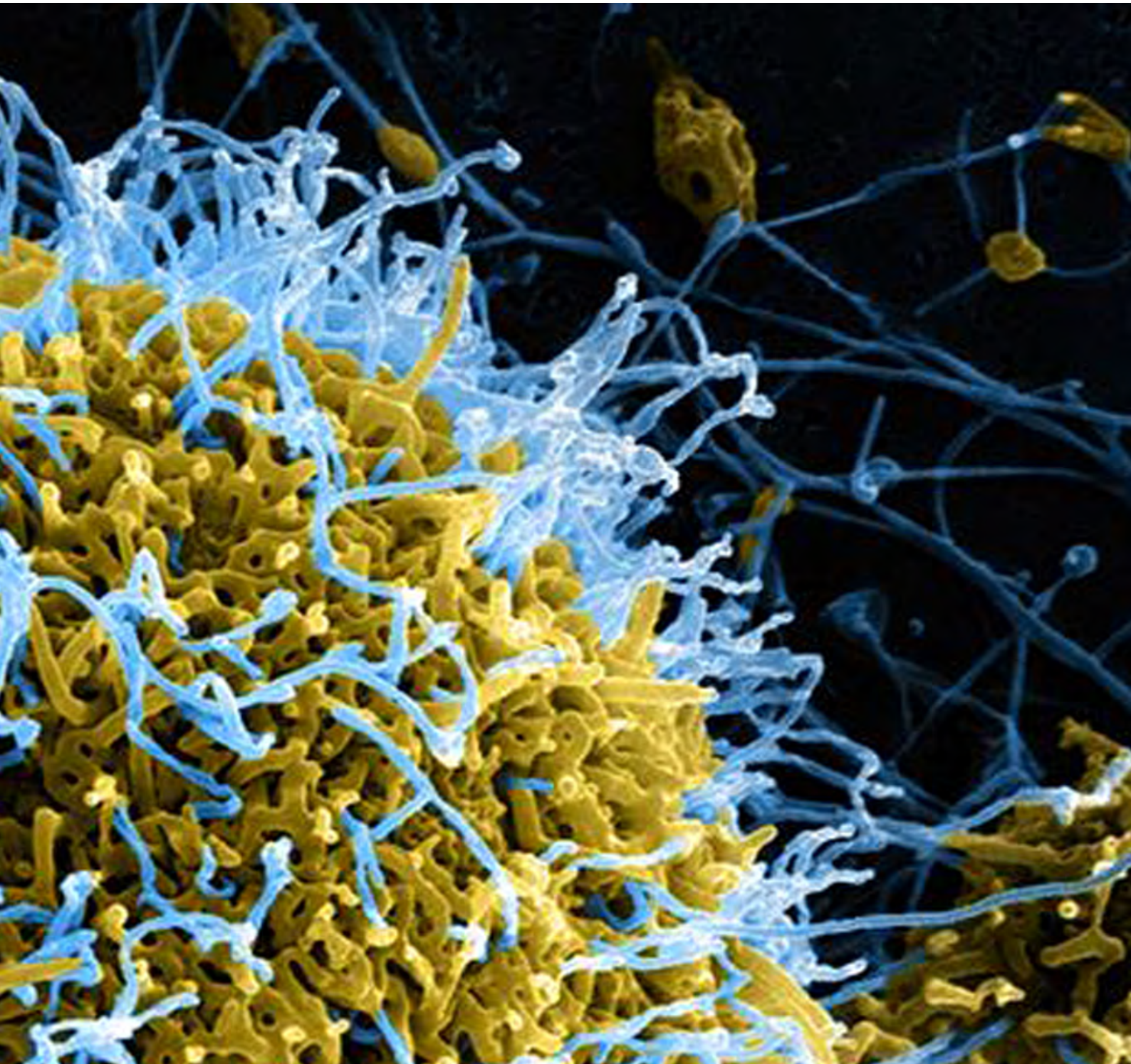
DZIF

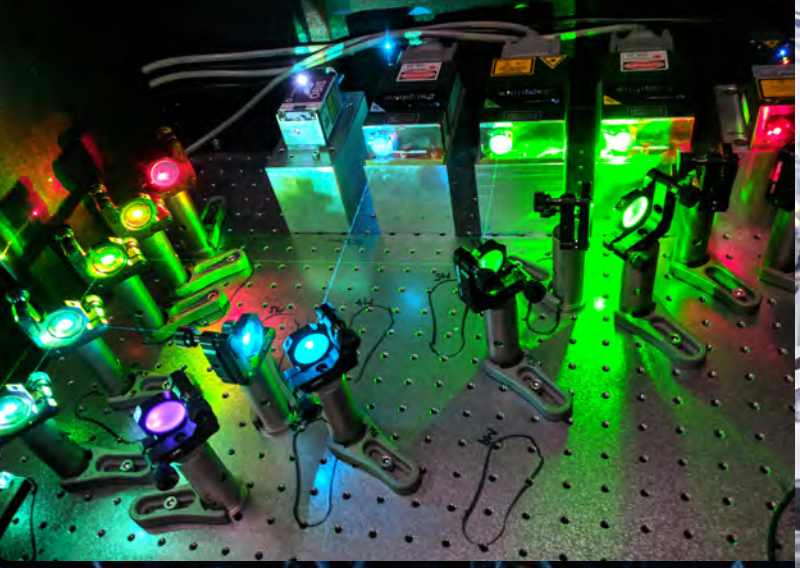
DZG DEUTSCHE ZENTREN DER GESUNDHEITSFORSCHUNG

GERMAN CENTER FOR INFECTION RESEARCH

Annual Report 2018



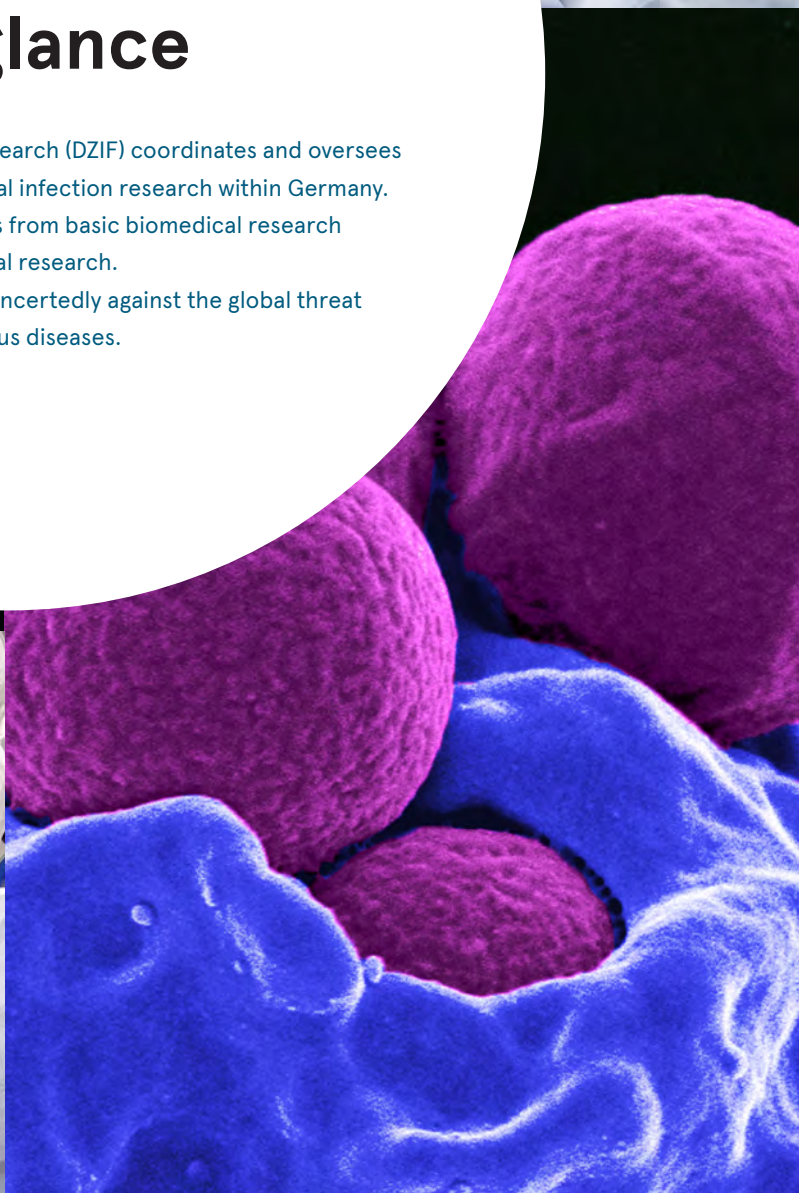
Cover image: This image shows a scanning electron microscope image of thread-like Ebola viruses (in blue) protruding from an infected cell.



ANNUAL REPORT 2018

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

Infectious diseases pose major challenges for science, medicine, politics in Germany and throughout the world. The German Center for Infection Research (DZIF) tackles these challenges through translational research. Since 2019, a new Executive Board comprising five members has been supervising the activities of the DZIF. The new Board inherited a successful network from its predecessors, the "founding" Executive Board, including numerous successful achievements. The DZIF's Scientific Advisory Board recently rated the DZIF as a "key player at an international global level", allowing the new Executive Board to build on a solid foundation and to continue the strategic development of the translational infection research. Special thanks go to the predecessors Martin Krönke, Ulrike Protzer and Dirk Heinz, who contributed substantially to this development through their dedication.

The specific focus now is to further improve on these successful projects, to develop new themes and projects and to keep adapting the strategy in line with changing demands. In 2018, focus was placed on internationalisation which set the course for partnerships with globally active institutions: CEPI (Coalition for Epidemic Preparedness Innovation) and CARB-X (Combating Antibiotic Resistant Biopharmaceutical Accelerator). The development of new vaccines and new approaches towards managing multidrug-resistant bacteria, viruses and parasites will continue to play an important role in the future.

Prevention, diagnostics and therapy are central themes at the DZIF which has categorised its activities into nine different research fields. This report will describe two vaccine research projects in detail: a therapeutic vaccination against hepatitis B for which preclinical development has been concluded and which is now ready for clinical testing, and a vaccine candidate against the Epstein Barr virus which is ready for the product development according to the Good Manufacturing Practice (GMP) guidelines.

Once again, our Annual Report illustrates the extensiveness of the thematic units dedicated to infection research at the DZIF. Firmly established themes within the DZIF include the development of new antibiotics, the fight against multidrug-resistant bacteria, research into infections that are prominent on a global scale such as HIV, malaria, tuberculosis and gastrointestinal diseases as well as newly emerging pathogens and how to combat them. There are several prime examples that should be of interest such as a new antibiotic against tuberculosis that is due to enter clinical phase II trials. DZIF researchers have also tested new antibodies with confirmed efficacy against HIV, a virus that continues to be a leading cause of death in many countries. The permanent control of HIV and eventually finding a cure for the infection continue to feature on the DZIF agenda.

We have selected various highlights from all fields of research for this report to give you a view of the scope of work carried out at the DZIF. You can read about what DZIF scientists have accomplished and achieved in the field of translational research in 2018. We hope you enjoy reading this report.

Yours sincerely
The DZIF Executive Board


Prof. Hans-Georg Kräusslich


Prof. Dirk Busch


Prof. Ingo Autenrieth


Prof. Maura Dandri


Prof. Dirk Heinz

ABOUT THE DZIF

United in tackling major challenges

Infection researchers at the DZIF are currently confronted with four major challenges: tropical and emerging infections, antibiotic resistance, chronic infections, immunoprevention and treatment. Rapid action is required in order to effectively bring new drugs, diagnostics and treatments to patients. The mission of the German Center for Infection Research (DZIF) is to translate research results into clinical practice. 35 institutions have come together under the DZIF umbrella and over 500 doctors and scientists work closely together in order to curb infectious diseases.

THE GOAL: TRANSLATION

Scientists and doctors work together at the DZIF– carrying out basic research on results obtained from patient treatments and bringing laboratory results faster to patients with severe diseases. In order to facilitate translational research processes, the DZIF is structured thematically encompassing projects within certain categories that operate across various institutions. Consequently, scientists and physicians conduct research on infectious diseases according to the research field categories of: “Tuberculosis”, “Malaria”, “HIV”, “Hepatitis” and “Gastrointestinal Infections” and also focus on specific problem areas such as “Emerging Infections”, “Infections of the immunocompromised Host”, “Healthcare-associated and Antibiotic-resistant bacterial Infections” and “Novel Antibiotics”.

IN-HOUSE SERVICE FACILITIES FOR SCIENTISTS

Eight “translational infrastructures” support scientists at the DZIF. Experts in “Product Development”, for example,

Ready for the stage: For the DZIF Annual Meeting 2019 scientists came together in the city hall of Heidelberg.

answer questions regarding approvals and clinical demands. The "Clinical Trial Unit" coordinates clinical trials for infectious disease research. DZIF scientists can obtain tissue, body fluid and cell samples from the DZIF's "Biobanking" infrastructure. Defined strains of bacteria are collected and analysed in the "Pathogen Repository". Experts and establishments remain accessible internationally: DZIF experts can conduct research on infectious diseases that are rare in Germany at "African Partner Institutions" where they are more common.

STRATEGIC NETWORKING

One of the strengths of the DZIF lies in its networking. Scientists and clinicians work together across the boundaries of their establishments and professions. Universities, research institutes, hospitals, authorities and establishments exchange information and work closely with clinical practices and industrial companies. Expertise is pooled together and managed internally within the DZIF's research fields and infrastructures. In addition, the DZIF is a member of the all-encompassing national German Centers for Health Research (DZG) alliance. Last but not least, the DZIF has also become a renowned partner in research networks across Europe and the world.

THE DZIF: A STRONG PARTNER FOR INDUSTRY

In many cases, developing new drugs is often not of economic interest to the pharmaceutical industry. This applies in particular to novel antibiotics as they often are last resort drugs which must be used as sparingly as possible for difficult-to-treat patients. This has led to a significant gap in drug development which continues to worsen, particularly for this group of drugs. Research companies need partners willing to share economic risks and make substantial scientific contributions. This is precisely where the DZIF steps in: over the past few years, the DZIF has become an important player in infection research in Germany and a reliable partner for the biotechnology and pharmaceutical industry.

NEW YOUNG TALENTS IN INFECTION RESEARCH

Previously, little support was available for research at the interface between the laboratory and clinical treatment of infectious diseases. The DZIF has created incentives for young scientists to specialise in infection research and offers scholarships to doctors, enabling them to dedicate themselves more to research. The DZIF Academy, for example, offers clinical leave stipends to support young doctors who would like to temporarily reduce their routine clinical work and focus more on research. Maternity leave stipends, which support young parents returning to research, are also very successful.

INTERNATIONAL PARTNERSHIPS

Emerging pathogens such as Zika, Ebola and MERS viruses underline the need for infection researchers to think, network and act internationally: pathogens know no boundaries. The DZIF has been working with partner institutions in Africa and Europe since it was founded. It works in partnership with the French institute INSERM (Institut national de la santé et de la recherche médicale) for AIDS and hepatitis research. It is also one of nine founding members of the CARA Initiative (Conscience of Antimicrobial Resistance Accountability) and is involved in the vaccine initiative CEPI (Coalition for Epidemic Preparedness Innovations). The DZIF is also involved with the establishment of the new "Global Antimicrobial Resistance Research and Development Hub" with its headquarters in Berlin. Since the beginning of 2019, the DZIF has also become one of ten partners in the CARB-X accelerator network. CARB-X accelerates new drug development projects worldwide in the fight against antibiotic-resistant drugs.

