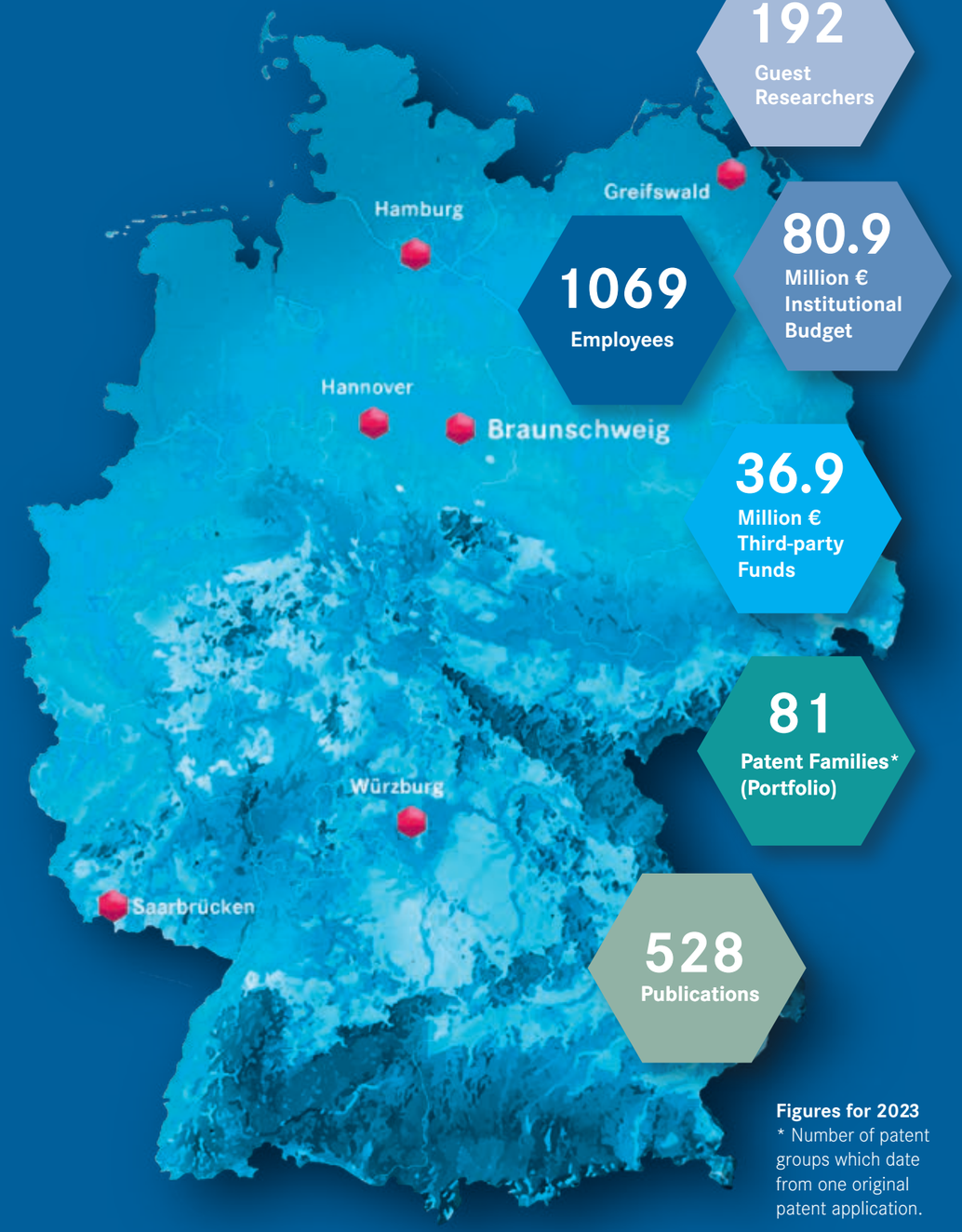
HZI HELMHOLTZ
Centre for Infection Research

RESEARCH REPORT

HZI 2022/2023

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



Figures for 2023
* Number of patent groups which date from one original patent application.

RESEARCH REPORT HZI 2022|2023

SITES

Science Campus Braunschweig-Süd

- Headquarters of HZI
- Central administration
- Research infrastructure
- Basic research on bacterial and viral infections, immunology, anti-infective agents, epidemiology
- Cooperation with the Technical University (TU) Braunschweig, in particular within the Braunschweig Integrated Centre of Systems Biology **BRICS**

Centre for Individualised Infection Medicine (CiiM), Hannover

- Joint initiative of HZI and Hannover Medical School (MHH)
- Elucidation of individual characteristics relevant for infection susceptibility, disease progression and therapeutic outcome
- Bridging clinical practice with state-of-the-art profiling technologies and latest data science technologies

Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), Saarbrücken

- Founded jointly by HZI and Saarland University (UdS) in 2009
- Research on novel anti-infectives from natural products and medicinal chemistry to fight antimicrobial resistance
- Combining pharmaceutical research with computer science and medicine to drive findings from basic research to application

Clinical Research Centre Hannover (CRC)

- Co-established with Hannover Medical School (MHH) and Fraunhofer ITEM
- Safety and efficacy testing of new medications
- Hosts the HZI Study Centre inside the framework of the German National Cohort NAKO

Photographs of HZI's sites:
Science Campus Braunschweig-Süd | Verena Meier
CiiM: HDR IMAGINA Visual Collaboration
CRC: Fraunhofer ITEM
CSSB: CSSB | Tina Mavric
HIOH: Jan Meßerschmidt
HIPS: UdS | Jörg Pütz
HIRI: University of Würzburg | Pressestelle
TWINCORE: TWINCORE Collection

Photo cover: © Adobe Stock | Ilja

TWINCORE, Hannover

- A joint venture of HZI and Hannover Medical School (MHH)
- Experimental and clinical infection research
- Life scientists and clinicians perform translational research together
- Bridge between basic research and clinical practice

Helmholtz Institute for RNA-based Infection Research (HIRI), Würzburg

- Founded jointly by HZI and Julius-Maximilians-Universität Würzburg (JMU)
- Research on RNA-based mechanisms of virulence and host defence
- Exploitation of RNA research for the development of new diagnostics, preventives and anti-infectives

Centre for Structural Systems Biology (CSSB), Hamburg

- Located on the campus of DESY (Deutsches Elektronensynchrotron) in Hamburg
- Jointly operated by ten North German research institutions and universities
- Structural elucidation of molecular infection processes using uniquely powerful photon sources

Helmholtz Institute for One Health (HIOH), Greifswald

- Founded by HZI in close cooperation with the University of Greifswald, the University Medicine Greifswald and the Friedrich-Loeffler-Institut
- Holistic research approach, considering human and animal health within their environment
- Addresses the threat posed by the emergence of novel pathogens, antimicrobial resistance as well as the evolution of known pathogens

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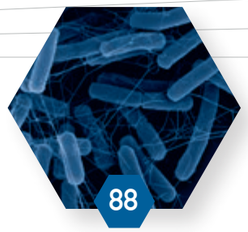
IN AND AROUND HZI

HIGHLIGHT PUBLICATIONS



HZI’S SITES

FACTS AND FIGURES

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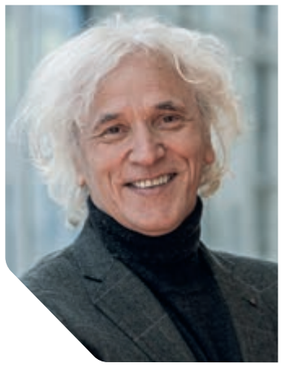
DEAR READERS,

the past two years brought many changes – to the entire world as a whole, but also to our center. Last summer, I took over as Scientific Director of HZI from Dirk Heinz, whom I sincerely thank for 13 years of outstanding work and for gently guiding me into this new challenge. Dirk Heinz has laid the foundation for world-class research, executed by an amazing group of dedicated researchers and embedded in a culture of support. Everybody at HZI has an integral and key role in the past, current, and future success and the translation of basic discoveries to human health. Now it is time to walk the next steps: to transform HZI into one of the top three centers for infection research on the planet.

In a world constantly confronted with evolving challenges, the pursuit of knowledge and innovation becomes paramount. As we navigate the complexities of our time, the challenges of pandemic resilience, climate change, precision infection medicine, and antimicrobial resistance emerge as a nexus of urgent concern that is imperative to all of us.

The COVID-19 pandemic has starkly illustrated the importance of pandemic resilience. As we confront the immediate threat of infectious diseases, we must also heed the lessons learned to fortify our defenses against future pandemics. From bolstering healthcare infrastructures to advancing surveillance and early warning systems, science-guided measures are essential to safeguarding public health and minimize the toll of future outbreaks. As COVID-19 has taught us again, health is not everything but without health everything is nothing.



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Climate change stands as a defining crisis of our era, with far-reaching consequences for ecosystems, economies, and human well-being. Its impacts reverberate across the globe, underscoring the imperative for decisive action. Climate change affects our health, not only through heat waves and storms, but also through new or differently occurring infectious diseases. With our Helmholtz Institute for One Health (HIOH) in Greifswald and our research stations in Africa and Germany, but also several other research groups at HZI, we are getting ready to meet the challenge how climate change affects and accelerates the next outbreaks.

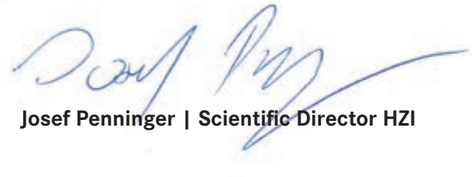
The dawn of personalized infection medicine heralds a paradigm shift in healthcare, offering tailored approaches to prevention, diagnosis, and treatment. By leveraging advances in genomics, AI-based data analytics, and digital technologies, we can now unlock the potential for precision medicine to revolutionize healthcare delivery and improve patient outcomes. A few years ago, HZI has recognized the importance of patient-centered infection medicine in the future and, together with Hannover Medical School (MHH), established an institute specializing in this field: the Centre for Individualized Infection Medicine (CiiM). The foundation-stone laying ceremony of the CiiM building took place in Hanover in 2022, and we are looking forward to move in with our research groups.

Antimicrobial resistance poses a grave threat to global health, undermining the efficacy of life-saving antibiotics and escalating the risk of untreatable infections. Addressing this challenge demands a multi-faceted approach, encompassing antimicrobial stewardship, infection prevention, and the development of novel therapeutics. Our researchers, in particular at the Institute for Pharmaceutical Research in Saarland (HIPS), play a pioneering role worldwide in the development of new anti-infectives, one testament of which is the recent inclusion in the Tuberculosis Drug Accelerator of the Bill & Melinda Gates Foundation.

HZI has always been at the forefront at recognizing and meeting new challenges, as demonstrated by the founding and success of TWINCORE as an institution for translational medicine and of the Helmholtz Institute for RNA-based Infection Research (HIRI). Both institutes celebrated anniversaries in 2022/2023: 15 years of TWINCORE and 5 years of HIRI.

Overall, I look forward to shaping HZI over the next years and working with talented researchers to face those above metioned challenges and make groundbreaking discoveries.
I would like to express my gratitude to all who contributed and are still contributing to our success, including scientific, administrative and technical support personnel, both within HZI as well as our network of national and international advisors and partner institutions.

Thank you for your interest in HZI – stay tuned and enjoy reading!



Josef Penninger | Scientific Director HZI

ABOUT HZI

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PORTRAIT OF THE RESEARCH CENTER

Continued or even increasing deficiencies in global health systems, world-wide mobility, as well as demographic and climate change facilitate the emergence and re-emergence of pathogens, accelerating their spread, enhancing the susceptibility to infectious diseases. From 2020 to 2022, the COVID-19 pandemic has vividly shown the alarming speed at which novel pathogens can spread all over the world, leaving unforeseen and dramatic consequences for human wellbeing and global economy. The need to define effective strategies to counteract and better contain future disease outbreaks ('pandemic preparedness') has become increasingly urgent.

Likewise, the increase in antimicrobial resistance (AMR) of hospital-associated pathogens - the so-called 'silent pandemic' - continues to pose a major challenge for public health, threatening to reverse the enormous progress made in infection control during the last century.

In addition, the role of pathogens as potential causes of other severe diseases – including cancer, metabolic syndrome and neurodegeneration – is becoming increasingly evident, offering a chance to overcome these diseases by preventing or curing the underlying infections.

In line with Helmholtz Association's mission to address major societal, scientific, and economic challenges, the Helmholtz Centre for Infection Research (HZI), Germany's largest scientific institution dedicated to infection research, employs cutting-edge research and next-generation technologies to investigate new approaches to preventing, diagnosing and treating infectious diseases. At HZI, we pursue an integrated and highly interdisciplinary research strategy based on profound expertise in the mechanistic exploration of host-pathogen interactions, seamlessly integrating state-of-the-art computational advancements, while focussing on bacterial and viral pathogens of high clinical relevance. Utilizing a multi-scale approach, scientists at HZI acquire in-depth understanding of the complex mechanisms underlying infection processes, from molecules via cells and organisms to populations and patient cohorts.

At HZI, we focus on translational infection research: By capitalizing on strong partnerships with universities, clinics, and industry, we aim to expedite transfer of fundamental research findings into clinical practice and precision medicine. Our unique combination of interdisciplinary expertise, collaboration, and state-of-the art technologies distinguishes the centre as a frontrunner in the relentless fight against global infection challenges.

The Center and its Sites

HZI's more than 1000 employees and about 200 guest scientists from over 70 countries work at different sites throughout Germany.

This de-centralised structure is a direct result of HZI's long-term strategy: Throughout the years, HZI has partnered with sites of excellence in selected, future-oriented research fields with a high potential for innovation with high clinical and societal relevance. In joint ventures with leading universities, university hospitals and research institutes, HZI is systematically building up the appropriate structure best suited for driving the development of these fields. This unique framework enables world-class translational research, making HZI an increasingly attractive partner for national and international collaborators, including industry partners.

Historically, the main campus in Braunschweig – with scientists covering all disciplines of infection research – has emerged as the central research hub. Over the years, branch sites with different specializations have been established, complementing and strengthening the scientific portfolio of the center.

HZI's Braunschweig site and the Foundation Campus

The center's headquarters lies in in Braunschweig; and the surrounding campus provides a site well suited to HZI's interdisciplinary approach. High-level foundational research is pursued and novel concepts for combatting infectious diseases are jointly developed and implemented via both in-house and external collaborations.

