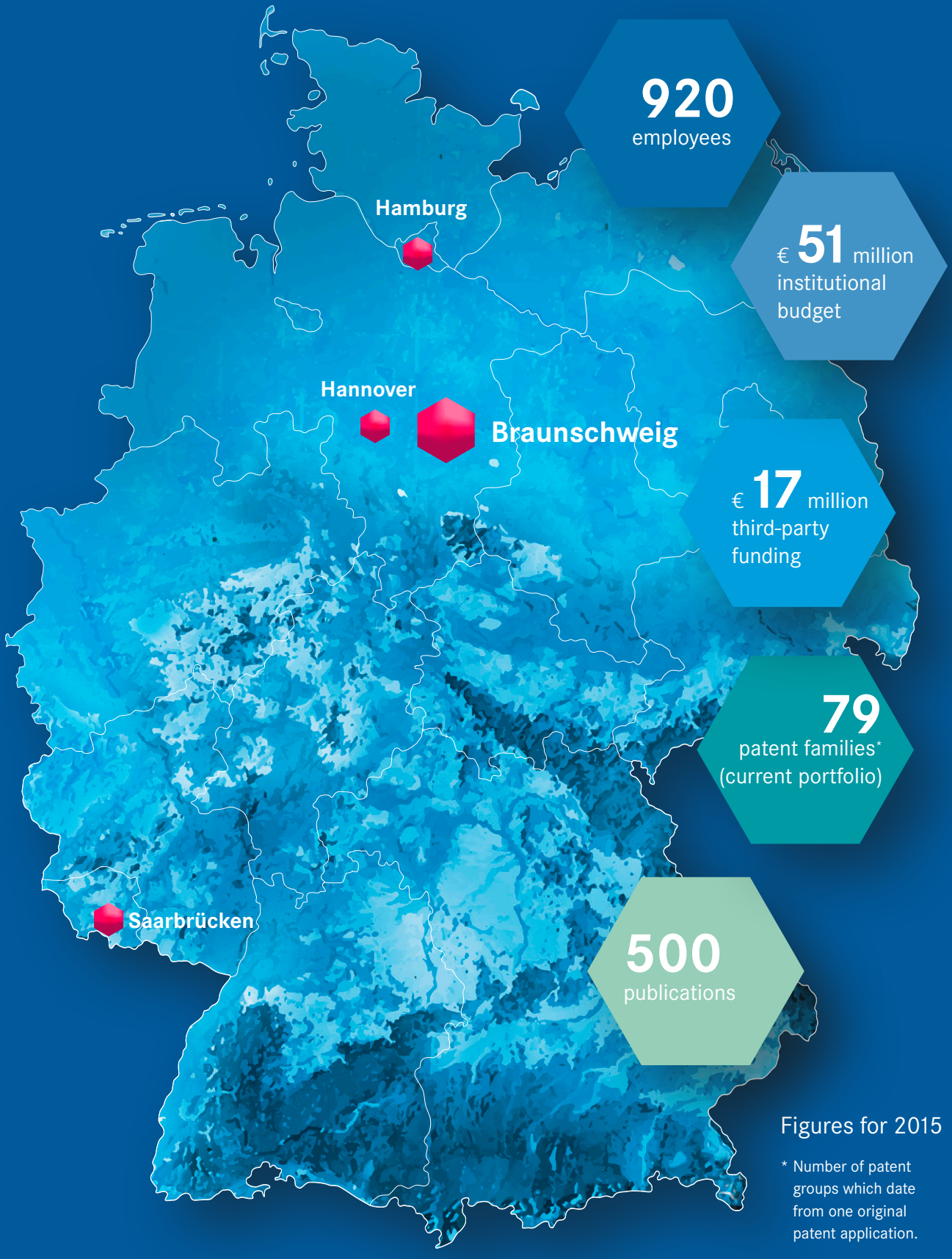
HZI 2025

A STRATEGIC ROADMAP FOR
THE HELMHOLTZ CENTRE FOR INFECTION RESEARCH

THE HELMHOLTZ CENTRE FOR INFECTION RESEARCH (HZI) AT A GLANCE



920 employees

€ **51** million institutional budget

€ **17** million third-party funding

79 patent families* (current portfolio)

500 publications

Figures for 2015

* Number of patent groups which date from one original patent application.

HZI campus – Braunschweig

- HZI headquarters
- Central administration
- Research infrastructure
- Basic research on bacterial and viral infections, pathogen-host interactions, anti-infective agents, epidemiology
- Partnership with Technische Universität (TU) Braunschweig, in particular: cooperation within the Braunschweig Integrated Centre for Systems Biology (BRICS)

Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), Saarbrücken

- Established jointly by the HZI and Saarland University (UdS)
- Investigation of natural compounds, optimisation for pharmaceutical application
- Bridging the gap between basic research and the pharmaceutical industry

TWINCORE, Hannover

- Founded jointly by the HZI and Hannover Medical School (MHH)
- Translation, joint research projects carried out by physicians and scientists
- Experimental and clinical infection research
- Bridging the gap between basic research and clinical practice

Centre for Structural Systems Biology (CSSB), Hamburg

- Located on the campus of DESY (Deutsches Elektronensynchrotron)
- Jointly operated by several north German research institutions
- Elucidation of molecular processes in infections using highly specialised photon sources


HELMHOLTZ
CENTRE FOR
INFECTION RESEARCH

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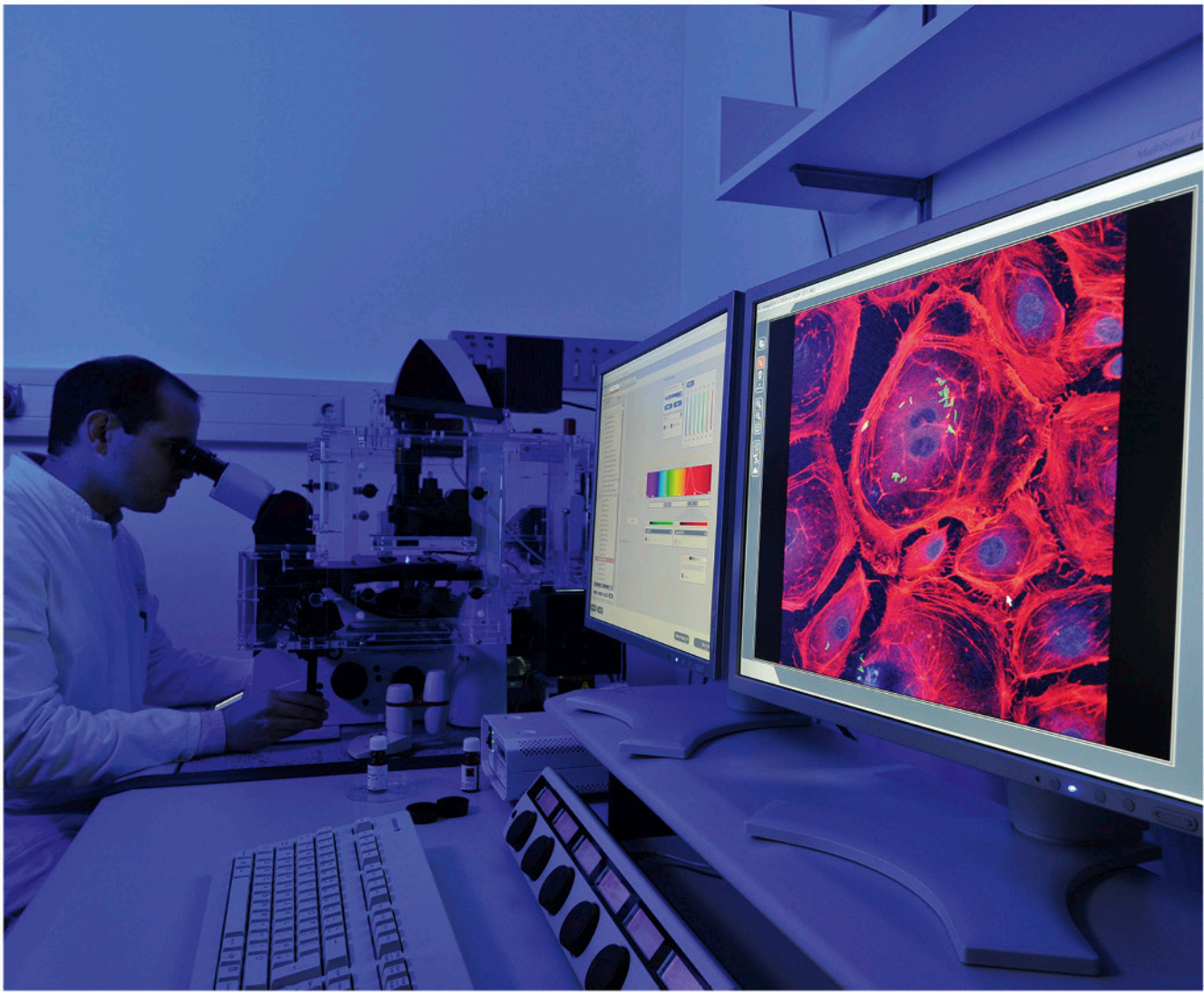


SUMMARY A

UNDERSTANDING INFECTIONS – FIGHTING PATHOGENS

In the 21st century, infectious diseases still pose a global threat to human health and are the cause of one-fifth of all deaths. In Germany, too, they are the source of many unsolved problems facing society and medicine. The Helmholtz Centre for Infection Research (HZI) is responding to this major challenge: in line with the Helmholtz Association's mission to help solve the important and pressing questions facing society, science and industry, it investigates the fundamental principles underlying infection processes. It uses state-of-the-art technologies to pursue its aim of developing innovative approaches to prevent, diagnose and treat infectious diseases.

HZI scientists conduct research on bacterial and viral pathogens of high clinical relevance. The analysis of the infection strategies of pathogens and the defence mechanisms of hosts leads to the identification of potential new target structures for therapeutic interventions. At the same time, based on its unique expertise in the area of natural compounds, the centre also focuses on systematically investigating potential candidates for novel anti-infective drugs. The HZI scientists therefore pursue a cross-disciplinary and integrated research approach, which addresses infection processes on many levels – from molecules through cells and organisms to populations.

A culture of mutual exchange between basic research and clinical as well as pharmaceutical application is of fundamental importance to the sustainable development of infection medicine. To promote this exchange, the HZI is constantly elaborating concepts and structures for translational infection research. The centre works closely with clinical and industry partners and, in cooperation with universities, trains the next generation of infection researchers. It collaborates strategically with regional, national and international research institutions and universities and participates actively in associations like the German Centre for Infection Research (DZIF).

The following are the key elements of the HZI strategy for the upcoming decade:

- "Innovation first": Choosing, establishing and expanding into new and **promising fields in infection research** with particularly high potential for innovation
- Setting up a **research and development platform for therapeutic interventions** (anti-infectives, vaccines and immunomodulators) from discovery to preclinical and early clinical trials (proof of concept)
- Establishing the basis for an increasingly **personalised infection medicine**, ideally in a new "Centre for Individualised Infection Medicine" (CIIM), which is yet to be set up

This roadmap, HZI 2025, shows how the HZI, with its translational focus, will help to facilitate a faster and more targeted approach when it comes to fighting and preventing existing, emerging or recurring infectious diseases.

Its aim is to keep pace with the rapidly evolving pathogens and thereby create the preconditions for a significant reduction of the disease burden caused by infections.

1. INFECTIOUS DISEASES – A GLOBAL THREAT

Infectious diseases are responsible for one-fifth of all fatalities worldwide[1]. While industrialised countries were able to reduce the burden of such diseases in the 20th century with vaccines, improved hygiene and antibiotics, they, too, are now facing new medical, economic and societal challenges. The rapid spread of emerging and recurring pathogens, chronic infections, increased resistance to drugs as well as demographic and climatic change make the issue of infectious diseases a topic of major concern.

DIFFICULT TO PREDICT: EMERGING AND RE-EMERGING INFECTIONS

Human populations are constantly confronted with pathogens. Some of these already emerged in the past, others cause new types of infectious diseases, for example by crossing species boundaries.

According to World Health Organization (WHO) statistics, between 250,000 and 500,000 people die every year from influenza. The devastating outbreaks of Ebola in Central and West Africa resulted in the deaths of more than 10,000 people in 2014. Approximately 35 million people carry the HIV/AIDS virus. Coronaviruses caused new types of infectious diseases such as SARS (2003 saw a total of 8,500 cases and 800 fatalities) and MERS (in July 2015, more than 1,300 people contracted this disease – almost 40 percent of whom died)[2].

Recent studies show that the number of registered outbreaks of infectious diseases has been increasing since the 1980s[3] (Fig. 2). More than 50 per cent of these are zoonoses – infectious diseases that can affect both animals and humans[4]. Currently, around 200 such zoonoses are known[5].

Germs which are frequently present in the human body and usually cause only mild symptoms can – for example due to genetic changes – engender life-threatening variants. Enterohaemorrhagic *Escherichia coli* (EHEC), for instance, are pathogenic strains of the otherwise mostly harmless gut bacterium *E. coli*. In 2011, EHEC bacteria caused a wave of illness in northern Germany, affecting 4,000 people and leading to 50 deaths[6]. The pathogens were spread by contaminated bean sprouts – an example of the huge significance of infections that can be transmitted through food. In Germany, particularly intestinal disorders of zoonotic origin, caused by *Salmonella, Campylobacter* and pathogenic *E. coli*, represent a constant threat.

The increasing mobility of a large proportion of the world's population boosts the spread of new and existing infectious diseases. Moreover, the lack of willingness to vaccinate may constitute a “gateway” for the return of infections that had been virtually eradicated.

With many of these infectious diseases, the question of why they pose a greater risk to certain individuals or populations than to others remains unanswered. An understanding of the underlying defence mechanisms of the host, particularly at a genetic and immunological level, could contribute significantly to new treatment and prevention approaches for the at-risk population groups.

