and bird carcasses, which we routinely test for both viruses to elucidate virus spread," says Dr Ute Ziegler. Hotspots for WNV are Berlin-Brandenburg, Saxony and Saxony-Anhalt, but virus intensity fluctuates from year to year. "So far, we don't see any clear spread towards the west, south or north of the country."

Prof. Rainer Ulrich—also at the FLI site in Greifswald and on the island of Riems—conducts One Health research on viruses transmitted by rats, mice and other small mammals. Pet rats are very popular, but can transmit pathogens to humans: in 2019, a human was infected with Seoul orthohantavirus for

Microscopic examination of the viability of Lassa virus-infected cells in the high security category BSL-4 laboratory of BNITM.



the first time in Germany by a rat kept as a pet and went on to develop haemorrhagic fever.

The lymphocytic choriomeningitis mammarenavirus (LCMV) is transmitted by house mice and can cause cerebral meningitis in primates and humans. In 2022, Ulrich's team was involved in identifying the origin of fatal LCMV disease of a lion monkey in pest rodents at the zoo. It is hoped that future systematic studies in rodent reservoirs as well as obligatory virus screening of pet rats will contribute to a better understanding of the pathogen spread and the risk to humans and animals.



“The young scientists Marie Weskamm and Anahita Fathi were able to demonstrate that vaccination with the MVA-MERS-S vaccine developed at DZIF induced long-lasting immunity”

Prof. Dr Marylyn Addo, Hamburg
Coordinator

LASSA VIRUS—PERSISTENCE AND DRUG STUDY

Together with partners at the Irrua Specialist Teaching Hospital (ISTH) in southern Nigeria, Prof. Stephan Günther from the Hamburg Bernhard Nocht Institute for Tropical Medicine (BNITM) is working on two Lassa projects. The region is highly endemic for the virus, which is transmitted by the African multimammate mouse and can persist for a long time in the human body after infection has resolved. High concentrations of the virus RNA are found for up to 12 months after acute infection, in particular in human seminal fluid, as discovered by the researchers in a study with 200 treated patients. Since Lassa can therefore still be transmitted sexually, patients at ISTH are now being advised on safe sex practices.

There is still no approved drug for Lassa fever. Patients are therefore treated off-label with the virostatic drug ribavirin, which is effective against hepatitis C, influenza, respiratory syncytial virus (RSV) and herpes. In a phase II study, Günther's team, together with the ISTH, compared the new drug favipiravir, which has been very successful in a mouse model, with ribavirin. “The therapeutic goal is to reduce the mortality rate of 15 percent,” Günther says. Based on the virological and pharmacological data obtained from the blood samples of the test persons, a phase III trial with a total of 600 patients will follow, for which eight million euros have already been raised from the EDCTP 3 (European and Developing Countries Clinical Trials Partnership) programme.



Birds of prey like the goshawk serve as reservoir and amplification hosts for the West Nile virus.

GOALS FOR 2022: OUTCOMES

- Development of a Marburg virus mouse model and a recombinant Marburg virus (Guinea isolate).
- Development of a Modified Vaccinia Ankara (MVA) vaccine against the Marburg virus.
- Development of in vitro assays for characterisation of infections with monkeypox virus (MPXV; virus load measurements and monitoring of the immune response).
- Characterisation of MPXV/Orthopoxvirus-specific immune responses in persons with MPXV infection or following vaccination with MVA-based recombinant vaccines (MVA-MERS, MVA-SARS/SARS-ST).
- Goal partially achieved/Project is ongoing
- Goal achieved

GOALS FOR 2023:

- Expansion of international translational activities with the main focus on the treatment and prevention of Lassa virus infections.
- Promotion of young scientific researchers: better integration of Early Career Researchers (ECR) into the Emerging Infections research area.
- Development of a vaccine against Nipah virus using previous work with the MVA platform as well as establishment of international collaboration with partners for clinical trials.



You can find more information at

TUBERCULOSIS

New methods for early diagnosis of tuberculosis disease

Tuberculosis, in addition to HIV and malaria, is one of the most common infectious diseases worldwide. In Germany, the number of cases rose again for the first time in 2022, after a downward trend in the previous five years. This is due to refugee movements from Ukraine.

DZIF researchers in Heidelberg and Borstel are working on how to track down antibiotic-resistant strains more quickly. Their Munich colleagues are looking for biomarkers to help diagnose tuberculosis disease earlier in the blood before the bacteria can be spread via aerosolic transmission.

Examples from research

DETECTING RESISTANCE PATTERNS THROUGH GENE SEQUENCING

Many strains of the tuberculosis (TB) bacterium *Mycobacterium tuberculosis* are already resistant to different antibiotics. It is therefore important to rapidly determine which drugs can actually help an individual patient. "The problem: it takes up to four weeks to grow the bacteria in the laboratory—and a further four weeks to test antibiotics against them," says PD Dr Claudia

Denkinger, Head of Infectious Diseases and Tropical Medicine at Heidelberg University Hospital. "We therefore investigated whether there is a link between certain changes in the genomes of the bacteria and their resistance profiles." To find that out, the scientist together with DZIF colleagues in Borstel, FIND—the Global Alliance for Diagnostics (Switzerland)—and partners in five countries analysed a large number of *M. tuberculosis* samples collected from patients across the world.

From this huge global dataset, the researchers filtered numerous mutation-resistance correlations, on the basis of which diagnostics can now be improved. And if the bacterial resistance profiles are quickly identified the most effective treatment for the patient can start immediately.

Rapid gene sequence analysis instead of tedious bacterial culture? "The COVID-19 pandemic has greatly advanced sequencing technologies, and even in resource-poor countries in Africa, South East Asia and the western Pacific region, where

Blood sample analysis within the framework of the African Cohort Study (AFRICOS).



around 85 percent of those infected with TB live, the availability of instruments and knowledge of how to use them have improved significantly,” says Denking.

BIOMARKERS FOR EARLY DIAGNOSIS OF ACTIVE TB IN THOSE INFECTED WITH HIV

Because their immune system is weakened, people living with HIV have a 20- to 30-fold higher risk of developing tuberculosis disease, particularly when living in regions where both pathogens are co-endemic. Early detection and treatment of tuberculosis reduces progression and transmission of this pulmonary disease. Scientists led by Prof. Michael Hoelscher and PD Dr Christof Geldmacher at the LMU Hospital Munich therefore searched for biomarkers that could be detected in the blood even before the disease was diagnosed and before TB bacteria are found in the sputum of patients.

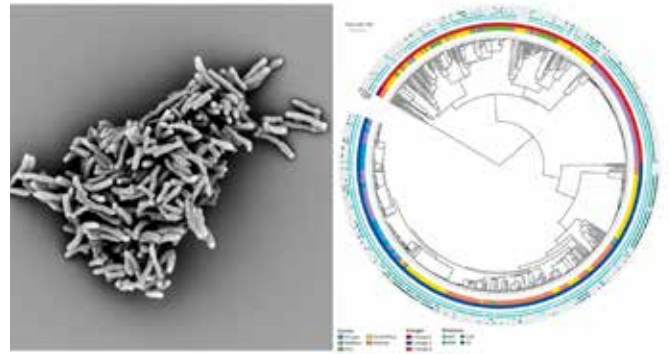


“In 2022, the establishment of MALDI imaging to analyse antibiotic penetration into granulomas in *Mtb*-infected mouse models was a major success.”

Prof. Dr Michael Hoelscher, München
Coordinator

Although according to the WHO around a quarter of the world population is infected with TB, only between five and 15 percent of cases of latent tuberculosis, which causes neither symptoms nor complaints, progress to active, transmissible TB. “To find predictive markers for these few patients who then progress to active TB, blood and sputum samples had to be collected and tested from many people over a long period of time,” stresses Geldmacher. This was possible within the framework of the US American AFRICOS study launched in 2013. HIV-positive and HIV-negative adults from eleven hospitals in Kenya, Tanzania, Uganda and Nigeria—countries in which *M. tuberculosis* infection is endemic—were taking part in this study.

Over a period of five years, working in close collaboration with the international AFRICOS study team, blood and sputum samples were collected every six months from over 2,000 HIV patients and subsequently analysed and compared. During this period, 70 study subjects developed active tuberculosis. In 68 percent of these active TB patients, activated *M. tuberculosis*-specific CD4+ cells were found already in the preceding six to 12 months. „Based on the activation of these immune cells, which recognise the pathogen, a reliable distinction can be made between latent and active TB,” Geldmacher says. If they are present, the patients’ risk of developing the disease increases significantly.



Electron microscopy image of *Mycobacterium tuberculosis* (left); circular phylogenetic tree showing the relationship, lineage and resistance profiles of the individual 900 isolates belonging to the *M. tuberculosis* complex—a genetically related group of mycobacteria species (right).

GOALS FOR 2022: OUTCOMES

- ① Evaluation of biomarkers of the multicentre mEX-TB cohort comprising patients with extrapulmonary tuberculosis.
- ① “Breaking down the wall”: Determination of the penetration of antibiotics in centrally necrotising granulomas on immunomodulatory treatment.
- ① Establishment of the optimal dose of BTZ-043 in combination with other TB drugs in patients.
- ① Goal partially achieved/Project is ongoing
- Goal achieved

GOALS FOR 2023:

- Establishment of laboratory methods and the first bio-marker analyses from longitudinally collected blood samples.
- Spread and evolution of multidrug-resistant TB bacteria—impact on diagnostics and therapy as well as modelling of the population efficacy of sequencing.
- Launch of the Paradigm Study: evaluation of BTZ-043 in five different drug combinations.

You can find more information at



MALARIA AND NEGLECTED TROPICAL DISEASES

Different causative species— same strategy?

Every year, around 250 million people contract malaria. 630,000 die each year from this easily treatable tropical disease—three quarters of them are less than five years old. Only a vaccination could stop this constant cycle of infection, treatment and reinfection. Although *Plasmodium falciparum* is by far the most common causative species of malaria, it is not the only one.

At the University Medical Center Hamburg-Eppendorf (UKE), DZIF researchers are testing the efficacy of a drug against the less commonly implicated species. At the University of Tübingen, their colleagues are working on an alternative to prophylaxis.

generally not cause organ complications, such as kidney failure or cerebral malaria,” says Prof. Michael Ramharter, Head of the Department of Clinical Research at the Bernhard Nocht Institute for Tropical Medicine and the Section of Clinical Tropical Medicine at UKE.

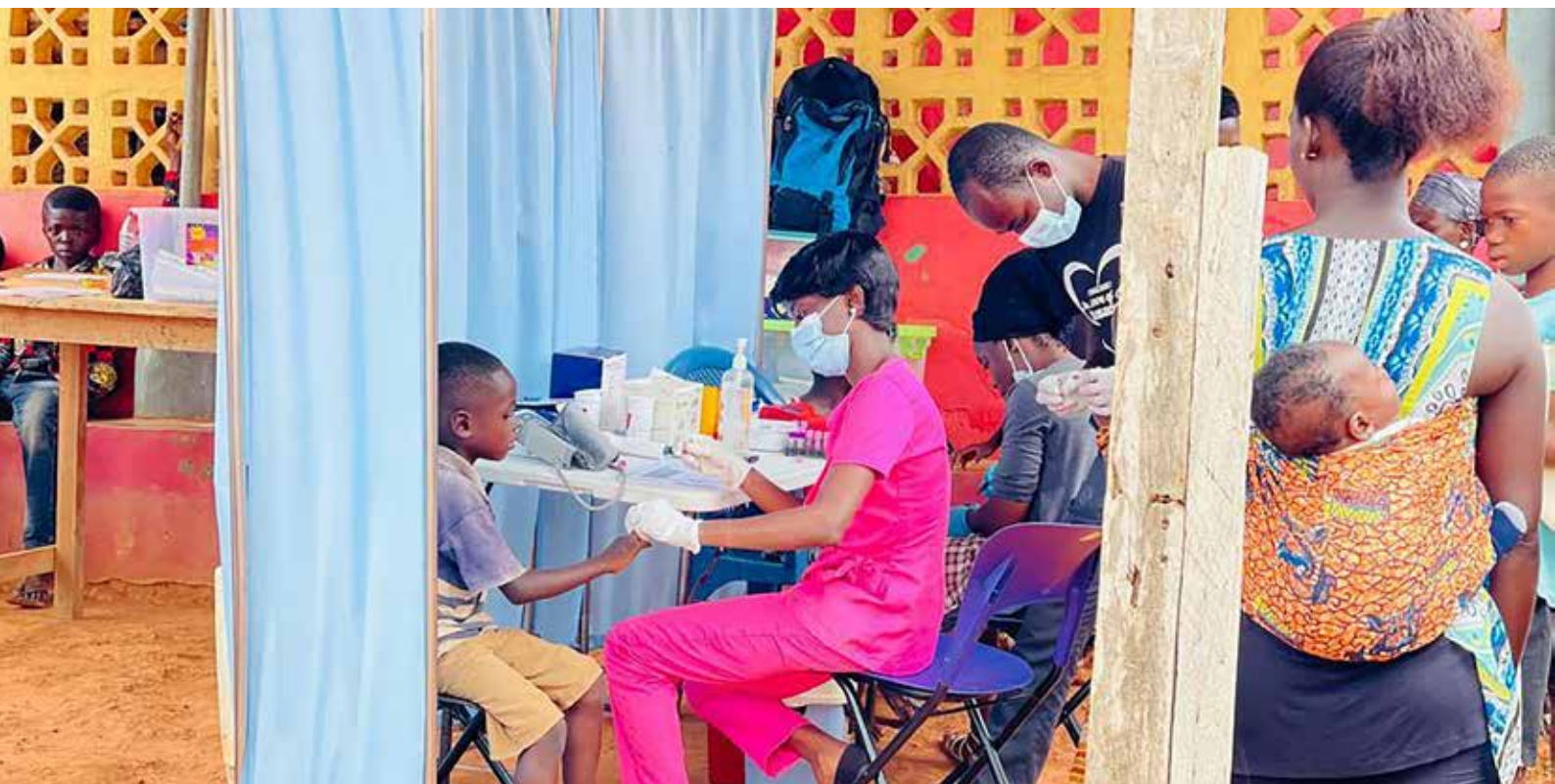
Since 95 percent of infections and virtually all deaths worldwide are caused by *P. falciparum*, there are hardly any studies on other pathogenic *Plasmodium* species or even mixed infections. Most rapid malaria tests are also designed for *P. falciparum*, cannot distinguish between the species and sometimes give false-negative results. Differences between species can only be seen under the microscope. To find out with which species the test subjects had actually been infected with, Ramharter’s team took another look at clinical data from CANTAM-Pyramax, a Phase IIIb/IV trial of pyronaridine-artesunate in Central Africa.

Examples from research

PYRONARIDINE-ARTESUNATE IS ALSO EFFECTIVE AGAINST MIXED INFECTIONS

Small differences in the life cycles of various malaria pathogens are also evident in the course of the disease. *Plasmodium ovale*, for example, forms dormant liver forms (hypnozoites), which months or years later can lead to malaria episodes. “However, unlike *P. falciparum*, the less common species do

Malaria screening of the Ghanaian population.



“In 1,502 randomly selected blood samples, we found that 12.8 percent, a relatively large percentage of those infected, had mixed infections or mono-infections caused by less common species,” states the physician. In addition, the researchers were able to demonstrate that pyronaridine-artesunate had worked as reliably in these cases as it had against *P. falciparum* alone.



“In 2022, the research area’s work was recognised by high-profile international project grants such as a platform study on new worm drugs and an ERC Starting Grant.”