The infrastructure on-campus exploits technology platforms, including facilities for fermentative and total synthesis of natural compounds that make it possible to identify and develop new molecules intervening in the infection process. Structural biology permits detailed analysis of interactions between virulence factors, host cell targets and small molecules. Units for omics technologies allow genotyping of pathogens and expression profiling. A cutting-edge animal facility, with around 300 different mouse strains, allows HZI scientists to analyze virulence mechanisms and immune modulation concepts in state-of-the-art biosafety level 1-3 (BSL1-3) laboratories. Furthermore, infection epidemiology conducts research on the occurrence and spread of infectious diseases at the population level.

Photo: © HZI | Verena Meier

A dedicated facility provides laboratory space for functional genomics research in collaboration with the Technical University Braunschweig (TU-BS) and the Leibniz Institute DSMZ – German Collection of Microorganisms and Cell Cultures (DSMZ, see below).

Together with neighbouring institutes and other partners on HZI premises, the centre has established the "Science Campus Braunschweig Süd", reflecting concentrated on-site collaborations in research, development, and education. Regional partners in this integrated campus include the Technical University Braunschweig (TU-BS), the German Collection of Microorganisms and Cell Cultures (DSMZ), the Fraunhofer Institute for Toxicology and Experimental Medicine (Fraunhofer ITEM), the German Center for Infection Research (DZIF), the "BioS" lab for school students and a number of start-up companies.

The head office of DZIF, which was initiated by the Federal Government of Germany in 2012 as one of the seven overarching German Centers for Health Research (DZG), is located on the HZI main campus and includes the DZIF project and funding management units. Scientifically, HZI plays a pivotal role in DZIF, coordinating the Research Area "Novel Antibiotics" as well as the Translational Project Management Office. DSMZ is the largest type culture collection in Europe. It offers longstanding expertise in fields like bacterial metabolism and functional genomics and provides HZI researchers with pathogen and compound producer strains. The modern sequencing units of HZI and DSMZ provide complementary services and offer a wide range of technologies and expertise, including gene expression analysis. Fraunhofer ITEM operates a specialised branch on the campus, including a GMP (Good manufacturing practice) facility for the production of biologicals and cells suitable for clinical testing, offering further opportunities for future cooperation on the campus.

HZI's Branch sites

In 2008, HZI founded the translational centre TWINCORE together with the Hannover Medical School (MHH). Since then, three Helmholtz Institutes, HIPS, HIRI, and HIOH, which significantly strengthen its expertise and critical mass in specific fields, have been founded. HZI has become an essential part of regional research institutions designed to foster unique expertise and technologies.

→ ***Clinically oriented translational research:*** The mission of the translation centre TWINCORE in Hannover is to promote clinically relevant, patient-oriented infection research. TWINCORE was founded in 2008 by HZI and Hannover Medical School (MHH) - one of Germany's leading university clinics. In line with its clinical focus on transplantation and regenerative medicine, one research pillar of MHH focuses on "infection and immunity", jointly developed in a strategic partnership with HZI. At TWINCORE, multidisciplinary teams of physicians and scientists pursue research motived by clinical needs and observations and translate their findings into clinical practice.

HZI and its sites (left).
The respective branch institutes complement the expertise on the HZI main campus in the strategically relevant fields indicated (right).

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→ ***Individualised infection medicine:*** TWINCORE currently also hosts the Centre for Individualised Infection Medicine (CiiM). This institute, jointly set up by MHH and HZI in 2015, performs transformative research via the development of increasingly patient-specific concepts and strategies in infection medicine. A dedicated new CiiM building is currently being constructed adjacent to TWINCORE.

→ ***Drug and pharmaceutical research:*** The Helmholtz Institute for Pharmaceutical Research Saarland (HIPS) in Saarbrücken focusses particularly on the discovery and development of novel anti-infectives from both natural sources, like soil bacteria or the human microbiota, as well as innovative synthetic approaches. HIPS was established jointly with Saarland University (UdS) in 2009 in order to combine the outstanding expertise of both institutes to advance pharmaceutical research, especially in the areas of natural compound research, medicinal chemistry and drug delivery. With its unique location on the UdS campus, HIPS acts as a catalyst for HZI's translational infection research. It currently houses six departments, including a thriving bioinformatics department, solidifying its position as a key asset for HZI's translational research pipeline.

→ ***RNA-based infection research:*** The role of non-coding RNAs in infection and immunity, and the study of infection processes at the single cell level are emerging and fast-growing areas with immense potential for novel diagnostics, therapeutics, and preventive strategies. In order to develop these fields sustainably, the Helmholtz Institute for RNA-based Infection Research (HIRI) was founded in collaboration with the Julius-Maximilians-University in Würzburg (JMU) in 2017. HIRI currently comprises two research departments and eight research groups. A dedicated HIRI building is under construction on the medical campus of JMU.

→ ***One Health:*** In 2021, the Helmholtz Institute for One Health (HIOH) was jointly established by HZI, the University of Greifswald, the Greifswald University Medicine and the Friedrich-Loeffler-Institut. HIOH addresses the ongoing threat posed by the emergence of novel pathogens as well as the adaptation of known pathogens, including the development of antimicrobial resistance (AMR). It focuses on investigating the interfaces between human, animal and environmental health through longitudinal and comprehensive sampling and data collection and analysis related to

emerging infections and AMR in two model regions: The African tropics and Mecklenburg-Vorpommern.

→ ***Information and data science:*** On its central campus, TU-BS together with HZI set up the Braunschweig Integrated Centre for Systems Biology (BRICS) in 2016. At BRICS, scientists from both partner institutes collaborate on bioinformatics and mathematical modelling of infectious disease processes. By integrating large data sets, they aim for a systems understanding of infections and immunity using state-of-the-art digital technologies. TU-BS has chosen "Infections and Therapeutics" as one of its main research fields, reflecting its long-term commitment to partnership with HZI.

→ ***Structural systems biology:*** In Hamburg, HZI has played a key role in establishing the Centre for Structural Systems Biology (CSSB), a joint initiative of ten research partners. In the CSSB building on the campus of the German Electron Synchrotron Centre (DESY), structural biologists and infection researchers investigate host-pathogen interactions at the highest possible spatial resolution using high-intensity photon sources, like the third-generation synchrotron source PETRA III and the European free electron laser X-FEL.

A structural biology department of HZI is located at CSSB to investigate supramolecular machines involved in bacterial infections.

→ ***Clinical trials:*** The Clinical Research Centre (CRC) in Hannover is staffed and equipped for safety and efficacy testing (Phase-I-to-IIa trials) of new medications. CRC was founded in 2014 by Fraunhofer ITEM and MHH together with HZI as a unique translational infrastructure. CRC also hosts the HZI Study Centre inside the framework of the German National Cohort (NAKO), where epidemiologists conduct long-term population studies with volunteers.

© HZI | Janos Krüger

HZI AND ITS SITES AT A GLANCE

Foundation Campus
HZI's headquarters on the Science Campus Braunschweig Süd

TWINCORE: Centre for Experimental and Clinical Infection Research, Hannover (co-established with Hannover Medical School), 2008

HIPS: Helmholtz Institute for Pharmaceutical Research Saarland, Saarbrücken (co-established with Saarland University), 2009

CRC: Clinical Research Center Hannover (co-established with Hanover Medical School and Fraunhofer ITEM), 2012

BRICS: Braunschweig Integrated Centre for Systems Biology (co-established with Technical University Braunschweig), 2016

HIRI: Helmholtz Institute for RNA-based Infection Research, Würzburg (co-established with University of Würzburg), 2017

CSSB: Centre for Structural Systems Biology, Hamburg (co-established with nine north German partners), 2017

CiiM: Centre for Individualised Infection Medicine, Hanover (co-established with Hannover Medical School), 2017

HIOH: Helmholtz Institute for One Health (co-established with University Greifswald, University Medical Centre Greifswald and Friedrich-Loeffler-Institut), Greifswald, 2021

THE HELMHOLTZ PROGRAM "INFECTION RESEARCH"

In order to address the infectious disease threats of the 21st century, HZI scientists have developed the interdisciplinary program "Infection Research". The program combines groundbreaking fundamental research with clinically oriented investigation and application-oriented research (Figure 1). HZI's unique interdisciplinary approach facilitates the development of innovative, increasingly patient-tailored solutions for diagnosis, prevention, treatment as well as surveillance and control of infectious diseases.

Pathogen research at HZI aims to promote the development of efficient treatment strategies against bacterial and viral pathogens. This endeavor requires a deep understanding of the complex interactions between pathogen and patient, with a focus towards possible treatment options (Figure 2). Reflecting this interplay, the HZI program INFECTION RESEARCH is composed of three integrated RESEARCH TOPICS.

Topic 1 focuses on the role of pathogenic bacteria and viruses in infectious disease processes.
The focus of Topic 2 is the response of the immune system to infections.
In Topic 3, researchers are discovering and developing new anti-infectives.

On the basis of challenges of high clinical and societal relevance and the special competences at HZI and its cooperation partners, HZI has established so-called Research Foci providing a synergistic, dynamic and flexible framework for the research program. The Research Foci aim to integrate expertise from different areas of HZI's research, namely from all three Topics. Within each Research Focus, HZI scientists contribute their expertise and facilitate the transfer of knowledge from the lab to clinical or pharmaceutical application. They offer the flexibility to rapidly adapt the research program to emerging and future challenges.

Currently, researchers at HZI and its partner institutions cooperate in seven Research Foci addressing the clinically relevant fields of Antimicrobial Resistance (AMR), Microbial Communities (MICO), Chronic Viral Infections (CVIR), Individualised Immune Interventions (INDI), Digital and Global Health (EPI), Respiratory Viral Infections (RVIR), and Infection and Neurodegeneration (INEU).

GOALS OF THE PROGRAM "INFECTION RESEARCH"

In recent years, HZI has taken several important steps towards achieving its strategic mission. Key strategic partnerships have been further strengthened to stay at the forefront of infection research and to advance the translational research program. HZI has achieved high international visibility in fields such as natural product-based drug discovery, data science and modelling, the use of RNA molecules in studying and controlling infections, disease outbreak control as well as integration of precision medicine into infection research.

Figure 1: From research to impact: the integrative research strategy of HZI

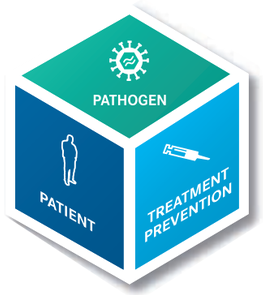


Figure 2: The triad pathogen-patient-therapy | prevention

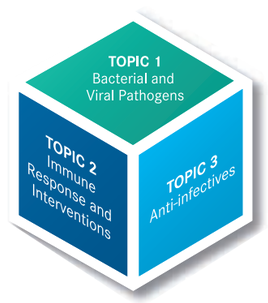


Figure 3: HZI's Research Topics

These achievements enable us to follow seven overarching goals for the upcoming years:

- Establishing HZI as a world-leading academic institution for the discovery and development of anti-infectives
- Positioning HZI as a frontrunner in translating early discoveries into patient-tailored infection medicine
- Pioneering an RNA-centric approach to understand infection processes and microbiomes on the single-cell level
- Addressing global health challenges dynamically by continually adapting the program, i.e. by establishing new Research Foci
- Transforming infection research through a digital revolution
- Strengthening HZI as a driver of and partner within global networks for translational infection research
- Contributing significantly to the prevention of future pandemics, in particular through groundbreaking research in the field of "One Health".

LONG-TERM PERSPECTIVE FOR SUSTAINABLE RESEARCH

The Helmholtz Association's Program-Oriented Funding (POF)

The Helmholtz Association, Germany's largest research organisation, invests its resources in research programs that compete with one another for institutional funding provided by the Federal and State Governments.

This "program-orientated funding" (POF) aims at and enables sustainable research with a long-term perspective, in line with the Helmholtz Association's mission to contribute to solving major and pressing issues facing society, science and industry,

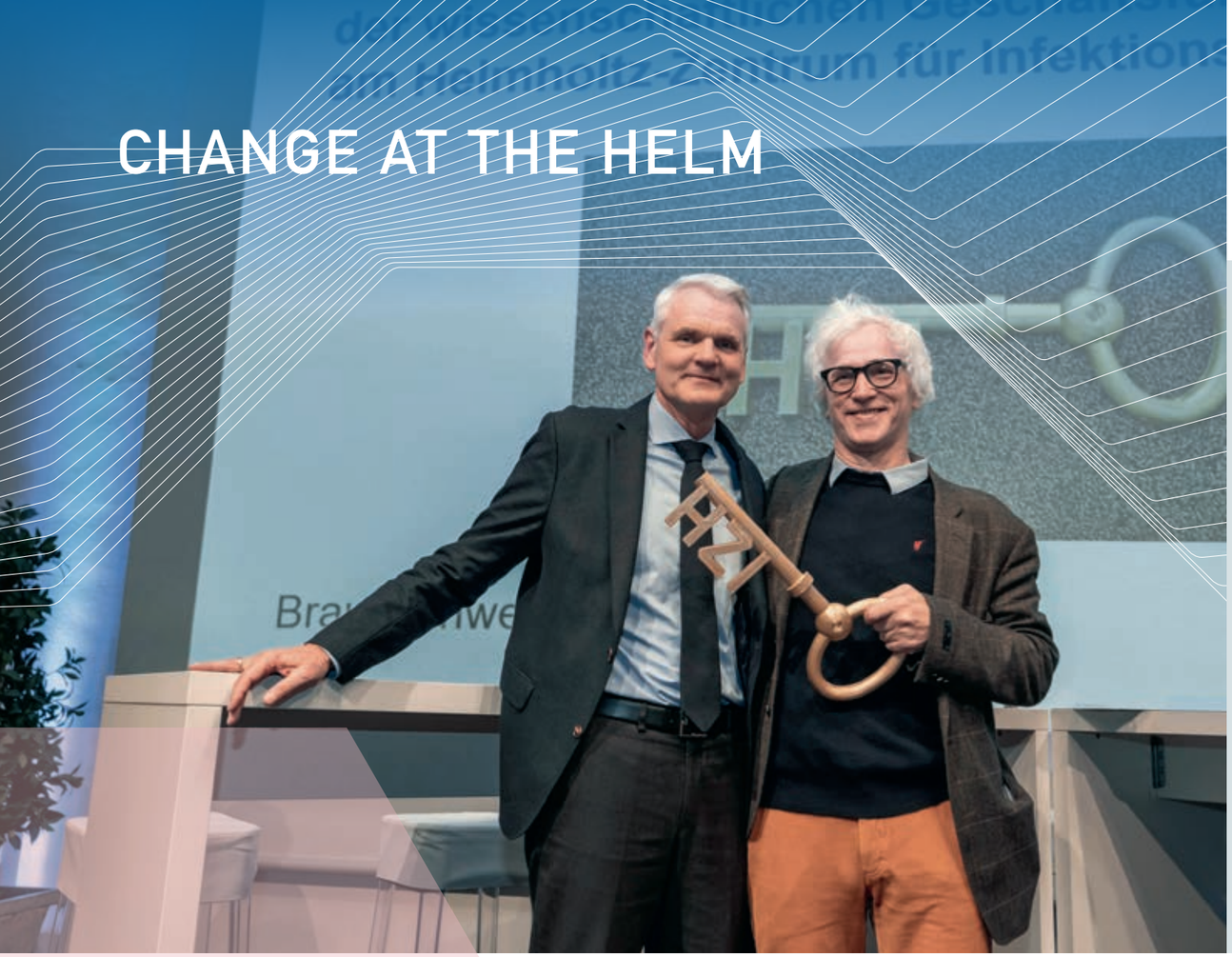
POF is based on a two-step procedure: A scientific evaluation of the existing program at the level of the research centre focussing on scientific performance, followed by a strategic evaluation of the new program proposals, which reviews program goals, work program, competences and potential future impact.

