DZIF
Deutsches Zentrum für Infektionsforschung

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Helmholtz Centre for Infection Research

DZIF

German Centre for Infection Research

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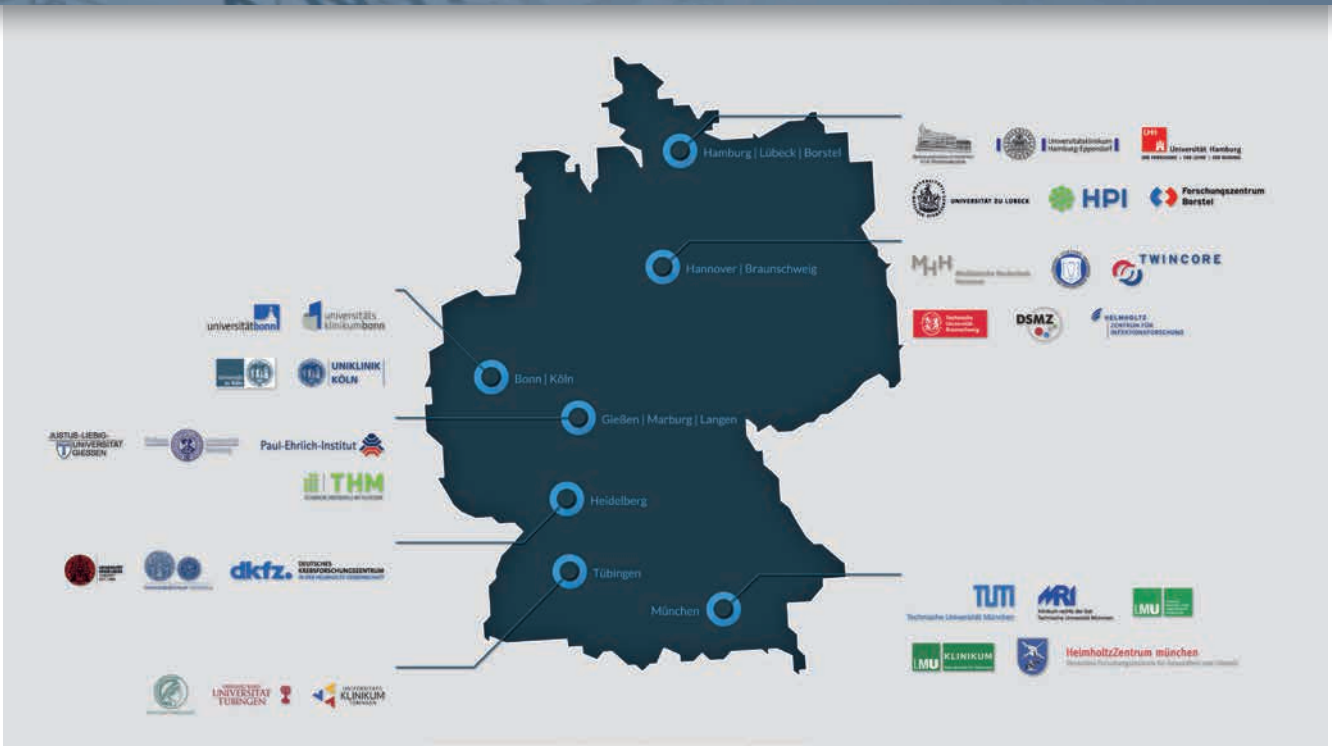
The German Centre for Infection Research (DZIF)

Seventy years after the onset of the antibiotic era, infectious diseases continue to be among the strongest contributors to morbidity and mortality worldwide. The Grand Challenges in infection research are caused by emerging and globally present pathogens, rapid development of resistance against anti-infectives and poverty-associated infectious diseases in developing countries. In addition, health care-associated infections challenge human health in industrialized societies, and immuno-suppression after transplantation or by state-of-the-art medical treatment of cancers paves the way for complicated infections.