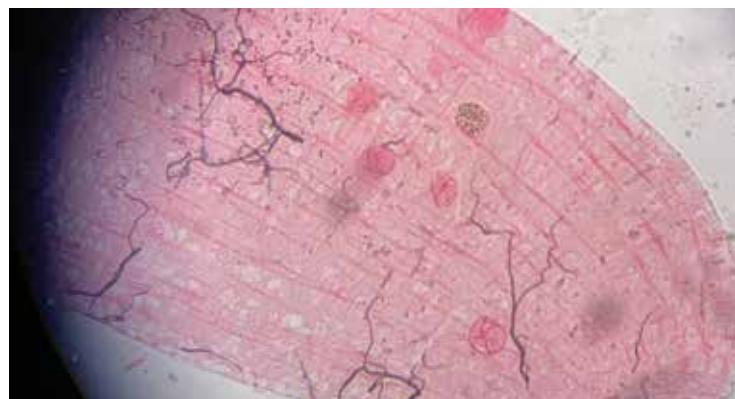
Prof. Dr Michael Ramharter, Hamburg
Coordinator

PFSPZ VACCINE ALSO HETEROLOGOUSLY EFFECTIVE

Despite intensive research, there is still no adequate approved malaria vaccine. Although people living in endemic areas can be treated effectively, they are not protected against reinfection once they have been cured. Due to side effects, there is also a lack of acceptance of malaria prophylaxis among the approximately 100 million travellers who visit the affected regions in Africa, South America and Southeast Asia every year. In the EU alone, 8,641 malaria cases were reported among returning travellers in 2019.

Prof. Peter Kremsner, Director of the Institute for Tropical Medicine, Travel Medicine and Human Parasitology at the University of Tübingen, is working on vaccines that could be a better choice for travellers. In 2022, his team successfully tested the efficacy and dosage regimen of a vaccine candidate (PfSPZ) in 45 subjects. Attenuated sporozoites of *P. falciparum* were used as vaccines. “After triple immunisation within 28 days, we see very good efficacy with excellent tolerability and few side effects,” Kremsner says.

Trial subjects were injected with 900,000 irradiated parasites from African *P. falciparum* strains on each of days 0–7–28. The vaccine strains, attenuated in this way, are still viable in the body for one to two days, but can no longer reproduce. “In the process, however, they spur the immune system on so strongly that it can cope well with an infection over a period of at least ten weeks,” says Kremsner, who subsequently tested this by means of controlled infection with a genetically distant *P. falciparum* strain from South America. 85 percent of those vaccinated were completely protected during the ten-week test phase in this so-called heterologous infection (different *P. falciparum* strains used in vaccination and infection).



The gut of an *Anopheles* mosquito infected with *Plasmodium* oocysts (round pink-coloured structures). Ruptured oocysts that have released sporozoites into the saliva of the mosquito are identifiable as black-coloured structures.

GOALS FOR 2022: OUTCOMES

- Development and testing of new methods and regimens for attenuation of malaria parasites for further development of the PfSPZ vaccine.
- Intensification of translational drug development for treatment of human filariasis.
- Investigation of the implications of insecticide resistance for vector competence.
- Development and evaluation of new diagnostics for neglected tropical diseases and for molecular point-of-care diagnosis of malaria.
- Goal partially achieved / Project is ongoing
- Goal achieved

GOALS FOR 2023

- The development of an affordable rapid diagnostic test with a very low detection limit for malaria parasites to be completed and preparations made for the pilot evaluation study in Africa.
- Establishment of robust mosquito infections with *Plasmodium falciparum* and production of a mosquito-infecting transgenic *Plasmodium falciparum* line.
- Initiation of first clinical trials for the evaluation of new therapies against loiasis.



You can find more information at

HIV

Deep insights into immune processes

Thanks to antiretroviral therapy, the replication of human immunodeficiency viruses (HIV) in the body can be effectively suppressed. However, this means having to take pills every day for the rest of one's life. In the quest for alternatives, research is delving deep into the complex immune responses triggered by the virus. In the process, the obstacles that stand in the way of a true cure are also becoming clearer.

At the University Medical Center Hamburg-Eppendorf (UKE), DZIF researchers are looking into how the virus manages to suppress the immune response of HIV patients. Their colleagues at the University Hospital Cologne are working on a therapy to attack hidden viruses.

Examples from research

HIV INFECTION DISTURBS THE ANTI-INFLAMMATORY EFFECT OF UNCONVENTIONAL T CELLS

HI viruses target the immune cells of their host. In particular, regulatory T cells, whose task it is to prevent an overreaction of the immune system. Prof. Schulze zur Wiesch, senior physician in the Division of Infectious Diseases at the UKE, and his team have looked at the expression of the surface

proteins CD39 and CD73 of γ - δ -T cells—an unconventional subset of T cells—in a comparative study of 86 HIV patients and healthy volunteers each.

“In infected people, the CD39/CD73 ratio shifts in favour of CD39. And the more CD39 we find, the worse the patient's health,” the physician explains. The unconventional T cells are primarily important for the immune defence of the intestinal mucosa, for which the CD39/CD73 ratio is normally finely balanced. Both conventional and unconventional T cells break down adenosine triphosphate (ATP), the body's molecular energy supplier. ATP is released when cells have been destroyed by inflammation and fuels inflammation outside of cells. “We now have a better understanding of why immune destruction occurs in the gut at the onset of HIV infection: the imbalance of CD39 and CD73 inhibits ATP breakdown,” says Schulze zur Wiesch. “With CD39 and

HIV cell cultures under the microscope.



CD73, we have now for the first time found markers for immunosuppressive cells that can tell us something about the inflammatory response in HIV infection but also in other diseases.”

KICK & KILL—AN APPROACH TO HIV THERAPY?

Even if viral particles are no longer detectable in the plasma of HIV patients, the virus remains dormant in many cells in the body. So far, this viral “reservoir” prevents a cure of HIV infection. Couldn’t the dormant virus be awakened in order to mark infected cells with antibodies and have them removed by the immune system? “Kick and kill” is the name of the concept tested by researchers from the University Hospital Cologne, Aarhus University (Denmark) and Rockefeller University (USA) in the ROADMAP study. Of 19 HIV patients taking romidepsin as a “viral alarm clock” in addition to antiviral therapy, eleven also received the neutralising antibody 3BNC117. The viral reservoir was then determined based on viral DNA and, after interruption of all therapies, the amount of virus in the blood of the study participants was measured by weekly PCR. The result was sobering: the additional antibody administration did not lead to a reduction of the HIV reservoir.



“A major achievement was the detailed immunological and virological characterisation of the ‘Düsseldorf patient’, who was successfully cured of HIV-1.”

Prof. Dr Marcus Altfeld, Hamburg
Coordinator

“Nevertheless, we gained important insights,” explains Dr Henning Grüll of the Institute of Virology at the University Hospital Cologne. “The result showed the difficulties of eliminating the HIV reservoir, especially in long-term existing infection.” However, the study also demonstrated the safety and good tolerability, and thus potential suitability, of HIV neutralising antibodies for other application scenarios. In a Danish follow-up study of patients just starting antiretroviral therapy, those receiving romidepsin plus antibodies were found to have lower viral loads after discontinuation of therapy. The researchers from Cologne also previously demonstrated that antibody combinations can effectively suppress viral loads for months. According to Dr Grüll, “these results indicate the potential of neutralising antibodies for the immunological control of HIV infection.”



Illustration of a HIV particle in the blood plasma being attacked by the immune system. Small Y-shaped antibodies bind to its surface.

✓ GOALS FOR 2022: OUTCOMES

- *Promotion of young researchers: better integration of young scientists into the HIV research area.*
- *Characterisation of surface molecules on novel regulatory gamma delta T cells in connection with the detection of HIV-infected cells and the course of HIV infection.*
- *Identification of mechanisms affecting the functions of natural killer (NK) cells, which are an important type of antiviral immune cell.*
- *Goal partially achieved / Project is ongoing*
- *Goal achieved*

🔄 GOALS FOR 2023

- *Promotion of young scientists: start of innovative new projects (Hölzemer, Schommers) with the help of the budget increase of the HIV research area.*
- *New insights from stem cell transplantation as a future perspective for the fight against HIV infection (publication by Schulze zur Wiesch, Nature Medicine).*
- *Organisation of a symposium of the DZIF research area HIV at the German-Austrian AIDS Congress 2023.*



You can find more information at

HEPATITIS

Hepatitis B, C and D in the spotlight

Some 325 million humans worldwide suffer from viral hepatitis. More than 1.5 million die from it every year—400,000 from infection with the hepatitis C (HCV), 820,000 from infection with the hepatitis B (HBV) virus. While there are vaccines against hepatitis A and B, a vaccine to prevent hepatitis C is lacking. Promising approaches are urgently sought—as well as curative therapies for hepatitis B and D.

Broadly neutralising antibodies against HCV as a means of prophylaxis are being investigated by DZIF researchers at University Hospital Cologne. Clinician scientists at Hannover Medical School conducted a successful multicentre study to treat hepatitis D.

Examples from research

HOPE FOR HEPATITIS C VACCINE DEVELOPMENT

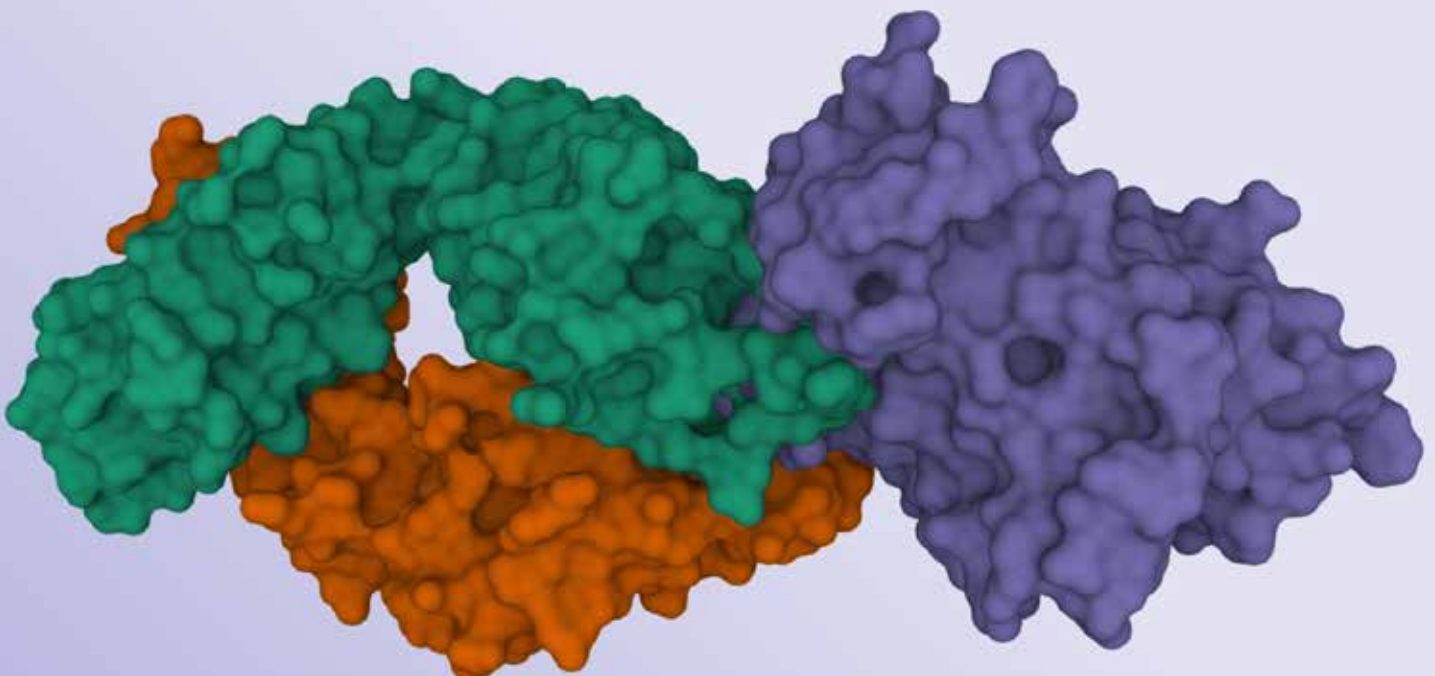
Although hepatitis C virus (HCV) infection can be cured with antivirals, it can go unnoticed for years and can thus progress to liver cirrhosis or even hepatocellular carcinoma. “Often, patients are diagnosed too late when liver damage already occurred. To overcome this problem, an effective HCV vaccine is needed,” says Prof. Florian Klein, Director

of the Institute of Virology at University Hospital Cologne. However, developing a vaccine is challenging. In particular, because the virus quickly mutates and can thus escape the immune system.

Notably, there are infected individuals whose immune system produces so-called broadly neutralising antibodies against the virus. These are able to attack many of the different HCV variants. Together with DZIF research partners in Hanover, Bonn, Tübingen and Lübeck, Klein’s team identified almost five percent of a cohort of 435 hepatitis C patients as “elite neutralisers”. From the blood of four of these individuals, his team isolated over 300 different HCV antibodies, some with outstanding activity.

Using bioinformatic structural and mutational analysis in cooperation with the team of Nico Pfeiffer, Professor of Medical Informatics at the University of Tübingen, the

Crystal structure: an antibody (red and green) binds to the HCV surface protein E2 (purple).



researchers discovered which properties and mutations in these antibodies have an influence on the neutralisation ability. “With the help of machine learning methods, it was possible to generate antibodies with neutralising activity against HCV. This is a first, but important step to pursue new approaches for effective HCV vaccine strategies,” Florian Klein says.

BULEVIRTIDE IS HIGHLY EFFECTIVE IN CHRONIC HDV INFECTION

The good news is that hepatitis B vaccines also protect from infection with hepatitis D (HDV), since the latter can only replicate in cells that are already infected with hepatitis B (HBV). However, persons already infected with HBV cannot be vaccinated anymore to prevent superinfection with HDV. “D to me stands for Devil because it is the worst of all chronic liver infections. In the end, the only option is often a liver transplant,” says Prof. Heiner Wedemeyer of Hannover Medical School.

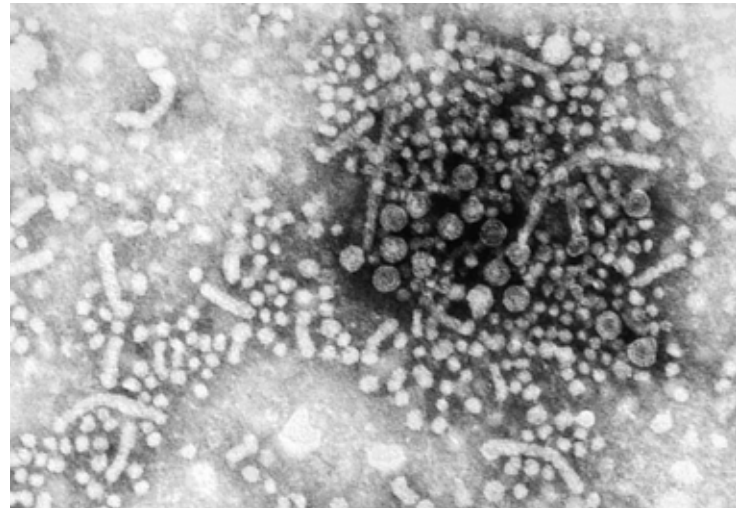


“*There has been great progress in bringing our therapeutic approaches to the clinic.*”

Prof. Dr Ulrike Protzer, München
Coordinator

Between ten and 20 million people worldwide are infected with HDV—and thus also with HBV. For a long time, there was no satisfactory treatment option for these patients until Stephan Urban, DZIF professor at Heidelberg University Hospital, developed the active agent bulevirtide. In a multicentre pivotal study, an international team around Wedemeyer demonstrated that the substance markedly reduces the viral load of HDV in the blood serum and blocks the viruses’ spread in the liver.