After an international expert panel acknowledged HZI's world-class scientific performance in the 2018/19 evaluation, its program "Infection Research" provides the guidelines for HZI research for the fourth period of program-oriented funding (POF IV), which started in 2021 and will last until 2027.

IN AND AROUND HZI

Streptomyces bacteria © HZI | Mathias Müsken

CHANGE AT THE HELM



Passing the key: Dirk Heinz (left) welcomed his successor Josef Penninger. © HZI | Marek Kruszewski

CEREMONIAL HANDOVER OF OFFICE AT HZI: FROM DIRK HEINZ TO JOSEF PENNINGER

In July 2023, the new Scientific Director, Josef Penninger, took over at HZI. He succeeds Dirk Heinz, who stepped down from his position after 13 years to establish the new research department „Molecular Structural Biology“ at the center.

On 4 December 2023, Dirk Heinz was officially honored for his many years of successful work. The handover to Josef Penninger was celebrated in the presence of renowned guests from Science and Politics. Greeting speeches were given by, among others, Stephan Weil, Minister President of Lower Saxony, Otmar Wiestler, President of the Helmholtz Association and Thorsten Kornblum, Mayor of Braunschweig.

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Josef Penninger, a geneticist who has received numerous international awards, previously headed the Life Sciences Institute at the University of British Columbia (Canada). As well as assuming scientific directorship of HZI, Penninger was also appointed Professor of Precision Medicine at the Medical University of Vienna, where he is to establish the new Eric Kandel Institute for Precision Medicine.

The first milestone at HZI under Penninger’s leadership was the launch of the “Microbial Stargazing - Research into Resilience Mechanisms of Microbes and Humans” (MICROSTAR for short) projects, with a total budget of around 30 million euros.

In his speech at the handover ceremony, Lower Saxony’s Minister President Stephan Weil stated:

“I am always impressed by the groundbreaking work of HZI, which has proved indispensable, especially during the pandemic. HZI plays a decisive role in research into bacterial and viral pathogens and the immune system; cutting-edge research from Lower Saxony - something we can all be proud of. Special thanks go to Prof Dirk Heinz for his outstanding achievements as Scientific Director to date. His vision and leadership have made the HZI what it is today. These successes are invaluable not only for the center, but for the whole of Lower Saxony. I am convinced that HZI will continue to play a key role in infection research under the new leadership of Prof Josef Penninger and will be a driving force in Infection Biology. The state will be happy to support this development. I wish the entire team continued success.”

> “
> **HZI HAS BEEN SET UP IMPRESSIVELY**

“HZI has been set up impressively. Dirk Heinz and his team have done a fantastic job together with all employees. Now to grasp the last few percent to play in the Champions League of research every year, that is my vision, which I am very much looking forward to,” said Josef Penninger. “I would like to take this opportunity to thank the BMBF and the state of Lower Saxony for their generous support.”

“In recent years, HZI has set the tone in infection research by establishing new institutes focusing on areas such as personalized medicine and RNA-based research,” said Dirk Heinz. “I am proud and grateful for what we have achieved together at HZI so far and will follow the further positive development of the Centre with excitement and joy.” ■

From left to right: Otmar Wiestler, President of the Helmholtz Association, Braunschweig’s First Mayor Thorsten Kornblum, Dirk Heinz, Josef Penninger, Minister President Stephan Weil, Annegret Ihbe, Deputy Mayor of Braunschweig, and Falko Mohrs, Lower Saxony’s Minister of Science.
© HZI | Marek Kruszewski

2017: Inauguration of the Science Campus Braunschweig Süd as a joint umbrella brand of the partners HZI, DZIF, DSMZ, Fraunhofer ITEM, TU-BS and BioS.
© HZI | Verena Meier

THE WILD 13: YEARS OF GROWTH AND CHANGE

THE ERA OF DIRK HEINZ AS SCIENTIFIC DIRECTOR

Dirk Heinz led the HZI for almost 13 years – longer than any other Scientific Director. Dirk Heinz, a structural biologist who started at HZI's predecessor organization, the GBF, in the late nineties, grew through all career stages at the center, from junior research group leader to group and department head to Scientific Director.

The years of his leadership (2010 to 2023) were marked by significant changes, strategic growth, and two comprehensive evaluations of the center's research. In particular, the second evaluation in 2018/19 is remembered as a tremendous success: HZI's program "Infection Research" achieved the highest possible rating, scoring the mark "outstanding" in the overall assessment by an international board of referees. This international appreciation proves that the HZI, under the leadership of Dirk Heinz, had completed the path laid out by Rudi Balling and Jürgen Wehland with its successful metamorphosis into an infection research center.

A dynamic young scientist in the lab (right) and on excursion with his team (left): Dirk Heinz as a research group leader in the early 2000s; photos from private sources.

It was not for nothing that I chose the image of "metamorphosis", because, as in nature, this change was predetermined, but by no means easy or free of resistance or challenges.

First of all, Dirk Heinz's term of office hit our center, and him in particular, unplanned, suddenly and at a difficult time. Jürgen Wehland had only just completed his first year as HZI Director when he tragically passed away far too early.

WILD YEARS – BUT NO WILD GROWTH

In this turmoil and shortly before the evaluation of our research program, Dirk Heinz, then spokesperson of our program and Jürgen Wehland's right-hand man, stepped up to lead the center.

This change certainly met with a complex situation at the center itself: Where does the center stand in the transition from the GBF to an infection research center? How ready are we for big data and systems in combination with hot topics in infection, immunity and drug research, and, more importantly, solutions? Which pathogens should be the focal points, what is the balance between basic research and translation?

Not only that, but there were also skeptical voices: Can a structural biologist define the directions in infection biology? Is he sufficiently anchored and networked in the community? Can he set the tone and ambition for the entire center?

Like many of us, I was able to experience this time over the past 13 years. We all could witness how answers to these questions were given. I myself associate three main characteristics of Dirk Heinz with this successful metamorphosis.

2011: State Secretary Georg Schütte (second from right) experiencing lab work during his visit at HZI, guided by his host Dirk Heinz (left).
© HZI | Susanne Hübner

Firstly, Dirk Heinz the structural biologist.
Without, of course, knowing first-hand what makes a true structural biologist (I am a humble virologist), I believe it must be a love for structure in its purest form, a love of precision and a love of detail. When others put their hands in their laps with satisfaction after three revisions, a structural biologist like Dirk Heinz, continues to fine-tune the finishing touches, the icing on the cake, the font size of the slides and, much more importantly, the details of the grand vision, the master plan.

Thus, the blueprint of the metamorphosis was in the hands of the capable and, as is well known, luck is with the capable and the prepared.

(It is, by the way, only logical that at the end of the long journey outlined here, Dirk has returned to his origins and resumed studying the building blocks of nature as a structural biologist once he stepped down as Scientific Director.)

Secondly, Dirk Heinz kissed by Kairos.
This requires some explanation: Kairos is an ancient Greek term and the name for the god of the favorable moment. In art, Kairos is depicted as a man with long hair at the front of his head and a bald head at the back. This symbolizes the fleeting nature of the moment, which can be grasped briefly, but once it is over, it is no longer graspable. In the sense of the aforementioned HZI metamorphosis, Kairos literally stands for the ability to recognize AND seize opportunities: Starting with the sudden take-over of office, the founding of HIRI, CiiM and HIOH and the remarkable growth of HIPS, a particularly good relationship between Dirk Heinz and this very Kairos becomes clear in my view.

During Dirk Heinz' term, HZI celebrated its 50th anniversary in 2015. © HZI

All this would not be enough, the brief moment recognized and seized but not built in and secured, were it not for a third feature:

Thirdly, Dirk Heinz has growth in his DNA – the growth mindset.
It is probably this characteristic that has impressed me the most over the years. It is the sheer will to grow, to make a difference and not to stand still. The ambition to build something in the spirit and for the cause (i.e. HZI and its mission) AND – importantly – to see setbacks as hints and support and not as failure or an insurmountable hurdle. Yes, and there were such setbacks and obstacles: the results of the first evaluation in his turn, just to name one of them, testifying an unsufficient focus and an unclear clinical orientation of our program, plus a lack of critical mass. Certainly, messages not easy to digest and, yet more difficult, to turn around and shape up.

Ultimately, I believe it was this triad for the cause of HZI that resonated with us at HZI (and beyond), that made us buy in and root along and has led us and me to where we are today.

Wild years? Yes, Wild growth? No.
Above all, strong will! Yes, and thank you.

Thomas Pietschmann

2013: Johanna Wanka, German Federal Minister for Education and Research, during her visit at HZI. © HZI | Hallbauer & Fioretti

2020: During the pandemic, Anja Karliczek, German Federal Minister for Education and Research, and Björn Thümler, Minister for Science and Culture in the State of Lower Saxony, visited the center. © HZI | Verena Meier

HZI HAS A NEW LEADERSHIP TEAM

The year 2023 saw changes in both scientific and administrative management. Together with their respective deputies, HZI's two directors constitute a four-person management team to discuss and make decisions jointly. In this report, the leadership duos of both science and administration explain their concepts and plans for the center in two comprehensive interviews.

© HZI | Andreas Holz

The new Scientific Director, Josef Penninger (left), started at HZI in July 2023. He shares responsibility with Thomas Pietschmann, who has gathered a wide range of experience at the center. In this joint interview, Penninger and Pietschmann outline their vision for HZI's research in the upcoming years, define their goals and give details on the transformative processes they have initiated.

HZI WILL BE ONE OF THE THREE TOP CENTERS FOR INFECTION RESEARCH ON THE PLANET

Prof. Penninger, you took up your new position as Scientific Director of HZI in July 2023. What were your first impressions? Was it as you had imagined before – or were there any major surprises?

JOSEF PENNINGER: My first impression was from the internal evaluation that Thomas was organizing in summer 2023. The group leaders presented their work, and I was very impressed. From the outside, HZI is sometimes perceived as a little bit conservative. But what I saw and heard was high-end, world-class research. I actually realized that HZI was populated with brilliant scientists doing brilliant science. Another very positive impression was the welcoming culture I experienced here. I really appreciate this.

You have seen how scientific research works in several countries. What are, in your point of view, main differences between North America, Austria, and Germany?

JOSEF PENNINGER: In North America, you have basically "scientific capitalism" – you live and die with the next grant. I have seen it in Canada – people who just write grant applications, nine months a year. They write ten, twelve grants to get on, to finance their laboratory. You could say, to survive you have to permanently hustle. Also, money from philanthropic sources – foundations or wealthy donors – plays an important role. In Europe, there is more government money spent in science. The North American system allows more translation. But in Europe, I think, you can expect a lot of innovation, because researchers have more freedom.

So, you appreciate the independence this system gives to scientists?

JOSEF PENNINGER: Absolutely. But of course, we need balance between safety and innovation. We have to spend the taxpayers' money well, and truly stimulate and maintain a culture of innovation; and our society will benefit from this in the long run. At Helmholtz – this is one of the aspects that attracted me – we have all the ingredients to be seriously competitive on the world-stage.

You have been here for six months now – what are the most important first steps which have been successfully initiated since your start?

JOSEF PENNINGER: The most important step was that we managed - with help from Thomas and many other people - to secure funding through our successful grant applications. The applications MICROSTAR and HUMAN allow us to hire, develop and nurture the next generation of scientists in Germany and Europe – the next superstars of infection research. People who, in 15 years from now, will populate the top positions in the field.

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Prof. Pietschmann, you have assumed responsibility as scientific co-director and are, along with Christian Scherf and Jörg Schinkel, part of the new leadership team of HZI. What is the benefit of this model and how do you divide your tasks?

THOMAS PIETSCHMANN: Actually, the division of tasks came quite naturally, because it is very obvious where we have our strengths. In the scientific management, Josef and I complement each other well. I am more familiar with the internal affairs of HZI, and am well connected in the German Center for the Infection Research - DZIF. Josef has a profound international experience, and he brings in the external view. It is always interesting to see what has been successful in other institutes or not.

On the administrative side, we have a similar constellation with Christian Scherf, bringing in his experience from several other centers, and Jörg Schinkel, who really knows the HZI inside out.

You are still heading your own research department. How do you handle the additional workload?

THOMAS PIETSCHMANN: Since taking up this position, we have begun redistributing responsibilities and tasks in my own lab – at the administrative, technical and scientific level. We improved our division of labor. I have members in my lab that are highly dedicated and experienced in long-term projects, like, for instance, the development of a Hepatitis C vaccine or the mechanisms of severe respiratory syncytial virus infections. They identify themselves with the projects, with our lab. They give stability to the team, help realize ideas, develop projects, nourish cooperation and train others in the lab. For me they are invaluable. I can depend on them anytime. They, I think, enjoy to work more independently and have more freedom to bring in their own ideas, and to get more merit, participation and visibility from the projects.

