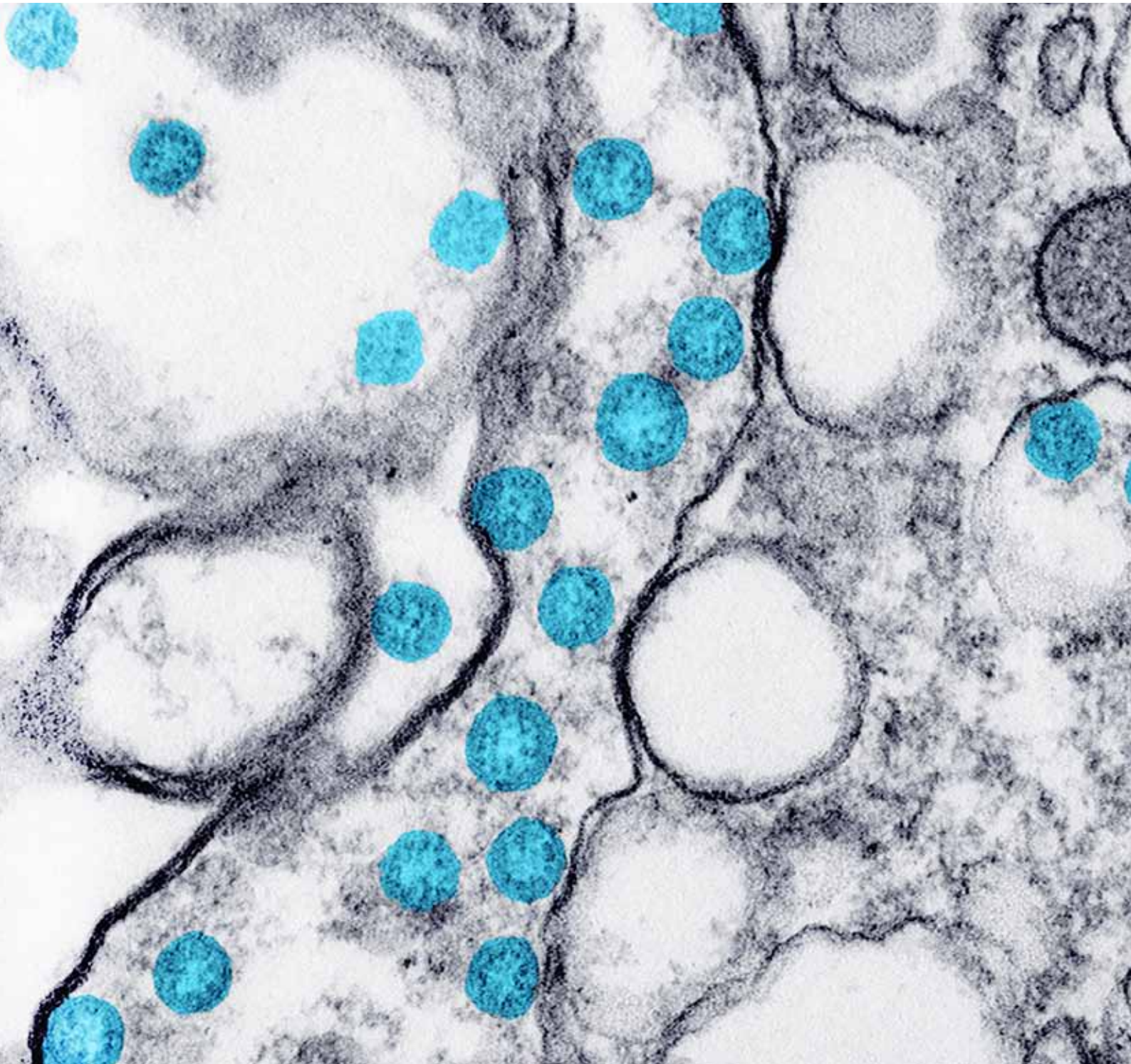
DZIF

DEUTSCHE ZENTREN DER GESUNDHEITSFORSCHUNG

GERMAN CENTER FOR INFECTION RESEARCH

Annual Report 2021



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Cover image: Since the beginning of the Corona pandemic, the DZIF has been working at full speed to contain and treat SARS-CoV-2/ COVID-19. The transmission electron microscope image on the cover shows an isolate from a person suffering from COVID-19. The spherical SARS-CoV-2 virus particles are coloured turquoise.

ANNUAL REPORT 2021

The DZIF at a glance

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

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Editorial

For the second year in a row, the topic of infectious diseases was the focus of public attention in 2021. For the DZIF this meant a continuation of the collective efforts initiated in 2020 to contain the COVID-19 pandemic at the national and international level. In addition to their research work, many researchers were also greatly involved in presenting knowledge and facts about the pandemic in a way that could be understood by the general public.

Many of the research projects launched within the space of a very short time in 2020 to gain a better understanding of the SARS-Coronavirus-2 as well as of the clinical effects of COVID-19-disease were continued at full speed in 2021. Several new projects were added. You can find a snapshot of the SARS-CoV-2/COVID-19 research activities undertaken in 2021 on pages 30 and 31 of this report.

Despite the additional pandemic-related tasks, the DZIF did not fail to keep sight of other infectiological challenges, such as for example increasing antibiotic resistance, hepatitis, tuberculosis or malaria (pages 6 to 23). Important progress was made for instance in the development of therapeutic agents against hepatitis B (page 14) as well as a new malaria vaccine (page 10). On page 9 you can read how a newly developed diagnostic technique could help to reduce by a third the duration and cost of treatment for tuberculosis patients. Using artificial intelligence, another research team is hoping to make a breakthrough in the treatment of onchocerciasis, also known as river blindness (page 11). And on pages 12 and 13, researchers track down the path of the human immunodeficiency virus (HIV) into the nucleus of certain immune cells.

2021 was record-breaking for the level of support given to DZIF scientists by the *Product Development Unit (PDU)* infrastructure: Never before did the *PDU* provide consultancy services to so many translational projects in one year. One of the areas of prime focus for these consultancy services was the further development of the DZIF vaccines against MERS and COVID-19 (page 27). With the newly established Advanced Clinician Scientist stipend, the *DZIF Academy* infrastructure expanded its programme to promote young scientific researchers (page 28).

The experiences gleaned since the outbreak of the pandemic show that infectious diseases can be effectively controlled only when working together and across national borders. In 2021, the DZIF continued to expand its research network and was involved in setting up new initiatives and collaborations. For example, the DZIF, among others, founded the European incubator INCATE to develop new technologies against multidrug-resistant bacteria. In collaboration with the Helmholtz Centre for Infection Research, it devised a concept to form a National Alliance for Pandemic Therapeutics (NA-PATH) geared at the development of broad-spectrum therapeutic agents against viral pathogens with pandemic potential. In the worldwide quest for novel, effective and affordable treatment strategies for tuberculosis, the DZIF is playing a pivotal role in the international UNITE4TB consortium.

In this annual report, you will of course again find all the important information on facts and figures from the past year at a glance. We wish you an interesting and entertaining read.

Yours sincerely, The DZIF Executive Board


Prof. D. Busch


Prof. H.-G. Kräusslich


Prof. M. Dandri


Prof. D. Heinz


Prof. A. Peschel

ABOUT THE DZIF

Pacesetter in infection research

The effects of the COVID-19 pandemic, which are still being felt today after more than two years, have shown what a central role infection research plays, especially in times of crisis. That still unknown viruses, such as recently SARS-CoV-2, emerge and spread to cause a pandemic is by no means a new phenomenon. Since its foundation in 2012, the more than 500 scientists from 35 member institutions and associated partners in the German Center for Infection Research (DZIF) have been working continuously together—and in new alliances—to be ever better prepared for a pandemic. However, the DZIF has not lost sight of the goal of rapid translation in other important areas either.

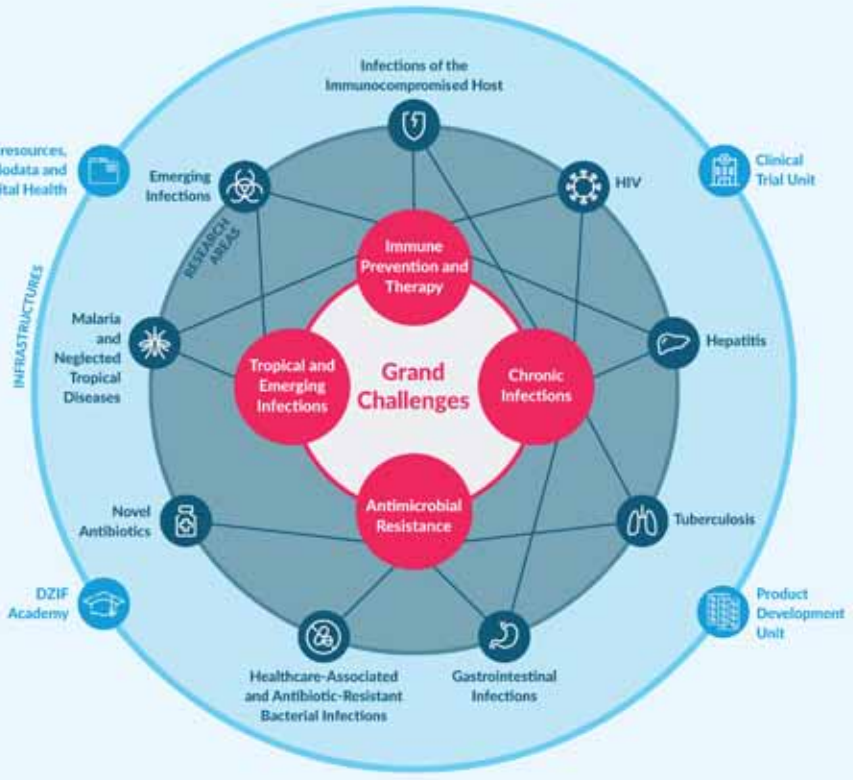
TRANSLATIONAL AND INTERDISCIPLINARY

The term "translation" is used to denote the effective transfer of the results of basic research to clinical application: Patients should be able to benefit as soon as possible from promising results of basic research in form of new drugs, vaccines or diagnostics. At the same time, experiences from patient treatments are taken up in basic research.

Our scientists engage in multi-institutional and interdisciplinary collaboration to drive forward translation and address the four major infectiological challenges of our time. These include antimicrobial resistance, chronic infections such as hepatitis, immune prevention and therapy as well as tropical and emerging infections such as COVID-19 (see figure). The DZIF's activities are strategically targeted at overcoming these grand challenges.

POOLING SYNERGIES: NINE RESEARCH AREAS ...

The DZIF pools projects in nine research areas, each of which focuses on one pathogen, one particular disease or one common topic within infection research. As of the beginning of 2021, the working group Neglected Tropical Diseases has been merged with the African Partner Institutions



Research at the DZIF focuses on the four grand infectiological challenges of our time: In nine research areas and four overarching infrastructures, the DZIF is working on new approaches to solutions and treatments for the major plagues of our time.

infrastructure and the research area Malaria to form the new research area *Malaria and Neglected Tropical Diseases*. This merger is intended to maximise synergies in order to develop a translational portfolio to combat malaria and neglected tropical diseases, such as for example river blindness (onchocerciasis), tailored to the health systems of low-income countries.

... AND FOUR INFRASTRUCTURES

DZIF researchers are supported by four translational infrastructures with their expertise. All DZIF scientists have access to these service areas. For example, they can seek advice from experts at the *Product Development Unit* on matters related to drug approval and clinical needs. The *Clinical Trial Unit* coordinates clinical infectiology studies and advises on all issues related to the design and content development of such studies.

Since 2021, the infrastructures Biobanking, Bioinformatics, Epidemiology and Pathogen Repository have been pooling their expertise in one large, overarching infrastructure: *Bioresources, Biodata and Digital Health*. The integration of these four infrastructures is intended as a means of achieving cross-cutting standardisation of biomedical data and interoperability of database systems. It provides improved access to relevant biomaterials, medical and analysis data as well as to digital tools and methods within the DZIF. This also takes into account the important aspect of digitalisation in infection research.

RECRUITING AND PROMOTING YOUNG RESEARCHERS

Infectiology was slow to evolve as a clinical discipline in Germany. With the *DZIF Academy* as its fourth infrastructure, the DZIF has since its foundation promoted young scientists and physicians to foster their enthusiasm for infection research and offer them long-term research perspectives: From MD stipends to support doctoral studies in the area of infection research to the stipends for Advanced Clinician Scientists announced for the first time in 2021—the DZIF is doing a lot to recruit young researchers and help them take the leap into independent research careers.

FORGING NEW ALLIANCES AND COOPERATING AT INTERNATIONAL LEVEL

Infectious diseases know no national borders. That was last impressively brought home to us by COVID-19. In the past 15 years alone, the World Health Organisation declared six infection-related global health emergencies. In order to be better prepared for pandemics, the DZIF in collaboration with the Helmholtz Centre for Infection Research formulated a concept in October 2021 for the creation of a National Alliance for Pandemic Therapeutics (NA-PATH). In doing so, we wish to boost research and development of broad-spectrum therapeutics to be better prepared for future outbreaks caused by viral pathogens with pandemic potential. The DZIF is also participating in the CEPI vaccine initiative for the development of protective measures against newly emerging infectious diseases.

As co-initiator of the UNITE4TB Consortium, the DZIF is accelerating research into the development of new treatment regimens for tuberculosis. The DZIF helped to set up INCATE, a European initiative to fight increasing antibiotic resistance. To develop drugs against antibiotic-resistant bacteria, the DZIF has also been involved as a partner in the CARB-X Global Accelerator Network. We engage in numerous other industrial and academic collaborations to meet the grand infectiological challenges of our time.

The DZIF pools together its activities in research areas and interdisciplinary infrastructures—internally referred to as Thematic Translational Units (TTUs) and Translational Infrastructures (TIs) (as of 2021):

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*

In January 2021, the former independent African Partner Institutions infrastructure was integrated into the expanded *Malaria and Neglected Tropical Diseases* research area and the Novel Antivirals infrastructure was integrated into the *Infections of the Immunocompromised Host* research area. The infrastructures Biobanking, Bioinformatics, Epidemiology and Pathogen Repository were merged to form one large, overarching infrastructure named *Bioresources, Biodata and Digital Health*.

EMERGING INFECTIONS

Looking ahead in the fight against new pathogens

Since 2020 the COVID-19 pandemic has held the world in check. But SARS-CoV-2 is just one of many pathogens that researchers must keep track of, if they want to be prepared in a timely and considered manner for new potential infectious diseases. Experts need to be familiar with the causative viruses and bacteria and also have in place comprehensive measures for rapid diagnosis and treatment in the event of an outbreak.

Berlin-based DZIF scientists investigated the genetic evolution of coronaviruses. Hamburg-based DZIF researchers launched a second vaccine trial of the MERS virus.

Examples from research

COVID-19 VACCINES MAY NOT NECESSARILY BE ADAPTED IN THE FUTURE

The SARS-CoV-2 pandemic continues, and most people in Germany have been vaccinated. But what happens next when immunity wanes? Must manufacturers update vaccines annually as in the case of, for example, influenza? Influenza viruses successfully evade the human immune system time and again through mutations. To investigate whether SARS-CoV-2 does something similar, virologists at the Charité – Universitätsmedizin Berlin and the DZIF compared the genetic evolution of influenza viruses with four species of coronaviruses that cause one in ten common colds worldwide.

"Up to the early 2000s, coronaviruses were considered harmless endemic viruses, hence there is a paucity of data," says Prof. Jan Felix Drexler, head of the Virus Epidemiology working group at the Charité Institute of Virology in Berlin. Comparison of the phylogenetic trees of corona- and influenza viruses revealed: "Indeed, coronaviruses evade the immune system similarly to the influenza virus—this is what we call antigenic drift," says the scientist. But influenza viruses mutate four times as fast; with regard to SARS-CoV-2, Drexler deems this a good sign. "If things turn out as we expect, SARS-CoV-2, too, will at some point only be seasonally active and become evolutionarily stable; then an annual adaptation of the vaccines may probably not be necessary," says the virologist. Besides, the cellular immune responses mediated by

Prof. Marylyn Addo (in the background DZIF junior group leader Dr Anahita Fathi) is heading the phase Ib trial to investigate the MVA-MERS-S vaccine.

the vaccines available in the meantime are much better than the currently available influenza vaccines. However, no one knows when the genetic evolution of SARS-CoV-2 will stabilise. "As long as the infection rates are still high worldwide, the virus will mutate more often and vaccines must continue to be adapted. This is confirmed by the currently circulating and rapidly evolving Omicron variant."