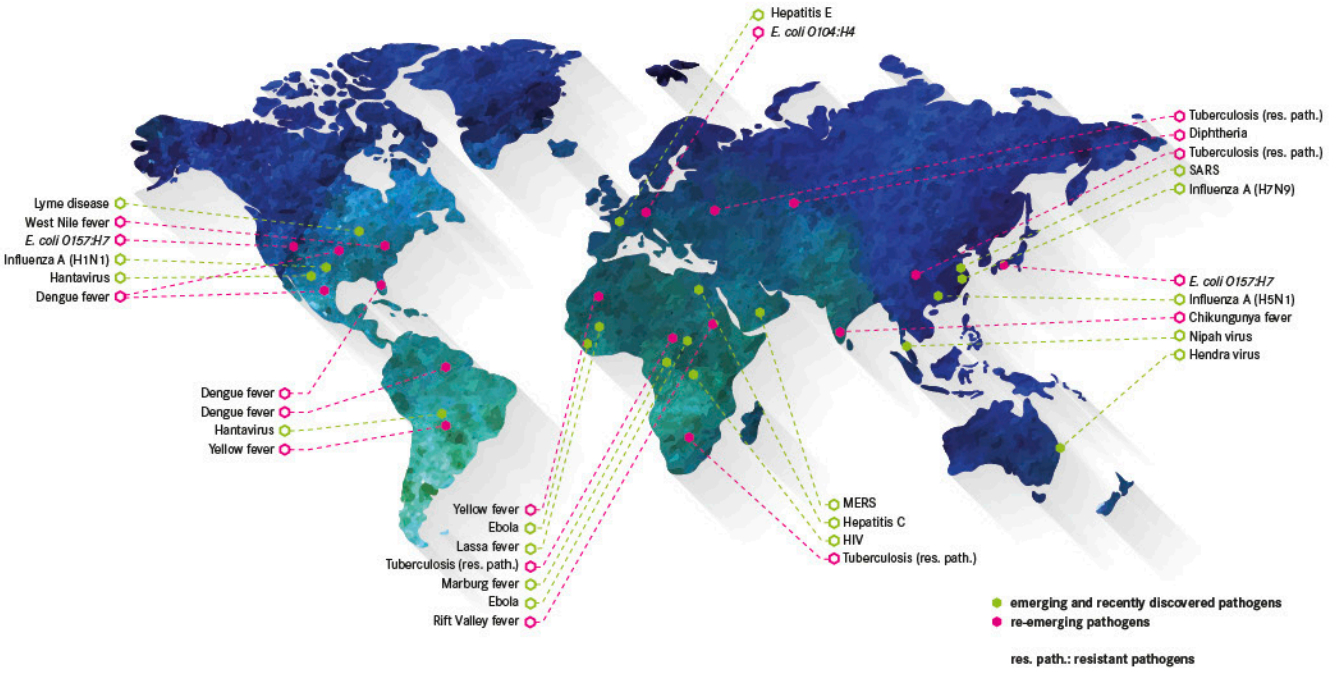


Fig. 1: New and recurring diseases: some of the major waves of illness in recent decades. (Sources: WHO, CDC, The Lancet)

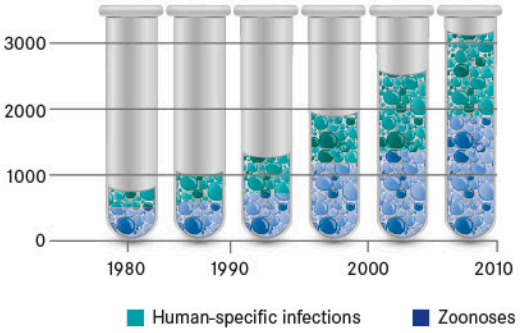


Fig. 2: A rising trend: the number of outbreaks of infectious diseases since 1980.
(HZI illustration based on: Smith et al., J R Soc Interface, 2014)

Through epidemiological studies, rapid analytics as well as future-oriented vaccination and drug research, infection research can play an important role in fighting emerging infections in the future.

1 *Lozano et al., The Lancet (2012) 380: 2095 doi: 10.1016/S0140-6736(12)61728-0.*

2 *Figures: WHO fact sheets and WHO situation reports: www.who.int (accessed on 8 September 2015).*

3 *Smith et al., J R Soc Interface (2014), 11 (101) doi: 10.1098/rsif.2014.0950.*

4 *Kahn, Emerg Infect Dis (2006) 12: 556.*

5 *WHO figures, see also: Jones et al., Nature (2008), 451: 990.*

6 *Grad et al., PNAS (2012) 109: 3065.*

INSIDIOUS DANGER: CHRONIC INFECTIONS

Some chronically persistent viruses play a major role as global health threats mainly due to their ubiquity. Besides the previously mentioned 35 million carriers of the HIV/AIDS virus[7], estimates indicate that more than 140 million people are affected by chronic infections with Hepatitis C virus (HCV)[8], but most of them have not been diagnosed with the infection. The number of people chronically affected by Hepatitis B virus infections is estimated to be as high as 250 million[9].

Between 1990 and 2013, global mortality[10] increased for just a few of the 235 most frequent causes of death, including HIV/AIDS and the liver carcinoma associated with the Hepatitis C virus. According to estimates, almost 360,000 people died from HCV-induced liver cirrhosis and more than 340,000 died from HCV-associated liver carcinoma in 2013[11].

Cytomegalovirus (CMV) appears extraordinarily frequently: in many countries, more than 50 percent of the population carry the virus[12]. Most people show no symptoms, but following organ transplantations the reactivation of persistent CMV is one of the most feared complications as it can lead to systemic infections with serious consequences. In pregnancy, a primary infection with CMV can cause serious birth defects in the unborn foetus[13].

Using a detailed analysis of the mechanisms of persistence, infection research can pave the way to curing chronic infections, as the example of HCV has shown: thanks to the use of combination therapy, which includes direct antiviral medications, the virus can now be eradicated completely from the body. Due to the high price of available drugs, potential re-infections and many as yet undiagnosed carriers of the virus, global efforts are needed in the healthcare sector to translate this scientific breakthrough into a significant reduction in the HCV-associated disease burden.

As the successful treatment of many diseases does not protect against a subsequent infection, it is crucial that prophylactic vaccines are researched and developed. In the long term they could make a significant contribution to the global control of chronically persistent pathogens.

URGENT NEED FOR ACTION: ANTIBIOTIC RESISTANCE

Across the EU, antibiotic resistance leads to 25,000 deaths every year and costs the health system 1.5 billion euros. The European Centre for Disease Prevention and Control (ECDC) estimates the number of hospital-acquired infections in the EU at 3.2 million each year[14, 15].

7 *WHO, fact sheet no. 360, July 2015.*

8 *Murray et al., The Lancet (2015) doi: 10.1016/S0140-6736(15)61340-X.*

9 *Schweitzer et al., The Lancet (2015) doi: 10.1016/S0140-6736(15)61412-X.*

10 *Age-standardised figures. To calculate age-standardised values, see Robert Koch Institute (2015) Infektionsschutz und Infektionsepidemiologie Fachwörter – Definitionen – Interpretationen, key word: Standardisation p. 121.*

11 *Forouzanfar et al., The Lancet (2015) 385: 117 doi: 10.1016/S0140-6736(14)61682-2.*

12 *Bundesgesundheitsbl. Gesundheitsforsch – Gesundheitsschutz (2000) 70:653–659. Springer-Verlag.*

13 *National Center for Immunization and Respiratory Diseases, Division of Viral Diseases, http://www.cdc.gov/cmv/risk (accessed on 8 September 2015).*

14 *European Centre for Disease Prevention and Control (ECDC) (2013), Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals 2011–2012.*

15 *European Commission, Antimicrobial resistance, http://ec.europa.eu/dgs/health_food-safety/amr/index_en.htm (accessed on 8 September 2015).*

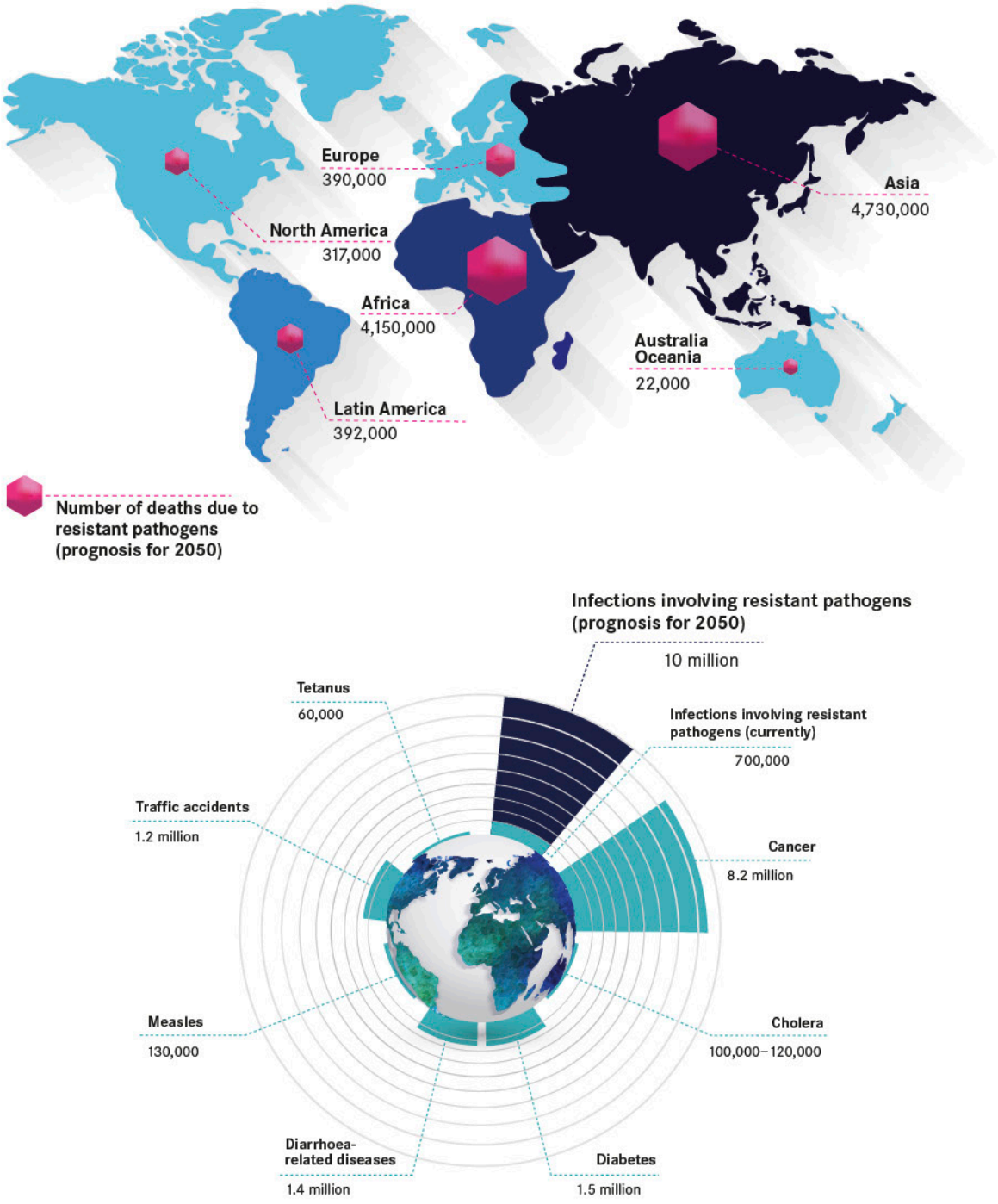


Fig. 3: An alarming trend: the number of fatalities caused by resistant pathogens could rise to 10 million per year by 2050 unless effective countermeasures are taken. In the bottom figure, each of the concentric rings represents one million fatalities from the relevant cause.

(Illustration based on: Review on Antimicrobial Resistance (2014). Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations)

A report recently commissioned by the British government estimates that resistant pathogens are currently implicated in 700,000 deaths worldwide each year. The same report warns that this figure could rise to 10 million by 2050 if this trend is not addressed immediately[16] (Fig. 3). The World Health Organization (WHO) even considers the scenario of a "post-antibiotic age" to be conceivable. In such a scenario, even trivial wound infections could once again be life-threatening[17].

The so-called "ESKAPE germs"[18] – an acronym for *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter* spp. – are among the most dangerous sources of hospital-acquired infections. Some of them are almost impossible to treat due to a lack of effective antibiotics. Another serious problem is the spread of the highly virulent, gram-positive *Clostridium difficile* strains, which now present similar difficulties as MRSA as hospital-acquired multi-resistant strains. Multi-resistance in the tuberculosis pathogen *Mycobacterium tuberculosis* (MDR-TB) is also limiting treatment options throughout the world for this potentially deadly lung infection.

For decades now, comparatively little progress has been made in developing new drug classes in the face of the growing number of multi-resistant and pandrug-resistant pathogen strains[19]. The most recent antibiotic with a fundamentally new mechanism of action to be launched on the market, the cyclic lipopeptide daptomycin, was discovered back in the 1980s. The development of urgently needed innovative antibiotics to combat gram-negative hospital-acquired germs has stagnated for decades due to a lack of suitable drug candidates. Recently, however, a slightly opposing trend can be observed: companies in the pharmaceutical industry are becoming increasingly involved in the development of new antibiotics[20].

The current situation regarding viral infections is similarly problematic in many respects. This relates in particular to pathogens associated with chronic infections, which are a global issue: the main concern here is the risk that the persistent use of a few drugs will promote the emergence of resistances. Combination therapies are now already being used to address this problem.

At their summit in 2015, the G7 countries declared the fight against antibiotic resistance to be a global challenge[21]. To meet this challenge in the coming years, it is hugely important that new anti-infectives with fundamentally new mechanisms of action are continuously researched and developed. At the same time, antibiotics need to be handled more responsibly and higher hygiene standards need to be guaranteed in hospitals.

16 *Review on Antimicrobial Resistance (2014), Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations*

17 *World Health Organization (WHO) (2014), Antimicrobial Resistance: Global Report on Surveillance (ISBN 978 92 4 156474 8).*

18 *Pendleton et al., Expert Rev Anti Infect Ther. (2013) 11: 297.*

19 *See, for example, Centers for Disease Control and Prevention (CDC) (2013), Antibiotic Resistance Threats in the United States.*

20 *Verband forschender Arzneimittelhersteller (VFA) (Association of Research-Based Pharmaceutical Companies) (2015), http://www.vfa.de/de/arzneimittel-forschung/woran-wir-forschen/neue-antibiotika-den-vorsprung-wahren.html.*

21 *German Federal Government (2015), Leaders' Declaration, G7 Summit.*

2. WEAK DEFENCES: IMMUNOSUPPRESSION AND AN AGEING SOCIETY

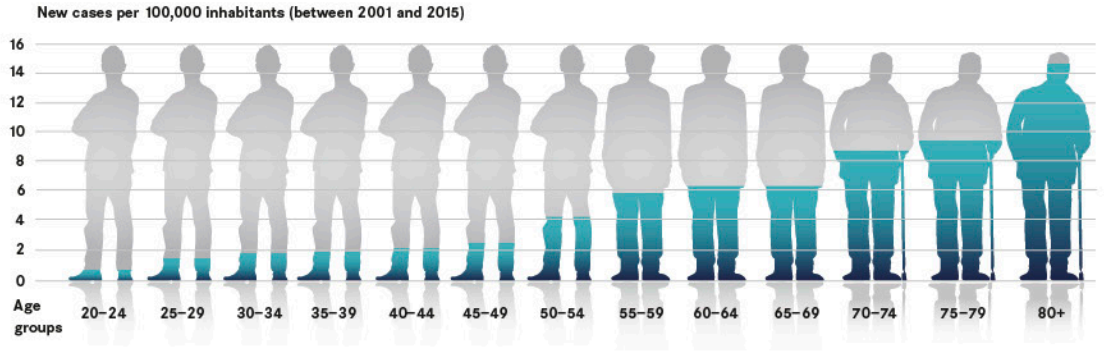


Fig. 4: Incidence of age-related invasive pneumococcal infections.
(HZI illustration based on: Robert Koch Institute: SurvStat@RKI 2.0, https://survstat.rki.de, deadline: 24/07/2015)

In Germany, the average life expectancy has more than doubled since the end of the 19th century. This increased life expectancy is accompanied by a rise in the number of multimorbid individuals whose immune system is no longer working at full capacity. Infections are therefore often more serious and this is paralleled by a rise in the incidence of many infectious diseases (Fig. 4). Another consequence of ageing is that vaccinations are less effective[22].

In addition, a rising number of patients must be continuously treated with immunosuppressant drugs. This can be seen primarily in the number of daily doses of immunosuppressant medications consumed in Germany: the figure rose from 21.5 million in 1999 to 141.7 million in 2013[23].

Patients receiving immunosuppressant drugs include organ transplant recipients and individuals with chronic inflammatory and autoimmune diseases[24]. Immunosuppression and immunomodulation are also elements of both conventional and innovative cancer treatments. Modern treatment concepts for the suppression of unwanted immune reactions, for example using therapeutic antibodies, usually go hand in hand with weakened defences. Such treatments are currently at a dynamic development stage and will become increasingly established in the upcoming years[25], leading to a rise in the risk of infection among affected patients.

