THE RACE AGAINST GERMS
Understanding Infections – Fighting Pathogens

HZI HELMHOLTZ Centre for Infection Research
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“At the HZI, interdisciplinary teams are developing innovative, increasingly patient-specific approaches for rapid diagnostic procedures, novel vaccines and antibiotics. The HZI has developed into an internationally recognised institution for translational infection research.”

Prof Dirk Heinz, Scientific Director of the HZI

TINY PATHOGENS, GLOBAL DANGER

Research for Patients

You read it every day in the papers or see it on the news: The fight against infections is a race against pathogens. Many pathogens have lost their scare thanks to improved hygiene and effective medication. But bacteria and viruses often develop creative evasion strategies. In the poorest regions of the world, infections continue to be one of the most frequent causes of death, but they also remain a serious threat in industrialised nations.

The Helmholtz Centre for Infection Research (HZI) is Germany’s largest government research institution addressing the global challenges posed by infectious diseases. The results of fundamental research have to be transferred quickly and systematically into clinical applications which can come to the patient’s benefit. This also reduces substantial costs to society caused by infections. This brochure gives you an overview of our most important research approaches.
Many bacterial pathogens develop so-called “resistance” and, accordingly, become less sensitive to antibiotics. We travel more often with infectious agents in our luggage. New infectious and rapidly spreading pathogens, such as the Ebola virus, EHEC bacteria or the corona virus SARS-CoV-2, pose new dangers. Chronic and poverty-related infectious diseases cause serious problems. Infection research, therefore, is instrumental in developing the basis for new approaches to the prevention and therapy of infectious diseases.
THE FIGHT AGAINST SUPERBUGS

In the race against resistant bacteria
A small cut on the finger or dental surgery could suddenly become life-threatening – because more and more bacteria are becoming resistant to available antibiotics.

More than 30,000 people in Europe and more than 700,000 people worldwide die every year from multi-resistant pathogens, which most often spread in hospitals.
In contrast to traditional culture-based methods, the molecular analysis of a pathogen enables the rapid diagnosis of resistance properties and also reveals its relationship to other clinical isolates.

“It still takes two to three days to isolate and identify the pathogens from an infectious site and to determine its antimicrobial resistance profile as the basis for the initiation of a targeted antimicrobial therapy in the infected patients. At HZI, we are therefore developing more efficient molecular analytical methods for resistance profiling in the clinic.”

Prof Susanne Häußler,
Head of the Department “Molecular Bacteriology” at HZI
“The proportion of multi-resistant pathogens in hospitals is constantly on the rise, while at the same time the development of genuinely new antibiotics has dramatically declined. It is feared that by 2050 more deaths worldwide will be caused by antibiotic resistance than by cancer. We therefore urgently need new, effective drugs.”

Prof Mark Brönstrup,
Head of the Department “Chemical Biology” at HZI

LIFE-SAVING NEW ANTIBIOTICS

Bacteria develop resistance to antibiotics as a natural consequence of their capacity for rapid evolution. Because bacteria can exchange their resistance genes with each other, several “superbugs” have developed against which almost no available antibiotic is effective. These antibiotic resistances are one of the greatest threats to global health.* They lead to prolonged hospital stays and, thus, to rising treatment costs and increased mortality. There are several reasons for their spread: For example, antibiotics are prescribed too readily to treat the common cold where they are usually ineffective, and are taken too briefly or used indiscriminately in mass livestock farming.

Scientists from the HZI and its site in Saarbrücken, the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), together with scientists from the Saarland University are investigating the mechanisms underlying resistance formation, and developing methods both for the early detection of resistant pathogens and for new treatment concepts that specifically address resistance. They are also investigating natural substances as potential sources for new drugs.

*WHO – World Health Organization
Myxobacteria (showing *Chondromyces croatus*) produce an enormous variety of chemical substances, many of which exert biological effects.
Almost all antibiotics originate from natural products. They are often derived from bacteria and fungi which have to compete for habitat and nutrients against other microorganisms. These active compounds work so precisely and effectively because evolution has developed them over millions of years.

Organisms on land and in water still possess a vast reservoir of potentially active substances yet to be discovered. HZI scientists are striving to exploit these treasures. They are searching for substances which have the potential to combat pathogens, notably in soil and in marine bacteria, tropical fungi and soil samples from all over the world.