These Grand Challenges can only be met by an integrative effort bundling the scientific expertise in basic research, epidemiology, translational research and clinical studies. In Germany, such expertise in infectious diseases is dispersed throughout the country, translational efforts are scarce and efforts tackling the Grand Challenges are fragmented and inefficient. The Federal Ministry of Education and Research (BMBF) founded the Deutsches Zentrum für Infektionsforschung (DZIF) as an integrated multi-centre structure bringing together selected universities, university hospitals and non-university research institutes and linking together their strong research portfolios as well as clinical infrastructures. The DZIF will foster the strategic coordination of concerted translational efforts aiming at novel diagnostic, preventive and therapeutic measures against the most important infectious diseases.

Members of the General Assembly of DZIF | DZIF



Map of the regional units of DZIF with their logos | DZIF

DZIF'S MISSION: TRANSLATIONAL RESEARCH

The DZIF will coordinate and strategically align translational infection research. Translational research means that results of basic research should systematically be developed further and should make new diagnostic, preventative and therapeutic methods for infectious disease treatment available. In return, the clinical staffs' knowledge about infectious diseases and the interests of patients will elucidate basic researchers' work. In total, translational research aims for effective interactions between basic and clinical research to benefit from each other.

In defined thematic units, DZIF researchers from different institutions work on specific pathogens and infectious diseases. Thus, DZIF members already achieved tremendous synergetic effects by. Indeed, this network of experts led to a pipeline with over 30 drug and vaccine candidates, which would not have arisen without the DZIF financial support and the combined know-how. For the first time, there is a real chance to implement these candidates on the market in the future.

The administrative group at the main office in Braunschweig (from left to right): Simone Friedrich, Dr. Jennifer Schmitz, Dr. Timo Jäger, Dr. Vivien Nagy, Janna Schmidt | DZIF

The Executive Board of the German Centre for Infection Research at the Opening Ceremony in December 2012 in Berlin (from left to right: Prof. Dirk Heinz, Prof. Ulrike Protzer, Prof. Martin Krönke) | DZIF

The Research Areas: Thematic Translational Units

EMERGING INFECTIONS

Outbreaks of emerging pathogens appear suddenly and a rapid response is crucial to contain the spread of the disease. Actions must be taken both to raise the awareness of the public health sector and to develop strategies to speed up biomedical research and production of candidate vaccines and therapeutics. The mission of the Thematic Translational Unit Emerging Infections is to establish a research infrastructure that contributes to rapid containment of emerging infections and to mitigate the consequences of such outbreaks for the public. To fulfil this mission, the Thematic Translational Unit Emerging Infections shall link expert individuals and research groups within three areas covering the entire response chain: i. pathogen detection, diagnostics and clinical management; ii. emergency vaccines; iii. broad-range antivirals.