Conducting research on the immune system will make an important contribution to tailored prophylaxes and therapeutic measures for older patients and those whose immune systems are compromised.

22 *Simpson et al., Eurosurveillance (2015) 20/8.*

23 *Consumption of immunosuppressant medication: http://de.statista.com/statistik/daten/studie/272482/umfrage/arzneimittelverbrauch-von-antidiabetika/ (accessed on 8 September 2015).*

24 *Pharmazeutische Zeitung, Issue 17/2011, "Immunsuppressiva: Den Teufel mit dem Beelzebub austreiben".*

25 *Aggarwal, Nat Biotechnol. (2010) 28: 1165.*

3. GRAVE CONSEQUENCES: INFECTIONS AS A CAUSE OF SERIOUS ILLNESSES

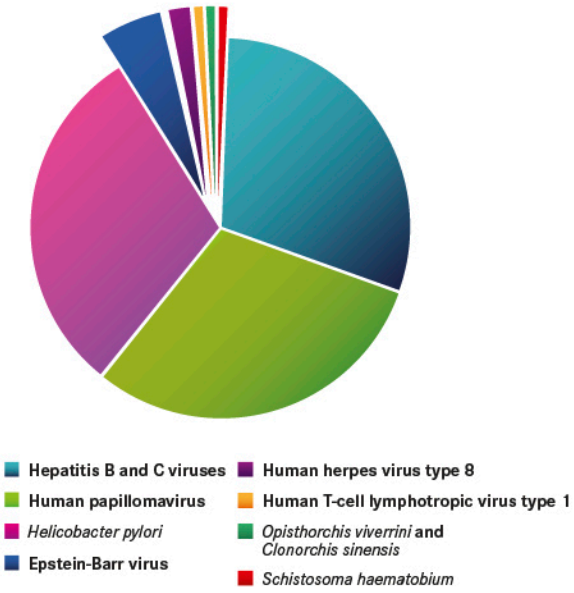


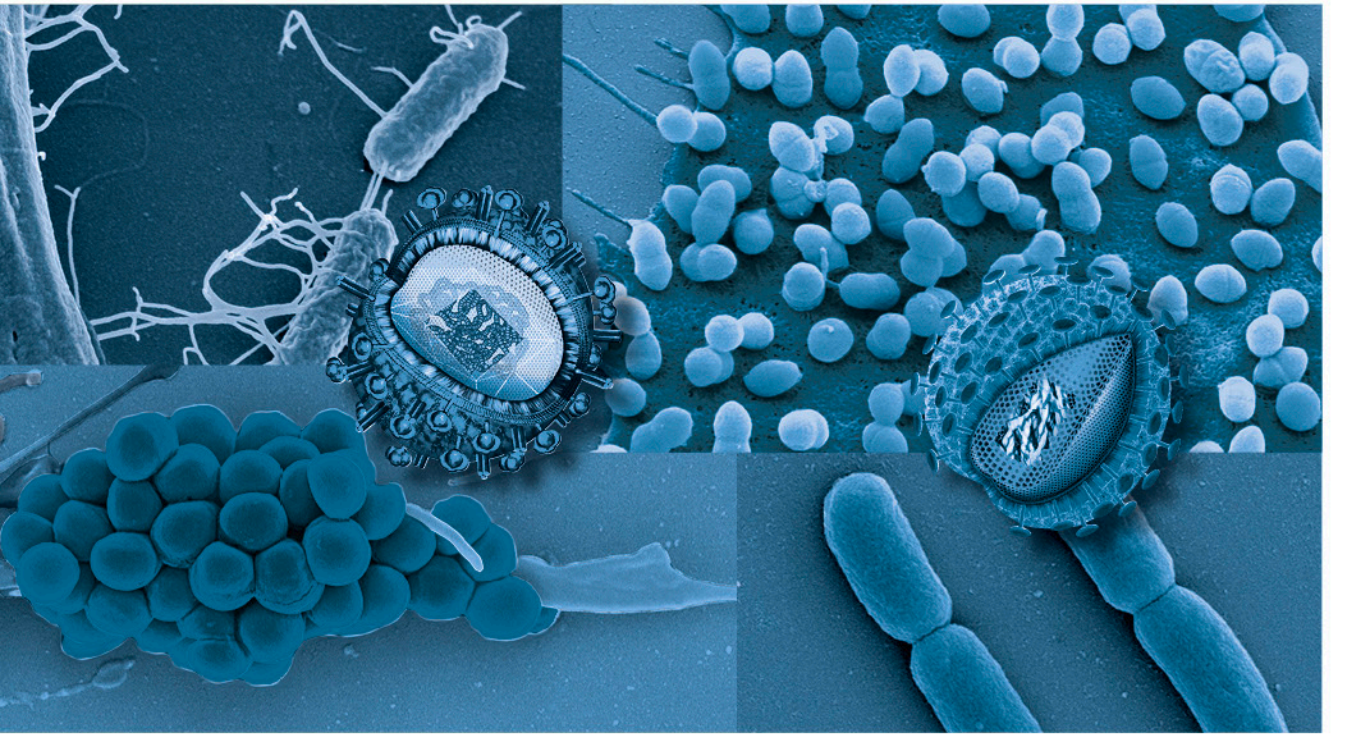
Fig. 5: Infections as a cause of cancer: hepatitis viruses, papillomaviruses and Helicobacter bacteria are among the most frequent triggers of cancerous tumours.
(HZI illustration based on: National Cancer Institute (USA), http://epigrants.cancer.gov/infectious-agents)

In recent decades, biomedical research has elucidated numerous links between infections and other diseases, which previously were not seen as causally connected to them. For example, cervical cancer is the result of an infection caused by the human papillomavirus[26], while some 75 percent of distal stomach tumours can be traced back to an infection caused by *Helicobacter pylori*[27]. Hepatitis viral infections are the culprits behind approximately 80 percent of all hepatic cancers[28]. The World Health Organization (WHO) estimates that more than 15 percent of all cases of emerging cancers could be prevented if the underlying infection could be curbed[29].

Diabetes[30] and cardiovascular disease[31] are also increasingly perceived to be associated with infections. Sometimes the immune responses triggered by the infection and the resulting chronic inflammation are the cause of such secondary diseases. There has also been growing evidence that neurodegeneration may correlate with infectious diseases or with inflammation caused by infections[32].

Comprehensive research into such correlations can in many cases create novel ways to treat or completely prevent non-contagious diseases by fighting the infection causing them. For example, treatment in the form of antibiotics for stomach tumours caused by certain strains of *Helicobacter* is now available, and the prevalence of virus-induced cervical carcinoma can be reduced by vaccination. In both cases, the underlying scientific discoveries were rewarded with the Nobel Prize.

26 *WHO fact sheet no. 380, updated November 2014.*
27 *De Martel et al., The Lancet (2012) 13: 607.*
28 *WHO in: http://www.who.int/immunization/topics/hepatitis/en/ (accessed on 8 September 2015).*
29 *De Martel et al., The Lancet (2012) 13: 607.*
30 *Schneider et al., Diabetologia (2014) 57: 2009.*
31 *Dunne (2004), Infectious agents and cardiovascular disease, in: The Infectious Etiology of Chronic Diseases. National Academies Press.*
32 *Iwashnyna et al., JAMA (2010) 304: 1787.*



Infections continue to pose a considerable threat to human health worldwide. The rapid spread of emerging and re-emerging pathogens, increasing resistance to drugs and the large number of chronic infections throughout the world make this a topic of major concern. Demographic trends, the growing number of patients with compromised immune systems and secondary illnesses caused by infections confront medicine and society with considerable challenges. Targeted infection research and the rapid and practical implementation of research findings are needed to keep pace with rapidly evolving pathogens.

TRANSLATIONAL INFECTION RESEARCH – THE KEY TO SUCCESS

Biomedical research has achieved several breakthroughs in recent years. The mechanisms underlying many diseases can now be elucidated at a level of detail never seen before. Nevertheless, the number of new and innovative medications addressing major common diseases is progressing comparatively slowly. In the case of infectious diseases this applies particularly to antibiotics.

The development process for a new drug often takes more than ten years and can cost more than one billion euros[33]. Of several thousand compounds processed in basic and pre-clinical research, just one or two candidates reach approval stage[34].

Publicly funded research institutions can significantly contribute to this development process only in the early stages. The pharmaceutical industry, on the other hand, prefers to invest in projects that have already demonstrated proof of concept (see Fig. 6). In the case of anti-infectives, particularly antibiotics, the situation is aggravated by the fact that marketing them is often not particularly lucrative[35]. A highly effective antibiotic is generally administered only over a short period of time while the industry's traditional blockbuster concepts are based mostly on years of treatment of chronic illnesses. The requirement to keep new antibiotics under wraps as drugs of last resort for particularly virulent multi-resistant germs also reduces their commercial attractiveness.

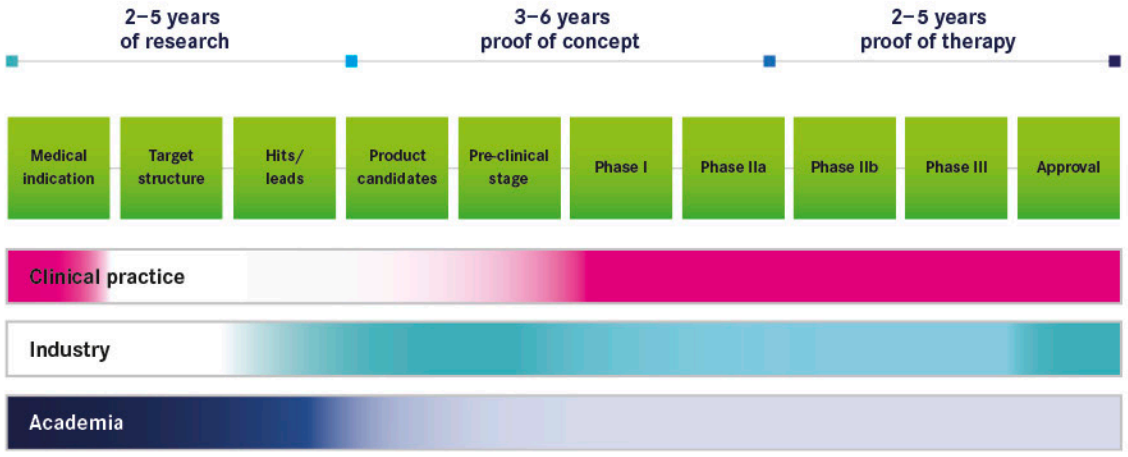


Fig. 6: The long road to drug approval.

Therefore, many pharmaceutical companies have gradually cut back their research and development of new antibiotic drugs since the 1980s. This trend has only started to reverse somewhat in the last few years. Accelerated approval and facilitated conditions are designed to mitigate the risk associated with developing innovative antibiotics. To this end, explicit economic incentives have been introduced. Such incentives include the Generating Antibiotics Incentives Now Act (GAIN) in the USA[36]. In the EU, the Innovative Medicines Initiative (IMI) supports pre-competitive research[37].

In many cases, prevention through vaccination is more effective than treatment – this is illustrated by the history of successful vaccination campaigns which led to the complete or almost-complete eradication of the respective pathogen, as with smallpox and polio. Vaccinations also prevent secondary diseases that arise from various chronic infections. The existence of effective vaccinations against the human papillomavirus and the Hepatitis B virus shows the significant role that infection research can play in reducing the global disease burden (→ "Insidious danger: chronic infections").

However, vaccines still have to battle acceptance problems as they are generally administered to healthy people and there is frequently a lack of awareness among individuals about the effective protection of the population provided by herd immunity. Most of the difficulties outlined in the development of therapeutic agents apply to a certain extent also to vaccines.

33 *See Tufts Center for the Study of Drug Development (2014), http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study.*

34 *VFA (2013), Forschung für das Leben; see also: Paul et al., Nature Reviews Drug Discovery (2010) 9:20 doi:10.1038/nrd3078.*

35 *For more on the cost-effectiveness of antibiotic development, see also: Review on Antimicrobial Resistance (2015), Securing new drugs for future generations: the pipeline of antibiotics.*

36 *Brown; Can J Microbiol. (2013) 59: 153.*

37 *http://www.imi.europa.eu/ (accessed on 8 September 2015).*

Research and new treatment options for Hepatitis C: a success story

The Hepatitis C virus (HCV) was discovered in 1989 and initially could not even be cultivated. A causal treatment was scarcely possible. But less than 25 years later, chronic HCV infections can be treated with a combination therapy.

The elucidation of the molecular mechanisms of HCV infection created the basis for this development. Given that more than 140 million people throughout the world are infected with HCV, huge international efforts were made to drive this development. Close cooperation between the basic researchers, their clinical partners and the pharmaceutical industry has been fostered by translational programmes. This has facilitated the swift identification of suitable targets for treatment and the successful search for innovative antiviral drugs and their testing in clinical trials.

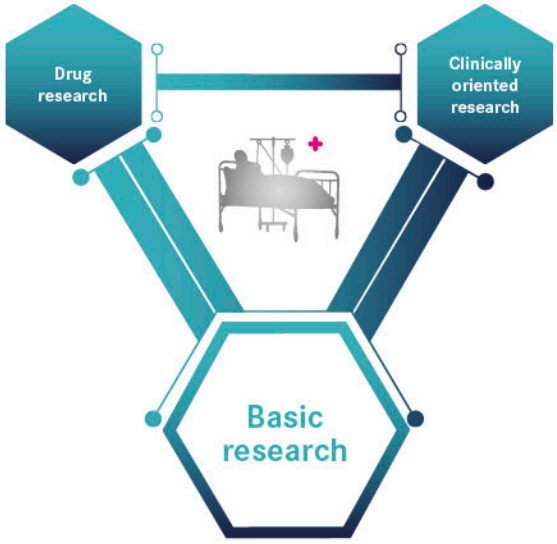


Fig. 7: Focus on the patient: the translational linking of basic, clinical and industrial research activities aims at resolving clinically relevant problems.

The aim of translational research is to help overcome the obstacles outlined above. The objective is to transfer the results obtained from biomedical fundamental research – in cooperation with hospitals and the pharmaceutical industry – as efficiently and systematically as possible to pre-clinical development so that they can then enter the clinical trial and approval phases. In addition, the direct communication between hospitals and research laboratories regarding the handling of clinically relevant issues is a key feature of modern translational research ("back translation").

This requires a structured, interdisciplinary approach in which experts from basic research, clinical medicine, industry and different disciplines work closely together. The establishment and development of productive and sustainable partnerships between the various parties involved – in the form of translation centres and product development partnerships, for example – is needed in order that new drugs can systematically travel the long path to the development of new medications and thus, in an ideal scenario, reduce development time.

A particular challenge facing publicly funded research institutions is the testing of product candidates in the pre-clinical evaluation stage: suitable financing and collaboration structures need to bridge the gap between fundamental research and clinical phase I. This applies in particular to critical steps such as pharmacokinetics and ADME studies[38] as well as GMP production[39] and regulatory safety pharmacology/toxicology, but also to aspects of medicinal chemistry (→ "Bridges/The transfer to application").

The HZI has recognised these challenges at an early stage and is developing concepts to effectively address them. The following pages outline the strategies that the HZI and its partners are pursuing in order to conduct and advance translational infection research.

In order to ensure the most effective translation of findings from biomedical basic research to application, sustainable collaboration structures need to be established between academia, clinics and industry – particularly for the purpose of developing innovative anti-infective therapies.