MERS VACCINE IN SECOND PHASE I STUDY

According to the World Health Organisation, the MERS (Middle East Respiratory Syndrome) coronavirus is especially dangerous due to its high case fatality rate of 30-40 percent. It occurs in particular on the Arabian Peninsula and causes severe respiratory tract infection. The virus—whose reservoir host is the dromedary camel—was first detected in humans in 2012.

"In addition to making important contributions to fighting COVID-19, our working groups in the research area Emerging Infections *also helped foster a better understanding of other viral diseases with epidemic potential, for example Lassa fever."*

Prof. Marylyn Addo, Hamburg

Coordinator

Fears about a global MERS pandemic did not materialise. To date, there are around 2,500 cases in 27 countries. MERS is currently not highly contagious, but one in three infected people dies. Those with chronic diseases are particularly at risk and can develop severe pneumonia and respiratory distress syndrome. To date, there is no drug or approved vaccine against MERS. The DZIF and IDT Biologika GmbH have been collaborating for several years now on the promising MVA-MERS-S vaccine candidate. Since May 2021, a randomised, double-blind phase Ib study with 145 participants is being conducted at the University Medical Center Hamburg-Eppendorf (UKE).

In addition to the safety and tolerability, the vaccine dose, optimal vaccination schedule and the immunogenicity are being investigated. "The results so far are very promising," says DZIF scientist Prof. Marylyn Addo, who heads the study. "We are happy that this further coronavirus vaccination trial can be carried out despite the special challenges posed by the COVID-19 pandemic and are grateful to the study participants for their extraordinary commitment." The head of the Infectious Diseases Division at UKE expects initial results and a decision on a subsequent phase II study at the end of 2022.

Dromedary camels (here: in Dubai) can spread the MERS virus to humans.

GOALS FOR 2021: OUTCOMES

● *Characterisation of optimised second generation measles virus (MeV) COVID-19 vaccine candidates.*

◐ *Implementation of the CoRoPa project "Monitoring of Norway (brown) rats and house mice at sites in southern and north-eastern Germany" and of the WBA-Zoo2 project "Phylogeographic analyses of West Nile virus infected birds from the 2020 season using next generation sequencing methods."*

● *Optimisation of alpha-ketoamides as broad-spectrum inhibitors of coronavirus and enterovirus replication.*

◐ *Goal partially achieved/Project is still ongoing*

● *Goal achieved*

GOALS FOR 2022

○ *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).*

You can find more information at

TUBERCULOSIS

Promising prospects for tuberculosis treatment

In 2021, tuberculosis was again the bacterial infectious disease that caused the most deaths worldwide. The number of new infections has remained stable at a high level with 10 million per year for a long time. But the intention was actually to eradicate tuberculosis by 2030.

DZIF researchers are leading the way as Europe takes up the fight against tuberculosis. They are searching for new and effective treatment regimens and biomarkers that can help to safely end tuberculosis treatment early.

Examples from research

FINDING NEW DRUG COMBINATIONS

Thirty partners, 13 countries, 185 million euros—these are the key data of the international research consortium "Academia and industry united innovation and treatment for tuberculosis (UNITE4TB)". The development partnership pools the tuberculosis expertise vested in academic institutions and pharmaceutical companies from across Europe. The goal: to quickly find effective drug combinations. "Regarding tuberculosis there is the major problem that the bacteria quickly become resistant even to new drugs," says Prof. Michael Hoelscher, director of the Division of Infectious Diseases and Tropical Medicine at the LMU University Hospital Munich and co-initiator of UNITE4TB. "We constantly need to search for novel effective regimens to avoid the emergence of extensively resistant tuberculosis bacteria from which up to 60 percent of patients die."

While partners from the pharmaceutical industry are contributing new drug candidates to the initiative, academic institutions are developing, for example, new biomarkers and study designs. "Both help us to make clinical trials more efficient

Prof. Michael Hoelscher collecting laboratory samples from a SARS-CoV-2 antibody study, which are stored in a biobank at -80°C.

and shorten product development that lasts many years," explains the coordinator of the DZIF *Tuberculosis* research area. Among the German project partners participating in the initiative are the DZIF and the LMU University Hospital Munich. In the past years they continued to develop BTZ-043, an antibiotic against tuberculosis discovered in Germany (see page 29). "With the support of UNITE4TB, we will be able to move forward with the further studies needed for early approval," says Hoelscher. The drug has already successfully passed early clinical tests.

BIOMARKERS FOR SUCCESSFUL TREATMENT OUTCOMES

Tuberculosis treatment is complex, expensive and has side effects. Because: Mycobacteria replicate only slowly; this protects the pathogen from drug attacks and necessitates the administration of several antibiotics. In the case of multidrug resistant tuberculosis the German guideline recommends an 18-month treatment course; a statistical empirical value to prevent recurrences. "We urgently need biomarkers that permit an individual treatment duration," says Prof. Christoph Lange, clinical director of the Research Center Borstel, Leibniz Lung Center. Not every patient needs to be treated for so long.

"The start of the world's largest clinical TB consortium UNITE4TB with the significant participation of the DZIF was a great success for us."

Prof. Michael Hoelscher, München
Coordinator

The Borstel researchers have now developed a diagnostic test, which determines the RNA of 22 genes in the blood. They code for inflammatory parameters, their activity correlates with the tuberculosis disease course. "If we identify a particular constellation of RNA in the blood, we can assume that the patient has been cured," stresses the infectious diseases clinician. First studies in patient cohorts have confirmed the stable predictive power of the marker. As a next step, the research team is planning with the support of UNITE4TB a comparative study: One half of patients will end treatment if the status of the new biomarker indicates this, while the other half will comply with the recommended treatment duration. Then the recurrence incidence will be explored. Lange is confident that the Borstel biomarker can shorten the treatment duration: "We estimate that, with the same efficacy, one third of the treatment duration and costs can be reduced and that there will be fewer side effects while on this treatment."

Prof. Christoph Lange examines a tuberculosis patient.

GOALS FOR 2021: OUTCOMES

- ● *Validation of pathogen biomarkers to guide treatment of multidrug-resistant tuberculosis patients.*
- ◐ *Identification of the mode of action of novel drug candidates with antituberculous activity as well as ex vivo/in vivo activity.*
- ◐ *Continuation of clinical evaluation of the DZIF's RNA signature (TB22) and of other biomarkers to predict the end of TB therapy as well as TB outcome.*

◐ *Goal partially achieved/Project is ongoing*
● *Goal achieved*

GOALS FOR 2022:

- ○ *Evaluation of biomarkers of the multicentre mEX-TB cohort comprising patients with extrapulmonary tuberculosis.*
- ○ *"Breaking down the wall": Determination of the penetration of antibiotics in centrally necrotising granulomas on immunomodulatory treatment.*
- ○ *Establishment of the optimal dose of BTZ-043 in combination with other TB drugs in patients.*

You can find more information at

MALARIA AND NEGLECTED TROPICAL DISEASES

New weapons in the fight against parasites

Parasites cause dangerous infectious diseases worldwide. In 2020 alone, there were an estimated 241 million malaria cases, of which 95 percent were in Africa. Besides, over 21 million people in Africa are infected with the filarial worm that causes river blindness. In both diseases, the causative parasites are transmitted to humans through bites of infected insect vectors.

DZIF scientists are working on new vaccines and effective measures to control the parasites.

Examples from research

LIVE MALARIA VACCINE WITH GOOD EFFICACY

Following a mosquito bite, the malaria parasite first goes to the liver and then to the red blood cells (erythrocytes), where it replicates. The infected erythrocytes then rupture, which is accompanied by high fever, bleeding, muscle and joint pain. No breakthrough has yet been made in vaccine research. Researchers at University Hospital Tübingen have now developed the PfSPZ-CVac vaccine, in collaboration with the US American biotech company Sanaria. Acting in the parasites' pre-erythrocytic stage, studies have demonstrated a 77 percent efficacy of the vaccine. "The live vaccine from attenuated infectious parasites is administered thrice in four weeks together with an antimalarial," says Prof. Peter Kremsner, director of the Institute for Tropical Medicine, Travel Medicine and Human Parasitology. "The immune system makes functional antibodies and the parasites are selectively killed even before they leave the liver." If immune protection is incomplete, the study participants are treated immediately. The study is a milestone in vaccine development, he says. "We are using here an infection model designed by us that is based on a standardised infection," states the professor. "The model makes it easy to test new potential vaccines in a small number of study subjects and quickly discard them if the results are insufficient." In the latest study, ten out of 13 vaccinated subjects were fully immune against infection. Kremsner is hoping for a first registration trial in one to two years.

Identification of a nodule with adult worms in a patient with onchocerciasis (river blindness) in Ghana. The worm nodules are palpable under the skin.

ARTIFICIAL INTELLIGENCE ANALYSES TREATMENT OUTCOME

River blindness results in blindness in one in ten infected people. The larvae of the threadworm (nematode) are transmitted through the blackfly bite to the subcutaneous tissues of humans and grow here in nodules to sexually mature adult worms. The adult female worm releases microfilariae that migrate via the lymphatic system to the eye, causing corneal inflammation. Therapy with current anthelmintic (worm) drugs is insufficient in that it could take until 2050 or even longer to eliminate this tropical disease, according to various modelling efforts. To eradicate the parasites in the future, parasitologists at University Hospital Bonn are therefore searching for more effective drugs that kill the microfilariae as well as the adult worms, of which three are undergoing trials in infected patients in Africa. "However, to rapidly analyse the efficacy of these drug candidates, we also need techniques that are able to analyse and evaluate potential active substances more quickly than before," says Prof. Achim Hörauf, director of the Institute for Medical Microbiology, Immunology and Parasitology at University Hospital Bonn.

"In the MULTIMAL clinical trial tested novel innovative malaria combination therapies demonstrated excellent treatment outcomes with a low rate of side effects."

Prof. Michael Ramharter, Hamburg
Coordinator

His team is working on optimising the analysis process with artificial intelligence (AI) and on automating the evaluation of histology specimens. This is because the manual analysis used hitherto is too time consuming and needs extensive experience. "While a human being needs 20 minutes to analyse a single specimen, a computer needs five seconds," says the scientist. The goal of the project is to use AI to expedite evaluation and, at the same time, develop an objective algorithm for analysis. For the automated analysis, the researchers draw on existing deep-learning models for object recognition. Using transfer learning, the AI system then learns to assess worms from microscopy images already evaluated in numerous clinical trials. Using AI, Hörauf hopes to significantly accelerate clinical trials of the active substances and bring them to approval more quickly, so that river blindness could be eradicated well before 2050.

The malaria vaccine PfSPZ-CVac is injected intravenously into a test subject.

GOALS FOR 2021: OUTCOMES

◐ *The Antimicrobial Resistance (AMR) Surveillance System at the African Partner Institutions will be further expanded and AMR baseline data from patient samples will be entered into an electronic database.*

◐ *Various methods for diagnosis of malaria, schistosomiasis and filariasis will be evaluated and compared in endemic areas.*

● *Patients participate in clinical trials of multi-drug combination therapies against malaria (MULTIMAL) to prevent the development of drug resistance.*

◐ *Goal partially achieved/Project is ongoing*
● *Goal achieved*

GOALS FOR 2022

○ *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.*

You can find more information at

HIV

Gaining a better understanding of the biology of HIV in host cells

By 2030, the AIDS epidemic should no longer be a global health threat, demand the United Nations. A laudable goal. In 2020 alone, 680,000 people worldwide died as a result of infection with the human immunodeficiency virus (HIV). In Germany, there are currently 90,000 HIV-positive persons.

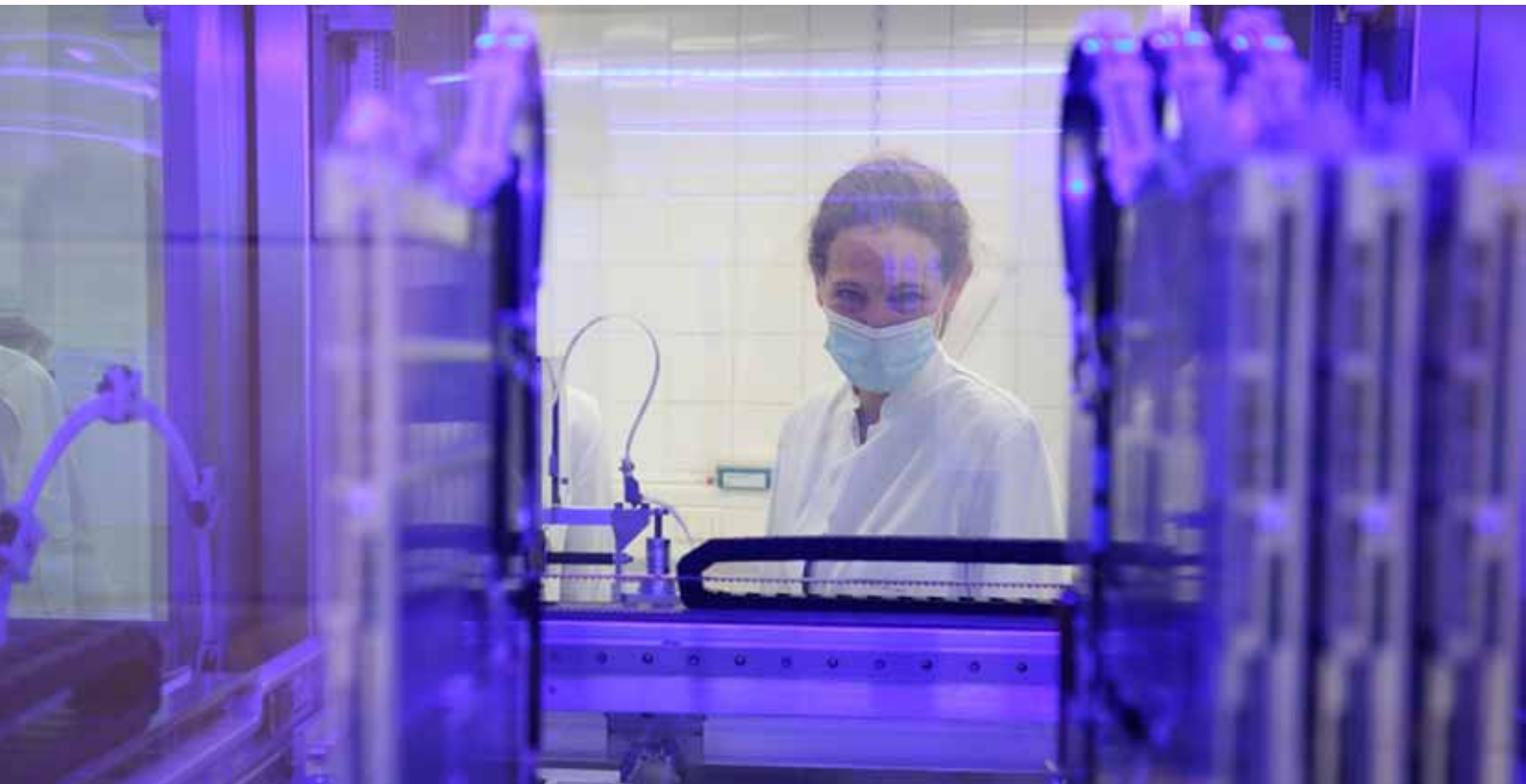
In the fight against the immunodeficiency disease, DZIF researchers are particularly interested in CD4-positive (CD4+) T-cells, the most important target cells for HIV in infected people.

