DZIF
Deutsches Zentrum
für Infektionsforschung

Translational Research at the German Center for Infection Research

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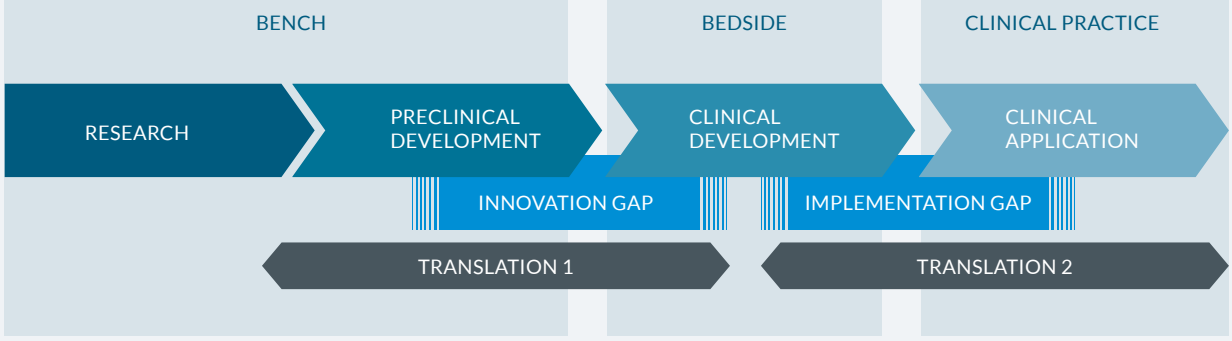
Translational medicine in the context of global challenges caused by infectious diseases

Infectious diseases still account for the most frequent causes of disease and death worldwide. Increasing resistance to antibiotics, the rapid spread of pathogens across national borders, poverty-related infections, emerging viruses and bacteria, as well as an increasing number of immunocompromised patients constitute some of the greatest economic, medical and political challenges of our time (Grand Challenges).

These Grand Challenges caused by infectious disease pathogens call for new collaborative structures and concerted global action plans to transfer knowledge from basic research to clinical studies more effectively, and to subsequently implement this into clinical practice. Translation, i.e. transferring findings from basic biomedical research to clinical studies takes the centre stage of DZIF's mission.

What does the term 'translational medicine' mean precisely? Although slight variations of the concept exist, in the end all definitions lead to the common notion of the rapid and targeted transfer of accumulated knowledge from (basic) laboratory research to innovative diagnostic methods, effective preventive measures, and new therapies that can be applied clinically in the mid- to long term (figure 1). Translational research necessitates collaboration between many disciplines, ranging from pharmacology, medical chemistry, quality-assured manufacturing and preclinical development, clinical trials, epidemiology and clinical guideline development to market-driven activities. In the first translational step (from bench to bedside), knowledge and data from research are integrated into the development of new preventive, diagnostic and treatment methods and products for infectious diseases in order to close the gap of innovation. In clinical trials, these are subsequently tested for safety and efficacy in humans for the first time (proof-of-concept). The second translational step (from bedside to clinical practice) involves further clinical trials and the implementation into medical practice. Accordingly, the term 'implementation gap' has been coined for the second translational step.

Figure 1: First and second translational step



Translational research at the DZIF

DZIF's translational research areas have been selected according to pressing unmet medical needs and to the specific challenges associated with combating infectious diseases. In particular, new therapeutic agents such as antibacterial, antiviral and antiparasitic compounds, and vaccines are in urgent need. Due to the strong withdrawal of the pharmaceutical industry over the past 20 years, earlier stages of product development, ranging from preclinical to clinical phase I and II trials, have shifted to the responsibility of public academic research institutions such as DZIF. Thus, the development of new anti-infective agents is an absolute imperative for DZIF, which aims to focus its research activities on the first translational step. DZIF combines a wealth of multidisciplinary expertise and experience from 35 universities, university hospitals, and external non-university research institutes as well as specialized federal research institutions and regulatory authorities and is, therefore, in an excellent position to meet this translational responsibility.

