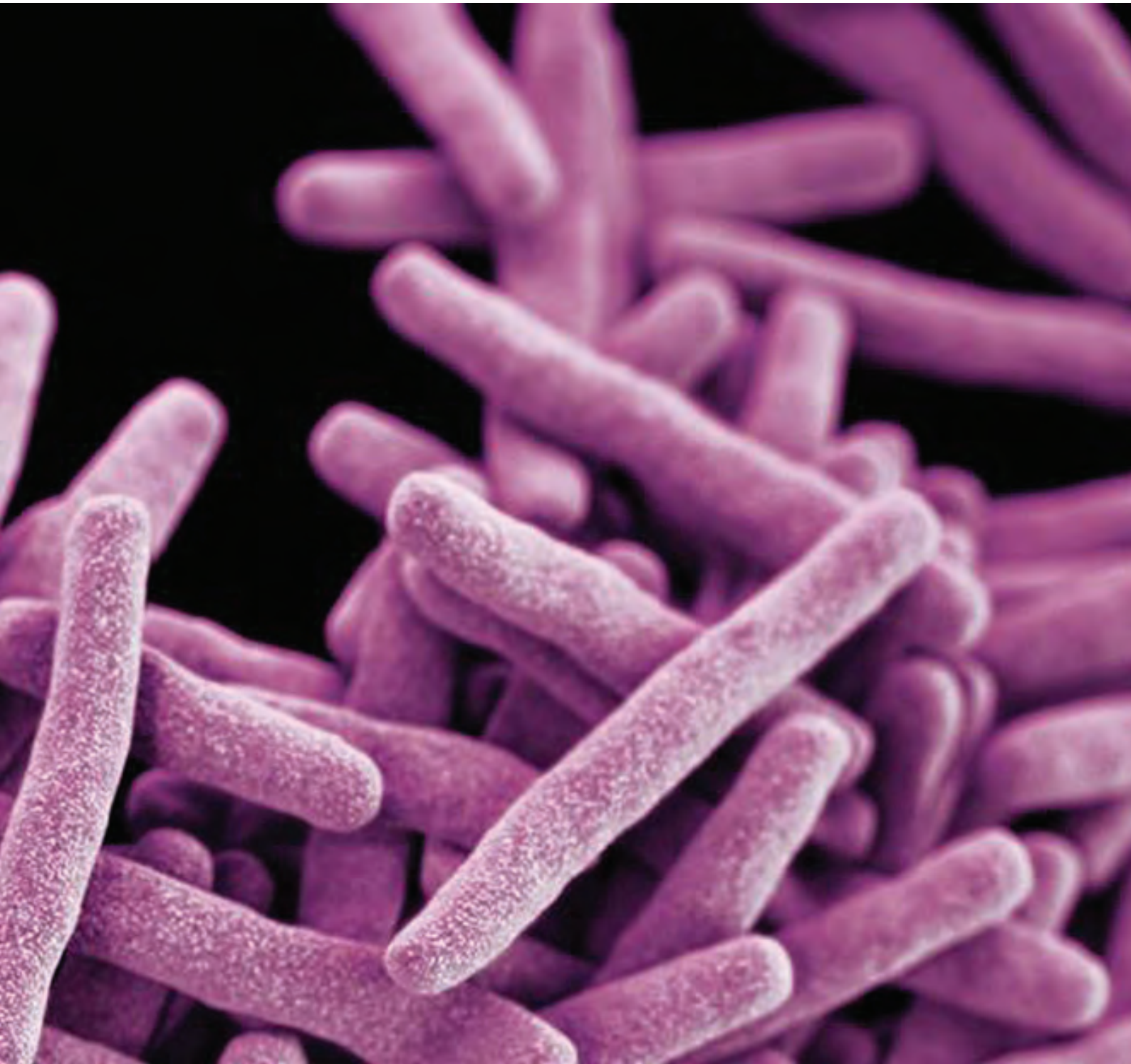
DZIF

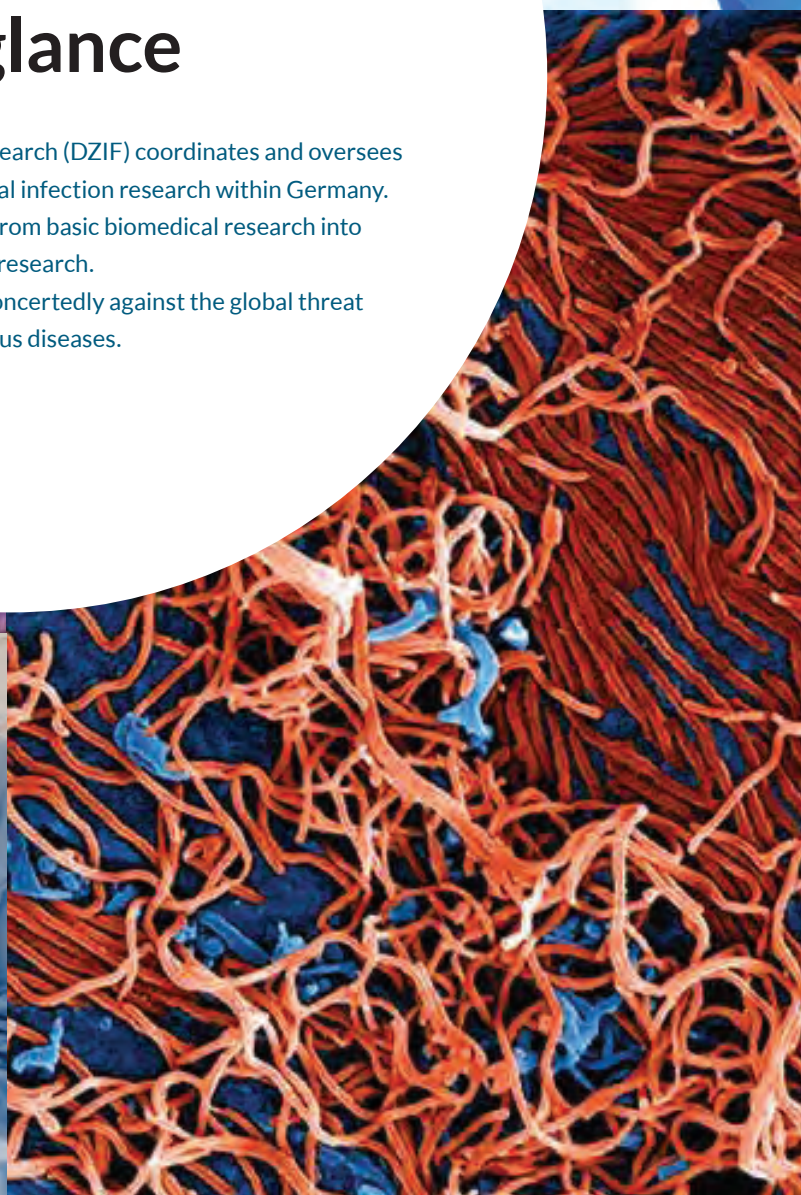
DZG DEUTSCHE ZENTREN DER GESUNDHEITSFORSCHUNG

GERMAN CENTER FOR INFECTION RESEARCH

Annual Report 2017



Title image: This shows an electron microscope image of a cluster of rod-shaped tuberculosis bacteria visible in pink.



ANNUAL REPORT 2017

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

Martin Krönke, Ulrike Protzer, Dirk Heinz

As part of an assessment spanning several centres in 2017, the German Council of Science and Humanities dealt intensively with the past and future development of the German Research Centres (DZG). It substantiates that the German Center for Infection Research (DZIF) can already demonstrate considerable success in terms of the expansion and advancement of translational infection research in Germany just a few years after its founding, and highlights the need for long-term orientation and institutional funding of the DZIF.

The global challenges posed by infectious agents actually demand patience and persistence. One of the highly debated health policy issues in 2017 was the rapid spread of antibiotic resistance–an issue that was discussed at both the G7 and G20 summits. At the G20 summit in Hamburg, the Global Antimicrobial Resistance Research and Development Hub was created to coordinate the development of new antibiotics and vaccines worldwide. The formation of the Global AMR R&D Hub in Berlin is supported by the DZIF.

The DZIF can already demonstrate tangible results. The Ebola epidemic in West Africa as well as the outbreak of the MERS coronavirus in Saudi Arabia have accentuated the need for new vaccines and drug therapy options for these previously untreatable viral diseases. In less than two years, DZIF researchers successfully designed a MERS vaccine that has been shown to be highly effective in camels. Further development of this vaccine to get it ready for clinical trial is carried out in cooperation with a German vaccine manufacturer (IDT Biologika GmbH) and is financially supported by the Coalition for Epidemic Preparedness Innovation (CEPI).

Myrcludex B is another example of successful translational research at the DZIF. This peptide therapeutic agent developed at the Heidelberg location blocks hepatitis B and D viruses from entering liver cells. The clinical trial of the novel peptide in hepatitis D patients (Phase II) showed resounding success and promptly received the "PRIME" seal from the European Medicines Agency (EMA): This distinguishes Myrcludex B as a particularly promising candidate for a new antiviral drug and its development is given priority by EMA.

DZIF scientists in Tübingen have achieved immunisation results of up to 100 percent in a clinical trial with an innovative vaccination approach against malaria. The vaccine is based on fully viable, non-attenuated malaria pathogens co-administered with an antimalarial drug. In 2017, we decided to dedicate even more attention to malaria and the neglected tropical diseases (NTD). Therefore, a new research focus on this topic is being established at the DZIF.

You can now read what the DZIF scientists were able to accomplish and achieve in 2017 in translational infection research. We hope you enjoy this exciting report.

DZIF e. V. Executive Board

Prof. Martin Krönke

Prof. Ulrike Protzer

Prof. Dirk Heinz

ABOUT THE DZIF

Think globally–operate in a network

The requirement for infection researchers to think beyond borders is greater than ever. Newly emerging pathogens such as Zika, Ebola or MERS viruses cause epidemics that require quick action, and increasingly resistant and multi-drug resistant bacteria call for new therapeutic options. The German Center for Infection Research (DZIF) is taking on these challenges: Thirty-five institutions across the nation have joined forces in order to develop new drugs, diagnostic products and vaccines faster. With partner institutions in Africa and Eastern Europe as well as through cooperation with international institutions, the DZIF is developing a globally unique infrastructure and opening up perspectives beyond the borders.

BUILDING BRIDGES: TRANSLATION AS A MISSION

The DZIF bridges the gap between basic research and clinical application: from test tube to patient, from testing to treatment. Scientists and physicians work closely together, therefore the lab results are getting faster to people suffering from a serious illness. For this process of so-called translation to work, the DZIF has organised and structured its work in projects spanning multiple institutions:

Scientists and physicians in nine research areas are researching infectious diseases such as "Tuberculosis", "Malaria", "HIV", "Hepatitis" or "Gastrointestinal Infections". The DZIF research areas also cover specific problem areas such as "Emerging Infections", "Infections in the immunocompromised Host", "Healthcare-associated and Antibiotic-resistant bacterial Infections", and "Novel Antibiotics".

Networking as a programme: At the annual DZIF meeting in 2017, the scientists met in Hamburg for a lively exchange.

IN-HOUSE SERVICE FACILITIES

For increased efficiency, the DZIF scientists are assisted by experts in eight "translational infrastructures". This gives them easy access to experts of the "Product Development Unit" when they have questions about drug approval and clinical requirements. The "Clinical Trial Unit" coordinates clinical trials on volunteers for infectious diseases. The "Bioinformatics" unit helps with special software. Sample material from tissues, body fluids or cells is retrieved from DZIF's own "Biobanking" unit. Defined bacterial strains are collected from the "Pathogen Repository" and analysed. In cooperation with "African Partner Institutions", the DZIF colleagues are able to research infectious diseases on location, which are less common in this part of the world. Since 2016, the "Epidemiology" unit has been supporting studies on the spread of pathogens in specific areas or populations.

YOUNG TALENTS FOR INFECTION RESEARCH

The DZIF has set up an academy specifically for the targeted support of young scientists in infection research. From the Technical University of Munich, it coordinates the selection of fellows, offers workshops, laboratory rotations, and other funding programmes. Clinical leave scholarships are particularly successful, as they offer young physicians the opportunity to leave the daily clinical routine so they can devote more time to research. With their clinical expertise and proximity to the patients, the young researchers are implementing the goal of translation: from Bench to Bedside.

STRONGER TOGETHER TO FIGHT INFECTIONS

The strength of the DZIF lies in the close network structure. Scientists and clinicians work together–beyond the boundaries of their institutions and professions. There is constant exchange between universities, research institutes, clinics, official authorities, and institutions as well as cooperation with medical practices and industrial companies. This expertise is bundled and coordinated internally in DZIF's own research areas and infrastructures. Furthermore, the DZIF is part of a superordinate national network of the German Research Centres (DZG). Last but not least, the DZIF has also established itself as a renowned partner in European and international research networks.

NATIONAL AND INTERNATIONAL

In addition to the traditionally set-up partnerships in Africa, the DZIF is consistently expanding its international contacts. A hospital in Romania has been integrated into the network for tuberculosis research. In cooperation with the French institute INSERM (Institut national de la santé et de la recherche médicale), the DZIF works on HIV and hepatitis. It is also one of nine CARA (Conscience of Antimicrobial Resistance Accountability) founding organisations.
This international alliance makes sure that effective antibiotics continue to be available worldwide in the future. The DZIF is also involved in the newly established vaccine initiative CEPI (Coalition for Epidemic Preparedness Innovations), where emergency vaccines are being developed. Furthermore, the DZIF is involved in the international fight against antibiotic resistance. The international initiative "Global Antimicrobial Resistance Research and Development Hub" (in short, Global AMR R&D Hub) will initially be based in Berlin under the patronage of the German Center for Infection Research.

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

Research areas

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

Infrastructures

- *African Partner Institutions*
- *Novel Antivirals (since 2018)*
- *Biobanking*
- *Bioinformatics*
- *Epidemiology*
- *Clinical Trial Unit*
- *Pathogen Repository*
- *Product Development Unit*
- *DZIF Academy*

Prepared for unknown pathogens

Viruses can change their genetic make-up in a short time. This leads to resistance to antiviral drugs or completely new viruses that can cause previously unknown infections in humans. To understand how quickly and unexpectedly these viruses can spread became evident in the Ebola crisis in West Africa and the Zika epidemic in South America. To contain such out-breaks, fast action is required.

This can only happen in an association of well networked experts who are prepared for emergencies. The DZIF scientists in this field are therefore exploring diagnostic methods for rapid and reliable identification of new pathogens. They establish platforms for the development of vaccines or antiviral drugs and observe changes in existing virus strains to facilitate prediction of impending outbreaks.

The DZIF scientists are developing a test platform for antiviral substances at seven locations. Here: Laboratory at the University of Heidelberg.

The tick *Ixodes inopinatus*, carrier of meningitis, spreads from the Mediterranean area to southern Germany.

FOCUSED ON THE SPREAD

For example, a group led by Dr Gerhard Dobler at the Munich Institute for Microbiology of the German Federal Armed Forces is investigating the spread of tick-borne encephalitis (TBE) viruses in Central Europe. The causative agent of TBE is transmitted by ticks to humans and can cause potentially fatal meningitis. These pathogens occur in constantly new regions of Germany and in 2016 for the first time in the Netherlands. The researchers from Munich suspect that birds are associated with the spread, because molecular biological results by scientists from different regions of Europe showed that the TBE viruses are spread along the known bird migration lines. In a project supported by the DZIF, they reported seeing *Ixodes inopinatus*, a tick previously only seen along the Mediterranean, and other previously rare species in southern Germany among known TBE herds. "The importance of these transfers across continents has hardly been researched so far and could be of great importance for the emergence of diseases transmitted by ticks," emphasises Dobler. The DZIF project provides a better understanding of the propagation mechanisms in order to prevent the transmission of infections together with the public health service.

BEING PREPARED FOR THE UNEXPECTED

In order to combat new infections, new vaccines and drugs have to be developed. However, antiviral substances usually have a highly specific effect and only against certain viruses. In order to prepare for unknown viruses, a virtual test platform for broadly effective antiviral substances was established as part of a DZIF project. DZIF scientists at seven different sites, including a coordinating headquarters in Heidelberg, are testing on location depending on the virus expertise, thus creating a networked test platform. "New viral diseases often occur very suddenly. Developing a specific drug often takes years. We are therefore looking for substances with broad-spectrum effect that can quickly be tested and used with new viruses", explains project coordinator Prof. Ralf Bartenschlager, Head of the Department of Molecular Virology at the University Hospital Heidelberg. The researchers are primarily focusing on agents already approved for other diseases or known to be tolerated in clinical trials to minimise time and development costs. "We were already able to identify a first lead compound, the cyclophilin blocker, as an inhibitor against many viral pathogens," says Bartenschlager. The platform could also be a useful testing tool for the industry, the virologist believes, adding: "We are already in negotiations with cooperation partners and would be very happy to welcome other partners, especially from the industry."