Examples from research

HIV ENTERS THE CELL NUCLEUS WITH THE HELP OF ITS PROTEIN ENVELOPE

One of the key functions of CD4+ T-cells is to direct other cells of the immune system in the defence against pathogens. HIV infection disrupts this vital function in that the virus destroys the CD4+ T-cells. The fewer T-helper cells, the less well the immune system is able to protect the body against disease. In HIV infection the virus enters the cell and then inserts its genetic material into the nucleus, where it replicates. Until now it was unclear at what point the virus sheds its protective protein envelope, known as the capsid. Now for the first time, using light and electron microscopy, researchers at Heidelberg University were able to track the path of the virus into the nucleus. “The entire HIV capsid enters the nucleus. Only then does it disintegrate into protein envelope and genetic material, releasing the viral genome,” explains DZIF researcher Prof. Hans-Georg Kräusslich, medical director of the Department of Infectious Diseases at Heidelberg University Hospital. Until now it was assumed that the virus sheds its protein envelope before passing through the nuclear membrane. “The assumption was that the capsid was not able to fit through the membrane pores,” says the virologist. With the new insights into the pathway of the virus into the nucleus, as published in the journal *Cell*, researchers are now hoping for new approaches for future treatments. To date, antiviral therapies are only able to prevent

The interaction between HIV and the host cells is being investigated at the Max von Pettenkofer-Institute of LMU Munich.



the virus from replicating inside the body but not to completely eliminate the virus. “Thanks to our microscopy images we have discovered a new piece of the HIV infection jigsaw, which may provide approaches for new target molecules.”

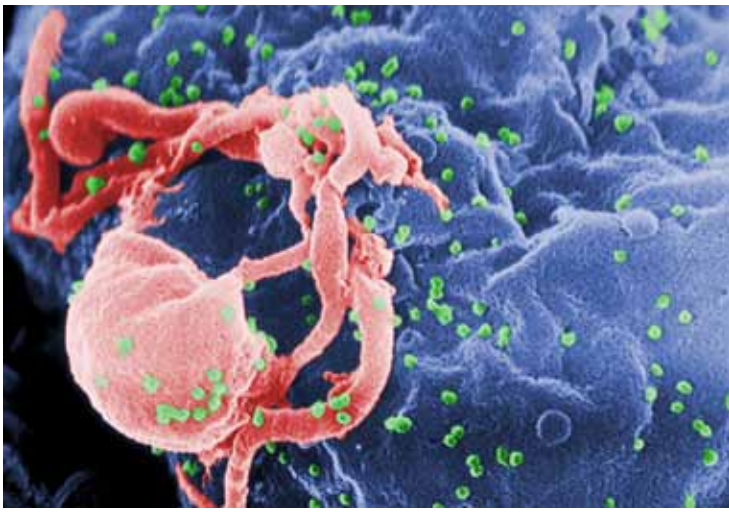
TRACKING DOWN HIV IN QUIESCENT CD4+ T-CELLS

Likewise, the working group led by Prof. Oliver Keppler at the Max von Pettenkofer-Institute for Hygiene and Medical Microbiology of the Ludwig-Maximilians-Universität (LMU) Munich focuses on CD4+ T-cells. Latently infected quiescent CD4+ T-cells constitute a “silent” virus reservoir. The virus evades the defence mechanisms of the immune system because in most cases it does not express any viral antigens. Until now it was not possible to selectively “wake” these dormant cells, so that they can be detected by the immune system and destroyed, or targeted by conventional antiviral treatments. Collaborating with Prof. Oliver Fackler from the Centre for Integrative Infectious Disease Research at Heidelberg University Hospital, Keppler has now managed for the first time to genetically manipulate quiescent CD4+ T-cells under physiological conditions and also gain a better understanding of how the virus interacts with these specific host cells. DZIF researchers have reported on the new technology in the journal *Nature Methods*.

“In 2021, we were particularly pleased by the achievements of Dr Dr Angelique Hölzemer and Dr Dr Ulrike Lange, both of whom were awarded highly competitive funding for HIV research by the German Federal Ministry of Education and Research (BMBF).”

Prof. Marcus Altfeld, Hamburg
Coordinator

“Using what is known as nucleofection, we introduced the CRISPR-Cas gene scissors tool into the cells and in this way were able to simultaneously knock out up to six different genes,” explains virologist Keppler. At the same time, the scientists incorporated new genes into the cellular genome in a targeted manner. “With this technique we were able for the first time to genetically investigate the biology of HIV in these quiescent CD4+ T-cells and thus characterise basic mechanisms of infection, latency and reactivation,” Keppler says. This better understanding could possibly lead to the development of new approaches for completely eliminating HIV from the body in the future.



Scanning electron microscopy image of HIV virions (green) on the surface of a white blood cell (red).

GOALS FOR 2021: OUTCOMES

- *Expansion of the cooperation with the French ANRS RHIVIERA consortium in the HIV-1 cure field.*
- *Development of synergies within the three main HIV research fields, focusing on immune control of HIV-1, the HIV reservoir and the clinical cohorts in HIV research.*
- *Characterisation of the role of Fc gamma receptor-mediated trogocytosis—a mechanism that facilitates HIV-1 infection of quiescent CD4+ T-cells.*

◐ *Goal partially achieved/Project is ongoing*
● *Goal achieved*

GOALS FOR 2022

○ *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.*

You can find more information at

HEPATITIS

New strategies for a cure

About 257 million people worldwide are chronically infected with the hepatitis B virus (HBV). Whether and when severe consequences such as liver cirrhosis or liver cancer develop depends on many individual factors. So far, infection is suppressed with antiviral therapy. The aim for the future is to find a cure for patients using novel therapeutics.

DZIF researchers are searching for new biomarkers and specific antibodies to make hepatitis B therapies more effective on an individual basis.

Examples from research

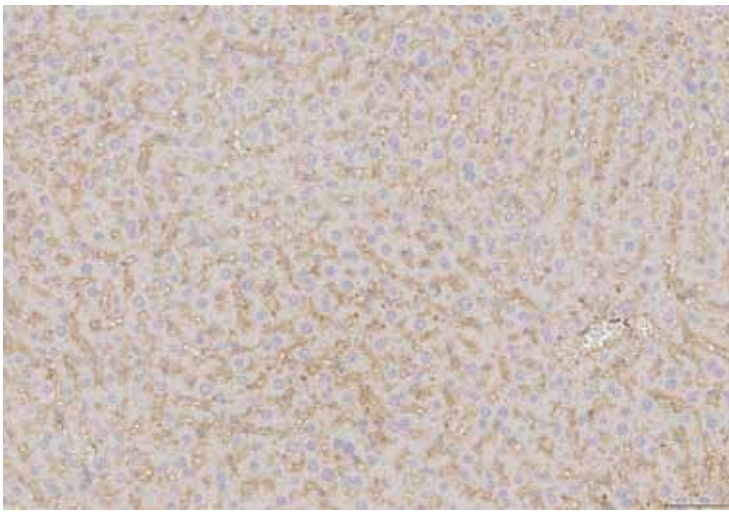
WHO BENEFITS FROM IMMUNOTHERAPY?

It is hoped that various potential immunotherapeutics will cure HBV infection in the future. "To assess their efficacy, we need biomarkers that show which patients will particularly benefit," says Prof. Markus Cornberg, deputy director of the Department of Gastroenterology, Hepatology and Endocrinology at Hannover Medical School. For example, cytotoxic T-cells and T-helper cells correlate with successful treatment outcomes. T-cells are continuously activated in patients with chronic infection, leading to T-cell exhaustion in the long term. Moreover, infected hepatocytes produce the HBsAg antigen (hepatitis B surface antigen). Until now it was assumed that high HBsAg levels were associated with a poor T-cell immune response. "We now demonstrate that the T-cell response is associated not only with the HBsAg blood levels, but tends to be more influenced by the patients' age," says the deputy coordinator of the DZIF's *Hepatitis* research area. This means: The older the patients, the poorer the immune response. "Younger people would therefore be more likely to benefit from immunotherapy," is how the scientist sums this up. Besides, T-cell response was better in infected persons with low HBcrAg (hepatitis B core-related antigen) blood levels. "The study showed for the first time that the HBcrAg virus marker could be an interesting alternative to HBsAg, in order to stratify patients for future studies," Cornberg states.

Prof. Ulrike Protzer is confident that specific antibodies could be used in the future to treat chronic viral hepatitis as well as HBV-associated liver cancer.

NEW ACTIVE SUBSTANCE CANDIDATE BOOSTS THE IMMUNE RESPONSE

Chronic HBV infection weakens patient immunity in the long term. The virus can thus persist in the body and after years lead to hepatocellular carcinoma. Experts are developing various new therapies to stop this process and eliminate the virus. Researchers at the Technical University of Munich (TUM) are trying, for example, to restore antiviral T-cell immunity in infected patients with bispecific antibodies. Clinical studies on these molecules have so far been conducted mainly in the case of cancer. "For the first time we are now using bispecific antibodies in human cell cultures and in a murine model also against infectious diseases," says Dr Oliver Quitt from the Institute of Virology at TUM. "We were able to demonstrate that so-called T-cell engager antibodies bind specifically to viral envelope proteins on the surface of infected cells and, at the same time, activate T-cells, and this both in HBV-infected hepatocytes and HBV-induced tumour cells," the postdoc says.



Immunohistochemistry staining showing the in vivo binding of T-cell engager antibodies (in beige) to hepatocytes expressing HBV-envelope proteins (grey with blue nuclei) in the liver of an HBV-transgenic mouse.

"Our greatest success in 2021 was the takeover by the US pharmaceutical group Gilead Sciences of the virus entry inhibitor Hepcludex (bulevirtide) developed by Prof. Stephan Urban within the Hepatitis *research area."*

Prof. Ulrike Protzer, München
Coordinator

The activated T-cells recognise and kill the cells and the virus is successfully eliminated. Therefore, specific antibodies could prove to be interesting active substances in future for the treatment of chronic viral hepatitis and also HBV-associated liver cancer. The initial results of the joint follow-up studies in the laboratories headed by Prof. Maura Dandri and Prof. Ulrike Protzer are likewise very promising. "Our T-cell engager antibodies are able to restore immunity," Quitt states. He is hoping for first clinical studies in three to four years, in collaboration with the biotechnology company SCG Cell Therapy.

GOALS FOR 2021: OUTCOMES

- ● *Development of bidirectional antibodies to direct T-cells to HBV-infected cells and eliminate them.*
- ● *Development of a point-of-care test for detection of infection with HDV.*
- ● *Identification and preclinical testing of therapeutic strategies affecting the in vivo activity of HBV-cccDNA.*

◐ *Goal partially achieved/Project is ongoing*
● *Goal achieved*

GOALS FOR 2022

- ○ *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 to better understand the efficacy and mechanism of action.*

You can find more information at

GASTROINTESTINAL INFECTIONS

Preventing gastrointestinal infections with microbiota

Around 100 billion microorganisms colonise the human gut—a gigantic treasure. The composition of the microbiota plays a role, for example, in obesity, type 2 diabetes and heart attack, and is a chief determinant of whether someone is more susceptible to pathogenic intestinal microbes.

Older and weakened patients, in particular, become infected with pathogenic intestinal microbes while in hospital. DZIF researchers understand now ever better how the intestinal microbiota can protect us against difficult-to-treat and resistant intestinal microbes.

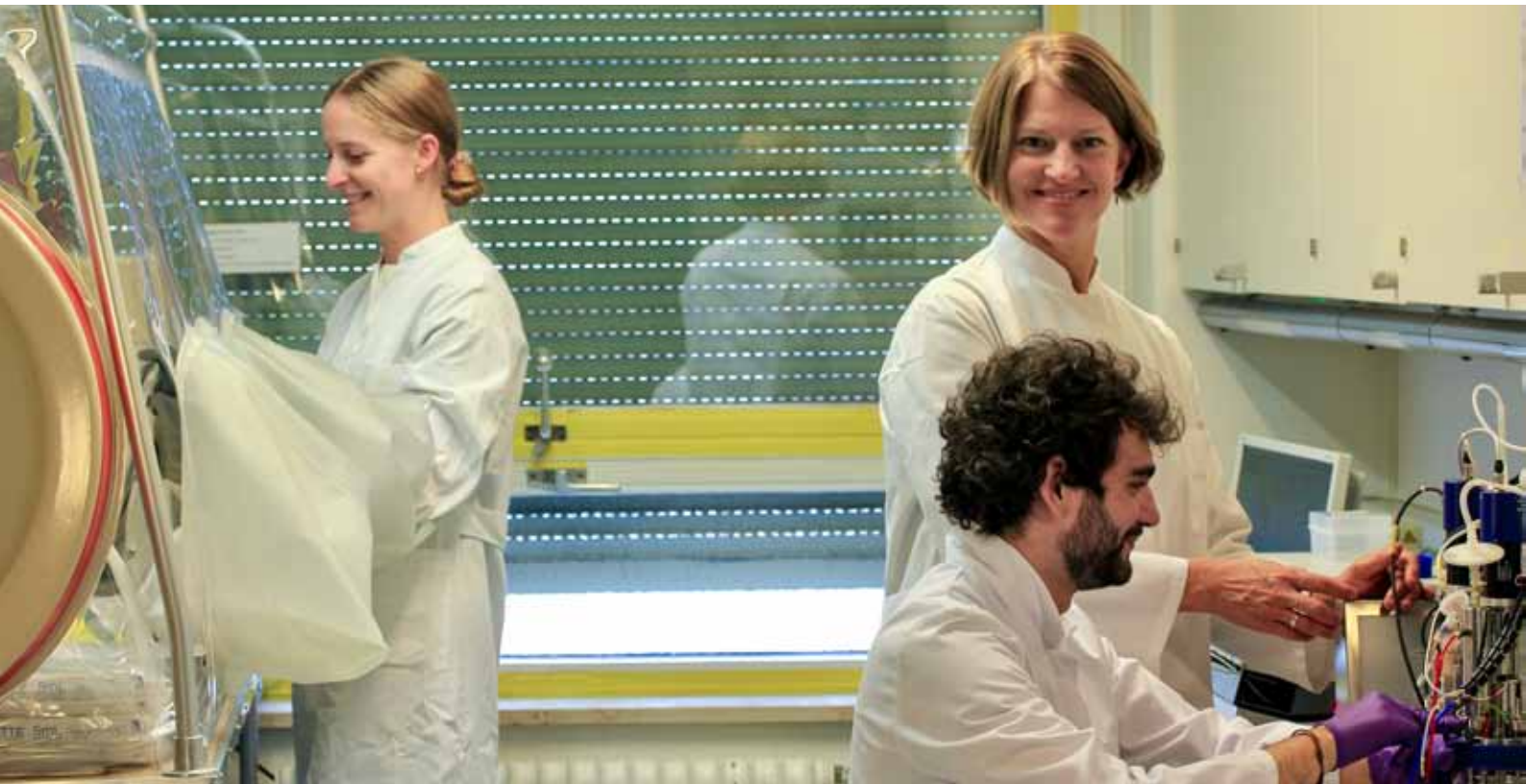
Examples from research

GOOD INTESTINAL MICROBES STARVE THE BAD MICROBES

The intestinal microbiota is able to keep pathogenic microbes in check. The bacterium *Klebsiella oxytoca*, for example, can displace the hospital pathogen *Klebsiella pneumoniae*, which causes pneumonia, urinary tract infections and sepsis. How is that possible? Both Klebsiella species use similar sugars as nutrition. The "good" *Klebsiella* species snatches away the sugar from the "bad" ones. "*Klebsiella oxytoca* displaces *Klebsiella pneumoniae* by starving it," says DZIF scientist Prof. Till Strowig from the Helmholtz Centre for Infection Research in Braunschweig. To demonstrate that, the researchers incubated stool samples with *K. pneumoniae*. The pathogenic bacterial species grew less well when the stool also contained many benign *Klebsiella* species. Conversely, in the mouse model it was demonstrated that the addition of *K. oxytoca* made the rodents less susceptible to the hospital pathogen. "The intestinal microbiome regenerates faster as a result," says Strowig.

The situation is similar with *Escherichia coli*: pathogenic strains contaminate drinking water and cause infections. Other strains have a beneficial effect in that they protect us, for example, against *Salmonella*. Prof. Bärbel Stecher and her team from the Max von Pettenkofer Institute at Ludwig-Maximilians-

Prof. Bärbel Stecher (right) and her team develop microbiome-based therapeutic strategies against gastrointestinal infections.