Unlike other antivirals, bulevirtide does not prevent replication of HDV but rather blocks its entry into, as yet, uninfected cells. Because the liver tissue is constantly regenerating, the viral load in the body continually declines. Sometimes, however, liver cells divide and thus pass the viruses on to the daughter cells, which makes a real cure very difficult. “So far, we therefore assume that treatment will be lifelong. But it has hardly any severe side effects,” stresses Wedemeyer. The primary goal of the treatment therefore is to reduce the number of patients who die from severe liver inflammation.



Transmission electron microscope image of hepatitis B viral particles.

GOALS FOR 2022: OUTCOMES

- *Optimisation of the formulation of the therapeutic hepatitis B vaccine TherVacB in terms of efficacy and stability.*
- ⌚ *In vivo proof of concept of the principle of T cell redirection through T cell engager antibodies.*
- *Detailed analysis of samples from clinical trials of the entry inhibitor Hepcludex (bulevirtide) to better understand the efficacy and mechanism of action.*
- ⌚ *Goal partially achieved / Project is ongoing*
- *Goal achieved*

GOALS FOR 2023

- *Provide data to support FDA approval for the cell entry inhibitor Hepcludex (bulevirtide), co-developed within the DZIF, for the treatment of chronic hepatitis D.*
- *Publication of an internationally agreed protocol for the determination of HBV cccDNA led by members of the Hepatitis research area.*
- *Start of the first clinical study on TherVacB.*



You can find more information at

GASTROINTESTINAL INFECTIONS

Improving *Helicobacter pylori* treatment

Ninety percent of all gastric cancers, more than 75 percent of gastric ulcers and nearly all duodenal ulcers are associated with *Helicobacter pylori* infection. Every infected person develops chronic active gastritis. But this obligate pathogenic stomach bacterium, too, is becoming increasingly resistant to antibiotics.

At the Ludwig-Maximilians-Universität München, a DZIF researcher is on the lookout for substances that do not act in the classical way—by directly inhibiting growth or killing the bacteria. Other LMU colleagues want to find out in a large-scale study how widespread the stomach germ actually is in the German population and to what extent antibiotic resistance exists.

Examples from research

SHACKLES FOR A FEISTY BACTERIUM

The ability to move around in the acidic, viscous gastric environment is essential for *H. pylori* to survive and multiply. To this end, the rod-shaped bacterium has a small bundle of rotating flagella at one end, which serves as a propeller to plow its way through the gastric mucus like a screw. Christine Josenhans, professor at the Max von Pettenkofer

Institute of the LMU, together with colleagues from the Helmholtz Centre for Infection Research in Braunschweig, the Hannover Medical School (MHH) and the Charité – Universitätsmedizin Berlin, is searching for substances that can paralyse the mini propellers by acting like a shackle.

The researchers tested more than 4,000 chemical substances *in vitro* for possible motility inhibition—and scored many hits. “Among these were a few that have a very strong effect on the germ’s locomotor system and were previously unknown to us,” Josenhans explains. Particularly promising is a group of aromatic compounds that may bind covalently to certain regulatory proteins and thus paralyse the flagella. Proof of the mode of action is in the works.

Through targeted evolution, the team also succeeded in modifying *H. pylori* in such a way that the active agents can now be studied not only in the test tube but also in the mouse model. This was no mean feat since the bacterium is specialised for humans and undergoes profound change

Dr Christian Schulz, project leader of the HelicoPTER study at LMU, performing endoscopic examinations.



if it does grow in rodents. “Initial tests show that the novel substances are very effective in driving the bacteria back out of the stomach—but are not toxic and also spare the intestinal microbiota,” says Josenhans. The best prerequisites, then, for an effective and gentle antibacterial agent.



“*HelicoPTER, the largest H. pylori prevalence and resistance study in Europe, was launched in 2022 at the four research area partner sites and is actively recruiting participants.*”

Prof. Dr Bärbel Stecher, München
Coordinator

HELICOPTER STUDY—STILL LOOKING FOR TEST PERSONS!

The bacterium’s exact transmission route is not known but it is thought that in the vast majority of cases it is spread already early in life from person to person (especially parents to children under ten years of age). Almost every second person on Earth is infected with *H. pylori*. But is this figure equally true in all regions? Eighty percent of infections remain almost asymptomatic and therefore undetected throughout life. But it’s good to know if you have it, because antibiotic therapy can easily prevent secondary diseases. Within the framework of the HelicoPTER Study, it is now possible to be tested, and, if positive, to be treated immediately and, at the same time, advance research. Since 2020, the study has been conducted jointly by the LMU and the Technical University of Munich as well as the MHH and University Hospital Tübingen.

HelicoPTER stands for “*Helicobacter pylori* prevalence, therapy success and resistance”. Register online and have a few millilitres of blood drawn—that’s all it takes. “We will then look for antibodies against the bacterium,” says Dr Christian Schulz, Head of the research group “Microbiome in the Gastrointestinal Tract” at LMU. To date, more than 2,500 people have registered for the study—20,000 are planned. If the test is positive, it often means the presence of chronic infection. “In this case, we additionally send the probands a ¹³C-urea breath test to their home address, which allows to diagnose the germs in the stomach.” Infected individuals are then offered antibiotic therapy. Based on an initial review of the data, less than 30 percent of test persons in the regions in Germany participating in the study are infected.



Helicobacter pylori under the electron microscope. Information on the HelicoPTER study and contact details for participation can be found at www.helicobacter-testen.de.

✓ GOALS FOR 2022: OUTCOMES

- Recruit at least 2,000 patients in the HelicoPTER study.
- ① Use of *Klebsiella oxytoca* for decolonisation of multidrug-resistant (MDR)-*Enterobacteriaceae*: identification of a safe and effective strain as candidate for GMP production.
- In vivo efficacy data for at least one further pathoblocker candidate.
- ① Goal partially achieved / Project is ongoing
- Goal achieved

🔄 GOALS FOR 2023

- Sequencing of over 800 human *Campylobacter jejuni* isolates for epidemiological studies and prediction of antibiotic resistance.
- Inclusion and sampling of 45 patients with liver cirrhosis and transjugular intrahepatic portosystemic shunt (TIPS) as well as 60 control patients (no TIPS) to study the role of the microbiome and the immune system in infections (TIPINF study).
- Characterisation of the role of drugs in susceptibility to gastrointestinal infections.



You can find more information at

INFECTIONS OF THE IMMUNOCOMPROMISED HOST

Viral triggers and infections in the immunocompromised

Some seemingly harmless viruses that almost everyone carries have the potential to cause serious diseases later on. Others, such as SARS-CoV-2, often cause severe symptoms immediately. In both cases, people whose immune defences are already weakened—by serious illness or immunosuppressive therapy—are particularly affected.

At Helmholtz Munich, DZIF researchers are on the home stretch for the first clinical trials with a vaccine against the Epstein-Barr virus. At the University Medical Center Hamburg-Eppendorf (UKE), scientists are learning amazing things from a SARS-CoV-2-infected cancer patient.

Examples from research

EPSTEIN-BARR VIRUS: VACCINE CANDIDATE READY FOR CLINICAL DEVELOPMENT

More than nine out of ten people worldwide become infected at some point with the Epstein-Barr virus (EBV), most already during childhood. Even though the acute infection often goes unnoticed: EBV has come to stay—for life. This is what it has in common with the other members of the herpesvirus family. If

the “first contact” occurs during puberty, it is usually not so harmless: Pfeiffer’s glandular fever, also known as infectious mononucleosis, monocyte angina or kissing disease, can break out, leading to weeks of fever and—in severe cases—exhaustion lasting for months.

Not least because EBV is suspected of playing a central role in the development of the chronic autoimmune disease multiple sclerosis and certain cancers such as Hodgkin’s lymphoma, Prof. Wolfgang Hammerschmidt’s team at Helmholtz Munich has been developing a vaccine against EBV for many years. To this end, a human cell line (HEK-293) was genetically reprogrammed to produce virus-like particles containing more than 50 proteins of the Epstein-Barr virus. “It’s virtually the original—but with biochemical tricks we have pulled its teeth out so that the particles incite the immune system but no longer trigger an infection,” explains Hammerschmidt.

Coronavirus researcher in a biosafety level 3 laboratory at Hannover Medical School.



In 2022, an important milestone was reached in the production of the vaccine: a total of 140 litres of the vaccine were produced in cell factories, amounting to around 100,000 vaccine doses. At the same time, a formulation was developed to stabilise and optimally store the particles. The vaccine is now ready for first clinical trials in humans.

UNEXPECTED IMMUNE RESPONSE TO SARS-COV-2 IN CANCER PATIENT

The adaptive immune system consists primarily of specialised white blood cells such as the B and T lymphocytes and can adapt well to novel pathogens. But how does it react in patients who are already immunocompromised? This is what Prof. Julian Schulze zur Wiesch from UKE pondered during the COVID-19 pandemic.

Cancer patients infected with the novel coronavirus often had a prolonged, almost chronic course. One female patient, who had received immunosuppressive antibody therapy, tested positive for the virus for over three months.

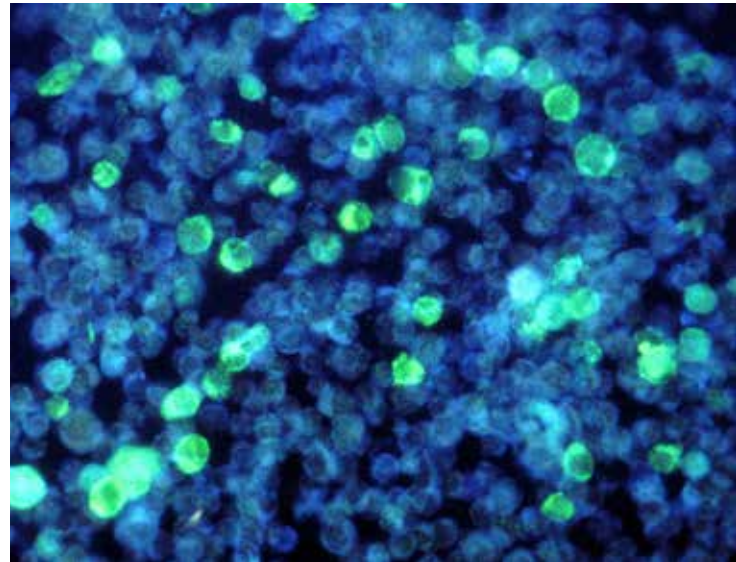


“The identification of the target structure for a new cytomegalovirus inhibitor was a major success for us.”

Prof. Dr Thomas Schulz, Hannover
Coordinator

She was seriously ill for 100 days. In a case study, the Hamburg team investigated how her T cell response differed from that of others with intact immune systems. It was known that cancer patients treated with antibodies no longer had B cells. The researchers expected that this COVID patient would also lack COVID-19-specific T cells. But on the contrary: her T cell response was actually increased! “This indicates that even in the absence of B cells a robust virus-specific T cell immune response is triggered,” Julian Schulze zur Wiesch explains. The immune system accordingly finds a fallback solution. Analysis of these T cells directed against COVID-19 revealed that their functional activity was reduced by inhibitory molecules on the surface, which could explain the long course of infection. They exhibited the exhaustion proteins TIGIT and LAG-3, which are also known from HIV and chronic hepatitis patients.

COVID-19, in particular, has taught us a lot about the immune response in immunosuppressed persons, emphasises Schulze zur Wiesch: “This will help us in future to improve treatment of at-risk-patients.”



Leukaemia cells infected with EBV glow green in this fluorescence micrograph.

GOALS FOR 2022: OUTCOMES

- ① First animal study with inhibitor of Kaposi's sarcoma-associated herpesvirus (KSHV).
- Submission of patent application for new inhibitor of human cytomegalovirus (HCMV).
- ① Definition of a GMP-conform manufacturing protocol for OTR (orthotopic T cell receptor (TCR) replacement).
- ① Goal partially achieved / Project is ongoing
- Goal achieved

GOALS FOR 2023

- Submission and approval of a FlexFund application for a new HCMV inhibitor.
- Submission of a patent for a new EBV inhibitor.
- Decision on the continuation of individual research projects beyond the current DZIF funding phase.



You can find more information at

HEALTHCARE-ASSOCIATED AND ANTIBIOTIC-RESISTANT BACTERIAL INFECTIONS

Of life-threatening resistant bugs and rescuing cleaners

Within the DZIF network “Multiresistant Bacteria” (R-Net), microbiological, genomic, epidemiological and clinical data on the prevention of infections during hospitalisation have been collected at six sites since 2014. A more recent project focusses on the implementation of bactericidal phages for therapeutic use.

In Lübeck, Cologne, Tübingen and Giessen, DZIF researchers are investigating the prevalence of certain drug-resistant bacteria. In Tübingen and Braunschweig, researchers are investigating effective phage therapies.

Examples from research

DRUG-RESISTANT KLEBSIELLAE AND ENTEROCOCCI

Which multidrug-resistant bacteria are on the rise in hospitals and which patient groups need special protection? To identify trends, patients presenting to the emergency departments of the university hospitals of Berlin, Freiburg, Giessen, Tübingen, Cologne and Lübeck are randomly selected within the framework of the R-Net and tested routinely for the most important pathogens with respect to antimicrobial resistance.

“We are focusing primarily on pathogens that the WHO put on the priority list years ago, because we could run out of treatment options for these in the near future,” explains Prof. Jan Rupp, Director of the Department of Infectious Diseases and Microbiology at the Universität zu Lübeck. In 2022, the team conducted two large cross-sectional studies on vancomycin-resistant *Enterococcus faecium* (VREfm) and on 3rd generation cephalosporin (3GCR)- and carbapenem-resistant *Klebsiella pneumoniae*, respectively. The results showed that 1.5 percent of 17,349 study participants tested between 2014 and 2018—though asymptomatic and hitherto undetected—were colonised with VREfm; 3GCR-*K. pneumoniae* was detected in 0.8 percent of the 11,885 persons tested between 2016 and 2019.

“These data, collected in several centres and over a long period of time, are extremely important to derive further research questions and translational studies on the prevention

Dr Ana Filipa Moreira Martins (left in the picture) and Anja Gatzemeier during laboratory work on the „EVREA-Phage“ project.



and therapy of infections with drug-resistant pathogens,” says Rupp. As the risk of enterococcal colonisation increases with age, and as more and more people live in nursing homes and receive antibiotics at older ages, the currently low numbers are expected to rise in the coming years. “The ageing of society cannot be brought to a halt. Therefore, we must try to stop the trend on the pathogen side.”



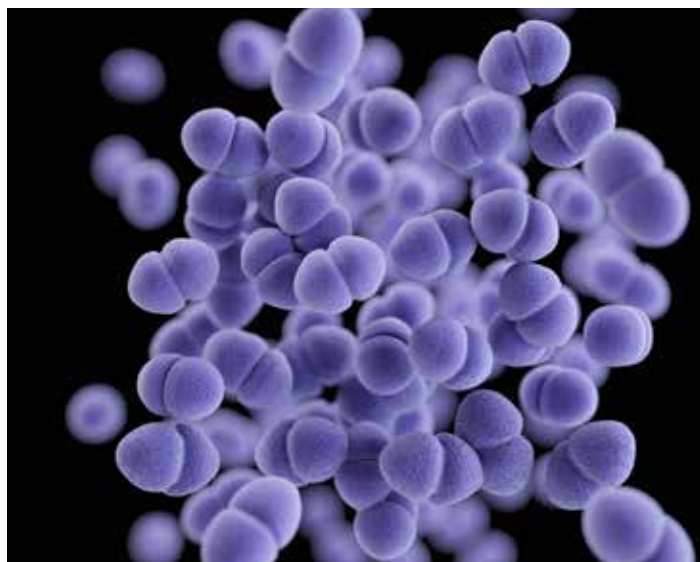
“We have established the development of novel microbiota-based therapeutic principles as a key competence of the research area.”