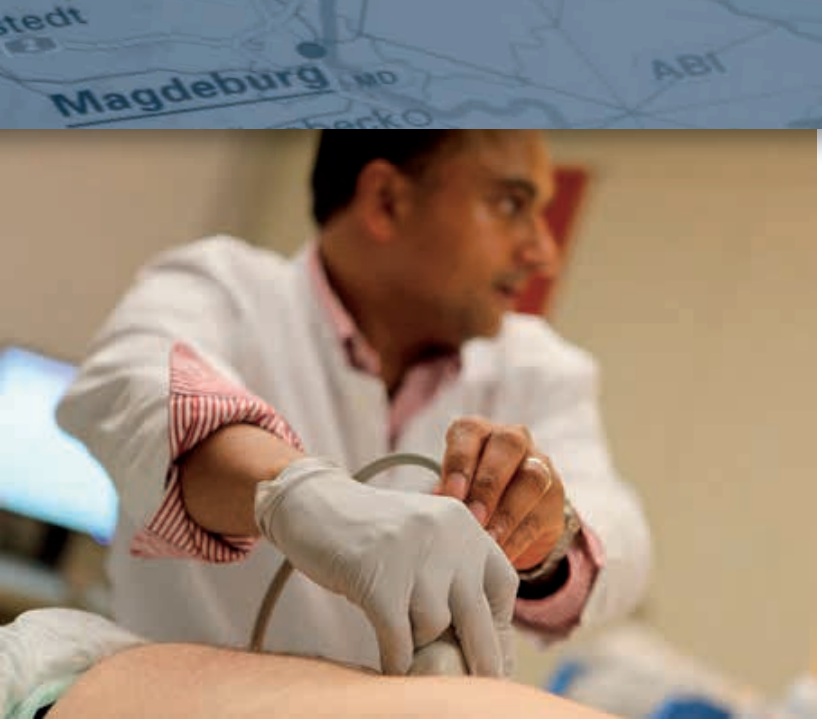
TUBERCULOSIS

Despite enormous efforts tuberculosis (TB) remains a prime global health threat, with at least 8 million newly infected individuals and 1.4 million deaths every year. The problem is compounded by HIV/TB co-infections and the emergence of multi- and extensively drug-resistant (MDR and XDR) strains of the *Mycobacterium tuberculosis* complex, particularly in Eastern Europe, Sub-Saharan Africa and Asia. TB control, on the global level, is faced with several challenges: There is currently no vaccine that efficiently protects against pulmonary TB in adults; the arsenal of anti-TB drugs is limited and there are only few new drugs in industrial pipelines; biomarkers to predict or monitor treatment success are virtually absent; and access to TB diagnostics is restricted in resource-poor settings. The mission of the Thematic Translational Unit Tuberculosis is to improve TB infection control, with a focus on M/XDR-TB.

MALARIA

Despite a multitude of actions taken to eradicate malaria, the disease still remains one of the top killers of African children under 5 years of age. An efficient vaccine for prevention has not been brought to the market yet, and the spread of resistance to the drugs currently administered makes it painfully clear that we need new medications to provide effective therapies for all target groups. Regional differences in parasite and human populations as well as co-infections are further obstacles impeding an efficient and correct treatment of patients. A continuous effort in epidemiological research is required to keep knowledge of current parasite distributions up-to-date as a prerequisite for efficient intervention design. The mission of the Thematic Translational Unit Malaria is to fight malaria with preventive and therapeutic measures using disease modelling to optimise interventions in Africa.

Researchers at TTU “Malaria” in Tübingen are making significant headway in finding a vaccine against malaria.



Sonography for hepatitis diagnosis. | © DZIF/scienceRELATIONS.de

HEPATITIS

Worldwide, more than half a billion people are chronically infected with the hepatitis B (HBV), C (HCV) and/or D virus (HDV) and are at high risk of developing end-stage liver disease and hepatocellular carcinoma. A preventive vaccine and efficient antiviral drugs are available for HBV. However, current treatments merely suppress viral replication and no curative treatments are in the pipeline. For HCV, on the other hand, the first specific direct-acting antivirals (DAAs) have been approved and other promising compounds are in clinical development.

With an increasing number of therapeutic options and the emergence of viral resistance, therapy will become much more complex in the coming years. There is an urgent need to establish treatment standards that consider all patient groups including in particular the difficult-to-treat patients, *e.g.* those with end-stage liver disease who are excluded from most clinical trials. Finally, specific treatments are lacking for certain forms of chronic viral hepatitis such as HDV/HBV co-infection, the most severe form of the disease.

GASTROINTESTINAL INFECTIONS

Gastrointestinal infections kill around three million people globally each year. Diarrheal infections are responsible for approximately 2.5 million deaths per year (4.3 % of all deaths, and 10 % of deaths in children up to four years; WHO 2011). The most important gastrointestinal (GI) pathogens that cause acute diarrhea include *Campylobacter jejuni/coli, Salmonella, Shigella, Escherichia coli, Yersinia enterocolitica, Vibrio cholerae, Clostridium difficile*, rotaviruses, noroviruses, and *Entamoeba histolytica*. In addition to the diarrheal pathogens, one of the most important GI pathogens is *Helicobacter pylori*. Approximately half the world population is infected with this pathogen which is the main cause for gastric cancer. No effective vaccines are available for any of the leading GI pathogens and treatment options are unsatisfactory for most of them. Thus, there is an urgent need for novel vaccines and therapeutic interventions.