Universität München discovered that the protective *E. coli* consume the sugar needed by the *Salmonella* to survive. How well *E. coli* does this depends on the composition of the other bacteria in the gut: "If Lachnospiraceae, which also metabolise simple sugars, were present, *E. coli* is protective, otherwise not," says the microbiologist. This also has implications for treatment: Depending on the intestinal colonisation, probiotics help, or they don't. "Therefore, an effective cocktail should always contain more than one bacterial species."

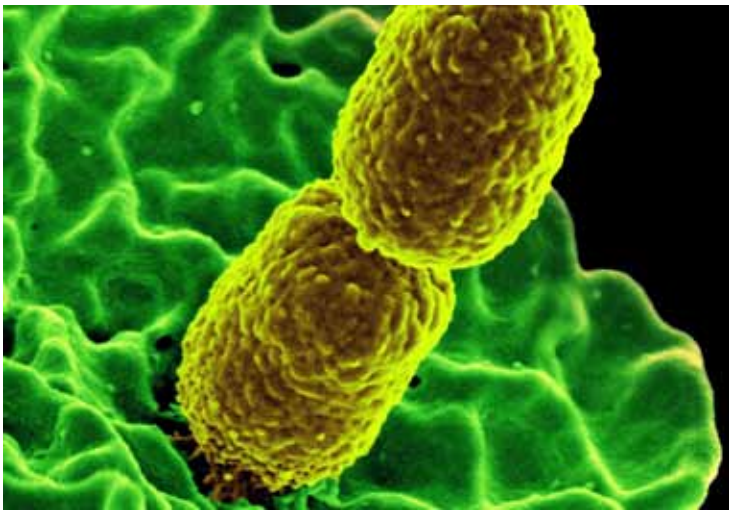
INTESTINAL MICROBIOTA PROTECT AGAINST CLOSTRIDIA INFECTION

Depending on its composition, the intestinal microbiome can prevent infection with *Clostridioides difficile*, as demonstrated by DZIF researchers in a prospective study published in 2021 in the journal *Clinical Infectious Diseases*. In most cases, *C. difficile* is harmless. If the bacterium is growing because, for example, antibiotics have displaced the good microbiota, *C. difficile* can produce toxins, causing intestinal inflammation and severe diarrhoea. "Several studies have shown that faecal transplant once or twice can effectively treat recurrent *C. difficile* infection, with few side effects," says Prof. Oliver Bachmann,

"The publication of the study on the efficacy of Klebsiella oxytoca *as a probiotic in an animal model and the international patent filing were a great success for us."*

Prof. Bärbel Stecher, München
Coordinator

chief physician Internal Medicine at Siloah St. Trudpert Hospital in Pforzheim, who until the end of 2018 was senior physician and DZIF scientist at Hannover Medical School and is one of the lead authors of the study. To understand, which microbes protect against Clostridia, scientists of the DZIF *Gastrointestinal Infections* and *Healthcare-Associated and Antibiotic-Resistant Bacterial Infections* research areas, under the direction of Prof. Bachmann and Prof. Sebastian Suerbaum from the Max von Pettenkofer Institute at Ludwig-Maximilians-Universität München, investigated stool samples from 1,500 patients. "We found *Gemmiger* spp., *Odoribacter splanchnicus, Ruminococcus bromii* and other *Ruminococcus* spp. to be protective factors," states Prof. Suerbaum. In the future it may be possible to prevent *C. difficile* infection by giving high risk persons specific mixtures of intestinal microbiota, for example, when administering a broad spectrum antibiotic.



The intestinal resident Klebsiella pneumoniae *can cause severe pneumonia, urinary tract infections or even sepsis in debilitated individuals.*

GOALS FOR 2021: OUTCOMES

◐ *Expansion of the HelicoPTER trial to at least two additional trial centres outside München.*

◐ *Filing of another patent from the Pathoblocker Development project area.*

● *Completion of the trial protocol for characterisation of human tissue samples for the potentially protective commensal bacterium* Mucispirillum *spp. and granting of the ethics vote.*

◐ *Goal partially achieved/Project is ongoing*
● *Goal achieved*

GOALS FOR 2022

○ *Recruit at least 2,000 patients in the HelicoPTER study.*

○ *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.*

You can find more information at

HEALTHCARE-ASSOCIATED AND ANTIBIOTIC-RESISTANT BACTERIAL INFECTIONS

New strategies to fight sepsis

Bloodstream infections are life threatening diseases and account for 150,000 deaths each year. Since infections are often severe despite effective antibiotics, new approaches are needed for a better understanding, earlier diagnosis and more effective treatment of sepsis.

DZIF researchers are devising new strategies to boost the immune system to fight sepsis and are developing the first prognostic score for long-term risk patients.

Examples from research

STRENGTHENED IMMUNE DEFENCES AGAINST SEPSIS

Sometimes septicaemia (blood poisoning) is mild, sometimes fatal. The reasons for this remain unclear. Researchers at University Hospital Tübingen have come one step closer to an answer. Using cell cultures and a murine model, the infection biology team has discovered a new therapeutic strategy, which relies on a strengthened immune response instead of antibiotics. Mice were given acetate (in the form of sodium acetate), whereupon marked alleviation of sepsis caused by the bacterium *Staphylococcus aureus* was observed. "We were surprised how dramatic the effects are: we found that the immune response had increased by several orders of magnitude in the mice that had been given acetate," says the institute head Prof. Andreas Peschel. What is the exact role of the short chain fatty acid acetate? It is known that during digestion, bacteria of the intestinal microbiome produce acetate in different concentrations, depending on nutrition and genetics. Acetate is also produced by staphylococci. In the event of infection, the short chain fatty acid in the bloodstream then activates the so-called GPR43 receptor on white blood cells, enabling the immune cells to effectively fight the bacterial infection.

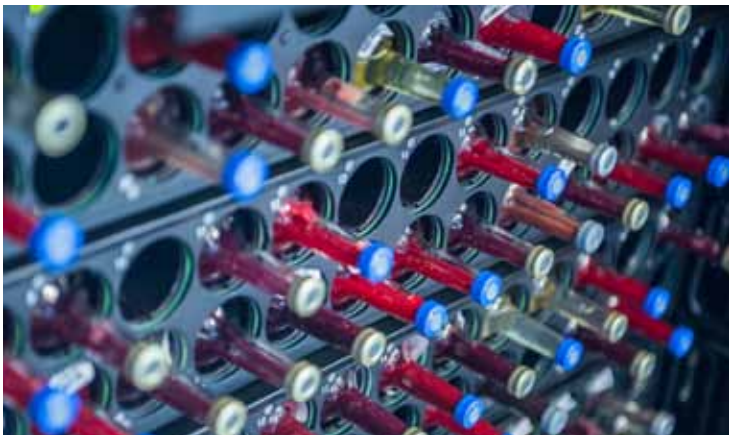
"Acetate may be a booster that activates the immune cells and puts them on alert," says the scientist. "It is possible that people who have many, nutritionally mediated, activated GPR43 receptors experience milder sepsis, while conversely those with fewer activated receptors are more likely to die."

Culturing multidrug-resistant Escherichia coli *bacteria on a selective agar plate.*

The researchers have already been able to impressively demonstrate this in mice. “With optimised acetate blood levels, the immune system was able to effectively kill staphylococci more quickly and the mice no longer died from sepsis,” says Peschel. It is conceivable that in the future, acetate will be administered as a sepsis prophylaxis.

NEW SCORE IDENTIFIES LONG-TERM RISK

Based on European data, over five percent of all hospitalised patients contract a bloodstream infection during their hospital stay. The associated mortality rate is high, not only in the short term, but the body of evidence supporting longterm effects on mortality even months after discharge is constantly growing.



Blood culture bottles in an automated blood culture system. Blood cultures are used to detect bloodstream infections.

“Our projects give scientists from a broad range of disciplines the opportunity to develop joint strategies against multidrug-resistant pathogens.”

Prof. Maria Vehreschild, Köln
Coordinator

The mortality risk during sepsis or bloodstream infection is estimated using risk scores. However, all established prediction models are tailored specifically to certain microorganisms, exclusively on intensive care patients, or they predict only short-term mortality risks. Tübingen researchers led by Prof. Eva Tacconelli have now devised two prognostic scores that help to estimate the risk for all patients (in both standard wards and the intensive care unit and regardless of the causative organism) in the first 14 days of hospital admission and beyond. “Older data demonstrate that many persons affected have a higher mortality risk even after overcoming a bloodstream infection compared with patients who did not experience infection,” says Dr Siri Göpel, head of clinical infectiology at the University of Tübingen. The prediction model was developed with the help of a prospective, multicentre cohort study with around 2,500 patients. The evaluation results of relevant prognostic parameters, such as age, malignant pre-existing diseases, microorganism species and number as well as the platelet and leucocyte counts, were converted into scores and then combined into two clinical scores. The study showed that, already in the early stages of infection, the models can be used to make accurate predictions of the mortality risk at 14 days and six months.

GOALS FOR 2021: OUTCOMES

- *Development of a new project in collaboration with the* Bioresources, Biodata and Digital Health *infrastructure to identify lytic phages for treatment of vancomycin-resistant enterobacterial infections.*
- *Enrolment of the first patients in the recently launched TIARA cohort (The Impact of Colonisation and Infection with MDRO in a Cohort of Complex Surgical Patients).*
- *Establishment of a DZIF-wide culturomics platform with which the dynamics of microbial communities can be analysed after co-cultivation.*
- *Establishment of an overarching “DZIF Bacteriophage Task Force”.*

◐ *Goal partially achieved/Project is ongoing*
● *Goal achieved*

GOALS FOR 2022

○ *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 for microbiota-based decolonisation in collaboration with the* Gastrointestinal Infections *research area.*

○ *Conduct of a national workshop on implementation of phage therapy in Germany.*

You can find more information at

INFECTIONS OF THE IMMUNOCOMPROMISED HOST

With expertise for the immunocompromised

It is not just during the pandemic that people with a compromised immune system are at an increased risk. Viruses that are mostly harmless to healthy individuals hit them hard too. Often they cannot be vaccinated either. This makes innovative therapies that focus on infections in the immunocompromised host all the more important.

DZIF researchers identify new antibodies to treat COVID-19 in immunocompromised patients and investigate hitherto unclear links between transplantation and infections.

Examples from research

VIRUS VARIANTS CALL FOR NEW ULTRAPOTENT ANTIBODIES

COVID-19 disease can be effectively treated with neutralising monoclonal antibodies (nMAbs), in particular in the early phase. Furthermore, nMAbs protect immunocompromised kidney or cancer patients who have no, or ineffective, antibodies. However, as the number of virus variants rises, currently available nMAbs are becoming increasingly less effective. "Following SARS-CoV-1, MERS and SARS-CoV-2, there is likely to be another coronavirus outbreak at some point in the future," says Prof. Florian Klein, director of the Institute of Virology at University Hospital Cologne. "The research goal is therefore to discover new ultrapotent antibodies that are effective against as many SARS-CoV-2 variants and SARS-CoV-2-related coronaviruses as possible." In a recent study with 963 COVID-19 convalescent individuals, the team led by the virologist identified ten people whose immune system exhibited a particularly potent antibody response to SARS-Coronavirus-2. "In these elite neutralisers we carried out single B cell analysis and discovered antibodies that effectively neutralised all virus variants tested, even with low activity," says Klein. The next step is to use these nMAbs in the clinical setting.

Similar research is being conducted by Prof. Thomas Schulz at the Institute of Virology at Hannover Medical School. "Our task is to find solutions for immunocompromised patients," states the director of the Institute. "Even though the situation is very complex

Dr Saskia Stein from Prof. Thomas Schulz's research group developing a new inhibitor of Kaposi's sarcoma-associated herpesvirus.

because of the pandemic and industry is currently cautious, there is a high demand for broadly effective antibodies. There is a need to prepare for the next coronavirus outbreak," he says.

OVERARCHING COHORT IMPROVES SITUATION FOR TRANSPLANT RECIPIENTS

Following organ or stem cell transplantation, patients must take immunosuppressants for their entire life to prevent their body from rejecting the transplanted organ. More than 3,500 organ transplants and 7,000 stem cell transplants are carried out in Germany each year. However, the weakened immune system increases the risk of serious infections in transplant recipients. Every second death after a transplantation is due to infection. The DZIF therefore established the so-called DZIF Transplant Cohort back in 2014. Meanwhile, more than 2,000 patients are registered in the database and more than 27,200 blood samples and 8,500 other samples such as urine or stool have been collected.

The DZIF Transplant Cohort provides comprehensive medical data and biological samples from transplanted patients for research.

"Prof. Martin Messerle and Prof. Mark Brönstrup developed small-molecule inhibitors of cytomegalovirus with nanomolecular activity that disrupt viral genome packaging."

Prof. Thomas Schulz, Hannover
Coordinator

In 2021 the team led by Dr Daniela Schindler published a first study describing the set-up and specific goals of the DZIF Transplant Cohort. Another study with authors from all cohort sites reporting on the incidence of infections in kidney transplant cohort patients was published in 2022 and further studies are underway.

"By cooperating with several large transplant centres, we are growing an overarching robust dataset that can help to identify any causal links between transplantation, pre-existing illnesses, medication, and infections and complications, and verify them in follow-up studies," says Schindler, the coordinator of the transplant cohort who conducts research at the Klinikum rechts der Isar of the Technical University of Munich. "The better we understand the relationship between transplantation and infections, the sooner we can identify risk patients and improve prevention, diagnosis and treatment." The goal of those involved is to enrol 3,500 patients in the cohort by 2023 and follow them up until at least 2025.

GOALS FOR 2021: OUTCOMES

◐ *Start with in vivo trials of new antiviral inhibitors in an animal model.*

● *Continue patient recruitment in the DZIF Transplant Cohort.*

● *Publications from the "Biomarkers" and "New antiviral therapies" research themes.*

◐ *Goal partially achieved/Project is ongoing*
● *Goal achieved*

GOALS FOR 2022

○ *First animal study with inhibitor of Kaposi's sarcoma-associated herpesvirus (KSHV).*

○ *Submission of patent application for new inhibitor of human cytomegalovirus (HCMV).*

○ *Definition of a GMP-conform manufacturing protocol for OTR (orthotopic T-cell receptor (TCR) replacement).*

You can find more information at

NOVEL ANTIBIOTICS

New antibiotics urgently needed

The development of new antimicrobial substances is lengthy and expensive and has rarely been successful in recent decades. Currently, 1.2 million people die worldwide because of multidrug-resistant germs. In a few years there could be ten to fifteen times that number if no new agents are found.

The DZIF is successfully participating in the search for antibiotics within an international research community. In Tübingen, DZIF researchers are using bacterial bioreporter cells to search for new antibacterial agents.

Examples from research

FILLING THE PRODUCT PIPELINES

For Prof. Rolf Müller, a natural products' researcher at the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), things could not be more serious: "We saw in the case of SARS-CoV-2 how bad it was not having any effective drugs. We could shortly be facing a similar threat with multidrug-resistant bacteria if we do not soon discover new substances." Academic research alone will not be able to develop these, simply because it does not have the resources. Therefore, the coordinator of the DZIF *Novel Antibiotics* research area has joined forces with academic institutions and the pharmaceutical industry from the field of antibiotics research in the International Research Alliance for Antibiotic Discovery and Development (IRAADD). The network will bridge the gap between basic research and industrial development to generate new, effective antibiotics for the future. "The idea is to give academic research groups access to the knowledge and methods needed for product development as early as possible," says Müller. "We must use the resources at our disposal in a much more efficient and coordinated way to advance the translation pipeline for the benefit of future generations." The strategy paper published by IRAADD in *Nature Review Chemistry* cites three approaches to that effect: new antibiotics from natural

Dr Walid Elgaher synthesising inhibitors of bacterial virulence factors.

products, synthetic drugs that bind to key molecules of pathogens as well as methods to optimise the process from the drug candidate to the final drug.