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

Research fields

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

Infrastructures

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

Research curbs the rise of highly contagious viruses

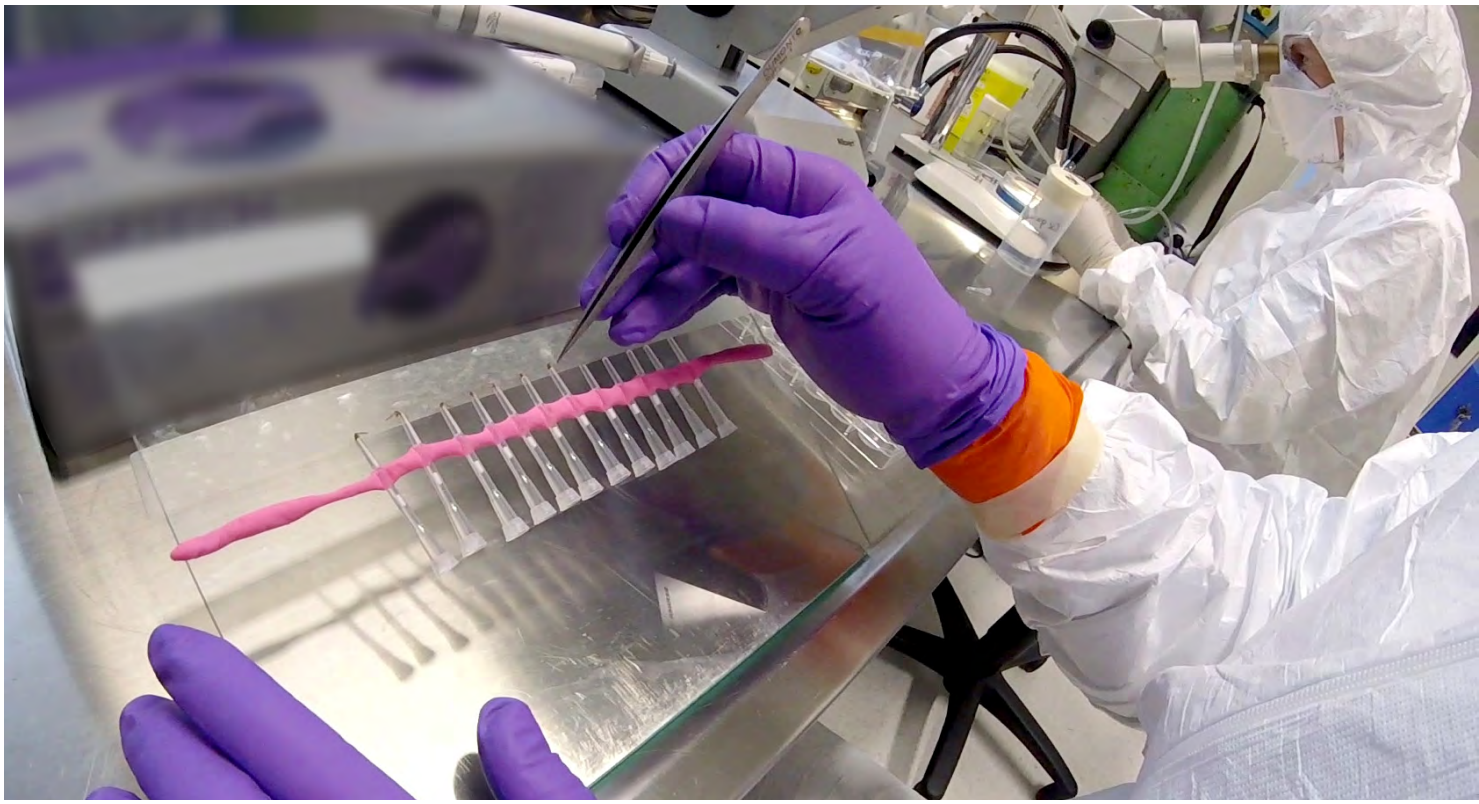
Often, no solution is available to treat tropical virus-associated diseases. The highly contagious Ebola virus, for example, caused the largest known epidemic with 11,000 deaths in West Africa in 2016. Chikungunya viruses, which are also endemic in South East Asia and Southern India, cause symptoms such as fever, petechial rash and severe joint pain. People acquire immunity only after infection. There are currently no drugs available to treat these diseases.

Viruses have very adept mechanisms for mass replication. Several DZIF teams are working on stopping the dangerous spread of viruses. For example, they have developed an artificial inhibitor which stops the replication of Ebola viruses in infected cells. They are also carrying out research to determine whether tropical Chikungunya viruses can spread to this part of the world.

UNITED IN THE FIGHT AGAINST EBOLA

Ebola infections are usually fatal within a very short period of time. DZIF researchers and cell biologists from Denmark have created an artificial inhibitor which prevents the virus from "kidnapping" an enzyme in the infected cell using it for its own purposes. "Each virus requires certain cellular proteins in order to replicate," says Prof. Stephan Becker from

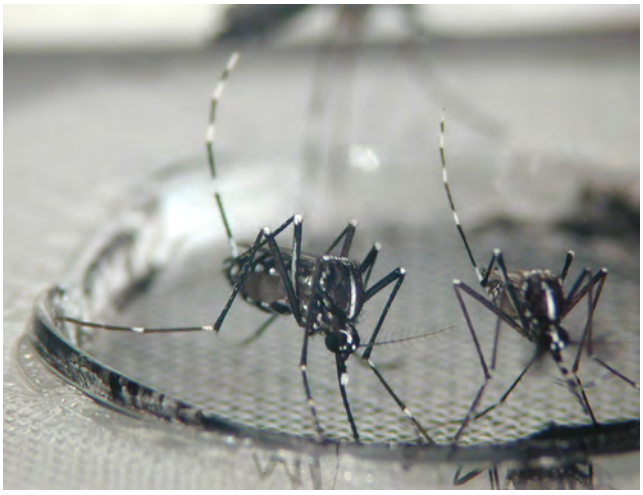
Female mosquitoes have to be stuck on a dish, in order to obtain and test their saliva. The saliva is obtained with the tip of a pipette filled with fluid. (Back right of the image: A scientist is sedating and sorting mosquitoes)



Philipps University of Marburg. One of these is the host cell's own phosphatase PP2A. "When this enzyme approaches VP30, a protein in the virus, VP30 becomes activated and the virus starts working," explains Becker. VP30 is one of the key proteins needed for viral transcription. In order to become active, PP2A requires a contact site on another viral protein, NP, which guides it to the virus particle inside of the infected cell. Becker and his team have now developed a molecular duplicate of NP that possesses the same viral contact site for PP2A and lures it away from VP30. "Consequently, PP2A is no longer able to dock onto the virus particle in the close vicinity of VP30 which inhibits viral activation." Thus, the Ebola virus inhibitor acts on cellular proteins and specifically targets cellular processes. "With this approach we are pursuing a new strategy to fight viruses which had previously been avoided due to potential side effects," says Becker. "Nowadays, it is becoming increasingly evident that intercepting cellular processes in short-term acute viral infections is justifiable." Using this approach, scientists hope to find an agent that has broad-spectrum efficacy which can be used for several viruses simultaneously.

PREVENTING TROPICAL PATHOGENS FROM COLONISING THIS PART OF THE WORLD

Up to now, the climatic conditions in our part of the world have been unattractive for tropical pathogens such as West Nile, Dengue and Zika viruses. These viruses usually only spread in warm climatic regions and need specific insects for their transmission such as the tiger mosquito. "In Germany, we usually do not have high average temperatures of between 25 and 27 degrees over periods of 2 to 3 weeks," says Prof. Egbert Tannich, Head of the National Reference Centre for Tropical Pathogens at the Bernhard Nocht Institute for Tropical Medicine (BNITM). However, some pathogens, for example chikungunya viruses, do not follow these climatic rules. In the past few years, despite moderate temperatures, there have been repeated outbreaks in Italy and France. Researchers at the BNITM have now been able to demonstrate that these outbreaks could also occur in Germany. In a special high-safety insectarium, indigenous mosquitoes from Germany were exposed to blood containing viruses and kept in climate chambers set at 18, 21, and 24 degrees over a 14 day period. "The viruses replicated very well in tiger mosquitoes from Germany, even at 18 degrees," says Tannich. "After 2 weeks, over half of the mosquitoes had infectious viruses in their saliva." However, Tannich and his team of experts currently deem an outbreak unlikely in the near future. "Up to now, we have only found a few individual tiger mosquitoes restricted to certain local regions. Their low prevalence has prevented tropical pathogens from spreading up to now." Potentially affected regions should, however, establish surveillance systems to monitor transmitting insects and enable them to be targeted early on.



The Asian tiger mosquito transmits the tropical chikungunya virus.

GOALS FOR 2018: OUTCOMES

- 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 outreach of the DZIF through intensive collaboration with the Coalition for Epidemic Preparedness Innovations (CEPI) as part of developing the MVA-MERS vaccine.

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

GOALS FOR 2019

- ○ Launch of the DZIF Virus Test Platform and acquisition of new industrial partners.
- ○ Development of a vaccine platform based on self-replicating RNA together with industrial partners.
- ○ Expansion of a surveillance system to monitor known and unknown virus infections / zoonoses in rats and wild birds.

Coordinator:
Prof. Stephan Becker
Marburg

Improved testing, new drugs

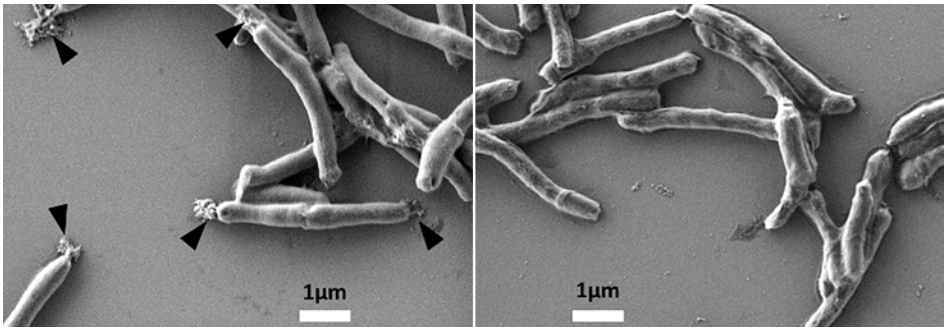
With nine million new infections each year, tuberculosis is one of the top most infectious diseases worldwide. According to estimates by the World Health Organisation, one third of the human population–approximately two billion people–is infected with the tuberculosis pathogen. One in ten to one in twenty of those infected are developing active tuberculosis and consequently require effective treatment.

Doctors treat tuberculosis (TB) with a cocktail of four to eight antibiotics. A combination of drugs is necessary to prevent resistance development and achieve successful treatment outcome. Prior to treatment initiation, drug-susceptibility testing must be carried out so as to rule out the use of ineffective drugs from the start. DZIF researchers have now developed a more rapid method of testing for resistance. In addition, with the support of the DZIF, scientists have succeeded in developing a new antibiotic.

NEW DRUG IN CLINICAL TRIALS

A first trial on patients with tuberculosis, examining the new tuberculosis antibiotic BTZ043, will be initiated in Cape Town, South Africa, in the coming months. Trials on healthy volunteers have already been carried out. “With the help of this trial, we would like to ascertain the dose for optimal efficacy and which is still tolerated well,” explains DZIF scientist Prof. Michael Hoelscher, Director of the Tropical Institute of the Ludwig-Maximilians-Universität München (LMU). “We would subsequently

Professor Stefan Niemann, Research Center Borstel, believes in genome sequencing for drug-susceptibility testing.



Tuberculosis bacteria: cells leak when treated with BTZ043 (left); (right) untreated bacterial cells.

like to conduct further tests on three promising dosages in larger patient groups." BTZ043 was tolerated well in the first clinical trials. The molecule irreversibly binds to an enzyme mycobacteria need to build their bacterial cell walls. It destroys the outer envelope and consequently kills the bacteria. "Investigations into over 300 isolates with particularly high resistance have shown that there is currently no resistance to BTZ043 as it is the first agent in a new class of antibiotics," says Hoelscher. BTZ043 was discovered at the Hans Knöll Institute (HKI) in Jena. Since 2014, researchers from LMU Munich and HKI have been working on developing the agent at various locations including the DZIF and the InfectControl 2020 consortium. In the future, BTZ043 is to replace one of the agents used in the drug combinations for tuberculosis treatment. Future trials will show the most effective combination of BTZ043 with previously used agents.

GENOME SEQUENCING REPLACES CONVENTIONAL DRUG-SUSCEPTIBILITY TESTING

Prof. Stefan Niemann is Head of the Molecular Mycobacteriology Group at the Research Center Borstel (FZB). The main aim of his research work is to develop effective resistance diagnostic guiding individualized TB therapy. Drug-susceptibility testing (DST) is usually conducted before treatment in order to ensure effective treatment regimens for patients. Up to now, DST is mainly carried out by culture based methods, which takes several weeks. "This testing is work intensive, requires quite a large number of staff and ample experience in working in laboratory infrastructures with high biosafety levels," says Niemann. Consequently, scientists are looking for molecular alternatives to carry out the resistance testing. An international consortium, also involving scientists from Borstel, carried out the so-called CRYpTIC study, published in the *New England Journal of Medicine* in 2018, which showed that genome sequencing of tubercle bacteria can be used to predict resistance directly from the genome of the pathogens. In this study, scientists analysed the genomes of over 10,000 pathogen strains from 16 countries. The FZB provided 600 data sets and was involved in the data analysis. "Conventional susceptibility testing of standard drugs could soon be replaced by genome-based methods," Niemann hopes. In Germany, a pilot study is currently underway to evaluate the suitability of the method for both, diagnostic and surveillance purposes. "We are expecting initial results by end of 2019," says Niemann. In Great Britain, however, molecular diagnostics have already been well established over the past few years.

GOALS FOR 2018: OUTCOMES

◐ The individual adaptation for treatment of TB patients based on the exact genome of the tuberculosis pathogens was evaluated in the clinic.

● An initial selection of biomarkers was made available for assessing the course of therapy for M/XDR therapy.

● The first test subjects were included in the study for a potential tuberculosis drug.

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

GOALS FOR 2019

○ Molecular biology methods that confirm mutations coding for resistance in the TB pathogen's genome will be evaluated in a pilot study.

○ Evaluation of defined biomarkers for assessing treatment success in TB patients.

○ First TB patients to receive BTZ043, the new antibiotic for tuberculosis.

Coordinator:
Prof. Stefan Niemann
Borstel

Tracking the pathogen's tactics

Malaria is caused by parasites of the species Plasmodium, which are transmitted by bites of infected mosquitoes. They infect red blood cells–with life threatening consequences. According to the WHO, 219 million people contracted this tropical disease in 2017. Of the 435,000 people that died, most were children under 5. Malaria is endemic in Africa as well as in tropical and subtropical regions in Asia and South America.

Symptoms of malaria include fever, anaemia and signs of organ dysfunction such as coma and respiratory distress. However, not all of those infected develop symptoms as some people develop immunity to the pathogen. Scientists at the DZIF are developing a new method in order to investigate this naturally acquired immunity in humans. They aim to identify mechanisms of the parasite in order to protect itself and remain under control of the immune system of infected people, without causing any symptoms during the dry season.

USING A NEW AND PRECISE RESEARCH METHOD

People with the sickle cell gene have innate immunity to malaria and people who have frequently been exposed to the malaria parasite during childhood acquire natural immunity. This means that these people, despite being infected, develop less frequent or less severe symptoms. Scientists at the Institute of Tropical Medicine of the University of Tübingen, the DZIF and Sanaria Inc. have investigated the mechanisms behind this. They developed a method to infect volunteers under controlled conditions and treat them effectively before symptoms or complications can develop. "We have now used this method in a clinical trial for the first time in order to research the interactions between the immune system and changes in the parasite's genome," says Professor Bertrand Lell, Director of the Centre de Recherches Médicales de Lambaréné (CERMEL) in Gabon, Central Africa. A total of eleven

The University of Tübingen works closely with the CERMEL in Lambaréné, Gabon, for studies on malaria.

Intensive exchange: Professor Peter G. Kremsner and Dr Rella Manego.

semi-immune people in Gabon with normal haemoglobin levels, nine semi-immune people with the sickle cell gene and five non-immune Europeans with normal haemoglobin levels were included in the clinical trial. Adults who have been exposed to the pathogen all their lives, as is the case in Gabon, are considered to be semi-immune. "We wanted to find out which people develop symptoms and when, in addition to what controls the infection and how the immune system responds to infection." In people with naturally acquired immunity, the pathogens appeared in the blood later and symptoms also either occurred later or did not occur at all. In four of the people infected, no pathogens could be detected in the blood at all. "The parasites have probably already been eliminated in the liver through cellular immune responses," explains Lell. This study confirms that natural immunisation starts in the liver. "It would therefore be worthwhile to develop vaccinations that target malaria at the liver stage."