The mission of the Thematic Translational Unit Gastrointestinal Infections is to improve the diagnosis, treatment and prophylaxis of bacterial gastrointestinal infections, and thereby aims at reducing the morbidity and mortality from these diseases. Uniquely, all interventions developed will be selective for specific pathogens or groups of them, rather than broadly attacking pathogens and commensals alike. Another important research focus is to develop therapies that protect the microbiota during interventions against GI pathogens.

INFECTIONS OF THE IMMUNOCOMPROMISED HOST

As a consequence of our aging population and the growing prevalence of chronic diseases, infections in patients with immunodeficiencies are a serious issue in clinical practice. Furthermore, temporary or in many cases even long-term alterations of immune functions must be factored into the development of new therapies in modern medicine, *e.g.* organ transplantation or cancer treatment. In immunocompromised patients microbes that are normally efficiently controlled by a healthy immune system can suddenly become life-threatening pathogens that are difficult to treat with currently available anti-infectives. Risk stratification to identify clinically relevant immunodeficiencies and associated pathogens is still highly limited.

In clinics such as the University Hospital of Cologne, nasal swabs are currently being taken from every patient to test for MRSA germs. | © DZIF/scienceRELATIONS.de

However, since immune alteration is a major contributor to disease in immunocompromised patients, active and passive immunotherapies as well as immune modulation provide promising options for the development of novel and highly effective anti-infective therapies.

HEALTHCARE-ASSOCIATED AND ANTIBIOTIC-RESISTANT BACTERIAL INFECTIONS

A phenomenal increase in infections caused by antibiotic-resistant bacterial pathogens has become one of the biggest public health concerns over the last ten years. Most severe cases result from healthcare-associated bacterial infections which are increasingly caused by methicillin-resistant *Staphylococcus aureus* and extended-spectrum beta lactamase (ESBL)-producing enterobacteria. Unfortunately, most pharmaceutical companies have shifted their R&D activities towards chronic infections and diseases and only very few new compounds are expected to become available in the next decade. The Thematic Translational Unit Healthcare-Associated and Antibiotic-Resistant Bacterial Infections will support translational research to develop novel anti-infective strategies. It will also foster the establishment of clinical studies to assess the suitability of improved infection control measures and appropriate use of antibiotics (*e.g.* antibiotic stewardship) for reducing the burden of healthcare-associated and antibiotic-resistant bacterial infections.

NOVEL ANTI-INFECTIVES

Antibiotics have improved the life expectancy of mankind. However, multi-drug resistance has become common place in pathogenic bacteria and our “magic bullets” are losing their efficacy. Current medical standards in infectious disease management, intensive care and transplantation medicine rely heavily on efficacious classical anti-infective chemotherapeutics, yet the antibacterial development pipeline is drying up and the number of innovative drugs reaching the market is dwindling rapidly. In spite of the strong medical need, the economic viability of antibiotic R&D programmes is being questioned and the interest of the private sector is waning. R&D is increasingly dependent on the biotech sector which, due to financial limitations, focuses on single small-scale and short-term projects. The absence of strong industrial commitments reflects back onto the academic sector and provides little incentive for either researchers or institutions to invest in translational activities. The mission of the Thematic Translational Unit Novel Anti-Infectives is to bridge the gap between basic research and current anti-infective development activities.

DZIF infrastructures: From bench to bedside

The DZIF mission is to coordinate and strategically align translational infection research. Basic research should result in new diagnostic, preventative, and therapeutic methods for treatment of infectious diseases. Therefore, a modern infrastructure is essential – from the laboratory through clinics and pharmaceutical companies to patients.