DISCOVERING EFFECTIVE NATURAL PRODUCTS FASTER

Likewise, the working group led by Prof. Heike Brötz-Oesterhelt from the Institute of Microbiology and Infection Medicine at the University of Tübingen is searching for new antibacterial agents. The scientist says that a major challenge in natural product research at present was to rapidly detect and sort out already known substances, to free capacities for the investigation of new agents, "We need prompt information on the bioactivity and mode of action, so that we can concentrate on the isolation of compounds with unknown modes of action," says the microbiologist. To that effect, the researchers have developed a new bioreporter approach which they published in the journal *Cell Chemical Biology*. Bioreporters are genetically engineered microbial cells that are able to generate a measurable signal in reaction to a particular substance in their environment—in this case a coloured circle around the bacterial colonies. This approach generates information on the mode of action of bioactive compounds already during primary screening without the need for substance enrichment or purification.

"The identification of cystobactamides, which are very active against carbapenem-resistant A. baumannii*, led to the achievement of desired target product profiles for drug development."*

Prof. Rolf Müller, Braunschweig/Saarbrücken
Coordinator

The method works along the entire purification pipeline, such as with culture supernatants, extracts, fractions and pure substances. When used together with high resolution mass spectrometry, the biosensor panel is an efficient and sensitive tool for deciphering compounds. It provides prompt information on the inhibited metabolic pathway to permit the targeted selection of follow-up assays for elucidation of the molecular target structure.

Prof. Heike Brötz-Oesterhelt (centre) and colleague Katharina Wex validating the bioreporter assay.

GOALS FOR 2021: OUTCOMES

◐ *In the Corallopyronin A development, completion of transfer to the industrial Clinical Research Organisations and upscaling of the production to large scale (15,000 litres), as well as key toxicology studies in dogs.*

● *Elaboration and publication of a roadmap for antibiotic development from translational academic research within the framework of the DZIF participation in JPI-AMR.*

● *Demonstration/confirmation of in vivo proof of concept for adjuvant treatment of* Pseudomonas aeruginosa *infections using PqsR inverse agonists in combination with an aminoglycoside antibiotic.*

◐ *Goal partially achieved/Project is ongoing*
● *Goal achieved*

GOALS FOR 2022

○ *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.*

You can find more information at

BIORESOURCES, BIODATA AND DIGITAL HEALTH

Creating comprehensive biomedical service structures

Since 2021, the former infrastructures Biobanking, Bioinformatics, Epidemiology and Pathogen Repository have been pooling their expertise in the new translational infrastructure *Bioresources, Biodata and Digital Health (BBD)*. All DZIF researchers can benefit from the services, training courses and workshops: The infrastructure provides support in the areas of biomaterials, medical data and bioinformatics, among others.

The *BBD* is aiming for DZIF-wide standardisation of biomedical data and interoperability of database systems and for improved access to relevant biomaterials, medical and analysis data as well as to digital tools and methods.

AVAILABLE BIORESOURCES AND BIODATA

The DZIF Biobanking, based at Helmholtz Munich and the University Hospital Heidelberg, is responsible for all issues relating to the collection of human biosamples. It also offers researchers support in collecting their own high-quality biosamples. At the Munich site the Central Biosample Register (DZIF-ZBR) merges biomaterial data from the local systems and consolidates data from the various studies, making it a valuable data harmonisation tool. As of June 2022, some 200,000 biosamples and associated data have been entered and can be used to answer research questions.

Within the *HIV* research area, the open source biobanking tool HEnRY is being developed by the working group led by Prof. Jörg Janne Vehreschild at University Hospital Cologne. In collaboration with the DZIF-ZBR, an automated interface was created and users are now able to send their biosample data in HEnRY at the click of a mouse to the DZIF-ZBR, where they can be used for search queries.

The central DZIF Tissue Bank at the Heidelberg site provides collections of relevant tissue samples for research projects and offers state-of-the-art tissue analysis methods and technology for tissue-based investigations. Under the management of the DZIF Heidelberg site, the COVID-19 Autopsy and Biosample Registry Baden-Wuerttemberg has been granting scientists since 2020 quick access to standardised tissue samples from SARS-CoV-2-positive patients or from patients vaccinated against SARS-CoV-2, in order to analyse the pathophysiological mechanisms as well as adapt treatment of severe disease courses.

The DZIF Pathogen Repository is located at the Leibniz Institute DSMZ-German Collection of Microorganisms and Cell Culture in Braunschweig. In recent years, the number of microbial pathogen strains and active substance producers has rapidly grown to include over 3,000 strains. In addition to bacteria, the Pathogen Repository also includes fungi and bacteriophages. In 2021 around 300 new strains were added including, among others, high priority pathogens such as multidrug-resistant gram-positive and gram-negative bacteria (e.g. *Staphylococcus aureus* or *Escherichia coli*). The Pathogen Repository is continually expanding its strain collections that are important for certain research questions: Thanks to collaboration with the *Gastrointestinal Infections* research area and other partners, it now contains for example

Dr Vanessa Melhorn (left in the photo) explains the application possibilities of the "PIA" monitoring and management app, which makes it easier to collect epidemiological data.

microbiome strain collections from the gastrointestinal tract of mice, pigs, chickens and humans.

BIOINFORMATICS AND MACHINE LEARNING

Computer-assisted analysis of large biomedical datasets is an essential component of modern research into pathogens. In particular, the fast-paced development of Omics technologies has led to an increased need for informatics-based methods in biological and clinical research. The *BBD* has extensive expertise in the evaluation of bioinformatics and machine learning methods for analysis of microbial pathogens and communities or for implementation of bioinformatics pipelines and their application in DZIF-relevant translational research.

CONSULTING, TRAINING AND WORKSHOPS

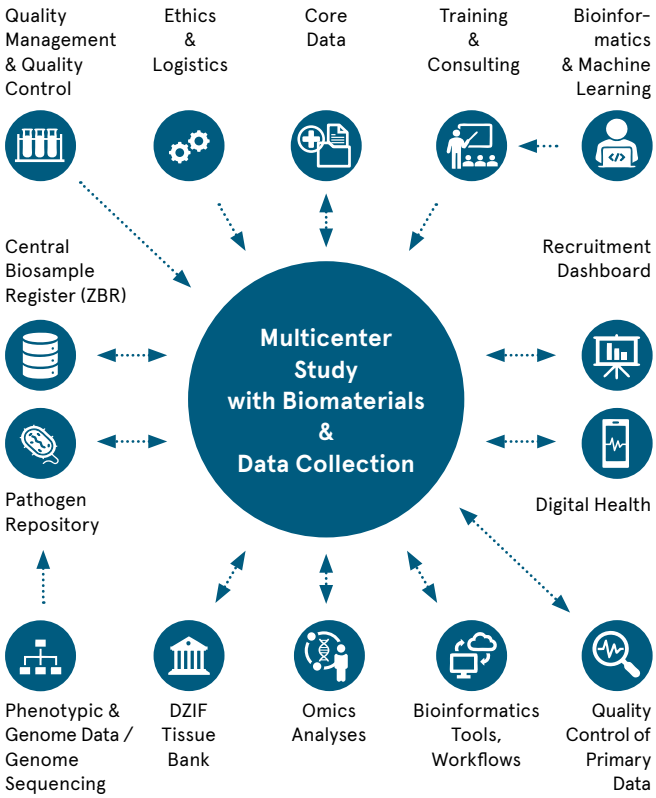
Oriented to the questions and problems faced by the DZIF researchers, the *BBD* infrastructure is imparting its knowledge in consulting talks, training courses, webinars, workshops and at conferences. Here, researchers can acquire specific knowledge or discuss and master research methods based on specific examples from their routine research activities: The topics range—among others—from the storage and logistics of biomaterials and pathogens through bioinformatics methods to systematic reviews and meta-analyses as well as the monitoring of outbreak activities.

BBD CONTRIBUTIONS IN 2021—A FEW EXAMPLES

In 2021, the *BBD* made valuable contributions to further research into COVID-19 outbreak activities: Within the framework of the National Network of University Medicine (NUM), the infrastructure participated in the German Research Network on Autopsies in Pandemics and, through its involvement in the Lean European Open Survey on SARS-CoV-2-Infected Patients, it contributed to the study by the German National Pandemic Cohorts Network. Furthermore, the department led by Prof. Alice McHardy, based at the Helmholz Centre for Infection Research (HZI) in Braunschweig, developed among other things the CoVerage web-based resource: a tool for evaluation of the epidemiological dynamics of SARS-CoV-2. The SORMAS app, which was developed with the involvement of the *BBD* also at HZI, has been used worldwide for monitoring outbreak activities. The *BBD* provided methodical support to Germany's largest MuSPAD seroprevalence study.

OUTLOOK: A NEW PLATFORM FOR DZIF RESEARCHERS

The *BBD* was commissioned in 2021 by the DZIF Executive Board to develop an IT or data platform for the DZIF-wide exchange of bioresources, biodata and bioinformatics tools and workflows. "Our vision is to make the availability and exchange of biomaterials, biodata, tools, documents and templates for evaluations and study planning more efficient.



The graphic shows an overview of the service structures of the BBD*: The facilities offer DZIF researchers, for example, new analysis options for multicentre studies.*

We will achieve this through standardisation, methodical support and, in particular, through the creation of a central and broad digital platform," says Prof. Jörg Overmann, scientific director of the Leibniz Institute DSMZ and *BBD* coordinator in 2021. It is intended that from 2022 DZIF researchers will have access via an integrated online platform to a large number of services, facilitating information and data exchange.

Prof. Alice McHardy, Braunschweig
Coordinator

CLINICAL TRIAL UNIT

Clinical trials to the highest standards

New medicines and vaccines must be tested for tolerability and efficacy in humans before they are placed on the market. This is done in phase I to III clinical trials. DZIF has 12 clinical trial centres specialised in infectious diseases and organised in the *Clinical Trial Unit (CTU)* infrastructure. This is coordinated by the central Coordinating Office (CO) based in Cologne, which also supports DZIF scientists in the planning and implementation of clinical trials.

To design, develop and coordinate the content of clinical trials is a multifaceted and time-consuming challenge. In its *Clinical Trial Unit*, DZIF has an important platform for conduct of clinical studies: DZIF is able to implement clinical infectiology trials to the highest standards—including multicentre trials at several locations or sites. In collaboration with the Board of Trustees for Dialysis and Kidney Transplantation, the *CTU* conducted, for example, the DOPPIO observational study. DOPPIO investigates the protective effects of pneumococcal vaccination in dialysis patients. The results are expected to be available by the end of 2022.

CLINICAL RESEARCH ON SARS-COV-2 AND COVID-19

"Our infrastructure contributes to the transparent presentation of clinical research activities for the interested public and researchers. Likewise, it lends decisive support to the pan-European coordination of clinical research on fighting the pandemic," is how Prof. Oliver A. Cornely, coordinator of the infrastructure, summarises the *CTU* activities.

The registry for people interested in participating in COVID-19 vaccine trials, initiated by the Coordinating Office in 2021 as part of the VACCELERATE platform, already included more than 35,000 volunteers in nine European countries at the end of the year. VACCELERATE is an important interface for bringing those willing to participate in COVID-19 vaccination trials into contact with the clinical trial sponsors: Some 13,000 persons were referred to clinical studies through the platform within the first year.

In November 2021, the first of three planned VACCELERATE trials on the effects of COVID-19 booster vaccinations on the immune response in different age groups has been initiated at the *Clinical Trial Unit* in Cologne. In the multinational phase II trial EU-COVAT-1 AGED data on the effect are collected in older adults (75+). The three clinical trials are intended to provide information on who, and when, is most likely to benefit from a booster vaccination.

Moreover, the infrastructure has set up the EUVAP platform. EUVAP allows for a Europe-wide mapping of experienced clinical trial sites and handles study enquiries from vaccine manufacturers. Around 400 trial sites have been identified and registered in all EU and neighbouring countries.

Prof. Oliver A. Cornely, Köln
Coordinator

For the Clinical Trial Unit*, 2021 was again dominated by the COVID-19 pandemic. At the same time, studies from other research areas were also continued or completed as planned in the second pandemic year.*

PRODUCT DEVELOPMENT UNIT

Highly innovative drug development

The SARS-CoV-2 pandemic highlights the urgency of the prospective need for new vaccines and antivirals. This is compounded by the need for novel antimicrobial products due to the worldwide spread of multidrug-resistant pathogens. The *Product Development Unit (PDU)* team supports DZIF scientists from product conception to the first clinical trials of innovative drug candidates to identify short-term as well as long-term prevention and treatment options.

OSRA AND TPMO AS TRANSLATION DRIVERS

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), located at the Paul-Ehrlich-Institut (PEI) and the Federal Institute for Drugs and Medical Devices (BfArM), and the Translational Project Management Office (TPMO) at the Helmholtz Centre for Infection Research (HZI) in Braunschweig are both part of the *PDU* infrastructure. OSRA assists in clarifying regulatory and technical issues in scientific advice procedures. TPMO helps with operative and commercial aspects of drug development.

2021 was a record year for scientific and regulatory discussions: The *PDU* attended 15 discussions with experts at the PEI and BfArM—around three times more than in previous years. In this context, the COVID-19 and MERS vaccine projects continued to receive strong support. HY-133, TherVacB, anti-CgoX-D3 and Corallopyronin A are examples of four product development projects on the way to their first clinical trials for which the *PDU* is providing intensive consulting support.

OPENING THE METHODS REPERTOIRE

With regard to the projects receiving ongoing support in the areas of vaccine and antibody development as well as the treatment of infections caused by antibiotic-resistant bacteria, Dr Thomas Hesterkamp, Head of TPMO, emphasises: "We see a great interest in new therapeutic modalities and technologies." As examples, he cites the approaches based on anti-bacterial pathoblockers, therapies with phages and Live Biotherapeutic Products, where live bacteria are used to dispel harmful bacteria from colonisation.

Within the framework of the Combating Antibiotic-Resistant Bacteria Accelerator (CARB-X) funding initiative, the *PDU* as an Accelerator has provided support to international product developers with technical project management and scientific regulatory advice since 2019. In 2021, two projects supported by the *PDU* were successfully added to the CARB-X portfolio.

Prof. Klaus Cichutek, Langen
Coordinator

Without expert support, such as offered by the PDU, *the development of new drug candidates often fails before the first clinical trial.*

DZIF ACADEMY

Offering long-term research perspectives

The DZIF attaches great importance to the promotion of young researchers in translational infection research. Since its foundation, the DZIF has been running attractive sponsorship programmes within the framework of the *DZIF Academy* for physicians and scientists. The aim is to enable distinguished young researchers to make a career in widely diverse areas—including clinical infectiology, medical microbiology and virology, immunology as well as molecular medicine. Prof. Jan Rupp and Dr Nadja Käding at the Universität zu Lübeck coordinate and manage the *DZIF Academy*.

DZIF ACADEMY WITH A NEW PROGRAMME: ADVANCED CLINICIAN SCIENTIST

The Academy's programme was expanded last year to also support medical specialists who have already achieved academic success on their way to setting up their own working groups or attaining management roles or professorships: In the autumn, the first two places were awarded within the Advanced Clinician Scientist programme.

The *DZIF Academy* programmes established many years ago were again very popular in 2021 (see page 48). Unlike the Advanced Clinician Scientist programme, they are targeted more at infection researchers starting out in their research careers: The Clinical Leave Stipends are open to clinicians who, thanks to the programme, can leave their routine clinical duties for up to a year and a half and devote themselves to infection research. Medical students are sponsored at DZIF partner sites through MD Stipends to support doctoral studies in the area of infection research. The MD/PhD Stipend enables medical doctors to obtain an additional doctoral degree—combined with three years of research time without clinical duties. The Maternity Leave Stipends make it easier for women to re-enter research after parental leave.

DZIF ACADEMY AS A STEPPING STONE

All *DZIF Academy* stipendiaries who have received funding so far have gained a permanent foothold in infection research. Last year, Dr Dr Angelique Hölzemer and Dr Dr Ulrike Lange took the leap into an independent research career: They received funding from the German Federal Ministry of Education and Research for their own junior research groups—"Infection and Immune Regulation" (Hölzemer) and "Genomics of Retroviral Infections" (Lange). In 2022, their working groups at the UKE and the Leibniz Institute for Virology in Hamburg could officially start up their activities. The two Academy alumni are unanimous: "Our DZIF stipends made a decisive contribution to this success. We were able to concentrate fully on infection research for some time and learned an incredible amount about methodology, which still benefits us today!"