GOALS IN 2017: OUTCOMES

◐ Conduct a first-in-man clinical phase I trial using the investigational drug MVA-MERS-S produced in 2016.

◐ Test cyclosporine analogues and silvestrol in animal models for antiviral effects against coronaviruses.

◐ Preparation of a FlexFund application to strengthen the DZIF's international presence through a clinical trial to be conducted in the African partner institutions.

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

GOALS FOR 2018

○ Immunological follow-up experiments in the context of a first-in-man clinical phase I trial using the investigational drug MVA-MERS-S produced in 2016.

○ Expansion of the DZIF virus test platform through inclusion of physiological primary cell culture systems.

○ Strengthening the international reach of the DZIF through intensive collaboration with the *Coalition for Epidemic Preparedness Innovations* (CEPI) as part of developing the MVA-MERS vaccine.

Coordinator:
Prof. Stephan Becker
Marburg

Responses to Refugees and Resistance

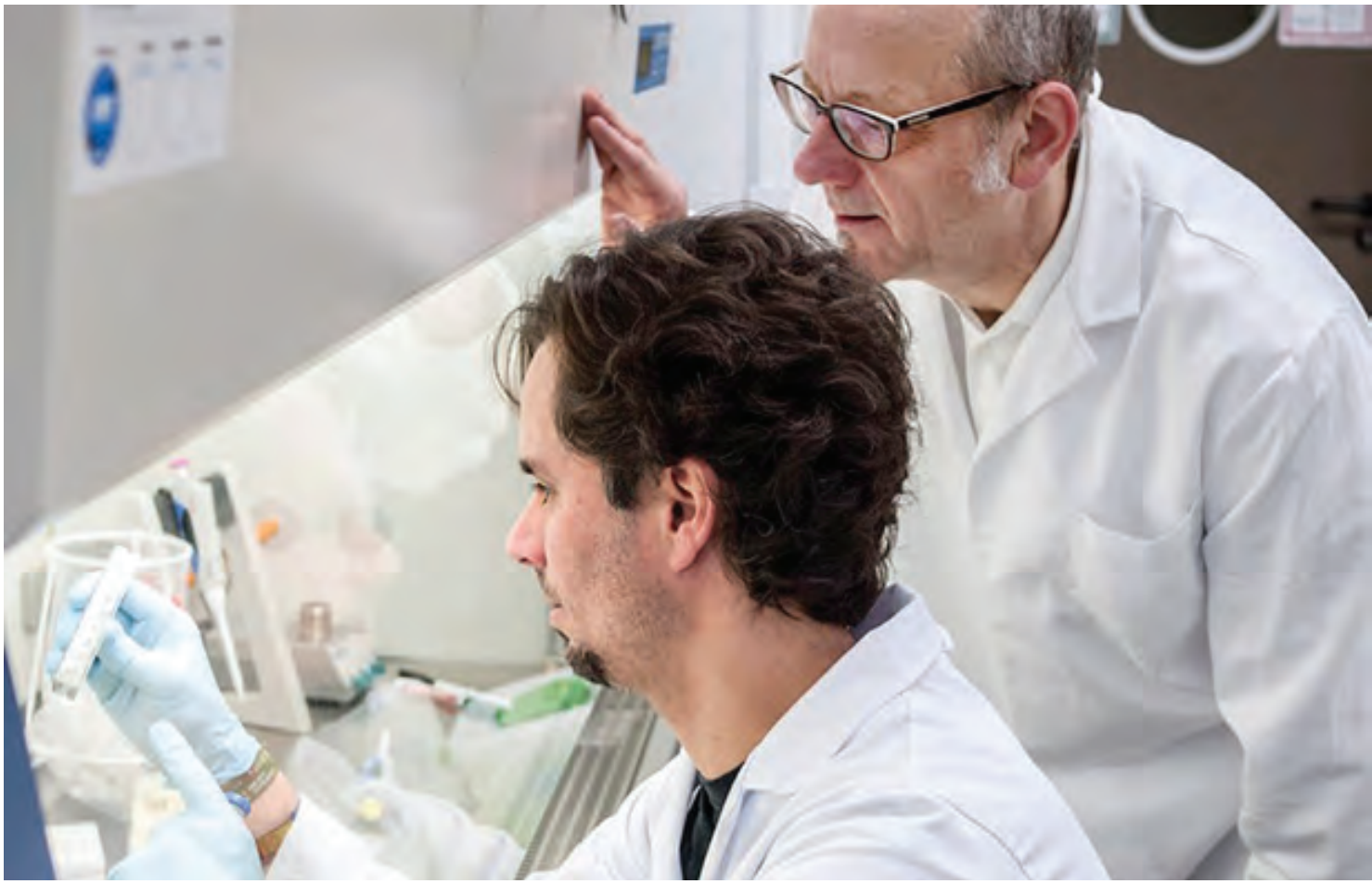
Tuberculosis (TB) is caused by an infection of the lung with mycobacteria and can spread to other organs. According to the WHO, 10.4 million people worldwide suffer from it each year. 1.7 million died in 2016 as a result of TB. It is the infectious disease that causes most deaths worldwide. The DZIF scientists specialising in "Tuberculosis" research are investigating the spread of the pathogens, testing new drugs and developing diagnostic biomarkers for individual treatment.

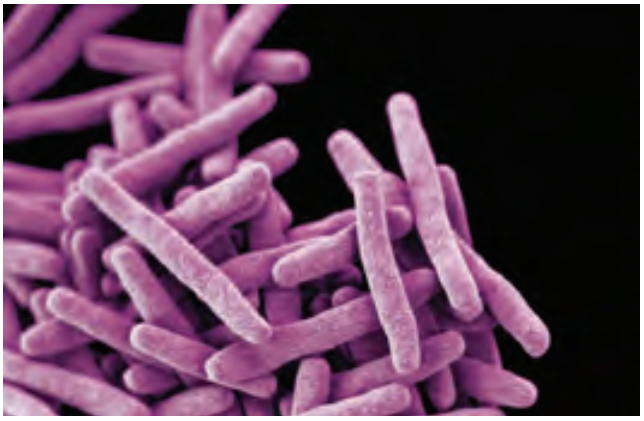
Problems with the diagnosis are the main cause as to why tuberculosis is difficult to contain. Currently used methods such as conventional X-ray images of the lungs are more than 100 years old and in parts do not allow safe differentiation from other lung diseases. Especially during examination of children or larger groups, a TB infection is difficult to distinguish from other diseases. On the other hand, early detection and targeted treatment of TB is a decisive factor to avoid serious illnesses, deaths and the spread of antibiotic-resistant germs.

RESPOND FASTER WITH NEW DIAGNOSTIC METHODS

How important a rapid and reliable diagnosis is was demonstrated by the recent influx of refugees to Germany. "The familiar diagnostic method in the admission examinations

Dr Tobias Dallenga (left) and Prof. Ulrich Schaible are developing an alternative treatment method for tuberculosis.





Tuberculosis bacteria; aesthetics of the dreaded germs under the electron microscope.

often led to false results," said Dr Norbert Heinrich from the University of Munich. In case of TB suspicion, those affected spent weeks in infectiological specialist clinics until the findings were clarified. In order to establish faster and better TB diagnostics, the DZIF scientists working with Heinrich at the LMU Munich and the Research Centre Borstel are testing new methods. In the "RefuScreen" study, they are studying several new tests on children and adults who tested positive for TB at the initial visit. The tests also include an immunological procedure developed by DZIF researcher Dr Christof Geldmacher at the Tropical Institute of the University of Munich, which has already been tested on approximately 130 children at the African Partner Institution in Mbeya (Tanzania). This TAM-TB test allowed differentiation of TB infectious disease from non-infectious latent infection. "In Tanzania, the blood test showed active tuberculosis more precisely and more specifically, including in children. With this method, test results can be delivered the very next day," explains project coordinator Heinrich. As part of the "RefuScreen" study, the test is now being evaluated in Germany and combined with other methods.

RESPONDING TO RESISTANCE WITH NEW THERAPEUTIC APPROACHES

An individual procedure also requires the treatment of tuberculosis, especially because of the increase of resistant pathogens. Patients infected with these germs receive treatment with specific antibiotic combinations. Their treatment time is often significantly prolonged, the side effects are amplified and the risk of death is increased. Therefore, in addition to new antibiotics, alternative therapies are urgently needed. One promising approach is host-oriented therapy, which targets the patient's immune system. The DZIF scientists led by Dr Tobias Dallenga and Prof. Ulrich E. Schaible from the Borstel Research Centre found that neutrophil granulocytes are a promising target for this purpose: Human defence cells play a key role in disease development as they are most affected by TB bacteria in the lungs. The granulocytes are manipulated by the pathogens so that they destroy themselves and their defence effect fails. It creates a vicious cycle of cell death, bacterial spread and finally tissue destruction. The Borstel team has now shown that inhibiting the cell death of infected granulocytes helps other host cells break the vicious cycle. "With this therapeutic approach, we want to contain the tissue damage and remove the tuberculosis pathogens growth base," said Prof. Ulrich Schaible, promising that "there are already drugs in clinical trials for other diseases that could soon be tested for tuberculosis."

GOALS IN 2017: OUTCOMES

- ● The specific hereditary information of a patient's tuberculosis pathogens was to be determined in order to enable individual treatment adjustments.
- ◐ Identify biomarker candidates in order to individualise the duration of M/XDR-TB treatment.
- ● Submit a clinical phase I protocol for a potential tuberculosis drug to BfArM.

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

GOALS FOR 2018

- ○ The individual adaptation for treatment of TB patients based on the exact genome of the tuberculosis pathogens is evaluated in the clinic.
- ○ An initial selection of biomarkers is available for assessing the course of therapy for M/XDR therapy.
- ○ The first test subjects will be included in the study for a potential tuberculosis drug.

Coordinator:
Prof. Stefan Niemann
Borstel

Advances in prevention

Malaria is one of the world's leading infections. According to the WHO, in 2016 about 216 million people were diagnosed with the tropical disease, which is transmitted by the bite of infected mosquitoes. Typical symptoms of malaria are alternating fever and fever-free phases. Around 445,000 people died in 2016, 90 percent of them in Africa. Almost three quarters of all deaths affect children under the age of five.

Single-cellular parasites called plasmodia cause malaria; they are genetically highly adaptable and therefore partially resistant to common drugs. Co-infections with other pathogens additionally complicate the treatment. Therefore, the DZIF researchers focused on "Malaria" are taking unconventional routes, developing parasite inhibitors, testing alternative vaccination methods and investigating the regional spread of pathogens. This also improves malaria infection prevention.

A NEW ACTIVE INGREDIENT FOR PROPHYLAXIS

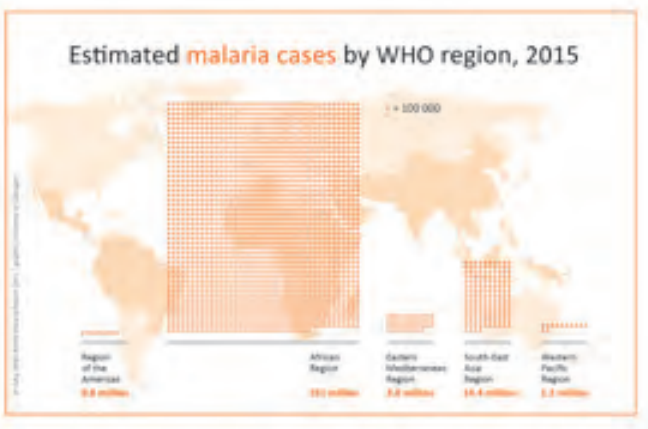
Although various medicines already exist for malaria

In the fight against malaria, the DZIF scientists are investigating multiple avenues.

prevention, they sometimes cause serious side effects. Others are more tolerable, but must be taken daily. For people from non-tropical regions, forgetting to take the drug is the biggest risk factor for malaria. The DZIF scientists headed by Prof. Peter Kremsner and Prof. Benjamin Mordmüller from the Institute of Tropical Medicine at the University of Tübingen have recently clinically tested a new substance called DSM265. The study, supported by the Medicines for Malaria Venture (MMV) Network and the DZIF, involved 21 healthy volunteers who were previously unaffected by malaria. They received one dose of DSM265, an established malaria drug or a placebo. One or seven days after ingestion, all were infected with malaria pathogens under controlled conditions. The new remedy inhibits the metabolism and thus the multiplication of the parasites. "The volunteers who had taken DSM265 the day before were protected from the infection. The intake seven days before the infection was only partially effective," summarises Mordmüller. By increasing the dosage, which will be tested in a second clinical trial, the physician sees opportunities to achieve sufficient protection with a single dose even for a longer period of time. If this turns out to be successful, it would mean that there is an important means of malaria prophylaxis, especially for tropical travellers.

A VACCINE FOR PREVENTION AND RESISTANCE PREVENTION

For more than 100 years scientists have urgently been looking for a vaccine. It would not only protect travellers but also people in malaria areas and prevent the spread of resistant strains. For the first time ever, Prof. Kremsner and Prof. Mordmüller have now tested a new vaccination method in a clinical trial involving 67 healthy test subjects, achieving vaccination protection of up to 100 percent. Unlike previous vaccines, the vaccine is based on fully viable non-attenuated malaria pathogens that are co-administered with the antimalarial drug chloroquine. "By vaccinating with a living pathogen that was only attenuated once it was inside the body, we managed to trigger a very strong immune response," said study director Benjamin Mordmüller. "The protection was probably caused by specific T-lymphocytes and antibody responses against the parasites," added Peter Kremsner. The study results indicated a relatively stable and long-lasting vaccination protection. Moreover, the vaccine was very well tolerated. Next, its effectiveness will be tested in several clinical trials in the African partner institute of Tübingen in Gabon for several years. Malaria is one of the biggest health issues in this region. If these studies are successful, the newly developed vaccine could become an important component of malaria prophylaxis.



According to estimates by the WHO, Africa has to contend with most malaria cases.

GOALS IN 2017: OUTCOMES

- ● The Tübingen malaria vaccination schedule was supposed to be further improved, and initial implementation in Africa was scheduled.
- ◐ The research on the experimental malaria agent's mechanisms of action and resistance was supposed to be continued.
- ● Diagnostic biomarkers that enable a differentiation between malaria and sepsis in ill children and adolescents in Africa were to be selected from well-defined clinical samples.

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

GOALS FOR 2018

- ○ The Tübingen vaccination schedule for malaria will be optimised and defined for further clinical development. A first-time application in Africa will be implemented.
- ○ Continue research on the experimental malaria agent's mechanisms of action and resistance.
- ○ Clearly defined reference samples are collected to evaluate or confirm the forecast performance of the identified diagnostic biomarkers.

Coordinator:
Prof. Peter Kremsner
Tübingen

New Approaches to Prevention and Treatment

Human immunodeficiency virus (HIV) continues to cause a global health problem. According to the WHO, around 37 million people currently live with the virus, which is the cause of AIDS (*acquired immunodeficiency syndrome*). In 2016 alone, one million people worldwide died of HIV. Africa is the hardest hit continent, as it accounts for almost two-thirds of all new HIV infections worldwide.

Medicinal antiretroviral therapy (ART) extends the life expectancy of affected patients and reduces new infections. However, only about half of the affected people worldwide receive these therapies. Although the disease has become treatable with ART, the pathogen remains in the body and becomes active again when the therapy is discontinued. So far, there is neither a cure nor a vaccine that protects against HIV infection, and the mutability of the virus makes new therapeutic approaches difficult. The DZIF scientists focusing on "HIV" research rely on gene therapy methods to break through the resistance of the viruses, so they can more easily attack them, or they use neutralising antibodies for treatment.

At the University of Cologne, the task forces around Florian Klein and Gerd Fätkenheuer develop antibodies for the treatment of HIV.