> WE ARE CONTINUOUSLY ENGAGED IN AN INTERNATIONAL COMPETITION.

You are also speaker of the Helmholtz program Infection Research. How would you evaluate the program?

THOMAS PIETSCHMANN: We have had a productive and meaningful first part of the funding period, with some real world-class achievements – strong publications in different fields from different sites. But I also realize that this is not the end of the journey. We are continuously engaged in an international competition. We had an internal midterm evaluation last year, which marks the middle of the 7-year funding period. We did this, because we realized how important it is to get valuable external feedback from what we like to call critical friends. These were reviewers that know us, and know how HZI works as a Helmholtz center. They recognized our strengths, but they were also honest enough to detect and speak about our weaknesses.

What were the main results and how will this shape HZI in the future?

THOMAS PIETSCHMANN: I was elated to see that, overall, the reviewers appreciated what HZI has achieved. Our work in the COVID pandemic was highly valued. The successful research at our sites such as HIPS, HIRI and HIOH, was highlighted. Their work is appreciated nationally but also has reached international recognition. On the other hand, the reviewers emphasized: Try to make even more of this multi-site HZI, and foster interdisciplinary, inter-site interaction.

Another point was to try to be more successful in spin-offs, licensing, founding companies. Create real economic value, and make sure to bring these products to the clinics and the patients.

The reviewers also encouraged us to really embrace breakthroughs in computer sciences, such as AI. This is well taken advice that we are working on.

Besides the reviewers' recommendations, what are your most important plans for the years to come?

JOSEF PENNINGER: From my point of view, there are five main tasks to address now.

The most important task for 2024 and 2025 is the recruitment of our young talents. We are hiring up to 20 junior investigators. This means finding the right people and convincing them to come here, to set up their research groups, to find space for them – this is a major transformation for HZI.

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Secondly, we need to implement changes to accommodate the many new researchers. They need onboarding, organization, support, and a motivating environment. Everything should be set in place, so they can start work immediately. We are expanding science support structures, with grant writing and other services, so that scientists can focus on what their core activity should be - research and being innovative.

> WE ARE HIRING UP TO 20 JUNIOR INVESTIGATORS.

THOMAS PIETSCHMANN: One thing I want to emphasize: We have a strong and highly talented staff here. The value comes from bringing the existing expertise and the new people together, and making them harmonize, and to create a culture out of this. Clearly, this also means that we have to move together, share resources and help each other. While this will not always be easy, I am confident that we will generate a spirit of cohesion, generosity and friendship on the basis of which strong and lasting cooperation will grow. This will be extremely rewarding in the end. Winston Churchill put it in a nutshell: "We make a living by what we get. We make a life by what we give."

JOSEF PENNINGER: HZI is a large place with many different sites – to find ways to integrate them even better as is done already: this is the third objective on our agenda. It is already done very well, but of course one can always do better. As a fourth point, we are currently having a closer look at our infrastructures and the technologies that we have to offer. Where do we have strong core units and what technologies can all of us benefit from? Are these technologies internationally competitive? Do we really need to do everything ourselves, or could we perhaps save money by collaborating with other centers and institutes? Optimizing these infrastructures and having competitive core units can really improve our overall performance significantly.

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And, last but not least, I also want to develop my own research department. I want to keep in touch with scientific research and not just tell others how to do it. I am currently establishing an organoid research unit, which will fit in the HZI context quite nicely, where many groups will benefit from this work.

So, there are plenty of tasks we want to accomplish this year – or at least make the first steps to get there.

THOMAS PIETSCHMANN: What we are aiming at is a sort of domino effect: these new talents, our people and strong technologies - when you achieve something visible, you have much stronger international ties, leaders want to collaborate with you, and then you can attain even more and create additional value.

> ***You both mentioned the multi-site structure of the center. You have to administer a lot of different people, sites and structures over large distances. What is your approach to cope with that?***

JOSEF PENNINGER: This decentralized structure is actually one of the key strengths we have. With HIPS in Saarbrücken we have probably one of the best institutes on the planet for pharmaceutical research based on bacterial molecules. The HIRI in Würzburg was the first institute for RNA-based infection research in the world, as far as I know. Hannover is clearly a world center for infection medicine, with TWINCORE and CiiM providing hubs for translational research and personalized infection medicine. At the HIOH in Greifswald, we have one of the world-leading centers for One Health. And of course, our site in Braunschweig has always been a strong center.

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> THESE ARE FIVE VERY POWERFUL UNITS.

These are five very powerful units! Instead of thinking how complex it might be to work together, I think we just have to see it as a unique opportunity.

> ***Yet still, you mentioned the integration of HZI's various sites as one of your five major tasks ...***

JOSEF PENNINGER: When you go to a job interview and are asked, "What is your biggest strength?", we all know your biggest strength is also one of your biggest weaknesses. Knowing this, we can actively address it. The question for the near future is - how could we make this even better, make people work together more?

THOMAS PIETSCHMANN: Cooperation grows when people know and trust each other, have shared goals and can complement each other. Thus, we want to bring our people together at all levels. Moreover, we want to reorganize the scientific advisory boards.

JOSEF PENNINGER: Yes, we will give the advisory boards at the different sites more power and integrate them. Besides acting locally, they also receive influence in the central, overarching, HZI-wide advisory board we are now setting up anew.

The interview continues on page 28 →

Holistic Approach for Novel Medicines

Learning from microbes to improve human health: The programs MICROSTAR and HUMAN

Clostridioides difficile © Manfred Rohde

Over the course of approximately four billion years evolution, all organisms from viruses and unicellular microorganisms to humans have developed defense mechanisms at the molecular, genomic, cellular, and ecosystem levels that protect them against external and internal challenges.

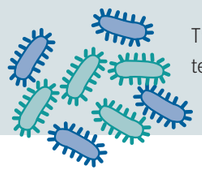
These resilience mechanisms enable organisms to react effectively to change, thrive in existing habitats and colonize new ones. Microbes in particular have successfully adapted to a whole gamut of ecosystems and hosts.

With the new project MICROSTAR – short for "Microbial Stargazing" – HZI aims to learn from the microbial world and unravel their secrets of resilience and adaptability in order to use these principles for the benefit of mankind and nature. MICROSTAR is funded by the German Federal Ministry of Education and Research (BMBF) and includes the establishment of several junior research groups as well as substantial measures to promote and foster young scientists. The MICROSTAR concept was first developed in 2023, the program having started last October.

Human diversity is a key determinant of our health and our responses to microbes. This diversity is influenced by age, socio-environmental and behavioral factors, the immune system, medication, prior exposure to pathogens, genetic and epigenetic traits plus microbial colonization. Each of us is a "superorganism" that comprizes and coordinates a multitude of factors that shape our health and responses to microbes.

Exploring this human ecosystem is the main objective of the complementary project HUMAN (Human Microbe Alliance for Universal Health). HUMAN aims to advance our understanding of human health, particularly in relation to infectious diseases, and exploit these insights for the development of innovative strategies to protect, restore and preserve its integrity. The key steps of HUMAN have now been planned and outlined; and funding applied for from the Ministry of Science and Culture in Lower Saxony and the VolkswagenStiftung.

The alliance of HUMAN and MICROSTAR with its focus on microbes forms a holistic and multifaceted strategy with the potential to yield groundbreaking insights and fresh solutions to human health in the context of its microbial environment.



The long-term goal is to develop new and innovative drugs and novel technologies to combat global challenges of today and tomorrow.

WHAT CAN WE LEARN FROM VIRUSES AND BACTERIA?

In a sense, future has already started with the new projects HUMAN and MICROSTAR. Can you explain the intention and contents of these programs?

THOMAS PIETSCHMANN: These two projects stem from Josef's vision – from what he communicated to the ministries when he was recruited. In a sense, you can put it on two sides of a coin. On the one side, there is the MICROSTAR project. In short, it's about microbial diversity. Microbes have populated this planet ever since life arose, and adapted to changing environments, thereby evolving effector and resilience mechanisms. The other side of the coin is the human being – a universe in itself. And that is the second project, HUMAN, which puts a focus on each of us and our microbes and how they shape our health, our response to infection in the acute, post-acute and long-term. Together, these two projects have brought us considerable funding, and they provide us with the framework for many new recruitments and potential developments we have already mentioned.

JOSEF PENNINGER: There's 3.8 billion years of evolution of microbes, and one thing they certainly did is adapt – to sometimes very hostile environments on our planet. What can we learn from viruses and bacteria? How can they help us developing new medicines? I think we are very well placed to answer these questions.

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THOMAS PIETSCHMANN: In the long term, we want to take this knowledge even beyond the human being, for other applications where microbes could be useful. Think of the entire biosphere, climate change, the global challenges confronting us. I think that's a fantastic long-term perspective and may have a tremendous impact.

JOSEF PENNINGER: Yes, this is how we came up with this project and defined it – to try to think outside the box, go to totally new directions, meet grand challenges, discover new medicines. The vision is set – now it is important to execute. I hope this will be the year of execution.

To break this down to everyday research at HZI: what is going to change in the new program you will have to set up for the next Helmholtz-wide evaluation? How will it differ from the current program?

THOMAS PIETSCHMANN: First of all, we delivered to the ongoing project and funding period. We can report impressive success stories. But while we prepare for this evaluation, we also look into new fields and challenges we already have identified, and which will be the core of our next program proposal.

Can you already name these new research areas?

THOMAS PIETSCHMANN: They are not all new, actually. Antimicrobial resistance, or AMR, is a challenge that we have been working on for a long time. However, adding to this, we want to transform the center towards global infectious disease related challenges directly. So that we join forces to address, besides AMR, also Climate and Infection as a second, Pandemic Resilience as a third, and Precision Medicine as a fourth new area.

JOSEF PENNINGER: The issue always is, one has to look in the mirror; where are we, where do we want to go? And equally important, what are the others doing? There are many great research centers on the planet dedicated to particular topics. So, one always has to aspire to be a little different to be ahead of the game.

WE LOOK INTO NEW FIELDS AND CHALLENGES WE ALREADY HAVE IDENTIFIED.

In the next evaluation for the Helmholtz Association's Program-oriented Funding, or POF for short, you will have to convince the reviewers of this concept. One could say that the bar is hanging quite high, because the last evaluation results were remarkably good. Are you confident that the center will make it in the same way?

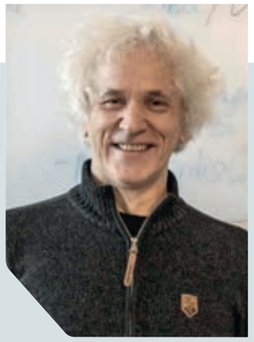
THOMAS PIETSCHMANN: I see so much that has happened in the current funding period that we have reason to be optimistic and confident. We have gained a lot of support and trust from the ministries – also from Josef, for choosing us and joining us. There is a lot of interest and trust in the HZI and its potential. The expectations are rising, that's right. But I don't see a reason why we should not live up to them.

JOSEF PENNINGER: I actually like to be evaluated because evaluations are opportunities. It is great to look into the mirror of competent international evaluators because this is our challenge. Either we want to play in the international league, or we don't. And if you want to play in the international league, you have to play against the best teams.

Where do you want the center to stand in, say, ten or fifteen years?

JOSEF PENNINGER: HZI will be one of the three top centers for infection research on the planet, which has started multiple new companies and won multiple prizes. I want HZI to be seen from a spacecraft, because we are giants.

THOMAS PIETSCHMANN: I want that talented young people say: HZI is the place I want to go as an infectious disease researcher.



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JOSEF PENNINGER born in Gurten, Austria, is the Scientific Director of the HZI since July 1, 2023. At the same time, he was appointed part-time Professor for Precision Medicine at the Medical University of Vienna. Josef Penninger studied medicine at the University of Innsbruck. From 1990 to 1994 he worked as post-doctoral fellow at the Ontario Cancer Institute, thereafter until 2002 at the Department of Immunology and Medical Biophysics at the University of Toronto. As Principal Investigator at Amgen, his independent lab contributed to the development of the antibody Denosumab for bone loss and found the first connection for RANKL to mammary gland development in pregnancy and breast cancer. In 2002 he moved to Vienna, to start and develop the Institute of Molecular Biotechnology. In 2018 he returned to Canada as Director of the Life Sciences Institute (LSI) at the University of British Columbia (UBC). His major accomplishments include pioneering insights into the molecular basis of osteoporosis and breast cancer. Furthermore, he demonstrated a critical role for ACE2 as the cellular receptor for SARS Coronavirus infections and linked ACE2 to lung failure in such infections.

Is there a message you want to deliver to the readers, especially inside the center?

THOMAS PIETSCHMANN: One important message that Josef said at his first day was: Everybody is important and valuable at HZI. We are more than 1000 people here, and everybody has their role.

JOSEF PENNINGER: Everybody can contribute – we mean it, and we will live it.

Interview: Manfred Braun ■

> "I WANT HZI TO BE SEEN FROM A SPACECRAFT, BECAUSE WE ARE GIANTS.

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THOMAS PIETSCHMANN, born in Würzburg, studied biology at the Julius-Maximilians-Universität of Würzburg and Duke University, Durham USA. In 2000 he received his doctorate at the Institute of Virology at the University of Würzburg on mechanisms of virus morphogenesis in retroviruses and joined Professor Ralf Bartenschlager's group at the Institute of Virology in Mainz as a postdoc. In 2002 he moved to the Department of Molecular Virology at Heidelberg University together with Bartenschlager. In 2006 Thomas Pietschmann founded an Emmy Noether junior research group that focused on the morphogenesis and entry mechanism of the Hepatitis C virus. In spring 2007, he and his working group were appointed to TWINCORE. Since 2012 Pietschmann is head of the Department of Experimental Virology at TWINCORE and has been spokesman for the Helmholtz program "Infection Research" since 2021. In 2023 he joined the HZI management team as scientific co-director and was elected to the executive board of the German Center for Infection Research (DZIF).