Prof. Jan Rupp, Lübeck Coordinator

After a break because of COVID-19, the popular DZIF Autumn School in Lübeck took place again, where DZIF Academy *stipendiaries presented their work and networked.*

SUCCESSFUL TRANSLATION

New drug substance BTZ-043 against tuberculosis

Translation is the goal of the DZIF: The effective implementation of research results into practice is the focus of all German Centers for Health Research. BTZ-043, a novel candidate for an antibiotic against tuberculosis (TB), is currently evaluated in a clinical trial. BTZ-043 is one of ten flagship projects in 2021, which have already achieved success on the path to translation and are in different clinical trial phases.

According to the World Health Organisation (WHO), around 1.5 million people died from TB in 2020 alone. The growing incidence of multidrug-resistant mycobacteria is an enormous challenge in the treatment of TB (see page 8). Therefore, new drugs are urgently needed. BTZ-043, an organic compound from the benzothiazinone group, is such a completely new drug candidate. BTZ-043 was investigated in a phase IIa clinical trial in Cape Town, South Africa. In addition, a phase I clinical trial with ^{14}C-labelled BTZ-043 investigating the absorption, metabolism and elimination of BTZ-043 in humans was conducted in 2021 in the Netherlands. BTZ-043 binds irreversibly to the enzyme DprE1 needed by mycobacteria for their cell wall synthesis. It blocks the enzyme, leading to holes in the mycobacteria's cells walls and to their death.

ON THE DEVELOPMENT OF BTZ-043

The substance was discovered by researchers at the Leibniz Institute for Natural Product Research and Infection Biology – Hans Knöll Institute (Leibniz-HKI) in Jena. Since 2014, the drug has been developed in a collaboration between the LMU University Hospital Munich and the Leibniz-HKI within the DZIF and the InfectControl 2020 consortium, among others. Since June 2021, preclinical and clinical development has continued within the framework of the UNITE4TB consortium.

The drug substance for the clinical trials is produced at HAPILA GmbH in Gera. The clinical development process is closely coordinated with the *Product Development Unit* at the DZIF and at the Federal Institute for Drugs and Medical Devices. The substance has been successfully tested in three phase I to IIa clinical trials.

WHAT'S NEXT?

After phase IIa, TB drugs can only be developed in combination with other drugs, because one substance alone is not able to eliminate the pathogens. Within the framework of UNITE4TB, Europe's largest TB network, several phase IIb/c clinical trials are set to start at the beginning of 2023 to evaluate the optimal dosage, correct drug combination partners and shortest possible treatment duration. "The development of BTZ-043 illustrates that successful translation needs a long breath and partners in both science and industry," says Prof. Michael Hoelscher from the Division of Infectious Diseases and Tropical Medicine at the LMU University Hospital Munich, who leads the drug development programme. "In the foreseeable future, BTZ-043 might be able to replace one of the conventional, often resistance-prone, antibiotics in combination therapy and significantly shorten the tuberculosis treatment duration," Hoelscher is certain.

Pilot plant for production of BTZ-043 at HAPILA GmbH, which is responsible for manufacturing the active pharmaceutical ingredient in accordance with Good Manufacturing Practice (GMP).

DZIF RESEARCH ON SARS-COV-2 AND COVID-19

United against SARS-CoV-2

Since the pandemic outbreak, DZIF scientists have been working at full speed to contain and treat the infectious disease COVID-19. Right from the time of its foundation, collaboration beyond the boundaries of one's own research areas has been a matter of course at DZIF in order to successfully overcome the major infectiological challenges of our time, in particular the global challenge of a pandemic.

The common focus on the newly emerging pathogen SARS-CoV-2 has deepened this cooperation and also given rise to new collaborations and alliances. In addition to the DZIF research areas, the DZIF infrastructures also made important contributions to coping with the pandemic in 2021 (see pages 24 to 27).

With the *Emerging Infections* research area, the DZIF has from the outset paid particular attention to the fight against new pathogens. Several studies from this research area have helped gain a better understanding of the virus and develop approaches for the diagnosis and treatment of COVID-19 disease (see page 6f.). But outstanding contributions were also made by DZIF researchers in other research areas. On this double page, we show a snapshot of the DZIF SARS-CoV-2/COVID-19 research activities over the past year. The focus is on studies by scientists who do not belong to the *Emerging Infections* research area but who, thanks to their expertise, played a pivotal role in successfully fighting the virus, and continue to do so.

LEARNING TO UNDERSTAND THE VIRUS BETTER

A team led by Andreas Pichlmair, a DZIF professor in the *Hepatitis* research area at the Technical University of Munich, documented in parallel the interaction between virus and cell at five levels. To this end, more than 1,200 samples were analysed using state-of-the-art mass spectrometric techniques and bioinformatics methods. The result is a freely accessible dataset that provides information on which cellular proteins the viral proteins bind to and the effects of these interactions on the cell. Among other things, the dataset can serve as a tool to find new drugs.

Luisa Ruhl (left) and Prof. Christine Falk at the Hannover Medical School analysed which actors of the immune system influence the course of COVID-19 disease.

Dr Jan Rybniker from the *Tuberculosis* research area and his team at University Hospital Cologne demonstrated that COVID-19 causes long-lasting activation of immune cells. They investigated the effect of the virus spike protein on the innate immune system. The research team found that macrophages from COVID-19 patients were stimulated by the virus spike protein to produce massive amounts of the proinflammatory cytokine interleukin-1 and that they continued to be strongly activated even weeks to months after SARS-CoV-2 infection. Since macrophages have a very short life span of only a few days, this argues for changes in the genetic material of the macrophage progenitor cells and could explain why some infected people exhibit an exaggerated immune response to the virus.

Prof. Christine Falk from the Hannover Medical School and DZIF scientist in the *Infections of the Immunocompromised Host* research area investigated together with other research teams why some persons develop life-threatening COVID-19 disease. Severe courses of disease were characterised by, in addition to strong immune activation and inflammatory reactions, in particular by dysregulation of the vascular system. Progressive damage to the blood brain barrier—signalled by the release of certain inflammatory plasma proteins—is associated with deterioration of the patient's condition. This insight is of significant importance both for the identification of biomarkers for severe COVID-19 courses and for the development of new treatment approaches.

EMERGENCY DRUGS

Neutralising antibodies are an important mainstay in the fight against COVID-19: They are able to selectively inactivate the virus and have great potential to be used effectively to protect against and treat the disease. At University Hospital Cologne the DZIF research group led by Prof. Florian Klein isolated neutralising antibodies from the blood of SARS-CoV-2 recovered persons. The inhaled and intravenous administration of the DZIF-10c antibody was investigated in phase I and IIa studies. Here, Florian Klein applied his expertise gleaned from the *HIV* research area.

The research group led by Prof. Rolf Hilgenfeld at the University of Lübeck in 2020 identified the main viral protease, which is a key enzyme in SARS-CoV-2 replication, thus paving the way for the targeted development of active substances. Based on his previous work activities in the *Emerging Infections* research area, he and his team developed the inhibitor RHCDS-13b, an alpha-ketoamide compound. This protease inhibitor was investigated by Dr Katharina Rox at the Helmholtz Centre for Infection Research in Braunschweig to further improve its pharmacokinetic properties, such as residence time in the body and distribution in tissues. Dr Rox heads the DZIF Pharmacokinetics and Pharmacodynamics (PK/PD) Unit in the *Novel Antibiotics* research area. The aim of further development is to modify the inhibitor into a broad spectrum antiviral entry inhibitor, which is also expected to be effective against other corona- and enteroviruses. Several new derivatives of the inhibitor were produced and tested here in 2021. The medicinal chemistry pharmacokinetics of these derivatives is being currently further optimised.

VACCINE DEVELOPMENT

One of the main focus areas of the *Product Development Unit* in 2021 was the further development, including possibly the marketing authorisation, of DZIF vaccines against COVID-19 and MERS. Within the DZIF, the Modified Vaccinia Ankara (MVA) platform, in which genetic information for viral antigens is introduced into an attenuated and thus harmless poxvirus (MVA) vector has already been investigated for many years and demonstrated initial successes against the MERS coronavirus. In 2021, the DZIF began a study in which an MVA-SARS-2-ST vector vaccine developed by DZIF scientists is being tested for its efficacy for booster vaccination. Independently of this, a phase Ib trial with the optimised vector vaccine in unvaccinated people continued. The *Product Development Unit* in discussions with the European Medicines Agency clarified important issues regarding, among others, using the MVA-SARS-2-ST as a booster-only vaccine.

NEW COLLABORATIONS AND ALLIANCES

SARS-CoV-2 has revealed areas where there is still a need for improvement in the event of a pandemic: for example, in early cross-border detection of new pathogens or the development of uniform data infrastructures. The DZIF is participating in international collaborations aimed at being better prepared for any new pandemic.

DZIF working groups have been conducting research for many years now on early detection and outbreak management, emergency vaccines and broad-spectrum antivirals, among others. Within the framework of special measures, this research at DZIF has been intensified since 2020. In collaboration with the European platforms VACCELERATE and EUVAP, the *Clinical Trial Unit* put in place important structures in 2021 for cross-border organisation of clinical trials. The infrastructure *Bioresources, Biodata and Digital Health* made, for example, significant contributions to infection modelling and to the activities of the European COVID-19 Forecast Hub committees.

In collaboration with the HZI, DZIF also began setting up in 2021 the National Alliance for Pandemic Therapeutics (NA-PATH). NA-PATH aims to expedite the development of broad spectrum therapeutics to contain new viral pathogens more quickly in the future.

You can find more information at

DZIF HIGHLIGHTS 2021

News in Focus

JANUARY

DZIF scientists at the University Hospital Cologne have developed a new vaccination strategy against multi-resistant strains of the hospital pathogen *Staphylococcus aureus*. Passive immunisation with a monoclonal antibody is based on an innovative antimicrobial principle. It is considered a potentially valuable alternative or addition to antibiotic therapy.

JUNE

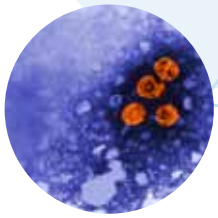
In some people, infection with SARS-CoV-2 leads to an excessive immune response associated with severe inflammation of the lungs and other vital organs. The viral spike protein is a major contributor to the stimulation of the innate immune system, whose activity is associated with severe disease progression, as DZIF researchers at the University Hospital Cologne have discovered.

MAY

The malaria vaccine PfSPZ-CVac, developed by the Institute for Tropical Medicine, Travel Medicine and Human Parasitology at the University Hospital Tübingen in collaboration with the biotechnology company Sanaria, results in 77% protection against malaria parasites. The study was conducted by researchers from the Tübingen Institute and the DZIF.

FEBRUARY

Researchers at the University Medical Center Hamburg-Eppendorf have developed a combination therapy that was highly effective in a model and promises to cure chronic infections with the hepatitis B virus, which causes liver cirrhosis and liver cancer.



MARCH

The vaccine research network VACCELERATE, led by the DZIF *Clinical Trial Unit* at the University Hospital Cologne, serves to coordinate SARS-CoV-2 vaccine studies on issues of vaccine safety, efficacy and adaptation to viral variants. The pan-European network is funded by the European Union for three years with a total of 12 million euros.

APRIL

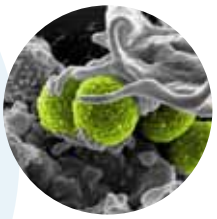
The higher pathogenicity of SARS-CoV-2 and the closely related virus SARS-CoV compared to other coronaviruses is based on their ability to strongly stimulate the production of their proteins and thus the propagation of virus particles in infected cells. This was found by DZIF researchers at the Universität zu Lübeck and LMU Munich.

JULY

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

AUGUST

New antibiotics and strategies against deadly infectious diseases and multi-resistant bacteria are urgently needed. In the newly founded incubator INCATE (INCubator for Antibacterial Therapies in Europe), founding member DZIF, together with partners from academia, industry and the public sector, supports start-up teams in the development of new drugs.



SEPTEMBER

Enterobacteria such as *Escherichia coli* or *Klebsiella pneumoniae* can lead to severe infections in the intestine and urinary tract and are increasingly developing resistance to a group of antibiotics that serve as an emergency reserve—the carbapenems. Hopes for a new therapy with two antimicrobial substances capable of overcoming carbapenem resistance when used in combination have been put into perspective by a study conducted by the DZIF and Justus Liebig University Giessen. The researchers discovered bacteria that are already resistant to the new combination therapy.

OCTOBER

If the balance of the microbiome in the gut is disturbed, for example by antibiotic therapy, pathogens such as *Salmonella* or *Klebsiella pneumoniae* can gain the upper hand. In several studies, DZIF researchers from the Helmholtz Centre for Infection Research (HZI) and LMU Munich succeeded in identifying commensal—positively acting—bacterial strains in the gut that are collectively able to displace pathogenic bacteria by depriving them of sugar food.

To address the lack of antiviral agents needed to overcome the current COVID-19 as well as future pandemics, the DZIF together with the HZI has developed a concept to establish a National Alliance for Pandemic Therapeutics (NA-PATH). The aim is to boost research and development of broadly effective therapeutics in order to be better prepared for future outbreaks caused by viral pathogens with pandemic potential.

NOVEMBER

Since immune protection of the vaccine against the coronavirus decreases over time, a booster vaccination is intended to further increase protection against the disease and a severe COVID-19 course. In a study started by the University Medical Center Hamburg-Eppendorf and DZIF, the MVA-SARS-2-ST vector vaccine developed by DZIF researchers is tested for its booster effect.

DECEMBER

In 2021, the DZIF awarded the physician and clinical virologist Prof. Ulrike Protzer for her translational infection research, in particular her developments of therapeutic vaccines, antibodies and T-cell therapy to combat hepatitis.

SCIENCE AND THE PUBLIC

Together for open science

In 2021, COVID-19 became a topic with the potential to divide society. Caught in the crossfire between fake news, disinformation and evidence-based information, DZIF researchers made valuable contributions to facts-based scientific communication: In podcasts, television appearances, interviews in leading newspapers or on their own social media channels, DZIF scientists enriched the debate with factual information on the most diverse issues around SARS-CoV-2. The DZIF Press Office developed new formats to reach the public on matters related to and beyond the current pandemic.

Scientific knowledge gleaned from infection research plays a pivotal role in evidence-based decision-making, especially in times of pandemic. DZIF experts were therefore last year very often called upon when it came to weighing up political decisions. With the NDR (Northern German Broadcasting) podcast “Coronavirus Update”, which in 2021 was awarded the “Heinz Oberhummer Award for Scientific Communication”, among others, Prof. Christian Drosten and Prof. Sandra Ciesek played a key mediation role between science and the public.

However, our scientists were often also massively attacked when they presented their scientific knowledge to the public. Lay persons often struggle to understand the statistical uncertainties arising from scientific methods. A key task of the Press Office was therefore to collect and disseminate information from various sides and serve as an interface between research and the public.

With new formats we are trying to reach even more people and make them aware of what scientific work involves and how scientific knowledge can be processed.

The DZIF research group led by Prof. Florian Klein at the University Hospital Cologne isolated neutralising antibodies from the blood of SARS-CoV-2 convalescents. Still from the DZIF video “New antibody against SARS-CoV-2 in clinical studies”.

NEW FORMATS IN SCIENTIFIC COMMUNICATION

In June 2021, the first DZIF science news video from the "Science in Motion" series was launched. The DZIF has been involved in the development of this format of the "Informationsdienst Wissenschaft" (scientific information service) for several years. The first DZIF YouTube video from this series presents the research findings of the working group led by Prof. Florian Klein at University Hospital Cologne. By the end of the year, the video had almost 26,000 views (see video still on the left).

In 2021, we once again produced our own films in German language. In a short film Prof. Mark Brönstrup explains how the DZG Expert Center for Medicinal Chemistry supports all researchers within the German Centers for Health Research on the way from academic concept to drug development. At the last DZIF Academy Autumn School, we interviewed three stipendiaries. The resulting films show what motivates young researchers and inform about the opportunities offered by DZIF Academy stipends.