Prof. Dr Maria Vehreschild, Köln
Coordinator

BACTERIOPHAGES—AN ALTERNATIVE TO ANTIBIOTICS

Bacteriophages—viruses that replicate in and kill bacteria—are found wherever bacteria live: in soils, lakes, sewage water and in large quantities in the human gut. Phages, which have specific preferences for certain types of bacteria, can be employed to target antibiotic-resistant bacteria. In July 2022, the team led by Dr Christine Rohde and Dr Johannes Wittmann from the Leibniz Institute DSMZ—German Collection of Microorganisms and Cell Cultures launched the “EVREA-Phage” project. Within the scope of this project, phages are isolated from the wastewater systems of participating hospitals and their effect is tested on a collection of nearly 300 *Enterococcus faecium* strains. “Our goal is to use selected phages to prevent VRE-*E. faecium* colonisation of blood cancer patients whose intestinal mucosa is often destroyed after chemotherapy,” Rohde explains. These bacteria preferentially colonise the intestine and can lead to life-threatening sepsis.

Sometimes, an active agent produced by “clean-up phages” can also lead to decolonisation success. HY-133, a phage lysine developed by Prof. Andreas Peschel at the University of Tübingen, is a “killer enzyme” that cuts the cell walls of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteria that have colonised the nasal mucosa—much faster than the hitherto available antibiotic-containing creams do. “In a human skin model, a gel containing HY-133 at concentrations as low as 0.1 mg/ml was able to completely kill the bacteria within 30 minutes,” Peschel explains. In the future, immunocompromised and intensive care patients could be protected from pneumonia, sepsis, wound or implant infections by a formulation that delays the release of the active agent over a period of time. A first exploratory trial is being planned.



Microscopic image of vancomycin-resistant *Enterococci sp. bacteria*.

GOALS FOR 2022: OUTCOMES

- ① *Conduct of the first study on decolonisation of multidrug-resistant bacteria using the in vitro intestinal model developed by the Healthcare-Associated and Antibiotic-Resistant Bacterial Infections research area.*
- *Development of a joint project on microbiota-based decolonisation in collaboration with the Gastrointestinal Infections research area*
- *Conduct a national workshop on the implementation of phage therapy in Germany.*
- ① *Goal partially achieved / Project is ongoing*
- *Goal achieved*

GOALS FOR 2023

- *EVREA-Phage: development of an orally applicable phage cocktail against vancomycin-resistant *Enterococcus faecium* for targeted gut decolonisation.*
- *Establishment of the world’s first animal model of a humanised nasal microbiome for preclinical studies of antibiotic-resistant pathogens in the nose.*
- *Simple immunochromatographic detection method for rapid diagnosis of potentially fatal infections with carbapenem-resistant *Acinetobacter baumannii*.*



You can find more information at

NOVEL ANTIBIOTICS

Exploiting hitherto unknown potential in a targeted manner

More and more bacterial strains are becoming resistant to once highly effective antibiotics. According to the WHO, 100,000 deaths a year worldwide are caused by methicillin-resistant *Staphylococcus aureus* (MRSA) alone. There is a frenzied search underway for novel active agents, especially those that attack previously unused weak points of the pathogens.

DZIF researchers in Bonn and Braunschweig are developing a tissue-permeable antibiotic. Their colleagues in Tübingen are combing through bacterial genomes and finding immense, hitherto unused biosynthetic potential.

Examples from research

CORALLOPYRONIN A IS MORE VERSATILE THAN THOUGHT

Corallopyronin A, an antibacterial natural product derived from myxobacteria that targets the polymerase of pathogenic germs, is being actively developed to treat tropical worm diseases, particularly those caused by the thread-like worms known as filariae. These worms maintain a symbiotic relationship with intracellular bacteria called *Wolbachia*. Corallopyronin A kills the “co-residents” and subsequently

the worm also dies. A detailed pharmacokinetic analysis showed that high levels of the active ingredient were not only achieved in the blood. “What was striking, was that a great deal of it also reaches the lungs and bones,” says Prof. Achim Hörauf from the University Hospital Bonn, deputy coordinator of the DZIF research area *Malaria and Neglected Tropical Diseases*.

Bacteria can form dangerous plaques in inflamed joints and bone. Supported by the DZIF, the European Union and the BMBF, Hörauf’s team, together with colleagues in Braunschweig, now wants to develop corallopyronin A for additional indications: against *Staphylococcus aureus* in general, and specifically against osteomyelitis, an inflammation that goes into the bone and can lead to the loss of a leg in diabetics, for example, as well as against sexually transmitted infections caused by *Gonococci*. In cooperation

Establishing the manufacturing process and production of corallopyronin A in the Biotechnology centre of the Helmholtz Centre for Infection Research (HZI). From a bird’s eye view, Dr Miriam Große, Head of HZI fermentation, keeps an eye on the processes.



with a Belgian company, the active agent could be produced at kilogram scale in 15m³ fermenters in 2022. This marks a major milestone in the project: coralopyronin A is now available in sufficient quantities for extensive toxicity studies and other preclinical investigations.

HUGE DRUG POTENTIAL OF BACTERIA DISCOVERED

Whether penicillins, cephalosporins or carbapenems—most antibiotics are natural substances produced by bacteria or fungi, or at least derived from them. The single-celled organisms use them to keep other microorganisms at bay. In the search for new antibiotics, Nadine Ziemert, Professor for Natural Product Genome Mining at the University of Tübingen, and her team do not take a shovel to the field to isolate bacteria from the soil, but instead comb through large gene databases.

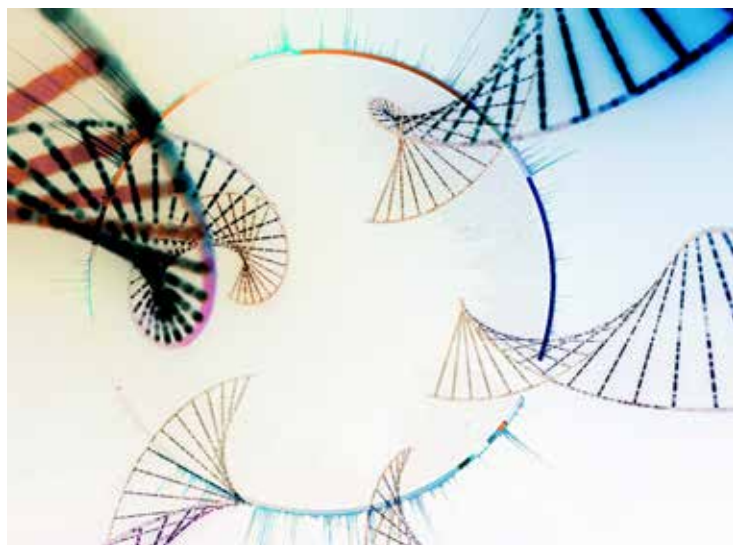


“*In 2022, Alexander Titz’s team demonstrated for the first time in an animal model that lectin inhibitors improve the therapy of Pseudomonas aeruginosa infections.*”

Prof. Dr Rolf Müller, Braunschweig/Saarbrücken
Coordinator

To find out how large and diverse the natural product synthesis potential of a microorganism is, the scientists searched for biosynthesis gene clusters in 170,000 bacterial genomes. These contain the “blueprints” for all the substances that a bacterium produces—or, to be more precise, could produce! This is because microorganisms usually do not fully exploit their synthesis potential.

Up to 75 genes are involved in the assembly of a complex natural product. “The comparison of known biosynthesis clusters with newly discovered ones showed, on the one hand, that barely three percent of the genetic potential for the production of natural products has been discovered so far,” says the researcher. “On the other hand, we were able to identify bacterial groups that have a particularly high and diverse natural product potential.” Most prominent among these are the streptomycetes. But other well-researched genera of actinomycetes, which are among the main producers of classical antibiotics, can also produce far more substances than previously known. The challenge now is to find culture conditions and genetic manipulation options under which the bacteria actually produce the new substances.



Bioinformatic comparison of many different bacterial genomes helps discover new gene clusters with potential antibiotic activity.

✓ GOALS FOR 2022: OUTCOMES

- *Demonstration/confirmation of in vivo proof of concept for adjuvant treatment of Pseudomonas aeruginosa infections using LecB inhibitors in combination with a standard-of-care antibiotic.*
- *Nomination of a guide structure to use against Pseudomonas aeruginosa infections.*
- *Identification and use of central transcription regulators for activation of silent gene clusters and identification of novel antibiotically active natural products.*
- *Goal partially achieved / Project is ongoing*
- *Goal achieved*

🔄 GOALS FOR 2023

- *Demonstration of anti-staphylococcal activity of CorA in vivo and against bacterial plaques.*
- *Validation of cystobactamides for use against Neisseria.*
- *Nomination of a pre-candidate and a backup candidate in haemolysin development.*



You can find more information at

BIORESOURCES, BIODATA AND DIGITAL HEALTH

FAIR data for the DZIF

The *Bioresources, Biodata and Digital Health (TI BBD)* translational infrastructure assures cross-cutting standardisation of biomedical data and interoperability of database systems within the DZIF and improves access to biosamples, biodata, (digital) tools and methods relating to bioinformatics and infection epidemiology. The data are made available in accordance with the FAIR principles, i. e. Findable, Accessible, Interoperable and Reusable.

In 2021, the DZIF's existing translational infrastructures were merged to form the *TI BBD* infrastructure and create a comprehensive IT and data platform for DZIF-wide exchange of bioresources, biodata and digital tools and workflows, making these available to all DZIF scientists. This IT platform makes data and (digital) tools available within the DZIF in accordance with the FAIR principles to facilitate access to research data and improve the quality of the research projects. Data harmonisation and quality assurance are needed to implement such a platform, enable meaningful interoperability in the first place and make interoperated data and biosamples interpretable. Furthermore, the interoperability of the most diverse data (population-based and clinical data, data on pathogens, human omics data) and biosamples from the same patient cohort opens up prospects for comprehensive and new analysis possibilities, helping to identify correlations and generate new insights.

ON THE WAY TO A COMPREHENSIVE IT PLATFORM

The communications and collaboration Research Project Suite (RPS), which was developed by the University of Cologne, serves as a basis for the future IT platform. All tools can be presented on this platform using the same navigation and a uniform design. The platform has been designed as a DZIF intranet and will contain all access-restricted services, which will be made available to DZIF members.

To map the resources already available in the *TI BBD*, the "DZIF Data & Tools Hub" web portal was established in 2022. The beta version is freely accessible at <https://dt-hub.dzif.de>. The registry of the DZIF *Clinical Trial Unit* will also be integrated as a new searchable use case resource. This will allow searching for clinical and population based DZIF studies, among others.

DZIF Data & Tools-Hub

Please select one of the available modules to use the desired function.

The screenshot shows a web interface with three main modules, each with a 'START' button and a right-pointing arrow:

- Search:** Features a magnifying glass icon. Text: "Search allows you to search the entire Data & Tools Hub and apply filters. Here you will find an overview of available resources, with the option of immediate availability (download) or further information (forwarding or contact)." A 'START' button is at the bottom.
- Use Cases:** Features a briefcase icon. Text: "Under Use Cases you will find resources developed for specific use cases and which are already established, they are stored in the Data & Tools Hub and are intended to show you how we have answered specific topic-related questions. Among them are e.g. analysis tools, work instructions for multi-center studies, sample texts (ethical) or epidemiological APPs." A 'START' button is at the bottom.
- Databases:** Features a database icon. Text: "The search item Catalogues / Databases will take you to our information resources, such as the DZIF-ZBR (Central Biospecimen Register) as an overview tool for biospecimen collections at the DZIF, Enterobase, a bacteriological genome database or BacDive, a worldwide information collection for bacterial phenotypes. You can directly access the respective services, forms and contact persons here." A 'START' button is at the bottom.

The Data & Tools Hub can be accessed in future via Single Sign On (SSO) and is thus also connected with the DZIF intranet. This will facilitate navigation for DZIF researchers.

IMPROVING THE POSSIBILITIES FOR REUSING DATA THROUGH CORE DATASETS

To make large amounts of medical research data readily available and usable, the data must be assigned a standard meaning. This is a core task of the *TI BBD*, which formulates core datasets for the DZIF, after which they are then available in a DZIF Metadata Repository (DZIF-MDR).

In a first version, the *TI BBD* has implemented a publicly accessible MDR, based on the approach taken by the German Center for Lung Research (DZL). It already contains the current search dataset of the Central Biosample Register (DZIF-ZBR) and thus provides descriptions, metadata as well as aligned clinical search datasets for biosample data from various DZIF studies. At a later date, the iDEX core dataset of the German network for data exchange on infectious diseases as well as various existing population-based study items will be identified and, as additional module elements, will map datasets for population-based studies. These will be prospectively summarised in a DZIF core dataset, organised in modules and jointly published in the DZIF-MDR.

In addition, the *TI BBD* is analysing in this context the existing and emerging clinical Research Data (kFDI) infrastructures in other networks to determine the optimal solution for implementation of the core datasets, in particular of the other German Centers for Health Research (DZG). Here, the focus is on the implementation via decentralised, federated components with interfaces to the routine data.

NEW PREDICTION POSSIBILITIES THROUGH INTEGRATION OF PATHOGEN DATA

The *TI BBD* uses the deep-learning platform deepG developed by the Helmholtz Centre for Infection Research (HZI) to devise and test genome-based prediction tools, e.g. for antibiotic resistance. Synergies within the infrastructure are used to achieve this, including having recourse to data from the EnteroBase database for genome sequences from *Mycobacterium tuberculosis* isolates and associated metadata (pathogen source, clinical symptoms, etc.) as well as to the experimentally collected phenotype data in the BacDive database. Here, the genomes of 12,754 bacterial strains have already been analysed and up to seven characteristics integrated into the database. The EnteroBase database is in the process of being developed further and will contain around 90,000 genome sequences.

DZIF TISSUE BANK WANTS TO BE ACCREDITED IN ACCORDANCE WITH THE NEW BIOBANK STANDARD

In 2022, the DZIF tissue bank at the Pathology Institute of Heidelberg University Hospital in collaboration with the tissue bank of the National Centre for Tumour Diseases (NCT) and the DZL Lung Biobank at Heidelberg University Hospital successfully worked towards becoming the first biobank in Germany to be accredited in accordance with the biobank



Over 3,000 pathogen strains are stored in nitrogen tanks at the Leibniz Institute DSMZ-German Collection of Microorganisms and Cell Cultures. Tissue collections are valuable resources for scientific projects and investigations.

standard DIN ISO 20387. The biobank standard was compiled in 2018 at international level and accreditation by the German Accreditation Body (DAkkS) has been possible since 2022. The tissue collection is a valuable resource for scientific projects and investigations and is available upon request to all DZIF scientists. Accreditation underscores the high quality demands that are of decisive importance for the reproducibility of analysis results. Since October 2022, the DZIF tissue bank has also been providing data to the Central Biosample Register (DZIF-ZBR) and is thus a blueprint for tissue collections to be added in future within the DZIF. Before that, the COVID-19 Autopsy Registry had already been added to the DZIF-ZBR as another tissue collection.



Dr Gabriele Anton München
Coordinator

CLINICAL TRIAL UNIT

Prepared for a pandemic: continuing education and networking

New medicines and vaccines must be tested for tolerability and efficacy in humans before they are placed on the market. The DZIF has twelve clinical trial centres specialised in infectious diseases and organised in the *Clinical Trial Unit* infrastructure. This is coordinated by the central Coordinating Office based in Cologne, which also supports DZIF scientists in the planning and implementation of clinical trials.

With the *Clinical Trial Unit (CTU)*, the DZIF is able to implement infectiology clinical trials to the highest standards—including multicentre trials at several institutions or partner sites. Besides, the *CTU* provides consultancy services to DZIF researchers: as an overarching research infrastructure, it provides support, for example, on design, budgeting or strategy development for local study implementation. The number of consultation requests received by the *CTU* sharply rose in 2022: 16 applications were submitted in 2022, compared with nine in the previous year. Moreover, the Coordinating Office (CO) provided advice on ten preliminary applications for newly planned DZIF study projects. Since its foundation in 2012, 151 feasibility requests were submitted to the DZIF up to the end of 2022. In 2022 alone, 24 clinical trials with around 13,600 subjects were conducted based on DZIF projects.