DZIF research areas are of global significance

DZIF's central mission is to align translational research with unmet global medical needs caused by infectious diseases. The centre coordinates infection research work in Germany to address national as well as global challenges with great societal impact as defined by the WHO health agenda. DZIF's translational mission, therefore, includes the implementation gap as an integral part of its strategy.

DZIF's research activities focus on nine thematic research areas, each dedicated to specific pathogens or important disease entities including tuberculosis, hepatitis, malaria as well as gastrointestinal infections, infectious diseases in immunocompromised patients, hospital-borne infections, antibiotic resistance and emerging infectious diseases. The most straightforward activities include product development and clinical studies with the aim of bringing novel biomarkers, anti-infectives and vaccines to the patient. This involves the classical 'bench to bedside' approach as well as disease-oriented infection research (bedside to bench) that is driven by the feedback from clinical observations. DZIF research areas are supported by newly established translational infrastructures which provide technical and regulatory assistance: a Product Development Unit (PDU), a Clinical Trial Unit (CTU), African Partner Institutions, Biobanking, Natural Compound Libraries, Bioinformatics, Epidemiology and Vaccine Development.

First translational step – innovation gap: from bench to bedside

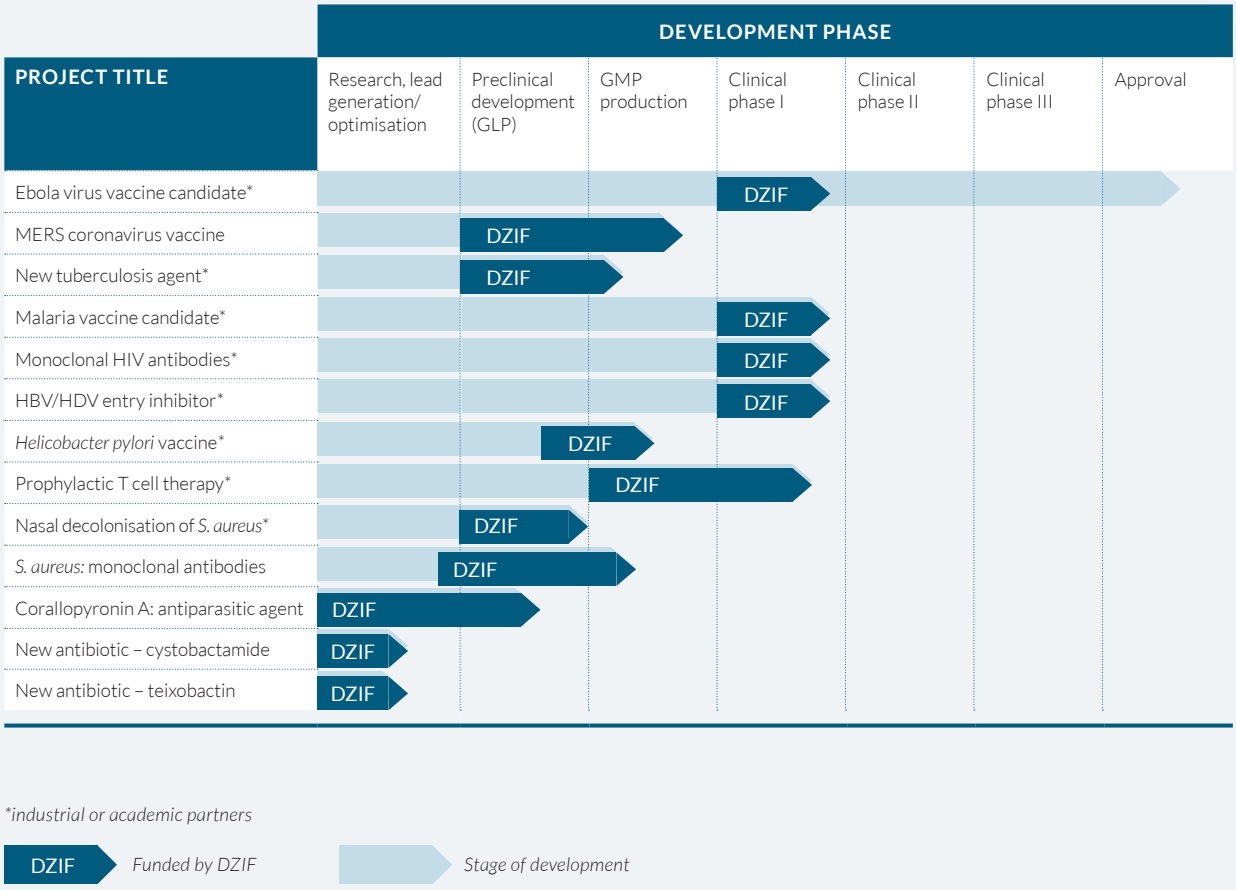
DEVELOPING NEW ANTINFECTIVES AT DZIF – IN COOPERATION WITH INDUSTRIAL PARTNERS

The development of new antibacterial, antiviral and antiparasitic agents as well as vaccines is a high-risk, long-term and costly venture. DZIF's portfolio ranges from identifying new targets for anti-infectives and vaccines, the discovery of new active agents and biomarkers, to conducting preclinical research as well as clinical phase I and II trials. Complete closure of the innovation gap requires greater resources than those available in DZIF, a fact that emphasizes the importance of industrial collaborations, especially for clinical phase IIb and III trials and successful applications for drug approval. Developing new synthetic chemical agents, particularly confirmatory clinical phase III trials and filing these for drug approval, requires investments ranging in the hundreds of millions of Euros and are hence far beyond DZIF's financial and organizational capacities. Thus, the interface between academic and industrial product development projects is a most critical subject for due diligence, where pharmaceutical companies must come to momentous decisions on taking over new product candidates for further development. Therefore, it is mandatory that translational research at DZIF fulfills quality standards along the product development chain that have been set by the pharmaceutical industry.