PLAYING HIDE AND SEEK IN THE DRY SEASON

Malaria pathogens need the Anopheles mosquito to enter the human body. In turn, mosquito larvae need water in order to develop. How does the parasite survive the long dry season? Dr Silvia Portugal at the Centre for Infectious Diseases of the University of Heidelberg is addressing this question. "The parasite may possess so-called "sensing" mechanisms which help it recognise presence or absence of mosquitoes," Portugal suspects, "and it probably adapts its growth accordingly." One thing is certain: during the dry season, the parasites "hide" in infected, asymptomatic people. During this time the parasite changes in such a way that the infection does not cause symptoms. "Children in particular seem to be an efficient silent reservoir," says Portugal. "Their range of immune responses is not as advanced as compared to adults and they are consequently less able to completely eliminate the parasites." Portugal's team also investigates the degree to which the human immune system can control the pathogen and the precise mechanisms the pathogens use to make themselves invisible. "We are interested in what causes the differences in the parasites' gene expressions during the dry season, when it causes no symptoms, and during the rainy season, when it causes malaria." Portugal's work is being funded by DZIF and an European Union ERC starting grant worth 1.5 million euro.

GOALS FOR 2018: OUTCOMES

- The Tübingen vaccination schedule for malaria was optimised and defined for further clinical development. First studies in Africa were initiated.
- The mechanism of action and resistance development against a new antimalarial compound were further explored.
- Exactly defined reference samples were collected to evaluate the predictive capacity of newly established biomarkers.

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

GOALS FOR 2019

○ Progressing the clinical development of the malaria vaccine developed in Tübingen. Tolerability and efficacy of the vaccine will be tested in children in a Phase II trial in Gabon.

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

○ Development of immunity against the malaria pathogen in the first twelve months of life will be investigated. A birth cohort will be established in Ghana for this purpose.

Coordinator:
Prof. Benjamin Mordmüller
Tübingen

Understanding and conquering the virus

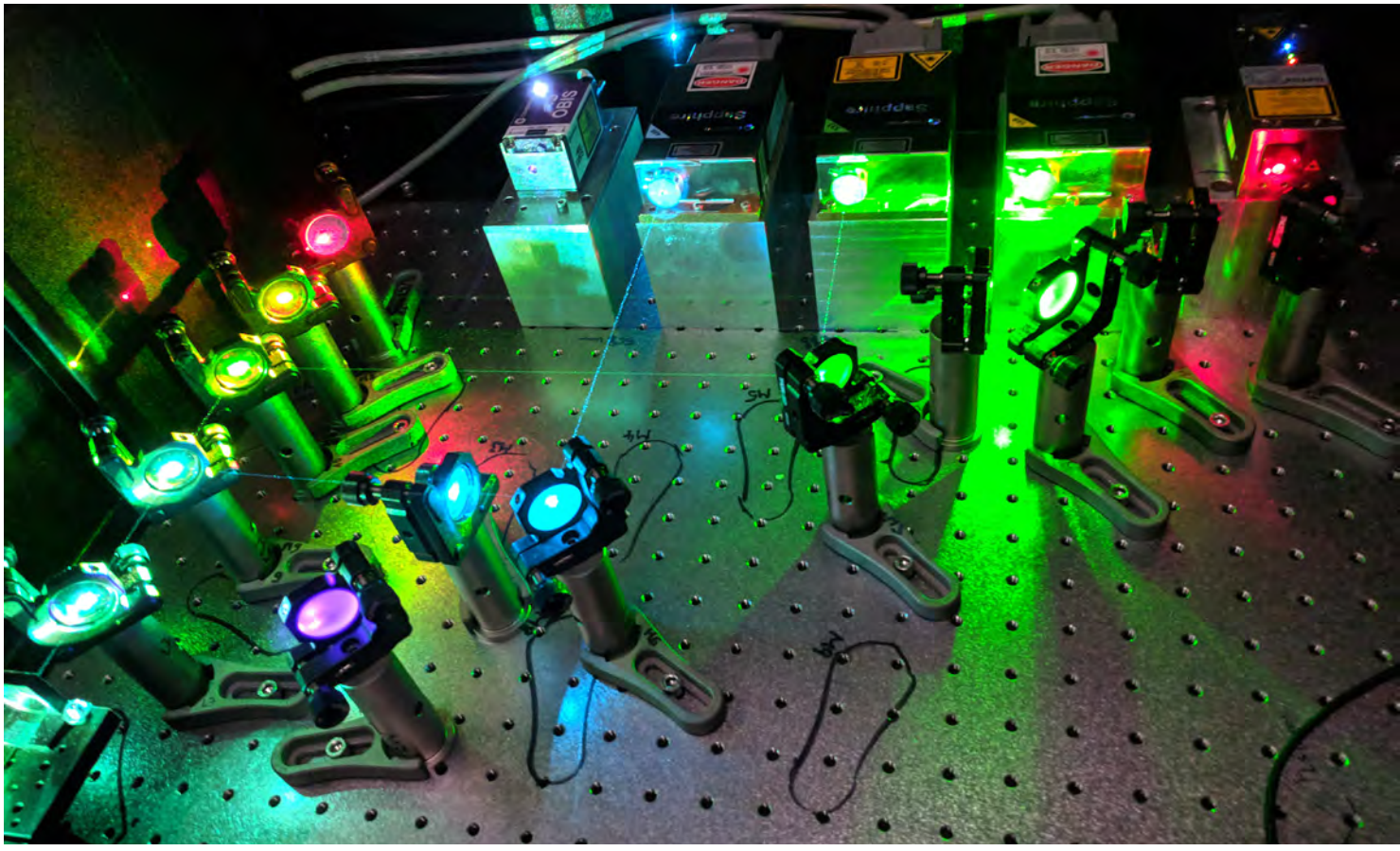
Patients infected with the human immunodeficiency virus type 1 (HIV-1) are usually treated with antiretroviral treatment (ART). This combination of drugs prevents viral replication and disease manifestation. However, despite effective treatment, people are still dying from the consequences of HIV infection, often because they do not have regular access to the drugs. Alternatives to the classic antiretrovirals are urgently needed.

Treatment with ART renders the HIV virus dormant. However, as soon as treatment is discontinued, the virus resumes replication. In initial trials, DZIF researchers from Cologne used a new approach to potentially reduce the frequency of treatment required in the future, going from daily to occasional treatment periods. An imaging platform at the University of Heidelberg also provides new insights into the disease as it depicts detailed pathobiological processes of infectious diseases by means of microscopy.

USING BROADLY NEUTRALISING ANTIBODIES FOR HIV-1

In the past few years, so-called broadly neutralising antibodies have undergone clinical testing as a potentially

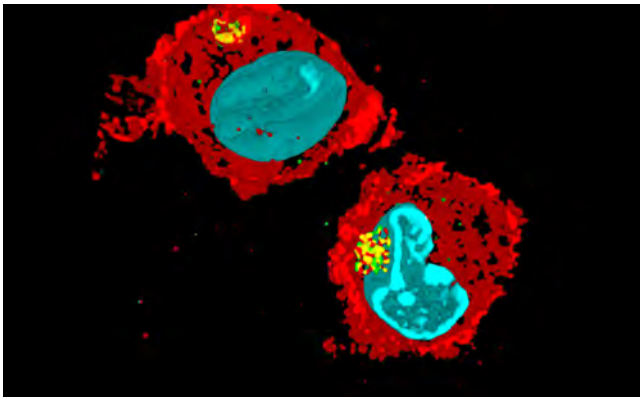
An imaging platform for infectious diseases in Heidelberg permits realistic insights into living systems.



new treatment approach for HIV-1. These antibodies neutralise the virus and consequently reduce viral loads. DZIF researcher Prof. Florian Klein from Cologne University Hospital co-developed this approach. In collaboration with various partners, his team demonstrated that patients who were administered a combination of two broadly neutralising antibodies had virus-free intervals lasting over a period of several months. "The antibody combination resulted in long-term control of HIV replication." The antibodies were originally isolated and cloned from so-called elite neutralisers. Elite neutralisers are individuals who develop very potent antibodies against HIV-1. Meanwhile, the approach of administering broadly neutralising antibodies to target HIV viruses has reached clinical research stages. "The efficacy and safety of about a dozen broadly neutralising antibodies are currently being investigated by colleagues in over 60 trials all over the world," says Klein. The antibodies not only prevent viral replication, but also support the immune system in killing infected cells.

PRECISE EXAMINATION OF THE PATHOBIOLOGY

Basic and clinical research on HIV have not been sufficiently combined in Germany so far. The Infectious Diseases Imaging Platform (IDIP) could change this and support the development of new therapeutic strategies in the future. "Many findings drawn from basic research have not been transferrable to humans as they only represent simplified and potentially distorted perspectives of important pathobiological processes," says Dr Vibor Laketa, who heads the IDIP for HIV research. "If it were possible to transfer infectious disease research to more complex biological systems such as the human organism, we would be able to better predict pathogenicity as well as both immunological and drug-induced pathogen control in the infected host." Microscopic imaging is the only method that can demonstrate molecular events in complex biological systems and investigate these quantitatively. For the first time now, the IDIP offers the safety standards required for such an extensive analysis of HIV. "Microscopy will enable us to realistically depict a living system," says Laketa. In the future, the newly established microscopy infrastructure could help clarify open questions regarding HIV pathophysiology. Rare cells relevant for HIV research could be identified and isolated. Alongside studies on the mechanism of action of new therapeutic strategies, microscopic screening approaches to identify new therapeutics or therapeutic goals could also be developed.



In human dendritic cells HIV is mostly localized in an invagination of the plasma membrane (blue: cell nucleus, red: plasma membrane, green: HIV).

GOALS FOR 2018: OUTCOMES

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

◐ *Ziel teilweise erreicht/Projekt läuft noch*
● *Ziel erreicht*

GOALS FOR 2019

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

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

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

Coordinator:
Prof. Marcus Altfeld
Hamburg

Preventing hepatitis B and C for good

More and more people are dying from hepatitis infections even though treatment has improved. According to mortality statistics, the virus is ranked first of the top most infectious diseases worldwide. The World Health Organisation (WHO) aims to achieve a drastic reduction in the incidence and mortality rate of hepatitis by 2030. The DZIF "Hepatitis" research field is contributing to this objective through the development of new vaccines.

There are five known hepatitis viruses classified as hepatitis A to E. The hepatitis B and C viruses are particularly dangerous and account for 96 percent of the 1.34 million hepatitis-related deaths recorded worldwide each year. DZIF researchers are consequently searching for new strategies to fight these two types of viruses in particular. They are working to develop specific vaccinations against hepatitis B and C to improve treatment or prevention of infection by the viruses.

HEPATITIS C PREVENTION

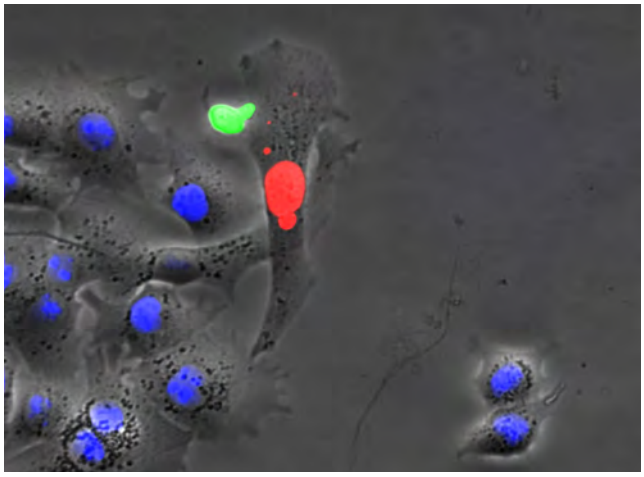
Hepatitis C has become a curable disease as new treatment has been available for the past few years. However, a vaccine preventing the disease in the first place would be preferable to any kind of therapy. Researchers at TWINCORE, part of the Hannover Medical School (MHH) and the Helmholtz Centre for Infection Research (HZI), are working intensively to develop a preventive vaccine. "We first searched for a

Strict safety procedures are in place for hepatitis research.

suitable target site on the viral envelope protein which can be used to generate an immune response," says Prof. Thomas Pietschmann, Head of the Department for Experimental Virology at the HZI. This is not an easy task because, similar to influenza viruses, hepatitis C viruses change continuously which is how they elude the immune system. The researchers selected a protein that the virus needs in order to enter liver cells. "This protein has important receptor binding sites that do not change, despite the virus being highly variable. The protein is consequently a target molecule that is well-suited for inducing immune responses," Pietschmann explains. However, the immune system develops an insufficient number of antibodies, despite this potent target site. Why is this so? "We now know that the selected surface protein is very mobile," says Pietschmann, "so figuratively speaking, it is constantly being blown about in the wind but we need for it to be windstill in order to induce good immune responses." The researchers are currently looking into how to fixate the region in question in such a way that it becomes recognisable to the immune system and therefore induces a response. Pietschmann is certain that once this has been accomplished, the immune system will also develop sufficient antibodies against hepatitis C and a vaccine will consequently make the disease preventable.

USING VACCINATION THERAPY AS A CURE

Prof. Ulrike Protzer of the Institute of Virology of the Technical University of Munich (TUM), has completed the experimental drug development phase of a therapeutic hepatitis B vaccine. The agent is to be tested on first trial subjects in 2020. Instead of preventing an infection, Protzer's vaccine aims to cure infected patients. Up to now, hepatitis B has been incurable. The virus begins to replicate again as soon as antivirals have been discontinued, the reason being that the virus deposits DNA into the nuclei of infected liver cells which allows it to remain undetectable by innate immune receptors. This new immune therapy has a double effect: firstly, as is the case with any vaccination, the immune system develops neutralising antibodies against specific hepatitis B proteins whilst raising the alarm for T cells. Secondly, with the help of a viral vector, the vaccination boosts cytotoxic T cells which kill the infected liver cells. This DZIF vaccine has successfully combined both response pathways for the first time in the world. Preclinical proof-of-concept experiments demonstrated that sufficient neutralising antibodies and T cells were produced in order to kill the hidden viruses, which consequently led to a cure. The vaccine is currently being produced under strict specifications so as to be used in clinical trials on healthy trial subjects. Virologist, Ulrike Protzer, is optimistic: "If all goes well, this therapeutic vaccine could become a reality within the next ten years." For this, however, still a lot of work is required.



The image shows an HBV-specific T cell (green) targeting a cell which is producing virus proteins (red) and HBV negative cells (blue).

GOALS FOR 2018: OUTCOMES

- ● Next generation sequencing methods (NGS) were to be introduced into the online-based platform Geno2pheno for the identification of viral resistance.
- ◐ 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 through 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.