PRODUCT DEVELOPMENT UNIT

From target discovery to approval of new drugs, 95 % or more get stuck in the 'valley of death' and fail to reach clinical phase. All too often, this is not because of shortcomings with the innovative product, but rather due to an inadequate translational development process. The mission of the Product Development Unit (PDU) is to bridge the translational gap and to catalyse and regulate the rapid transformation of research discoveries into products including their preclinical development, manufacture and initiation of a first-in-man clinical trial.

CLINICAL TRIAL UNIT

In 2011, the DZIF's respective sites already had excellent clinical trials units (CTUs), yet their activities were restricted to a narrow spectrum of indications. The CTUs rarely reflected the full range of diseases the DZIF is dedicated to. However, the potential weakness of this heterogeneity is counterbalanced by a particular strength of the DZIF: Its network combines expertise in all clinical infectious disease indications with direct access to these clinical trial units, albeit to a varying extent at each site.

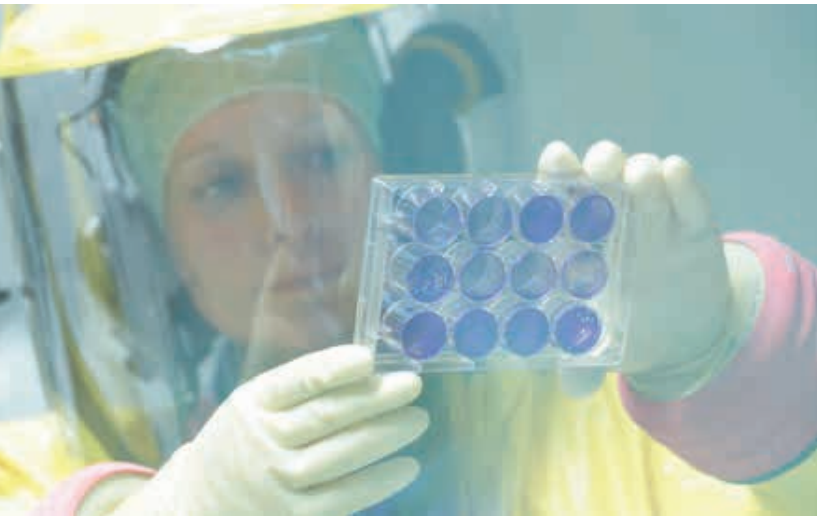
Thus, the strategic plan for increasing the value of the DZIF CTU started with the exchange of expertise between sites. A central coordinating office supports a mutual strategy for clinical trial performance at the DZIF in accordance with BMBF Standard Operating Procedures.

The nationwide DZIF platform reduces the cost of conducting clinical trials by mobilizing an unprecedented recruitment potential. With high-level data quality and performance rates, the DZIF clinical trial structure aims to become the preferred partner for academic and industrial clinical trials.

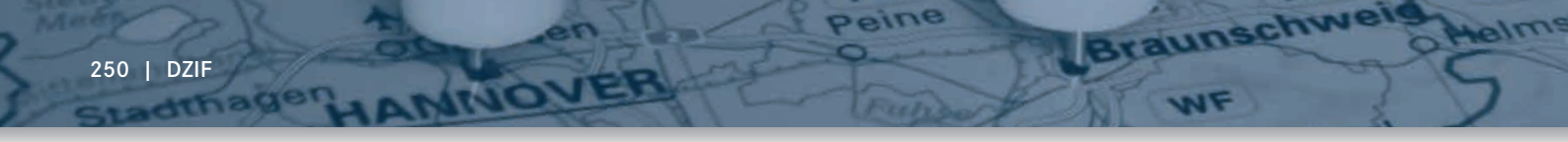
AFRICAN PARTNER SITES

This infrastructure shall establish and strengthen a sustainable North-South collaboration with African institutions of infectious disease research. Long-lasting collaborations between some of these centers and DZIF partners already exist. Yet, most of these sites run on a project basis leaving few resources for sustainable investments. Working together with these partner sites is crucial since most of the diseases endemic to these sites are also an issue in developed countries, albeit at much lower frequencies.