Key to professionalizing DZIF's translational research has been the establishment of the Translational Project Management Office (TPMO). The Product Development Unit (PDU) is headed by an expert with in-depth pharmaceutical industry experience, who provides proficient support for product development at early preclinical and clinical project stages. The PDU also negotiates intellectual property and contract issues between academia and pharmaceutical companies. In addition, DZIF has established an independent Office for Scientific and Regulatory Advice (OSRA) that supports product development projects from their start into preclinical and clinical stages. As DZIF member institutions, regulatory national authorities such as the Paul Ehrlich Institute and the Federal Institute for Drugs and Medical Devices (BfArM) have proven instrumental for the organization of this service, as their combined expertise allows for early identification of regulatory requirements. The formulation of objective criteria is key for the selection of the most promising product development projects which show increased prospects of finding industrial partners for out-licensing the further development into clinical proof-of-concept studies and market approval stages.

Meanwhile, DZIF has established numerous strategic partnerships with industry and non-governmental organizations (NGOs) as well as Product Development Partnerships (PDPs), which have contributed further to the professionalisation of the product development at DZIF. Clearly, translational product development is no longer just a vision at DZIF, but a reality. This is illustrated by the portfolio of novel anti-infectives and vaccine candidates shown in figure 2.

Figure 2: DZIF's development pipeline



Second translational step – implementation gap: from bedside to clinical application

The second translational gap entails the risk of missing the conversion of new clinical proofs of concepts into improved healthcare, i.e. of failing to reach the patient. The process of implementing new translational developments in long-term medical routines is extremely complex and shaped by many interests. In general, it is the given responsibility of federal states' institutes to secure public health. Translational science can help to implement and guide novel medical treatment methods, thereby contributing to the maintenance and improvement of public health. By combining state-of-the-art scientific technologies with the tremendous collective of multidisciplinary expertise, DZIF is prepared to advance evidence-based medicine. Thus, new clinical knowledge and discoveries generated within DZIF will be integrated into medical recommendations and treatment guidelines. That said, decision-making in the organization and advancement of patient care is often determined by non-scientific factors.