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

GOALS FOR 2019

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

Coordinator:
Prof. Ulrike Protzer
Munich

Tracking *Helicobacter pylori*

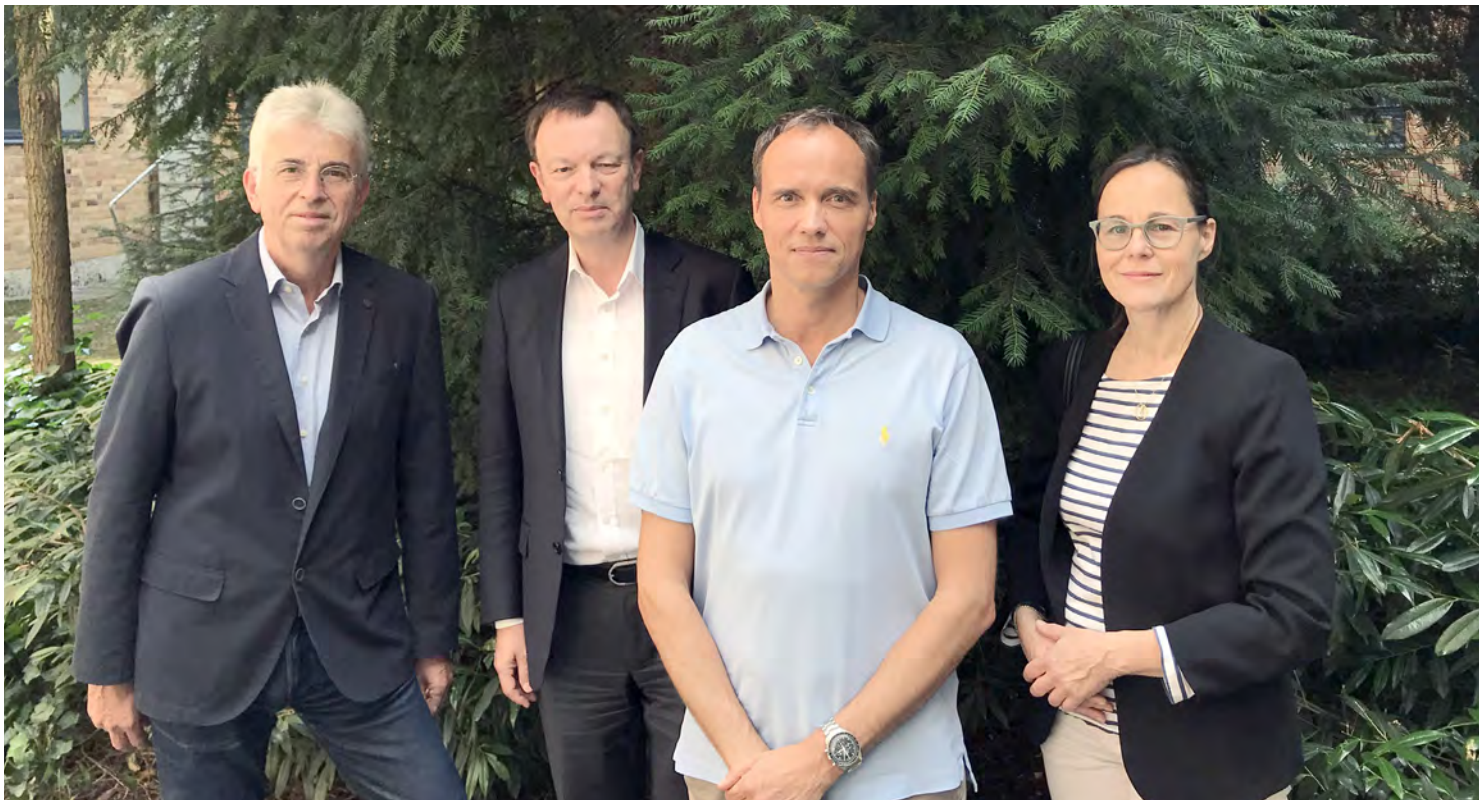
Helicobacter pylori is globally endemic and the most frequent cause of chronic bacterial infections in humans. Infections usually occur during childhood and approximately one in two people are affected worldwide. H. pylori causes gastritis in almost all cases, of which just under a fifth require symptomatic treatment. Since 1994, it has been officially recognised that the bacteria cause gastric cancer in approximately one percent of all those infected.

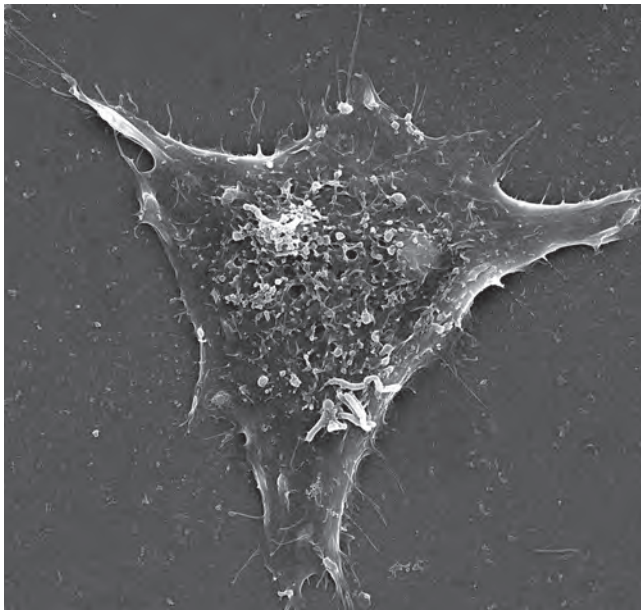
H. *pylori* infections do not provoke any overt symptoms, consequently most people do not realise that they carry the bacteria. DZIF researchers look for solutions to better understand the mechanisms of infection in order to improve prevention and treatment. Two teams at the Ludwig-Maximilians-Universität München (LMU Munich) jointly analysed the genetic mechanisms the bacteria use to spread worldwide. Two further research groups at the LMU and the Technical University Munich (TUM) were able to show how the bacteria reach the gastric mucosa in humans and how this could perhaps be prevented.

ENZYME REGULATES EPIGENETIC ADAPTATION

A typical trait of *Helicobacter pylori* is its genetic adaptability. It is able to spread on a global scale due to its ability to genetically adapt to different environments. LMU microbiologists are investigating which precise role the bacteria's flexible gene expression plays in infection of the human stomach. Research groups led by Professors Sebastian Suerbaum and Christine Josenhans at the LMU's Max von Pettenkofer Institute, identified an enzyme that plays a fundamental role in this process. The enzyme, known as methyltransferase JHP 1050, regulates the bacteria's entire

United against Helicobacter pylori: (from left) Rainer Haas, Sebastian Suerbaum, Markus Gerhard, Christine Josenhans.





Helicobacter pylori under the electron microscope.

gene expression by transferring methyl groups onto specific DNA sequences. Genes are switched on or off depending on whether the enzyme methylates a DNA sequence or not. In almost all organisms, methyltransferases play a crucial role in epigenetic processes that regulate adaptation to the environment. Methylation of DNA, as a mode of regulating gene expression, was originally discovered in humans. "Epigenetic regulation in bacteria, however, has not been researched much," says Sebastian Suerbaum. "Our work demonstrates that almost all important features of interaction between the bacteria and their human hosts such as bacterial metabolism, interaction with host cells, motility and stress resistance are regulated by global gene methylation," says Josenhans. "This process gives the bacteria the high flexibility required in order to continuously adapt to changing environmental conditions."

NEW TARGET STRUCTURES FOR *H. PYLORI'S* POISONOUS INJECTION

Gastric cancer develops in one to two percent of *H. pylori* infections worldwide. "The strains involved in the development of cancer are particularly pathogenic and possess a complex molecular structure and important virulence factor called Cag type IV secretion system (T4SS)," explains Prof. Rainer Haas from the LMU's Max von Pettenkofer Institute. The bacteria use these molecular injection needles to squirt CagA, a signalling molecule, into the cells of the gastric mucosa, consequently destroying signalling pathways which can ultimately result in the development of cancer. Current scientific consensus is that T4SS binds to a surface protein called integrin in order to inject CagA into the cells. "However, our latest results show that it is not the binding to integrins but an interaction between *H. pylori* and so-called CEACAM receptors on human gastric epithelium cells that enables the Cag type IV secretion system to function," the microbiologist says. The DZIF researcher's long-term goal is to block this molecular injection or selectively inhibit the bacteria themselves with new drugs. The research team consequently developed a high-throughput method to screen for potential new agents. Prof. Markus Gerhard's research group (TUM) has additionally been able to show that it is possible to prevent injection of CagA into gastric mucosa cells by intercepting bacterial binding to the receptor using antibodies or small peptides, for example. "These findings are an important starting point for developing new vaccines and therapeutics," says Gerhard.

GOALS FOR 2018: OUTCOMES

◐ 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 CROSS-DIFF, 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.

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

GOALS FOR 2019

○ Status analysis of all pathoblocker projects with regard to patentability and timelines for patenting, determining targets for identified "actives" and acquisition of additional funding for the development of a hit-to-lead.

○ Prioritisation of antigens for prophylactic vaccines against *H. pylori*.

○ Identification of microbiome biomarkers for susceptibility to EHEC infection and for the risk of developing haemolytic uraemic syndrome (HUS).

Coordinator:
Prof. Sebastian Suerbaum
Munich

Improved protection for immunocompromised patients

The human immune system defends the body against pathogens consequently preventing severe infections. If the immune system is compromised, as is the case with diseases such as AIDS or following transplantation surgery or tumour therapy, even “harmless” viruses and bacteria can cause serious infections. Infections in immunocompromised patients are on the increase in hospitals.

Scientists are therefore working to find new solutions for the effective and timely treatment of patients who are at risk. DZIF researchers at the Helmholtz Centre Munich, have developed an analytic procedure in order to identify cytomegalovirus infections based on immune responses. Scientists at Hannover Medical School (MHH) and the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), discovered new inhibitors for viral targets which, when blocked, prevent latent replication of Kaposi’s sarcoma-associated herpesvirus (HHV-8) which causes the cancer Kaposi Sarcoma.

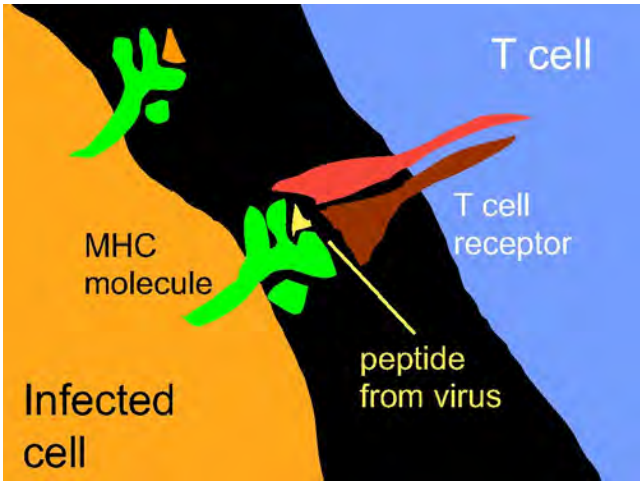
Much laboratory research is still required to improve protection of immunocompromised patients from infections.

KILLER CELLS DETECT VIRUS FRAGMENTS

The cytomegalovirus (CMV) is a widespread herpesvirus. Following an infection, the virus hides in the body for a lifetime, usually going unnoticed. "In healthy people, viral replication is kept in check by T cells. However, when the immune system is weakened, insufficient T cell responses often put patients at a higher risk of permanent damage to a range of different organs including the nervous system," says Dr Andreas Moosmann, chemist and Head of the DZIF research group at Helmholtz Centre Munich. Transplant patients and unborn babies are particularly at risk. Moosmann's team has now developed an analytic procedure that indicates whether the human T cell repertoire is responding to the virus and the exact type of T cells involved. "We analyse the ribonucleic acid (RNA) of millions of T cells and can subsequently identify the different T cell receptors, each of which is specific to a certain portion of the CMV," Moosmann explains. "To start with, we analysed 1,052 CMV-specific T cell receptors in eight healthy virus carriers and subsequently measured the prevalence of these sequences in a group of 352 donors, enabling us to very accurately predict infected donors." The next step is RNA sequencing applied to stem cell patients. In the medium-term, the team intends to develop a biomarker. "We suspect that certain T cells will be more reliable in predicting whether a patient will develop the disease than others," says Moosmann. In the long-term patients will be administered with the specific T cells they lack.

NEW TARGET STRUCTURES FOR TREATMENT OF KAPOSI'S SARCOMA

Kaposi's sarcoma is a type of skin cancer caused by a virus. In immunocompromised patients it spreads into various organs and can quickly become life-threatening. DZIF researchers at Hannover Medical School and the HIPS have discovered new molecules that can curb the Kaposi's sarcoma-associated herpesvirus (HHV8) which is responsible for causing skin cancer. "In collaboration with virologists at Hannover Medical School we have identified and optimised very small, synthetic compounds that block an important viral mechanism in HHV8's life cycle," says Dr Martin Empting, HIPS. "It involves a specific interaction between the so-called latency-associated nuclear antigen (LANA) and DNA, which has been difficult to target on a pharmacological level up to now." LANA is responsible for the virus' ability to remain in the human body and replicate over a long period of time. "We used biophysical methods to screen small, structurally diverse molecule libraries to identify the first LANA inhibitors," says Empting. "These fragments are very well suited for generating future active agent molecules." The long-term goal is to use these fragments as a base from which to develop new agents to treat HHV8 infections.



A T cell receptor recognises a small fragment of a specific pathogen.

GOALS FOR 2018: OUTCOMES

- ◐ First biomarker projects using the Tx cohort.
- ● Advancement of a prophylactic EBV vaccine.
- ● PACT trial: Expansion to additional locations.

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

GOALS FOR 2019

- ○ Development of a method for predicting graft-versus-host disease in stem cell transplant receivers with cytomegalovirus infections.
- ○ Identification of target sites for new antiviral compounds currently being developed, which demonstrate activity against the human cytomegalovirus, herpes simplex virus, Kaposi's sarcoma-associated herpesvirus and BK virus.
- ○ Proof of efficacy of a new antiviral substance developed at the DZIF.

Coordinator:
Prof. Thomas Schulz
Hanover

Targeted detection and prevention of resistance

Antibiotic exposure results in selection of antibiotic-resistant bacteria that are no longer susceptible to many or sometimes all available antibiotic treatments. Infection researchers are extremely concerned about the rise in multidrug resistance since even so-called last resort antibiotics originally reserved for use in emergencies, are becoming increasingly ineffective. People with compromised immune systems are particularly at risk of infections caused by multidrug resistant pathogens.

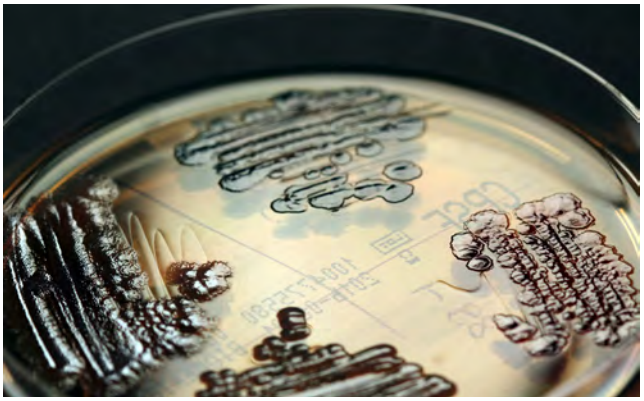
Which structures do bacteria use to protect themselves against antibiotics? Which mechanisms confer resistance? DZIF researchers are constantly contributing to solving these key questions. Researchers at the University of Bonn for example disproved a hypothesis that had been well established over the past few years. DZIF scientists from the University Hospital Cologne have developed new methods that can detect multidrug resistance in bacteria more rapidly.

SULPHIDE SOLELY PROTECTS BACTERIA AGAINST AMINOGLYCOSIDES

In an article published in 2011 in "Science", researchers postulated that bacteria secrete sulphides which protect them against different antibiotics. They suggested that hydrogen sulphide reduces the oxidative stress which is thought to occur during all antibiotic treatments. Dr Fabian Grein has disproved this hypothesis. He leads a research group at the University of Bonn which investigates new target structures that could enhance the efficacy of antibiotics against *Staphylococcus aureus*, a common hospital pathogen. The research group tested whether inhibiting sulphide production improves antibiotic efficacy. Using a modified agar diffusion test permitting continuous incubation with sulphide, they systematically exposed staphylococci to the most relevant antibiotics. Grein made a surprising discovery: sulphide solely protects bacteria against aminoglycosides and not against other antibiotics. Aminoglycosides are the only class of antibiotics that require energy to pass through the bacterial cell membrane. "Hydrogen sulphide partially poisons the cell, making insufficient energy available for uptake of the

Accelerated diagnosis of resistance enables individual treatment and may be life-saving.

antibiotic," says Grein. Consequently, aminoglycosides cannot enter the cell. "Therefore, the sulphide hypothesis does not apply to antibiotics not requiring energy to enter the bacterial cell or acting on the surface of the cell." Grein and his colleagues also showed that the amount of sulphide produced by *S. aureus* is too low to provide effective protection. Grein is now searching for other target structures for antibiotics against staphylococci.



Confirmation of multidrug-resistant Enterobacteriaceae in a Petri dish.