NEW HIV-NEUTRALISING ANTIBODIES TESTED

A team led by DZIF scientist Prof. Florian Klein at the University of Cologne has been researching in recent years new, broadly neutralising antibodies against HIV. "These antibodies can effectively neutralise a large amount of different HIV viruses, thus rendering them harmless, and are therefore of particular importance in the search for and development of an HIV vaccine," explains Klein. Together with the DZIF researchers led by Prof. Gerd Fätkenheuer from the Clinical Infectious Diseases Department of the University of Cologne and scientists from Rockefeller University in New York, Klein investigated whether these broadly neutralising antibodies are also suitable for HIV therapy. They recently tested the antibody "10-1074" in a phase I clinical trial. In the phase I study, the antibody was well tolerated and displayed high antiviral activity, which significantly reduced viral strain in the blood of HIV-infected individuals. The scientists owe the basic understanding of the pathogen-host interaction of these antibodies to their *in vivo* studies on mice in the Humanised Mouse Core Cologne (HMCC), a newly established mouse core at the University of Cologne that is funded by the DZIF.

NEW DISCOVERIES ABOUT INFECTION AND IMMUNE SYSTEM

The interplay between HI virus and human immune cells is also the focus of research performed by Prof. Marcus Altfeld and Dr Angelique Hölzemer at the Hamburg Heinrich Pette Institute (HPI). Both DZIF scientists proved that HIV-1 peptides can inhibit the defence function of certain human immune cells, the natural killer cells (NK cells). The HI virus can use this mechanism to evade the immune system. In addition, the DZIF scientists and their colleagues at Harvard Medical School have identified a long-sought messenger (ligand) for activation of the NK cell receptor, which is associated with slower progression of HIV-1 infection. For this work, the two DZIF researchers were awarded the "Hector Research Award HIV 2017". "Many of the immunological factors that can positively influence the course of HIV-1 infection are still unknown. We hope that a better understanding of these factors will contribute to the development of new treatment strategies," said Prof. Altfeld at the award ceremony. "This award is certainly an additional motivation boost," added Hölzemer, who is supported by the DZIF Academy with an MD/PhD fellowship.

Dr Angelique Hölzemer explains her outstanding work about the course of HIV infection.

GOALS IN 2017: OUTCOMES

- ● Preparatory (non-clinical) studies to conduct a first-time clinical study on HIV removal.
- ● The Humanised Mouse Core in Cologne is supposed to start its work on preclinical HIV trials.
- ● Opening of the new "Center for Integrative Infectious Disease Research (CIID)" with a Europe-wide unique imaging platform for HIV research.

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

GOALS FOR 2018

- ○ Combination therapy with two broadly neutralising antibodies in HIV patients.
- ○ Preparation of a first-time clinical anti-HIV gene therapy study in Hamburg.
- ○ The DZIF imaging platform in Heidelberg starts operations in the new research building.

Coordinator:
Prof. Hans-Georg Kräusslich
Heidelberg

Tackling challenges in hepatitis

According to estimates by the WHO, approximately 257 million people worldwide have chronic hepatitis B (HBV) and 71 million suffer from a chronic hepatitis C virus (HCV) infection. The frequently unnoticed liver inflammation can lead to liver cirrhosis and cancer. According to the WHO, 1.34 million people worldwide die every year from viral hepatitis. There is a prophylactic vaccine against HBV infection and antiviral drugs to be used at the onset of the disease, but there is no cure. In most cases of hepatitis C this is possible thanks to novel antiviral drugs, but a preventive vaccine is still missing.

In the DZIF research field "Hepatitis", the focus is on improving the prevention and treatment of viral hepatitis. For example, DZIF scientists are focusing on optimising hepatitis C treatment as well as epidemiological studies in countries with high disease rates. These studies are necessary to determine the frequency and the associated treatment needs.

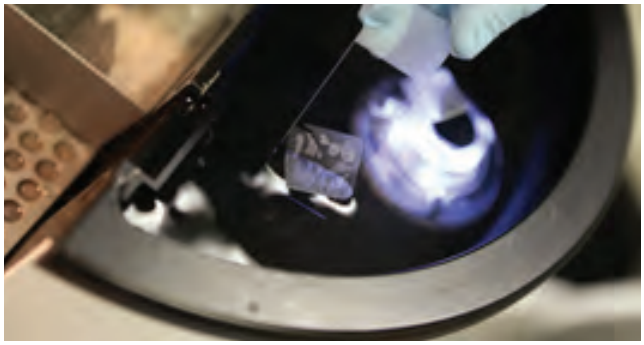
Laboratory tests are necessary to detect viral hepatitis.

COLLABORATION AND CAPACITY INCREASE ACROSS CONTINENTS

Chronic hepatitis B virus infections are common in many West African countries. To collect more detailed data on risk factors and affected populations, the DZIF scientists collaborated with their African Partner Institution "Centre de Recherche de Santé de Nouna (CRSN)" to conduct a major epidemiological study on chronic HBV infection. In field surveys, the scientists collected baseline data on the prevalence of HBV infection as well as sociodemographic information. They also took blood samples from a representative population of over 4,000 people. "According to initial analyses, the prevalence is around five percent, and as expected, significantly higher in older people," reports Dr Jördis Ott from the HZI. "These types of studies are important to obtain real data on the burden of chronic HBV infections that are absent in sub-Saharan Africa, and even more so in Burkina Faso," confirms Dr Ali Sié, head of the partner institution and director of the CRSN. The DZIF study is significant for the research partnership and local capacity increase. He therefore hopes to continue the collaboration with other hepatitis projects and beyond.

RELIABLE PREDICTABILITY DEPENDING ON VIRUS VARIANT

There are also challenges in this country when it comes to the treatment of chronic hepatitis C. Since there is availability of treatment opportunities with direct antiviral agents (DAAs), more and more patients can be cured. However, cure rates vary depending on the virus genotype and condition of the liver. "Especially patients with cirrhosis or concomitant infections as well as carriers of the HCV genotype 1a and 3 are more difficult to treat," explains Dr Julia Dietz from the University Hospital Frankfurt. This is due to the development of resistance of the virus to certain drugs. In 10 to 20 per cent of patients, so-called resistance-associated virus substitutions (RASs) are apparently already be present before the start of therapy. In an ongoing cohort study, the Frankfurt-based DZIF researchers and their colleagues from the Hannover Medical School and other European physicians are collecting samples from previously untreated and treatment failure patients. Based on their data, the researchers are investigating which agents work best for which virus type and for which variant of resistance. "Through genotypic resistance tests, we can make more reliable predictions about the therapeutic success and provide physicians with recommendations for choosing the optimal medication, even in difficult cases," says Dietz. Initial applications according to these guidelines already showed significantly higher healing rates, even in patients for whom therapy had previously failed.



The smallest liver slices are examined in the laboratory.

GOALS IN 2017: OUTCOMES

- ● The tests for eliminating HBV infection in humanised mice by means of immunotherapies are supposed to be continued.
- ● A new study on treating chronic hepatitis E is supposed to be initiated at the German Liver Foundation's HepNet Study House.
- ◐ A large epidemiological chronic HBV study is being conducted in Burkina Faso. The goal was to attain representative conclusions and generate evidence on seroprevalences in the general population of a low-income country.

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

GOALS FOR 2018

- ○ Next generation sequencing methods (NGS) will be introduced into the online-based platform Geno2pheno for the identification of viral resistances.
- ○ Development of a standard protocol for the polymerase chain reaction (PCR) of cccDNA in hepatitis B viruses: Comparison of different DNA preparation and detection methods in an international consortium.
- ○ Establishment of a set of hepatitis C virus isolates representing the full range of antibody responses to HCV as the basis for the development of a prophylactic vaccine.

Coordinator:
Prof. Michael Manns
Hanover

Targeting and stopping stomach and intestinal germs

Gastrointestinal infections are caused by numerous bacteria, viruses and parasites. They often cause diarrhoea with soft stools and vomiting and can lead to malnutrition if the disease persists. According to the WHO, there are nearly 1.7 billion diarrhoea cases each year worldwide–in children alone. For children under the age of five, diarrhoea is the second leading cause of death.

The DZIF research field "Gastrointestinal Infections" aims to improve diagnosis, treatment and prevention of bacterial infections of the gastrointestinal tract. The scientists are exploring the natural gastrointestinal flora and trying to figure out how to strengthen them. They are developing new therapeutic approaches that block certain pathogens, as well as new vaccines for prevention and treatment.

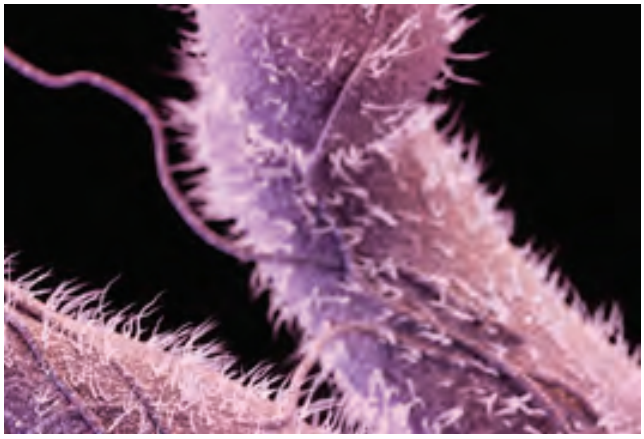
The diagnosis of blood cultures plays a major role in infections.

MUTATION MECHANISMS OF THE GASTRIC GERM ANALYSED

One of the most important pathogens of the gastrointestinal tract is *Helicobacter pylori*, which infects about one in two people. The bacterium is the main cause of gastritis (gastric mucosal inflammation) and gastric or duodenal ulcer and is considered a risk factor for gastric cancer. Typical of *Helicobacter pylori* is its genetic diversity, which was studied in detail by a team led by DZIF scientist Prof. Sebastian Suerbaum at the Max von Pettenkofer Institute of LMU Munich. Using freshly infected samples, the researchers were able to observe at the molecular level exactly what changes the bacterium undergoes in its early adaptation phase: "The mutation rate is very high–right from the start," explains Suerbaum. Together with researchers at the Hannover Medical School and the University of Magdeburg, the team from Munich showed how individual components of the genetic material of the bacterium change at the beginning of the infection. "High genetic diversity is a challenge for the development of a vaccine," Suerbaum emphasises. A badly needed vaccine against the gastric germ is already being worked on at the DZIF. "The results of the study will have an impact on the selection of potential vaccine antigens," Suerbaum is convinced.

INHIBITOR OF MOLECULAR SALMONELLA SYRINGE IDENTIFIED

DZIF scientists led by Prof. Samuel Wagner of the University of Tübingen are investigating the pathogenic properties of the pathogens. They pay particular attention to the type III secretion systems (T3SS), a protein complex found in Salmonella, for example. T3SS enable bacteria to inject proteins into their hosts through a molecular needle. Based on their discoveries of the structure and function of the system, the DZIF researchers looked for a suitable inhibitor. Using bioinformatic methods, they screened 250,000 small molecule compounds of a compound library and studied 50 selected compounds in laboratory assays. "In the subsequent tests in cell cultures, only compound C26 showed strong inhibition of bacterial pathogenicity and low toxicity," explains Wagner. The researchers were able to demonstrate that C26 blocks the formation of the entire T3SS. "It works by preventing bacteria from producing the building blocks of the injection needle and the injected proteins, thus preventing an infection," explains Wagner, who may have found a new class of inhibitors. Supported by DZIF experts in product development and the research field "Novel Antibiotics", drug development and other preclinical tests are now pending.



The DZIF scientists in Tübingen are focussing on salmonella.

GOALS IN 2017: OUTCOMES

- Completion of the SPECTRUM study including bioinformatic evaluation of the data.
- Identification of first microbiota-associated biomarkers for gastrointestinal infections, particularly *Clostridium difficile* infections.
- Initiation of the CROSSDIFF trial (follow-up trial to the SPECTRUM trial).

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

GOALS FOR 2018

- ○ Revalidation of the successfully completed high-throughput screen using structure-effect relationships and launch of the hit-to-lead programme.
- ○ Identification of new vaccine antigens for a prophylactic vaccine against *Helicobacter pylori* in the infection model.
- ○ Completion of the recruitment phase of CROSSDIFF, a multicentric cross-sectional study on the association of clinical and microbial risk factors for *C. difficile* infection and correlation with the complementary data of the prospective SPECTRUM study.

Coordinator:
Prof. Sebastian Suerbaum
Munich

Strengthening the immune system – protection against infections

Modern cancer therapies, transplants and intensive care increase the life expectancy of many patients. But these methods come with a price. They often weaken the immune system of the treated patient. Due to the demographic change with more and more elderly and chronically ill people, the proportion of immunocompromised patients in clinics is also increasing. Pathogens that are harmless to healthy individuals can become life-threatening for this group of patients.

Which risk factors particularly weaken the immune system of the respective patient is currently unclear. The DZIF scientists in this area of research are looking for biomarkers for risk assessment, developing vaccines and novel therapies to strengthen the immune defence and to protect immunocompromised patients from infection. How significant this research is can be seen in humans after organ transplantation, for example.

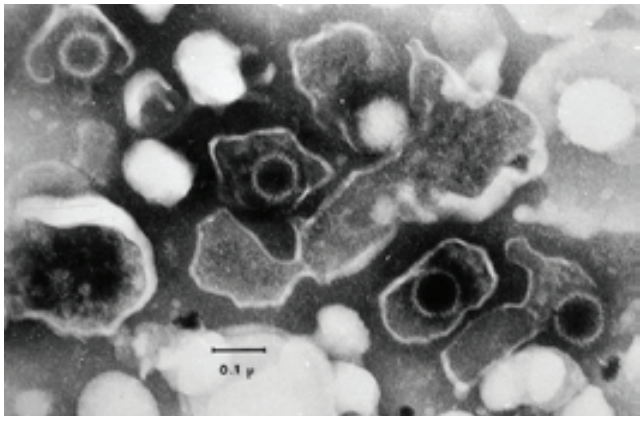
Bioprobes of transplant patients are collected and conserved in the DZIF.

PROTECTING ORGAN RECIPIENTS–MINIMISE HARMFUL INFLUENCES

Many organ recipients have to take lifelong "immunosuppressants" that prevent rejection of the transplanted organ. These drugs intentionally weaken the body's immune system and thereby promote infections. "The more we understand the relationships between transplantation, pre-existing conditions, medication and infections, the more effectively we can protect patients," explains Dr Daniela Schindler, project manager of the "DZIF-Transplantationskohorte e. V." at University Hospital rechts der Isar in Munich. An essential part of the cohort is the database. It contains up to 5,000 different parameters such as age, pre-existing conditions, type of transplant, infections, and medications. Following strict data protection guidelines, patient data is centrally documented, while the associated blood, stool or urine samples are collected and stored in biobanks at the transplantation sites in Hannover, Munich, Heidelberg and Tübingen. "By May 2018, we were able to gather 6,160 blood samples and a total of 758 patients for the cohort," said Schindler. Their health progression will be monitored through routine check-ups, infections, diseases or therapies over the next few years. The data and samples serve as an important basis for later DZIF studies. "They could reveal how the patient's immune response changes after transplantation, thereby improving the care of future transplant patients," says Schindler.

PROTECTING IMMUNOCOMPROMISED INDIVIDUALS WITH A NOVEL EBV VACCINE

The team led by Prof. Wolfgang Hammerschmidt at Helmholtz Centre for Infection Research Munich is focussing on the development of a vaccine against Epstein-Barr virus (EBV). Named after the people who first discovered it, the virus is present in 90 percent of adults and is kept at bay by a healthy immune system. In immunocompromised individuals, however, it can cause life-threatening B-cell lymphoma. The DZIF scientists have developed a vaccine from virus-like particles (VLPs). Although they have the same structure as the virus, they do not have its genetic material and are therefore not infectious. "With the VLPs, we can produce a strong immune response that protects against infections with EBV," says Hammerschmidt. It does not only benefit patients with a reduced immune system. In recent years significantly more adolescents than ever before have been affected by the virus, which is often transmitted by kissing. For them, the vaccine could offer protection against Pfeiffer's glandular fever, which is characterised by flu-like symptoms and lymph node swelling and also increases the risk of cancer. In preclinical trials, the vaccine of choice has already been successfully investigated. "As soon as we find a suitable industrial partner for vaccine production, we can start with the clinical trials," says Hammerschmidt.



DZIF scientists are developing a vaccine against Epstein-Barr virus (electron micrograph).

GOALS IN 2017: OUTCOMES

- ● New biomarkers were supposed to be identified to assess pathogen-specific risks of infection in immuno-compromised patients.
- ◐ Complete recruitment of the Tx cohort and first cohort-associated projects.
- ◐ Identify new inhibitors for clinically relevant viral infections during immunosuppression.
- ◐ Recruit the target number of patients for the PACT Trial (adoptive T cell therapy trial for the prophylactic treatment of infections in allogenic stem cell transplants).
- ◐ Develop a GMP-compatible manufacturing process for a prophylactic vaccine against the Epstein-Barr virus.