38 *ADME: Acronym for absorption, distribution, metabolisation and excretion, the key factors in pharmacokinetics.*

39 *See Good manufacturing practice (GMP) guidelines (vol. 4): http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm (accessed on 8 September 2015).*

1. HOW DOES TRANSLATIONAL INFECTION RESEARCH WORK?

The HZI defines itself as a centre of innovation-driven infection research with a strong focus on translation. Over the next ten years the centre will play a major role in tackling the current and future challenges posed by infectious diseases.

The centre's excellent scientific and strategic starting position, its research programme and its concepts for continuous advancement through expertise, infrastructure and partnerships (“Brains”, “Bricks” and “Bridges”) will be key factors in achieving this goal.

THE STARTING POINT

Scientists at the HZI and its partner institutions conduct research on infectious diseases at all resolution levels to gain an in-depth understanding of the underlying mechanisms, which are often highly complex. The primary objective – to develop innovative approaches for the prevention, diagnosis and treatment of infectious diseases – calls for collaboration between a variety of scientific disciplines and areas of expertise. This not only relates to science but also involves experts in research management and administration.

A comparable concentration of expertise, ranging from structural biology, through bacteriology and virology, to epidemiology and covering areas such as natural compound and pharmaceutical research, immunology, the development of predictive animal models and systems biological modelling is rarely found within one research centre and its immediate environment.

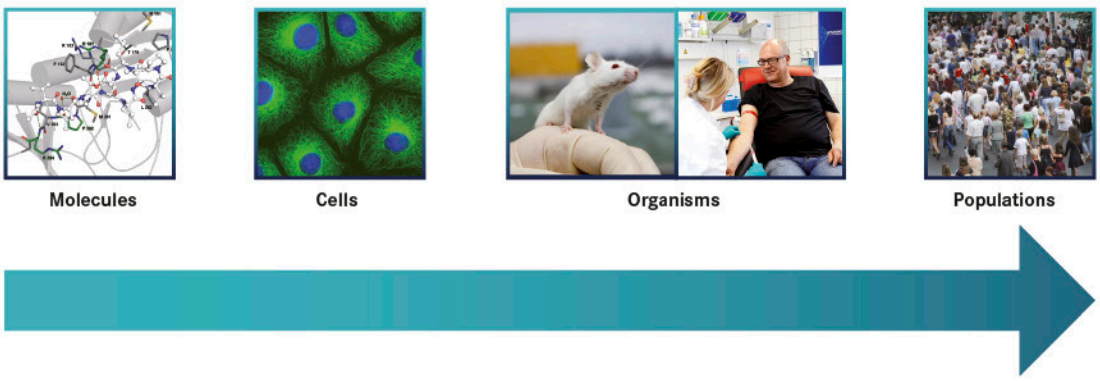


Fig. 8: From molecules to population groups: the HZI researches infections at all “resolution levels”. Molecular biology, structural biology, cell biology, animal models and clinically oriented research play key roles in this process; systems biologists and IT specialists model infection processes at all levels.

The HZI has consistently built on its strengths. Its combination of strengths provides the centre with several distinctive features and puts it at the forefront of translational infection research in Germany:

- **Excellent basic research and a high level of interdisciplinary cooperation:** The study of the basic mechanisms of pathogenicity and immune defence processes is just as much a part of the HZI's expertise as its many years of experience in researching new anti-infectives. Over the years, this has resulted in the establishment of particularly predictive infection models, the elucidation of infection mechanisms at high resolution, the decoding of basic principles of immunity and immune evasion strategies of pathogens, the characterisation of new target structures and the identification and advancement of novel immunomodulators and antibiotics.

- **Integrated approach:** At the HZI and its partner institutions, experts in life sciences, IT, pharmacy and medicine work together on infection-related issues. The portfolio of their research activities covers all levels of an integrated approach to basic, drug and clinical research. The researchers study molecules and their interactions, genomes, cells and organisms to gain a better understanding of the interactions between host and pathogens. They elucidate mechanisms of pathogen invasion and immune defence, model infection processes, devise clinically relevant research projects, contribute to (pre)clinical studies for product development projects and conduct research that includes specific patient and population cohorts. The expertise concentrated within the HZI and its network of partners creates synergies and provides scientists with unique opportunities to contribute to the fight against infectious diseases.

- **Internationally outstanding expertise in drug research:** The vast majority of antibiotics used in human medicine are derived from microbial natural products. Experts estimate that the stock of potential anti-infectives of this type is not yet exhausted, but that the discovery of new classes of drugs has become significantly more challenging from a technical perspective. Few other research institutions can match the HZI's many years of natural products research and the experience that it has gained. The centre now conducts drug research and pharmaceutical research at a top international level. Its aim is to discover and develop more natural compounds with anti-infective properties. The elucidation of biosynthetic pathways in the producers of natural compounds and their genetic basis helps to modify naturally occurring molecules using synthetic biology and to generate novel, deliberately modified basic chemical structures.

- **Strong partners in clinical research:** In terms of translation, scientists at the HZI have the opportunity of collaborating with excellent clinical partner institutions, especially Hannover Medical School (MHH). As one of Germany's leading university hospitals in the field of infection medicine, MHH commands particular expertise in numerous areas relevant to the HZI's research. Large patient cohorts in the area of regenerative medicine, including transplantation, provide the opportunity to acquire valuable information about patient groups that are particularly vulnerable to infection in daily clinical practice. In 2008, the HZI and MHH jointly founded TWINCORE in Hannover. Their aim was to consolidate translational infection research (→ "Bricks/Clinically oriented research"). In cooperation with the medical faculty at Otto-von-Guericke University (OVGU) in Magdeburg, infection-related inflammation processes and their role in neurological diseases are researched. In order to further strengthen clinical expertise at the centre, positions for clinician scientists were created in cooperation with the MHH and OVGU. Thus, physicians are given the opportunity to spend time conducting research at the centre. The recently established Clinical Advisory Board - as a consultative committee for the HZI - supports the centre in making decisions on issues of particular clinical relevance.

- **Member of the German Center for Infection Research (DZIF):** Established in 2012, the DZIF is a network of 35 research institutions based at seven locations throughout Germany. All member institutions have outstanding expertise in infection research. As one of six German Centres for Health Research (DZG), the DZIF was established with the objective of strengthening and strategically aligning translational infection research in Germany. In cooperation with industry, new procedures are to be developed to prevent, diagnose and treat infectious diseases which are nationally and internationally perceived as "Grand Challenges". As a Helmholtz Centre, the HZI plays a prominent role within the DZIF at the Hannover-Braunschweig site and beyond, both in administrative and research terms. Continuing into the future, the HZI recognises its responsibility to support this important national initiative in order to pursue and implement its objectives in the long term. The HZI already avails of many new and unique partnership opportunities within the DZIF.

- **Member of the Helmholtz Association:** Together with the other centres in the Helmholtz Association, the largest non-university research organisation in Germany, the HZI contributes to identifying and exploring major challenges to society, science and economy by conducting top-level research in strategic programmes. Like seven other centres, it is part of the research field "Health", which investigates the causes and progression of major common diseases in order to develop new strategies for their effective prevention and timely diagnosis as well as effective treatments. In this research field and beyond, Helmholtz centres deploy synergies in expertise and infrastructure to conduct comprehensive research projects and thereby best fulfil this mission. The programme "Infection Research" contributes to various interdisciplinary research fields, including drug research, structural and systems biology, metabolic dysfunction and synthetic biology. In virtual institutes and cross-programme networks such as the "iMed" initiative for individualised medicine, the centres work together in clinically relevant fields. These include long-term and jointly implemented major projects such as the largest prospectively designed health study in Germany, the National Cohort[40]. Close cooperation is in place with the Helmholtz Centre in Munich (HMGU) in drug research; together with the German Cancer Research Center (DKFZ) the HZI is studying the links between infections and cancer. The aim of a partnership with the German Centre for Neurodegenerative Diseases (DZNE) is to investigate the effect of infection and inflammation on neurodegenerative processes.

- **HZI as an attractive partner:** One of the HZI's particular strengths is its close cooperation with clinical and academic partners. In addition to the clinical partners previously mentioned – MHH and the medical faculty of OVGU – the HZI also maintains strong links with a number of other institutions, among them Technische Universität (TU) Braunschweig, Saarland University (UdS), University of Veterinary Medicine Hannover (TiHo), Leibniz Universität Hannover (LUH), Leibniz Institute German Collection of Microorganisms and Cell Cultures (DSMZ), and the Robert Koch Institute (RKI). This highly efficient network of partners, together with the continuity and structure of a publicly funded research centre, enables the HZI to pursue long-term and high-risk research approaches and to bridge the gaps in innovation. This knowledge-driven innovative capacity makes the HZI itself an attractive partner, not just in the specified academic environment, but also for pharmaceutical companies in order to initiate the development of new anti-infective medications in joint projects.

40 *Information on the study: http://www.nationale-kohorte.de*

The HZI's characteristic strengths include interdisciplinarity and integrated research approaches, outstanding expertise particularly in pathogen research, immunology and drug research, as well as its involvement in highly efficient partnerships and networks. This combination of unique strengths places the centre at the forefront of future translational infection research.

THE RESEARCH PROGRAMME

Together, scientists at the HZI and its partner institutions have developed the internationally competitive programme “Infection Research”. It specifies the direction for the further development of the centre and its main research areas (Fig. 9). The programme's objectives also meet requirements in health research that have been identified by the Federal Government and specified in funding policy documents[41].

In accordance with the strategic guidelines stipulated by the Federal Ministry of Education and Research for the research field “Health” in the Helmholtz Association, the programme places particular importance on translational approaches, concepts for individualised medicine and networking with other Helmholtz centres and university partners.

The programme is divided into three topics: “Bacterial and Viral Pathogens”, “Immune Response and Interventions” and “Anti-Infectives”. Across all three topics, the research activities concentrate on selected clinically relevant pathogens (focus pathogens), areas of research for which the HZI is particularly well set up. The focus is therefore on chronic viral infections, especially on hepatitis and herpes viruses; infections involving antibiotic-resistant bacterial pathogens such as *Pseudomonas aeruginosa, Klebsiella pneumoniae* and *Staphylococcus aureus*; gastrointestinal bacterial infections, for example with Enterobacteriaceae and *Clostridium difficile*; and respiratory viral infections, for example those involving influenza viruses. The bacterial co-infections that often occur in conjunction with respiratory viral infections also play a central role.

A number of criteria were crucial in the selection process: the clinical relevance of the underlying pathogens; available expertise at the HZI and its partner institutes (particularly MHH and the DZIF); scientific excellence; and an optimal position within the German infection research community.

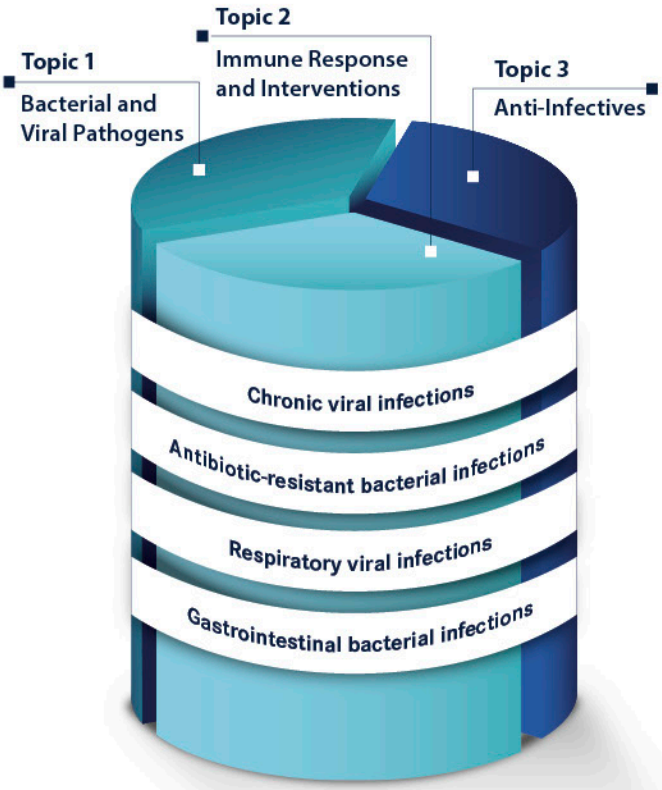


Fig. 9: Three topics and various cross-topic activities: The HZI research programme.

41 *1.) Federal Ministry of Education and Research (BMBF, 2010); Health Research Framework Programme of the Federal Government.*

2.) Federal Ministry of Health (BMG) / Federal Ministry of Food and Agriculture (BMEL) / Federal Ministry of Education and Research (BMBF) (2015), DART 2020 – Fighting antibiotic resistance for the good of both humans and animals.

3.) German Federal Government (2015), Leaders' Declaration, G7 Summit.

BACTERIAL FOCUS PATHOGENS

Pathogen	Widespread or clinically relevant resistance
Staphylococcus aureus	Methicillin (MRSA)
Klebsiella pneumoniae	Carbapenem (metallo-beta-lactamase-producing strains / MBL)
Pseudomonas aeruginosa	Constitutionally resistant to several penicillins and cephalosporins
Enterobacteriaceae	Extended-spectrum beta-lactamase-producing strains (ESBL), resistant to penicillins and cephalosporins
Clostridium difficile	Erythromycin, clindamycin and others

VIRAL FOCUS PATHOGENS

Pathogen	Particular challenge
Hepatitis viruses	Acute and chronic disease, chronic persistent hepatitis, trigger for secondary diseases
Herpes viruses (area of focus: cytomegalovirus, CMV)	Wide distribution, chronic persistence, trigger for secondary diseases, reactivation after immunosuppression
Pathogens causing respiratory infections (e.g. influenza viruses)	High pandemic potential, high variability, co-infections

The programme “Infection Research” sets out the present and future direction of research at the HZI. It covers the topics “Bacterial and Viral Pathogens”, “Immune Response and Interventions” and “Anti-Infectives”. Within the framework of these overarching areas, the HZI concentrates on researching and fighting selected pathogens that are clinically highly relevant.

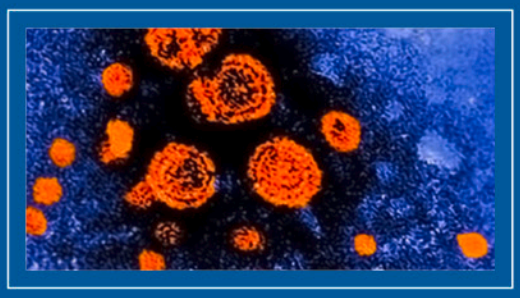
RESEARCH HIGHLIGHTS:
CURRENT SUCCESS STORIES AT THE HZI

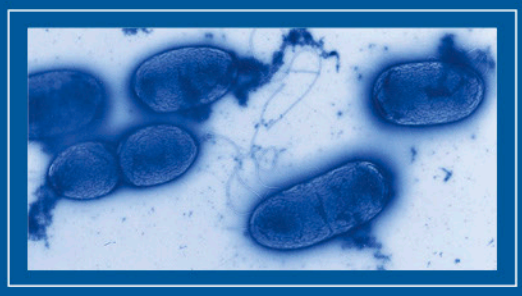
Scientists at the HZI and TWINCORE have gained many new insights into infections caused by the Hepatitis C virus (HCV). For example, their research on host specificity (species tropism) and how pathogens enter cells established a basis for developing new small animal models for HCV infections. This opens up the possibility of developing vaccinations to prevent infection.

Nandakumar et al., Gastroenterology (2013) 145: 6.
Frentzen et al., Hepatology (2014) 59: 1.