WEBSITE TRAFFIC, MEDIA RESPONSE & REACH

With some 840,000 visitors from the entire world, the DZIF website once again proved to be a central contact point for those seeking information. Almost half of new German-speaking visitors landed on one of our glossary pages; the search term most commonly entered was "vector vaccine". Likewise, the continuously high interest in the DZIF is reflected in the media response: While, with 3,431 online articles, DZIF content was accessed less frequently in the online media we monitored than in the previous year, the potential reach was, at the same time, nearly three times as high. Spread over the entire year, national and international online media alone potentially reached 19.4 billion people. Not included here are the contributions by DZIF researchers in the traditional print media as well as in radio and television appearances. DZIF reports on COVID-19 studies had the highest reach, potentially reaching over 200 million readers per news. These reports were picked up and disseminated by online editorial departments, e.g. *Daily Mail*, *Yahoo! News* or *The Independent*, to name just a few examples.

PRESS RELEASES, TWITTER & LINKEDIN

In the past year we issued 43 press releases, of which 17 were on SARS-CoV-2/COVID-19. Other topics included the hopes for a vaccine against *Staphylococcus aureus*, how to prevent infection risks following a transplant, novel therapeutic options for hepatitis B and tuberculosis, MERS and malaria vaccine development or antibiotic resistance.

We continue to have a large social media presence: With 161 tweets and 83 LinkedIn posts, we got a total of 419,246 impressions and gained around 1,000 new followers.

DZIF Academy MD stipendiary Lennard Meiwes spent several months in Eswatini (Africa) for his tuberculosis research project and reports on his research and experiences in the blog "The Flying Lab" (https://adobe.ly/3z7swqa) maintained by the DZIF Press Office.

INTERNAL AND EXTERNAL NETWORKING & COOPERATION

Just as important as communication with the media is the consideration of other target groups: In regular DZIF newsletters and internal emails to all DZIF staff members we share important addressee-specific information. We support the internal and external DZIF project communication, for example, through public relations activities for conferences and congresses and continually engage in networking within the DZIF as well as with our numerous cooperation partners in external research institutions and industry. In collaboration with the other five German Centers for Health Research we continue to develop cross-cutting communication within the DZG. A prominent example of this is the DZG magazine *SYNERGIE*, whose print version was awarded the *Berlin Type in Silver* design prize in 2021.

From left: Tatiana Hilger, Martina Lienhop, Karola Neubert, Janna Schmidt, Dr Nicola Wittekindt (since 2022)
Braunschweig, Press Office

COLLABORATIONS

External Partnerships

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

ASSOCIATED PARTNERS

Charité – Universitätsmedizin Berlin
The Charité Institute of Hygiene and Environmental Medicine is one of six partners in the DZIF network "Multidrug-resistant Bacteria" (MDRO Network: R-Net 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 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 centers 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

In addition to its 35 member institutions at seven locations in Germany, the DZIF cooperates with numerous other academic institutions and industrial partners in Germany and abroad.

cooperation partners, it creates a platform for conducting clinical studies. The DZIF can use infrastructures and cohorts for its projects.

Johann Wolfgang Goethe-Universität Frankfurt
The Goethe-Universität Frankfurt is active in the DZIF research areas *Hepatitis* and *Healthcare-Associated and Antibiotic-Resistant Bacterial Infections* and was involved in several SARS-CoV-2 projects in 2021.

In the *Hepatitis* research area, a collaborative project is taking place, among others, to optimise the treatment of hepatitis C patients with novel agents—so-called Directly Acting Antivirals (DAA)—and to develop a prophylactic vaccine. The Universität Frankfurt is also involved in a DZIF study on the treatment of hepatitis E.

Julius Maximilians-University 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 defence functions. Some of the study patients will be treated in Würzburg, as well as at the DZIF partner sites in München (coordination), Tübingen and Hannover-Braunschweig.

Leibniz Institute for Natural Product Research and Infection Biology—Hans Knöll Institute (Leibniz-HKI), Jena
The Leibniz-HKI provides various natural products to the DZIF. Scientists of the Leibniz-HKI and the Ludwig-Maximilians-Universität München (LMU) 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 Universität 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.

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* (MTB) is the focus of a large tuberculosis screening project in which the University of Bayreuth is participating. The aim is to develop a preclinical model that provides a basis for the identification of new active agents against tuberculosis and for efficacy-testing of known and newly discovered active substances.

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

Medical Center – University of Freiburg
The University of Freiburg Medical Center 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 hospital-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 and *Clostridioides difficile*-infections have been studied longitudinally over a period of several years. A monitoring system is also being developed to provide timely indication of outbreaks of multidrug-resistant bacteria in the hospital.

Greifswald University Medicine
Greifswald University Medicine 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 highly effective against methicillin-resistant *Staphylococcus aureus* bacteria in the nasal cavity. Currently, the promising compound is being investigated in preclinical studies to ensure safety in subsequent human clinical trials.

Münster University
Collaborating in a project in the research area *Gastrointestinal Infections*, Münster University is working on new pathogen-specific inhibitors, for example against Salmonella.

Scientists 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.

Boehringer Ingelheim
In this DZIF collaboration, the virology institutes of the University Hospital Cologne (UKK) and Philipps Universität Marburg are cooperating with Boehringer Ingelheim to test a SARS-CoV-2 neutralising antibody preclinically and early clinically. The project was discontinued after Phase I testing at UKK.

Coris BioConcept, Gembloux (Belgium)
DZIF scientists from the Institute of Medical Microbiology, Immunology and Hygiene at the University Hospital Cologne have developed 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 working group "Antibacterial Vaccine Development" of Dr Alexander Klimka is funded by the DZIF.

HYpharm GmbH, Bernried
HYpharm GmbH and a DZIF-funded consortium are cooperating in the field of production and preclinical development of the phage lysine protein HY-133 (see also University of Greifswald). 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, formerly Stage Cell Therapeutics, is the collaboration and commercialisation partner of Prof. Dirk Busch's research group at 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. The DZIF supports the group around Dirk Busch.

Gilead Sciences, Inc., Foster City (USA)
Together with Heidelberg University, an active agent was developed that can prevent the entry of hepatitis B viruses into the cell and will be used against hepatitis B and D. The overall project was coordinated by MYR GmbH. At the end of July 2020, the European Commission approved the active agent under the name Hepcludex—initially for hepatitis D. In March 2021, the full acquisition of MYR GmbH by Gilead Sciences, Inc. became public.

INTERNATIONAL ALLIANCES (DZIF-INITIATED)

INCATE
Multidrug-resistant bacteria are spreading worldwide and new antibiotics and strategies against deadly infectious diseases are urgently needed. With INCATE (INCubator for Antibacterial Therapies in Europe), a consortium is now being launched 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.

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). Their aim is to drive forward the research and development of broadly effective therapeutics in a targeted manner 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.

AFRICAN PARTNER INSTITUTIONS

The DZIF has been cooperating for many years with the Centre de Recherches Médicales de Lambaréné (CERMEL, Gabon), the Centre de Recherche en Santé de Nouna (CRSN, Burkina Faso), the Kumasi Centre for Collaborative Research in Tropical Medicine (KCCR, Ghana), and the Mbeya Medical Research Center (MMRC, Tanzania). Joint projects focus on prevention, diagnosis and treatment of malaria, tuberculosis, HIV/AIDS and neglected tropical diseases such as worm diseases.

ABOUT THE DZG

German Centers for Health Research

A key objective of the German government's health research programme is the ability to combat widespread diseases more effectively. With the establishment of the German Centers for Health Research (DZG), the federal and state governments have created the conditions for this.

The German Centers for Health Research are long-term, equal partnerships of non-university research institutions—such as the Max Planck, Helmholtz and Leibniz Institutes—and universities with university hospitals. The DZIF is one of six DZGs established between 2009 and 2012 at the initiative of the German 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. Basic research and clinical research are closely interlinked.

The Centers are dedicated to the following diseases: cancer (DKTK), neurodegenerative diseases (DZNE), infectious diseases (DZIF), diabetes (DZD), lung diseases (DZL) and cardiovascular diseases (DZHK). Two additional centres for child and adolescent health and for mental health are in planning.

The strategic collaboration of leading researchers in the DZGs strengthens Germany's position as a science location in international competition and at the same time increases its attractiveness for young scientists in Germany and abroad. The bundling of different disciplines and competencies has already led to a significantly increased international visibility of translational, clinical application-oriented research in Germany.

The six DZGs have been working closely together from the outset in order to exchange experiences and create synergies. In quarterly joint meetings of the DZGs' boards as well as biannual DZG forums (involving the BMBF and state representatives), the focus is on the strategic development and collaboration of the DZGs. In recent years, the DZGs have grown closer together: A DZG office has been established, while the existing working groups for biobanking, data management, promotion of young researchers, public relations, prevention, global health and regulation of clinical trials continued their work. A new working group deals with the topic of patient participation. With the DZG Innovation Fund (DZGIF), the concept for a joint research funding programme was developed, which will start in 2022 with the research topic "Cell & Gene Therapy". With the help of the fund, interdisciplinary synergies between the DZGs are to be exploited and promising cross-disease research projects advanced.

As part of the promotion of young scientists, the DZG offered very well-attended courses for young talents last year, for example the workshop "Translating Science into Clinical Practice" and several lectures on the topic of science communication and career development. In addition, intensive work was done to support scientists in the balancing act between clinical practice and research and to exchange their research data and biosamples on the basis of common standards.

The joint research magazine SYNERGIE of the DZG was continued in 2021 with two issues on the topics "Genome" and "Precision Medicine"—as a high-quality print product as well as an online edition at www.dzg-magazin.de.

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 (TTUs)

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

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

TRANSLATIONAL INFRASTRUCTURES (TIs)

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

- 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.

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

SCIENTIFIC ADVISORY BOARD

Dr H. Feldmann (Chair), *National Institute of Allergy and Infectious Diseases, USA*

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 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

Prof. Dr G. Sutter (Chair), *Ludwig-Maximilians-Universität München*

Prof. Dr H. Brötz-Oesterhelt (Vice Chair), *University of Tübingen*

Dr Berit Lange (on behalf of Dr S. Castell), *Helmholtz Centre for Infection Research, Braunschweig*

Prof. Dr K. Cichutek, *Paul-Ehrlich-Institut, Langen*

Prof. Dr O. A. Cornely, *University Hospital Cologne*

Prof. Dr S. Herold, *Justus Liebig University Giessen*

Prof. Dr F. Klein, *University Hospital Cologne*

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*

as of August 2022

PARTNER SITES AND MEMBER INSTITUTIONS

Partner sites and member institutions

Germany-wide infection research

BADEN-WÜRTTEMBERG

The research areas *Hepatitis* and *Infections of the Immunocompromised Host* 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 banks. Methodologically, one of the focal points of Heidelberg's activities is imaging techniques for visualising infection in systems of varying complexity: from clonal cells and mixed cell populations to organs and animal models. Research on HIV is also conducted here.

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)

TI Coordination:

- Biobanking—since 1/2021 part of the TI Bioresources, Biodata and Digital Health (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*. 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-coordination. 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 Zentrum München – German Research Center for Environmental Health, Bundeswehr Institute of Microbiology, LMU University Hospital Munich, Klinikum 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-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.

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 for Experimental Virology (HPI), University of Hamburg, University Medical Center Hamburg-Eppendorf, Universität zu Lübeck

TTU Coordination:

- HIV (coordination)
- Malaria and Neglected Tropical Diseases (coordination)
- Emerging Infections (co-coordination, since 01/2022 coordination)
- Tuberculosis (co-coordination)
- Healthcare-Associated and Antibiotic-Resistant Bacterial Infections (co-coordination)

TI Coordination:

- DZIF Academy

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 at the Paul Ehrlich Institute (PEI) in Langen and the Microbial Genome Research Center (MGRC) 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 infrastructure *Product Development Unit*.

GIESSEN – MARBURG - LANGEN

Spokesperson: Prof. Dr Stephan Becker (Philipps-Universität Marburg) since 1/2021

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

TTU Coordination:

- Emerging Infections (coordination until 12/2021, since 01/2022 co-coordination)
- Healthcare-Associated and Antibiotic-Resistant Bacterial Infections (co-coordination until 11/2021, since 12/2021 PD Dr Can Imirzalioglu (Gießen) is site representative with voting rights on the TTU coordination committee)

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 antibiotics.

HANNOVER – BRAUNSCHWEIG

Spokesperson: Prof. Dr Thomas Pietschmann (TWINCORE)
Institutions: Helmholtz Centre for Infection Research, Braunschweig, 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)

TI Coordination:

- Bioresources, Biodata and Digital Health (coordination)

NORTH RHINE-WESTPHALIA

Experts at the **Bonn – Köln** partner site focus on combating viral and bacterial infectious diseases. In the area *Novel Antibiotics*, the preclinical development of the new antibiotic Corallopyronin A is being advanced in cooperation with the TPMO and the BfArM. Vaccines against bacterial pathogens such as *S. aureus* and *A. baumannii* as well as activities on neglected tropical diseases are further focal points. In the area *Healthcare-Associated and Antibiotic-Resistant Bacterial Infections*, the focus is on therapies for infections with multidrug-resistant pathogens as well as infection control measures. The development of nucleic acid-based adjuvants, analysis of mechanisms of action of mRNA vaccines and targeted activation of innate antiviral immunity make important contributions to the area *Infections of the Immunocompromised Host*. In HIV research, T cell-mediated immunity is being explored and antibody-mediated therapeutic approaches are being taken into translation. Other foci include SARS-CoV-2 research and the newly established VACCELERATE clinical research network.

BONN – KÖLN

Spokesperson: Prof. Dr Oliver A. Cornely (University Hospital Cologne)
Institutions: Federal Institute for Drugs and Medical Devices (BfArM), University of Bonn, University Hospital Bonn, University of Cologne, University Hospital Cologne
TTU Coordination:

- Healthcare-Associated and Antibiotic-Resistant Bacterial Infections (coordination since 12/2021)
- HIV (co-coordination)
- Novel Antibiotics (co-coordination)
- Tuberculosis (co-coordination)
- Malaria and Neglected Tropical Diseases (co-coordination)

TI Coordination:

- Clinical Trial Unit (coordination)

Member institutions of the German Center for Infection Research

Bernhard Nocht Institute for Tropical Medicine
Bundeswehr Institute of Microbiology
Federal Institute for Drugs and Medical Devices
Friedrich-Loeffler-Institut
German Cancer Research Center
Hannover Medical School
Heidelberg University
Heidelberg University Hospital
Helmholtz Centre for Infection Research
Helmholtz Munich - German Research Center for Environmental Health
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 research with high impact

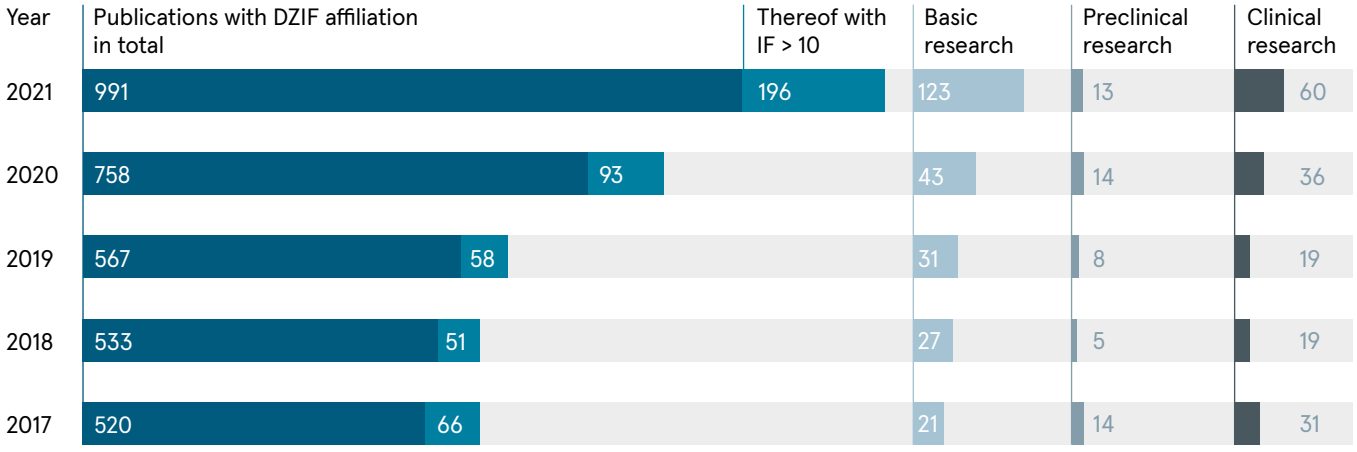
Publications allow researchers worldwide to access the results of others, to critically reflect on them and to take them up in their own research work. At the same time, published works are important for scientific reputation: Publications in renowned journals with a high impact factor are often regarded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

The journal impact factor 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 impact factor (IF) of at least ten is generally considered excellent.