ACCELERATED DIAGNOSIS OF MULTIDRUG-RESISTANT BACTERIA

Septicaemia caused by multidrug-resistant pathogens can be life-threatening. Even carbapenems, a group of last-resort antibiotics, are often no longer effective in these cases. Up to now, it has taken from 16 to 72 hours to determine whether a pathogen is resistant to carbapenems. "We have now developed a procedure by which we can determine within 20 to 45 minutes whether bacteria possess a protein called carbapenemase, responsible for the resistance," says Prof. Axel Hamprecht from the Institute for Medical Microbiology, Immunology and Hygiene at University Hospital Cologne.

"The test detects 99 percent of all carbapenemases found in this part of the world," explains Hamprecht. Previously, isolates had to be cultured on a solid growth medium (agar). "This new test detects carbapenemase directly from blood cultures, consequently saving a whole day in time." A second research group led by Dr Alexander Klimka is focussing on rapid detection of the carbapenemase OXA-23 by means of antibodies. Carbapenemase OXA-23 is produced by 80 percent of all multidrug-resistant *A. baumannii* strains worldwide. The antibody test uses a method similar to that used in pregnancy tests: a solution containing isolates of a bacterial strain is applied to a test strip. The solution flows over two specific antibodies in the test strip, both of which bind to OXA-23. When both are bound, a line appears on the test strip. The treating physician thus knows immediately which antibiotics can be considered for treatment. DZIF scientists from the microbiology, immunology and molecular biology fields partnered with a Belgian company to develop this diagnostic kit. It is quick and easy to use and suitable for every clinical microbiology laboratory.

GOALS FOR 2018: OUTCOMES

◐ 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").

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

GOALS FOR 2019

○ Utilisation and expansion of previously established infrastructures (R-NET, CONTROL study, SurvCARE) to determine current dynamics and mechanisms of multidrug-resistance on a national scale with a focus on vancomycin-resistant enterococci (VRE).

○ Establishment and validation of a scoring system for rapid identification of patients with a high risk of developing blood stream infections.

○ Developing new eradication strategies for antibiotic-resistant pathogens infecting high-risk patients.

Coordinator:
Prof. Maria Vehreschild
Cologne

Fighting resistance through new strategies

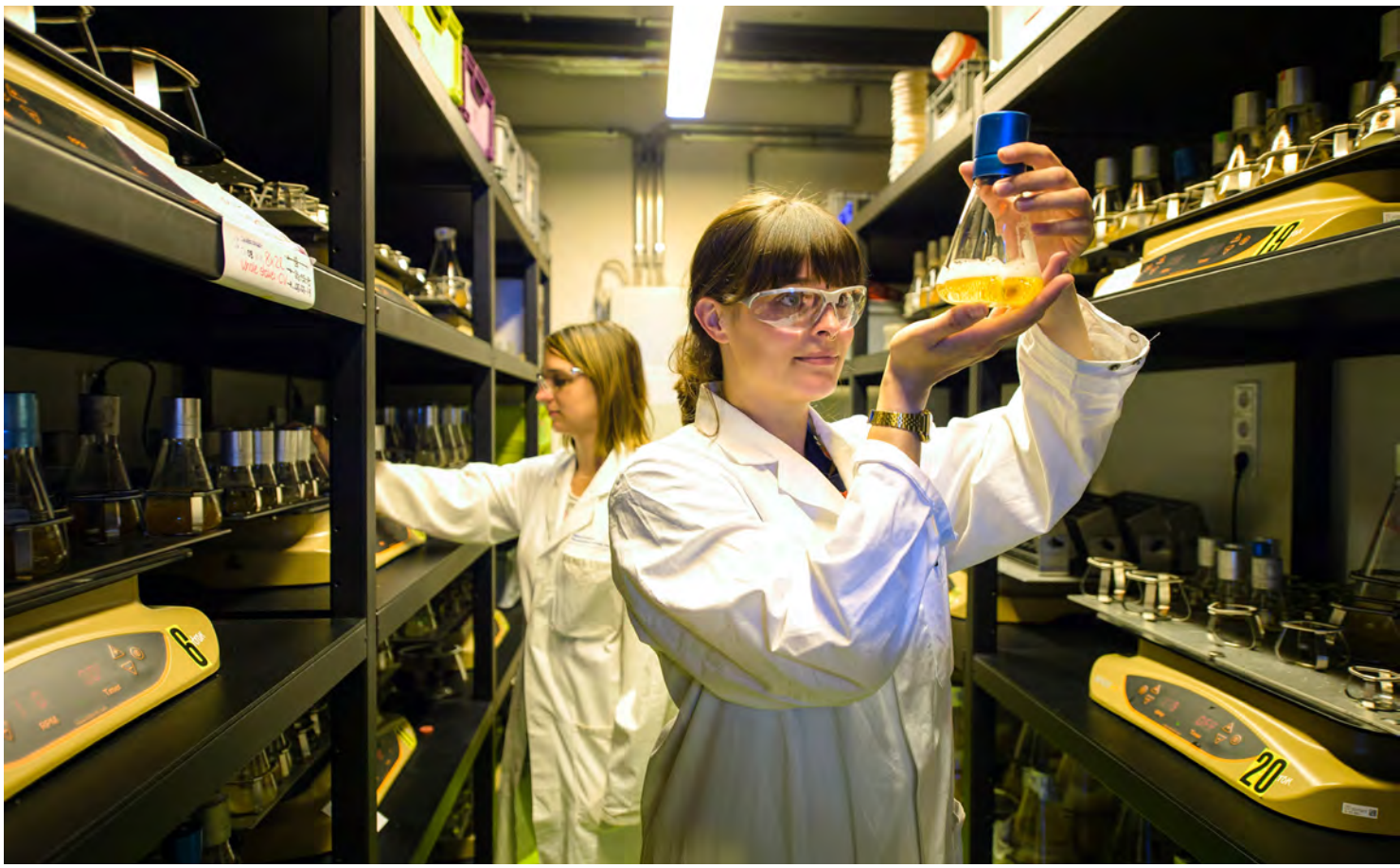
According to the WHO, 25,000 patients worldwide die of infections with multidrug-resistant pathogens per year. The uncontrolled use of antibiotics is making more and more bacteria become insensitive to conventional drugs. In a weakened body, bacteria colonise all organs and many also produce a substance known as biofilm which effectively shields growing bacterial colonies from drugs and from the immune system.

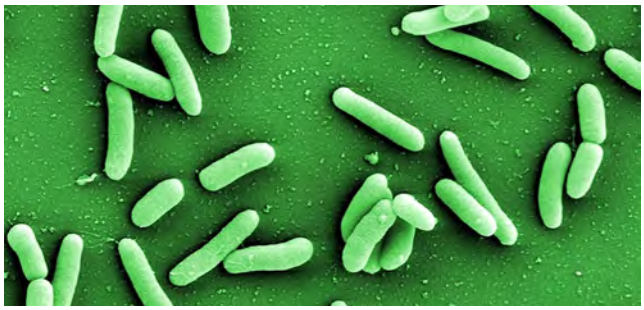
Several research groups at the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS) are searching for strategies to curb resistant pathogens and their production of biofilm. One team is developing a small molecule that prevents the development of biofilm and which can be administered orally. Another group is carrying out research to identify new potential antibiotic agents within natural compounds.

NEW INHIBITOR OF PERSISTENT BACTERIAL BIOFILMS

Once bacteria such as *Pseudomonas aeruginosa* have developed a biofilm in the human body, there is little hope of eradication. Hidden in thick mucus, this obstinate hospital superbug shields itself from antibiotics and immune cells. Infections of tissues and implants consequently become untreatable. Researchers at the HIPS recently developed a new molecule that successfully prevents the formation of

At the HIPS new antibiotics are isolated from soil samples. In the image: Kathrin Andres (front) and Viktoria Schmitt.





Bacteria such as Pseudomonas aeruginosa are resistant by hiding in thick mucus.

Julian Thimm from the HIPS assesses bacterial growth in Petri dishes.

bacterial biofilm. It inhibits the LecB protein, which is released by the bacteria in order to bind to sugar molecules in the host. Without it, the bacteria do not have a matrix for adhering to the tissue and no protected environment within which they can replicate. "We chemically modified the sugar molecule mannose, a natural binder of LecB, in such a way that it remains as stable and active as the original sugar," says Dr Alexander Titz, Head of the Medicinal Chemistry of Natural Compounds research group at the DZIF. "The molecule specifically binds to LecB and consequently blocks it." Numerous research groups worldwide are working on similar objectives. "However, all previous molecules have been too large in size to be absorbed after oral administration," Titz says. "We are the first to have developed a small molecule which is suitable for oral intake." The molecule only targets biofilm. "The agent does not have antibiotic activity so there will hopefully be no development of resistance," adds Titz. However, numerous studies will have to be conducted before it can be used clinically.

FROM BACTERIAL TO CHEMICAL DIVERSITY

Natural compounds are a promising source of novel antibiotics, for example, myxobacteria which live in soil. "Myxobacteria produce an extraordinary large number of structurally diverse natural, biologically active agents," says Prof. Rolf Müller, Managing Director of Helmholtz Institute for Pharmaceutical Research Saarland (HIPS). However, isolating potential substances from typical raw myxobacteria cultures is challenging. Using mass spectrometry and statistical methods, a study investigated 2,300 myxobacteria extracts for new and previously unidentified natural substances. The study showed that: "The likelihood of finding previously unknown classes of chemical agents increases considerably when a new phylogenetic group is used to represent familiar species," says Dr Daniel Krug, who researches natural compounds by means of mass spectrometry at the HIPS. "The less the investigated bacterial strains are related to each other, the higher the potential of making surprising chemical discoveries." Scientists describe this as the phylogenetic paradigm. These findings give valuable insights into how new types of bacteria can be isolated effectively from soil samples in the future.

GOALS FOR 2018: OUTCOMES

- 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 Corallopyronin A antibiotic up to phase I clinical trials.

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

GOALS FOR 2019

○ Toxicological evaluation of potential kidney toxicity of chelocardin and amidochelocardin as part of the ongoing preclinical drug development.

○ Genome-based reactivity probes for the specific identification of novel antibiotics.

○ Establishment of a biotechnological production process for high quality Corallopyronin A, which can be transferred to an external producer.

Coordinator:
Prof. Rolf Müller
Brunswick/Saarbrucken

PRODUCT DEVELOPMENT UNIT

Support in the development of new agents

"Product developers" support scientists on the long road to the development of new drugs and vaccines.

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

In 2018, a total of five PDU workshops were held for DZIF scientists. The PDU was elected as one of the top ten global supporters of the CARB-X network.

Coordinator:

Prof. Klaus Cichutek *Langen*

CLINICAL TRIAL UNIT

Specialised in infectious diseases

Clinical trials on humans are systematically planned at the DZIF's Clinical Trial Unit.

New vaccines and medicines need to be tested on humans before being launched. The DZIF has clinical trial centres specialised in infectious diseases under the "Clinical Trial Unit" (CTU) infrastructure. The infrastructure's central coordinating office is based in Cologne. Twelve clinical trial centres are currently working together under the umbrella of this network. To date, the CTU has conducted 111 clinical trials. The CTU offers DZIF scientists consultation services for the planning of clinical trial projects and answers questions on study design and planning, budget calculations, approval procedures and the selection of trial centres. It also co-develops recruitment strategies. As part of the DZIF FlexFunds procedure, the CTU provides advice for clinical trial applications.

The CTU has been conducting its own multicentre observational study since December 2017: "DOPPIO" investigates the protective effects of pneumococcal vaccines in dialysis patients. For this group of patients, the current RKI vaccination guidelines recommend a pneumococcal vaccination every six years. However, some studies challenge this recommendation. By the end of 2018, a total of 654 out of 884 patients were included in the study. The twelve clinical trial centres work together with dialysis clinics of the Dialysis and Kidney Transplant Board of Trustees e.V. (KfH).

Coordinator:

Prof. Oliver Cornely *Cologne*

AFRICAN PARTNER INSTITUTIONS

Global Partnerships

People are always in the focus of research. In the Image: Children in Lambaréné.

The DZIF "African Partner Institutions" infrastructure strengthens longstanding partnerships between the German DZIF establishments and their African partners so as to conduct joint projects in infection research. Projects are being conducted in hospitals and research centres in Kumasi (Ghana), Lambaréné (Gabon), Nouna (Burkina Faso) and Mbeya (Tanzania). These countries have a high prevalence of numerous infectious diseases and increasing multidrug-resistance.

Within the existing network, valuable investments have been made towards personnel and laboratories. Several of these laboratories already serve as diagnostic reference centres for local hospitals. In 2018, diagnostic tests were compared across different centres, which notably confirmed the benefit of multicentre trials. In addition, the DZIF established a new research group for neglected tropical diseases.

In 2018, internal audits were conducted with the aim of improving quality in laboratories. Equipment for microbiology laboratories and the methods used for identifying susceptibility to antibiotics were both improved. Consequently, current biosafety standards have been met and preparations are underway for the launch of a hospital-based antibiotic resistance surveillance system.

Coordinator:

Prof. Jürgen May *Hamburg*

NOVEL ANTIVIRALS

Optimising promising candidates

DZIF scientists look for substances with antiviral activity.

Successful treatments are still pending for emerging viruses such as Ebola or Zika in addition to many other well-known viral diseases such as hepatitis B or the flu. At the end of 2017, the DZIF set up an overarching infrastructure dedicated to the research of new substances with antiviral activity. In the search for new agents, focus has increasingly been on screening biobanks containing small molecular substances for use as potential drug candidates. All DZIF partner sites will have access to appropriate screening platforms as well as substance banks and, upon request, support in carrying out screening experiments. Screening platforms can be found in Munich, Heidelberg, Hanover and Brunswick.

In 2018, particular focus was placed on intensifying partnerships between medicinal chemists to advise and support DZIF scientists in the "Novel Antivirals" infrastructure. Even during the early stages of a project, they provide assessments as to whether active substances identified in screenings could be so-called "hits", i.e. promising candidates for drug use from a chemical perspective. In 2018, medicinal chemists synthesized the first hit derivatives from different screenings, which DZIF scientists subsequently successfully tested for antiviral efficacy. Therefore, the path to further development of the substances has been paved.

Coordinator:

Prof. Thomas Schulz *Hanover*

BIOBANKING

Quality management of biosamples

DZIF research projects can access tissue samples in biobanks.

Infection researchers often require human sample material, such as tissue or body fluids for their studies. At the DZIF, a centrally managed biobanking infrastructure provides access to high quality, accurately identified and systematically recorded biomaterials including accompanying clinical information. A central biosample register (ZBR) at the Helmholtz Centre Munich simplifies the search for infectious disease sample material.

Obtaining comparable and high-quality biosamples plays an essential role for multicentre trials in particular. The DZIF "Biobanking" infrastructure implemented a 3-stage quality management system (QM system) for the DZIF transplant cohort which specifically focuses on quality and comparability. In 2018, biosample quality was checked with regard to the use of state-of-the-art technology such as metabolomics and microRNA analyses. Other multicentre trials at the DZIF can now draw on these experiences to optimise their own collections.

In 2018, a collaborative biobanking and data management initiative, jointly led by the DZIF "Biobanking" infrastructure and the DZHK, was expanded to include the other German Centers for Health Research.

Coordinator:

Prof. Peter Schirmacher *Heidelberg*

PATHOGEN REPOSITORY

Pathogens for research

Over 2,000 pathogen strains are stored at the DSMZ.

How do antibiotics affect different bacterial strains? Are newly occurring bacteria related to known common ones? What role do microorganisms play in humans? To answer these and other questions, infection researchers require pathogen isolates. As a result, 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 Brunswick. Bacteria, fungi or bacteriophages undergo quality control, are well documented and subsequently made available for use in research. Training for the professional handling of pathogens is provided.

Over the past few years, the DZIF collection of pathogens has expanded to include over 2,000 microbial pathogen strains and active agent producers. Multidrug-resistant bacteria and antibiotic-sensitive "negative control strains" also play an important role. To date, almost 200 genome sequencings have been performed in collaboration with the "Healthcare-associated and Antibiotic-resistant bacterial Infections" and "Gastrointestinal Infections" research fields. A so-called mouse microbiome, i.e. a collection of bacteria from the intestinal tract of mice, is stored in Munich thanks to collaborations with the "Gastrointestinal Infections" research field. Currently, collections of strains from the intestinal tracts of the pig and chicken are being created.