In order to cure infections and aid patients in hospitals in the future, however, these substances must first be optimised for clinical use: They should, for example, be able to reach their target destinations in the body by means of suitable “active substance taxis” and unfold their effect only there. Scientists at the HZI and HIPS in Saarbrücken are working on this challenge.

“About 80 percent of antibiotics are based on natural products. The challenge for the coming years is to make them usable in medicine. Currently, the development of new antibiotics is unattractive for large pharmaceutical companies. Non-university research institutions such as the HZI are left to fill this gap.”

Prof Rolf Müller,
Managing Director of the HIPS in Saarbrücken
STOWAWAYS

When herpes, hepatitis & co. become chronic

We still need effective vaccines against the widespread hepatitis C virus and most herpes viruses.
The hepatitis C virus is transmitted mainly via blood contact. It is carried by approximately 70 million people worldwide in the liver as a stowaway sometimes with grave, often fatal long-term damage such as cirrhosis of the liver and hepatic cancer.
“The treatment of chronic hepatitis C infections with antiviral agents works very well. However, the treatment does not protect against repeated infections. In addition, many people do not know that they are infected and continue to transmit the virus. For these reasons, we are looking for a universal vaccine to prevent the transmission of the virus in the future.”

Prof Thomas Pietschmann, Head of the HZI Department and the TWINCORE Institute “Experimental Virology”

HEPATITIS VIRUSES: HIDDEN KILLERS

More people worldwide die from viral hepatitis than from tuberculosis, AIDS or malaria. Five hepatitis viruses – A, B, C, D and E – are known to cause infections. In 2016 alone, 1.34 million deaths were caused by this liver-destroying disease. The insidious circumstance about hepatitis C is that those affected often don’t notice it for years, because the symptoms only become apparent after the liver has already been severely damaged.

A vaccine against hepatitis C infection, which affects 1.7 million people every year, is urgently needed.*

This cleverly adapted virus exclusively infects humans and chimpanzees. Therefore, it has been difficult to develop new vaccination strategies since the infection can only be investigated in cell cultures and therefore without an intact immune system present.

Scientists from the HZI and TWINCORE, which was established jointly with the Hannover Medical School (MHH), laid the foundations for new humanised mouse models for the infection. This will make it possible to develop urgently needed vaccines against the pathogen. In the long term, an effective vaccine could eradicate hepatitis C worldwide.

* WHO, RKI – Robert Koch Institute
Global Strategy

There is still no effective treatment for some forms of hepatitis, while others lack any vaccine. Many people in poorer countries rarely have any access to the expensive therapies or vaccinations currently available. The WHO has set itself the goal of testing 90 percent of people for hepatitis by 2030 and reducing deaths by 65 percent.

Virus attack under the magnifying glass

Our researchers are currently investigating in detail how the host cell is attacked by the virus and how special “cell entry inhibitors” make infections less likely.
Doctors have been using the basic principle of vaccination for centuries: They specifically expose the body to weakened or dead pathogens. Our awakened immune system then prevents a severe course of the disease in the event of any subsequent infection. The art of vaccine researchers is to find substances which prevent us from contracting diseases such as influenza, viral hepatitis or HIV/AIDS. But what should a vaccine have to do to protect us effectively? To this end and in order to develop new, better vaccination strategies, HZI scientists are investigating how the immune system reacts to new vaccine prototypes. Hitherto, there are no therapies or vaccinations available against many infectious diseases. People with a weakened immune system are particularly at risk. Researchers are currently learning from patients who defeat a disease naturally, i.e. whose immune system spontaneously produces a suitable reaction.

“Every autumn, a new flu vaccine is needed. Viruses are constantly changing their components to which our immune protection responds. At HZI, we are trying to create artificial antigens from stable parts of the flu virus. Our vision is to develop a universal influenza vaccine 2.0 based on the designer antigens.”

Prof Carlos A. Guzmán, Head of the HZI Department “Vaccinology and Applied Microbiology”
Safe and painless: Vaccinate with nasal spray
Researchers at the HZI and its HIPS site are looking for alternatives to vaccination by syringe, such as creams or sprays. Without the painful prick with the needle, vaccinations would be much better accepted.