As a centre for translational medicine, DZIF aligns its research activities with societal needs, including the 'One Health' concept, which recognizes that many infectious diseases are caused by pathogens transmissible between animals and humans (zoonoses). Zoonoses constitute around two thirds of all infectious disease pathogens, and translational research on these pathogens is of major societal, political, and economic importance. One pressing question to be answered, for example, is whether the use of (last-resort) antibiotics in agriculture results in the development of antimicrobial resistance and if this has an impact on human healthcare. As integral members of DZIF, the Federal Research Institute for Animal Health, the Friedrich Loeffler Institute, and the central national public health authority, the Robert Koch Institute, add a political dimension to the novel medical insights elaborated at DZIF. Furthermore, the Robert Koch Institute ensures that aspects of public health and epidemiological concerns are appropriately considered in DZIF. In this context, epidemiological aspects are firmly anchored into all individual research fields within the overarching translational DZIF infrastructure 'Epidemiology'. Aligning and connecting translational research with emerging public health needs remains an integral part of DZIF's central mission.

Investing in the future: DZIF promotes the next generation of physicians and scientists in translational infection research

A fundamental goal of the centre is to improve the implementation of new treatment modalities and advance general clinical care. Young, dedicated people who work at the centre and shape DZIF's mission are needed to ensure this for the future to come. Training in translational research therefore plays an important role at DZIF, preparing future generations of scientists and physicians for working at the interface between research and medical practice. In collaboration with DZIF´s Product Development Unit, the DZIF Academy systematically promotes academic careers, offering scientists and physicians attractive translational research and product development training programmes including clinical trials. Different stipend programmes support MD and PhD students, enable clinical leave for research purposes and facilitate the combining of career and family. Furthermore, structured and certified training programmes (workshops and Academy Schools) are in place to educate the next generation of translational researchers. The increase in the critical mass of experts in infectious diseases will ultimately enhance the recognition of infectious disease medicine as an independent scientific and clinical discipline.

DZIF sets ambitious goals

From the very beginning, the participating institutions and scientists have shaped the outreach of DZIF with exceptional motivation, determination, dedication and responsibility. With the objective of facing the global Grand Challenges in a most concerted and effective way, DZIF physicians and scientists consistently perform at the highest level to achieve accomplishments in translational infection research. The institute and hospital directors' unbounded commitment to DZIF has furthered close collaborations between physicians and scientists, and intensified their programmes in translational infection research. Owing to DZIF's national responsibility, the scientists have naturally taken on the mandate of tackling existing and emerging infectious disease challenges that are of global and societal relevance. DZIF's stories of success have by far exceeded initial expectations and attracted international attention. Over the past five years, DZIF has achieved scientific

breakthroughs, developed new drugs, therapies and innovative technologies, curbed epidemics and brought about long-term changes in clinical practice – all for the benefit of patients. The translational value of DZIF's work is measurable: in order to quantify its achievements, DZIF has defined specific key performance indicators (see appendix).

DZIF continues in the endeavour to enhance its position and its impact in translational infection research along the specific lines of infectious diseases: One Health - One World. Consequently, DZIF has entered close partnerships with African partner institutions in order to reinforce collaborative investigations in countries with epidemic tropical diseases. In addition, the centre is part of international alliances like CEPI (Coalition for Epidemic Preparedness Innovations) and CARA (Conscience of Antimicrobial Resistance Accountability), who enable global and concerted actions against neglected tropical diseases and antibiotic resistance. To further advance and ensure a long-term framework for translational infection research, DZIF will continue building on excellence. At the same time, the centre is continuously developing its strategies to respond to new developments in science and medicine as well as to the continuously changing and emerging societal and medical challenges caused by infectious diseases.