INTERNATIONAL VISIBILITY FOR CTU AND DZIF

The VACCELERATE platform established at the beginning of the COVID-19 pandemic coordinates as a pan-European network vaccine research and promotes knowledge exchange, in order to be able to respond rapidly in an emergency. "The proximity of the platform to the DZIF gives DZIF researchers access to phase II and III vaccine trials and enhances the international visibility of both the DZIF and the CTU," emphasises the coordinator

Prof. Dr Oliver A. Cornely. This is greatly underpinned by the Volunteer Registry initiated by the CO in 2021 and which already included more than 106,000 volunteers in 18 countries by the end of 2022. "If we don't have to painstakingly look for new subjects for every study, this saves valuable time," says Cornely. The CO has established yet a second database, which will be further developed within the framework of VACCELERATE: the Site Network had 489 trial sites in 39 countries in 2022. In addition, training courses have been run by the VACCELERATE Academy since 2022 on various topics relating to clinical (vaccine) research to establish uniform quality standards.

The three VACCELERATE trials on the effects of COVID-19 booster vaccinations in different age groups are underway and initial findings are expected in 2023. "The structures laid down by VACCELERATE were very valuable when implementing the trial," adds Cornely. "We therefore want to maintain and further develop these also beyond COVID-19."



Prof. Dr Oliver A. Cornely, K&Oln
Coordinator



From planning to management of samples: well-trained personnel at all levels are essential in clinical trials. Since 2022, the VACCELERATE Academy has been developing and expanding the field of continuing education.

PRODUCT DEVELOPMENT UNIT

Translating science into products

Many infectious diseases have yet to be countered by preventive vaccines or therapeutics. Multidrug-resistant bacterial pathogens are spreading worldwide, while new or emerging viruses cause epidemics or even pandemics.

There is a great need for innovative antimicrobial therapeutics, antivirals, and vaccines in order to protect the population. The *Product Development Unit* supports DZIF researchers in implementing translational projects and developing product candidates.

Without expert support, the development of new product candidates often fails already before the first clinical trial. "With the *Product Development Unit (PDU)*, the DZIF offers important added value in the field of drug development from academic research to overcome the widely criticised translational gap," says *PDU* coordinator Prof. Klaus Cichutek.

WORK ON THE STRONG DZIF PORTFOLIO CONTINUES

After focusing on SARS-CoV-2 and COVID-19 during the pandemic, in 2022 the *PDU* was able to turn its attention back to the other portfolio projects within the DZIF. "We provide targeted support to these projects in their steps from preclinical to early clinical development," says Dr Thomas Hesterkamp, Head of Drug Development at the Translational Project Management Office (TPMO). With the phage lysin HY-133, the anti-CgoX-D3 antibody and the vaccine candidate EBV-VLP, it was possible to bring promising DZIF projects supported by the *PDU* to late preclinical development.

The *PDU* works closely within the DZIF research areas to identify appropriate approaches to new vaccines, therapeutics, and diagnostics. The Office for Scientific and Regulatory Advice (OSRA) at the Paul-Ehrlich-Institut (PEI) and at the Federal Institute for Drugs and Medical Devices (BfArM) as well as the TPMO at the Helmholtz Centre for

Infection Research (HZI) and at the DZIF are all part of the *PDU*. OSRA assists in clarifying scientific and regulatory issues in scientific advice procedures. TPMO helps with operative and commercial aspects of drug development and forges or coordinates research and development collaborations with third parties, including industry partners.

TPMO WITH NEW HEAD OF VACCINE DEVELOPMENT

Within the German Centers for Health Research, the *PDU* is a distinguishing feature of the DZIF. The *PDU* was further strengthened in October 2022 when Dr Klaus Schwamborn became the new Head of Vaccine Development at TPMO. "We want to focus as far as possible on product-relevant aspects and involve collaboration and industrial partners as early as possible to enable, apart from translation, also the further development of vaccine candidates," says Dr Klaus Schwamborn, who brings his many years' experience in the industry to the DZIF.



Prof. Dr Klaus Cichutek, Langen
Coordinator



The path to a product is often a long one: the PDU supports new approaches and technologies on their way to successful translation, also within the framework of international collaborations (see page 29).

DZIF ACADEMY

Building bridges: multidisciplinary career pathways

At the time of its foundation ten years ago, it was already clear that the promotion of young researchers would play an important role within the DZIF because the best investment is in excellent talent. Since successful translation needs interdisciplinary thinking and well-connected researchers, DZG-wide career development opportunities have become more important. Prof. Jan Rupp and Dr Nadja Käding coordinate and manage the *DZIF Academy* at the Universität zu Lübeck and also provide decisive impulses for the development of DZG young researchers.

LOST IN TRANSLATION? NOT WITH THE DZIF ACADEMY PROGRAMMES!

Dr Julia Pagel is a paediatrician with a research focus in infectious diseases in infants. Three *DZIF Academy* funding programmes helped her to manage the balancing act between clinical tasks, research and everyday life as a mother. Julia Pagel was initially able to benefit from the Clinical Leave programme. This was followed by MD/PhD funding and until May 2022 she was supported by the Maternity Leave programme, which aims to facilitate the return to research after parental leave. "Translation succeeds in the DZIF," says Pagel, looking back on her own career. "The path from the clinic to science and back again has worked well for me," she adds. The excellent support from the DZIF also enabled her to take the next career step, a German Federal Ministry of Education and Research (BMBF) grant over six years, to set up her own working group within the framework of the iSTAR programme. She sees a funding gap where most traditional programmes for young researchers come to an end: in transition to the "senior phase", when many exciting research projects are in danger of petering out due to the strong clinical involvement.

The Advanced Clinician Scientist programme aims to close precisely this gap. Since last year, the first four senior

medical specialists have been supported by the programme in setting up their own working groups, leadership roles or professorships. In addition to the other *DZIF Academy* programmes (see page 48), the Summer and Autumn Schools give young researchers the opportunity for continuing education and networking. Regular coaching opportunities round off the comprehensive *DZIF Academy* programme portfolio. A mentoring programme is under preparation.

The *DZIF Academy* also provides important impulses across the German Centers for Health Research (DZG). In 2023, Dr Nadja Käding will assume the role of spokesperson of the DZG working group for the promotion of young scientists. The common objective of the working group is to set up a multidisciplinary network of scientists in translational health research.



Prof. Dr Jan Rupp, Lübeck
Coordinator



Dr Julia Pagel (second from right) during the 10th anniversary ceremony. As a DZIF Academy sponsorship recipient, she views herself as a good example for the success of the translational approach.

SUCCESSFUL TRANSLATION

INCATE—a partnership for novel antibacterial therapies

Translation has been the DZIF's mission for the past ten years: the effective implementation of research results into practice is the focus of all German Centers for Health Research (DZG). In close collaboration with the Translational Project Management Office (TPMO), projects are supported within the DZIF on the path to successful translation. Likewise, in international partnerships the DZIF funds new translational technologies and approaches. With INCATE, the DZIF is participating in an initiative that is taking up the fight against increasing antibiotic resistance.

Antimicrobial resistance (AMR) presents an increasing threat to health systems: novel antibiotics and strategies are urgently needed to effectively treat bacterial infectious diseases. The global antibiotics pipeline is rather meagre and innovative treatment approaches often are not sufficiently developed to secure follow-up funding for subsequent product development. Bridging this gap between basic research and industrial implementation to achieve novel therapies is the declared goal of the INCATE (INCubator for Antibacterial Therapies in Europe) funding initiative. A growing number of partners now support the INCATE initiative—including the CARB-X Accelerator (Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator), which funds projects in later stages of development.

DIRECT EXCHANGE WITH THE PHARMACEUTICAL INDUSTRY

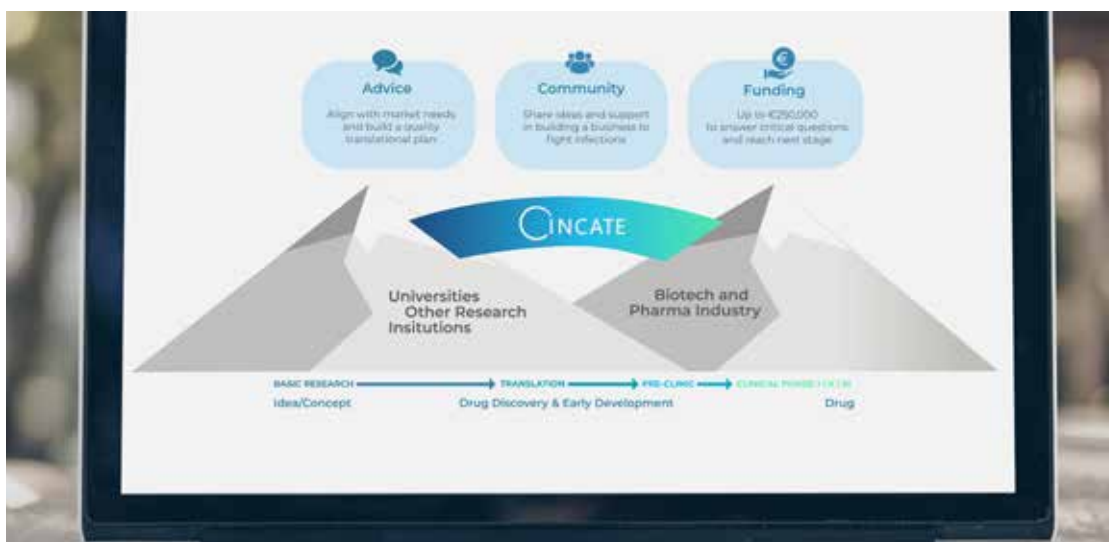
The DZIF has been a founding member of INCATE since 2021. Together with the Hans Knöll Institute (Leibniz-HKI), the University of Basel and the Swiss AntiResist Network as well as partners in the pharmaceutical industry (Roche, MSD Germany, Boehringer Ingelheim Venture Fund, Shionogi), the DZIF identifies innovative projects in the AMR area within the framework of INCATE and funds early product development to build up a stable

antibiotics pipeline. The focus here is on academic research groups working towards spin-offs and young start-ups. INCATE helps these by providing advice, networking opportunities and financial support. A special feature of the INCATE incubator is that it offers direct exchange with the pharmaceutical industry in order to ensure that medical and market needs are met right from the start of product development and to help start-ups develop into interesting companies for investors.

THREE SUCCESSFUL DZIF PROJECTS IN 2022

Thanks to good networking with DZIF scientists, INCATE has already been able to support innovative AMR projects in Germany. In 2022, three DZIF projects were successfully supported: an alpha-haemolysis inhibitor from the working group led by Prof. Mark Brönstrup at the Helmholtz Centre for Infection Research in Braunschweig, darobactin analogs by Prof. Till Schäberle's working group at Giessen University as well as the antibiotic chlorotoniil by Prof. Rolf Müller at HIPS in Saarbrücken.

Further innovative projects from the DZIF are also to be advanced in the future within the framework of INCATE.



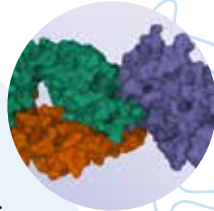
As a transnational incubator, INCATE wants to bridge the development gap on the path to novel antimicrobial therapies and concepts to effectively help patients.

News in Focus

JANUARY

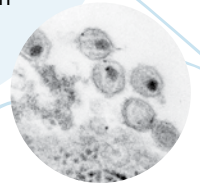
Vaccine development for the hepatitis C virus, which causes about 400,000 deaths worldwide each year, has so far failed due to the genetic diversity and high mutation rate of the virus. The characterisation of broadly effective antibodies that act as “elite neutralisers” attacking many viral variants simultaneously could advance the development of a vaccine.

As a founding member of the European initiative INCATE (INCubator for Antibacterial Therapies in Europe), the DZIF is involved in the fight against increasing antibiotic resistance. In a first round of applications, a committee of experts from industry, academia and the public sector selected four companies to receive funding of 10,000 euros each for the development of new technologies.



JUNE

Researchers from the DZIF and the University Medical Center Hamburg-Eppendorf (UKE) demonstrated in a large-scale comparative study the critical role of a group of specialised immune cells in suppressing the antiviral immune response of HIV-infected patients. The findings could help pave the way for curing chronic human immunodeficiency virus (HIV) infections.



MAY

New antibiotics are urgently needed to counter the rapidly increasing spread of resistance. The German Network against Antimicrobial Resistance (DNAMR) was founded to promote the development of new, resistance-breaking antibiotics and the necessary political willingness to act.



FEBRUARY

After a total of three contacts with the viral spike protein of SARS-CoV-2, the immune system develops a high-quality antibody response that also efficiently neutralises the omicron variant. A breakthrough infection with SARS-CoV-2 after two vaccinations achieves the same protective effect as a third vaccination, as a DZIF study at Munich universities and clinics showed.



APRIL

The joint magazine SYNERGIE of the German Centers for Health Research (DZG) has received an iF DESIGN AWARD 2022 in the field of communication—already the second design award for the magazine after receiving the Berlin Type Award in Silver 2021.



MARCH

Increasing resistance of the bacterium *Helicobacter pylori*, which is responsible for gastric ulcers and cancer, to currently available antibiotics makes the development of new active substances urgently needed. DZIF researchers at Ludwig-Maximilians-Universität München were able to identify substances that can inhibit the bacteria’s motility and thus their proliferation and pathogenic activity.



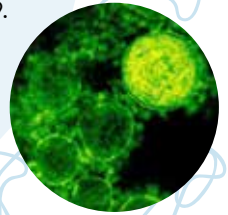
JULY

Specific biomarkers in blood can indicate the onset of tuberculosis (TB) in HIV-infected individuals six to 12 months earlier than TB diagnosis by sputum. Early diagnosis via blood-based biomarkers followed by medical treatment could prevent progression and transmission of the disease. This is the conclusion of an international research group with DZIF participation in a longitudinal study.



AUGUST

To be better prepared for future outbreaks of the highly pathogenic Middle East Respiratory Syndrome Coronavirus (MERS-CoV), DZIF researchers at UKE had developed the recombinant vector-based vaccine MVA-MERS-S and successfully tested a basic immunisation regime consisting of two vaccinations in the years 2017-2019. Two studies now showed that a third booster vaccination with the MVA-MERS-S vaccine leads to a long-lasting immune response.



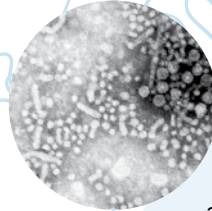
OCTOBER

Almost 30 percent of tuberculosis cases in Germany affect extrapulmonary organs. The disease, triggered by the bacterium *Mycobacterium tuberculosis* and often initially undetected, first affects the lungs and later the lymph nodes, bones or brain. A multicentre and prospective study of the DZIF, funded with almost 680,000 Euros, aims to help improve early detection and treatment of this difficult-to-treat form of tuberculosis.



SEPTEMBER

Worldwide, 10-20 million people are affected by hepatitis D virus infection, the most severe form of chronic viral hepatitis, which is always associated with hepatitis B virus infection. In a multicentre phase II clinical trial, an international research team was able to show that the 24-week application of the active agent bulevirtide, developed by DZIF virologist Prof. Stephan Urban and approved in the European Union since August 2020, significantly reduced the hepatitis D viral load in the blood serum and liver of the test subjects.



NOVEMBER

A team led by Prof. Ulrike Protzer from Helmholtz Munich and Technical University of Munich is researching a new therapeutic vaccine—called TherVacB—for curing chronic hepatitis B. The team has now developed an optimal formulation to make the vaccine heat stable and thus avoid the need for continuous cold chains for transportation and storage.