Of the 991 publications in 2021 with DZIF affiliation, i.e. mention of the DZIF by at least one contributor to a publication, 196 had an IF > 10 (Impact Factor from 2020), including 67 articles related to SARS-CoV-2/COVID-19.

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 2021 is available at: http://bitly.ws/tPVW



Graphical representation of the number of scientific publications with DZIF affiliation since 2017 (sources: PubMed, Scopus and Web of Science). The number of publications in the areas of basic research, preclinical research and clinical research refers to publications with IF > 10.

INDICATORS 2021

The DZIF in figures

FLEXFUNDS*

12 Number of FlexFunds projects approved in 2021 thereof one Fast-Track project for SARS-CoV-2

6,252,590 total budget in euros. Corresponding to

16.49 % of the annual DZIF budget

*funds available at short notice for translational projects

DZIF ACADEMY PROGRAMMES

14 Clinical Leave Stipends

04 MD/PhD Stipends

12 Maternity Leave Stipends

76 MD Stipends

01 Lab Rotation

04 Travel Grants

WORKSHOPS AND SYMPOSIA

09 mostly online events

PUBLICATIONS WITH DZIF AFFILIATIONS

991

PUBLICATIONS WITH IMPACT FACTOR >10

196

CONFERENCE CONTRIBUTIONS

275 mostly online events

PRESS RELEASES/ NEWS

43

PATENTS AND PROPERTY RIGHTS

36

INDUSTRY COLLABORATIONS

7

CLINICAL STUDIES

25

DATA- AND BIOBANKS

23

CONFIRMATORY PRECLINICAL STUDIES

26

COHORTS

51

WEBSITE VISITORS

840,423

SOCIAL MEDIA*

1,107 New Followers

419,246 Impressions

244 Social Media Posts

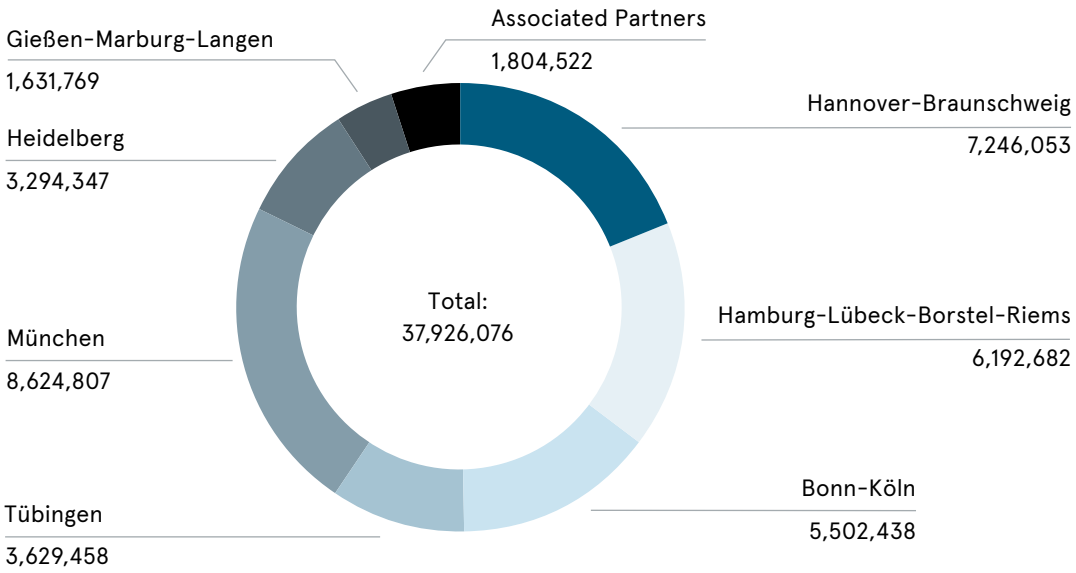
* Cumulative figures from the presences on Twitter and LinkedIn

FINANCES

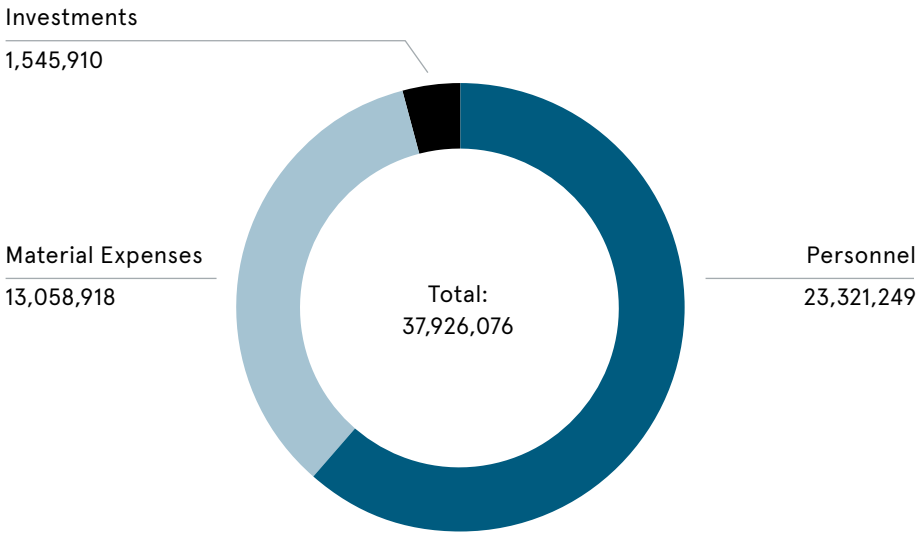
DZIF financial data 2021

REPORTED EXPENDITURE IN EUROS

BY PARTNER SITE



BY TYPE OF EXPENDITURE



BY FIELD OF WORK

FIELD OF WORK	Euro
Emerging Infections	4,992,208
Tuberculosis	1,716,949
Malaria and Neglected Tropical Diseases	2,884,678
HIV	2,082,012
Hepatitis	3,792,373
Gastrointestinal Infections	1,736,962
Infections of the Immunocompromised Host	5,762,127
Healthcare-Associated and Antibiotic-Resistant Bacterial Infections	2,442,747
Novel Antibiotics	3,971,364
Bioresources, Biodata and Digital Health	1,060,914
Clinical Trial Unit	403,596
Product Development Unit	784,003
DZIF Academy	2,427,752
Cross-DZG projects	92,616
Administration	3,775,776
Total	**37,926,076**

BY FUNDERS

FUNDER	Euro
Baden-Württemberg	714,575
Bavaria	876,022
Hamburg	447,512
Hesse	119,547
Lower Saxony	640,841
North Rhine-Westphalia	551,744
Schleswig-Holstein	174,420
Financial contributions from associated partners	180,019
Federal Government	34,221,397
Total	**37,926,076**

In 2021, the German Center for Infection Research's reported expenditure amounted to approximately 37.93 million Euros. 224 research projects, along with 111 projects of the DZIF Academy, were funded within DZIF in 2021.

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 2021 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 2021 are preliminary and refer to the audit status as of 16.05.2022.

PERSONNEL AND AWARDS

Awards and commendations

Prof. Dr Marylyn Addo

University Medical Center Hamburg-Eppendorf

- Citizen Award (Senate of Hamburg)
- Hammonia (State Women's Council Hamburg)

Prof. Dr Christian Drosten

Charité – Universitätsmedizin Berlin

- Leibniz Medal
- Member of the German National Academy of Sciences (Leopoldina)
- University Teacher of the Year
- Urania Medal

Prof. Dr Ralf Bartenschlager

Heidelberg University Hospital

- M. W. Beijerinck Virology Prize 2021 of the Royal Netherlands Academy of Arts and Sciences

Dr Cindy Hörner

Dr Christoph Schürmann

Paul-Ehrlich-Institut

- Langen Award for Young Scientists

Prof. Dr Sandra Ciesek

Johann Wolfgang Goethe-Universität Frankfurt

- University Teacher of the Year
- Urania Medal
- Hessian Culture Prize

Prof. Dr Rolf Müller

Helmholtz Institute for Pharmaceutical Research Saarland (HIPS)

- Gottfried Wilhelm Leibniz Prize

PD Dr Claudia Denkinger

Heidelberg University Hospital

- Memento Research Award

Dr Julia Pagel (on the right in the photo) at the award ceremony of the Dorothea Erxleben Female Investigator Award. Prof. Gabriele Gillessen-Kaesbach, President of the Universität zu Lübeck, presented her with the prize.

Prof. Dr Stefan Niemann

Research Center Borstel, Leibniz Lung Center

• Gardner Middlebrook Award

Prof. Dr Jürgen Ruland

Technical University of Munich

• Gottfried Wilhelm Leibniz Prize

Dr Julia Pagel

Universität zu Lübeck
University Medical Center Hamburg-Eppendorf

• Dorothea Erxleben Female Investigator Award

Dr Dr Philipp Schommers

University Hospital Cologne

• German Thesis Award

Prof. Dr Ulrike Protzer

Technical University of Munich
Helmholtz Munich

• DZIF Prize for Translational Infection Research

Prof. Dr Stephan Urban

Heidelberg University

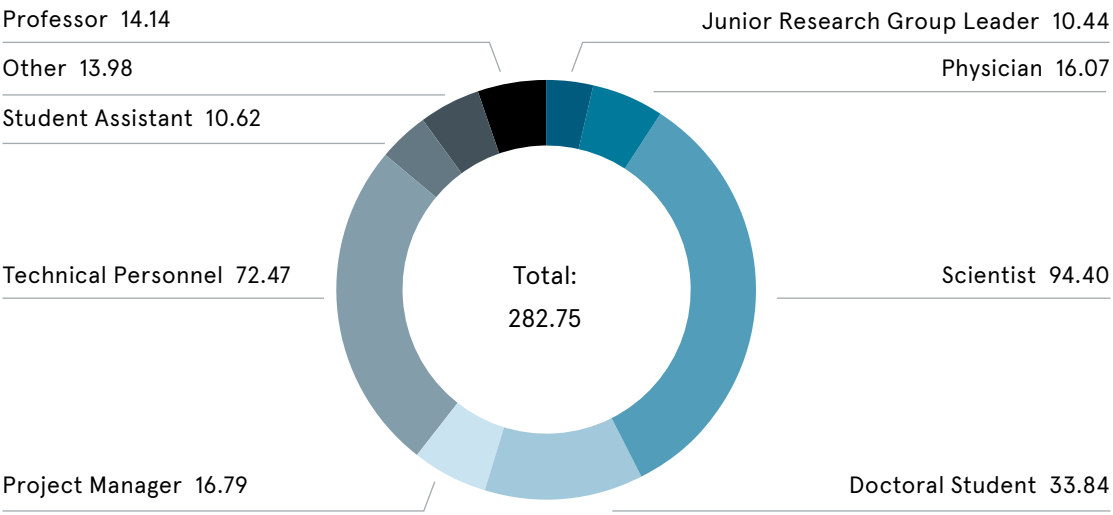
• The Distinguished Award in Hepatitis B Research

Prof. Ulrike Protzer received the 2021 DZIF Prize for Translational Infection Research. Prof. Jan Rupp (left in the photo) and Prof. Hans-Georg Kräusslich presented her the prize at the joint Annual Meeting of DGI and DZIF in 2022.

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	16	14	30
Scientist	69	110	179
Doctoral Student	38	41	79
Project Manager	10	27	37
Technical Personnel	29	133	162
Student Assistant	11	26	37
Other	4	24	28
Total	**196**	**386**	**582**

In 2021, the DZIF recruited seven employees from abroad and assisted 16 mothers and fathers respectively on their return from parental leave.

IMPRINT

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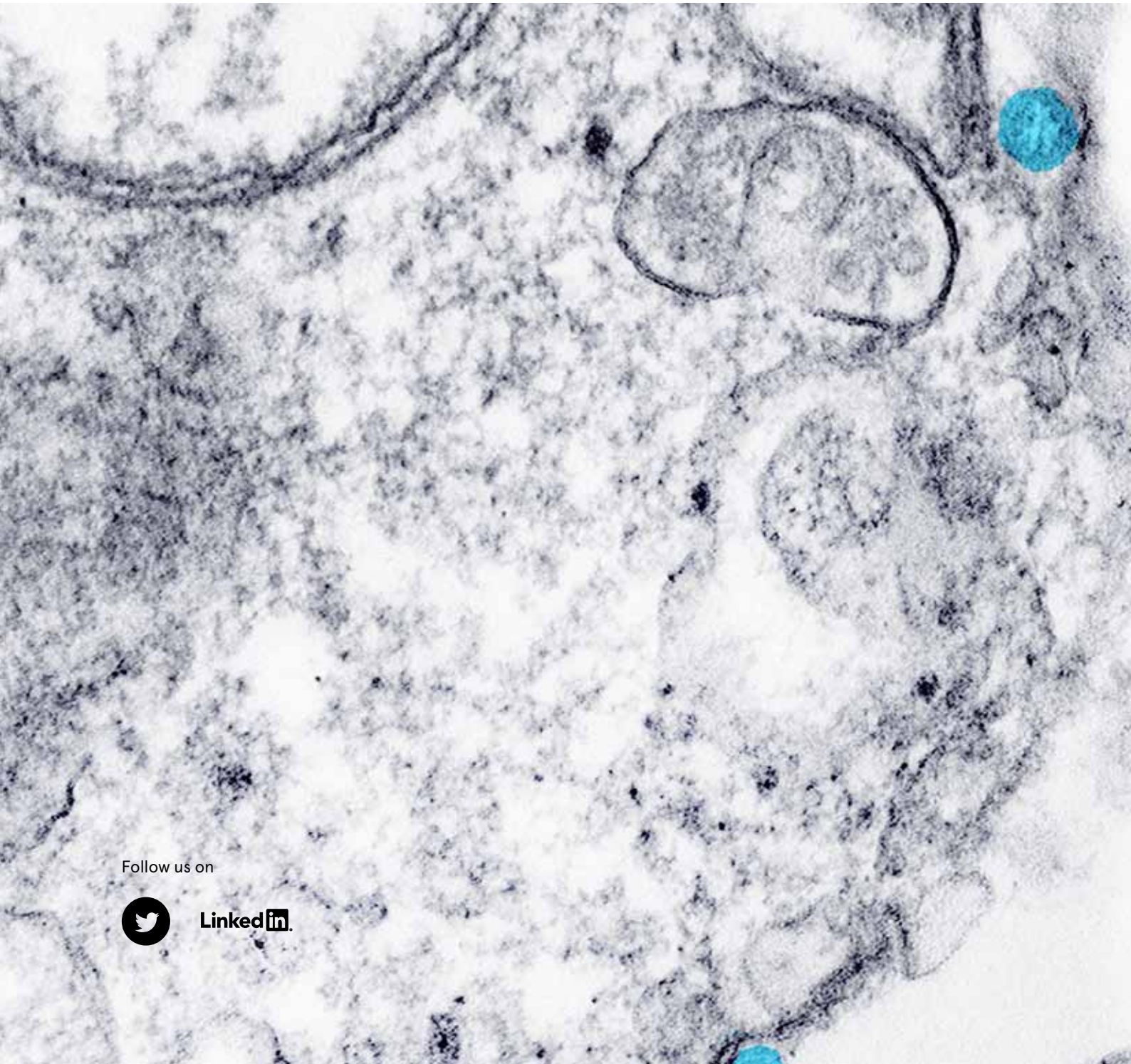

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