In the most extensive systematic analysis carried out on Hepatitis B viruses (HBV) to date, epidemiologists at the HZI showed how great the global disease burden caused by Hepatitis B actually is – and how different regions in the world are unequally affected by it. The disease has a prevalence of more than 20 percent in some parts of Africa. According to estimates, almost 250 million people worldwide suffer from HBV infections.

(Source of figure on the right: Erskine Palmer, CDC)
Schweitzer et al., The Lancet (2015) 386:1546-55.



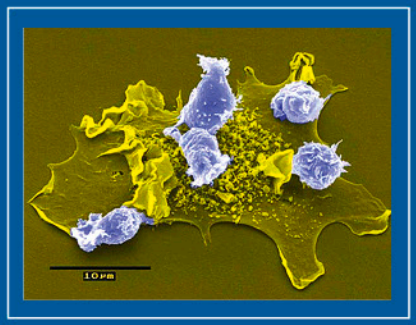


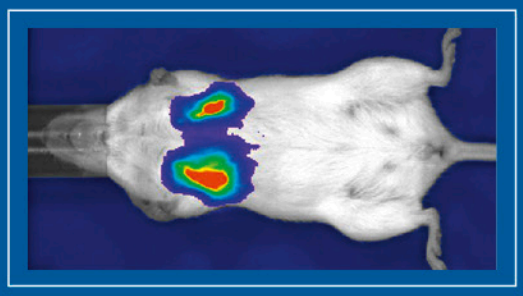
Researchers at HIPS and TWINCORE have elucidated which genetic factors and which regulation mechanisms facilitate the formation of biofilms by the pathogenic bacterium *Pseudomonas aeruginosa*. They were able to block biofilm formation by inhibiting the biochemical exchange of signals between the bacteria – a first step towards developing a specific anti-infective drug.

Lu et al., Angew Chem. (2014) 53: 1109.
Blanka et al., Sci Signal. (2015) 8: 372.

Regulatory T-cells (Tregs) are important modulators of the immune system. HZI and TWINCORE scientists discovered how their maturity and differentiation can be affected by drugs – knowledge that could help to systematically modulate immune responses to infections.

Milanez-Almeida et al., Eur J Immunol. (2015) 45: 153.
Khailaie et al., J Immunol. (2014) 193: 5983.
Huang et al., Eur J Immunol. (2014) 44: 460.
Berod et al., Nat Med. (2014) 20: 1327.



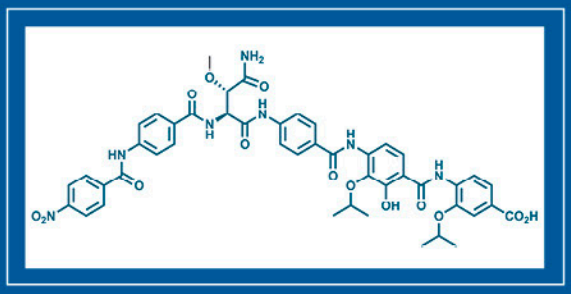


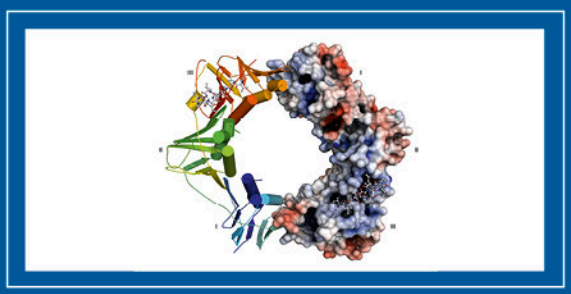
Virologists and immunologists at the HZI have contributed to the elucidation of the interplay between virus and host and studied the key role played by interferons. New target structures for anti-infectives have been revealed and vaccination strategies improved.

Nair et al., PLoS Pathog. (2014) 10: e1003999.
Dag et al., PLoS Pathog. (2014) 10: e1003962.
Rand et al., Nucleic Acids Res. (2014) 42: e109.
Anggakusuma et al., Hepatology (2015) 62: 702.

In order to contain epidemics, particularly in developing countries, finding alternative ways to administer vaccines would represent considerable progress. Scientists at the HZI and HIPS were able to show that it is possible, in a mouse model, to trigger significant immune responses by applying vaccines to the skin. To accomplish this, antigens are attached to nanoparticles and combined with adjuvants. In future, it is conceivable that vaccination could be as simple as putting on skin lotion.

Mittal et al., J Control Release. (2015) 206: 140.
Mittal et al., Nanomedicine (2015) 11(1): 147



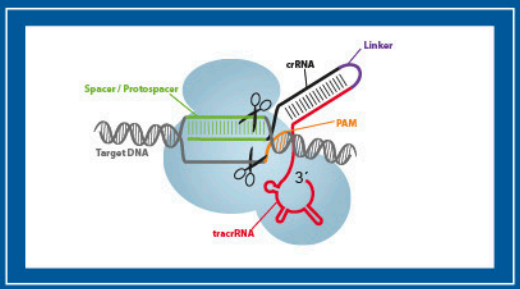


Drug researchers at HIPS and the HZI have discovered new antibiotic candidates, for example cystobactamides; these could be used to fight gram-negative pathogens which are particularly difficult to treat. Together with partners in the pharmaceutical industry, the researchers optimised the natural compound griselimycin which targets the tuberculosis pathogen. Using structural biological methods, they elucidated its mode of action.

Baumann, et al., Angew Chem. (2014) 53: 14605.
Kling et al. Science (2015) 348: 1106.

The CRISPR/Cas system, which bacteria use to defend themselves against viruses, was developed into a unique molecular tool for genome editing within a very short time. It has quickly gained worldwide acceptance. The pioneering discovery by an HZI scientist has been acknowledged with several prestigious science awards.

Doudna & Charpentier, Science (2014) 346: 6213.
Heckl & Charpentier, Mol Cell. (2015) 58: 560.



BBB

BRAINS, BRICKS, BRIDGES

Scientific expertise (“brains”), first-class infrastructure (“bricks”) and collaborations with excellent partners, together with the transfer to application (“bridges”), will continue to be the focus of the HZI's strategic development in the future. Successful translational infection research requires specific measures and initiatives in all three areas. To this end, the HZI has developed a number of long-term concepts.

B*rains: The best talents for infection research*

In addition to ensuring scientific excellence at an international level, the most important objective of staff development at the HZI is to increasingly create and consolidate skills for the scientific exchange between basic research, clinical practice and industry. In order to accomplish this, new cross-disciplinary approaches need to be explored.

In addition to the academic excellence of candidates, the strategic fit of their research is important in the appointment of new research staff. The HZI will strengthen its research foci through new appointments, while at the same time systematically developing new fields that are strategically relevant for the centre. A balanced mix of departments or working groups led by experienced scientists and junior research groups has proved successful at the centre. Junior research groups offer selected young scientists the opportunity to carry out research for a period of five to seven years. The young researchers have access to excellent facilities in a stimulating environment and thereby obtain the qualifications for careers both inside and outside the centre. Leading scientists at the HZI are generally professors or lecturers co-appointed with partner universities and are actively involved in teaching, joint training programmes and the acquisition of third party funding.

Close cooperation with clinicians is essential to address clinically relevant issues. Co-appointments of experienced and junior clinicians, the establishment of clinical expert panels and training programmes for scientists as well as physicians help to promote this exchange. To this end, the HZI and TWINCORE have cooperated with MHH and Magdeburg University Hospital to successfully develop a variety of measures: clinicians now have the opportunity to be released temporarily from their clinical duties in order to concentrate on infection research in the lab. The establishment of a Clinical Advisory Board as an integral part of the HZI's Scientific Advisory Board has greatly helped to focus the research programme on clinically relevant pathogens (focus pathogens). A Clinical Director will incorporate the increasingly important clinical aspects even more comprehensively into the centre's strategic mission. The inclusion of clinical themes in the curricula of the graduate schools will enable scientists to acquire a deeper understanding of clinically relevant issues.

The recruitment of scientific experts with many years of industry experience is vital, particularly for drug research. On the one hand, it helps to consolidate highly specific expertise in the academic environment and facilitates the progress of promising product candidates along the development pipeline; on the other hand, it contributes to the establishment of partnerships between the centre and the pharmaceutical industry through personal contacts and networks.

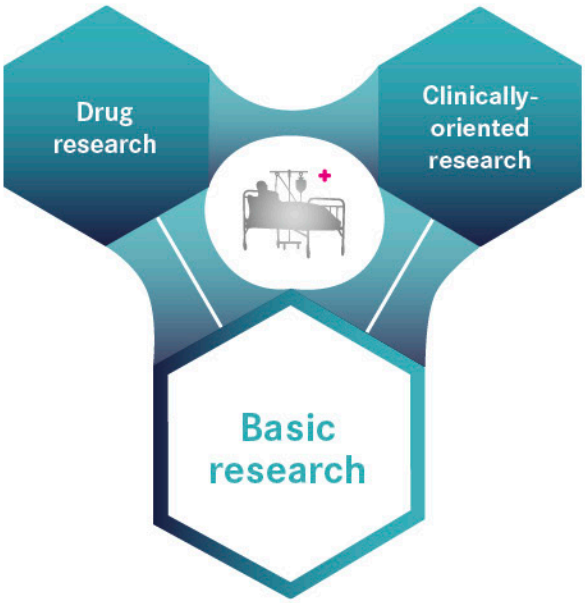


Fig. 10: An integrated approach: the centre's recruitment and HR development strategy pursues the objective of combining basic research, drug research and clinically-oriented research.

Moreover, to create a translational culture, suitable indicators of success must be defined and established. Thus, in research projects, in addition to publication and external funding statistics, patents and progress along the various stages of the development pipeline are incorporated as criteria of success.

Specific training and professional development programmes, as designed and structured by the Translation Alliance in Lower Saxony (TRAIN) in cooperation with the HZI, are used for staff development at the centre. Specific incentive systems and the availability of established scientists as role models are also expedient.

Finally, the translational objectives of the centre must be reflected in recruitment in the administrative area so that new opportunities can be availed of and, as a result, scientific research can be supported as effectively as possible.

To link basic research with the development of new approaches in prophylaxis, therapy and diagnosis of infectious diseases, the HZI invests in attracting the best talents and in training the next generation of translational infection researchers. In particular, the HZI is continuously developing new strategies to systematically attract expertise from clinical practice and industry to the centre.

Bricks: First-class research infrastructure

State-of-the-art technology, an internationally competitive infrastructure and its constant development are essential requirements for achieving outstanding results and for attracting highly qualified staff as well as excellent research partners to the centre. New infrastructure projects will complete the HZI's portfolio and facilitate the development of new and promising research fields.

a. Infection biology basic research

In order to be best equipped to face the challenges of an experimentally oriented infection research programme, the HZI has consistently expanded and, together with its partners, strategically enhanced its infrastructure. A range of systems (technical installations, large-scale facilities and instrumentation) which have already been established or will be available in the future facilitate close interaction between basic research, clinical practice and drug development.

Cutting-edge technologies: Infection research laboratories at the HZI.

- By expanding its laboratory space, modifying an entire laboratory building to meet the S2 safety standard, modernising genomic and proteomic facilities and imaging technologies on a variety of scales, the HZI has created the conditions for modern infection research at a high technical level.

- **S3 laboratories** facilitate research on highly pathogenic organisms, including airborne germs. Such high-security laboratories are also available in the HZI's animal facilities. These are among the most modern in Europe, accommodating several hundred breeding lines and enabling researchers to work with sophisticated mouse models and to study the interaction between pathogens and hosts.

- In the field of structural biology, the HZI is involved in establishing an important national research institution, the **Centre for Structural Systems Biology (CSSB)**, as a partner. The CSSB is currently under construction on the DESY campus in Hamburg. It will provide unique technologies for the high-resolution structural analysis of bio-macromolecules using powerful synchrotron radiation and innovative X-ray laser sources. Structural biologists will apply these technologies systematically to precisely resolve details of complex infection processes.

- In the **Braunschweig Integrated Centre for Systems Biology (BRICS)** (→ "Towards quantitative biology"), research groups from the HZI and TU Braunschweig work together on areas involving systems biology and systems medicine. The close cooperation between infection researchers, bioinformaticians and modelling experts allows meaningful integration and interpretation of complex biological data. The researchers at BRICS analyse infection processes using bioinformatic and biostatistical methods. The results will be incorporated into quantitative models to examine the dynamics of the origin and development of diseases. This will help in future to predict the course of diseases and optimise treatment strategies.

- A new Helmholtz Institute for RNA-based Infection Research (HIRI) is to be established in Würzburg. Currently at an early planning stage, this facility will be jointly established by the HZI and the University of Würzburg. Its purpose will be to study the role of non-coding RNA molecules in pathogens and in the host with regard to the origin, course and treatment of infections. HIRI would thereby open up completely new avenues for prevention and treatment of diseases (→ "Innovative fields in infection research").

b. Clinically oriented research

With its specific infrastructure for clinically oriented research, the HZI, together with its partners, is creating the conditions in which basic researchers and clinicians can devise and implement joint projects aimed at elucidating key processes in infectious diseases in humans.

- **TWINCORE** in Hannover: In the translational research centre founded jointly by the HZI and MHH in 2008, basic researchers work side by side with clinicians. This allows researchers to gain access to clinically relevant issues, and opens physicians the door to the latest analytical methods. Furthermore, the close proximity of TWINCORE and MHH means that joint studies involving patient information can be designed and conducted. Such studies can then provide information about mechanisms in infectious diseases that are relevant to humans. For example, researchers can examine why different people respond very differently to infections. The findings obtained will provide the basis for the establishment of an increasingly individualised infection medicine (→ "Individualised infection medicine").

Dedicated to translational research: The TWINCORE in Hannover.

- The **Clinical Research Centre (CRC)** in Hannover, established jointly with MHH and the Fraunhofer Institute for Toxicology and Experimental Medicine (ITEM), will in future enable early ("first-in-human") clinical studies to test new medications and therapeutic approaches. Epidemiologists at the HZI are also working on projects such as the long-term "National Cohort" population study. Thanks to the CRC, the HZI and other institutions in the region will be in a position to accelerate the translation of their own research projects. This will also help to foster industrial partnerships in order to expand translational infection research and optimise output over the next 10 years.

- **Clinics** in the HZI partner network: The infrastructure of hospitals collaborating with the HZI in investigating key areas can in some cases also be used by HZI scientists. Researchers thus gain access to patient information and medical expertise, particularly in relation to clinically relevant immunological issues and to the investigation of the previously mentioned focus pathogens. In addition to its most important partner, MHH, the HZI also cooperates with Magdeburg university hospital, the university hospitals in the DZIF and Braunschweig Medical Centre (Klinikum Braunschweig). In line with the HZI's strategic focus on translational infection research, these partnerships will increase in importance in the coming years.

c. Drug research

The technology and laboratory equipment used in the HZI's intensive drug research will be expanded further in the coming years. By 2018, the HZI and its partners will operate four state-of-the-art drug research centres in Braunschweig, Hannover and Saarbrücken. An expansion of the natural compound libraries and fermentation capacities will further enhance the capability of the institutes so that their unique expertise and interdisciplinary competence can be exploited even more effectively.

- The **Helmholtz Institute for Pharmaceutical Research Saarland (HIPS)** in Saarbrücken: HIPS was established in 2009 as a joint venture with Saarland University (UdS), renowned for its tradition of outstanding pharmaceutical research. In August 2015, the institute's new building was opened. Scientists at HIPS are working with groups at the HZI main campus in Braunschweig to find new anti-infective natural compounds, optimise them for pharmaceutical use and, using medicinal chemistry methods and the development of suitable formulations, optimise drug delivery to facilitate their entry in preclinical and clinical studies. Based on rational approaches, both natural products and synthetic molecules are identified and optimised in order to address target structures in infection research.