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

GOALS FOR 2018

- ○ First biomarker projects using the Tx cohort.
- ○ Advancement of a prophylactic EBV vaccine.
- ○ PACT trial (see above): Expansion to additional locations.

Coordinator:
Prof. Dirk Busch
Munich

Hospital pathogens under control

Almost one million people become infected in Germany each year during their hospital stay, according to the German Society for Hospital Hygiene (DGKH). Approximately five per cent of hospital patients are affected by these nosocomial infections and up to 30,000 die from it each year. The leading cause is the increase in resistant bacterial pathogens, which are insensitive to common antibiotics.

These hospital-borne germs lead to higher treatment costs, longer hospital stays and increase the mortality for those affected. The DZIF research area "Healthcare-associated and Antibiotic-resistant bacterial Infections" is therefore coming up with new strategies to combat the development and spread of resistant bacteria, for example through responsible use of antibiotics (antibiotic stewardship) and improved infection control.

IMPROVED DIAGNOSIS OF RISKY DRUG RESISTANCE

A major task of infection control is to uncover sources of infection and transmission pathways. For example, in 2016, DZIF scientists from the Giessen University first demonstrated multi-resistant bacteria in Germany with the mobile resistance gene mcr-1. These germs could not be made innocuous, even by the reserve antibiotic colistin.

Responsible use of antibiotics is also on the agenda at the University Hospital of Cologne. In the picture: DZIF scientist Maria Vehreschild.

Detection of resistant genes as quickly as possible can protect against spread.

Distribution of the mcr-1 gene is readily accomplished via plasmids, small circular DNA molecules that can be transferred between different bacterial species. "Therefore, it is important to detect mobile mcr-1 resistance as quickly as possible to prevent further transmission," emphasises Dr Linda Falgenhauer, DZIF scientist at the Institute of Medical Microbiology of the Giessen University. Together with DZIF colleagues and other scientists in the RESET research network, she has tested a rapid molecular test in a study. The test clearly differentiated between conventional and plasmid-localised colistin resistance. "The results for a sample are already available after just twenty minutes", explains Dr Judith Schmiedel from the Giessen team. In addition, the test is apparently so uncomplicated that it could be further developed in the future for diagnostics in hospitals or livestock farming.

RESPONSIBLE USE OF ANTIBIOTICS

Another strategy against multidrug-resistant pathogens is the targeted and responsible use of antibiotics in hospitals– also known as antibiotic stewardship (ABS). DZIF scientists led by Prof. Evelina Tacconelli from the University of Tübingen conducted a meta-analysis based on literature data to assess the influence of antibiotic stewardship measures in the treatment of clinical patients. For this systematic review, the researchers evaluated publications from 1960 to 2017. "The results confirm that certain areas of the clinic can no longer function without antibiotic stewardship programmes," Tacconelli is convinced. Intensive care patients benefited the most. Overall, the programmes would significantly reduce the frequency of infections and colonisation with antibiotic-resistant bacteria in patients. The best results were achieved in combination with infection control measures such as proper hand hygiene. "This study provides policy makers and health care professionals with important recommendations for antibiotic stewardship interventions, effectively reducing infections caused by antibiotic-resistant bacteria," Tacconelli says emphatically.

GOALS IN 2017: OUTCOMES

◐ Establish a nationwide network in Germany and collect first samples for monitoring the prevalence of multidrug-resistant pathogens, bloodstream infections and Clostridium infections.

◐ Evaluate study data from the enterococci contact isolation study and define variables and parameters that promote infection and colonisation with enterococci.

◐ Introduction of Antibiotic Stewardship measures and monitoring their impact on the use of antibiotics and the development of antibiotic resistance.

◐ *Goal partially achieved/project is still ongoing*

● *Goal achieved*

GOALS FOR 2018

○ Further development of promising eradication and anti-virulent agents against *Staphylococcus aureus*.

○ Publication of a multicentric analysis on the influence of contact isolation in single-bed rooms on the acquisition of colonisation with vancomycin-resistant enterococci in high-risk patients.

○ Establishment of an interactive database network, a collection of key pathogens, including blood cultures, and innovative whole genome sequencing technology to develop an early warning system for the identification of new resistant strains of bacteria (so-called "high-risk clones").

Coordinator:

Prof. Evelina Tacconelli

Tübingen

Promising active ingredients from natural substances

Antibiotics can be used to treat and often cure many infectious diseases. They facilitate modern intensive care medicine and have increased the life expectancy of many people. But excessive use of antibiotics is making more and more germs insensitive to conventional drugs.

The rise in these resistant bacteria poses major challenges for medicine: New antibiotic classes are urgently needed but their development is expensive and takes decades. The DZIF scientists researching "Novel Antibiotics" are looking for new points of attack and chemically new antimicrobial compounds. For example, they rely on the biochemical synthesis of substances and the natural product screening with the assistance of genome sequence analyses.

At the HZI in Braunschweig, the production of promising antibiotic candidates is being optimised.

DIGITAL TOOLS FROM THE WEB

The deployed natural products are small bioactive molecules that are produced by microorganisms. Ninety per cent of all clinically used antibiotics are derived from such secondary metabolites. "To date, about 900,000 gene clusters have been identified that encode secondary metabolites. But we still don't know which ones produce what, "says DZIF professor Nadine Ziemert from the University of Tübingen. Exploring each one individually would be like searching for a needle in a haystack. The microbiologist and her interdisciplinary team therefore rely on genome mining methods at the interface between microbiology and bioinformatics. Accordingly, they created their own web server: ARTS (Antibiotic Resistant Target Seeker). It automates the screening of large quantities of sequence data and focuses on the most promising bacterial strains that produce antibiotics with new modes of action. The web tool has been available to the DZIF colleagues and other scientists for a year via the website https://arts.ziemertlab.com. "The valuable thing about this tool is that you can proceed in a much more systematic and time-saving manner when you search for the needle in the haystack," explains Ziemert. The interest is correspondingly high: So far over 3,000 bacterial genomes have been analysed.

ACTIVE INGREDIENT PRODUCTION IN APPROPRIATE BACTERIAL HOSTS

The natural product Corallopyronin A, which has been investigated at the HZI as a promising candidate for a new antibiotic since the 1980s, also originates from an environmental bacterium. In 2009, DZIF scientists led by Prof. Achim Hörauf at the University of Bonn showed that the substance is effective against worms from the group of filariae. Together with the DZIF scientists, a research group has recently proven its effectiveness against tsutsugamushi fever, a typhoid-like tropical disease. In order to be able to use the drug candidate for preclinical and clinical tests, Prof. Rolf Müller from the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS) and Prof. Marc Stadler from the Helmholtz Centre for Infection Research (HZI) have advanced substance development in a DZIF project. "Corallopyronins are α-pyrone antibiotics made by myxobacteria, which represent a promising class of compounds for the development of broad-spectrum antibacterial therapeutic agents," explains the natural product expert. Corallopyronin inhibits the enzyme RNA polymerase in bacterial cells, which transcribes the cell´s genetic material into RNA molecules. Due to the blockage, the bacterium can no longer multiply. The team led by Stadler and Müller has now managed to optimise the production process for Corallopyoronin A with the help of an engineering platform and changes in the culture medium in such a way that a practical and high-yielding active substance production is achieved specifically for this purpose from host bacteria.

The search for new antibiotics and their development is time consuming.

GOALS IN 2017: OUTCOMES

- Establish protocols that will lead to further optimised yields and purity of Corallopyronin A for preclinical testing.
- Profiling of 300 preselected actinomycetes strains with regard to the antibiotic modes of action of their products.
- *In vivo* and *ex vivo* investigations of the aminochelocardins in preclinical urinary tract models. Additionally, first evidence of *in vivo* efficacy for a further antibiotic substance was supposed to be ascertained.

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

GOALS FOR 2018

○ Development of a production platform for the biotechnological production of Pseudomonas-effective mureidomycins to facilitate subsequent preclinical studies.

○ Generation of new synthetic derivatives of cystobactamides with optimised properties.

○ Establishment of a roadmap for the antibiotic Corallopyronin A until phase I clinical trials.

Coordinator:
Prof. Rolf Müller
Brunswick/Saarbrucken

PRODUCT DEVELOPMENT UNIT

Support on the way to the final product

DZIF scientists are developing drugs and vaccines.

95 per cent of new pharmaceutical products fail even before the first clinical trial, partly because there is a lack of professional support in the development. Therefore, experts in the "Product Development Unit" (PDU) support DZIF scientists from the project idea through to clinical trials of finished pharmaceutical products. The PDU works closely with the various DZIF research areas in order to identify appropriate approaches to new vaccines or therapies. The goal is to support the development of innovative active ingredients all the way to the pharmaceutical industry, which then takes over the late development stages up to approval and marketing. The Office for Scientific and Regulatory Advice (OSRA) is part of the PDU. It is located at the Paul-Ehrlich-Institut and at the BfArM, Federal Institute for Drugs and Medical Devices. OSRA assists in clarifying regulatory and technical issues within scientific discussion and consulting events. In June 2017, a workshop was also held at the BfArM for the DZIF scientists on the topics "The new Clinical Trial Regulation" and "First-in-Man Studies". Support for commercial aspects of drug development is provided by the Translational Project Management Office (TPMO) at the Helmholtz Centre for Infection Research in Braunschweig. Currently, the PDU is working intensively with scientists in eight DZIF projects.

Coordinator:

Prof. Klaus Cichutek *Langen*

CLINICAL TRIAL UNIT

Clinical trials planned systematically

Scientists and physicians are being trained for clinical trials at the DZIF.

New vaccines and medicines also need to be tested on humans before being launched. The DZIF has specialised clinical trial centres which are organised in the infrastructure "Clinical Trial Unit" (CTU). Twelve clinical trial centres are currently collaborating under the umbrella of this network. To date, the CTU has conducted 107 clinical trials and processed more than 100 feasibility requests. Clinicians and interested scientists are trained to systematically conduct clinical trials. The central coordinating office is based in Cologne. CTU has been conducting its own multicentric observational study since December 2017: "DOPPIO" will investigate pneumococcal vaccines in dialysis patients. Pneumococcal pneumonia is one of the most frequent causes of death in this patient group. The scientists want to achieve an improved, individualised vaccination protection with the findings obtained in the study. By the end of 2017, a total of 53 of the planned 884 patients had been enrolled. The twelve clinical trial centres cooperate with dialysis clinics of the Dialysis and Kidney Transplant Board of Trustees e.V. (KfH).

Coordinator:

Prof. Oliver Cornely *Cologne*

AFRICAN PARTNER INSTITUTIONS

Intercontinentally networked

The collaboration with African partners enables larger clinical trials and experiences in infection areas.

Many infections such as malaria, tuberculosis or AIDS are a bigger problem in Africa than they are here. The DZIF scientists are working closely with African partners to research these diseases more intensively where they frequently occur. These collaborations enable larger clinical trials and epidemiological investigations to be conducted in regions with high incidence of infectious disease.

The DZIF infrastructure "African Partner Institutions" establishes and reinforces long-term collaborations with institutions in Africa. These include hospitals and research centres in Kumasi (Ghana), Lambaréné (Gabon), Nouna (Burkina Faso) and Mbeya (Tanzania). DZIF scientists have long-standing collaborations with these four partner institutions.

In 2017, the laboratories and techniques in all African partner institutions were modernised to a high degree. This encompassed training staff on new methods, including the initial diagnostics, such as rapid tests for the detection of diarrhoea pathogens, to assess their accuracy. Ayola Akim Adegnika shows just how closely the German and African scientists are converging. The director at CERMEL, the clinical research facility in Lambaréné, has also been appointed to a DZIF professorship at the University of Tübingen.

Coordinator:

Prof. Jürgen May *Hamburg*

NOVEL ANTIVIRALS

With screening platforms and medical chemistry

The search for new substances with antiviral activity will be strengthened in the DZIF by a new infrastructure.

The recipe for success is missing for the treatment of emerging viruses such as Ebola or Zika just like for many well-known viral diseases such as hepatitis B or the flu. At the end of 2017, the DZIF set up an overarching infrastructure especially for the research of new substances with antiviral activity. In the future, biobanks containing small molecular substances will be screened for potential drug candidates. All DZIF locations will have access to appropriate screening platforms as well as substance banks and, upon request, support in carrying out screening experiments. Screening platforms can be found in Munich, Heidelberg, Hanover and Brunswick.

In particular, medical chemists will provide advice to the DZIF scientists in the "Novel Antivirals" infrastructure. Even in the early stages of the project, they will provide their assessment as to whether active substances identified in screenings would be promising candidates for drug use from a chemical perspective. They propose how the substances could be chemically optimised and who, inside or outside of the DZIF, could carry out corresponding syntheses. The collaboration with the product development team is very tight: It advises on the selection of drug candidates, considers market opportunities and, where appropriate, establishes contact with the industry.

Coordinator:

Prof. Thomas Schulz *Hanover*

BIOBANKING

Patient samples of the highest quality

High-quality biomaterials are indispensable for research.

Infection researchers often require human sample material, such as tissue or body fluids, for their projects. At the DZIF, a centrally coordinated biobanking infrastructure provides access to high quality, precisely characterised and systematically recorded biomaterials including the accompanying clinical information.

A central biosample registry (ZBR) at the Helmholtz Centre Munich has simplified the search for infectious disease sample material.

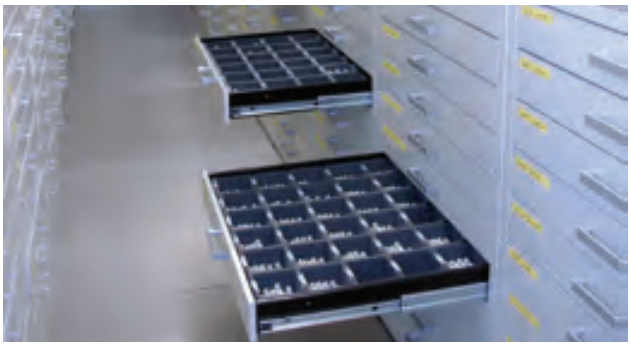
In order to achieve a comparable, high-quality collection of biosamples, the biobank infrastructure establishes a 3-stage quality management system (QM system), in 2017 initially in the DZIF transplant cohort. Biosamples of patients with solid organ transplants are collected as well as samples of stem cell transplants. The 3-level QM system is based on minimum standards, which are subsequently checked in internal audits. As a third step, quality control of the biosamples will be used to check whether deviations in the process are also reflected in the sample itself. In the future, the quality management system should make it possible to transfer it to other multicentric studies.

Coordinator:

Prof. Peter Schirmacher *Heidelberg*

PATHOGEN REPOSITORY

Preserving for research



Bacteria, fungi or bacteriophages are preserved long-term in the pathogen repository.

How do antibiotics affect different bacterial strains? Are newly occurring bacteria related to familiar ones? What role do microorganisms play in humans? To answer these and other questions, infection researchers need potential pathogens. Accordingly, a broad range of pathogens is stored in the DZIF "Pathogen Repository" which is hosted by the German Collection of Microorganisms and Cell Cultures (DSMZ) in Braunschweig. Bacteria, fungi or bacteriophages undergo quality control and are made available for use in research.

In the last one and a half years, Pathogen Repository collections have been expanded to include over 750 microbial pathogen strains and active substance producers. Multidrug-resistant bacteria and antibiotic-sensitive negative control strains, which can be used as test organisms, are playing an important role in this case. To date, almost 200 genome sequences have been performed. Thanks to the collaboration with the research area "Gastrointestinal Infections" in Munich, there is a collection of bacteria from the intestinal tract of the mouse. In the future, there will also be a collection of strains from the intestinal tract of the pig. The collaboration with the research field "Novel Antibiotics" provides a set of indicator strains for the screening of drug candidates in antibiotic development.

Coordinator:

Prof. Jörg Overmann *Brunswick*

BIOINFORMATICS

Understanding biomedical data

Bioinformaticians support the scientists with the evaluation and interpretation of huge amounts of data.

Bioinformatics plays an extremely important role in medical research. New methods are used to sequence genomes in continuously shorter time, while functional analyses (proteomics, metagenomics) generate huge amounts of data. Properly collecting and evaluating this data requires the expertise of bioinformaticians as well as specialised soft- and hardware.

The infrastructure "Bioinformatics" supports DZIF scientists with evaluating and interpreting their infection research data. This includes developing and providing software and analysis pipelines for the DZIF researchers to use independently as required. Automated and reproducible, complex analyses, such as the genome-based prediction of bacterial phenotypes and resistance mechanisms, can be performed simultaneously for thousands of isolates "at the push of a button". The bioinformaticians use seminars and workshops to pass on their know-ledge. The need for these training sessions is rising. The Metagenomics Workshop, an annual highlight of bioinformatics, was again in great demand, and in 2017 it was executed for the first time in cooperation with renowned microbiome researchers from University of California, San Diego. The "Bioinformatics" infrastructure will continue to offer training, support and infrastructure for all interested DZIF scientists and will be available as an application partner for DZIF projects.