DECEMBER

The 2022 Prize for Translational Infection Research of the DZIF went to the epidemiologist Gérard Krause. The DZIF scientist was honoured for his outstanding contributions in the field of translational infection epidemiology and especially for the development of the epidemic management system SORMAS, which is used worldwide.



New challenges for science communication

The past pandemic years have underlined the importance of good science communication. They have also highlighted the sometimes devastating effects of intransparency and communication that is not properly tailored to the target audience. Filter bubbles, selective fake news or the fast publishing pace in online and social media channels in pursuit of the public's favour—all phenomena, with which science communicators have to deal with. In the DZIF press office, we want to continue to disseminate high-quality information and support our scientists in making their research findings visible and understandable to as many people as possible.

Public interest in the DZIF rose sharply during the years of the COVID-19 pandemic: in both 2020 and 2021, some one million people worldwide visited the DZIF website—well over 13-fold more than in the year before the pandemic. In 2016, we launched our YouTube channel and since 2019 the DZIF operates Twitter and LinkedIn as additional social media channels, reflecting the growing importance of digital and especially social media for science communication. The number of followers on our social media channels also grew rapidly in 2020.

The prospect of being able to harness artificial intelligence (AI), for example to create texts, images or videos, presents a major challenge in the realm of communications (and not just there). This could lead to an exponential growth in fake news and fake images. Already today, it is sometimes almost impossible to distinguish images created by an AI from “real” images—especially if manual image processing is used in addition to digital processing. For this annual report's cover design, we have used an AI image in combination with manual image processing. Even though this is a rather playful AI-

There was no need for AI for this photo: members of the public, including also the Executive Board members Prof. Dirk Heinz (2nd from left) and Prof. Maura Dandri (4th from left), are obviously having a lot of fun during the ceremony to mark the 10th anniversary jubilee in Berlin. This was also a success for the DZG press offices which jointly organised the event and accompanying public relations measures.



generated birthday motif for the DZIF’s tenth anniversary, at first glance it is no longer possible to distinguish with certainty between AI-generated and „real“ images here either (in fact, only the photos in the picture frames are real photographs, everything else is produced by the AI). Recognising AI components in media is likely to become even more difficult when we navigate scientifically abstract (image) worlds of which we have little or no idea from our everyday experience. At the same time, the large AI language models and image generators could also make communication work a lot easier in many places and possibly even lead to more researchers communicating their work. In any case, it is clear that AI technologies will bring completely new challenges for science communication.

WEBSITE TRAFFIC, MEDIA RESPONSE & REACH

Despite a slight decrease in COVID-19-related topics, the DZIF regularly reaches a broad public via its communication channels: around 760,000 visitors from across the world used the DZIF website in 2022 as a key source of information. While German-speaking information seekers landed particularly frequently on one of our glossary pages, the pages on hepatitis B research and therapy were among the most frequently visited English-language content.

The continuous interest in the DZIF’s work is also reflected in the media response beyond the DZIF’s own media channels. In around 1,500 online articles, DZIF reports were picked up, DZIF experts were quoted or the DZIF was mentioned as a source. Around a quarter of these articles were published outside the German-speaking countries. In 2022, articles about COVID-19 still achieved the widest coverage. The article with the broadest coverage and a reference to the DZIF came from the online editorial team of the British medium „The Independent“. It potentially reached over 49 million readers.

PRESS RELEASES, TWITTER & LINKEDIN

In the past year we issued 49 press releases and other news: all nine research areas were represented with at least two news articles each. We reported most frequently news from the research areas *Emerging Infections*, *Tuberculosis* and *Hepatitis*, with eleven and twice seven reports, respectively.

Our social media posts were again extremely successful in 2022, with 153 tweets and 139 LinkedIn posts generating 296,590 impressions and gaining over 1,500 new followers.

INTERNAL AND EXTERNAL NETWORKING & COOPERATION

In 2022, we were able to meet once again face to face, celebrate together the 10th anniversary or participate in scientific exchanges at the DZIF annual meeting. In addition to coordinating these events, the DZIF press office participated in the conception and implementation of the social media campaign and the information films for the ten-



From the logo to the typeface and colour scheme to implementation in concrete applications such as the DZG website: as part of the DZG Public Relations working group, members of the DZIF Press Office contributed to the development of the DZG’s corporate design and regularly participated in DZG-wide communication campaigns and events.

year anniversary as well as in corporate design development for the German Centers for Health Research (DZG). Within the framework of the DZG public relations working group, the press office also contributes to the planning of DZG events as well as to the conception and contents of the DZG website and the biannual issues of the DZG magazine SYNERGIE.

In regular DZIF newsletters and internal emails we share essential information tailored to specific audiences. We continuously work on the strengthening of networks within the DZIF and with its numerous external cooperation partners in academia and industry. Because only when research results are made public can patients, interested citizens and, last but not least, external researchers find out which new developments are on the way.



From left: Tatiana Hilger, Martina Lienhop, Karola Neubert (until 2023), Dr Nicola Wittekindt

Braunschweig, Press Office

ABOUT THE DZG

German Centers for Health Research

A key objective of the German government's health research programme is to be able to combat widespread diseases more effectively. With the establishment of the German Centers for Health Research (DZG) since 2009, the federal and state governments have laid the groundwork for this. Four of the six centers celebrated their tenth anniversary in 2022 under the motto "10 years of DZG: Pacesetters in Health Research".

The German Centers for Health Research are long-term, equal partnerships of non-university and university research institutions, such as Max Planck, Helmholtz and Leibniz Institutes, universities and university hospitals. The DZIF is one of six DZG Centers established between 2009 and 2012 at the initiative of the Federal Ministry of Education and Research (BMBF). They pool existing expertise and ensure that new scientific findings on prevention, diagnosis and therapies for common diseases benefit patients more quickly. Thereby, basic research and clinical research are closely networked.

The DZG Centers are dedicated to the following diseases: cancer (DKTK), diabetes (DZD), cardiovascular diseases (DZHK), infectious diseases (DZIF), lung diseases (DZL) and neurodegenerative diseases (DZNE). Two more centres will be added in the next two years: the German Center for Mental Health (DZPG) will start its work in May 2023, and the German Center for Child and Adolescent Health (DZKJ) is expected to start at the end of 2023 or in 2024.

The strategic cooperation of the leading researchers in the DZG Centers strengthens Germany's position as a

Lively discussions during the round-table talks at the ceremony marking the 10th anniversary of the four centres DKTK, DZHK, DZIF and DZL. Pictured are DZG junior researchers Dr Julia Pagel (1st from left, DZIF), Dr Theresa Suckert (4th from left, DKTK), Dr Meshal Ansari (1st from right, DZL) and Dr Djawid Hashemi (6th from right, DZHK); the DZG Executive Board Chairmen Prof. Michael Baumann (6th from left, DKTK), Prof. Stefanie Dimmeler (5th from right, DZHK), Prof. Dirk Busch (2nd from left, DZIF), Prof. Werner Seeger (4th from right, DZL), Prof. Martin Hrabě de Angelis (3rd from right, DZD) and Dr Sabine Helling-Moegen (2nd from right, on behalf of Prof. Pierluigi Nicotera, DZNE); as well as former German Federal Minister Annette Schavan (7th from left), former State Secretary for Health Dr Thomas Götz (5th from left), and Prof. Christian Drosten (3rd from left, Director of the Institute of Virology at Charité - Universitätsmedizin Berlin).



science hub in international competition and at the same time increases its attractiveness for young scientists at home and abroad. The bundling of different disciplines and competences has already led to a significantly increased international visibility of translational, clinical application-oriented research in Germany.

The six DZG Centers have been working closely together from the very beginning in order to exchange experiences and create synergies. In quarterly joint meetings of the DZG executive boards as well as biannual DZG forums (involving representatives of the BMBF and state governments), the focus is on the strategic development and cooperation of the DZG Centers. In recent years, the DZG Centers have grown closer together: a DZG main office was established, while the existing working groups for Global Health, Promotion of Young Scientists, Public Relations, Patient Participation and Regulatory Aspects of Clinical Trials continued their work. The Data Management working group was further developed in 2022 and renamed the Research IT working group. It works on harmonising processes and IT systems for efficient and secure data exchange between the differently specialised centres.

“For 10 years, the German Centers for Health Research have been carrying out valuable work for an important goal: they bundle research on widespread diseases. This way, new findings on prevention, diagnosis and therapies reach patients more quickly. I congratulate them very warmly on this!”

Bettina Stark-Watzinger

German Federal Minister of Education and Research

STRONG JOINT COMMITMENT TO THE PROMOTION OF RESEARCH AND YOUNG SCIENTISTS

With the DZG Innovation Fund (DZGIF), the concept for a joint research funding programme was developed, which started in 2022 with a first call for proposals on the research topic “Cell & Gene Therapy”. With the help of the fund, the DZG Centers want to strengthen the networking of their members within the German research landscape and create interdisciplinary synergies to tackle the challenges of common diseases. Researchers from five of the six DZG Centers are involved



In the series of the successful jointly-designed health research magazine SYNERGIE, two issues on the topics “The Immune System” and “Clinical Research” were published in 2022 as high-quality print products as well as online editions at www.dzg-magazin.de (in German). In 2022, the magazine received an iF DESIGN AWARD in the field of communication—already the second design award for the magazine after the Berlin Type Award in Silver 2021.

in the successful funding application of the first call. In a second round of calls on the topic of “Microbiome”, eight full proposals were received by the submission deadline at the end of November 2022.

As part of the promotion of young scientists, the DZG offered very well-attended courses for young talents last year, for example the virtual DZG symposium for young scientists on the topic of “single cell analysis” and several lectures on the topics of science communication, career development and setting up a company. In addition, intensive work was done to support scientists in balancing clinical and research activities and to help them exchange their research data and biosamples on the basis of common standards.

The joint public relations work was also continued with commitment: in October 2022, the German Centers for Health Research DZHK, DZD, DZL, DZIF and DZNE organised a scientific symposium on post-COVID syndrome in Frankfurt, which was followed by a public citizens’ event with a panel discussion on late effects of COVID-19.

“PACESETTERS IN HEALTH RESEARCH”

With a ceremony in Berlin and around 300 guests from politics and science, four of the six DZG Centers celebrated their tenth anniversary on 19 May 2022 under the motto “10 years of DZG: Pacesetters in Health Research”. During the event and by digital means, congratulations were extended by, among others, the current German Federal Minister of Education and Research, Bettina Stark-Watzinger, and the former German Federal Minister of Education and Research, Annette Schavan, who played a leading role in the founding of the DZG.

External Partnerships

Numerous associated partnerships and other external collaborations strengthen the DZIF's position as an outstanding institution in the field of infection research.

ASSOCIATED PARTNERS

Carl von Ossietzky University Oldenburg

Since 2022, the Institute for Medical Microbiology and Virology at the University of Oldenburg has been involved in a project to characterise carbapenem resistance in carbapenemase-producing Enterobacterales (CPE). Together with the group of Dr Andreas Wendel at the Kliniken der Stadt Köln, the Oldenburg group led by Prof. Axel Hamprecht is providing CPE isolates as well as epidemiological data for the pilot study "Dissemination of carbapenemase genes by mobile genetic elements (DIOGENES)", which is being conducted under the leadership of the University Hospital Tübingen.

Charité – Universitätsmedizin Berlin

The Charité Institute of Hygiene and Environmental Medicine is one of six partners in the DZIF network "Multiresistant Bacteria" (MDRO Network: R-Net 2.0). Investigations in the network focus on the epidemiology of multidrug-resistant bacteria as well as of bloodstream and *Clostridioides difficile* infections.

The Charité Institute of Virology hosts the working group "Virus Detection and Preparedness", an essential infrastructural component of the DZIF research area *Emerging Infections*. The group, led by Prof. Christian Drosten, is responsible for the detection of emerging viruses and the development of diagnostic tests for novel and epidemic pathogens. The Institute of Virology is also home to the research group "Innate

The Kumasi Centre for Collaborative Research in Tropical Medicine (KCCR) in Ghana—an African Partner Institution of the DZIF—celebrated its 25th anniversary and its successful research on infectious diseases in the tropics with a ceremony and scientific symposium on 29 and 30 November 2022.



Immunity and Viral Evasion” of Prof. Christine Goffinet, which characterises mechanisms of intrinsic cellular defences and HIV-1-mediated antagonisation strategies in the DZIF research area *HIV*. The research group “Virus Epidemiology”, headed by Prof. Jan Felix Drexler, coordinates the work of several DZIF partner sites on Zika outbreaks in Latin America and collaborates closely with the *Hepatitis* research area on novel hepatitis viruses from animal reservoirs.

German Liver Foundation/HepNet Study-House, Hannover

The HepNet Study House networks study centres and establishes contacts with practices and physicians throughout Germany who are interested in participating in hepatitis research studies. As a central contact point for scientists and cooperation partners, it creates a platform for conducting clinical trials. The DZIF can use infrastructures and cohorts for its projects.

Goethe University Frankfurt a. M.

The Goethe University Frankfurt is active in the DZIF research areas *Hepatitis* and *Healthcare-Associated and Antibiotic-Resistant Bacterial Infections*. In the *Hepatitis* research area, a joint project is taking place, among others, to optimise the treatment of hepatitis C patients with novel agents—so-called Directly Acting Antivirals—and to develop a prophylactic vaccine. The Goethe University Frankfurt is also involved in a DZIF study on the treatment of hepatitis E.

Greifswald University Hospital

The Greifswald University Hospital is partnering in a project in 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. Currently, the promising compound is being investigated in preclinical studies to ensure its safety in subsequent clinical trials in humans.

Kliniken der Stadt Köln

In the research area *Healthcare-Associated and Antibiotic-Resistant Bacterial Infections*, the Kliniken der Stadt Köln are involved in a pilot study on the spread of carbapenemase genes through mobile genetic elements. The study will comprehensively characterise carbapenem-resistant enterobacteria isolated from 2014 to 2019 in the Kliniken der Stadt Köln and at three other partner sites in Germany.

Leibniz Institute for Natural Product Research and Infection Biology—Hans Knöll Institute (Leibniz-HKI), Jena

The Leibniz-HKI provides the DZIF with various natural products. Researchers of the Leibniz-HKI and the Ludwig-

Maximilians-Universität München are leading a project for the clinical testing of a newly developed antibiotic against tuberculosis. The new test substance, called BTZ-043, is also effective against multidrug-resistant pathogens.

Leibniz University Hannover

The Institute of Organic Chemistry at Leibniz University Hannover is participating in a joint project in the research area *Novel Antibiotics*, which is being coordinated by the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS) in Saarbrücken. The project focuses on amidochelocardin, an antibiotic from the tetracycline class. The lead structure of this compound is to be optimised using medicinal chemistry and biosynthetic methods.

Medical Center—University of Freiburg

The Medical Center—University of Freiburg is a partner in several DZIF projects in the research areas *Hepatitis*, *Infections of the Immunocompromised Host* and *Healthcare-Associated and Antibiotic-Resistant Bacterial Infections*. Reducing healthcare-associated infections is an important goal of these projects. To this end, for example, antibiotics are used in a more targeted manner and hygiene measures are improved. Freiburg is one of six partner sites where the epidemiology of multidrug-resistant bacteria as well as of bloodstream infections and *Clostridioides difficile* infections have been studied longitudinally over a period of several years. A monitoring system is also being developed that will indicate outbreaks of multidrug-resistant bacteria in the clinic in good time.

Ruhr University Bochum

The Ruhr University Bochum is participating in a project on hepatitis E. On the one hand, new antiviral treatment options are being researched, on the other hand, manifestations outside the liver. Among other things, neurological cell culture systems are being developed in Bochum for this purpose.