- **DRFG and BMWZ drug research centres in Lower Saxony:** A new Drug Research and Functional Genomics Centre (DRFG) will be established on the HZI campus in the coming years and will harness the latest technologies for drug research and chemical biology. Construction was scheduled to begin at the end of 2015. The centre will work in close cooperation with the Centre of Biomolecular Drug Research (BMWZ) on the campus of Leibniz University of Hannover (LUH), whose main expertise is in the chemical synthesis of complex natural compounds.

- A closer connection between drug research at the HZI and the new **Centre of Pharmaceutical Engineering** (Zentrum für Pharmaverfahrenstechnik, **PVZ**) at TU Braunschweig will expand the HZI's research spectrum to include process technology and engineering aspects in particular.

Through collaborations, the BMWZ (whose area of expertise is synthetic chemistry), the DRFG (which focuses on chemical biology), the PVZ (where process engineering is the area of interest) and HIPS (as a centre for pharmaceutical research) will combine all the competences needed for academic drug discovery and development.

Once construction of the DRFG is complete, the highly efficient clustering of synergy-based, closely integrated, state-of-the-art drug research institutions will be unique in Europe. The structure of this network will facilitate the enhanced development of innovative therapeutic interventions in the coming years (→ "Therapeutic interventions").

A home to pharmaceutical research: The new HIPS building in Saarbrücken was completed in 2015.

d. Towards quantitative biology

The synergetic use of large quantities of data from very different sources will fundamentally change the life sciences in the coming years. New technologies, increasing automation and miniaturisation will lead to the exponential growth of data ("big data"). In particular, the omics technologies[42] – genome, proteome and metabolome analytics – as well as image analysis, structural biology and epidemiology will contribute to this flood of data. The aim of collecting the relevant data is to capture and record biological systems as far as possible in their entirety. It is only by meaningfully linking the data that an overall picture emerges, revealing fundamentally new information. In medicine, this provides the opportunity to develop innovative therapeutic and diagnostic approaches that are not accessible using traditional methods. In particular, systems medicine, as it is known, will play a key role in the development of personalised medicine (→ "Individualised infection medicine").

Mathematical and bioinformatic modelling for infection research: The Braunschweig Integrated Centre for Systems Biology (BRICS).

The HZI is convinced that the systems biology and systems medical approach requires continuous investment in modern IT infrastructure, whose development should be fostered as a top priority in the coming years. Systems biology and systems medicine are highly interdisciplinary. It is only through close cooperation between infection researchers, bioinformaticians and modelling experts that meaningful integration and interpretation of complex biological data records is possible. For this reason, the HZI is significantly involved in the establishment of the **Braunschweig Integrated Centre for Systems Biology (BRICS)**, which TU Braunschweig is constructing on its campus. In this centre, scientists from TU and HZI will conduct research together under one roof, investigating systems biology and systems medical issues (→ "Bricks/Infection biology basic research").

The planned Centre for Individualised Infection Medicine (CIIM) in Hannover is also intended to harness the very latest technologies and approaches in bioinformatics to create the basis for personalised diagnoses and treatments (→ "Individualised infection medicine").

Through long-term, strategically designed structural measures, the HZI is establishing a chain of synergistically collaborating institutions that will enable the investigation of infections, immune defences and treatment options "from molecules to patients". Very few centres worldwide have the prerequisites needed to integrate the aforementioned areas in this way and thereby ensure academically driven innovation processes with an "added value" to fight infectious diseases.

42 *"Omics": Collective term for genomics, proteomics, metabolomics and related fields of study.*

Bridges: Closing the gap to application through strong collaborations

The HZI is continuously building a network of closely aligned strategic partnerships with universities, research institutions, hospitals and pharmaceutical companies. Its primary objective is to create synergies which establish the optimal conditions for an efficient transfer of knowledge from basic research to medical application.

a. Interconnected HZI: Academic partners at regional, national and international levels

Collaboration between scientists at an individual level has always been the basis for successful research at the HZI. Furthermore, the centre is also focused on strategically expanding its institutional partnerships at national and international levels.

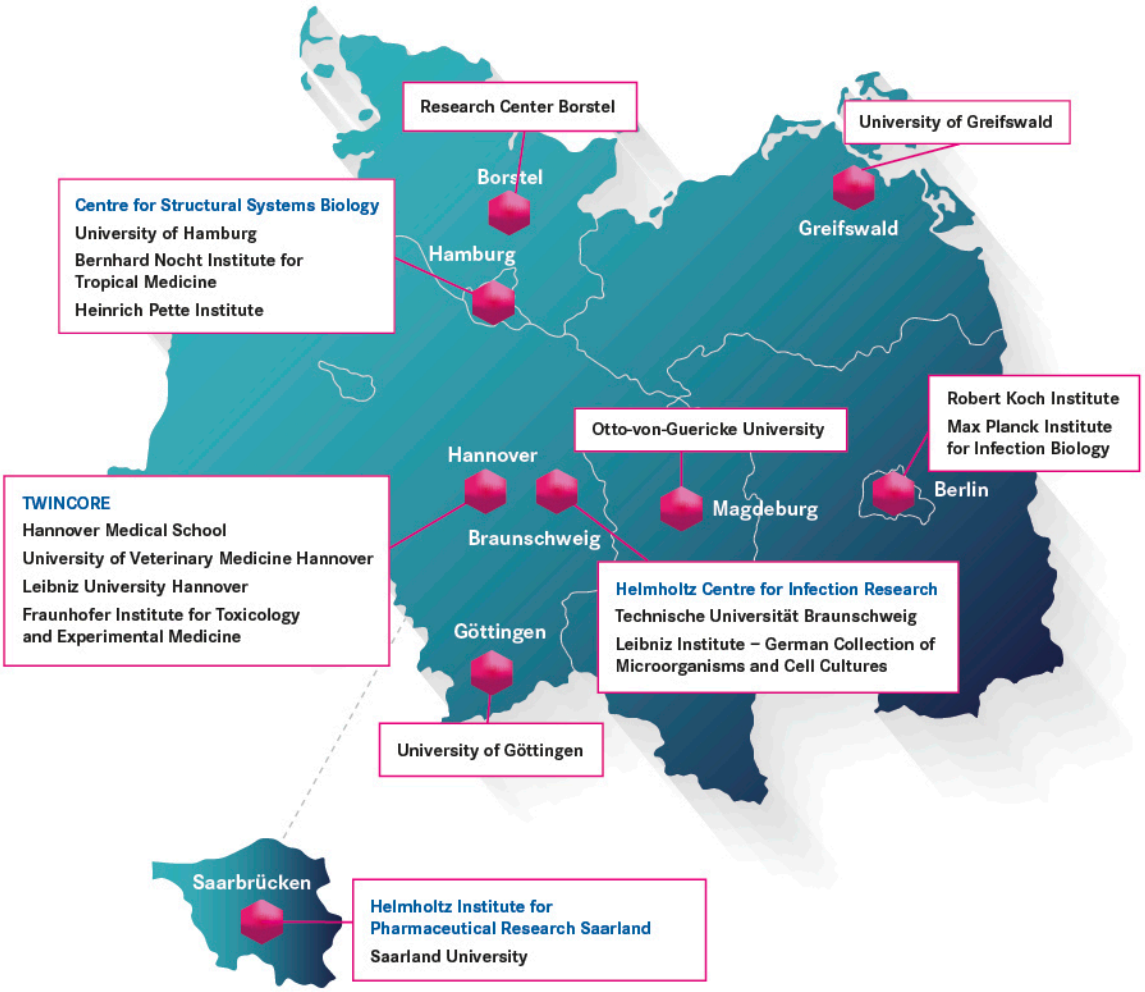


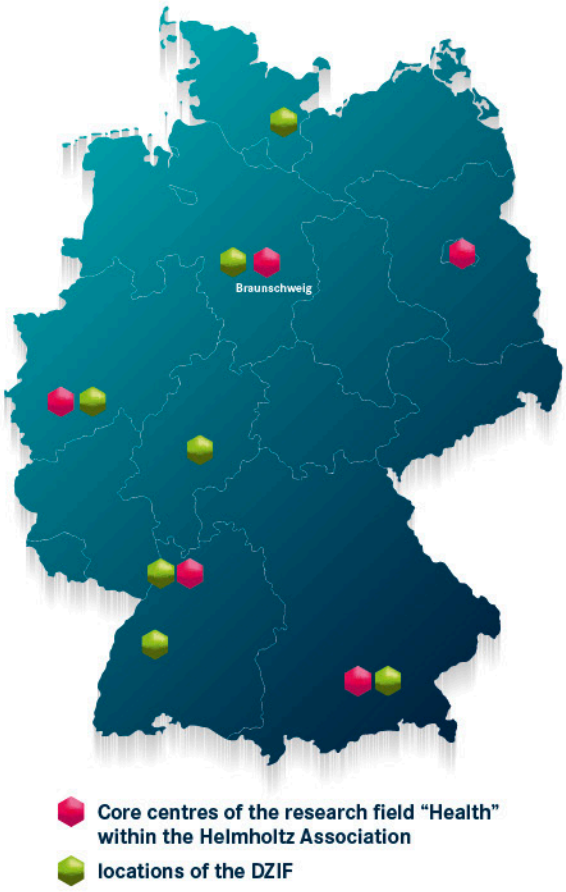
Fig. 11: Strong North German network: the HZI's regional partnerships.

The HZI will continue to make an important impact within the framework of **regional partnerships** and play a vital role in shaping the research landscape in northern Germany. The HZI provided the impetus for several pioneering projects that have already been implemented in accordance with the recommendations of the Academic Advisory Council of Lower Saxony (Wissenschaftliche Kommission Niedersachsen, WKN) to strengthen infection research in the region. The projects include the establishment of the Centre for Structural Systems Biology (CSSB) as part of a consortium of north German research institutions, and the North German Center of Microbial Genomics (NZMG), a network that shares the infrastructure and technology used to analyse bacterial genomes. Many of the institutions involved in these initiatives are also partners of the DZIF.

The HZI provides a forum for scientists, particularly those based in northern Germany, and hosts the North Regio Day on Infection, NoRDI, a regular symposium addressing current issues. Thanks to its expertise and commitment, the HZI contributes significantly to strengthening the region as a location for infection research.

The centre plays an important role as a driving force in the biomedical Translation Alliance in Lower Saxony (TRAIN), an initiative supported by the federal state of Lower Saxony. TRAIN pools the expertise and infrastructure of university and non-university research institutions for therapeutic developments. These interactions are to be expanded in order to structure the highly efficient infection research environment in northern Germany even more effectively and to optimise it for translation.

At a national level, the centre's specific infrastructure, focused approach and willingness to network place the HZI in an ideal position to take on an integrating role as organiser, driving force and technology leader in translational research. The HZI intends to play a key role in the national associations and networks involved in infection-related health research. The DZIF network provides direct access to the most distinguished partners in all areas of infection research. Over the coming years, within



National alliances: Partners of the HZI in the DZIF and the Helmholtz Association

the DZIF, the HZI sees itself in the role of an "intermediary" between academic research and the pharmaceutical industry.

Networking with other Helmholtz centres involved in health research is to be expanded, particularly with regard to researching the role of infections in the devel-

opment of non-communicable diseases. In the medium term, from the point of view of the HZI, Helmholtz alliances on important overarching issues such as "infection and inflammation as a cause of non-communicable diseases" could be established.

At an **international level**, the HZI focuses on three strategic criteria:

- *Networking*, especially within the *European infection research community*: Partnerships at this level enable the HZI to participate in projects supported by the EU and to initiate and drive internationally focused concepts for training and promoting young talents (examples: the Institut Pasteur in Paris, the Karolinska Institutet in Stockholm and the University of Umea (Sweden), with whom partnerships and research alliances have already been established).

- *Targeted synergies:* Selected partners with internationally recognised expertise in areas that complement the HZI portfolio are integrated systematically into cooperations (examples: hepatitis research with the University of Alberta in Edmonton, Canada; the search for new antimicrobial drugs under the umbrella of the Shandong University – Helmholtz Joint Institute of Biotechnology, SHIB).

- *Focal points:* With regard to globally significant infections, the HZI is cooperating closely with partners in selected regions to deal with issues concerning epidemics and is striving to contain and eliminate them (examples: East Asia as the point of origin for influenza pandemics; South Africa, where large numbers of cases of infectious diseases are encountered).

b. Transfer to application

Strategic partnerships with hospitals and the pharmaceutical industry are particularly important for meeting the challenges of transferring research results to pharmaceutical development and clinical practice.

Applied basic research

The development of new and disease-specific infection models at the HZI helps to better represent and predict the conditions in humans. Thus, more conclusive decisions can be made at an early stage of drug development. This can save considerable amounts of time and money during the research and development stages. This aspect of translational research can only be performed to a limited extent by industry and is therefore one of the key functions of academic research. With therapies frequently focused on the pathogen, infection models in rodents offer excellent translational prospects for the further pre-clinical and clinical development of novel anti-infectives.

Interaction with hospitals

Experts who possess both research experience and direct experience with patients play a key role in the interaction with university hospitals. To a large extent, this expertise still needs to be established: the aim of the clinician scientist programmes jointly organized by the HZI and its partners is to familiarise clinicians with the specific demands of basic research (→ "Brains"). Other initiatives undertaken by the HZI and the Translation Alliance in Lower Saxony (TRAIN) introduce basic researchers to clinically relevant issues in infection medicine.

Dynamic institutes with the appropriate focus, and in which the HZI is involved, serve as bridges between basic research and clinical practice and therefore as an experimental ground for clinically relevant research. This was the intention behind the creation of TWINCORE, whose scope and size will be expanded following the establishment of the planned CIIM (→ "Individualised infection medicine").

Academic alliances between research and clinical units such as the German Centres for Health Research (DZG), including the DZIF, play a pioneering role in the development of innovative, publicly funded collaboration structures to strengthen translational research.

Interaction with industry

To drive collaboration in the field, the HZI relies increasingly on partnerships with the pharmaceutical industry. Project-related interactions are continuously maintained with both large and small to medium-sized enterprises (SMEs) in the pharmaceutical industry and, where required, with contract research organisations (CROs). A "Screening Panel" composed of internal and external experts monitors the progress of drug development projects within the HZI and makes recommendations about their prioritisation and implementation, including the patentability of results and potential industry partnerships. The HZI is actively engaged in the transfer of technology and maintains a portfolio of intellectual property rights for drug candidates.

Pre-clinical development phases to evaluate product candidates must be successful in order to reach clinical phase I. The analysis of pharmacokinetics and pharmacodynamics (PK/PD) plays a key role; ADME studies, toxicology, safety pharmacology and, ultimately, the GMP production of clinical trial materials are crucial steps along the way. This is where the HZI contributes its highly efficient infection models, its infrastructure and its expertise in medicinal chemistry and pharmaceutical research to various collaboration arrangements. At the same time, it also relies on partners like the Fraunhofer ITEM, CROs and the pharmaceutical industry. The HZI has attracted project funding from the DZIF in competitive applications, which it uses for the pre-clinical development of innovative drug candidates.

In the long term, it is envisaged that strategic partnerships will facilitate the development of anti-infectives and diagnostic agents based on research findings, for example within the framework of public-private partnerships (PPPs) or product development partnerships (PDPs). Examples of such partnerships include the EU programme "New Drugs for Bad Bugs" (ND4BB[43]), which comprises a number of projects such as "European Gram-Negative Antibacterial Engine" (ENABLE), in which academic partners and pharmaceutical companies work on projects that have been selected through competition.