Coordinator:

Prof. Jörg Overmann *Brunswick*

BIOINFORMATICS

Understanding big data

Bioinformaticians pass on their expertise and provide support with the analysis of vast amounts of data.

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

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

The bioinformaticians pass on their knowledge and experience through seminars and workshops. The need for these training sessions is rising. Specific workshops on microbiome data analytics and viral sequencing analytics have been particularly popular, as well as introductory workshops for linux pipelines and statistical data analysis in free software such as "R".

Coordinator:

Prof. Alice McHardy *Brunswick*

EPIDEMIOLOGY

Detecting infectious diseases faster

Epidemiologists at the DZIF help to rapidly identify and curb infectious diseases.

Epidemiology is the study of the occurrence, spread and distribution of diseases within a given population. The prevalence of infectious diseases varies in different regions. They spread differently depending on the pathogen and the route of infection affecting some population groups more than others. Epidemiologists can recognise and curb the spread of infectious diseases more rapidly and prevent the occurrence of other diseases by taking these factors into account. The DZIF "Epidemiology" infrastructure supports the different DZIF research fields in dealing with epidemiological issues, thus bridging the methodological gap between individual research fields and infrastructures.

In addition, the infrastructure offers various workshops, writes reviews and develops new instruments for clinical and epidemiological research studies. These include, for example, the development of a mobile network app to record and control pathogen outbreaks in real time (SORMAS).

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

Coordinator:

Prof. Gérard Krause *Brunswick*

DZIF ACADEMY

Investing in young talent

An important part of the DZIF programme is to intensively promote young talent. The DZIF Academy was established specifically for this purpose and supports young doctors and scientists who are interested in working in the field of infection research. From the Technical University of Munich, the Academy coordinates the selection and supervision of stipend holders who work at the different partner sites. The past few years have shown that the programmes have been successful with young talents building on their careers.

The DZIF Academy's Autumn School provides both training and networking opportunities for young scientists.

RECONCILING WORK AND FAMILY LIFE

The DZIF offers an exceptional Maternity Leave Stipend, which enables mothers or fathers to return to research work after parental leave by funding half of their salary. Maria Vehreschild and Sandra Ciesek are examples of the importance of this measure in building a scientific career. Both currently hold professorships and have headed a department or an institute at large university medical centres since 2018 and 2019, respectively. Both have children. "Two DZIF Maternity Leave Stipends enabled me to return to my medical and scientific career after the birth of my children. This was critical for me," emphasizes Maria Vehreschild. Sandra Ciesek also explains "I would never have started working again so early after the birth of my daughter. The stipend not only helps financially, it also inspires courage and the self-confidence to continue with research work and temporarily put routine clinical work aside."

FURTHER TRAINING AND NETWORKING FROM THE START

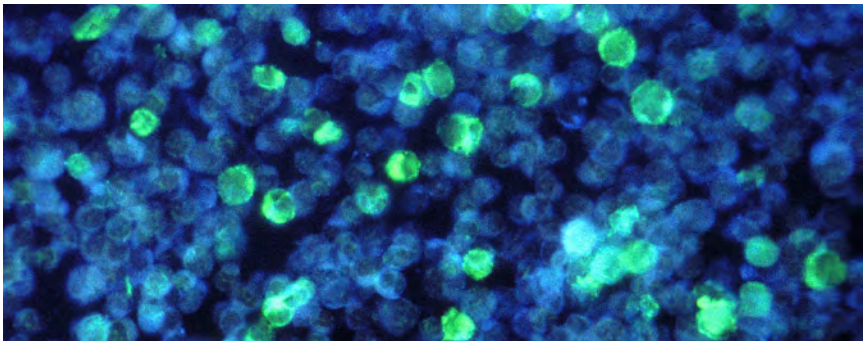
Alongside the Maternity Leave Stipends, which support women to return to scientific and medical careers, the Academy also awards so-called Clinical Leave Stipends. These enable young physicians to temporarily put routine clinical work aside and consequently have time for research activities and to qualify for scientific careers in infection research. In 2018, 19 young physicians benefited from these stipends. In addition, the DZIF awards PhD stipends to medical students and doctors who wish to complete a PhD, either to attain a German MD title or an internationally recognised PhD. In 2018, a total of 59 of these stipends were awarded. The DZIF Summer and Autumn Schools not only provide training opportunities but also networking opportunities with other infection researchers. Laboratory rotations provide lively exchange platforms for scientists and opportunities to work in different laboratories. Travel grants for events are also awarded. Special courses, jointly organised and conducted by DZIF experts, provide basic training in different fields ranging from bioinformatics to clinical trials and science communication. In 2018, the DZIF Academy awarded a total of 87 stipends, a figure which speaks for itself.

Coordinator:
Prof. Ulrike Protzer *Munich*

SUCCESSFUL TRANSLATION

Epstein Barr Virus: a vaccine candidate on the road to production

The Epstein Barr virus (EBV) is widespread: over 90 percent of the adult population are lifetime carriers of this herpesvirus. Infection is usually asymptomatic, however, this can be misleading as EBV can cause various other diseases such as glandular fever and certain types of cancer, particularly in delayed infection. The virus poses a particularly high risk for immunocompromised patients. At the DZIF, EBV research has been ongoing for years and now a promising vaccine candidate is ready for product development.



The image shows leukaemia cells infected with Epstein Barr viruses. The infected cells are marked green.

There is a mounting need for an EBV vaccine as the carcinogenic effects of the virus are becoming increasingly well known. The virus causes approximately 200,000 cases of cancer worldwide each year. The risk of contracting glandular fever (infectious mononucleosis), which is particularly common amongst youngsters and adolescents, is also being taken very seriously as it increases the risk of developing multiple sclerosis and Hodgkin lymphoma. "A vaccine against EBV would be of great help against these diseases," explains Prof. Wolfgang Hammerschmidt, virologist at the Helmholtz Zentrum München (HMGU). It would also be a lifesaver for transplant patients for whom the virus can become life-threatening due to their compromised immune systems.

VIRUS-LIKE PARTICLES FEIGN INFECTION

"We now have a vaccine candidate ready for submission to the process development for production," explains Hammerschmidt, the project coordinator. First steps towards the development of the candidate vaccine started approximately 20 years ago at the HMGU with the construction of a first generation of virus-like particles (VLPs) which were subsequently refined both at the HMGU and the German Cancer Research Center in Heidelberg. VLPs are empty virus protein envelopes lacking the viral genome but mimicking a real EBV infection to the immune system. Consequently, VLPs are safe and promising vaccine candidates as they efficiently induce both EBV-specific humoral and cellular immune responses. A company has now been commissioned with the development process for production according to Good Manufacturing Practice (GMP) guidelines. This transfer of technology is the first critical step on the path towards obtaining a vaccine candidate.

"In 2018 at the DZIF, we completed the development of a producer cell line which is able to generate these VLPs in large quantities," says Hammerschmidt, summarising the current state of research. "This is a critical milestone for further vaccine manufacturing. We have confirmed the important features required for developing such a cell line which include product safety, stability and scalability, and we can proceed now with the process of production according to the Good Manufacturing Practice (GMP) guidelines," he says happily. It is estimated that the development process will take approximately two years after which the vaccine can go into preclinical and early phase clinical trials.

Project Coordinator:
Prof. Wolfgang Hammerschmidt *Munich*

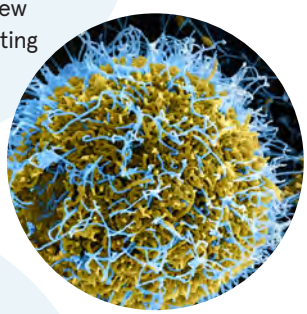
DZIF HIGHLIGHTS 2018

News Ticker

JANUARY

A first trial jointly conducted by all twelve clinic trial centres is initiated at the DZIF. The aim is to improve vaccine protection in dialysis patients.

In an experiment, a European research team succeeds in specifically inhibiting Ebola virus replication. A new imaging method enables testing of potential drugs.



FEBRUARY

Scientists from the DZIF and the TU Dresden discover multidrug-resistant bacteria in Lower Saxony's waterways. The German Federal Ministry for the Environment consequently advocates for the systematic investigation of multidrug-resistant bacteria in the environment.

MARCH

The DZIF researchers from Tübingen Bernhard Krismer, Andreas Peschel and Alexander Zipperer, receive the Rudolf Schülke Foundation's renowned Hygiene Prize worth 15,000 euro for the discovery of lugdunin, a promising antibiotic agent.

The European Research Council awards Silvia Portugal, a young DZIF scientist, 1.5 million euro to track the malaria pathogen in the dry season.

APRIL

The Research Center Borstel has succeeded in developing a new rapid test to diagnose lung tuberculosis. With this test, doctors obtain correct results in only three days.

MAY

Thanks to a new initiative, the BMBF intends to advance research on resistance to antimicrobial agents. The „Global Antimicrobial Resistance Research and Development Hub", or "Global AMR R&D Hub", was launched on 22 May 2018. Its offices are based at the DZIF.

JUNE

The first antibiotic for tuberculosis to be developed in Germany goes into clinical testing. The newly developed investigational agent BTZ043 is also effective against multidrug-resistant pathogens. DZIF scientists from the LMU Munich and Hans Knöll Institute in Jena are leading the project.

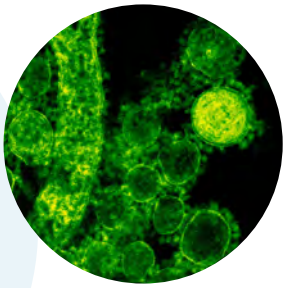
Information about ticks spread through the media. Using a new model, DZIF scientists in Munich predict a "year rich in ticks".

JULY

In a new research group, the DZIF focuses on neglected tropical diseases, the majority of which are caused by worms, as well as viruses and bacteria.

AUGUST

The development of a MERS vaccine at the DZIF has now been funded for over five years by the internationally active vaccine initiative Coalition for Epidemic Preparedness Innovations (CEPI).



SEPTEMBER

Major advances in Zika research: DZIF scientists demonstrate how the Zika virus causes severe malformation of the brain in newborns. Other long-term consequences on children of Zika infections during pregnancy are also being investigated.

Using a combination of antibodies, researchers at the University Hospital Cologne, accomplish long-term viral suppression in HIV patients.

OCTOBER

DZIF researchers at the PEI show how protective antibodies against emerging viruses can be produced rapidly in animals and in large quantities when required.

NOVEMBER

A current study at the Research Center Borstel shows how multidrug-resistant bacteria spread in Central Asia. The first multidrug-resistant TB bacteria in Central Asia are likely to have developed in the Soviet Union and propagated through ineffective treatment, self-treatment and poor diagnostics.

DECEMBER

Volker Lohmann and Marylyn Addo are in the limelight at the DZIF Annual Meeting: they each received a DZIF Prize for Translational Research in honour of their scientific accomplishments.

SCIENCE AND PUBLIC

Transparency for the wider public

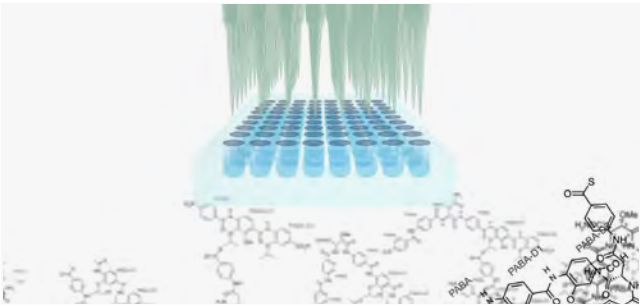
Large research organisations are responsible for making science accessible to all those that may have an interest in the subject. With the rise in social media channels, the possibilities and modes of communication have changed and have overtaken the role of the journalist as being the sole source for the sharing and distribution of information. Information is available through many channels but not all of it is reliable. As an organisation in direct communication with the public, we therefore hold an increasingly important responsibility for providing reliable and understandable information regarding research on infections in the most efficient way and in the most appealing formats possible. The DZIF Press Office aims to fulfil these objectives through the use of digital and analogue media channels, both new and old.

The DZIF recently launched a new website which is more than just a visual facelift as it also includes improved content. The broad spectrum of themes being researched at the DZIF has, for the first time, been presented externally through the website.

CURRENTLY ONLINE: FROM A LIKE "ACINETOBACTER" TO Z LIKE "ZIKA" VIRUS

The diversity of research themes at the DZIF is reflected in the new website glossary. Technical terms have been "simplified" so as to make general research information available to the

Members of the German Center for Health Research introduce themselves at the GAIN Annual Meeting in Boston in 2018. In the discussion (from left): State Secretary Dr Georg Schütte, DZG representatives Dr Astrid Glaser and Dr Timo Jäger.



Top: DZIF Project Managers Dr Benjamin Stottmeier and Dr Andrea Kühn present the DZIF "Biobanking" infrastructure at the Annual Meeting. Bottom: A special video explaining the meaning of translational research.

larger public in a comprehensible format. Those interested in more detail can click on each project and research group link in order to obtain more specialised information. Twitter and LinkedIn provide a networking interface for the DZIF and a platform for the rapid exchange of information.

MEDIA EFFECTIVE: TREACHEROUS VIRUSES AND RESISTANT BACTERIA

In science, the traditional press release continues to play an important role for announcing research findings. In 2018, approximately 40 press releases were uploaded onto the DZIF website and circulated externally via press mailing lists. Major topics in the media included multidrug-resistant bacteria and emerging viruses. Be it Zika, Ebola or hepatitis, viral pathogens take up a lot of space in research and media broadcasting. In 2018, as was the case in the previous year, research information about ticks received much media coverage. Understandably, the public was particularly interested in a model used for predicting the density of ticks in certain areas.

WHAT IS TRANSLATIONAL RESEARCH?

Over 500 scientists, doctors, technical assistants, project managers, doctoral students and students conduct translational research at the DZIF. What does translational research mean? This central term is clearly explained in a video that is accessible via the website. It also highlights the characteristics of the German Center for Health Research. Currently, a total of six centres are involved in investigating widespread diseases with translational research as their mission. Recently, the research centres jointly published the journal "SYNERGIE". Its neon-orange colour makes it stand out from other print journals. It is also widely available online. The journal has been well received and a second issue, entitled "Prevention", is currently in preparation. The research centres are also involved in jointly publishing their findings in the BMBF newsletter: "Aktuelle Ergebnisse der Gesundheitsforschung (Current Findings in Health Research)", which is directed at approximately 1,500 editorial teams and/or journalists. In a 2018 edition of this newsletter, the DZIF focused on neglected tropical diseases and the development of a new MERS vaccine.

INTERNAL AND EXTERNAL NETWORKING

Scientists and clinicians must work together as a network in order to conduct translational research thus bringing research findings to the patient faster. This network requires effective internal communication which plays an important role within the DZIF. In order to support the regular exchange of information, the Press Office regularly publishes a newsletter and provides information via the DZIF intranet platform which is accessible to all members of staff. At the 2018 Annual Meeting in Heidelberg, DZIF members from all partner sites came together to discuss the progress of their respective projects. New partnerships are formed and project ideas are often developed further thanks to this Annual Meeting.

BEING APPROACHABLE: THE DZIF AT FAIRS

In 2018, the DZIF was once again an exhibitor at various scientific congresses in order to increase its national and international visibility. These congresses included the European Congress on Clinical Microbiology and Infectious Diseases (ECCMID) in Madrid and the annual GAIN meeting: a network of German scientists in North America, in which the German Center for Health Research presented their junior programmes in particular.

UPDATED PRINT MATERIALS

A high proportion of information is communicated via computers or mobile phones using social media platforms such as Twitter, LinkedIn, YouTube etc. Despite this, young scientists still seem to like to refer to hardcopy print materials. High-quality brochures, information flyers and magazines are still being used frequently. Therefore, alongside the digital information provided on the DZIF website, you will find all information and journals, including this report (which you may be holding in your hands right now), in a printed hardcopy version. We would like to thank all DZIF staff members for their contributions and for their commitment and support towards this.

Press and Public Relations:
Karola Neubert
Janna Schmidt
Brunswick

COLLABORATIONS

External Partnerships

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

THE DZIF'S ASSOCIATED PARTNERS

Charité – Universitätsmedizin Berlin

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

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

German Liver Foundation/HepNet Study House, Hanover

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 for carrying out clinical trials. The DZIF can use the infrastructures and cohorts for its projects.