DZIF at a glance

The German Center for Infection Research uses an integrative approach to meet the major infectious disease challenges. DZIF's mission is to translate research results from the laboratory to clinical practice and medical care rapidly and effectively. In doing so, DZIF has paved the way for developing innovative vaccines, diagnostics and drugs that will benefit patients over the coming years. Over 500 scientists and physicians from 35 member institutions are networked closely within the centre, resulting in a synergistic alliance between all participating member institutes and unique setting for unfolding DZIF's potential and capacity for the accomplishment of its translational mission.

An international audit committee selected the founding establishments and institutions (universities, university hospitals, clusters of excellence, collaborative research centres (SFBs), non-university research institutes and specialized federal research institutions; see figure 3) for their outstanding and specific expertise, both in basic infection research and clinical infectious diseases. Meanwhile, further institutions in Germany and Africa specialised in infectious diseases have joined as associated DZIF partners, enabling an even more successful translation of results from basic research into preclinical development programmes and clinical trials. A budget of €38.8 million euros is annually made available to DZIF by the Federal Ministry of Education and Research (BMBF) and the federal states.

Figure 3:
DZIF partners

GERMAN CENTER FOR INFECTION RESEARCH (DZIF)

> 150 hospital and institute directors

7 partner sites

35 partner establishments

Basic research	Clinical expertise	Regulatory expertise	Public health
· 5 "elite" universities · 4 clusters of excellence · 19 collaborative research centres (SFBs) · 6 priority programmes · S3 and S4 laboratories	· Clinical trial units · Departments of clinical infectious diseases	· Paul-Ehrlich-Institut · Federal Institute for Drugs and Medical Devices	· Robert Koch Institute · Friedrich-Loeffler-Institut

APPENDIX

The German Center for Infection Research's specific key performance indicators

INNOVATIVE PRODUCT DEVELOPMENT, TREATMENT MONITORING, GUIDELINE OPTIMISATION	
INDICATOR AND TRANSLATIONAL MISSION	**PROCESS DEFINITION (measurable parameters: type and number)**
Diagnostics and biomarkers	
· Rapid, economic and precise diagnostics for infectious diseases · New, validated biomarkers for rapid, economic and precise treatment of infectious diseases · Targeted and personalised treatment management	· Development and validation of new diagnostics · Identification of new biomarkers · Preclinical and clinical trials on biomarkers and diagnostics · Industry collaborations · Spin-offs, industry licensing · Implementation in hospitals · Incorporation into clinical guidelines
New anti-infectives (antibacterial, antiviral and antiparasitic agents)	
· Preclinical proof-of-principle · Clinical proof-of-concept · Approval and implementation of new agents for treating infectious diseases	· Development/validation of new methods/technologies · Development of new preclinical disease models · Identification of target sites for new agents · Identification of new agents · Development of target product profiles for new agents · Project progress in hit-to-lead, lead-optimisation phases · Establishing new drug candidates · Preclinical and non-clinical trials relevant to approval (pharmacology, toxicology, safety pharmacology) · Clinical phase I/II trials · Spin-offs, industry licensing · Product development partnerships
New vaccines	
· Preclinical proof-of-principle · Clinical proof-of-concept · Approval and implementation of new vaccines for infectious disease prevention in clinical practice	· Identification of new vaccine candidates · Identification of new adjuvants · Efficacy testing in preclinical vaccine trials · Clinical phase I/II trials · Spin-offs, industry licensing · Product development partnerships
Pandemics, Epidemics and Endemics	
· Set up of a prevention and response centre · New management standards for detecting, preventing and controlling pandemics, epidemics and endemics	· Epidemiological studies on known pathogens · Detecting emerging pathogens · Development of new diagnostic detection methods · Development of new vaccines for outbreaks · Collaborations with national and international public health institutions (ECDC, CDC, WHO)