It is vitally important that the most suitable industry partners are identified for the respective research projects. Both parties can jointly decide in a second step which stages of product development – also in terms of adding value – will be handled by which partner in the project (→ "Therapeutic interventions").

From research to company start-ups

Successful start-ups initiated by HZI scientists prove the centre's experience in translational research. Examples of such start-ups include companies like BIOBASE, InSCREENeX and GlycoThera, as well as companies established in cooperation with HIPS, the Saarbrücken-based HZI institute: PharmBioTec, Pharmaelsus and Across Barriers. Another successful start-up initiated by the HZI using public funding is Vakzine Projekt Management GmbH (VPM). As a translational project management organisation, VPM identifies promising vaccination and drug development projects around the world. The company then develops these projects to the stage of clinical proof of concept. VPM has already facilitated the development of an innovative tuberculosis vaccine to phase IIb clinical studies. It is also working on an immunotherapeutic agent to fight bladder cancer (phase I/II) and on drugs to combat heart failure and various viral infections. In the meantime, VPM is economically self-financing.

Start-ups in the area of antimicrobial drugs are of particular strategic importance, as they open up additional options for the pre-clinical and early clinical development of innovative drug candidates. This is a key element of the compatibility of publicly funded research vis-a-vis industrial companies, which are acquiring licences later and later in the process in an effort to minimise their risk. Start-ups are also crucial for mobilising urgently needed risk capital.

43 *http://www.nd4bb.eu (accessed on 8 September 2015).*

Consequently, a key element of the future HZI strategy will be to give young scientists the opportunity to advance their own discoveries to the product stage as independently as possible. The DZIF has established a Translational Product Management Office (TPMO) on the HZI campus. Its role is to identify promising approaches in medical research and to realistically evaluate the chances of further development. Intellectual property (IP) management at the HZI is professionally supported by an IP asset management company with special expertise in life sciences. Its primary objective is to transfer the results of scientific research into practical application. Funding instruments offered by the Federal Ministry of Education and Research and the Helmholtz Association are also used.

Additional incentives are expected to further promote the establishment of start-ups in the coming years and make them more attractive. The HZI provides start-ups with lab and office space, regularly informs them about funding and financing opportunities, facilitates organisational support and protects scientists from the existential risks associated with company start-ups by offering them the option of returning to research.

The transfer of knowledge from basic research to medical application is the long-term objective of infection research. Its requirements are incorporated into each strategic decision made by the HZI. In addition to maintaining existing strategic partnerships with hospitals and industry and establishing new partnerships, these requirements include the systematic promotion of start-up companies.

2. TOWARDS THE INFECTION RESEARCH OF TOMORROW

INNOVATIONS, INTERVENTIONS, INDIVIDUALISATION

Based on its existing expertise and the success it has achieved, the HZI will continue to consistently develop and strategically complement its key areas in the upcoming years, primarily in order to further increase the translational "output" of its research. As milestones for its future development, the centre is developing cutting-edge fields with a special potential for researching and fighting infections. In particular, it will build capacity for an increasingly individualised infection medicine and explore new avenues when researching therapeutic interventions.

a. Innovative fields in infection research

As part of its mission, the HZI is constantly identifying and working on new areas of research from which crucial innovations and breakthroughs in infection medicine are to be expected. On the one hand, certain existing activities are being further enhanced; on the other hand, selected new fields are being developed in order to expand the portfolio of seminal expertise and to embrace promising topics at an early stage. One example of how existing projects are readjusted and realigned is the work performed on analysing gene expression in bacterial and animal cells: the results – combined with findings from systems biology – are used to design new genetic modules with the aim of decoding and harnessing cellular regulation networks (synthetic biology). In the case of bacteria, the HZI optimises biosynthetic pathways for natural products and utilizes them for the production of new antibiotics; in mammalian cells, synthetic interventions into existing networks create new cell and animal models.

Another example relates to microbiome studies, which are based on the analysis of genomes and transcriptomes from bacteria and hosts. It provides information on the status of the microbiome and its interaction with the immune system and the pathogens, and helps to understand the effect of this interaction on the development of infections. In the case of other topics for which the expertise at the HZI is not yet sufficiently established, new research groups are being set up by external recruitment.

In addition to researching innovative therapeutic interventions and the fundamentals of personalised infection medicine (→ following chapters), the centre has also identified other cutting-edge fields as options for its future development.

This includes, for example, the role of infections and inflammatory processes in the development of neurological disorders, which the HZI and Otto-von-Guericke University in Magdeburg will continue to analyse in detail.

Research on sensory and non-coding ribonucleic acids (RNAs) will form another area of focus at the HZI in the near future. Non-coding RNAs and other RNA-based control mechanisms critically affect the course of infectious

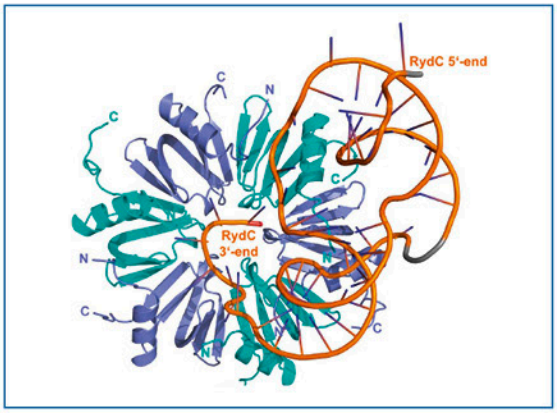


Figure 13: Untapped potential: RNAs (orange structure in the image above) are a versatile multifunctional class of biomolecules. Source: Dimastrogiovanni et al., eLife 2014;3:e05375. doi: 10.7554/eLife.05375.001.

diseases both on the host side and on the pathogen side. RNA-mediated processes play a crucial role in regulating and controlling virulence. An understanding of such processes will therefore contribute significantly to the development of new forms of treatment, diagnosis and prevention.[44, 45]

At the HZI, RNA research, e.g. the study of RNA-mediated genome editing and regulation processes, is increasing in importance.
This has been strengthened in a number of ways, including the appointment of the co-developer of the CRISPR/Cas9-based genome editing technology[46], which is derived from bacterial defence mechanisms against viruses and is now used worldwide.

In Germany, the Research Center for Infectious Diseases (ZINF) at Julius Maximilian University in Würzburg is internationally renowned for its research on RNA and infection, in particular with respect to the aforementioned fields of sensory and other non-coding RNAs.
The HZI is therefore planning to set up a new Helmholtz Institute in Würzburg dedicated to RNA-based infection research as a joint institution with this university. The establishment of such an institute would allow the development of this very new area of research in Germany and Europe as a prerequisite for the exploitation of the potential of RNAs for therapeutic purposes.
Thus, development of new RNA-based intervention strategies is one of the priorities. The planned institute will also work on new aspects of quantitative biology and exploit single cell-based RNA analyses for the whole field of infection research.

The centre will focus on promising areas of research, which can fundamentally advance infection research and can be systematically promoted and developed if required. One example of this is RNA-based infection research, which the HZI intends to significantly expand in collaboration with the University of Würzburg.

44 *Westermann et al., Nat Rev Microbiol. (2012) 10: 618.*

45 *L'Hernault et al., Curr Opin Virol. (2015) 15: 41.*

46 *Emmanuelle Charpentier headed the HZI department "Regulation in Infection Biology" from 2012 to 2015. Charpentier helped develop the CRISPR/Cas9-based genome editing method. Since October 2015, she has held the position of a director at the Max Planck Institute for Infection Biology in Berlin.*

b. Therapeutic interventions

Drug research is a main focus at the HZI. It establishes the basis for the discovery and development of innovative therapeutic interventions. The HZI does not restrict itself to just anti-infective compounds; in fact, work on new therapeutic interventions – including prophylactic measures – runs as a guiding principle throughout all areas of the research programme.

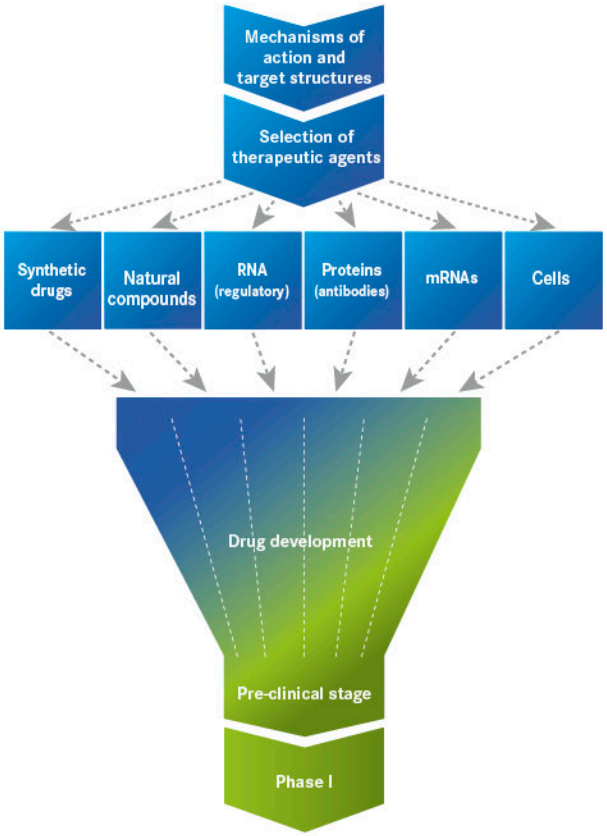


Fig. 14: Identifying and developing therapeutic agents: the point at which projects are "transferred" to industry partners depends to a high degree on the centre's expertise in researching the respective agents (blue: academia; green: industry partners).

Most "conventional" anti-infectives target the pathogen directly. A better understanding of the immune system, which combats most pathogens using its innate and adaptive mechanisms, opens up an alternative approach. It provides an increasing number of molecules, cells and signalling paths, which can serve as new targets for interventions. Elucidating the molecular and cellular mechanisms involved in the immune response is therefore as important as identifying the relevant target molecules on the pathogen side. In addition to traditional vaccines and adjuvants, the focus in future will also be on immunomodulators, which are promising substances for fighting infections.[47]

The identification and molecular analysis of new targets will show which types of potential drugs or interventions are best suited for prophylaxis or treatment. The HZI will continue to consolidate and strategically expand its portfolio of molecules and agents. In addition to low-molecular substances, particularly natural compounds, proteins (e.g. antibodies), RNA molecules, other nucleic acids and cells in the immune system are investigated to assess their therapeutic potential (Fig. 14).

Suitable drugs or agents can be found using a number of methods, e.g. by screening chemical libraries or through chemical or biological synthesis procedures. In terms of a "proof of concept platform", the HZI aims not only to identify these drugs and agents, but also where possible to transfer them to the pre-clinical and early clinical trial phases. The requirements differ and are specific to the various classes of agents that are studied: whereas the previously mentioned steps of ADME/toxicology, pharmacokinetics and pharmacodynamics play a key role for small molecules and natural products (→ "Bridges"/"Transfer to application"), the focus for biopharmaceutical therapeutic agents ("biologicals") may initially be on other criteria. In the case of antibodies, for example, it is their specificity and optimisation.

47 *One example is the immunomodulator Ipilimumab, which releases a "brake" on the body's own defence cells and is already used to treat malignant melanoma, see http://www.aerzteblatt.de/nachrichten/56024/Melanom-Langzeitueberleben-unter-Ipilimumab-moeglich.*

The HZI draws on many years of expertise in researching and developing natural products. This was a major factor in ensuring that epothilone, a natural compound discovered at the centre, could be developed as a commercially viable cancer treatment. This special expertise allows the HZI to actively drive the development of new anti-infectives from natural compounds to an advanced stage.

In any case, particularly with regard to the development of high-molecular substances (proteins, nucleic acids) or cellular agents, additional expertise, which cannot be provided by the centre alone, is needed.

Many of the research projects conducted at the centre are still at an early stage. In order to progress these projects in terms of translation, the HZI is currently developing internal validation procedures. These procedures are to be financed by the Helmholtz Innovation Fund and by funding from the Life Science-Stiftung (a foundation established by a number of German research centres) and should pave the way for public-private partnerships (PPP) or product development partnerships (PDP).

In addition to these models, participation in future-oriented Open Innovation networks (see Fig. 15), in which partners from industry and academia pool and share their expertise, will become increasingly important in the future.

In many cases, the HZI's cooperations with industry consist of project-driven development partnerships, some of which have already been initiated but not yet made public (→ “Bridges”/“Interaction with industry”). These partnerships can frequently be established in the early development stages and even during the research phase. Such cooperations can take a variety of forms. For example, the HZI may be in a position to provide certain pharmacologically relevant infection models, or the partnership may involve the joint research and optimisation of innovative drug or therapeutic classes. Industry licensing mostly relates to intellectual property rights that have been registered by the HZI for innovative or optimised therapeutic agents. Typical transfer points at which the industry partner acquires a licence and then takes on further development may be at the level of a pharmaceutical lead structure or after supplying the first clinical proof of concept.

In developing innovative models for industrial partnerships, the HZI will also take advantage of appropriate development programmes offered by the public sector. The Innovative Medicines Initiative (IMI), a research alliance between the European Commission and leading European companies in the pharmaceutical industry, initiates public-private partnerships. It thus opens up interesting options for infection research, which the HZI is already actively pursuing. Likewise, the Helmholtz Validation Fund can contribute to the development of innovative collaboration structures; a similar function is performed by the Federal Ministry of Education and Research's “VIP+” funding instrument, which facilitates cooperation with CROs by providing the relevant funding.

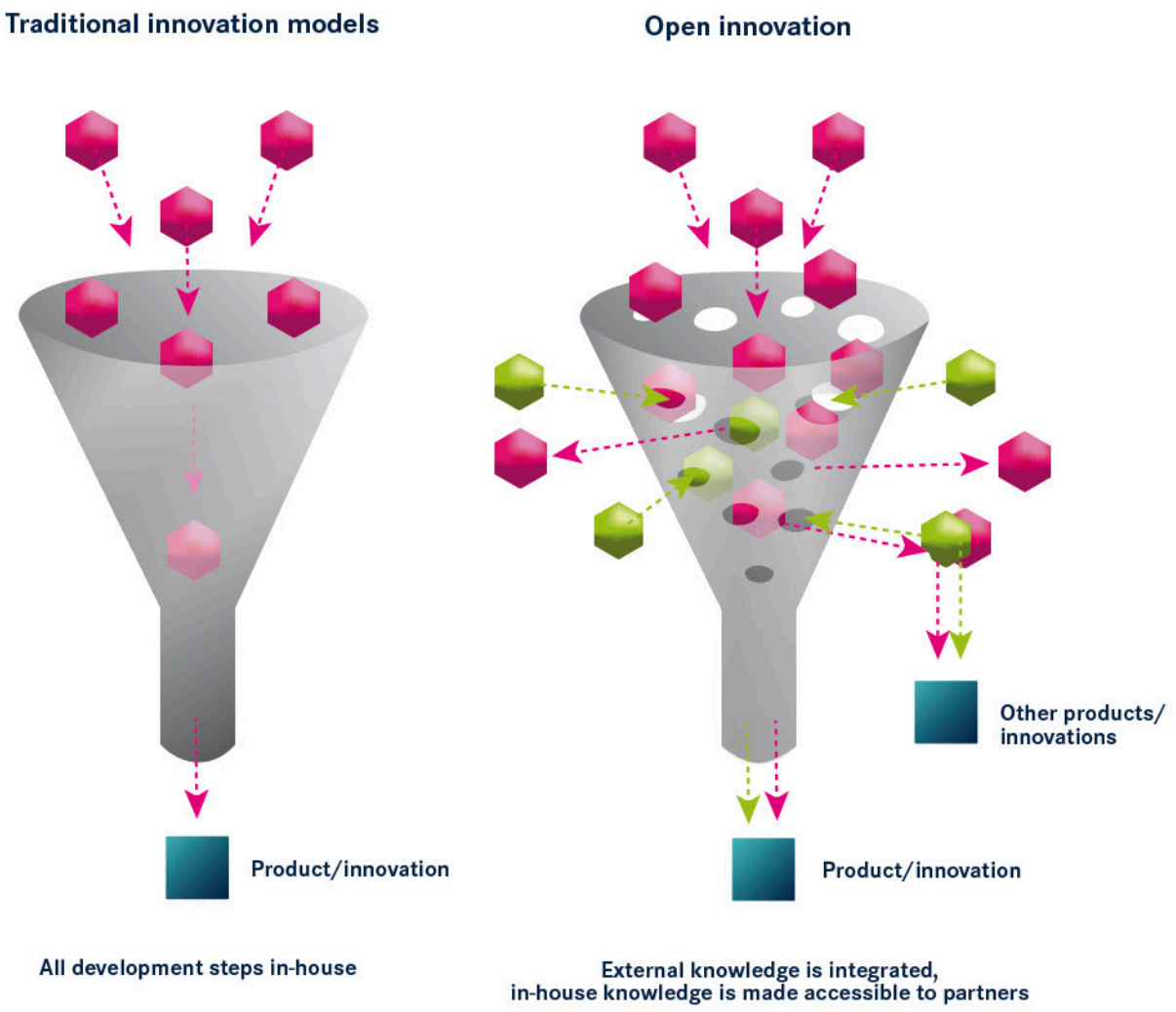


Fig. 15: Permeable structures: linking internal (red symbols) and external knowledge (green symbols) – along the lines of "Open Innovation" cooperation models – facilitates a beneficial exchange between partners when developing new technologies or procedures. Research institutions and companies can also be part of Open Innovation networks.