University of Bayreuth

The pathogen *Mycobacterium tuberculosis* is the focus of a large tuberculosis screening project in which the University of Bayreuth is involved. The aim is to develop a preclinical model on the basis of which new active agents against tuberculosis can be identified and known and newly discovered active agents can be tested for effectiveness.

University Hospital of Düsseldorf

The University Hospital of Düsseldorf is involved in a study on the control of hepatitis C and contributes to the patient cohorts. The aim of the study is to identify those patients who need treatment and to develop a prophylactic vaccine.

University Hospital of Würzburg

In a clinical trial in the DZIF research area *Infections of the Immunocompromised Host*, leukaemia patients receive specially purified cells of the immune system, so-called memory T cells, after bone marrow transplantation. The special immune cells are intended to protect the patients from infections until their own immune defences function. Some of the study patients will be treated in Würzburg, as well as at the DZIF partner sites in Munich (coordination), Tübingen and Hannover-Braunschweig.

University of Münster

Collaborating in a project in the research area *Gastro-intestinal Infections*, the University of Münster is working on new pathogen-specific inhibitors, for instance, against *Salmonella*. Researchers at the University are also involved in the development of new antibiotics against multidrug-resistant tuberculosis bacteria. The aim of this project is to develop a drug candidate that proves its efficacy against tuberculosis in preclinical studies.

INDUSTRY COOPERATIONS**BioNTech AG, Mainz**

In collaboration with BioNTech and the biopharmaceutical research institute TRON at the Johannes Gutenberg University Mainz, the DZIF is investigating RNA-based vaccines for selected virus families with human pathogenic potential and subsequently bringing them into preclinical and early clinical development.

Coris BioConcept, Gembloux (Belgium)

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

HYpharm GmbH, Bernried

HYpharm GmbH and a consortium funded by the DZIF are cooperating in the field of production and preclinical development of the phage lysine protein HY-133 (see also Greifswald University Hospital). A joint early clinical development for the nasal decolonisation of *Staphylococcus aureus* is concretely planned.

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 scientific and clinical partners. The company IDT Biologika developed its own cell line for the production of the vaccine on a larger scale. IDT Biologika is also a partner and consortium leader in the currently ongoing clinical trial of the vaccine candidate MVA-SARS-2-ST.

Juno Therapeutics GmbH, a Bristol Myers Squibb Company, Göttingen

Juno Therapeutics is the cooperation and commercialisation partner of the DZIF-funded group led by Prof. Dirk Busch, Technical University of Munich, in the field of GMP quality-assured production of central memory T cells for clinical application in infection and tumour therapy.

INTERNATIONAL ALLIANCES (DZIF-INITIATED)**INCATE**

Multidrug-resistant bacteria are spreading worldwide and new antibiotics and strategies against deadly infectious diseases are urgently needed. INCATE (INCubator for Antibacterial Therapies in Europe) is a consortium in the start-up phase that aims to boost the development of new drugs. To this end, partners from the academic, industrial and public sectors are working together. The DZIF is one of the founding members. The industrial partners are Roche, Boehringer Ingelheim Venture Fund, MSD Germany and Shionogi (see also page 29).

NA-PATH

The DZIF and the Helmholtz Centre for Infection Research have developed a concept to establish a National Alliance for Pandemic Therapeutics (NA-PATH). With this, they want to specifically boost research and development of broadly effective therapeutics in order to be better prepared for future outbreaks caused by viral pathogens with pandemic potential.

UNITE4TB

To advance research in the fight against tuberculosis (TB) and enable new, safe and affordable treatment solutions for TB patients worldwide, a new consortium of 30 partners from 13 countries has officially started its work. The LMU University Hospital Munich and the DZIF are centrally involved in this consortium called "Academia and industry united innovation and treatment for tuberculosis", or UNITE4TB for short.



Malaria research at the Centre de Recherches Médicales de Lambaréné (CERMEL), an African Partner Institution of the DZIF in the Central African country of Gabon.

PARTNERSHIPS WITH INTERNATIONAL UNIVERSITIES

McMaster University

In order to better prepare for future pandemics, the DZIF has signed a partnership agreement with Canada's McMaster University. In addition to joint research projects and workshops on "Pandemic Preparedness", the fight against increasing antibiotic resistance is another topic of the planned cooperation.

AFRICAN PARTNER INSTITUTIONS

In long-term collaborations with four partner institutions in Africa, DZIF scientists are researching preventive measures as well as new diagnostics, therapies and vaccines for malaria, tuberculosis, HIV/AIDS and neglected tropical diseases such as worm diseases. Institutions in Africa include clinics and research centres in Kumasi (Ghana), Lambaréné (Gabon), Nouna (Burkina Faso) and Mbeya (Tanzania).

KCCR

At the Kumasi Centre for Collaborative Research in Tropical Medicine (KCCR) in Ghana—an external research and training institution of the Bernhard Nocht Institute for Tropical Medicine in Hamburg—research focuses on malaria, tuberculosis, salmonellosis and Buruli ulcer, an infectious disease of the skin and soft tissues common in the tropics.

CERMEL

At the Centre de Recherches Médicales de Lambaréné (CERMEL) in the Central African country of Gabon, scientists conduct research primarily on parasitic diseases such as malaria, schistosomiasis (also known as bilharzia), intestinal infections with parasitic worms, tuberculosis and bacterial infections. In collaboration with the DZIF and the University of Tübingen, a large number of phase I-III clinical trials have been conducted over the past 30 years for the development of new drugs and vaccines.

CRSN

The Centre de Recherche en Santé de Nouna (CRSN) in Burkina Faso was founded in the early 1990s as a cooperation project between Heidelberg University and the Ministry of Health of Burkina Faso. Joint projects with the DZIF focus on researching and treating malaria, HIV/AIDS and bacterial meningitis.

NIMR-MMRC

The Mbeya Medical Research Center (MMRC) in Tanzania, one of eight medical research centres of the National Institute for Medical Research (NIMR), conducts research on HIV/AIDS, tuberculosis, malaria and other tropical diseases. Together with the DZIF, the MMRC carries out clinical trials on tuberculosis vaccines and drugs, among other things.

ORGANISATION AND BODIES

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 institutions. The General Assembly elects the Executive Board members and the Executive Director, and decides on the allocation of funds to the research areas 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 Braunschweig 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 areas 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 (TTU)

The nine 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 and Neglected Tropical Diseases
- HIV
- Hepatitis
- Gastrointestinal Infections
- Infections of the Immunocompromised Host
- Healthcare-Associated and Antibiotic-Resistant Bacterial Infections
- Novel Antibiotics

TRANSLATIONAL INFRASTRUCTURES (TI)

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

- Bioresources, Biodata and Digital Health
- Clinical Trial Unit
- Product Development Unit
- DZIF Academy

PARTNER SITES

The DZIF conducts its research in 35 research institutions 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 (see pages 36-39).

Bonn-Köln

Gießen-Marburg-Langen

Hamburg-Lübeck-Borstel-Riems

Hannover-Braunschweig

Heidelberg

München

Tübingen

Associated Partners

ORGANISATION AND BODIES

Central bodies

EXECUTIVE BOARD

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

MANAGING DIRECTOR

Dr T. Jäger, *DZIF, Braunschweig*

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Prof. Dr C. Rooney (Vice Chair), *Baylor College of Medicine, USA*
Prof. Dr D. Bumann, *University of Basel, Switzerland*
Dr L. Fraisse, *Drugs for Neglected Diseases initiative, Switzerland*
Dr Dr Delia Goletti, *Lazzaro Spallanzani, National Institute for Infectious Diseases, Italien*
Dr K. Klumpp, *Riboscience, LLC, USA*
Prof. Dr D. Moradpour, *Lausanne University Hospital, Switzerland*
Dr E. Pamer, *The University of Chicago, USA*
Dr J. Reinhard-Rupp, *Merck Global Health Institute, Switzerland*
Prof. Dr A. Trkola, *University of Zurich, Switzerland*
Prof. Dr R. Wallis, *The Aurum Institute, South Africa*
Prof. Dr Dr A. Zinkernagel, *University Hospital Zurich, University of Zurich, Switzerland*

INTERNAL ADVISORY BOARD

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Prof. Dr O. A. Cornely, *University Hospital Cologne*
Prof. Dr S. Herold, *Justus Liebig University Giessen*
Prof. Dr F. Klein, *University Hospital Cologne*
Dr B. Lange, *Helmholtz Centre for Infection Research, Braunschweig*
Prof. Dr C. Meier, *Universität Hamburg*
Prof. Dr T. Pietschmann, *TWINCORE, Centre for Experimental and Clinical Infection Research, Hannover*
Prof. Dr H. Rohde, *University Medical Center Hamburg-Eppendorf*

PARTNER SITES AND MEMBER INSTITUTIONS

Partner sites and member institutions



Germany-wide infection research



BADEN-WÜRTTEMBERG

The research areas *Hepatitis, Infections of the Immunocompromised Host* and *Tuberculosis* are co-managed from **Heidelberg**. Furthermore, Heidelberg scientists coordinate the DZIF-wide Biobanking unit—since 2021 part of the DZIF infrastructure *Bioresources, Biodata and Digital Health*—with a focus on tissue banking. In addition to participating in the DZIF *Clinical Trial Unit* with a “First-In-Human (FIH)” unit for early clinical trials, Heidelberg researchers are working on combating malaria, developing antiviral therapy concepts for viral emerging infectious diseases, controlling HIV, as well as healthcare-associated and antibiotic-resistant bacteria, and developing imaging methods to visualise infections in systems of varying complexity.

HEIDELBERG

Spokesperson: Prof. Dr Stephan Urban (Heidelberg University Hospital)

Institutions: 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)
- Tuberculosis (co-coordination)

At the DZIF partner site **Tübingen**, research is conducted in the areas *Gastrointestinal Infections, Healthcare-Associated and Antibiotic-Resistant Bacterial Infections, Novel Antibiotics*, and *Malaria and Neglected Tropical Diseases* (NTDs). The Tübingen focus is on the translation of research results into drug and vaccine development as well as on infection models and epidemiology. In the case of infections caused by antibiotic-resistant bacterial pathogens, the focus is on multidrug-resistant pathogens such as methicillin-resistant staphylococci (MRSA) and gram-negative pathogens (e.g. the so-called ESBL producers).

TÜBINGEN

Spokesperson: Prof. Dr Peter Kremsner (University of Tübingen)

Institutions: University of Tübingen, Max Planck Institute for Biology, University Hospital Tübingen

TTU Coordination:

- Malaria and Neglected Tropical Diseases (co-coordination)
- Gastrointestinal Infections (co-coordination)
- Healthcare-Associated and Antibiotic-Resistant Bacterial Infections (co-coordination)
- Novel Antibiotics (co-coordination)

BAVARIA

The research areas *Gastrointestinal Infections*, *Hepatitis* and *Tuberculosis* are coordinated from **München**, as is the field of *Infections of the Immunocompromised Host* in co-ordination. Scientists at the DZIF site in München are also working on immune control of infections, defence against emerging infectious diseases and the development of new therapeutic methods. Pathogen-specific immunotherapies (e.g. vaccinations or (adoptive) T cell transfer) are aimed at strengthening the body's own immune defence system in order to better control or completely prevent infectious diseases. Further focal points at the München site are HIV and the infrastructure Biobanking (since 1/2021 part of the *TI Bioresources, Biodata and Digital Health*), as well as the International Clinical Trials Unit—a central service facility of the DZIF for the coordination of global studies on various research topics (e.g. tuberculosis, HIV, hepatitis B and SARS-CoV-2).

MÜNCHEN

Spokesperson: Prof. Dr Michael Hoelscher (LMU University Hospital Munich)

Institutions: Helmholtz Munich – Environmental Health Center, Bundeswehr Institute of Microbiology, LMU University Hospital Munich, University Hospital rechts der Isar of the Technical University of Munich, Ludwig-Maximilians-Universität München, Technical University of Munich

TTU Coordination:

- Gastrointestinal Infections (coordination)
- Hepatitis (coordination)
- Tuberculosis (coordination)
- Infections of the Immunocompromised Host (co-ordination)

TI Coordination:

- Bioresources, Biodata and Digital Health (coordination)

**HAMBURG/
SCHLESWIG-HOLSTEIN**

The **Hamburg - Lübeck - Borstel - Riems** partner site concentrates a unique wealth of expertise and infrastructure to study infectious diseases and emerging pathogens of national and global relevance and to develop control strategies. Scientists at the site are involved in clinical, entomological and virological studies; medicinal chemistry for drug discovery is based here, as are the epidemiology of malaria or translational studies on tuberculosis, viral haemorrhagic fevers and hepatitis. The site is strongly linked to the DZIF's African Partner Institutions through many cooperation projects.

HAMBURG - LÜBECK - BORSTEL - RIEMS

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

since February 2022: Prof. Dr Julian Schulze zur Wiesch (University Medical Center Hamburg-Eppendorf)

Institutions: Bernhard Nocht Institute for Tropical Medicine, Research Center Borstel – Leibniz Lung Center, Friedrich-Loeffler-Institute, Leibniz Institute of Virology, University of Hamburg, University Medical Center Hamburg-Eppendorf, Universität zu Lübeck

TTU Coordination:

- HIV (coordination)
- Malaria and Neglected Tropical Diseases (coordination)
- Emerging Infections (coordination)
- Tuberculosis (co-ordination)
- Healthcare-Associated and Antibiotic-Resistant Bacterial Infections (co-ordination)

TI Coordination:

- DZIF Academy (coordination)

HESSE

In **Gießen - Marburg - Langen**, emerging infectious agents are identified, new diagnostics and active agents are developed, and new active agents and vaccines are produced for scientific and industrial partners. The aim is to develop strategies to combat new or modified infectious diseases in order to be able to act quickly in the event of outbreaks of new infectious agents, e. g. through the development of vaccines. The focus in Marburg is on viral pathogens, in Gießen on bacteria and antibiotic resistance, and in Langen on research into novel vaccine concepts. The participating institutions contribute existing infrastructures such as the BSL-4 high-security laboratory in Marburg, the BSL-3 laboratory and animal facilities at the Paul Ehrlich Institute (PEI) in Langen and the Microbial Genome Research Center in Gießen. The PEI contributes to the rapid translation of research results into practice with its expertise in the field of drug approval and development. Accordingly, the PEI is home to the Office for Scientific and Regulatory Advice (OSRA) as part of the DZIF *Product Development Unit*.

GIESSEN - MARBURG - LANGEN

Spokesperson: Prof. Dr Stephan Becker (Philipps-Universität Marburg)

Institutions: Giessen University, Paul-Ehrlich-Institut – Federal Institute for Vaccines and Biomedicines, Philipps-Universität Marburg, Mittelhessen University of Applied Sciences

TTU Coordination:

- Emerging Infections (co-ordination)

TI Coordination:

- Product Development Unit (coordination)

LOWER SAXONY

Seven partner institutions cooperate in the DZIF at the **Hannover - Braunschweig** site. The research areas *Infections of the Immunocompromised Host* and *Novel Antibiotics* are coordinated from here. The scientists are involved in the establishment of a national transplant cohort and make a significant contribution with research projects on new therapies and diagnostic methods for infections with various herpes and hepatitis viruses as well as vaccine development against the hepatitis C virus. New approaches for effective treatment and control of resistant bacteria are also being pursued, and various molecular targets for active agents are being investigated. An important role is played by the identification and development of drug candidates with potential as antiviral agents or antibiotics.