Coordinator:

Prof. Alice McHardy *Brunswick*

EPIDEMIOLOGY

Mobile monitoring of diseases

Epidemiologists offer various methodical workshops at the DZIF.

Infectious diseases have different prevalence in different regions. They spread differently depending on the pathogen and the route of infection and affect some population groups more than others. Epidemiologists can recognise and curb the spread of infectious diseases more rapidly and prevent other diseases when they take these factors into account. In light of the growing importance of this field in an increasingly globalised world, the DZIF established the infrastructure "Epidemiology". It brings epidemiological aspects to research areas, supports DZIF projects and develops new tools for clinical and epidemiological studies. An example of this is the development of mobile apps which enable real-time recording and control of pathogen outbreaks called SORMAS.

In December 2017, this type of a mobile information system helped to fight a monkey pox outbreak in Nigeria for the first time. In 2017, epidemiologists also started their own study as part of the NAKO Health Study, the largest long-term population study on the causes of common diseases in Germany. A DZIF infection cohort will be integrated, with real-time monitoring based on mobile applications. This may help detect unknown associations between infections and non-communicable chronic diseases.

Coordinator:

Prof. Gérard Krause *Brunswick*

DZIF ACADEMY

Flexible and dedicated

For the future of infection research, DZIF relies on intensive promotion of young talent. The DZIF Academy offers targeted training and career opportunities to selected physicians and scientists. From the Technical University of Munich the Academy coordinates the selection and supervision of stipend holders who work at the locations. In 2017 alone, the Academy supported 59 fellows in four different programmes, and even paid for travel and lab exchanges.

A rotational fellowship enabled Esther Ludwig (front, 2nd from the right) to collect the samples in Lambaréné with Prof. Akim Adegnika (front, 1st from the left).

LABORATORY CHANGE FOR GREATER INSIGHT

Esther Ludwig did not see much of Gabon, but the four months spent at CERMEL, the research centre in Lambaréné, were extremely valuable to her. "It was incredibly exciting and also successful," says the DZIF fellow of the TU Munich, who was able to collect samples on site in Africa as part of her doctoral thesis. In her work, for which she received an MD scholarship from the DZIF for one year, she examines the impact of certain worm diseases on pregnant women and their newborns. Since these worm diseases occur especially in Africa, there should also be investigations there. A rotational lab fellowship made it easy to switch and the doctoral student made the best of her time. For four months she was in the lab seven days a week, now the doctoral thesis is completed and the state examination is her last hurdle on the way to becoming a doctor and scientist.

SUCCESSFUL THROUGH EXCHANGE AND NETWORKING

In addition to the laboratory rotation, an active exchange of young scientists was also made possible for the first time in 2017 via "Travel Grants". The DZIF Academy awards these travel grants for certain events. The goal of the funding is to give the first or last authors of DZIF-funded projects the opportunity to present their research project at a national or international scientific conference or similar event outside the DZIF network. With the "Clinical Leave", the DZIF Academy supports physicians who would like to qualify for a scientific career in infection research. Scholarships for young mothers along with support from technical staff facilitate re-entry after parental leave and the reconciliation of work and family. Doctoral scholarships are awarded by the Academy to medical students and physicians who wish to obtain a doctoral degree or the internationally recognised PhD degree. In a joint effort with the expert associations for infectiology, microbiology and hygiene as well as virology, the Academy annually awards prizes for the best doctoral theses. Furthermore, there are the "DZIF Spring, Summer and Autumn Schools", which aim to connect and train junior staff. Specialised courses, organised and implemented in collaboration with the DZIF experts, provide basic knowledge in a variety of areas, from bioinformatics to clinical studies and science communication. In 2017, 59 fellows were funded and 20 travel grants were awarded.

Coordinator:

Prof. Ulrike Protzer *Munich*

SUCCESSFUL TRANSLATION

MERS coronavirus: First vaccine is being clinically tested

In 2012, the MERS coronavirus was discovered in humans. In 2018, a clinical trial of a vaccine will commence at the German Center for Infection Research. The research into the virus that causes severe respiratory diseases is a true success story.

Getting a vaccine into camel noses was a challenge for the DZIF scientists.

So far, there is no effective vaccine or a specific drug against MERS Coronavirus (MERS stands for Middle East Respiratory Syndrome). More than 2,000 MERS cases have been confirmed since its discovery. Originally the pathogen came from Saudi Arabia and adjacent regions, where it is primarily found in dromedaries. Transmission from the dromedary to humans is possible and transmission from human to human could also be demonstrated.

FIRST VACCINE IN CLINICAL TRIAL

MVA-MERS-S is the scientific abbreviation for the first promising vaccine candidate, which has been tested for safety and tolerability since the beginning of 2018 at the University Hospital Hamburg-Eppendorf under the direction of Prof. Marylyn Addo. MVA stands for "Modified Vaccinia Virus Ankara" and it is based on an attenuated pox-virus, which is supposed to boost the defence against MERS with a component of the MERS virus.

FROM THE DISCOVERY OF THE VIRUS TO THE VACCINE

28 September 2012: "Scientists at the German Center for Infection Research (DZIF) today released the first detection method for the mysterious new virus, which caused a patient to die in Jeddah and made another patient who had flown out of Qatar to London seriously ill." This was the beginning of a press release, published by the DZIF as one of the first about the MERS coronavirus. Prof. Christian Drosten and his team from Bonn had identified the coronavirus as a new virus that did not correspond to the SARS virus. In a very short time, they developed a secure detection method, which is now used as the standard method worldwide. Exactly one year after the discovery, scientists from the DZIF reported the development of a potential vaccine. A team led by Prof. Gerd Sutter of the Ludwig Maximilian University in Munich developed it in cooperation with the Erasmus Medical Centre in Rotterdam and the Philipps University in Marburg.

In the subsequent years, the scientists were able to test the vaccine in the animal model and start a project in which the human clinical trial was prepared. In parallel, Sutter and his team tested the vaccine in a unique study of eight young dromedaries. The animals had to be less than one year old, because they usually get the virus very early; experts call this "Kindergarten sniffling for camels". "As cute as the little camels are, putting a vaccine into 40-cm-deep noses was a challenge," Sutter recalls with a grin. The experiment was successful and attracted attention in the Middle East and also at the World Health Organisation (WHO).

DZIF HIGHLIGHTS 2017

News ticker

JANUARY

The recent Ebola crisis has triggered global rethinking: The global community wants to prepare better than before for imminent epidemic outbreaks of infectious diseases. Correspondingly, the international vaccine initiative "**Coalition for Epidemic Preparedness Innovations**" (CEPI) was founded, in which the DZIF is also involved.

The Heidelberg virologist **Ralf Bartenschlager** receives the Hector Foundation Science Award, which is worth 150,000 euros.

JUNE

Myrcludex B receives the "PRIME" seal from the European Medicines Agency (EMA)–making it a drug whose development is treated with priority by the EMA. The virus inhibitor against the hepatitis B and D viruses was developed by DZIF scientists at Heidelberg University Hospital.

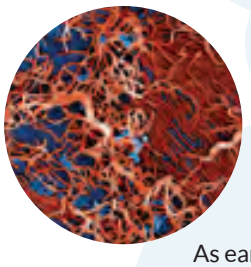
MAY

Researchers at the Cluster of Excellence ImmunoSensation at the University of Bonn have succeeded in what many scientists only dream of: In a joint effort with scientists from the USA, they were able to patent a new molecule that can be used to direct the **immune system against cancer cells**.

FEBRUARY

Which antibiotics are needed most? The World Health Organisation (WHO) published a list of 12 groups of bacteria to be given priority in the research and development of new antibiotics. A DZIF scientist from the University of Tübingen was significantly involved in developing this **priority list**.

Scientists at the DZIF and Justus Liebig University in Giessen have evaluated a **rapid test** that detects the dreaded mobile colistin resistance gene within twenty minutes. Use in clinics as well as in livestock husbandry is possible.



APRIL

As early as 2016, the Phase I clinical trial of a **potential vaccine against the dreaded Ebola virus** was successfully completed. For the first time, DZIF scientists at the University Medical Centre Hamburg-Eppendorf (UKE) were now able to demonstrate in a study how the vaccine boosts our immune system.

MARCH

Physicians specialising in tropical medicine of the University of Tübingen and the DZIF prove the efficacy of a novel active ingredient – DSM 265 – for the **prevention of malaria.**

JULY

The DZIF is joining the University and the University Hospital Tübingen to open a **training centre in Lambaréné, Gabon**. The state-controlled healthcare school is designed to train physicians and medical professionals.

The German Centres for Health Research (DZG) have received the **highest accolade from the German Council of Science and Humanities**. It considers them to be a suitable model to promote translational research in specific disease.

AUGUST

Chronic lung infections caused by the bacterium *Pseudomonas aeruginosa* require complex and, in most cases, long-term treatment with antibiotics. DZIF scientists at the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS) are now improving an **anti-infective active ingredient with a new mode of action**.

SEPTEMBER

Around 500 scientists and physicians from the DZIF and DGI come together in Hamburg to discuss current discoveries and results from infection research. On the occasion of the annual meeting Prof. Andreas Peschel from Tübingen receives the **DZIF Prize for Translational Infection Research 2017**. With lugdunin and a phage lysine he developed two new antibiotic agents.

OCTOBER

Common causes of difficult-to-treat hospital infections are the multidrug-resistant *Escherichia coli* bacteria, which have developed special enzymes to make antibiotics ineffective. The DZIF scientists at the University of Giessen studied these bacteria more closely and found a multidrug-resistant ***Escherichia coli*** **strain that has been spreading rapidly in Germany since 2010**.

NOVEMBER

The DZIF scientists in Munich are investigating the spread of tick-borne encephalitis (TBE) in Germany and are encountering a new potential carrier of the dreaded **meningitis**: the tick species *Ixodes inopinatus*.

DECEMBER

DZIF scientists from the Helmholtz Centre for Infection Research (HZI), together with Nigerian researchers, are fighting a **monkey pox outbreak** in Nigeria for the first time with a new **mobile information system**.

SCIENCE AND PUBLIC

From analogue to digital: Communication on all channels

Bringing information to the public in a timely manner–the website makes it possible. Appearance on the worldwide net is one of the most important communication channels in the digital age. In 2017, it was a focal point of the efforts in the DZIF Press Office because the original website, created at the time of the founding of the DZIF in 2012, was clearly getting old and dated. The changes in media usage behaviour was no longer suitably reflected, so a "relaunch" meant more than just a visual facelift. After intensive planning, a new design emerged–the new site will go online in 2018.

A strong website that is always up-to-date is the pillar of press offices; however, contact with journalists and the public requires far more communication channels: Telephone inquiries from journalists must be answered, experts arranged, annual reports and press releases or portraits written, congresses and internal meetings organised and supported.

TICK ALERT: *IXODES INOPINATUS* BITES ITS WAY THROUGH THE MEDIA FOREST

The broad research spectrum at the DZIF is also reflected in the 2017 press releases. "Risk of Zika transmission by mosquitoes in Germany" started in January; "New epidemic management system fights monkey pox outbreak in Nigeria" was the last press release in 2017. In between were antibiotic

During a lively panel discussion, the DZIF scientists (Ansgar Lohse on the left) and representatives from politics and industry talked about bacterial resistance in Germany.

resistance, tuberculosis and malaria, hepatitis and HIV. Particularly successful was a press release on the discovery of a new tick species, *Ixodes inopinatus*, which repeatedly appeared in the media long after its initial release. The topic "Ticks as transmitters of meningitis and Lyme disease" will be continued in the DZIF in 2018 and the DZIF Press Office will continue its efforts to provide the public with reliable information.

PEOPLE AT THE DZIF

More than 500 scientists and physicians, technical assistants and project managers, doctoral students and students work at the DZIF and bring the centre to life. We want to make that visible–in portraits of individual scientists as well as in short films. In 2017, in addition to a few portraits, short cinematic interviews were conducted, in which young scientists talk about their work and their goals at the DZIF. A playful way to understand complicated research topics–and to stimulate the desire to do research.

HEALTH-RELATED RESEARCH IN SIX CENTRES

The DZIF is one of six German Centres for Health Research (DZG) that deal with the widespread diseases and make the translation their own as a goal. In a joint effort with the other five centres, the importance of translational research is communicated to the outside world. In 2017, the centres started planning for a new magazine with focus on research in the six centres. This year, the magazine will be released for the first time, initially as a high-quality print edition, then online. Analogue and digital–here again, working different channels is key.

Together with the other German Centres for Health Research as well, research topics are regularly presented in the BMBF newsletter which reports the latest results and is directed at approximately 1,500 editorial offices and journalists. In 2017, the DZIF presented exciting news about the Epstein-Barr virus and research on Pfeiffer's glandular fever.

THE DZIF GOES OUTDOORS

To increase visibility both nationally and internationally, the DZIF was represented at scientific congresses with a fair stand again in 2017. Interested parties received well-prepared information at the European Congress on Clinical Microbiology and Infectious Diseases (ECCMID) in Vienna. At the annual GAIN meeting, a network of German scientists in North America, the German Centres for Health Research reported on their junior programmes. The interest in the special programmes at the DZG was enormous.

SYNERGIES THROUGH NETWORKING

Successfully creating synergies requires continuous exchange of information. In support of this information exchange, the Press Office publishes a quarterly digital newsletter and informs via the DZIF intranet, an exchange platform for all

Top: Young talented scientists in front of the camera.
Bottom: Fun to visit: Translational DZIF School in Lübeck.

DZIF staff. At the annual meeting in 2017, directly at the Port of Hamburg in close proximity to the Bernhard Nocht Institute of Tropical Medicine, the DZIF members convened to talk about current projects and discuss strategies for the future.

RESEARCH FOR HUMANS

The DZIF's goal of conducting research close to the patient and accomplishing faster access to applicable drugs and therapies also requires great transparency. Patients, interested citizens and third-party scientists can only find out what new developments are available to them if research results are made public. This process also facilitates feedback and speedier progress in research. Last but not least, the annual report you are holding in your hand is an informative contribution to science at the DZIF. The fact that it even came together is owed to the commitment of the employees at the DZIF.

Press and Public Relations:
Karola Neubert
Janna Schmidt
Brunswick

COLLABORATIONS

External collaborations

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

THE DZIF'S ASSOCIATED PARTNERS

Charité – Universitätsmedizin Berlin

The Charité Institute of Hygiene and Environmental Medicine is one of six partners in the DZIF network "Multidrug-resistant Bacteria" (MDRO Network: R-Net). This network is focussing on investigating the epidemiology of multidrug-resistant bacteria, bloodstream infections and *Clostridium difficile* infections over a period of four years. In 2017, 500 patients were examined at the Charité. Moreover, the hospital is involved in a project to support hygiene management in hospitals. In mid-2017, the working group "Virus Detection and Readiness" from the research field "Emerging Infections" moved from Bonn to the Charité. The working group is responsible for projects serving the detection, occurrence and description of emerging viruses.

German Liver Foundation/HepNet Study House, Hannover

The HepNet Study-House has been networking study centres for ten years now and is expanding nationwide networking across Germany with medical practices and physicians who are interested in taking part in hepatitis research. As a central point of contact for scientists and cooperation partners, it creates a platform to carry out clinical studies. The DZIF can use the infrastructures and cohorts for its projects. The German Liver Foundation has established a global registry of patients with chronic hepatitis D (www.hepatitis-delta.org), which is being continuously expanded; in 2017, further study centres were added, including one in Vietnam. In addition, a multicentre study on hepatitis E was recently launched.

Goethe University Frankfurt am Main

At the Goethe University of Frankfurt am Main, there is a project focussing on hepatitis research, which aims to

The DZIF regularly has exhibition stands at scientific conferences in order to be more visible both nationally and internationally.

improve the treatment of hepatitis C patients with novel drugs (Directly Acting Antivirals, DAA). It will define treatment algorithms that will maximise clinical success while simultaneously minimising healthcare costs. In particular, for difficult-to-treat hepatitis C patients in whom a virus resistance analysis was performed, it should facilitate establishing improved treatment recommendations.

Julius Maximilians University of Würzburg

In a clinical trial at the DZIF, leukaemia patients are administered specially purified immune cells, so-called memory T cells, after a bone marrow transplant for the first time. These special immune cells are to protect patients from infection until their own immune systems function. Some of the trial patients are being treated in Würzburg and others at the DZIF partner sites Munich (coordination), Tübingen and Hanover. The intake of new stem cell donors was expanded in 2017 in consultation with the German Bone Marrow Donor Database, so that more patients are expected to participate in the current year.