The DZIF intends to reinforce the networking between the existing collaborations. The goal is to improve and harmonize the link between DZIF partner sites and selected African research sites and to facilitate access to well-characterized clinical samples of specific interest.



In labs of the highest safety level, DZIF research on pathogens such as the Marburg virus and Ebola.



NATURAL COMPOUND LIBRARY

Numerous small molecule pharmaceuticals derived from natural microbial sources have been proven to play a key role in combatting infectious diseases. Such compounds account for the vast majority of antibiotics currently on the market. A particular shortcoming of drug discovery in recent decades is that only a small share of the currently known bacteria or fungi have been explored for their potential to produce novel drug leads. Furthermore, no state-of-the-art molecular biological methods have yet been systematically applied to screen the potential of microbial producers.

The DZIF Natural Compound Library will be combining isolation methods for obtaining and pre-selecting hitherto unexplored “creative” organisms and functional genomics with systems biology approaches, fermentation optimization, assay development, and bioprofiling in order to establish and optimise a highly diverse chemical compound library. This will render natural products accessible for screening and ultimately enable subsequent compound development in different Thematic Translational Units.

BIOBANKING

Access to a comprehensive biobanking infrastructure is mandatory for multi-site infectious disease research and its translation into practical application. Biomaterials of interest to the DZIF include culture collections of infectious pathogens and microbial producers, liquid biological samples such as serum, plasma and urine, and characterized tissue samples from infected patients. A biobank coordination and technology platform will be established within this infrastructure with specific emphasis on an interactive platform as well as high level preanalytical and storage quality.

BIOINFORMATICS PLATFORM

Major technological advances during the last decade have resulted in massively decreased prices for DNA sequencing, while quality and information density have rapidly increased. These advancements will directly impact a multitude of research areas: investigation of host-pathogen interaction, genomic epidemiology, transcriptomics and regulatory networks, metagenomics, and the identification of epidemiologically distinct clones and their potential to develop into outbreak strains with extended pathogenic capabilities – all of those areas will benefit from these improvements.

Scientific interpretation of data will only be possible by efficient preprocessing and analysis of data. Systematic collation technologies will be required to deal not only with the huge quantity of data generated but also to deal with the heterogeneity of the formats involved. The challenge is to generate aggregated information that can be used for further scientific interpretation. The unit will establish and provide tools to supply access to new technologies for respective research areas. In parallel to data management, statistical analysis methodologies will be implemented to deal with multi-dimensional data. The integration and comparative analysis of data generated within the DZIF network is the basis for both interdisciplinary and translational research. Bridging the gap between established genome bioinformatics and the medical data from clinical research will represent the main challenge for the DZIF Bioinformatics Platform.

THE DZIF ACADEMY

Education and training of next generation talents are among the most rewarding investments to strengthen and develop infection research in Germany. The DZIF Academy aims at attracting young medical doctors and scientists into infection research by establishing innovative and highly attractive educational programmes for students and post-graduates and to train next generation clinician scientists. By exchange programmes, structured doctoral programmes and collaborative spring and autumn schools, the DZIF Academy reflects and emphasizes the synergistic nature of DZIF and shares its mission to close the gap between basic research and clinical development.

DZIF ORGANIZATION

DZIF partners are members of DZIF e.V. (eingetragener Verein, incorporated society) under German Law. The General Assembly and the Executive Board are mandatory bodies of the DZIF. Further bodies of the DZIF are the Commission of the Funding Authorities and the Scientific Advisory Board. The Administrative Office, located at the Campus of Helmholtz Centre for Infection Research, is responsible for managing and coordinating all research funding procedures and it organizes General Assembly meetings, reporting and review procedures.

Contact and more information

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Certain therapies, for instance bone marrow transplants, require the immune system of the patient (child) to be artificially suppressed. Even harmless infections can then become a threat.