HANNOVER - BRAUNSCHWEIG

Spokesperson: Prof. Dr Thomas Pietschmann (TWINCORE)

Institutions: Helmholtz Centre for Infection Research, Leibniz Institute DSMZ-German Collection of Microorganisms and Cell Cultures, Hannover Medical School, Robert Koch Institute, University of Veterinary Medicine Hannover, 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)

NORTH RHINE-WESTPHALIA

In **Bonn - Köln**, broad-spectrum antivirals are being developed in the DZIF research area *Emerging Infections*. New therapeutic approaches, active agents and diagnostic procedures are in focus of the research area *Healthcare-Associated and Antibiotic-Resistant Bacterial Infections*. In the research area *Infections in the Immuno-compromised Host*, the therapy of viral infections is a key subject. In the research area *Novel Antibiotics*, the antibiotic coralopyronin A is being advanced in cooperation with the Translational Project Management Office (TPMO) and the Federal Institute for Drugs and Medical Devices (BfArM). In HIV research, T cell and antibody immunity as well as treatment approaches are being taken into translation and the Translational Platform HIV is being supported. The TTU *Hepatitis* is working on predicting the therapeutic success of chronic HBV and HDV infections. The partner site also conducts research on multidrug-resistant tuberculosis pathogens and neglected tropical diseases. Other focus areas include SARS-CoV-2, the DZIF *Bioresources*, *Biodata* and *Digital Health* infrastructure and the VACCELERATE clinical network in the *Clinical Trial Unit*.

BONN - KÖLN

Spokesperson: Prof. Dr Oliver A. Cornely (University of Cologne)

Institutions: 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)
- Tuberculosis (co-coordination)
- Malaria and Neglected Tropical Diseases (co-coordination)

TI Coordination:

- Clinical Trial Unit (CTU) (coordination)

MEMBER INSTITUTIONS

Member institutions of the German Center for Infection Research

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

PUBLICATIONS

DZIF publications with a broad reach

From around 30 publications with DZIF affiliation in the first year after the founding of the DZIF and around 200 publications in 2014, the number of publications rose to almost 1,000 per year from 2021 onwards. At the end of the anniversary year 2022, there were a total of around 5,000 publications with DZIF affiliation. According to analyses based on the Web of Science platform, eleven DZIF researchers were among the most cited scientific authors in their field worldwide in 2022.

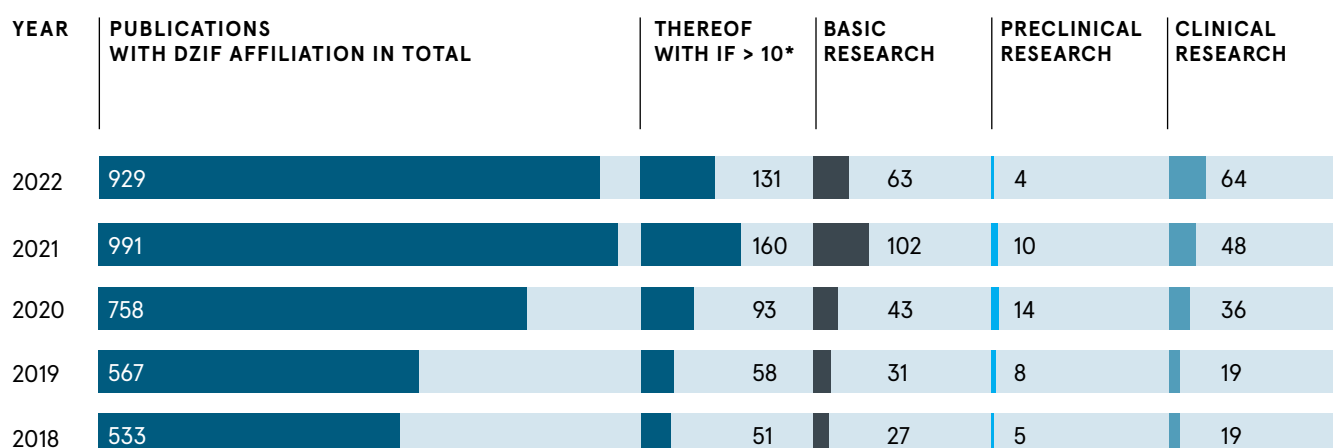
Publications allow researchers to access the results of others, to critically reflect on them and to incorporate them in their own research work. At the same time, published works are important for scientific reputation. Publications in renowned journals with a high impact factor (IF) are often used as an important measure of scientific success.

The IF is calculated as the ratio of the number of articles published in a journal to the number of citations in a defined period of time. An IF of at least ten is generally considered excellent.

Of the 929 publications in 2022 with DZIF affiliation, i. e. mention of the DZIF by at least one author, 170 had an IF > 10, including 39 journal articles classified as reviews.

Further information on the development of publication numbers over the last five years as well as on the shares of publications in the areas of basic, preclinical and clinical research are summarised in the diagram below.

The complete DZIF publication list for 2022 is available at: <http://bitly.ws/lhra>.



Graphical representation of the number of scientific publications with DZIF affiliation since 2018 (sources: PubMed, Scopus, and Web of Science). The publication numbers from the categories basic research, preclinical research and clinical research refer to publications with IF > 10. *Reviews are not included in the publications with IF > 10 in this diagram.

The DZIF in figures



FLEXFUNDS*

13 FlexFunds applications, including one FastTrack application for the implementation of Mpox measures.

6,143,257 total budget in euros. Corresponding to **15.96 %** of the annual DZIF budget

*funds available at short notice for translational projects



DZIF ACADEMY PROGRAMMES

04 Advanced Scientist programmes

16 Clinical Leave programmes

03 MD/PhD programmes

16 Maternity Leave programmes

76 MD Stipends

04 Lab Rotations

01 Travel Grant



WORKSHOPS AND SYMPOSIA

33



PUBLICATIONS WITH DZIF AFFILIATIONS

929

PUBLICATIONS WITH IMPACT FACTOR >10

170



CONFERENCE CONTRIBUTIONS

449



PRESS RELEASES/
NEWS

49



PATENTS

24



INDUSTRY
COLLABORATIONS

4



CLINICAL STUDIES

24



DATA- AND
BIOBANKS

27

PRECLINICAL
EFFICACY
STUDIES

26



COHORTS

49



WEBSITE VISITORS

761,697



SOCIAL MEDIA*

1,551 New followers

296,590 Impressions

292 Social media posts

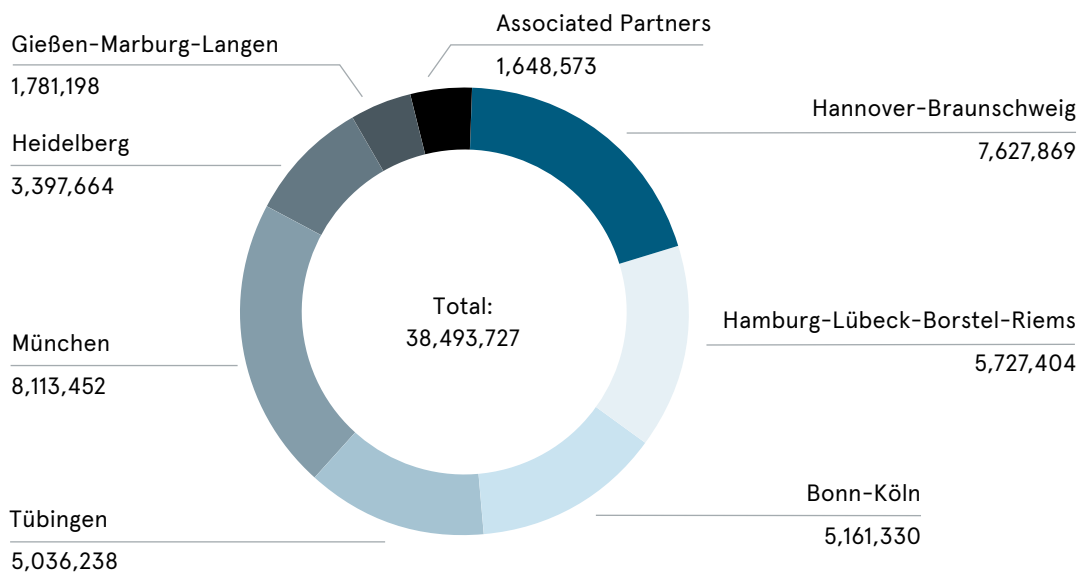
* Cumulative figures from the presences on Twitter and LinkedIn

FINANCES

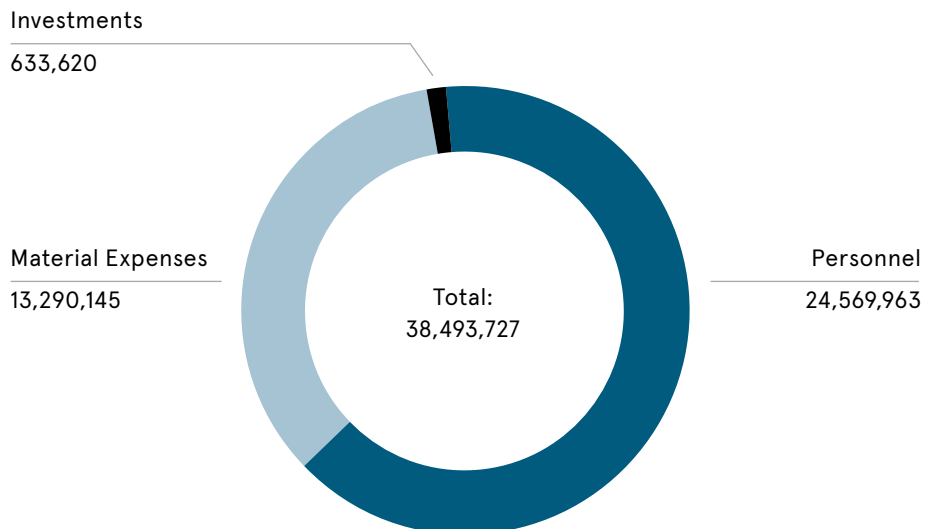
DZIF financial data 2022

REPORTED EXPENDITURE IN EUROS

BY PARTNER SITE



BY TYPE OF EXPENDITURE



BY FIELD OF WORK

FIELD OF WORK	Euro
Emerging Infections	3,350,405
Tuberculosis	2,275,068
Malaria and Neglected Tropical Diseases	2,915,938
HIV	2,379,296
Hepatitis	3,159,564
Gastrointestinal Infections	2,002,255
Infections of the Immunocompromised Host	5,393,960
Healthcare-Associated and Antibiotic-Resistant Bacterial Infections	4,337,365
Novel Antibiotics	4,158,804
Bioresources, Biodata and Digital Health	1,302,864
Clinical Trial Unit	350,550
Product Development Unit	907,233
DZIF Academy	2,254,274
Special measures for the development of antiviral therapeutics	498,835
Cross-DZG projects	110,700
Administration	3,096,617
Total	38,493,727

BY FUNDERS

FUNDER	Euro
Baden-Württemberg	871,159
Bavaria	828,229
Hamburg	384,097
Hesse	147,461
Lower Saxony	680,001
North Rhine-Westphalia	520,187
Schleswig-Holstein	192,377
Financial contributions from associated partners	164,857
Federal Government	34,705,360
Total	38,493,727

In 2022, the German Center for Infection Research's reported expenditure amounted to approximately 38.5 million Euros. 200 research projects, along with 120 projects of the DZIF Academy, were funded within DZIF in 2022. 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 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 2022 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. The calculated expenses for 2022 are preliminary and refer to the audit status as of 24.07.2023.

PERSONNEL AND AWARDS

Awards and honours 2022



MARCH

Bavarian Order of Merit

–
Prof. Michael Hoelscher,
Prof. Oliver Keppler,
Prof. Ulrike Protzer

–
*Ludwig-Maximilians-Universität
München; LMU University Hospital
Munich; Technical University
of Munich and Helmholtz
Munich*



MAY

Ernst Jung Prize for Medicine 2022

Honorary Doctorate of the University Medicine Mainz

–
Prof. Ralf Bartenschlager

–
*Heidelberg University
Hospital*



APRIL

Josef Adolf von Arx Award of the Westerdijk Fungal Biodiversity Institute, Netherlands

–
Prof. Marc Stadler

–
*Helmholtz Centre for Infection
Research,
Braunschweig*

MAY

Award for Clinical Research of the German Society of Pneumology and Respiratory Medicine (DGP)

–
Prof. Jan Heyckendorf
and Maja Reimann

–
*Research Center Borstel –
Leibniz Lung Center*



APRIL

Loeffler Frosch Prize of the Society of Virology e. V. (GfV)

–
Prof. Victor Corman

–
*Charité – Universitätsmedizin
Berlin*





SEPTEMBER

**Johann Lucas Schönlein
Plaque of the the German-
speaking Mycological Society**

–
Prof. Oliver A. Cornely
–
*University Hospital
Cologne*



JULY

**Emil von Behring Award of the
University of Marburg**

–
Prof. Andreas Peschel
–
University of Tübingen



NOVEMBER

**ERC Starting Grant of the
European Research Council
(ERC)**

–
Dr Victoria Ingham
–
*Heidelberg University
Hospital*



NOVEMBER

**Science Award of the German
Stifterverband ‚Research with
Responsibility‘**

–
Prof. Jörg Overmann
–
*Leibniz Institute DSMZ–German
Collection of Microorganisms
and Cell Cultures,
Braunschweig*



DECEMBER

**DZIF Prize for Translational
Infection Research 2022**

–
Prof. Gérard Krause
–
*Helmholtz Centre for Infection
Research,
Braunschweig*



DECEMBER

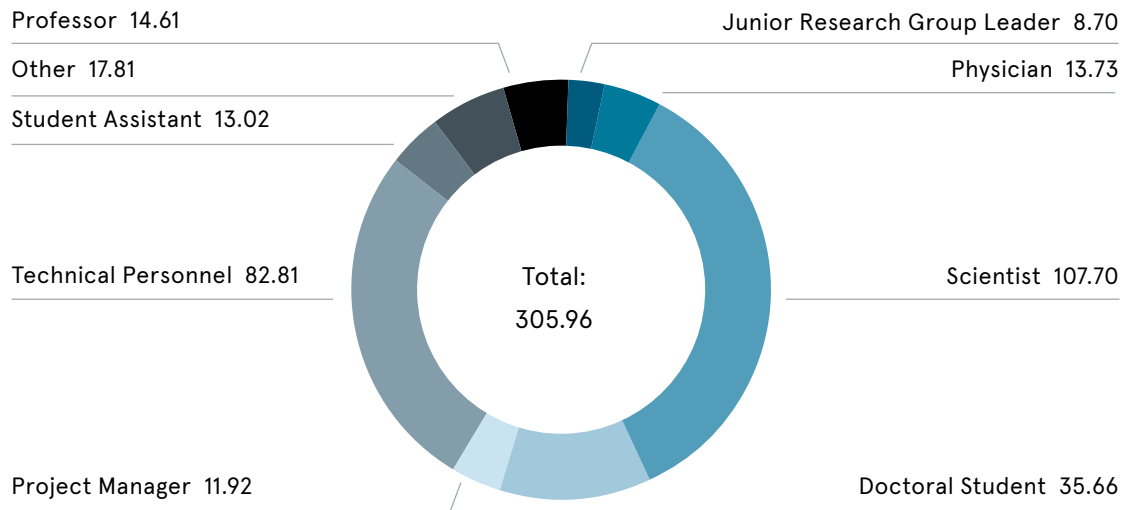
**2022 PHOENIX Pharmaceutical
Science Award in the category
Pharmaceutical Biology of the
PHOENIX group**

–
Prof. Harald Groß
–
University of Tübingen

PERSONNEL AND AWARDS

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	5	6	11
Physician	12	20	32
Scientist	80	138	218
Doctoral Student	29	43	72
Project Manager	6	25	31
Technical Personnel	39	152	191
Student Assistant	22	41	63
Other	7	23	30
Total	214	453	667

In 2022, the DZIF recruited five employees from abroad and assisted 11 mothers and fathers respectively on their return from parental leave—in addition to the 16 persons supported by the Maternity Leave Programme of the DZIF Academy.

IMPRINT

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