Optimal vaccine booster
Following a standard vaccination against influenza, only a small proportion of people over 60 years of age develop sufficient protection. If the vaccine is administered with an oil-water emulsion or other adjuvants, its effectiveness is significantly improved. Accordingly, researchers at the HZI are striving to develop the optimal vaccine booster.
GOOD GERMS, BAD GERMS?

Understanding microbial languages better

Billions of microorganisms inhabit our body – notably the intestine – and thus contribute to our wellbeing, but also to disease. How exactly this happens remains a puzzle, but has emerged as a major research topic.
In patients with chronic inflammatory bowel diseases, such as Crohn’s disease or ulcerative colitis, the diversity of intestinal microbes is reduced. As a result, the immune system reacts excessively to germs. Inflammatory intestinal diseases, for which therapies are still lacking, are thus aggravated.
In order to better understand how we humans interact with our microbial colonisers, we need model systems that allow for experimental changes – both in the host and in the microbes.”

Prof Till Strowig, Head of the HZI Department “Microbial Immune Regulation”

COLON MICROBES - LITTLE HELPERS AGAINST INFECTIONS

The microbial community – often referred to as the microbiome or microbiota – that lives in or on a host, such as humans or animals, is a very diverse community. It inhabits many parts of the body, for example the skin and the intestine. The composition of the human microbiome is very variable and influenced by the organism and nutrition, but also by drugs and diseases. Current research findings indicate that many diseases are associated with changes in the balance of the microbiota. If, for example, the bacterial flora in the intestine is decimated, this disturbs the protective effect of benign intestinal bacteria against invading pathogens. HZI scientists are investigating how these microbial communities impact infectious diseases and are investigating new ways to exploit their findings therapeutically.
Diseases associated with an imbalance in the microbiota are connected to:

- asthma/allergies, excessive immune responses
- biliary disorders and liver function
- changes in the metabolism of medicines
- autism, depression, anxiety disorders
- cardiovascular diseases, hypertension
- obesity
- bowel cancer, inflammatory bowel diseases

Probiotic Bacteria against Salmonella

HZI scientists have discovered that the pathogen *Salmonella enterica*, which causes approximately 155,000 deaths worldwide can be slowed by other intestinal microorganisms – so-called probiotic bacteria – thus mitigating the infection. The studies provide valuable information on how people could better protect themselves against dangerous pathogens in future.
Good germs – bad germs

Life-threatening hospital germs on the march

The bacterium Clostridium difficile can occur naturally in peaceful coexistence with other microorganisms in the human intestine. However, if the intestinal microbiota is disturbed, for example by antibiotics, it can cause severe diarrhoea. The pathogen itself can develop resistance to antibiotics and is therefore difficult to treat.

In focus: Immune cells in the fight against Clostridia

HZI scientists are currently investigating the metabolism of human immune cells in the intestine: All metabolic products and any changes thereof are examined in detail during Clostridial infections. The aim is to find out whether the immune cells in the intestine switch to another metabolism when they detect pathogens. Do they produce substances that kill bacteria? And what do the bacteria do to undermine the immune system? The answers to these questions will help us to better understand the immune system – and perhaps control it more specifically in future.
Tens of thousands of molecules are constantly being modified in living cells – split, linked, rebuilt and reassembled. Researchers call the totality of all these metabolic products the metabolome. With sophisticated technologies such as mass spectrometry, isotope labelling and computer algorithms, researchers at the HZI and BRICS have been driving the development of individual molecules – such as nutrients or cellular building blocks. The result is a unique fingerprint for every type of cell or tissue. The metabolic processes can even reveal what happens in the body during an infection.

“We’re interested in the language in which bacteria and immune cells communicate. Its elucidation should allow us to control this interplay.”

Prof Karsten Hiller, Head of the Research Group “Immunometabolism” at the Braunschweig Integrated Centre of Systems Biology (BRICS)
“Single cell analysis is interesting for many applications in biomedicine. For example, infected and healthy cells can be analysed separately and with unprecedented accuracy. This will enable us in future to perform highly precise interventions regarding the interaction of pathogen and host.”