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Christian Scherf (right) started as HZI's new Administrative Director in January 2023. He shares responsibility with Jörg Schinkel, who has been leading the center's Human Resources department since 2010. Here, Scherf and Schinkel explain what they have in mind concerning the development of HZI's administration in the near future.

AS HZI, WE ARE NOW AT A CROSSROADS

Mr. Scherf, you started at HZI in January 2023. I would like to ask you the same question we asked your scientific counterpart, Josef Penninger, who started some months after you: Was it as you had imagined before – or were there major surprises?

CHRISTIAN SCHERF: Well, I was expecting a small size Helmholtz laboratory, located on different sites. I figured that the administration is well fitted to cope with its task, but has to struggle with the multi-site aspect. And this is exactly what I found. So that was not really a big surprise.

What are, in your point of view, the characteristic features of HZI?

CHRISTIAN SCHERF: Life science laboratories differ from physical laboratories, as I know them from my previous positions at DESY and in Geesthacht - smaller scientific groups, smaller lab spaces. But, having managed the EMBL for five years, I also have some experience in the life science sector. What is new to me at HZI is, again, the multi-site aspect - a structure that has been growing now for a long time, but growing at different places and at different speeds.

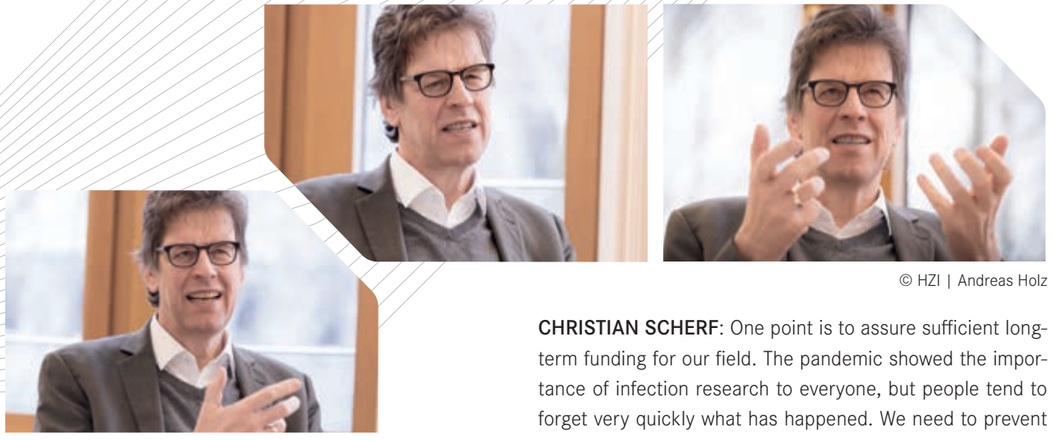
Looking from the outside, from places like EMBL or DESY: how is HZI perceived by other players in the research landscape?

CHRISTIAN SCHERF: I think it is seen as an important player in the field. For instance, that's why EMBL has set up a close cooperation with HZI. On the other hand, my impression is that great things are expected from HZI because the topic of infection research is so big. However, we are still a small size Helmholtz center.

Is that a disadvantage?

CHRISTIAN SCHERF: Not always, but it means that we have limited options to tackle huge problems. Just look at the subject of One Health: I think it would require a huge infrastructure, yet our One Health institute, HIOH in Greifswald, is still a small place. We address big issues, sometimes with very few people.

Mr. Schinkel, you have been working at HZI for one and a half decades. Is this your impression as well?



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JÖRG SCHINKEL: On the one hand, yes, we still are comparatively small for Helmholtz standards. On the other hand, in the 15 years which I have spent at the center I have seen many people coming and leaving – also in the top management – but, all in all, there has been a continuous growth. There was a temporary setback in the period of consolidation, which lasted for four years and affected science as well as administration. Apart from that, there was a steady increase in personnel, funding, and the number of sites. Therefore, in our new extended management team, it is very positive that the many issues we need to address are now not just resting on two shoulders, but are shared amongst a team of directors and their deputies. This helps to cope with the increasing workload.

> *Speaking of the new governance structure and the four heads of the center: How do you distribute the tasks on the administrative side? Have you already worked out a strategy for that?*

JÖRG SCHINKEL: We are still in the discovery phase, which is also necessary. But our mutual understanding assures good cooperation and a logical division of tasks. So, I think we do not need to discuss everything in the tiniest detail. Of course, we have set the big picture of who is responsible for what. But the details actually come along the way.

> *What do you see as the most important questions the new leadership of HZI has to address now?*

CHRISTIAN SCHERF: One point is to assure sufficient long-term funding for our field. The pandemic showed the importance of infection research to everyone, but people tend to forget very quickly what has happened. We need to prevent that – and to prepare ourselves for what may come up next. And, what I do see as a major challenge for us is that HZI has to define itself in its internal structure as a multi-site laboratory, and therefore has to function across its locations. That is a very high demand.

> *Why would that be a challenge?*

CHRISTIAN SCHERF: Our mission as a Helmholtz center is to address big questions with an organization that can tackle them. To achieve this, you need sufficiently strong structures. As HZI, we are now at a crossroads: we can either define ourselves as split into six or so different sites, all pursuing their own agenda, but too small to achieve what we are aiming for. The other road, which I believe we should take, is Helmholtz-like. That means, we act as a whole organization, and thus are able to cope with these big questions, give answers to them, and fulfil our mission within Helmholtz. This is the One Lab idea: that we function on different sites, but within one laboratory, the HZI. And this makes us strong.

> *The different sites of HZI act rather independently – do you want to change that?*

CHRISTIAN SCHERF: Not at all. It is good when a site is striving to be strong, to be attractive as a partner. We should encourage that. What we should do is think and act in a One Lab spirit. We have to make ourselves visible, because we are in a constant competition: Max Planck, Fraunhofer, the universities, all have their individual functions and claims. We need to position ourselves within that framework as a strong organization. And we can only do this together.

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> *What concrete measures will this include?*

CHRISTIAN SCHERF: One aspect is that we are going to discuss our branding, which will be an important step. In the meantime, we have already started with other activities. One example is Hannover. In order to become visible as Helmholtz there, we both – MHH and HZI – have agreed to create an umbrella for the Hannover site, which we want to call Helmholtz Infection Medicine. This will also strengthen the MHH as it shows that they are intensively cooperating in a strong Helmholtz partnership.

> *What about the main campus of HZI in Braunschweig?*

CHRISTIAN SCHERF: We need to care for every single site of the center. We can see that the other sites are growing. Hannover is growing because of CiiM. The others also are growing because they are being built up. Braunschweig is currently lacking new young leaders in science. Until recently, we didn't have the power to hire new staff. But we can do this now, and that will strengthen the site enormously.

> *You are talking about the new projects HUMAN and MICROSTAR, acquired by Josef Penninger, which will bring considerable growth to the campus. How are colleagues in the administration affected by the new scientific initiatives?*

JÖRG SCHINKEL: There definitely is a certain spirit which is kindled by these new developments – also in the administration. I notice that in my own team. It's the young people, the future scientists in the field for the next 30 years, that we are hiring here, which is a great opportunity. And during the onboarding process, I can see that there is a great common understanding, a common wavelength, between our young coworkers in the administration and the young researchers, which is also inspiring for us more experienced staff members. It helps us keep alert, dynamic and young.

> *But don't these recruitments also pose a significant additional workload to your HR department? Is HR – or the administration in general – prepared for this huge increase?*

JÖRG SCHINKEL: Indeed – up to 20 new groups in the next years, that comes close to an increase of 40 to 50 per cent in the number of research units. This is absolutely new to me and unique in the history of the HZI over the last 15 years. During my time at the Center, we have not had such a strong increase in a comparable time span. But we have created resources to deal with it. We have streamlined processes and are still refining them.

> **“**
> **THERE DEFINITELY IS A CERTAIN SPIRIT WHICH IS KINDLED BY THESE NEW DEVELOPMENTS.**

Will there be many new job profiles and new types of expertise which you have to get on board now? Is this a challenge for recruiters?

JÖRG SCHINKEL: It's not so much the different job profiles which call for attention – it's rather a new mindset, as the world out there has changed. For example, the importance of work-life balance is different nowadays. And the majority of young people - including researchers - have certain expectations, especially with regard to a family-friendly working environment.

CHRISTIAN SCHERF: I would put this in an even broader context: the way science is done is changing. It's not only new research subjects which are going to challenge us – the methodology of research is going to change dramatically in the next years. Digitalization and Artificial Intelligence are key factors in a radical change, which will affect our work in many ways. And we must respond – administration needs to cope with these challenges.

How can this be achieved?

CHRISTIAN SCHERF: We have to re-think what we are doing from scratch. The solutions that we have applied in the last fifty years may not be suitable for the next five. We have to consider tools, technology, working conditions, communication and many other aspects. Right now, we have outlined a two-year work program for ourselves, aiming to collect ideas, expertise, and suggestions on this subject. Then we will evaluate our results, and discuss them with HZI as a whole, in order to find answers to that. And we need to find these answers without spending too much money. So, getting prepared for the future and improving constantly will have to do a lot with our culture within the center.

Speaking of culture: the personnel departments of HZI – Human Resources and Personnel Development – are going to be merged and re-named "People and Culture". What is the intention behind that?

JÖRG SCHINKEL: First of all, it's important to bring together what belongs together. With this fusion, we are now pooling our experience and our skills. The goal is to present a single department that can be easily approached and coordinates HR-related procedures, especially the digital processes in Human Resources.

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CHRISTIAN SCHERF, born in Hoya in Lower Saxony, studied law in Freiburg /Brsg. and international and European law in Dijon, France. He completed both his state examinations and his legal traineeship in Frankfurt am Main. Christian Scherf's interest in international contacts began at a very early age. After graduating from high school, he worked for a year as a volunteer for the UN High Commissioner for Refugees in Costa Rica, helping refugees.

After later positions as a lawyer at the EU Commission in Brussels, as a government councillor of the City of Hamburg and various management positions in supra-regional education, science and research funding, he took over the commercial management of the GKSS Forschungszentrum Geesthacht GmbH (now HEREON) in 2000. In 2002, he moved to the German Electron Synchrotron DESY as Commercial Director. From 2015-2020, Scherf served as Administrative Director of the European Molecular Biology Laboratory in Heidelberg. In 2020, he took on a new challenge as Founding Chancellor and later Chancellor of the Berufliche Hochschule Hamburg. Since the beginning of January 2023, Christian Scherf has led HZI as Administrative Director.

© HZI | Andreas Holz

But where does culture come into play here?

JÖRG SCHINKEL: We use the term in the sense of corporate culture, of mapping processes, quality management, organization. For me, that would be the next stage of expansion.

CHRISTIAN SCHERF: Jörg Schinkel proposed the name, and I was immediately thrilled by it. To me, it makes clear that we understand HR not only as a department that just hires people, but that gives the main input what is important in our working relationship. Culture is not how to paint walls nicely, but how people work with each other. Therefore, I think this name really is a program.

What is your vision for the future? Where do you want to stand in ten years?

CHRISTIAN SCHERF: My wish is that in ten years' time, HZI has managed to achieve visible reputation worldwide, and that, internally, we use the most suitable, cutting-edge technologies, and support science in the best way possible.

JÖRG SCHINKEL: Yes, that HZI is renowned here as well as on a global scale – so, when you take a taxi from the airport in Hannover, you just say HZI and the driver knows where you want to go. And that scientists in the center tell everywhere how efficiently they are supported by their administrative colleagues.

CHRISTIAN SCHERF: What I would like to add, everything we have been talking about here will only work if we have the support of all employees at the center – be it on the scientific or the administrative side. It can't be just done top-down. It will only work if everyone participates. That is our message to all our coworkers.

Interview: Manfred Braun

© HZI | Andreas Holz

JÖRG SCHINKEL, born in Hamburg, studied social economics, specializing in business administration, at the University of Hamburg. After graduating with a degree in business administration with a focus on human resources management and labour law, he entered the non-university research world at the former Heinrich Pette Institute (now the Leibniz Institute for Virology) in Hamburg as head of human resources. He was also entrusted with the position of Deputy Administrative Director. After 7 years, Jörg Schinkel took the professional step to Braunschweig to take on the next challenge at a much larger research center, the Helmholtz Centre for Infection Research, and took over the center's HR department. Jörg Schinkel has been established there since 2009 and has also been deputy Administrative Director since November 2023.

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IT'S ABOUT THE BASIS OF OUR LIVES

With her newly established unit at HZI, Anne-Kathrin Winkler-Hanns is guiding development of concepts for sustainable research and management

Sustainable management in a research center – how does this work? Sterile workbenches, deep-freezing, autoclaves, disposable pipette tips, chemicals, laboratories, warehouses and offices under one roof: life science research consumes a wide variety of resources, such as energy, raw materials and space. Achieving significant savings here without restricting scientific output is a complex task. So is it better to concentrate on solar cells on the roofs – which are often already cluttered with building hardware – or on biodiversity measures in green spaces?

"These are all points that can be addressed," says Anne-Kathrin Winkler-Hanns. "The decisive factor is a coherent overall strategy that suits the center and its core task of infection research at the highest international level. To achieve this, we want to develop well thought-out concepts that are supported by the employees. And then we have to implement them together consistently, even if this means critically examining and, if necessary, changing familiar processes." Initiating, moderating and driving this development forward is the central task of the newly created Sustainability Department, which Anne-Kathrin Winkler-Hanns took over in April 2023.

The background to this are political requirements, but also the expectations of employees and potential junior staff. "The Helmholtz Association as well as politicians and funding bodies increasingly expect research institutions to contribute to climate and sustainability goals," explains Winkler-Hanns. In addition, employees are increasingly asking specifically about the meaningfulness of processes that waste resources; and junior staff now include the demonstrable sustainability performance of a potential employer in their job preferences. Centers like HZI will have to account for these aspects in the future: "From 2025, research institutions across the EU are expected to be subject to stricter reporting requirements for non-financial goals, known as sustainability reporting. This covers climate and environmental protection, biodiversity, plus governance and social sustainability within the company and along the supply chain."