The HZI is continually expanding its portfolio of agents with therapeutic or prophylactic effects to fight infections. The target points addressed for interventions are not only molecules and signalling pathways of the pathogen but increasingly also host processes playing an important role in fighting or eliminating pathogens. To develop these therapeutic agents towards application, the HZI will systematically expand its infrastructure and expertise in cooperation with partners in industry and clinical practice to establish a research and development platform.

c. Individualised infection medicine

The aim of individualised medicine is to improve the quality and efficacy of treatments through systematic diagnostics, targeted prevention and tailored therapeutic procedures designed to meet the needs of individual patients or patient groups[48]. The most important basis for individualised medicine is the molecular analysis of patient samples, employing modern omics methods among others. Remarkable success has been achieved in cancer medicine in recent times by the stratification of patients and subsequent improved individualised treatments[49].

Individualised treatments have also been successfully used in infectious diseases for some time now. One of the earliest applications was the risk stratification of AIDS patients. A small number of affected individuals react to a component in the well-established combination therapy used to treat HIV with adverse, in some cases life-threatening, symptoms. Research results showed that this intolerance correlated with the presence of a certain gene variant. A routine gene test can now check in advance whether the patient is at risk[50].

Nevertheless, there is considerable but so far unexploited potential in the concepts of individualised medicine used for the diagnosis and treatment of infections.

On the part of the host – in addition to pre-existing conditions, age, lifestyle and physiological parameters – genetic and epigenetic dispositions in particular have a considerable influence on how dangerous a specific pathogen can be to the organism. This affects not only the individually variable susceptibility to the pathogen itself but also the varying risk, depending on the patient, of developing serious inflammatory reactions with the corresponding long-term effects. Bacterial flora (microbiota), which also differs in type, has a significant bearing on infection and defence processes[51], thus opening up another important area of research. In addition, patients respond very differently to anti-infective therapies. The individual risk of a drug being ineffective or having side effects, as outlined in the example of the treatment for HIV infections, also frequently varies.

Fig. 16: The most suitable therapy for each patient: Individualised medicine aims to categorise patients and define groups based on the most promising treatment for the respective individual ("stratification").

On the pathogen side, the pathogenic potential of most viral and bacterial species also shows a high degree of variability. In many cases, molecular variations – some of them still unknown – play a crucial role in the severity and course of the infection.

Therefore, new, improved diagnostic criteria have to be developed so that the effects of these differences on the course of an infection can be predicted. In addition to the patient's diagnostic "signatures" (biomarkers), the specific molecular traits of a pathogen can also provide important clues. In the case of infectious diseases, moreover, the highly dynamic course of the disease is a critical factor and must be taken into consideration when individualising therapeutic approaches.

The HZI's objective, together with MHH and other clinical institutions, is to develop individualised approaches in the area of infection medicine. In addition to increasing data-based biological and clinical research, infrastructure must be created to allow reliable therapy recommendations by correlating the clinical and molecular data of individual patients with infections.

The construction of the new Centre for Individualised Infection Medicine (CIIM) in Hannover, whose swift establishment is jointly planned by the HZI, TWINCORE and MHH, is supposed to play a key role here. The planned centre will give this still-nascent area of research an important boost. It is intended to be built in direct proximity to TWINCORE, the MHH and the CRC to facilitate cooperation between clinicians, scientists and bioinformaticians under one roof. Together they intend to focus on identifying, validating and integrating important parameters in the interaction between patient, pathogen and microbiome. This would help to identify new biomarkers and lay the groundwork for new diagnostic procedures and innovative, tailored therapy concepts.

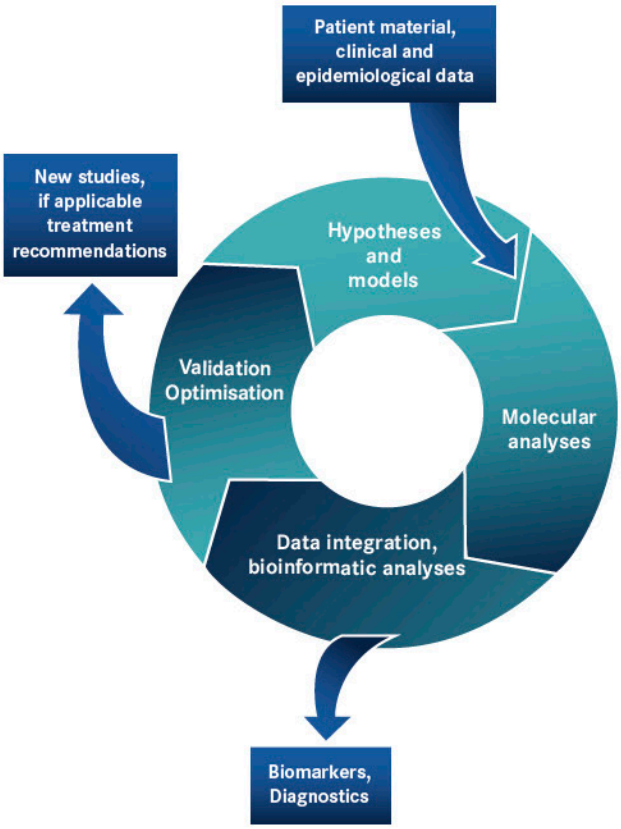


Fig. 17: Model for the future: the CIIM will integrate clinical and basic research findings and analysis methods to obtain new diagnostic agents and individualised treatment concepts.

48 *Definition adapted from: Nationale Akademie der Wissenschaften Leopoldina (2014): Individualised Medicine – Prerequisites and Consequences.*

49 *Perez et al., J Clin Oncol. (2014) 32: 3744; Institute for Quality and Efficiency in Health Care (2015), https://www.iqwig.de/en/press/press-releases/press-releases/afatinib-added-benefit-in-certain-mutations-confirmed.6817.html.*

50 *Mallal et al., N Engl J Med. (2008) 358: 568.*

51 *Willyard, Nature (2011), 479: S5 doi:10.1038/479S5a.*

The CIIM is supposed to be directly linked with the German National Cohort network (NaKo). The aim of this long-term prospective population study is to discover the causes of major common diseases, identify risk factors and improve the possibilities for early detection. The planned CIIM could contribute to and benefit from the comprehensive findings of this population study. The geographic and administrative proximity to the CRC in Hannover – the location of the HZI study centre, which coordinates the area of infectious diseases within the National Cohort – would offer the optimum conditions for fruitful interactions.

Further targeted studies on the epidemiology of infections and infection-associated diseases will be important in acquiring and systematically evaluating the relevant patient data. In interdisciplinary networks for individualised medicine, such as the Helmholtz initiative iMed, bridges are being built to other areas of research (cancer, neurodegenerative disorders, cardiovascular disease).

The merging of data, from a systems medical perspective, pertaining to a large number of patients can – once the models generated have been carefully validated – provide the basis for effective approaches to the personalisation of diagnosis and to treatment optimisation.

In addition to the research groups working on individualised infection medicine, the planned CIIM building will also accommodate the networks of excellence in infection medicine based at MHH, such as the Deutsche Leberstiftung (German liver foundation) and its hepatitis competence network (Hep-Net). The Hep-Net Study House is a DZIF study platform and has already generated exemplary therapy innovations in individualised infection medicine.

The long-term aim of the planned CIIM is to establish a precision medicine, which elucidates infection mechanisms at an individual level, and a “next-generation” systems medicine, which not only analyses data but also makes accurate predictions about complex infection processes and in this way contributes to the development of new therapy concepts.

In future, individualised procedures in the diagnosis and treatment of infectious diseases will become increasingly important. Together with its clinical partners, the HZI is ideally positioned to advance the field of individualised infection medicine. In the CIIM, which is currently at the planning stage, the groundwork will be laid for the precision medicine of the future.

OUTLOOK: NEW ANTI-INFECTIVES FROM THE HZI

By implementing the strategic concepts outlined in this roadmap, the HZI will have positioned itself by the year 2025 as an internationally prestigious infection research centre renowned for its innovative and excellent basic research and strong translational focus.

A sound understanding of the molecular and cellular mechanisms involved in infection will provide numerous new avenues for different applications. Novel antibiotics, vaccines, immunotherapeutic and RNA-based drugs, biomarkers and other diagnostic agents will emerge from the research conducted by the HZI and its partners. These will fill empty “development pipelines” and make them available for clinical application. Individualised approaches co-developed by the HZI and its partners will open up a new dimension in the treatment of infectious diseases. The research carried out by the HZI on the role of infection in the development of non-communicable diseases will provide information that can contribute to the elaboration of innovative concepts for the treatment and prevention of widespread major common diseases.

The work performed at the HZI will also benefit society in areas other than research results and therapeutic approaches. As a driving force in infection research and an intermediary between basic research, clinical and industrial application, the centre will help to advance Germany as a research location and ensure its innovativeness. New forms of collaboration will be developed with clinical and industry partners, and within the framework of these partnerships the centre will inject fresh momentum into the research on anti-infectives in particular. Together with its partners, the HZI will train the next generation of world-class infection researchers. Its translational research culture will provide a stimulus beyond its location and foster cross-disciplinary, creative collaboration structures.

The HZI's research strategy will thereby provide sustainable contributions at several levels to protect the population against infections, but also towards creating an interdisciplinary research culture in order to be better equipped for one of the greatest challenges facing society.

The ideas and expertise of many contributors both inside and outside the centre have been incorporated into the HZI 2025 roadmap. The HZI would like to thank everyone who provided content and/or suggestions for this document.

Figures

Photographs and architectural designs: TWINCORE (p. 1; p. 31);
HIPS (p. 1; p.32); hammeskrause architekten (p. 1);
thinkstock.com (p. 20; p. 27);
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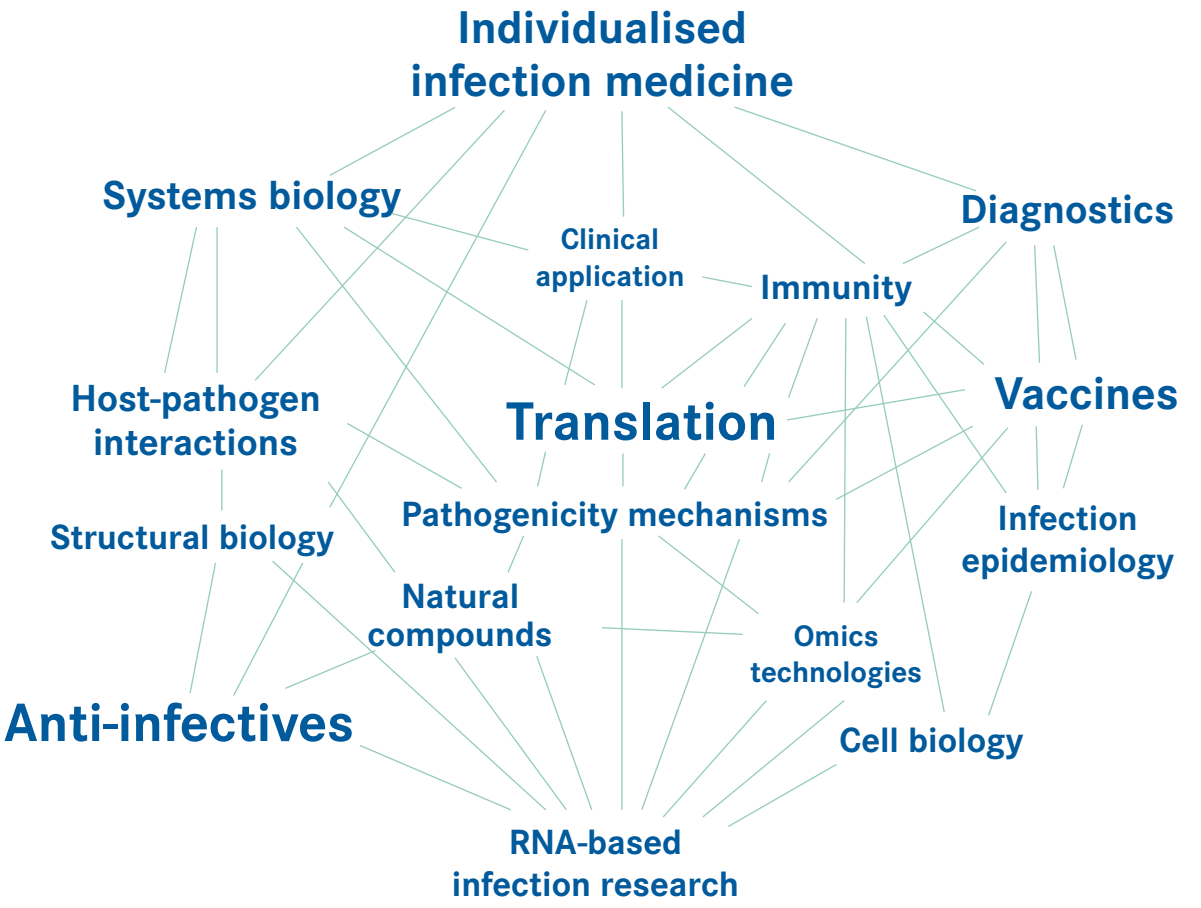
all others: HZI.

The diagrams were compiled by Jenko Sternberg Design GmbH, and in some cases were based on the data sources named in the legends.
RNA diagram on p. 40: Prof. Dr. Jörg Vogel, University of Würzburg.
Cloud image, inside cover, last page: ScienceRelations.


Individualised infection medicine
Systems biology
Diagnostics
Clinical application
Immunity
Host-pathogen interactions
Translation
Vaccines
Structural biology
Pathogenicity mechanisms
Infection epidemiology
Natural compounds
Omics technologies
Anti-infectives
Cell biology
RNA-based infection research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