Hans Knöll Institute, Jena

The Hans Knöll Institute (HKI) is a leading institute for natural compound research. As an associated partner, it provides the DZIF with natural compounds, particularly fungi. In a joint project, the first antibiotic for tuberculosis was developed in Germany by the HKI and is about to enter clinical trials.

Max Planck Institute for Informatics, Saarbrucken

At the Max Planck Institute for Informatics in Saarbrucken, data on hepatitis C patients who are undergoing treatment with new antiviral agents is being collected as part of a DZIF project. Sequencing, analysis and interpretation of both patient and viral genes, along with other parameters, will be used to evaluate the course of treatment. The analysis results are used to continually update a web-based tool called geno2pheno[hcv]: An update has been created to make the tool more sustainable and to develop new applications based on it: This is how it was possible to develop geno2pheno[ngs-freq] into what it is today. A programme that can detect resistance in viral populations in a matter of seconds with next-generation sequencing data.

Medical Faculty of Martin Luther University Halle-Wittenberg

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

Otto-von-Guericke University Magdeburg

With this approach, in 2016, the scientists discovered neosorangicin which is produced by the myxobacterium *Sorangium cellulosum*. It is similar to the previously developed sorangicin A, an RNA polymerase inhibitor. In comparison, *in vivo* test tube investigations demonstrated that the newly discovered substance had much higher antibacterial activity against both gram-negative and gram-positive bacteria incl. *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Consequently, neosorangicin could become a new drug candidate. However, the activity of this natural product is rather weak compared to conventional broad-spectrum antibiotics. At the Otto von Guericke University Magdeburg, the researchers are now looking for a way to synthetically produce the drug candidate on a gramme scale.

University of Bayreuth

The pathogen *Mycobacterium tuberculosis* (MTB) is the focus of a major screening project involving the University of Bayreuth. The goal is to create a preclinical model, based on which new drugs against tuberculosis can be identified, and known and newly discovered drugs can be tested for efficacy. Different active ingredients are tested on a mouse model, which has similar pathology to that of humans, and validated with available human data. This provides better predictability of the treatment success in humans. An imaging laboratory was set up in Bayreuth with which the tissue concentrations of active ingredients can be made visible.

University of Erfurt

A vaccine against the influenza virus is used to protect yourself from the flu. Hospital staff in particular should aim for 100% coverage in that sense. But the reality is quite different: In some cases, only one in five hospital employees has been vaccinated against influenza. The University of Erfurt is involved in a field experiment at the University Medical Centre Hamburg-Eppendorf, where nurses, nursing staff and physicians must decide to get vaccinated for their own protection and for the protection of patients and colleagues. In order to examine what the reasons are that prevent staff from vaccinating, structured interviews were conducted with the study participants in flu season 2017/18.

University Hospital Essen

The goal of the Hepatitis C project (see also Goethe University of Frankfurt), a collaboration of scientists from the University Hospital Essen, is to point out treatment options to the treating physician that are tailored to the individual needs of the patient. Both the genome sequences of the hepatitis C virus and the patient data are included in the therapy recommendation.

University Hospital Freiburg

The University Medical Center Freiburg is a partner of several DZIF projects. The clinic works on finding out which gene mutations are responsible for chronic mucocutaneous candidiasis, a chronic infection of the skin and mucous

membrane with candida fungi. Additionally, scientists are looking to find genetic factors associated with increased susceptibility to infection. They intend to identify biomarkers that permit better infection control. The clinic is working on two studies aimed at reducing hospital-associated infections. For example, antibiotics should be used more purposefully and hospital hygiene measures must be improved.

A multicentric study is currently in preparation with patients facing increased risk of infection with *Clostridium difficile* pathogens. Freiburg is one of six sites in which the epidemiology of multidrug-resistant bacteria and the epidemiology of bloodstream infections and *Clostridium difficile* infections are studied longitudinally over a four-year period.

Human cytomegalovirus (HCMV) infections pose a risk to immunocompromised individuals (such as AIDS or transplant patients). The researchers are looking for new drugs against HCMV, especially since two promising candidates have been determined in virological tests not to be effective enough.

Westphalian Wilhelm University of Münster

The University of Münster is partner in a project searching for new treatments for the haemolytic uraemic syndrome, which is caused by enterohaemorrhagic *Escherichia coli* (EHEC) bacteria and is the leading cause of acute renal failure. New strategies to combat methicillin-resistant *Staphylococcus aureus* bacteria in the nasal cavity are being developed in another project at Wilhelms University. And the first results are promising: Novel phage lytic proteins proved to be very effective.

INDUSTRY COLLABORATIONS

BioNTech AG, Mainz

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

Coris BioConcept, Gembloux (Belgium)

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

HYpharm GmbH, Bernried

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

ImevaX GmbH, Munich

The DZIF is funding a research group led by Prof. Markus Gerhard from the Technical University of Munich in the field of preclinical and early-stage clinical testing of the *Helicobacter pylori* vaccine candidate IMX-101. Together with other funders, the group founded a spin-off company from the university, ImevaX GmbH.

Juno Therapeutics GmbH, Göttingen

Juno Therapeutics, formerly Stage Cell Therapeutics, is collaborating and exploitation partner of the research group led by Prof. Dirk Busch, Technical University of Munich, working in the field of GMP quality-assured manufacture of central memory T cells for treatment of infections and cancer. The DZIF is funding the group led by Prof. Busch.

MMV–Medicines for Malaria Venture, Geneva (Switzerland)

An MMV portfolio substance is being clinically tested for chemoprevention of *Malaria tropica*, using a human infection model developed by DZIF colleagues in Tübingen.

Myr GmbH, Burgwedel

Together with the University of Heidelberg, an active agent (Myrcludex B) is being developed that inhibits hepatitis B viruses from penetrating cells and could potentially be used to prevent hepatitis B and D infections. Myr GmbH is coordinating the entire project and overseeing the clinical trial.

Sanaria Inc., Rockville (USA)

At the DZIF partner site Tübingen, scientists are developing a human malaria infection model. Here, the disease is induced under controlled conditions in order to test new active agents and vaccines. Sanaria Inc. in Rockville, USA, produces malaria parasites in GMP quality for immunisation purposes, which fulfil all the criteria for drug approval.

4SC Discovery GmbH, Martinsried

In the DZIF research field "Malaria", a candidate anti-malarial has gone into preclinical development. SC83288 is being tested as an inhibitor in animal models, and is being further developed in close collaboration with the company 4SC, which also produces the active agent.

ABOUT THE DZG

The German Health Research Centres

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

Translation as mission: The German Health Research Centres facilitate the faster transfer from laboratory findings into new drugs.

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

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

2009 already saw the foundation of the "German Centre for Neurodegenerative Diseases" and the "German Centre for Diabetes Research". In 2012, the "German Center for Cardiovascular Research", the "German Consortium for Translational Cancer Research" and the "German Center for Lung Research" were launched alongside the DZIF.

From the outset, the six German Health Research Centres have collaborated closely in order to share their findings and exploit synergies. To this end, a joint symposium at the World Health Summit (WHS) in Berlin was held for the fourth time in 2017–together with the Helmholtz Association. In addition, a joint magazine will be published for the first time in 2018–both in high-quality print and online. Last but not least: since 2015, the DZG have been taking turns to present exciting research themes in the BMBF newsletter.

The DZIF's structure

General Assembly

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

Commission of Funding Authorities

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

Executive Board

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

Scientific Advisory Board

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

Main Office

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

Internal Advisory Board

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

Thematic Translational Units (TTUs)

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

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

Translational Infrastructures (TIs)

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

- Product Development Unit
- African Partner Institutions
- Biobanking
- Pathogen Repository
- Bioinformatics
- Novel Antivirals (since 2018)
- Epidemiology
- Clinical Trial Unit
- DZIF Academy

Partner Sites

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

Bonn-Cologne	Giessen-Marburg-Langen	Hamburg-Lübeck-Borstel -Riems	Hanover-Brunswick
Heidelberg	Munich	Tübingen	Associated Partners

Central bodies

EXECUTIVE BOARD

- Prof. M. Krönke, University of Cologne and University Hospital Cologne (Chair)
- Prof. U. Protzer, Technische Universität München und Helmholtz Zentrum München (Vice Chair)
- Prof. D. Heinz, Helmholtz Centre for Infection Research, Brunswick

MANAGING DIRECTOR

- Dr T. Jäger, DZIF e.V.

SCIENTIFIC ADVISORY BOARD

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

INTERNAL ADVISORY BOARD

- Prof. I. Autenrieth, University of Tübingen and University Hospital Tübingen
- Prof. K. Cichutek, Paul-Ehrlich-Institut, Langen
- Prof. C. Drosten, Charité - Universitätsmedizin Berlin
- Prof. M. Hoelscher, Ludwigs-Maximilians-Universität München and Klinikum der Universität München
- Prof. R. Horstmann, Bernhard Nocht Institute for Tropical Medicine, Hamburg (Vice Chair till the end of 2017)
- Prof. H.-G. Kräusslich, Heidelberg University and University Hospital (Chair)
- Prof. C. Meier, Universität Hamburg (since 2018)
- Prof. T. Schulz, Hannover Medical School (Vice Chair since 2018)
- Prof. T. Welte, Hannover Medical School

Partner sites and member establishments

Germany-wide infection research

BADEN-WÜRTTEMBERG

Heidelberg is responsible for coordinating the TTU *HIV* at the DZIF. In order to control HIV infections, DZIF researchers at this location research factors of the innate immune system and identify DNA sites for viral DNA integration. Alongside HIV, Heidelberg co-coordinates the TTUs *Hepatitis*, *Malaria* and *Infections of the Immunocompromised Host*. The Heidel-berg scientists also coordinate the DZIF-wide translational infrastructure *Biobanking*, with a focus on establishing tissue banks.

Heidelberg
Spokesperson: Prof. Klaus Heeg (Heidelberg University Hospital)
Establishments: German Cancer Research Center in the Helmholtz Association, Heidelberg University, Heidelberg University Hospital
TTU coordination:
- Hepatitis (co-coordination)
- HIV (coordination)
- Infections of the immunocom-promised Host (co-coordination)
- Malaria (co-coordination)

TI coordination:
- Biobanking (coordination)

Tübingen has assumed the role of coordinating *Malaria* and *Healthcare-associated and Antibiotic-resistant bacterial Infections*. Co-coordinators of *Gastrointestinal Infections* and *Novel Antibiotics* work at this location. The main focus in Tübingen is on translating research results into medicine and vaccine development as well as on infection models and epidemiology. Regarding infections caused by antibiotic-resistant, bacterial pathogens, the focus is on multidrug-resistant pathogens such as methicillin-resistant staphylococci (MRSA) and multidrug-resistant gramnegative pathogens (e.g. so-called ESBLs). In 2016, the University of Tübingen established a first DZIF professorship in Africa, funded by the DZIF and the Government of Gabon.

Tübingen
Spokesperson: Prof Ingo Autenrieth (University of Tübingen)
Establishments: University of Tübingen, Max Planck Institute for Developmental Biology, University Hospital Tübingen
TTU coordination:
- Gastrointestinal Infections (co-coordination)
- Healthcare-associated and Antibiotic-resistant bacterial Infections (coordination)
- Malaria (coordination)
- Novel Antibiotics (co-coordination)

BAVARIA

At the DZIF establishments in **Munich**, scientists have a special focus on immune control of infections and developing novel therapies. Pathogen-specific immunotherapies (e.g. vaccination or adoptive T cell transfer) aim to strengthen the body's natural defence system so that it is able to control specific infectious diseases more effectively or even avoid them entirely. Other research fields in Munich are *Gastrointestinal Infections (GI)*, *HIV*, *Hepatitis* and *Tuberculosis*. The research fields *GI* and *HIV* have been reinforced with two new professorships at the Max von Pettenkofer-Institute.

Munich
Spokesperson: Prof. Dirk Busch (Technische Universität München)
Establishments Helmholtz Zentrum München – German Research Center for Environmental Health, Bundeswehr Institute of Microbiology, Klinikum der Universität München, Klinikum rechts der Isar der Technischen Universität München, Ludwig-Maximilians-Universität München, Technische Universität München
TTU coordination:
- Gastrointestinal Infections (coordination and co-coordination)
- Hepatitis (co-coordination)
- HIV (co-coordination)
- Infections of the immunocompromised Host (coordination)
- Tuberculosis (co-coordination)

TI coordination:
- Biobanking (co-coordination)
- DZIF Academy (coordination)

HAMBURG/ SCHLESWIG-HOLSTEIN

The **Hamburg – Lübeck – Borstel – Riems** site combines a unique collection of expertise and infrastructure for studying infectious diseases and emerging infections of national and global relevance and for development of control strategies. Scientists at the location are involved in clinical, entomological and virological studies. It is the DZIF base for medical chemistry, for active ingredient development as well as for the epidemiology of malaria and translational studies on tuberculosis, viral haemorrhagic fever, and hepatitis. The TI African Partner Institutions is coordinated from here.

HAMBURG – LÜBECK – BORSTEL – RIEMS
Spokesperson: Prof. Rolf Horstmann (Bernhard Nocht Institute for Tropical Diseases); (until end of 2017)
Prof. Jürgen May (BNITM)
Establishments: Bernhard Nocht Institute for Tropical Diseases, Research Center Borstel - Leibniz Lung Center, Friedrich-Loeffler-Institute, Heinrich Pette Institute – Leibniz Institute for Experimental Virology, University of Hamburg, University Medical Centre Hamburg-Eppendorf, University of Lübeck
TTU coordination:
- Malaria (co-coordination)
- Emerging Infections (co-coordination)
- Tuberculosis (coordination)

TI coordination:
- African Partner Institutions (coordination)

HESSE

In **Giessen – Marburg – Langen**, DZIF researchers identify new active agents and vaccines and produce them in quality-assured production processes for scientific and industrial partners. Research activities are concentrated on developing strategies for combatting new or re-emerging infectious diseases in order to contain outbreaks of new pathogens, for example through quick, effective action and rapid vaccine development. Marburg focuses on viral pathogens, while Gießen concentrates on bacteria and antibiotic resistance.

Giessen – Marburg – Langen
Spokesperson: Prof. Trinad Chakraborty (Giessen University)
Establishments: Giessen University, Paul-Ehrlich-Institut Langen, Philipps-Universität Marburg, Mittelhessen University of Applied Sciences
TTU coordination:
- Emerging Infections (coordination)
- Healthcare-associated and Antibiotic-resistant bacterial Infections (co-coordination)

TI coordination:
- Product Development Unit (coordination)

LOWER SAXONY

Seven partner institutes collaborate within DZIF at the **Hanover – Brunswick** site. The research fields *Hepatitis* and *Novel Antibiotics* are coordinated from here. The scientists aim to improve access to viral hepatitis therapies and conduct research on new diagnostic markers for courses of infection and therapy, amongst other things. The researchers also develop new approaches to effective treatment and control of resistant bacteria and investigate different molecular target sites for agents. Identifying and developing agent candidates that can be used as antibiotics play an important role.

Hanover – Brunswick
Spokesperson: Prof. Thomas Schulz (Hannover Medical School)
Establishments: 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, Foundation, Technische Universität Braunschweig, TWINCORE – Centre for Experimental and Clinical Infection Research
TTU coordination:
- Emerging Infections (co-coordination)
- Gastrointestinal Infections (co-coordination)
- Hepatitis (coordination)
- Infections of the immunocompromised Host (co-coordination)
- Novel Antibiotics (coordination since 2017)

TI coordination:
- Bioinformatics (coordination)
- Epidemiology (coordination)
- Novel Antivirals (coordination), since 2018
- Pathogen Repository (coordination)

NORTH RHINE-WESTPHALIA

With the merger of the research field *Novel Antiinfectives* and the infrastructure *Natural Compound Library* to the research field *Novel Antibiotics* a concentration of activities has been achieved in relation to the research and development of new antibiotics. In cooperation with the TPMO and the BfArM, the preclinical development of the new antibiotic corallopyronin A remains the top priority for the **Bonn - Cologne** location. In the vaccine research department, vaccines against bacterial pathogens like *S. aureus* and *A. baumannii* are developed into the clinical application phase. Scientists in the research field *Healthcare-associated and Antibiotic-resistant bacterial Infections* research bacterial colonisations and infections with multidrug-resistant bacteria with regard to both type and prevalence, as well as treatment options and the effectiveness of infection control measures. In HIV research, the researchers bring new antibody mediated treatment approaches into translation. This site also coordinates the DZIF Clinical Trial Unit.