Prof Jörg Vogel, Director of the Helmholtz Institute for RNA-based Infection Research (HIRI)

EACH INFECTED CELL BEHAVES DIFFERENTLY

The microscope of the future – single cell analysis

So-called single cell analysis brings light into the darkness and was accounted the most important advance of the year 2018 by the journal Science. For the first time, it is now possible to make gene expression visible, the intracellular path from genes to gene products such as proteins. Researchers at the Helmholtz Institute for RNA-based Infection Research (HIRI) and the University of Würzburg have further developed the method in order to investigate the interaction between pathogens and humans in unprecedented detail. They are focusing in particular on RNA molecules. This provides unprecedented insights into the complex regulatory processes involved in an infection.

Many pathogens can remain hidden in their hosts throughout their lives and cause infections again and again. Salmonella, which are food-borne pathogens, have a particularly clever strategy: They infect the immune cells that are supposed to fight them. In these ecological niches, they are protected from the host’s defense and can hide from antibiotics. Single cell analysis enables researchers to better understand the different sites of infection. The aim is to identify disease characteristics in individual cells as early as possible in order to counteract them promptly with treatments tailored to individual patients.
What does a Salmonella infection do with an immune cell?
Single cell analysis shows a map of the active genes in a non-infected immune cell (left) in contrast to an infected immune cell (right). Different genes are active in both cells, as shown by the color change of the lines from orange to blue (top, not infected) and from blue to orange (bottom, infected). Each line represents a single gene.

How do bacteria manage to protect themselves from immune cells? How pathogens affect our immune system and spread despite its control remains poorly understood. HZI researchers are unveiling the secrets of individual cells – and entire tissues – using a groundbreaking new method.
INFECTIONS KNOW NO BORDERS

*Mobile Health* speeds the fight against epidemics
Increasing global mobility facilitates the spread of pathogens, too.

To better follow epidemics, innovative digital solutions that also include eHealth approaches for patients are necessary. Modern information technologies are opening up new ways of dealing with the massive amount of data in infection research. This enables infections to be identified more quickly and precisely leading to improved pandemic preparedness.
Infections know no borders
An outstanding example of a digital tool developed by HZI epidemiologists is SORMAS – the Surveillance Outbreak Response Management and Analysis System. Used as a fast-response epidemic management system, it can monitor the spread of dangerous pathogens in affected regions like countries in Africa in real time and thus prevent possible pandemics.

In Nigeria in 2018, SORMAS has already made a successful contribution to containing simultaneous epidemics of Lassa fever and monkey pox. The system can be extended to include many other diseases, such as measles and cholera, or emerging diseases like COVID-19. Several health authorities worldwide are planning to use SORMAS in future.

“To protect against epidemics, measures and information regarding infected persons and their contacts must be effectively coordinated. SORMAS works even in remote locations without mobile network. As soon as a network connection is established, the data are synchronised centrally. This means that the protection measures can be implemented without delay.”

Prof Gérard Krause, Head of the HZI Department “Epidemiology”
The course in which an infection will develop is difficult to determine on the basis of isolated measurements alone. Systems biologists therefore design mathematical models that can predict dynamic processes in the human body.

Resistance profiles of bacteria at the touch of a button

The bacterial pathogen *Pseudomonas aeruginosa* can cause severe acute infections and is characterised by a particularly high resistance to a variety of antibiotics. Detailed data collected by HZI researchers on this pathogen are fed into an automatic database. The aim is to make accurate predictions for antibiotic resistance of *Pseudomonas* in the future and thus to be able to choose a suitable therapy for patients.
Is it possible to predict the next flu epidemic? Computer-assisted analyses no longer remain a mere vision for more reliable statements about the influenza pathogen of the coming season: Researchers at HZI can already stratify the potential risk of certain influenza viruses at an early stage by observing and evaluating genetic changes in the pathogens.

Thanks to state-of-the-art mainframe computers and big data from laboratory experiments and clinical cohort studies, mathematical models and computer analyses are becoming increasingly important in infection research. At the Braunschweig Integrated Centre of Systems Biology (BRICS), scientists from HZI and the Technische Universität Braunschweig are exploring the approach of machine learning for the characterisation of infection processes. For example, they use their computers to analyse processes of our body’s immune defense. In close cooperation with partners, hypotheses are tested in the laboratory and will in future support medical diagnostics and treatment of infections.