Winkler-Hanns, who holds a humanities degree, has collected wide experience in the field of sustainability. For 15 years, she developed operational structures at Autostadt

> **THE DECISIVE FACTOR IS A COHERENT OVERALL STRATEGY.**

in Wolfsburg to anchor sustainability goals in practice, for example via the introduction of energy and environmental management as well as greenhouse gas reporting. She has implemented projects, such as the conversion of Autostadt catering to become "organic, seasonal and regional". She also designed high-profile formats, such as the exhibition LEVEL GREEN – The Idea of Sustainability as well as events, such as the Global Social Business Summit. To this end, she has developed and coordinated exchanges with researchers, NGOs and various departments within the company.

At the same time, she has continued to pursue her own research interests in cultural aspects of sustainability; completed her doctorate at Berlin's Humboldt University while working. She finally brought both aspects together as a project developer for new part-time courses in sustainability management at the Center for Sustainability Management at Leuphana University, Lüneburg, where she still works as a lecturer.

With this background, she applied for the newly established staff position at the HZI. Her interest about the center was initially piqued when she first became aware of HZI during the COVID-19 pandemic: "It provided balanced and far-sighted opinions on what was happening. I liked that and was impressed."

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> WE WANT TO INVOLVE EMPLOYEES AS CLOSELY AS POSSIBLE.

What she finds particularly exciting about infection research is that – from a sustainability perspective – light and shadow are closely interwoven: "The HZI has a very positive raison d'être in an ethical sense to research and combat diseases. We therefore contribute directly to the sustainability goal of global health through our work. On the other hand, many of the means and methods used to achieve this goal are unsustainable: a lot of waste is produced, energy is consumed, laboratory animals are used, research results are not always published in a way that is publicly accessible. However, this dialectical relationship between sustainable corporate purpose and partly non-sustainable practice is not God-given. It should – as is customary in science – be critically questioned, reflected upon and further developed with regard to its impact on planetary boundaries."

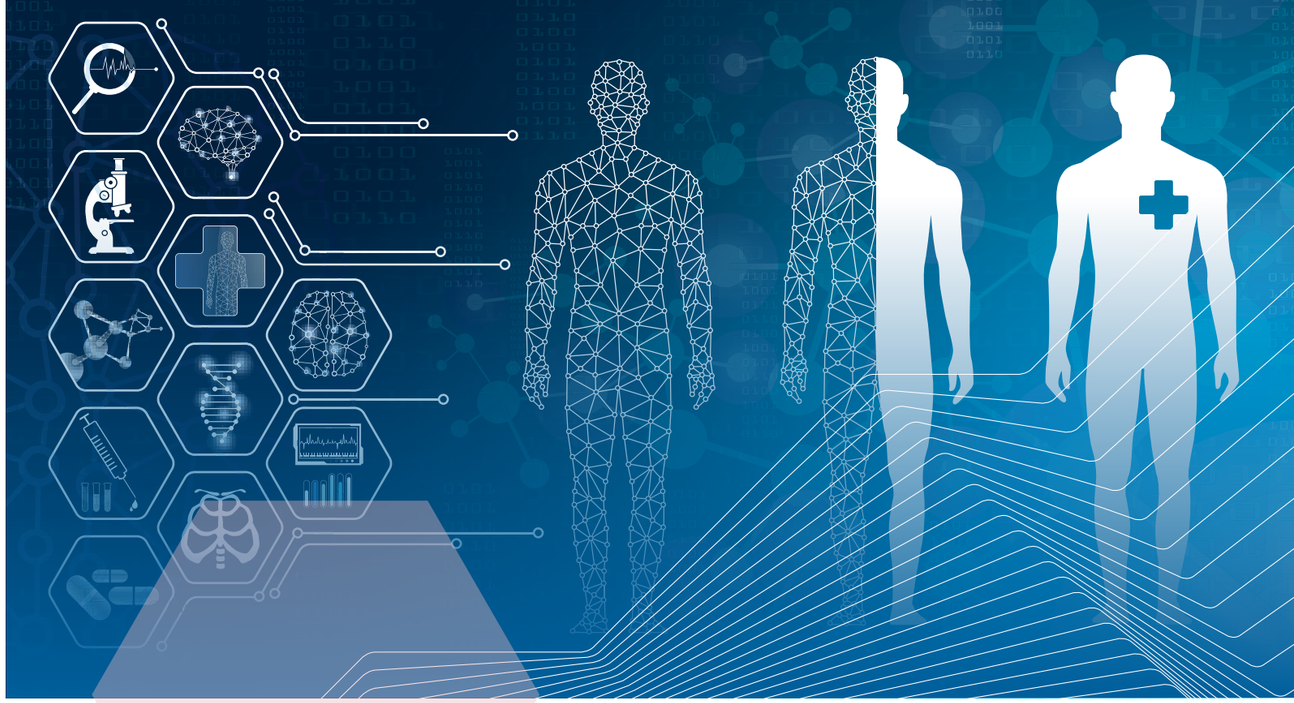
Winkler-Hanns further explains that she is aware that there is no quick and easy solution to many of the issues involved. This is why it is particularly important that measures be not simply "imposed from above": "We want to involve employees as closely as possible. This began with the development of the mission statement at the center, where we offered all relevant committees and interested parties the opportunity to participate in various event formats."

She was impressed by the response: "Fifteen percent of employees voluntarily took an active and committed part in developing the mission statement in writing, in discussions or workshops. That's really a lot, which wouldn't be the case everywhere." She likes the "highly developed culture of discussion" at the center: "Many colleagues who work here sense the importance of their work for the common good." The discussion of objectives has now been completed and 11 key fields of activity are defined. In addition to ecological sustainability aspects, such as climate protection and adaptation, energy-related emissions, water consumption, waste and biodiversity – social and ethical issues also play a role: human rights, diversity and equality are fundamental values that should guide future decisions and measures in administration and science, as well as governance-oriented corporate management.

Where do we go from here? "The guidelines and central goals are in place – now it's time to realize them," says Winkler-Hanns. She envisages a number of long-term projects. "For example, the architecture for the coming decades will soon be determined," she explains. "Climate neutrality and sustainability concepts will be very important here for economic reasons alone." The target of zero emissions by 2035 is on the table. "That is of course a very ambitious goal. This makes it all the more important to think carefully step by step on the way there. What should the organization achieve, what is it prepared to do, what can everyone do in their role to achieve this?" Equally central is how sustainability aspects are integrated into the center's future research strategy, for example by asking which viral and bacterial adaptation strategies can already be observed in current climate change hotspots.

Further steps include setting up a "green & colorful team" from all locations to advise on the process, identifying effective energy efficiency measures, converting green space management according to biodiversity characteristics, developing a diversity concept and establishing sustainable and human rights-oriented supply chain management.

"It is still difficult to estimate how far we will get in the next few years", says the sustainability officer. For her, developing an awareness of the fundamental issues involved is almost more important than individual measures and the implementation of legal and political requirements. "I think we should understand that ultimately it is not nature that is under threat and needs to be protected – it is constantly evolving anyway; rather, it is about the basis of our lives and work, and the desire for a successful life in a global world. Once we have understood this, we can approach changes with an open mind and agree on the right solutions for the HZI."



FROM BENCH TO BEDSIDE – FROM LAB TO CLASSROOM

INNOVATION MANAGEMENT AND TECHNOLOGY TRANSFER AT HZI

To effectively exploit research results for the benefit of society, technology transfer plays a central role at HZI. Based on its transfer strategy of November 2021, which is closely aligned with the research goals of the Pact for Research and Innovation, HZI has further developed its innovation ecosystem. Thus, innovative research results are continuously advanced along the technology readiness level towards application.

In addition to the establishment and professionalization of innovation management at HZI, existing structures, collaborations and alliances were further expanded, transfer culture and knowledge transfer strengthened and entrepreneurial thinking promoted.

Over the past two years (2022–2023) our office dedicated to Innovation Management and Technology Transfer (IMM) has been expanded to appoint an innovation officer in April 2023. The IMM team supports technology transfer (TT) activities within HZI and its sites. Collaboration with its long-standing TT service partner, Ascenion GmbH, has provided invaluable expertise and support for navigating the complexities of technology transfer and commercialization of research outcomes. The Life Science Foundation for the Promotion of Science and Research, a non-profit organization founded in 2001 where HZI was a founding member, supports research projects with TT potential from HZI.

Furthermore, to complement entrepreneurship activities at HZI, a full-time program manager position in entrepreneurship was established in summer 2023 to drive forward the H3 Health Hub - a Helmholtz Transfer Academy.

The **H3 Health Hub** (https://www.helmholtz-h3.de) was established in April 2023 by the six Helmholtz Health centers and funded by the Helmholtz Association for an initial three-year period led by HZI and DKFZ as co-coordinators. The H3 Health Hub will enable researchers, employees and aspiring entrepreneurs to successfully transfer results in the life sciences from lab into business (see box at the end of this article).

In addition, regular exchange with the technology transfer offices in the Helmholtz Association and especially Helmholtz Health as well as with the regional technology transfer offices at the Medical School Hannover (MHH), the University Medicine Göttingen (UMG) and Technical University Braunschweig (TU BS) were further intensified. Together with MHH and UMG, the **Institute for Biomedical Translation (IBT)** – an initiative funded by the Lower Saxony Advance Program administered by the Volkswagen Foundation to advance the transfer of biomedical innovations into application in the state of Lower Saxony - was established and its first portfolio conference held on June 16th 2023 in Hannover.

PRE-4D FUNDING HAS ENABLED MANY PROJECT TEAMS TO SUCCESSFULLY LEVERAGE ADDITIONAL THIRDPARTY FUNDING.

The HZI internal **Pre-4D** (Drug-Diagnostic-Discovery-Development) innovation fund, established at HZI in 2016 and consolidated in 2020, will continue at an annual funding level of Euro 390,000 with a gradually growing matching contribution by HZI of €300,000 until 2024. The objective is to increase the technology readiness level (TRL) of basic research projects along the TRL spectrum raising their attractiveness with regard to licensing for industrial partners or spin-off companies.

Over the 2022–2023 reporting period, 13 projects received funding through the Pre-4D innovation fund. Project topics range from diagnostic testing in Sars-CoV-2, hit-to-lead drug discovery, performing critical pharmacological studies and obtaining proof-of-concept to the evaluation of a mouse cytomegalovirus (MCMV) based vaccine vector against COVID-19. The Pre-4D funding enabled all projects to advance their TRL by mostly one level. This support has also enabled many project teams to successfully leverage additional third-party funding.

THE OBJECTIVE IS TO INCREASE THE TECHNOLOGY READINESS LEVEL.

For example, further funding could be secured for small-molecule sliding clamp (DnaN) inhibitors for the treatment of Gram-positive bacterial infections from the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator **CARB-X**, a global non-profit partnership accelerating antibacterial products to address drug-resistant bacteria, starting at the beginning of 2024.

Furthermore, various project teams were successful in attracting significant external funding for transfer related activities during 2022–2023.

Four transfer projects in the field of new antiviral agents started in 2021 with HZI participation (two as principal investigators and two as co-investigators), funded by the Federal Agency for Disruptive Innovation **SPRIN-D**. Three of them received funding for the second year in 2022, and finally two teams received funding for the remaining third year at the last interim evaluation in 2023 with the HZI team being in a subcontractor role.

With the **GO-Bio Initial Program**, the BMBF supports the identification and development of early life science research approaches with recognizable innovation potential. In the period 2022/2023, four projects were selected for the first stage of GoBio Initial in the conceptual phase. During this phase an idea for a potential commercialization pathway and an implementing strategy are developed over a term of up to 12 months. One project from the 2022 round received further funding for a subsequent feasibility stage during which the development work is taken forward to the proof-of-principle stage over a term of up to 24 months starting late 2023. One earlier project completed the feasibility phase in autumn 2023.

In 2022, two calls for proposals were issued by the Helmholtz Association as part of the Helmholtz Transfer Campaign. Three teams from HZI successfully secured funding for a two-year period.

Within the **Helmholtz Enterprise Program**, five HZI teams were each awarded a Field Study Fellowship in 2022/2023 and successfully completed the market research study with regard to their potential spin-off ideas. Four additional fellowships were acquired in 2023 to be conducted in 2024.

In 2023, four spin-off teams at HZI received funding for 14 months as part of the Helmholtz Enterprise Spin-off Program. One team had already spun off in summer 2023, the other three will start their projects in 2024.

The team developing the diagnostic tool **LEOPARD** at HIRI in Würzburg received support through the GO-Bio initial program from the BMBF in 2020 (conceptual phase) and 2021

Leopard™ Biosciences

Constantinos Patinios, Chase Beisel and Mikkel Noerholm from the spin-off company Leopard Biosciences.
© HIRI | Luisa Macharowsky

Meeting of the SORMAS Foundation's board of trustees at the WHO Hub in Berlin: The Managing Directors of the SORMAS Foundation, Jan Böhme (left) and Pilar Hernandez (second from right) with members of the board: Natalie Mayet (second from left) - Deputy director of the South African Public Health Inst., Paul Biondich (center) - Director, Global Health Informatics Program at the Regenstrief Institute, and Patrick Nguku (right) - Director of the African Field Epidemiology Network (AFENET) Nigeria. © SORMAS Foundation

(feasibility phase) as well as through the Medical Valley Award program in Bavaria (2021-2023). A successful application to the Helmholtz Enterprise Spin-off Program in 2023 enabled to spin off LEOPARD Biosciences GmbH in July 2023 in Munich as well as a subsidiary, LEOPARD Biosciences ApS, in Copenhagen, Denmark shortly thereafter. This was required since the team was accepted into the Denmark-based BII Venture Lab cohort 2023/2024 and is receiving a convertible loan of € 500.000 for the further development of the product.

Prominent speaker at the SORMAS conference in Berlin: Chikwe Ihekweazu, Assistant Director General at the World Health Organization WHO, with Rita Okonkwo - Project Director, Strengthening Global Health Security Agenda in Nigeria Project (SECURE-Nigeria) - Institute of Human Virology Nigeria (IRCE). © SORMAS Foundation

In July 2022, with the support of the Friends of HZI (Förderverein des HZI e.V.) the **SORMAS Foundation** (https://www.sormas.org) was founded as a non-profit organization to support local, national and international organizations worldwide in the development and implementation of SORMAS and other digital open-source systems for disease prevention and control. With its currently 15 strong team, SORMAS has a major contract with the health authorities from Luxembourg and is currently extending its work focus to sub-Saharan African countries in collaboration with the German Federal Development Agency.