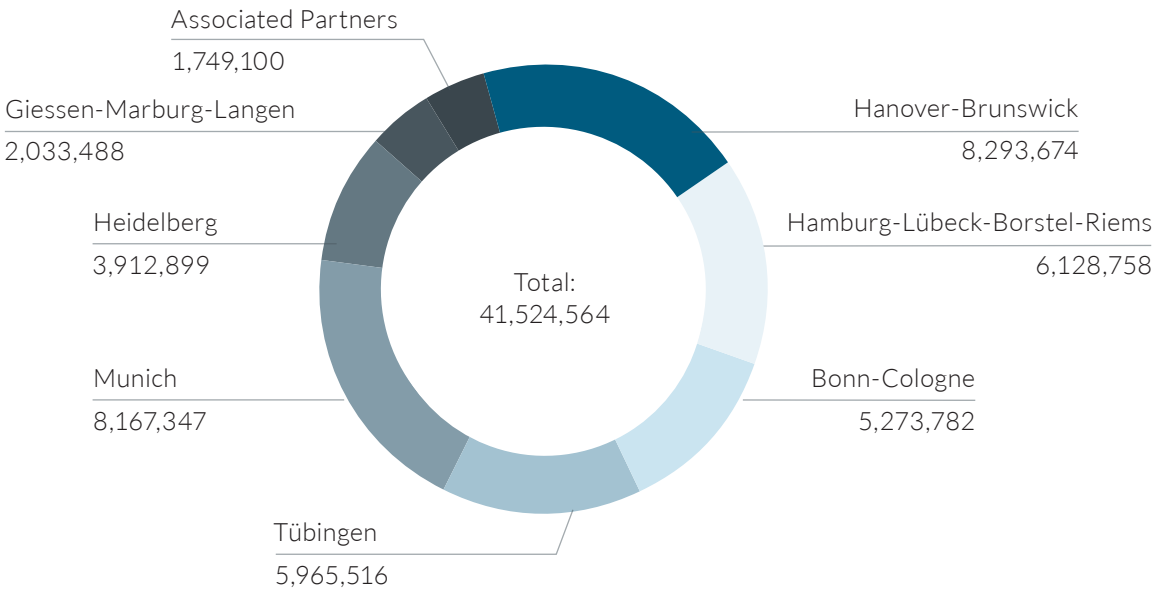
Bonn – Cologne
Spokesperson: Prof. Achim Hörauf (University of Bonn)
Establishments: Federal Institute for Drugs and Medical Devices, Rheinische Friedrich-Wilhelms-Universität Bonn, University Hospital Bonn, University of Cologne, University Hospital Cologne
TTU coordination:
- HIV (co-coordination)
- Emerging Infections (co-coordination)
- Healthcare-associated and Antibiotic-resistant bacterial Infections (HAARBI) (co-coordination)
- Novel Antibiotics (co-coordination)

TI coordination:
- Clinical Trial Unit (coordination)

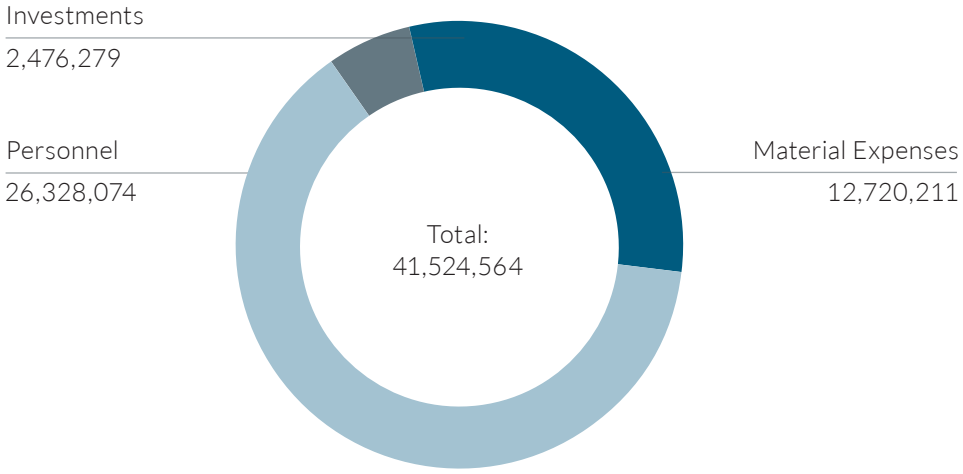
DZIF financial data 2017

REPORTED EXPENDITURE IN EUROS

BY PARTNER SITE



BY TYPE OF EXPENDITURE



BY FIELD OF WORK

FIELD OF WORK	Euros
Emerging Infections	3,347,338
Tuberculosis	3,598,676
Malaria	3,017,245
HIV	2,749,597
Hepatitis	3,284,185
Gastrointestinal Infections	2,059,959
Infections of the immunocompromised Host	5,895,716
Healthcare-associated and Antibiotic-resistant bacterial Infections	3,649,727
Novel Antibiotics	4,822,613
Product Development Unit	697,106
Clinical Trial Unit	471,796
African Partner Institutions	809,409
Biobanking	652,718
Vaccine Development	849,384
Bioinformatics	279,923
Pathogen Repository	231,587
Epidemiology	409,139
DZIF Academy	2,409,840
Administration	2,288,607
Total	**41,524,564**

BY FUNDERS

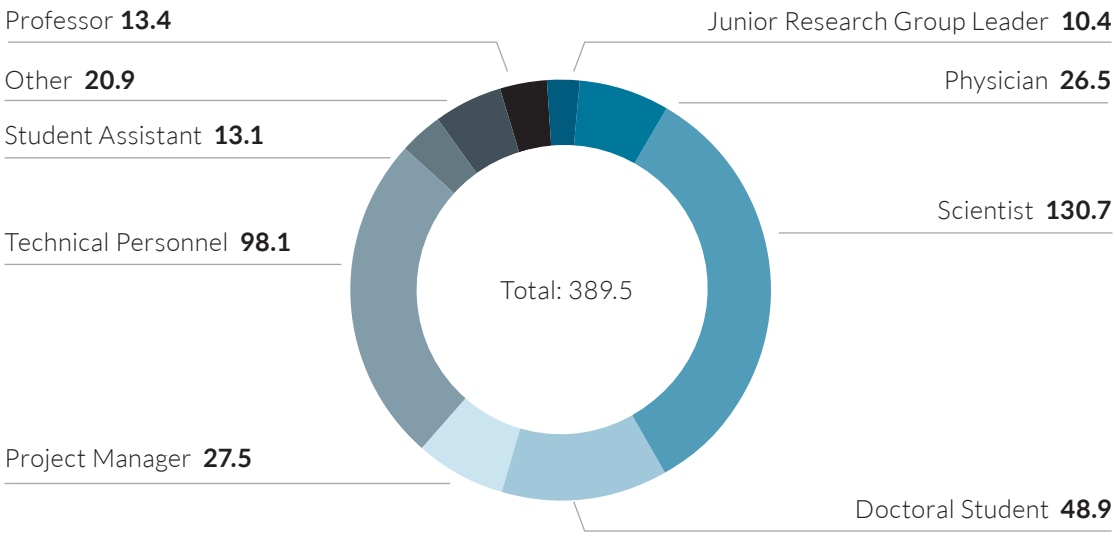
FUNDER	Euros
Baden-Württemberg	987,841
Bavaria	807,900
Hamburg	403,741
Hesse	152,285
Lower Saxony	803,271
North Rhine-Westphalia	519,580
Schleswig-Holstein	191,707
Financial contributions from associated partners	174,910
Federal Government	37,483,328
Total	**41,524,564**

In 2017, the German Center for Infection Research's reported expenditure amounted to approximately 41.5 million Euros. 169 projects and 64 stipends were funded within DZIF in 2017. The majority of funding came from the Federal Government (90 %) and from Länder funds (10 %). Only departmental research projects of the federal R&D institutions were fully funded by Germany's Federal Ministries. Funding management at the Helmholtz Centre for Infection Research in Braunschweig transfers the federal funds to the DZIF partner institutes for their projects.

The expenditures amounting to the BMBF funding were reported by the DZIF partners in the interim and final financial report 2017 and will be investigated by the DZIF Funding Management. The amounts of state and associated partner funding were calculated on the basis of these interim and final financial reports.

DZIF staff

FULL-TIME EQUIVALENT BY PROFESSIONAL GROUP



NUMBER OF EMPLOYEES BY PROFESSIONAL GROUP AND GENDER

PROFESSIONAL GROUPS	MEN	WOMEN	TOTAL
Professor	12	5	17
Junior Research Group Leader	7	4	11
Physician	23	27	50
Scientist	98	140	238
Doctoral Student	40	57	97
Project Manager	14	56	70
Technical Personnel	36	155	191
Student Assistant	7	34	41
Other	11	35	46
Total	**248**	**513**	**761**

In 2017, the DZIF recruited seven employees from abroad and assisted 27 mothers and fathers respectively on their return from maternity leave.

AWARDS AND COMMENDATIONS

AWARD RECIPIENT	AWARD
Prof. Marcus Altfeld and Dr Angelique Hölzemer *Hamburg-Eppendorf University Medical Centre*	Hector Research Award HIV
Christine Bächlein, PhD *University of Veterinary Medicine Hannover*	Gustav Rosenberger Memorial Award
Prof. Florian Klein *University Hospital Cologne*	Georges Köhler Award of the German Society of Immunology e. V.
Dr Jian Lei *University of Lübeck*	Sponsorship Award of the Gesellschaft Deutscher Chemiker (Department of Biochemistry)
Prof. Rolf Müller *Helmholtz Institute for Pharmaceutical Research Saarland*	Professorship appointment at the Academy of Sciences and Literature
Prof. Andreas Peschel *Eberhard Karls University of Tübingen*	DZIF Prize for Translational Infection Research
Dr Roman Sommer *Helmholtz Institute for Pharmaceutical Research Saarland*	Sponsorship Award of the Gesellschaft Deutscher Chemiker (Department of Medical Chemistry)
Prof. Bärbel Stecher *Ludwig-Maximilians University Munich*	Main Award from the Germany Society of Hygiene and Microbiology
Prof. Samuel Wagner *Eberhard Karls University of Tübingen*	Sponsorship Award from the Germany Society of Hygiene and Microbiology

The DZIF in figures

FLEXFUNDS*

36 Number of new FlexFunds projects approved in 2017

4.951.775 total budget in euros. Corresponding to

12 % of the annual DZIF budget

**funds available at short notice for translational projects*

DZIF ACADEMY PROGRAMMES

10 Clinical Leave Stipends

05 MD/PhD Stipends

04 Maternity Leave Stipends

40 MD Stipends

05 Lab Rotations

20 Travel Grants

WORKSHOPS AND SYMPOSIA

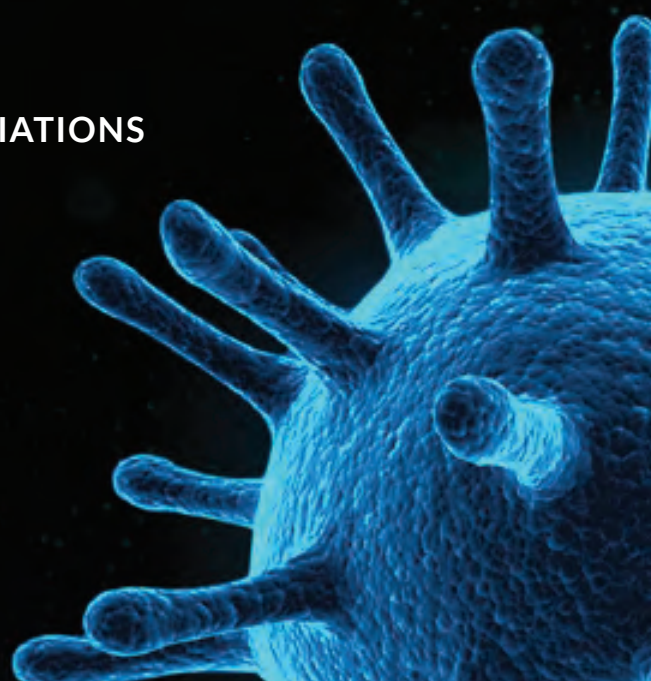
30

PUBLICATIONS WITH DZIF AFFILIATIONS

520

PUBLICATIONS WITH IMPACT FACTOR >10

66



CONFERENCE CONTRIBUTIONS
682

PATENTS AND PROPERTY RIGHTS
48

INDUSTRY COLLABORATIONS
9

PRESS RELEASES
44

BIOBANKS
57

CLINICAL STUDIES
37

CONFIRMATORY PRECLINICAL STUDIES
21

COHORTS
44

WEBSITE VISITORS
53.736

PUBLICATIONS

Scientific achievements 2017

The following shows a list of selected 2017 publications
(impact factor greater than ten*).
Please see our website for a complete list of DZIF publications.

Basic research

1. Alanjary M, Kronmiller B, Adamek M, Blin K, Weber T, Huson D, Philmus B, Ziemert N (2017) *The Antibiotic Resistant Target Seeker (ARTS), an exploration engine for antibiotic cluster prioritization and novel drug target discovery.* **Nucleic Acids Res**, 45(W1): W42-W48

2. Bankwitz D, Doepke M, Hueging K, Weller R, Bruening J, Behrendt P, Lee JY, Vondran FWR, Manns MP, Bartenschlager R, Pietschmann T (2017) *Maturation of secreted HCV particles by incorporation of secreted ApoE protects from antibodies by enhancing infectivity.* **J Hepatol**, 67(3): 480-489

3. Barthels C, Ogrinc A, Steyer V, Meier S, Simon F, Wimmer M, Blutke A, Straub T, Zimber-Strobl U, Lutgens E, Marconi P, Ohnmacht C, Garzetti D, Stecher B, Brocker T (2017) *CD40-signalling abrogates induction of RORgammat+ Treg cells by intestinal CD103+ DCs and causes fatal colitis.* **Nat Commun**, 8: 14715

4. Bugaytsova JA, Bjornham O, Chernov YA, Gideonsson P, Henriksson S, Mendez M, Sjostrom R, Mahdavi J, Shevtsova A, Ilver D, Moonens K, Quintana-Hayashi MP, Moskalenko R, Aisenbrey C, Bylund G, Schmidt A, Aberg A, Brannstrom K, Koniger V, Vikstrom S, Rakhimova L, Hofer A, Ogren J, Liu H, Goldman MD, Whitmire JM, Aden J, Younson J, Kelly CG, Gilman RH, Chowdhury A, Mukhopadhyay AK, Nair GB, Papadakos KS, Martinez-Gonzalez B, Sgouras DN, Engstrand L, Unemo M, Danielsson D, Suerbaum S, Oscarson S, Morozova-Roche LA, Olofsson A, Grobner G, Holgersson J, Esberg A, Stromberg N, Landstrom M, Eldridge AM, Chromy BA, Hansen LM, Solnick JV, Linden SK, Haas R, Dubois A, Merrell DS, Schedin S, Remaut H, Arnqvist A, Berg DE, Boren T (2017) *Helicobacter pylori Adapts to Chronic Infection and Gastric Disease via pH-Responsive BabA-Mediated Adherence.* **Cell Host Microbe**, 21(3): 376-389

5. Dulberger CL, McMurtrey CP, Holzemer A, Neu KE, Liu V, Steinbach AM, Garcia-Beltran WF, Sulak M, Jabri B, Lynch VJ, Altfeld M, Hildebrand WH, Adams EJ (2017) *Human Leukocyte Antigen F Presents Peptides and Regulates Immunity through Interactions with NK Cell Receptors.* **Immunity**, 46(6): 1018-1029.e1017

6. Fedry J, Liu Y, Pehau-Arnaudet G, Pei J, Li W, Tortorici MA, Traincard F, Meola A, Bricogne G, Grishin NV, Snell WJ, Rey FA, Krey T (2017) *The Ancient Gamete Fusogen HAP2 Is a Eukaryotic Class II Fusion Protein.* **Cell**, 168(5): 904-915.e910

7. Fu C, Auerbach D, Li Y, Scheid U, Luxenburger E, Garcia R, Irschik H, Muller R (2017) *Solving the Puzzle of One-Carbon Loss in Ripostatin Biosynthesis.* **Angew Chem Int Ed Engl,** 56(8): 2192-2197

