

THE RACE AGAINST GERMS

Understanding Infections – Fighting Pathogens



TINY PATHOGENS, GLOBAL DANGER



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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.

→ www.helmholtz-hzi.de/en









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.





"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

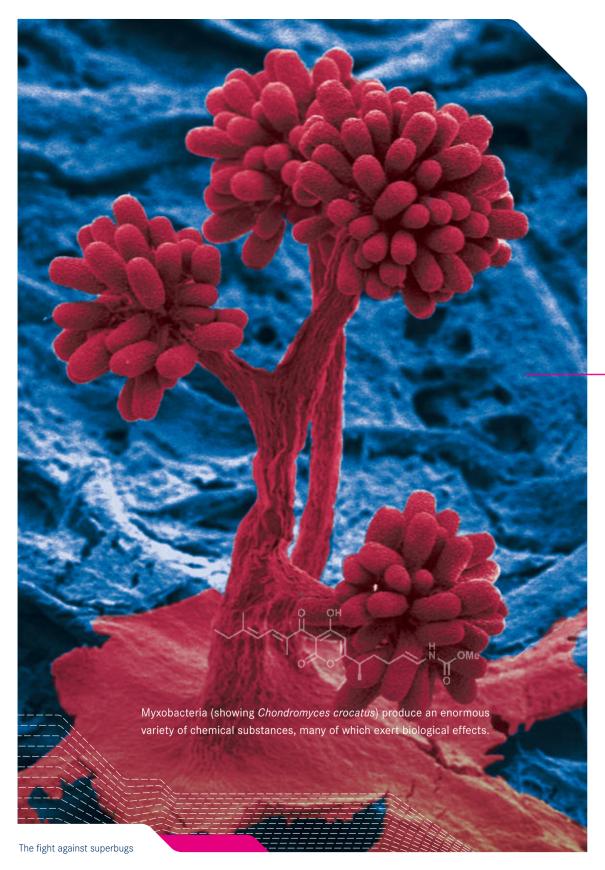
LIFE-SAVING NEW ANTIBIOTICS

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







"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

HEALING TREASURES FROM NATURE

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.



When herpes, hepatitis & co. become chronic







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

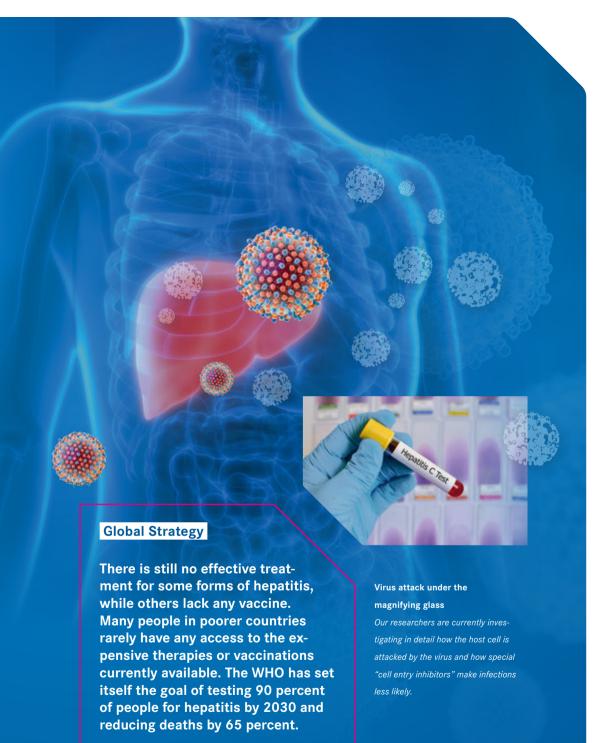
More people worldwide die from viral hepatitis than from tuberculosis, AIDS or malaria. Five hepatitis viruses – A, B, C, D and E – are known to cause infections. In 2016 alone, 1.34 million deaths were caused by this liver-destroying disease. The insidious circumstance about hepatitis C is that those 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



"Every a

"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"

VACCINES OF THE FUTURE

Tailor-made, efficient and universal

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.









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.







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.







HZI researchers cultivate and decipher the intestinal bacteria of mice, for example.

"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

autism, depression, anxiety disorders

cardiovascular diseases, hypertension

biliary disorders and liver function

changes in the metabolism of medicines obesity

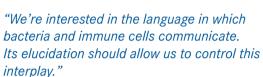
bowel cancer, inflammatory bowel diseases

Probiotic Bacteria against Salmonella

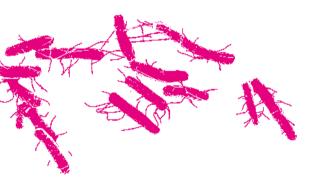
HZI scientists have discovered that the pathogen Salmonella enterica, which causes approximately 155,000 deaths worldwide can be slowed by other intestinal microorganisms – so-called probiotic bacteria – thus mitigating the infection. The studies provide valuable information on how people could better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







Prof Karsten Hiller, Head of the Research Group "Immunometabolism" at the Braunschweig Integrated Centre of Systems Biology (BRICS)





METABOLIC GAMES IN INFECTIONS

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.



"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."

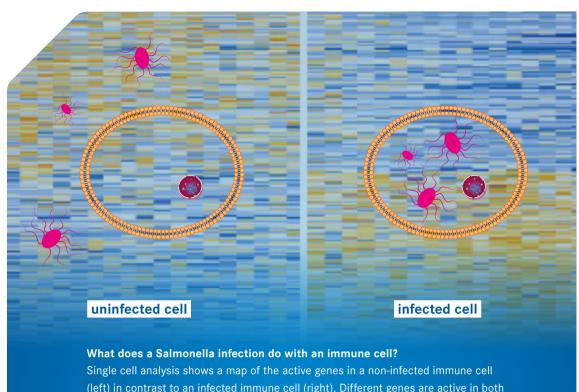
Prof Jörg Vogel, Director of the Helmholtz Institute for RNA-based Infection Research (HIRI)

EACH INFECTED CELL BEHAVES DIFFERENTLY

The microscope of the future – single cell analysis

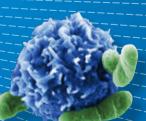
So-called single cell analysis brings light into the darkness and was accounted the most important advance of the year 2018 by the journal Science. For the first time, it is now possible to make gene expression visible, the intracellular path from genes to gene products such as proteins. Researchers 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.