Presenting SORMAS at the kickoff conference in Berlin, October 2023: Managing Director Pilar Hernandez © SORMAS Foundation

Speaker and guest at the SORMAS conference in Berlin: Rimamdeyati Usman Yashe – Head of the Event-Based Surveillance & Community-Based Surveillance (EBS/CBS) at the NCDC (Nigeria Centre for Disease Control) © SORMAS Foundation

At the international level, the project developing small molecule inhibitors of alpha-hemolysin for the treatment of *S. aureus* lung infections successfully acquired funding for the second phase (the lead optimization phase) of the CARB-X program to confront the challenge of growing antimicrobial resistance in close collaboration with the Lead Discovery Center GmbH. In the 2023 Oral Therapeutics round of CARB-X, four project applications were submitted in April of that year. Of these, the **project DnaN** by Anna Hirsch was awarded funding (see above).

SORMAS IS EXTENDING ITS WORK FOCUS TO SUB-SAHARAN AFRICAN COUNTRIES

To increase awareness within the broader research community at HZI regarding innovation and the value of technology transfer, several initiatives emerged during the reporting period. The transfer service partner Ascenion GmbH held a series of workshops exclusively for HZI members, related to transfer relevant aspects as, for example, from life sciences into business. The continuous education program **"Translational research & medicine: from idea to product"** offered by the Translational Alliance in Lower Saxony (TRAIN) in the TRAIN Academy is a joint initiative between HZI and various regional partners in the life sciences. HZI awarded several scholarships for this accredited training program on transfer relevant aspects in the biomedical field. Two complementary entrepreneurship programs by Young Entrepreneurs in Science (YES) for graduate level researchers were offered in 2022/2023 in collaboration with the Falling Wall Foundation.

Stefan Scherer & Heike Bauer ■

Making researchers fit for transfer: H3 workshop (left), H3 managers Silke Uhrig-Schmidt and Christian Brandstetter (right). © H3 Health Hub

TRAINING SCIENTISTS FOR THE BENEFIT OF SOCIETY

THE H3 HEALTH HUB – A HELMHOLTZ TRANSFER ACADEMY

When considering the transfer of research findings into applications for the benefit of society, entrepreneurship training increasingly plays a central role. Such training can provide crucial insights and meaningful skills for both established and junior researchers, thereby imparting expertise to commercialize their findings and maximize societal impact. Furthermore, it can help to establish first useful contacts relevant for successful transfer.

The *H3 Health Hub - A Helmholtz transfer academy* is a joint program of the Helmholtz Health Centers throughout Germany. It serves as a central platform for entrepreneurship training and development in the Life Sciences and fosters the establishment of an online community in the field.

Following the successful application in 2022 in response to a call for proposals as part of the Helmholtz Transfer Campaign, H3 started in mid-2023. In the beginning, it focused on refining objectives and goals using Design Thinking methods and bringing two full time Program Managers Entrepreneurship on board: Christian Brandstetter with expertise in entrepreneurship at HZI in Braunschweig, and Silke Uhrig-Schmidt with expertise in the life sciences at DKFZ in Heidelberg. They combine their complementary skill sets to set up the H3 platform involving all six Helmholtz Health Centers.

After the implementation of the relevant technical components and involvement of personnel from technology transfer, innovation management as well as human resource and career development, H3 combines entrepreneurship training with important opportunities for exchange between researchers from different research fields and active in various transfer projects. Thereby, it closely cooperates with regional partners, such as the Transfer Academy from the Translational Alliance in Lower Saxony (TRAIN), Young Entrepreneurs in Science (YES), and others. For details see the website https://www.helmholtz-h3.de launched in early 2024.

H3 provides diverse formats in entrepreneurship training at the various Helmholtz Health Centers. These include, e.g., the workshop *Roadmap to Transfer* event conducted by Ascenion and with support from the High Tech Gründer Fonds (HTGF) in November 2023 at HZI, which was open to all members in the community, as well as various formats jointly organized with partners from the life science ecosystem (TRAIN, YES etc., see above).

By participating in the H3 Health Hub, researchers benefit from a supportive and people-oriented environment that bridges academia and the economy, thereby enhancing the translation of scientific discoveries into application for impact in society.

Christian Brandstetter/Stefan Scherer/Heike Bauer ■

SCIENTIFIC EVENTS AT HZI 2022/23

SELECTED AWARDS TO HZI MEMBERS 2022

The Faculty of Medicine of the Julius-Maximilians-Universität Würzburg awarded an **honorary doctorate to Dirk Heinz**. The title recognises his extraordinary achievements in the fields of structural and infection biology as well as his commitment to shaping the German research landscape.

The highest honor for a scientist with outstanding contribution to the study of fungal biodiversity, the **Josef Adolf von Arx Award**, was awarded to **Marc Stadler** by the Westerdijk Institute in Amsterdam.

For the development of the diagnostic platform LEOPARD, **HIRI scientist Chase Beisel** and Cynthia Sharma from the Julius-Maximilians-Universität Würzburg received the **Pettenkofer Prize**, which is awarded annually by the Pettenkofer Foundation.

HIRI researchers **Mathias Munschauer** and **Alexander Westermann** were both awarded a prestigious ERC Starting Grant. Mathias Munschauer uses his **ERC Grant** to investigate the interplay between the RNAs of SARS-CoV-2 and factors of the host cell. Alexander Westermann aims to better understand the interaction between host cells, gut bacteria and pathogens and how the intestinal microbiota could be used to combat infections.

The list of **"Highly-cited researchers"** is published annually by Clarivate Analytics to honor scientists who have had a particularly great impact on their fields and are among the most cited 1 percent of the respective field. In 2022, three scientists of HZI were among the honorees on the list: Biochemist **Jörg Vogel**, bioinformatician **Alice McHardy**, and biotechnologist **Marc Stadler**.

Martin Korte and his project "Homeo Hirn" were awarded the second prize of the **North German Science Award** (Norddeutscher Wissenschaftspreis). In this project, the complex interplay of nerve cells in the brain is investigated to better understand the processes that cause a disturbed metabolic homeostasis in these cells, a possible cause for Alzheimer's disease and other forms of dementia.

Berit Lange was elected to the **Board of Directors of the German Society for Epidemiology** and will serve as a director for two years beginning in 2024.

This year, the Friends of HZI recognised with their annual PhD awards **Chantal Bader** (HIPS) and **Birthe Reinecke** (TWINCORE) for their outstanding PhD theses.

HIGHLY CITED RESEARCHERS 2022/23

PRIZES and AWARDS

Alexey Gurevich
@ HIPS | Dietze

Alice McHardy
© Yamel Photography

Yang Li
© Tom Figiel

Marc Stadler
@ HZI | Janos Krüger

Jörg Vogel
© HIRI | Nik Schölzel

Till Strowig
© HZI | Verena Meier

Andreas Keller
@ HIPS | Dietze

Josef Penninger
© HZI | Stephan Dublasky

SELECTED AWARDS TO HZI MEMBERS 2023

Anna Hirsch, head of the department "Drug Design and Optimisation" at HIPS, succeeded in acquiring a second ERC grant, this time under the "Proof of Concept" funding program. She receives funding to further optimise her most promising drug candidate against antibiotic resistant bacteria.

Gérard Krause was honored for his outstanding contributions to the field of translational infection epidemiology and in particular for the development of the epidemic management software SORMAS with the **DZIF prize for Translational Infection Research**.

The 2023 **PhD Awards** of the Friends of HZI went to **Alaa Alhayek** (HIPS), **Chunlei Jiao** (HIRI) **and Bernard Silenou** (Founding Campus Braunschweig).

In addition, **Chunlei Jiao** from the HZI site HIRI received the **Doctoral Prize of the Helmholtz Association** in the research field Health. He was honored in the category "application-oriented research" for his achievements in paving the way for the development of the CRISPR-based RNA detection and recording platforms known as LEOPARD and TIGER.

Neva Caliskan (HIRI) has been elected to the **Board of Directors of the RNA Society** and will serve as a director for two years beginning in 2024.

The Society for Industrial Microbiology and Biotechnology (SIMB) honored **Rolf Müller** (HIPS) with the prestigious **Charles Thom Award**. The prize recognizes his outstanding contributions to the scientific community, emphasizing the importance of his research in advancing industrial microbiology and biotechnology.

HZI scientist Rolf Müller (left in the picture, with SIMB Präsident Nigel Mouncey) during the award ceremony of the Charles Thom Award in Minneapolis. © SIMB, 2023 SIMB Annual Meeting

The Academy of Sciences and Humanities in Hamburg honored **Fabian Leendertz** (HIOH) for his achievements in the field of zoonotic infectious diseases applying the "One Health" concept with the **Hamburger Wissenschaftspreis 2023** (Hamburg Science Award).

The Hamburg Academy of Sciences awarded Fabian Leendertz (middle), the Hamburg Science Prize. Left: Eva-Maria Greve, Hamburgische Stiftung für Wissenschaften, Entwicklung und Kultur Helmut und Hannelore Greve, right: Mojib Latif, President of the Hamburg Academy of Sciences and head of the jury. Source: Jann Wilken |© AdWHH

The virologist and scientific co-director of HZI, **Thomas Pietschmann**, was elected to the **Executive Board of the German Center for Infection Research** (DZIF). He succeeds Dirk Heinz, who has served on this board since the establishment of the DZIF in 2012.

In 2023, seven HZI members were honored as **"Highly Cited Researchers"**: **Alexey Gurevich, Andreas Keller, Yang Li, Alice McHardy, Marc Stadler, Till Strowig** and **Josef Penninger**.

Katharina Schaufler (HIOH) received the **Sponsorship Award of The German Society for Hygiene and Microbiology**. She was recognized for her innovative research approaches and outstanding results for her research in analyzing the development of antibiotic resistances.

Jörg Vogel (HIRI) has been elected a full member of the **Bavarian Academy of Sciences and Humanities**. Becoming a member of this academy is one of the most prestigious scientific honors in Bavaria.

Jörn Piel (right) received the Inhoffen Medal 2023 from Klemens Rottner, Chairman of the HZI Förderverein (Friends of HZI). © HZI | Verena Meier

Christian Hertweck (second from left) and Sarah Reisman, awardees of the Inhoffen Medals 2020 and 2022, with their laudators Wilhelm Boland (left) und Alois Fürstner (right). © TU Braunschweig | Kristina Rottig

MEETINGS

Inhoffen Medal for outstanding pioneer work

The Inhoffen Medal, endowed with 8,000 euros, is considered the most prestigious German prize in the field of natural products chemistry. It is awarded since 1992 jointly by HZI, the Technische Universität Braunschweig (TU-BS) and the Friends of HZI (HZI-Förderverein).

The awarding ceremony is associated with the "Inhoffen Lecture" in honor of the biochemist Hans-Herloff Inhoffen, an event organized jointly by HZI and TU-BS. Inhoffen was director of TU-BS and co-founder of the Institute for Molecular Biology, Biochemistry and Biophysics (IMB), from which HZI subsequently emerged.

In 2022, the prize was awarded to Sarah Reisman, who is heading a research group at the California Institute of Technology and works on innovative syntheses of molecules with medical applications.

In addition, Christian Hertweck from the Hans Knöll Institut (HKI) in Jena was belatedly awarded with the Inhoffen Medal 2020. The ceremony for Christian Hertweck had been postponed several times due to the SARS-CoV-2 pandemic.

The Inhoffen Medal 2023 went to Jörn Piel, Swiss Federal Institute of Technology (ETH) Zurich. He was honored for his work on natural products from marine sources. He investigates how structurally complex molecules are produced.

One Health Conference and other meetings in Greifswald

In April 2022, more than 500 participants met virtually and in person in a hybrid format at the One Health conference, which followed the official founding ceremony of HIOH (*see chapter "A German Hub for One Health Research" in this Report*). The conference was held at the Alfried Krupp Wissenschaftskolleg in Greifswald and dealt with latest developments in One Health research.

A strategy development workshop on One Health surveillance was held on 1-2 December 2022 (funded by the German Alliance for Global Health Research GLOHRA). 35 guests from 14 local and international research institutions participated.

Six collaborative projects were approved and will be funded by HIOH seed grants to strengthen collaboration between HIOH and its collaborators. The third round of funding, focusing on One Health surveillance projects, started with a kick-off meeting on 7-8 December 2023 with around 50 participants.

Focus on Natural Compounds: The HIPS-Symposium

The HIPS symposium, organised by HZI's Saarbrücken branch, the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), brings together renowned scientists and young investigators from various pharmaceutical communities: natural products, medicinal chemistry, drug delivery and

clinical bioinformatics. It provides a forum for scientists to exchange ideas while crossing boundaries of classical disciplines. At the same time it gives young investigators the opportunity to obtain valuable feedback on their projects by international experts in the respective fields.

In May 2022, more than 350 participants joined the conference online. Speakers included Patrick Baumhof (CureVac), Wilhelm Boland (Max Planck Institute for Chemical Biology), Matthias Rarey (University of Hamburg), Christian Lerner (Hoffmann-La Roche), Wilfred van der Donk (University of Illinois), Emilie Racine (Nosopharm).

In May 2023, the HIPS symposium took place as a hybrid meeting. Altogether over 330 participants joined on-site and online. Speakers included Ruxandra Gref (Institut de Sciences Moléculaires D'Orsay), James Naismith (Rosalind Franklin Institute), Paul Wilmes (Luxembourg Centre for Systems Biomedicine), Caren Freel Meyers (Johns Hopkins School of Medicine), Sarah O'Connor (Max Planck Institute for Chemical Biology), and Jörn Piel (ETH Zürich).

HZI/EMBL Symposium

At the end of October 2021, a joint hybrid symposium was held between HZI and EMBL with around 200 participants. Talks focused on "Interfaces" at the organism, intercellular and intracellular level and their specific modulation.

TWINCORE Symposium

The annual TWINCORE Symposium has established itself as an important platform to present and discuss topics at the interface between basic and clinical research.

TWINCORE's Executive Director Ulrich Kalinke at the TWINCORE Symposium 2022. © TWINCORE | Carpentier

TWINCORE Symposium 2022 © TWINCORE | Carpentier

In September 2022, the 14th TWINCORE symposium was held, focusing on "Lessons from the pandemic for future infection research". It was jointly organized with the "International VPM Days", the annual symposium of the Vakzine Projekt Management GmbH (VPM; later renamed "Serum Life Science Europe GmbH", or SLS Europe).