“Through computer-aided analysis of large biological and epidemiological data sets, we construct hypotheses about the development of a disease, an effective immune response or the development of antibiotic resistance.”

Prof Alice McHardy, Head of the Department “Bioinformatics of Infection Research” at HZI and BRICS
TAYLOR-MADE MEDICINES

Man, woman, child, risk patient?
People react differently to therapies. For example, gastrointestinal diseases or lung infections can be much more severe in immunocompromised people. If researchers could identify high-risk patients in time, more effective therapies would be possible at an earlier stage.
INDIVIDUALISED THERAPIES AGAINST BACTERIA AND VIRUSES

Each person is unique with distinguishing characteristics which can also influence the course of infections. In recent years, it has become increasingly clear that the success of a treatment depends to a large extent on the molecular profile of a patient, i.e. on the molecular or cellular makeup of the patient. Individualised infection medicine, also known as personalised or precision medicine, seeks to apply this knowledge for the benefit of patients and derive the most effective treatment and with as few side effects as possible by making use of specific biomarkers.

Treating infections individually

Optimally, by analysing large amounts of data from patient groups, researchers will know even before treatment which therapy will prove unsuccessful or whether an antibiotic or vaccine is effective. At the newly founded Centre for Individualised Infection Medicine (CiiM) in Hannover, HZI scientists and MHH physicians will advance strategies for personalised medicine.

Artificial intelligence simulates hepatitis B therapy

Bioinformaticians from the BRICS and clinicians at the CiiM combine their expertise. Recently, using special software based on machine learning, they were able to identify a set of signalling substances that can be used to predict with 90 per cent certainty the consequence of terminating hepatitis B therapy.
“We are searching for biomarkers – characteristic properties or molecules – which we can use to stratify patients into different groups and thus make the most appropriate therapy decisions for each individual group in the future.”

Prof Yang Li, Head of the Department “Computational Biology for Individualised Medicine”, and Prof Markus Cornberg, Clinical Director of the HZI, are the dual leaders of the Centre for Individualised Infection Medicine (CiiM).

**Individualised medicine**

The susceptibility of the patient to infections and the severity of the disease course are determined by individual patient characteristics and the types of colonising microorganisms (microbiomes).

Pathogens can, for example, develop resistances that must be taken into account when choosing a therapy.

**Efficacy of drugs in each patient**

Differing efficacies of drugs and therapies depend on individual patient parameters and the pathogen causing the disease.
BRAUNSCHWEIG
Helmholtz Centre for Infection Research
www.helmholtz-hzi.de/en
Braunschweig Integrated Centre of Systems Biology
www.tu-braunschweig.de/en/brics

HANNOVER
TWINCORE – Centre for Experimental and Clinical Infection Research
www.twincore.de/en
CiiM – Centre for Individualised Infection Medicine
www.ciim-hannover.de
Study Centre Hannover
www.helmholtz-hzi.de/study-centre-hannover

SAARBRÜCKEN
Helmholtz Institute for Pharmaceutical Research Saarland
www.helmholtz-hips.de/en

WÜRZBURG
Helmholtz Institute for RNA-based Infection Research
www.helmholtz-hiri.de
ONE CENTRE - FIVE SITES

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NUMBERS & FACTS
Helmholtz Centre for Infection Research (HZI), 2019

840 Employees  200 Visiting scientists  50 Nationalities

65 MIO EUR core budget  15.5 MIO EUR third party funding

464 Publications  64 Patent families
The more than 800 employees at the Helmholtz Centre for Infection Research (HZI) use their expertise to bring closer a healthier society. Scientists at the HZI in Braunschweig and its other sites in Germany are investigating bacterial and viral infections as well as the body’s defense mechanisms. Their profound knowledge of natural substance research comprises an invaluable resource for driving forward development of novel anti-infectives. As a member of both the Helmholtz Association, Germany’s largest non-university research organisation, and the German Center for Infection Research (DZIF), the HZI conducts translational research to lay the foundation for new therapies and vaccines against infectious diseases. Together with clinical and industrial partners, the results of basic research are promptly and systematically transferred to application at the patient’s bedside.
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