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.



An immune cell in which bacteria have multiplied



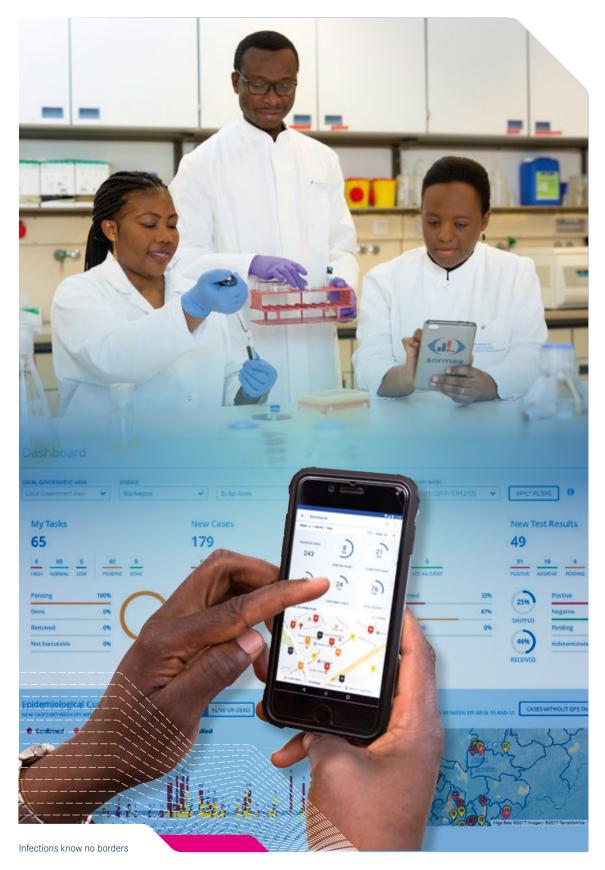
Mobile Health speeds the fight against epidemics



Innovative digital systems against epidemics in Africa The dramatic events which enfolded during the 2014 Ebola outbreak in West Africa showed how quickly a spreading virus can precipitate a globally relevant health crisis. Spread depends on how quickly national and international measures can contain the epidemic. A mobile eHealth system developed at the HZI offers valuable help in disease control.



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.





"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"

SORMAS THE FUTURE OF DISEASE SURVEILLANCE

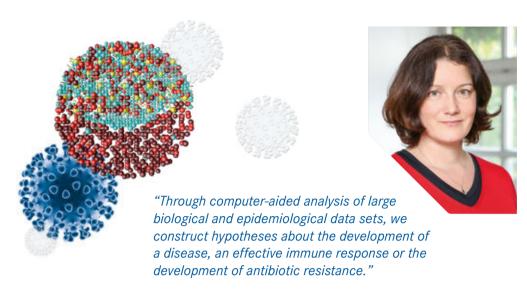
An outstanding example of a digital tool developed by HZI epidemiologists is SORMAS – the Surveillance Outbreak Response Management and Analysis System. Used as a fast-response epidemic management system, it can monitor the spread of dangerous pathogens in affected regions like countries in Africa in 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.

 \longrightarrow www.sormas.org





Prof Alice McHardy, Head of the Department "Bioinformatics of Infection Research" at HZI and BRICS

EARLY WARNING OF PATHOGENS

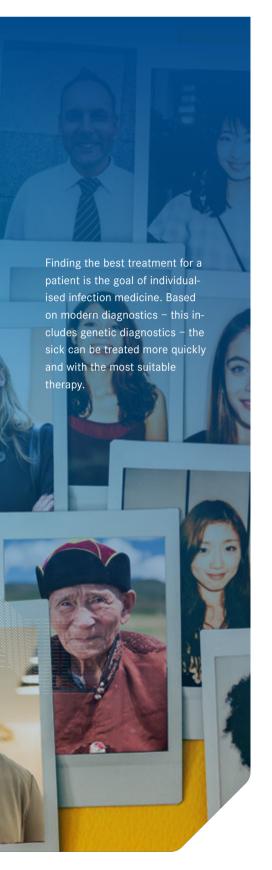
From prediction to therapy

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.







People react differently to therapies.

For example, gastrointestinal diseases or lung infections can be much more severe in immunocompromised people.

If researchers could identify highrisk patients in time, more effective
therapies would be possible at an
earlier stage.



Flu vaccination is less effective in the elderly

The immune system of older people reacts slower to vaccination and is less versatile than that of younger people. As a result, seniors are less well protected against new variants of the constantly changing flu virus. This relationship is being researched at the HZI and CiiM to design more effective vaccination strategies.

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.



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

biomes).

colonising microorganisms (micro-

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

Efficacy of drugs in each patient

Good efficacy up to no efficacy

The susceptibility of the patient to infections and the severity of the disease course are determined by individual patient characteristics and the types of



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

HAMBURG

Centre for Structural Systems Biology www.cssb-hamburg.de



WÜRZBURG

Helmholtz Institute for RNAbased 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 Visiting scientists

Nationalities



65 MIO 15.5 MIO

EUR core budget EUR third party funding







THE HELMHOLTZ CENTRE FOR INFECTION RESEARCH

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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