Acute hepatitis C and hepatitis D are two core themes. In addition, the first trial worldwide on the treatment of chronic hepatitis E was conducted in 2018. Samples obtained from this study are being used by different research groups in the "Hepatitis" research field.

During the breaks at the DZIF Annual Meeting, a few companies provided information about their offers and services.

Goethe University, Frankfurt am Main

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

The so-called Cosima study analyses carbapenem-resistant bacteria and was initiated in collaboration with the University of Cologne in 2018.

Hans Knöll Institute, Jena

The Hans Knöll Institute (HKI) provides the DZIF with natural compounds, particularly those derived from fungi. Scientists from the HKI and the Ludwig-Maximilians-Universität München (LMU) lead a project involving a clinical trial on a newly developed antibiotic against tuberculosis. The newly developed investigational agent, termed BTZ043, is also effective against multidrug-resistant pathogens.

Julius Maximilians University, 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.

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 based on which new applications will be developed. This enabled the development of geno2pheno[ngs- freq] into what it is today: a programme that can detect resistance in viral populations in a matter of seconds.

Medical Center – University of Freiburg

The Medical Center of the University of Freiburg is a partner of several DZIF projects. In these projects, scientists try to identify genetic and other risk factors that are associated with an increased susceptibility to respiratory infections and fungal infections in particular. They intend to identify biomarkers for improved infection control. The Medical Center is working on two studies that aim to reduce nosocomial infections, measures for which include a more targeted use of antibiotics and improved hygiene measures.

Freiburg is one of six partner sites at which the epidemiology of multidrug-resistant bacteria and the epidemiology of bloodstream infections and *Clostridium difficile* infections are being studied longitudinally over a four-year period.

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

Medical Faculty of Martin Luther University, Halle-Wittenberg

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

Otto-von-Guericke University, Magdeburg

In 2016, scientists discovered neosorangicin, a substance produced by *Sorangium cellulosum* myxobacteria. It is similar to the previously developed RNA polymerase inhibitor sorangicin A. 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 including *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Consequently, neosorangicin could become a new drug candidate. The production process has been optimised at the Otto von Guericke University in Magdeburg.

University of Bayreuth

The *Mycobacterium tuberculosis* (MTB) pathogen is in the focus of a major tuberculosis screening project in which the University of Bayreuth is involved. The goal is to create a preclinical model, based on which new drugs against tuberculosis can be identified, and both known and newly discovered drugs can undergo efficacy testing. The new agent BTZ043 is also being tested for tissue concentrations in mouse models.

University of Erfurt

Infuenza virus vaccinations provide protection against the flu. Consequently, hospital staff in particular should aim for 100% vaccination coverage. However, in reality the situation 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 Center Hamburg-Eppendorf in which nursing staff and physicians decide whether to get vaccinated in order to protect themselves as well as their patients and colleagues. Structured interviews were conducted with the study participants during the flu season 2017/18 to examine the reasons why staff do not get vaccinated.

University Hospital Essen

A hepatitis C project involving scientists from the University Hospital Essen and others (see also Goethe University of Frankfurt) aims to point out individually tailored patient treatment options to the treating physician. Therapy recommendations include both hepatitis C virus genome sequences and the patient data. Scientists at the University Hospital Essen also research hepatitis delta virus (HDV) infections, the most severe form of viral hepatitis. The aim is to better understand HDV life cycles and the interactions with human cells. The efficiency of a therapeutic vaccine against HIV is also being investigated. It induces an immune response that results in a reduction of latent viruses.

University of Münster

The University of Münster is partner in a project searching for new treatment options for the haemolytic uraemic syndrome, which is caused by enterohaemorrhagic *Escherichia coli* (EHEC) bacteria. It is the leading cause of acute renal failure.

A further project at the University confirmed that lytic phage lysin HY-133 is highly effective against methicillin-resistant *Staphylococcus aureus* bacteria in the nasal cavity. The promising agent is currently being investigated in preclinical trials so as to confirm its safety for subsequent clinical trials on humans.

INDUSTRY COLLABORATIONS

BioNTech AG, Mainz

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

BIRD-C GmbH & Co KG, Vienna (Austria)

DZIF scientists of the Technical University of Munich work together with the company BIRD-C GmbH to develop a vaccine against noroviruses. They use so-called bacterial ghosts as adjuvants (enhancers) which are administered together with minicircles that carry the norovirus capsid gene.

Coris BioConcept, Gembloux (Belgium)

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

Evotec, Hamburg

The company Evotec is conducting clinical efficacy and safety testing on antiviral substances against BK virus infections. The substances were discovered at the Heinrich Pette Institute. Kidney transplant patients with compromised immune systems are at a particularly high risk of contracting BK virus infections.

HYpharm GmbH, Bernried

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

IDT Biologika GmbH, Dessau-Rosslau

The international vaccine initiative CEPI (Coalition for Epidemic Preparedness Innovations) is funding the development of a vaccine against the dangerous MERS coronavirus. This promising vaccine candidate is being developed further together with the company IDT Biologika, in a consortium of scientific and clinical organisations.

Juno Therapeutics GmbH, Göttingen

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

MSD Sharp & Dohme GmbH, Haar

DZIF scientists from the Goethe University of Frankfurt worked together with this company in order to conduct a non-interventional study in the field of hepatitis C research.

Myr GmbH, Burgwedel

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

ABOUT DZG

German Centers for Health Research

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

With the jointly produced research magazine SYNERGIE, the German Centers for Health Research effectively present their objectives with regard to translational research.

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

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

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

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

The DZIF's structure

GENERAL ASSEMBLY

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

COMMISSION OF FUNDING AUTHORITIES

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

EXECUTIVE BOARD

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

SCIENTIFIC ADVISORY BOARD

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

MAIN OFFICE

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

INTERNAL ADVISORY BOARD

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

THEMATIC TRANSLATIONAL UNITS (TTUS)

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

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

TRANSLATIONAL INFRASTRUCTURES (TIS)

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

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

PARTNER SITES

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

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

Central bodies

EXECUTIVE BOARD

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

INTERNAL ADVISORY BOARD

- Prof. T. Schulz,
  Hannover Medical School
  (Acting Chair)
- Prof. K. Cichutek,
  Paul-Ehrlich-Institut, Langen
- Prof. C. Drosten,
  Charité - Universitätsmedizin Berlin
- Prof. M. Hoelscher,
  Ludwig-Maximilians-Universität
  München und Klinikum der Universität München
- Prof. C. Meier,
  Universität Hamburg
- Prof. T. Welte,
  Hannover Medical School

as at July 2019

Partner sites and member establishments

Germany-wide infection research

BADEN-WÜRTTEMBERG

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

HEIDELBERG

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

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

TI coordination:

- Biobanking (coordination)

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

TÜBINGEN

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

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

BAVARIA

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

MUNICH

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

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

TTU coordination:

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

TI coordination:

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

HAMBURG/ SCHLESWIG-HOLSTEIN

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

HAMBURG - LÜBECK - BORSTEL - RIEMS

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

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

TTU coordination:

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

TI coordination:

- African Partner Institutions (coordination)

HESSE

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

GIESSEN - MARBURG - LANGEN

Spokesperson: Prof. Trinad Chakraborty (Giessen University)

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

TTU coordination:

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

TI coordination:

- Product Development (coordination)

LOWER SAXONY

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

HANOVER - BRUNSWICK

Spokesperson: Prof. Thomas Schulz (Hannover Medical School)

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

TTU coordination:

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

TI coordination:

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

NORTH RHINE-WESTPHALIA

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

BONN - COLOGNE

Spokesperson: Prof. Achim Hörauf (University of Bonn)

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

TTU coordination:

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

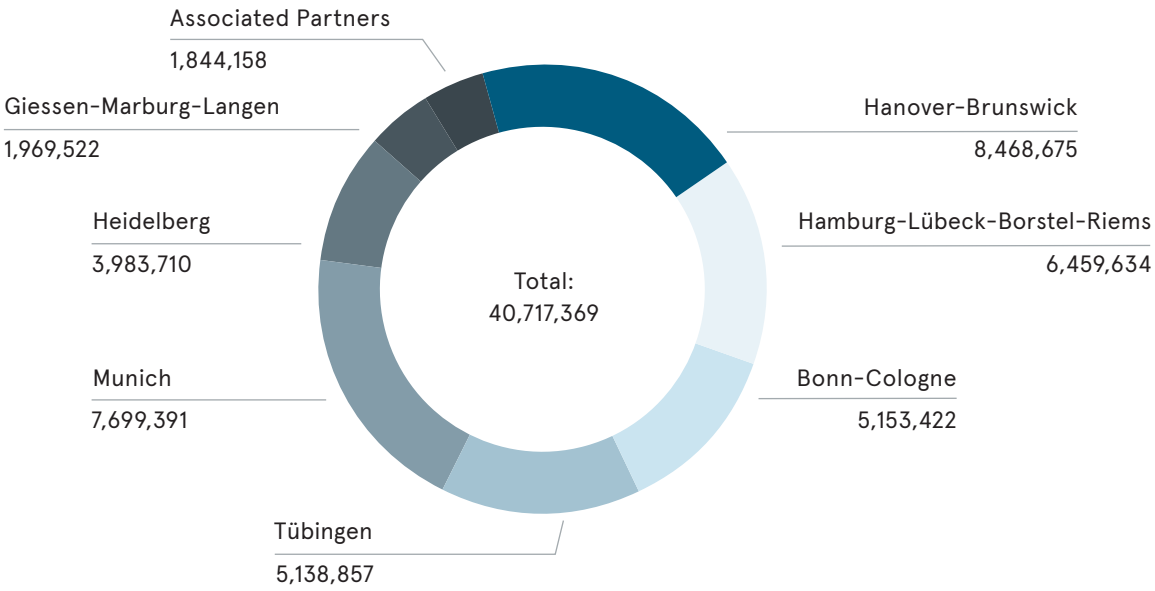
TI coordination:

- Clinical Trial Unit (coordination)

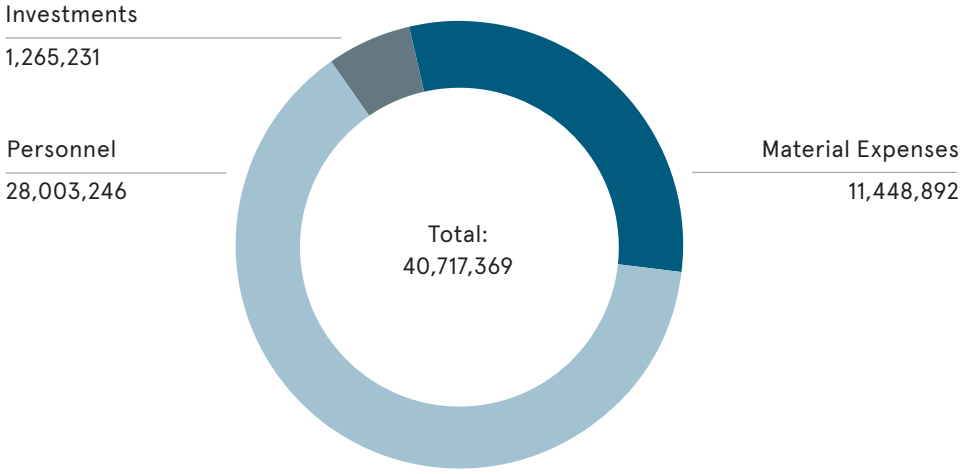
DZIF financial data 2018

REPORTED EXPENDITURE IN EUROS

BY PARTNER SITE



BY TYPE OF EXPENDITURE



BY FIELD OF WORK

FIELD OF WORK	Euro
Emerging Infections	3,894,048
Tuberculosis	2,667,957
Malaria	2,793,492
HIV	2,888,707
Hepatitis	3,568,688
Gastrointestinal Infections	1,834,314
Infections of the immunocompromised Host	5,315,666
Healthcare-associated and Antibiotic-resistant bacterial Infections	3,175,073
Novel Antibiotics	4,952,497
Product Development Unit	865,006
Clinical Trial Unit	547,779
African Partner Institutions	756,023
Biobanking	505.617
Bioinformatics	340,962
DZIF Academy	2,769,693
Pathogen Repository	254,979
Epidemiology	493,760
Vaccine Development	297,646
Novel Antivirals	304,727
Administration	2,490,735
Total	**40,717,369**

BY FUNDERS

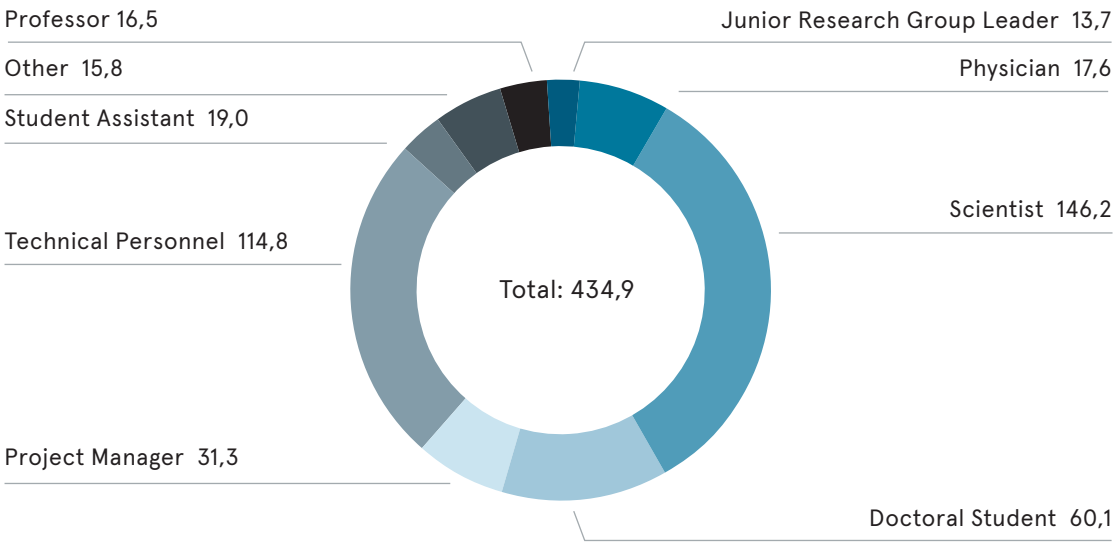
FUNDER	Euro
Baden-Württemberg	912,257
Bavaria	763,900
Hamburg	426,487
Hesse	148,783
Lower Saxony	822,446
North Rhine-Westphalia	499,780
Schleswig-Holstein	205,159
Financial contributions from associated partners	184,414
Federal Government	36,754,143
Total	**40,717,369**

In 2018, the German Center for Infection Research's reported expenditure amounted to approximately 40,7 million Euros. 172 projects and 92 stipends were funded within DZIF in 2018. 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 2018 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	13	5	18
Junior Research Group Leader	11	9	20
Physician	13	28	41
Scientist	104	148	252
Doctoral Student	46	77	123
Project Manager	14	53	67
Technical Personnel	41	188	229
Student Assistant	12	46	58
Other	11	31	42
Total	**265**	**585**	**850**

In 2018, the DZIF recruited five employees from abroad and assisted seven mothers and fathers respectively on their return from maternity leave.