INNOVATIVE PRODUCT DEVELOPMENT, TREATMENT MONITORING, GUIDELINE OPTIMISATION

INDICATOR AND TRANSLATIONAL MISSION	PROCESS DEFINITION (measurable parameters: type and number)
Multicentre clinical trials	
· Establishment of a DZIF Clinical Trial Unit · Establishment of the DZIF as a leading institution for clinical infectious disease trials in Germany	· Establishment of uniform quality criteria for clinical trials · Consultations, feasibility studies · Participation in clinical registration trials · Organization of clinical trials across DZIF
Development of recommendations and guidelines	
· Curbing the development of antibiotic resistance · Reducing the spread of multidrug-resistant pathogens · Reducing endogenous infections in risk patients · Guideline implementation	· Clinical trials and committee activities relevant to clinical guidelines · Clinical trials on optimising *antibiotic stewardship* · Clinical trials on *screening* and isolating infected patients/patients who have developed symptoms of infection · DZIF involvement in the formulation and/or alteration of diagnostic and treatment guidelines for infectious diseases
Development and utilization of translational platforms and infrastructures	
· Availability of biobanks with characterised samples · Insights into infectious diseases from defined cohorts of immunocompromised patients · Big data management · Collaborations with international institutions, to improve the prevention and treatment of neglected tropical diseases	· Biobanks (pathogens, patient samples and data sets, natural agents) · Quality management (SOPs), terms of use · Electronic data exchange with internal and external partners · Establishment of a transplant cohort for infection research · Quality management (SOPs), terms of use · Number of recruited patients, number of research projects · Bioinformatics · Training workshops, terms of use · Partnerships with African partner institutions and *Product Development Partnerships* (PDPs) · DZIF involvement in clinical trials on *neglected tropical diseases*

PROMOTING JUNIOR SCIENTIST STAFF, TRAINING AND RECRUITMENTS

INDICATOR AND TRANSLATIONAL MISSION	PROCESS DEFINITION (measurable parameters: type and number)
Training, stipends, mentoring, careers and positions	
· Increased number of scientifically and medically trained infection research staff · Attractive career opportunities at DZIF · Expansion of expertise in translational research · Increase in the number of women in leadership positions	· Establishment of the DZIF Academy for training and furthering careers in translational infection research · Stipends (MD, MD/PhD, clinical leave, maternity leave) · Alignment of DZIF Academy courses and workshops · DZIF Award for established translational infection researchers · Establishment of a fourth career path translational research in medicine and science · Appointment of DZIF professorships and heads of junior translational infection research groups · Promotion of scientific careers of women at DZIF · Specific mentoring for women

MANAGEMENT AND REPRESENTATION

INDICATOR AND TRANSLATIONAL MISSION	PROCESS DEFINITION (measurable parameters: type and number)
Internal	
· Collaboration agreements with member establishments · Quality assurance · Integration of external partners	· Internal process guidelines, regulation of IP rights · Quality control: - Internal and external project assessment - Milestones, deliverables - Project-specific advisory teams · Internal DZIF committee meetings: - Executive Board, partner site speakers, Internal Advisory Board - Funding authorities, BMBF - Scientific Advisory Board · Conferences with national infection research organisations

MANAGEMENT AND REPRESENTATION	
INDICATOR AND TRANSLATIONAL MISSION	PROCESS DEFINITION (measurable parameters: type and number)
International · Involvement in health programmes for specific infectious diseases, population groups and regions · Development of international guidelines to fight infectious diseases · DZIF contribution to efficient global healthcare	· Meetings and collaborations with international organisations (WHO, CDC, ECDC, PDPs, NGOs, etc.) · Collaborations and alliances with European and non-European partner institutions (NCATS, ANRS, MRC, CARA, etc.) · Conferences with international infection research organisations · Involvement in recommendations, assessments, strategic planning
Publications and public relations	· Publications · DZIF-organised national and international symposia · DZIF representation at national/international events · Press releases/statements/interviews · Media reports (press reviews) · DZIF website: development and update

DZG DEUTSCHE ZENTREN DER GESUNDHEITSFORSCHUNG

Imprint

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