8. Gabriel E, Ramani A, Karow U, Gottardo M, Natarajan K, Gooi LM, Goranci-Buzhala G, Krut O, Peters F, Nikolic M, Kuivanen S, Korhonen E, Smura T, Vapalahti O, Papantonis A, Schmidt-Chanasit J, Riparbelli M, Callaini G, Kronke M, Utermohlen O, Gopalakrishnan J (2017) *Recent Zika Virus Isolates Induce Premature Differentiation of Neural Progenitors in Human Brain Organoids.* **Cell Stem Cell**, 20(3): 397-406.e395

9. Gaertner F, Ahmad Z, Rosenberger G, Fan S, Nicolai L, Busch B, Yavuz G, Luckner M, Ishikawa-Ankerhold H, Hennel R, Benechet A, Lorenz M, Chandraratne S, Schubert I, Helmer S, Striednig B, Stark K, Janko M, Bottcher RT, Verschoor A, Leon C, Gachet C, Gudermann T, Mederos YSM, Pincus Z, Iannacone M, Haas R, Wanner G, Lauber K, Sixt M, Massberg S (2017) *Migrating Platelets Are Mechano-scavengers that Collect and Bundle Bacteria.* **Cell**, 171(6): 1368-1382.e1323

10. Holze C, Michaudel C, Mackowiak C, Haas DA, Benda C, Hubel P, Pennemann FL, Schnepf D, Wettmarshausen J, Braun M, Leung DW, Amarasinghe GK, Perocchi F, Staeheli P, Ryffel B, Pichlmair A (2018) *Oxeiptosis, a ROS-induced caspase-independent apoptosis-like cell-death pathway.* **Nat Immunol**, 19(2): 130-140. Epub 2017

11. Kjaerulff L, Raju R, Panter F, Scheid U, Garcia R, Herrmann J, Muller R (2017) *Pyxipyrrolones: Structure Elucidation and Biosynthesis of Cytotoxic Myxobacterial Metabolites.* **Angew Chem Int Ed Engl** 56(32): 9614-9618

12. Korner C, Simoneau CR, Schommers P, Granoff M, Ziegler M, Holzemer A, Lunemann S, Chukwukelu J, Corleis B, Naranbhai V, Kwon DS, Scully EP, Jost S, Kirchhoff F, Carrington M, Altfeld M (2017) *HIV-1-Mediated Downmodulation of HLA-C Impacts Target Cell Recognition and Antiviral Activity of NK Cells.* **Cell Host Microbe**, 22(1): 111-119.e114

13. Leipoldt F, Santos-Aberturas J, Stegmann DP, Wolf F, Kulik A, Lacret R, Popadic D, Keinhorster D, Kirchner N, Bekiesch P, Gross H, Truman AW, Kaysser L (2017) *Warhead biosynthesis and the origin of structural diversity in hydroxamate metalloproteinase inhibitors.* **Nat Commun**, 8(1): 1965

14. Miotto P, Tessema B, Tagliani E, Chindelevitch L, Starks AM, Emerson C,

** Impact Factor in 2016*

Hanna D, Kim PS, Liwski R, Zignol M, Gilpin C, Niemann S, Denkinger CM, Fleming J, Warren RM, Crook D, Posey J, Gagneux S, Hoffner S, Rodrigues C, Comas I, Engelthaler DM, Murray M, Alland D, Rigouts L, Lange C, Dheda K, Hasan R, Ranganathan UDK, McNerney R, Ezewudo M, Cirillo DM, Schito M, Koser CU, Rodwell TC (2017) *A standardised method for interpreting the association between mutations and phenotypic drug resistance in Mycobacterium tuberculosis.* **Eur Respir J**, 50(6)

15. Remy MM, Sahin M, Flatz L, Regen T, Xu L, Kreutzfeldt M, Fallet B, Doras C, Rieger T, Bestmann L, Hanisch UK, Kaufmann BA, Merkler D, Pinschewer DD (2017) *Interferon-gamma-Driven iNOS: A Molecular Pathway to Terminal Shock in Arenavirus Hemorrhagic Fever.* **Cell Host Microbe**, 22(3): 354-365

16. Sczyrba A, Hofmann P, Belmann P, Koslicki D, Janssen S, Droge J, Gregor I, Majda S, Fiedler J, Dahms E, Bremges A, Fritz A, Garrido-Oter R, Jorgensen TS, Shapiro N, Blood PD, Gurevich A, Bai Y, Turaev D, DeMaere MZ, Chikhi R, Nagarajan N, Quince C, Meyer F, Balvociute M, Hansen LH, Sorensen SJ, Chia BKH, Denis B, Froula JL, Wang Z, Egan R, Don Kang D, Cook JJ, Deltel C, Beckstette M, Lemaitre C, Peterlongo P, Rizk G, Lavenier D, Wu YW, Singer SW, Jain C, Strous M, Klingenberg H, Meinicke P, Barton MD, Lingner T, Lin HH, Liao YC, Silva GGZ, Cuevas DA, Edwards RA, Saha S, Piro VC, Renard BY, Pop M, Klenk HP, Goker M, Kyrpides NC, Woyke T, Vorholt JA, Schulze-Lefert P, Rubin EM, Darling AE, Rattei T, McHardy AC (2017) *Critical Assessment of Metagenome Interpretation-a benchmark of metagenomics software.* **Nat Methods**, 14(11): 1063-1071

17. Shumilov A, Tsai MH, Schlosser YT, Kratz AS, Bernhardt K, Fink S, Mizani T, Lin X, Jauch A, Mautner J, Kopp-Schneider A, Feederle R, Hoffmann I, Delecluse HJ (2017) *Epstein-Barr virus particles induce centrosome amplification and chromosomal instability.* **Nat Commun**, 8: 14257

18. Slijepcevic D, Roscam Abbing RLP, Katafuchi T, Blank A, Donkers JM, Van Hoppe S, de Waart DR, Tolenaars D, van der Meer JHM, Wildenberg M, Beuers U, Oude Elferink RPJ, Schinkel AH, van de Graaf SFJ (2017) *Hepatic uptake of conjugated bile acids is mediated by both NTCP and OATPs and modulated by intestinal sensing of plasma bile acid levels in mice.* **Hepatology**, 66(5): 1631-1643

19. Van Deun J, Mestdagh P, Agostinis P, Akay O, Anand S, Anckaert J, Martinez ZA, Baetens T, Beghein E, Bertier L, Berx G, Boere J, Boukouris S, Bremer M, Buschmann D, Byrd JB, Casert C, Cheng L, Cmoch A, Daveloose D, De Smedt E, Demirsoy S, Depoorter V, Dhondt B, Driedonks TA, Dudek A, Elsharawy A, Floris I, Foers AD, Gartner K, Garg AD, Geeurickx E, Gettemans J, Ghazavi F, Giebel B, Kormelink TG, Hancock G, Helsmoortel H, Hill AF, Hyenne V, Kalra H, Kim D, Kowal J, Kraemer S, Leidinger P, Leonelli C, Liang Y, Lippens L, Liu S, Lo Cicero A, Martin S, Mathivanan S, Mathiyalagan P, Matusek T, Milani G, Monguio-Tortajada M, Mus LM, Muth DC, Nemeth A, Nolte-'t Hoen EN, O'Driscoll L, Palmulli R, Pfaffl MW, Primdal-Bengtson B, Romano E, Rousseau Q, Sahoo S, Sampaio N, Samuel M, Scicluna B, Soen B, Steels A, Swinnen JV (2017) *EV-TRACK: transparent reporting and centralizing knowledge in extracellular vesicle research.* **Nat Methods**, 14(3): 228-232

20. Wagner S, Hauck D, Hoffmann M, Sommer R, Joachim I, Müller R, Imberty A, Varrot A, Titz A (2017) *Covalent Lectin Inhibition and Application in Bacterial Biofilm Imaging.* **Angew Chem Int Ed Engl**, 56(52): 16559-16564

21. Wen Y, Ouyang Z, Yu Y, Zhou X, Pei Y, Devreese B, Higgins PG, Zheng F (2017) *Mechanistic insight into how multidrug resistant Acinetobacter baumannii response regulator AdeR recognizes an intercistronic region.* **Nucleic Acids Res**, 45(16): 9773-9787

Preclinical research

1. Allweiss L, Volz T, Giersch K, Kah J, Raffa G, Petersen J, Lohse AW, Beninati C, Pollicino T, Urban S, Lutgehetmann M, Dandri M (2017) *Proliferation of primary human hepatocytes and prevention of hepatitis B virus reinfection efficiently deplete nuclear cccDNA in vivo.* **Gut**, 67(3): 542-552

2. Burwitz BJ, Wettengel JM, Muck-Hausl MA, Ringelhan M, Ko C, Festag MM, Hammond KB, Northrup M, Bimber BN, Jacob T, Reed JS, Norris R, Park B, Moller-Tank S, Esser K, Greene JM, Wu HL, Abdulhaqq S, Webb G, Sutton WF, Klug A, Swanson T, Legasse AW, Vu TQ, Asokan A, Haigwood NL, Protzer U, Sacha JB (2017) *Hepatocytic expression of human sodium-taurocholate cotransporting polypeptide enables hepatitis B virus infection of macaques.* **Nat Commun**, 8(1): 2146

3. Ferreira K, Hu HY, Fetz V, Prochnow H, Rais B, Muller PP, Bronstrup M (2017) *Multivalent Siderophore-DOTAM Conjugates as Theranostics for Imaging and Treatment of Bacterial Infections.* **Angew Chem Int Ed Engl** 56(28): 8272-8276

4. Fischer JC, Bscheider M, Eisenkolb G, Lin CC, Wintges A, Otten V, Lindemans CA, Heidegger S, Rudelius M, Monette S, Porosnicu Rodriguez KA, Calafiore M, Liebermann S, Liu C, Lienenklaus S, Weiss S, Kalinke U, Ruland J, Peschel C, Shono Y, Docampo M, Velardi E, Jenq RR, Hanash AM, Dudakov JA, Haas T, van den Brink MRM, Poeck H (2017) *RIG-I/MAVS and STING signaling promote gut integrity during irradiation- and immune-mediated tissue injury.* **Sci Transl Med**, 9(386)

5. Fu C, Sikandar A, Donner J, Zaburannyi N, Herrmann J, Reck M, Wagner-Döbler I, Koehnke J, Müller R (2017) *The natural product carolacton inhibits folate-dependent C1 metabolism by targeting FolD/MTHFD.* **Nat Commun**, 8(1): 1529

6. Giersch K, Bhadra OD, Volz T, Allweiss L, Riecken K, Fehse B, Lohse AW, Petersen J, Sureau C, Urban S, Dandri M, Lutgehetmann M (2017) *Hepatitis delta virus persists during liver regeneration and is amplified through cell division both in vitro and in vivo.* **Gut** 2017 Dec 7. Epub ahead of print

7. Hösel M, Huber A, Bohlen S, Lucifora J, Ronzitti G, Puzzo F, Boisgerault F, Hacker UT, Kwanten WJ (2017) *Autophagy Determines Efficiency of Liver-directed Gene Therapy with Adeno-associated Viral Vectors.* **Hepatology**, 66(1): 252-265

8. Huttel S, Testolin G, Herrmann J,

Planke T, Gille F, Moreno M, Stadler M, Brönstrup M, Kirschning A, Müller R (2017) *Discovery and Total Synthesis of Natural Cystobactamid Derivatives with Superior Activity against Gram-Negative Pathogens.* **Angew Chem Int Ed Engl**, 56(41): 12760-12764

9. Kah J, Koh S, Volz T, Ceccarello E, Allweiss L, Lutgehetmann M, Bertoletti A, Dandri M (2017) *Lymphocytes transiently expressing virus-specific T cell receptors reduce hepatitis B virus infection.* **J Clin Invest**, 127(8): 3177-3188

10. Kloss F, Krchnak V, Krchnakova A, Schieferdecker S, Dreisbach J, Krone V, Mollmann U, Hoelscher M, Miller MJ (2017) *In Vivo Dearomatization of the Potent Antituberculosis Agent BTZ043 via Meisenheimer Complex Formation.* **Angew Chem Int Ed Engl**, 56(8): 2187-2191

11. Levander S, Holmstrom F, Frelin L, Ahlen G, Rupp D, Long G, Bartenschlager R, Sallberg M (2017) *Immune-mediated effects targeting hepatitis C virus in a syngeneic replicon cell transplantation mouse model.* **Gut** 2017 Jun 23. Epub ahead of print

12. Pegoraro S, Duffey M, Otto TD (2017) *SC83288 is a clinical development candidate for the treatment of severe malaria.* **Nat Commun**, 8: 14193

13. Wildermuth R, Speck K, Haut FL, Mayer P, Karge B, Bronstrup M, Magauer T (2017) *A modular synthesis of tetracyclic meroterpenoid antibiotics.* **Nat Commun**, 8(1): 2083

14. Wolf F, Bauer JS, Bendel TM, Kulik A, Kalinowski J, Gross H, Kaysser L (2017) *Biosynthesis of the beta-Lactone Proteasome Inhibitors Belactosin and Cystargolide.* **Angew Chem Int Ed Engl**, 56(23): 6665-6668

Clinical research

1. Agnandji ST, Fernandes JF, Bache EB, Obiang Mba RM, Brosnahan JS, Kabwende L, Pitzinger P, Staarink P, Massinga-Loembe M, Krahling V, Biedenkopf N, Fehling SK, Strecker T, Clark DJ, Staines HM, Hooper JW, Silvera P, Moorthy V, Kieny MP, Adegnika AA, Grobusch MP, Becker S, Ramharter M, Mordmuller B, Lell B, Krishna S, Kremsner PG (2017) *Safety and immunogenicity of rVSVDeltaG-ZEBOV-GP Ebola vaccine in adults and children in Lambarene, Gabon: A phase I randomised trial.* **PLoS Med**, 14(10): e1002402

2. Bassetti M, Garnacho-Montero J, Calandra T, Kullberg B, Dimopoulos G, Azoulay E, Chakrabarti A, Kett D, Leon C, Ostrosky-Zeichner L, Sanguinetti M, Timsit JF, Richardson MD, Shorr A, Cornely OA (2017) *Intensive care medicine research agenda on invasive fungal infection in critically ill patients.* **Intensive Care Med**, 43(9): 1225-1238

3. Berg T, Simon KG, Mauss S, Schott E, Heyne R, Klass DM, Eisenbach C, Welzel TM, Zachoval R, Felten G, Schulze-Zur-Wiesch J, Cornberg M, den Brouw MLO, Jump B, Reiser H, Gallo L, Warger T, Petersen J (2017) *Long-term response after stopping tenofovir disoproxil fumarate in non-cirrhotic HBeAg-negative patients - FINITE study.* **J Hepatol**, 67(5): 918-924

4. Bjorn-Mortensen K, Lillebaek T, Koch A, Soborg B, Ladefoged K, Sorensen HC, Kohl TA, Niemann S, Andersen AB (2017) Extent of transmission captured by contact tracing in a tuberculosis high endemic setting. **Eur Respir J**, 49(3)

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6. Chesov D, Ciobanu N, Lange C, Schon T, Heyckendorf J, Crudu V (2017) *Lack of evidence of isoniazid efficacy for the treatment of MDR/XDR-TB in the presence of the katG 315T mutation.* **Eur Respir J**, 50(4)

7. Chotiwan N, Brewster CD, Magalhaes T, Weger-Lucarelli J, Duggal NK, Ruckert C, Nguyen C, Garcia Luna SM, Fauver JR (2017) *Rapid and specific detection of Asian- and African-lineage Zika viruses.* **Sci Transl Med** 9(388)

8. Crudu V, Chesov D, Ciobanu N, Lange C, Heyckendorf J (2017) *High-dose isoniazid in the shorter-course multidrug-resistant tuberculosis regimen in the Republic of Moldova.* Eur Respir J, 50(4)

9. Dedicoat MJ, Gunther G, Crudu V, Duarte R, Gualano G, Magis-Escurra C, Rumetshofer R, Skrahina A, Spinu V, Tiberi S (2017) *Tuberculosis Treatment Outcomes in Europe: Based on Treatment Completion, Not Cure.* **Am J Respir Crit Care Med**, 196(9): 1222-1224

10. Dietz J, Susser S, Vermehren J, Peiffer KH, Grammatikos G, Berger A, Ferenci P, Buti M, Mullhaupt B, Hunyady B, Hinrichsen H, Mauss S, Petersen J, Buggisch P, Felten G, Huppe D, Knecht G, Lutz T, Schott E, Berg C, Spengler U, von Hahn T, Berg T, Zeuzem S, Sarrazin C, HCV E (2017) *Patterns of Resistance-associated Substitutions in Patients With Chronic HCV Infection Following Treatment with Direct-acting Antivirals.* **Gastroenterology**, 154(4): 976-988

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