AWARDS AND COMMENDATIONS

AWARD RECIPIENT	AWARD
Prof. Marylyn M. Addo University Medical Center Hamburg-Eppendorf	DZIF Prize for Translational Infection Research
Prof. Christoph Lange Research Center Borstel - Leibniz Lung Center	Memento Research Prize for neglected diseases
Dr Volker Lohmann Heidelberg University Hospital	DZIF Prize for Translational Infection Research
Prof. Rolf Müller Helmholtz Institute for Pharmaceutical Research Saarland	Inhoffen Medal 2018
Dr Anne Rechtien University Medical Center Hamburg-Eppendorff	Meta-Alexander-Preis 2018
Dr Monika Schütz University of Tübingen	Sponsorship Award from the German Society of Hygiene and Microbiology
Melanie Stecher University of Cologne	International Investigator Award for the ID Week
Dr Alexander Titz Helmholtz Institute for Pharmaceutical Research Saarland	Innovation Prize Medicinal Chemistry (Gesellschaft Deutscher Chemiker and Deutsche Pharmazeutische Gesellschaft) and EFMC Prize for a Young Medicinal Chemist in Academia

INDICATORS 2018

The DZIF in figures

FLEXFUNDS*

7 Number of new FlexFunds projects approved in 2018

2.765.588 total budget in euros. Corresponding to

7 % of the annual DZIF budget

*funds available at short notice for translational projects

DZIF ACADEMY PROGRAMMES

19 Clinical Leave Stipends

13 MD/PhD Stipends

09 Maternity Leave Stipends

46 MD Stipends

05 Lab Rotations

16 Travel Grants

WORKSHOPS AND SYMPOSIA

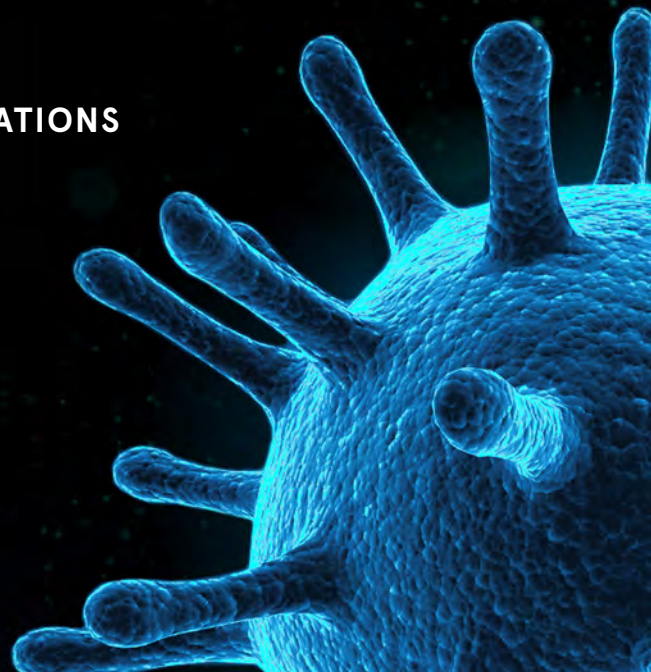
28

PUBLICATIONS WITH DZIF AFFILIATIONS

533

PUBLICATIONS WITH IMPACT FACTOR >10

51



CONFERENCE CONTRIBUTIONS
786

PATENTS AND PROPERTY RIGHTS
38

INDUSTRY COLLABORATIONS
9

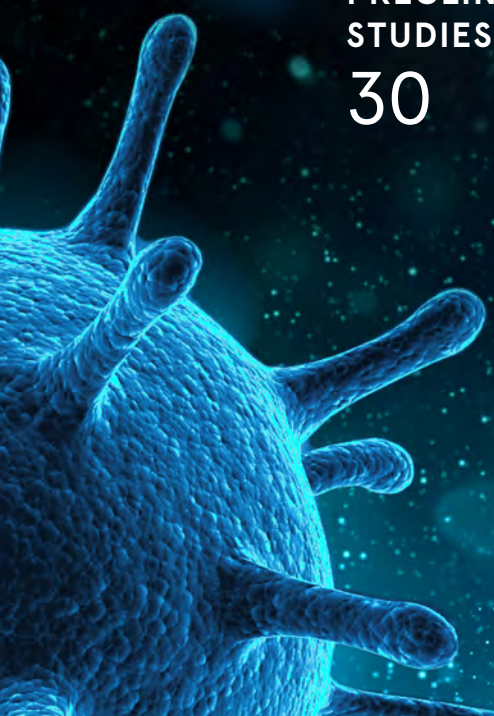
PRESS RELEASES
37

DATA- AND BIOBANKS
16

CLINICAL STUDIES
31

CONFIRMATORY PRECLINICAL STUDIES
30

COHORTS
38



PUBLICATIONS

Scientific achievements 2018

The following shows a list of selected 2018 publications
(impact factor greater than ten*).
Please see our website for a complete list of DZIF publications.

BASIC RESEARCH

1. Bubeck F, Hoffmann MD, Harteveld Z, Aschenbrenner S, Bietz A, Waldhauer MC, Borner K, Fakhiri J, Schmelas C, Dietz L, Grimm D, Correia BE, Eils R, Niopek D (2018) *Engineered anti-CRISPR proteins for optogenetic control of CRISPR-Cas9.* **Nat Methods**, 15(11): 924-927

2. de Carvalho Dominguez Souza BF, Konig A, Rasche A, de Oliveira Carneiro I, Stephan N, Corman VM, Roppert PL, Goldmann N, Kepper R, Muller SF, Volker C, de Souza AJS, Gomes-Gouvea MS, Moreira-Soto A, Stocker A, Nassal M, Franke CR, Rebello Pinho JR, Soares M, Geyer J, Lemey P, Drosten C, Netto EM, Glebe D, Drexler JF (2018) *A novel hepatitis B virus species discovered in capuchin monkeys sheds new light on the evolution of primate hepadnaviruses.* **J Hepatol**, 68(6): 1114-1122

3. Fanucchi S, Fok ET, Dalla E, Shibayama Y, Borner K, Chang EY, Stoychev S, Imakaev M, Grimm D, Wang KC, Li G, Sung WK, Mhlanga MM (2019) *Immune genes are primed for robust transcription by proximal long noncoding RNAs located in nuclear compartments.* **Nat Genet**, 51(1): 138-150

4. Gorges J, Panter F, Kjaerulff L, Hoffmann T, Kazmaier U, Muller R (2018) *Structure, Total Synthesis, and Biosynthesis of Chloromyxamides: Myxobacterial Tetrapeptides Featuring an Uncommon 6-Chloromethyl-5-methoxypipecolic Acid Building Block.* **Angew Chem Int Ed Engl**, 57(43): 14270-14275

5. Grunvogel O, Colasanti O, Lee JY, Kloss V, Belouzard S, Reustle A, Esser-Nobis K, Hesebeck-Brinckmann J, Mutz P, Hoffmann K, Mehrabi A, Koschny R, Vondran FWR, Gotthardt D, Schnitzler P, Neumann-Haefelin C, Thimme R, Binder M, Bartenschlager R, Dubuisson J, Dalpke AH, Lohmann V (2018) *Secretion of Hepatitis C Virus Replication Intermediates Reduces Activation of Toll-Like Receptor 3 in Hepatocytes.* **Gastroenterology**, 154(8): 2237-2251.e2216

6. Hoffmann T, Krug D, Bozkurt N, Duddela S, Jansen R, Garcia R, Gerth K, Steinmetz H, Muller R (2018) *Correlating chemical diversity with taxonomic distance for discovery of natural products in myxobacteria.* **Nat Commun**, 9(1): 803

7. Kasper L, Konig A, Koenig PA, Gresnigt MS, Westman J, Drummond RA, Lionakis MS, Gross O, Ruland J, Naglik JR, Hube B (2018) *The fungal peptide toxin Candidalysin activates the NLRP3 inflammasome and causes cytolysis in mononuclear phagocytes.* **Nat Commun**, 9(1): 4260

8. Khera T, Behrendt P, Bankwitz D, Brown RJP, Todt D, Doepke M, Khan AG, Schulze K, Law J, Logan M, Hockman D, Wong JAJ, Dold L, Gonzalez-Motos V, Spengler U, Viejo-Borbolla A, Stroh LJ, Krey T, Tarr AW, Steinmann E, Manns MP, Klein F, Guzman CA, Marcotrigiano J, Houghton M, Pietschmann T (2019) *Functional and immunogenic characterization of diverse HCV glycoprotein E2 variants.* **J Hepatol**, 70(4): 593-602

9. Ko C, Chakraborty A, Chou WM, Hasreiter J, Wettengel JM, Stadler D, Bester R, Asen T, Zhang K, Wisskirchen K, McKeating JA, Ryu WS, Protzer U (2018) *Hepatitis B virus genome recycling and de novo secondary infection events maintain stable cccDNA levels.* **J Hepatol**, 69(6): 1231-1241

10. Krampen L, Malmsheimer S, Grin I, Trunk T, Luhrmann A, de Gier JW, Wagner S (2018) *Revealing the mechanisms of membrane protein export by virulence-associated bacterial secretion systems.* **Nat Commun**, 9(1): 3467

11. Kuhlen L, Abrusci P, Johnson S, Gault J, Deme J, Caesar J, Dietsche T, Mebrhatu MT, Ganief T, Macek B, Wagner S, Robinson CV, Lea SM (2018) *Structure of the core of the type III secretion system export apparatus.* **Nat Struct Mol Biol**, 25(7): 583-590

12. Levander S, Holmstrom F, Frelin L, Ahlen G, Rupp D, Long G, Bartenschlager R, Sallberg M (2018) *Immune-mediated effects targeting hepatitis C virus in a syngeneic replicon cell transplantation mouse model.* **Gut**, 67(8): 1525-1535

13. Lunemann S, Schobel A, Kah J, Fittje P, Holzemer A, Langeneckert AE, Hess LU, Poch T, Martrus G, Garcia-Beltran WF, Korner C, Ziegler AE, Richert L, Oldhafer KJ, Schulze Zur Wiesch J, Schramm C, Dandri M, Herker E, Altfeld M (2018) *Interactions Between KIR3DS1 and HLA-F Activate Natural Killer Cells to Control HCV Replication in Cell Culture.* **Gastroenterology**, 155(5): 1366-1371.e1363

14. Manske K, Kallin N, Konig V, Schneider A, Kurz S, Bosch M, Welz M, Cheng RL, Bengsch B, Steiger K, Protzer U, Thimme R, Knolle PA, Wohlleber D (2018) *Outcome of Antiviral Immunity in the Liver Is Shaped by the Level of Antigen Expressed in Infected Hepatocytes.* **Hepatology**, 68(6): 2089-2105

15. Moonens K, Hamway Y, Neddermann M, Reschke M, Tegtmeyer N, Kruse T, Kammerer R, Mejias-Luque R, Singer BB, Backert S, Gerhard M, Remaut H (2018)

*Impact Factor in 2017

Helicobacter pylori adhesin HopQ disrupts trans dimerization in human CEACAMs. **Embo j**, 37(13)

16. Muhlemann B, Jones TC, Damgaard PB, Allentoft ME, Shevnina I, Logvin A, Usmanova E, Panyushkina IP, Boldgiv B, Bazartseren T, Tashbaeva K, Merz V, Lau N, Smrcka V, Voyakin D, Kitov E, Epimakhov A, Pokutta D, Vicze M, Price TD, Moiseyev V, Hansen AJ, Orlando L, Rasmussen S, Sikora M, Vinner L, Osterhaus A, Smith DJ, Glebe D, Fouchier RAM, Drosten C, Sjogren KG, Kristiansen K, Willerslev E (2018) *Ancient hepatitis B viruses from the Bronze Age to the Medieval period*. **Nature**, 557(7705): 418-423

17. Muller JA, Harms M, Kruger F, Gross R, Joas S, Hayn M, Dietz AN, Lippold S, von Einem J, Schubert A, Michel M, Mayer B, Cortese M, Jang KS, Sandi-Monroy N, Deniz M, Ebner F, Vapalahti O, Otto M, Bartenschlager R, Herbeuval JP, Schmidt-Chanasit J, Roan NR, Munch J (2018) *Semen inhibits Zika virus infection of cells and tissues from the anogenital region*. **Nat Commun**, 9(1): 2207

18. Scaturro P, Stukalov A, Haas DA, Cortese M, Draganova K, Plaszczyca A, Bartenschlager R, Gotz M, Pichlmair A (2018) *An orthogonal proteomic survey uncovers novel Zika virus host factors*. **Nature**, 561(7722): 253-257

19. Schott K, Fuchs NV, Derua R, Mahboubi B, Schnellbacher E, Seifried J, Tondera C, Schmitz H, Shepard C, Brandariz-Nunez A, Diaz-Griffero F, Reuter A, Kim B, Janssens V, Konig R (2018) *Dephosphorylation of the HIV-1 restriction factor SAMHD1 is mediated by PP2A-B55alpha holoenzymes during mitotic exit*. **Nat Commun**, 9(1): 2227

20. Senis E, Mosteiro L, Wilkening S, Wiedtke E, Nowrouzi A, Afzal S, Fronza R, Landerer H, Abad M, Niopek D, Schmidt M, Serrano M, Grimm D (2018) *AAVvector-mediated in vivo reprogramming into pluripotency*. **Nat Commun**, 9(1): 2651

21. Sikandar A, Cirnski K, Testolin G, Volz C, Bronstrup M, Kalinina OV, Muller R, Koehnke J (2018) *Adaptation of a Bacterial Multidrug Resistance System Revealed by the Structure and Function of AlbA*. **J Am Chem Soc**, 140(48): 16641-16649

22. Sommer R, Wagner S, Rox K, Varrot A, Hauck D, Wamhoff EC, Schreiber J, Ryckmans T, Brunner T, Rademacher C, Hartmann RW, Bronstrup M, Imberty A, Titz A (2018) *Glycomimetic, Orally Bioavailable LecB Inhibitors Block Biofilm Formation of Pseudomonas aeruginosa*. **J Am Chem Soc**, 140(7): 2537-2545

23. Tsay HC, Yuan Q, Balakrishnan A, Kaiser M, Mobus S, Kozdrowska E, Farid M, Tegtmeyer PK, Borst K, Vondran FWR, Kalinke U, Kispert A, Manns MP, Ott M, Sharma AD (2019) *Hepatocyte-specific suppression of microRNA-221-3p mitigates liver fibrosis*. **J Hepatol**, 70(4): 722-734

24. Uchil PD, Pi R, Haugh KA, Ladinsky MS, Ventura JD, Barrett BS, Santiago ML, Bjorkman PJ, Kassiotis G, Sewald X, Mothes W (2019) *A Protective Role for the Lectin CD169/Siglec-1 against a Pathogenic Murine Retrovirus*. **Cell Host Microbe**, 25(1): 87-100.e110

25. Wang X, Thompson CD, Weidenmaier C, Lee JC (2018) *Release of Staphylococcus aureus extracellular vesicles and their application as a vaccine platform*. **Nat Commun**, 9(1): 1379

26. Yu J, Duong VHH, Westphal K, Westphal A, Suwandi A, Grassl GA, Brand K, Chan AC, Foger N, Lee KH (2018) *Surface receptor Toso controls B cell-mediated regulation of T cell immunity*. **J Clin Invest,** 128(5): 1820-1836

27. Zhang Z, Filzmayer C, Ni Y, Sultmann H, Mutz P, Hiet MS, Vondran FWR, Bartenschlager R, Urban S (2018) *Hepatitis D virus replication is sensed by MDA5 and induces IFN-beta/lambda responses in hepatocytes*. **J Hepatol**, 69(1): 25-35

PRECLINICAL RESEARCH

1. Ernst CM, Slavetinsky CJ, Kuhn S, Hauser JN, Nega M, Mishra NN, Gekeler C, Bayer AS, Peschel A (2018) *Gain-of-Function Mutations in the Phospholipid Flippase MprF Confer Specific Daptomycin Resistance*. **MBio**, 9(6)

2. Gerlach D, Guo Y, De Castro C, Kim SH, Schlatterer K, Xu FF, Pereira C, Seeberger PH, Ali S, Codee J, Sirisarn W, Schulte B, Wolz C, Larsen J, Molinaro A, Lee BL, Xia G, Stehle T, Peschel A (2018) *Methicillin-resistant Staphylococcus aureus alters cell wall glycosylation to evade immunity*. **Nature**, 563(7733): 705-709

3. Pfeiffer A, Thalheimer FB, Hartmann S, Frank AM, Bender RR, Danisch S, Costa C, Wels WS, Modlich U, Stripecke R, Verhoeyen E, Buchholz CJ (2018) *In vivo generation of human CD19-CAR T cells results in B-cell depletion and signs of cytokine release syndrome*. **EMBO Mol Med**, 10(11)

4. Schneidt V, Ilecka M, Dreger P, van Zyl DG, Fink S, Mautner J, Delecluse HJ (2019) *Antibodies conjugated with viral antigens elicit a cytotoxic T cell response against*

primary CLL ex vivo. **Leukemia**, 33(1): 88-98

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CLINICAL RESEARCH

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