In 2023, the 15th TWINCORE symposium took place under the title "15 years of translational infection research".

The annual meeting of the Scientific Advisory Board of TWINCORE is regularly held on the day before the symposium to enable the Advisory Board members to attend the symposium.

Vaccine Workshop at HZI

In 2022/23, HZI scientists organized the meeting of the Vaccines Study Group of the German Society for Immunology (DGfI) on two occasions.

On January 12 to 13, 2022 the meeting took place online via Zoom with numerous updates on new scientific advances by the attending scientists. Focusing on "Vaccines in the Public Eye", a panel discussion addressed communication strategies to help improve general acceptance of vaccination, combat misinformation, and facilitate professional exchange within the scientific community.

In 2023, the workshop was on-site at the HZI campus in Braunschweig on January 12 to 14. Keynote lectures were interspersed with talks selected from abstracts, which were additionally presented as posters. Three students with best abstracts were awarded. The audience discussed the subject of "Public Communication for Scientists about Vaccines" under the moderation of Diana Dudziak.

Helmholtz Drug Discovery Conference HDDC 2023

In May 2023, the International Helmholtz Drug Discovery Conference (HDDC) took place on HZI's Braunschweig campus. New anti-infectives were the main topic, along with other areas such as "Artificial Intelligence in Drug Discovery", "Chemistry-driven Drug Innovation" and "From Biological Mechanisms to Novel Drug Targets". The conference attracted 13 international keynote speakers and welcomed more than 230 participants. Speakers included, among others, Erick Carreira (ETH Zürich), Christa Müller (Bonn University) and Stuart Conway (Oxford University / UC Los Angeles). The conference was financed by sponsors, including Roche as a "platinum sponsor".

CRISPR Conference at HIRI 2023. © HIRI | Luisa Macharowsky

CRISPR Conference

From June 27 to July 1, HIRI co-hosted the international conference "CRISPR 2023" with around 300 participants from all over the world. The event offered lectures, poster presentations and leisure activities and closed with a sightseeing day in Würzburg including a visit to the fair.

HIRI director Jörg Vogel at the Interacademy Conference "Microbiology 2023" in Würzburg. © HIRI | Luisa Macharowsky

HZI scientist Mark Brönstrup at the HDDC conference 2023. © HZI | Verena Meier

ISAM Conference in Saarbrücken

Pharmacists, physicians, biologists, physicists and engineers from all over the world met in Saarbrücken from 26 to 30 August, 2023. The 24th Congress of the International Society for Aerosol Medicine (ISAM) brought together more than 250 scientists from 20 countries on the campus of Saarland University. For five days, they exchanged ideas on respiratory diseases (for example caused by the corona virus), inhaled medicines and health risks caused by environmental aerosols.

The meeting was organized by the team of the conference chair Claus-Michael Lehr, Head of the Department "Drug Delivery" at HZI's Saarbrücken site HIPS and Professor for Biopharmacy and Pharmaceutical Technology at Saarland University.

Interacademy Conference "Microbiology 2023"

HIRI helped organize the Interacademy Conference "Microbiology 2023", which took place from September 20 to 22, attracting around 250 participants. In addition to interest-

Sandra Ciesek at the Alumni Event. © HZI | Verena Meier

Participants at the Alumni Event. © HZI | Verena Meier

ing lectures, visitors were treated to poster presentations, an editor session and a panel discussion. A special experience was a dinner in the historic wine cellar of the Würzburg Residence.

Alumni & Career Event

On 15 September 2023, around 60 former and current members of HZI met at HZI Science Campus for the Alumni & Career Event 2023. Alumnus Gérard Krause gave a lively overview of his career from being a trained medical doctor to becoming head of the department "Surveillance Systems" at the WHO. Afterwards, nine invited alumni with very different career paths in e.g. academia, industry or as entrepreneurs briefly presented themselves and were available for individual conversations at the following Career Fair. Young scientists of HZI used the chance to ask questions and become inspired for their own careers. Among the invited alumni was this years' prizewinner of the Jürgen Wehland Award, Stephanie Pfänder. The day was rounded off with a talk by alumna Sandra Ciesek, now director at the Institute for Medical Virology at the Universitätsklinikum Frankfurt, who also shared her experiences in the communication with the public in an entertaining way.

Jürgen Wehland Prize

Directly after the Alumni & Career Event (see above), virologist Stephanie Pfänder was awarded the Jürgen Wehland Prize 2023 to honor her outstanding contributions to the field of infection research. Stephanie Pfänder is a junior professor at the Ruhr-Universität Bochum. Her research focuses on emerging viruses such as coronaviruses and their interaction with the host.

Stephanie Pfänder, awardee of the Jürgen Wehland Prize 2023, with HZI's Administrative Director Christian Scherf (right) and Klemens Rottner, Chairman of the Friends of HZI. © HZI | Verena Meier

Thorsten Kornblum, mayor of the city of Braunschweig, Grant Hendrik Tonne, Lower Saxony's Minister of Education, and Dirk Heinz, Scientific Director of the HZI, talking to students in the BioS laboratory. © HZI | Verena Meier

20 YEARS OF SUCCESSFUL KNOWLEDGE TRANSFER

STUDENT LAB BIOS CELEBRATES ITS ANNIVERSARY

The Biotechnology Student Laboratory Braunschweig (BioS) offers high school students opportunities to learn basic bioscientific methods in a state-of-the-art laboratory setting under the guidance of scientists and researchers. The lab is funded and scientifically supported by HZI, the Technical University of Braunschweig (TU-BS), the Leibniz Institute DSMZ - German Collection of Microorganisms and Cell Cultures and the state of Lower Saxony on the Science Campus Braunschweig-Süd. The BioS sees itself as a bridge between schools, university and research.

In June 2022, this extracurricular place of learning celebrated its 20th anniversary.

BioS started with a single course in 2002. Today, schools can choose from 21 thematically different courses and programs. Most courses are offered as full day programs using educational content and provide an authentic laboratory experience for participants. More than 33,000 high school students have attended courses in the BioS program over the past 20 years.

From left to right: Jörg Overmann, Scientific Director of DSMZ, Minister Björn Thümler, Angela Ittel, President of TU-BS, Dirk Heinz, Mayor Thorsten Kornblum, Minister Grant Hendrik Tonne, Ralf-Rainer Mendel, Chairman of BioS e.V. © HZI | Verena Meier

The Ministry of Education and Cultural Affairs in Lower Saxony (*Kultusministerium*) supports the BioS by providing teaching positions, while HZI hosts the laboratory and provides additional support through a dedicated technical assistant. The other partners, namely TU Braunschweig and the Leibniz Institute DSMZ, cover the annual budget, which is used to finance consumables, new equipment or repairs as necessary.

Stefan Scherer | Heike Bauer | Andreas Plink ■

The founding partners of HIOH at the founding ceremony in April 2022: HIOH founding director Fabian Leendertz (front row, second from right), Katharina Riedel, rector of the University of Greifswald (back row, second from right), Thomas Mettenleiter, president of the Friedrich-Loeffler-Institut (FLI, Federal Research Institute for Animal Health; back row, left), Karlhans Endlich, dean of University Medicine Greifswald (back row, second from left) and Dirk Heinz, Scientific Director of HZI (back row, right) with Bettina Stark-Watzinger, Minister of Education and Research (front row, second from left), Bettina Martin, Minister for Science, Culture, Federal and European Affairs of the State of Mecklenburg-Vorpommern (front row, left) and Otmar Wiestler, president of the Helmholtz Association (front row, right). © Martin Pauer

A GERMAN HUB FOR ONE HEALTH RESEARCH

RESEARCH AT THE INTERFACE OF HUMANS, ANIMALS AND ENVIRONMENT: OFFICIAL FOUNDATION OF HIOH IN APRIL 2022

The Helmholtz Institute for One Health (HIOH) was ceremonially founded on 26 April 2022 in Greifswald. The HIOH is a new institute of HZI, established together with the University of Greifswald, the Greifswald University Medicine and the Friedrich-Loeffler-Institut/Federal Research Institute for Animal Health (FLI) as local founding partners. The founding director is the veterinarian and microbiologist Fabian Leendertz. Research at the new institute focusses on the threats posed by the emergence of pathogens, as well as on the epidemiology and ecology of antimicrobial resistance (AMR) to common medicines and vaccines.

In addition to the heads of the founding partners and the President of the Helmholtz Association, Otmar Wiestler, the Federal Minister of Education and Research, Bettina Stark-Watzinger, and the State Minister of Science, Culture, Federal and European Affairs, Bettina Martin, attended the founding ceremony, among others. Chikwe Ihekweazu, Deputy Director General of the World Health Organisation (WHO), and Lothar Wieler, President of the Robert Koch Institute (RKI), sent video messages. The founding ceremony was followed by a scientific meeting, the One Health Conference 2022, on 27 and 28 April 2022 (*see also section "Scientific Events" in this Report*).

> **HUMAN HEALTH CAN NO LONGER BE VIEWED IN ISOLATION. WE HAVE HAD TO LEARN IN RECENT YEARS THAT IT IS CLOSELY INTERTWINED WITH ANIMAL HEALTH, THE ENVIRONMENT AND ALSO ECOLOGICAL DIVERSITY.**

"Human health can no longer be viewed in isolation. We have had to learn in recent years that it is closely intertwined with animal health, the environment and also ecological diversity," said HIOH's Founding Director Fabian Leendertz in his programmatic speech.

The One Health research concept set up by the founding partners had been reviewed positively in November 2021 – "now it has to prove itself", Leendertz concluded.

Since its foundation, HIOH has grown with remarkable speed, established three departments, two core units and one junior research group, and initiated a range of ambitious projects (*see section "HZI's Sites" in this report for more details*).

HIOH director Fabian Leendertz welcoming guests at the foundation ceremony. © Martin Pauer

Group picture from left to right: Josef Penninger (HZI), Dirk Heinz (HZI), Renke Deckarm (EU Commission), Christian Scherf (HZI, Background), Judith Pirscher (BMBF), Markus Söder (Minister President of Bavaria), Jörg Vogel (HIRI), Rainer Post (doranth post architekten, Background), Otmar D. Wiestler (Helmholtz Association), Christian Schuchardt (Würzburg), Roland Weigert (StMWi), Matthias Frosch (JMU). © HIRI | Mario Schmitt

A NEW HOME FOR RNA RESEARCHERS

HELMHOLTZ INSTITUTE WÜRZBURG (HIRI) CELEBRATES LAYING OF FOUNDATION STONE

Attended by numerous guests, cooperation partners and associates, the Helmholtz Institute for RNA-based Infection Research (HIRI) in Würzburg celebrated its groundbreaking ceremony on July 6, 2023. The institute, a site of the HZI founded in 2017 in cooperation with the Julius-Maximilians-Universität (JMU), will occupy its own building on the Würzburg medical campus. The project will be completed with funds from the Free State of Bavaria, represented by the Bavarian State Ministry of Economic Affairs, Regional Development and Energy, and co-financed by the European Union.

In his address to more than 200 guests from science, business, politics and the media, Bavaria's Minister President Markus Söder highlighted the importance of research in Würzburg for the Free State's future and innovation strategy: "Research and science are a high priority in the Free State of Bavaria. We are investing in the future: The new building for HIRI and its infection research will provide space for 130 employees by 2026."

Judith Pirscher, State Secretary at the German Federal Ministry of Education and Research (BMBF), underlined the outstanding scientific work of the Federal Government-funded Helmholtz facilities and said: "In the field of infection research, the Würzburg Helmholtz Institute is making a significant contribution to preserving the basis for life in the long term. A space is being created for research, thinking, and scope for our future. At the same time, basic RNA research enables the development of new technologies, ensuring that our country remains competitive in the future."

At the groundbreaking ceremony, HIRI director Jörg Vogel presented Bavarian Minister President Markus Söder with a custom-made RNA gift. © HIRI | Mario Schmitt

State Secretary Roland Weigert from the Bavarian Ministry of Economic Affairs, Regional Development and Energy emphasized: "The pandemic years have shown us the crucial importance of outstanding basic research for the development of diagnostics and therapy in the field of infectious diseases. This research excellence requires bright minds as well as a cutting-edge working environment."

Otmar D. Wiestler, President of the Helmholtz Association, Josef Penninger, who introduced himself to the guests as the new Scientific Director of the HZI, and Jörg Vogel, Managing Director at the HIRI, expressed their gratitude to the funders. They allow research at the highest level. And the new building plays an important part in this, said Vogel: "After six years of growth at our institute, we are running out of space and laboratory capacity in our interim domicile."

> **"AFTER SIX YEARS OF GROWTH AT OUR INSTITUTE, WE ARE RUNNING OUT OF SPACE AND LABORATORY CAPACITY IN OUR INTERIM DOMICILE.**

In 2018, an architectural competition was held with the objective of creating a new building for the Helmholtz Institute that would be future-oriented and cost-effective. The contract was awarded to doranth post architekten, an architectural firm based in Munich. The firm, working in Germany and abroad, has designed several science buildings.

The design for the new HIRI building envisions a slender, longitudinally oriented structure that harmonizes with its surroundings on the medical campus in terms of shape and size. At the same time, the institute's transparent glass façade, its open main staircase flooded with natural light and its fragmented cubature form a contemporary juxtaposition to the adjacent historic buildings dating to the Wilhelmine period.

The new HIRI building © doranth post architekten

Laying of the foundation stone for the Center for Individualized Infection Medicine (CiiM). From left to right: Michael Manns, President of MHH; Falko Mohrs, Lower Saxony Minister for Science and Culture; Dirk Heinz, Scientific Director of HZI. © Karin Kaiser | MHH

BREAKING THE GROUND FOR PRECISION MEDICINE

JOINT INITIATIVE OF HZI AND MHH WILL GET ITS OWN RESEARCH BUILDING IN HANNOVER

A dedicated building is now being constructed in Hannover for the Centre for Individualised Infection Medicine (CiiM), a joint initiative of HZI and Hannover Medical School (MHH). The foundation-stone ceremony for the new building with 2100 square metres of effective space was held in November 2022 in the presence of numerous guests from politics and science.

CiiM, which was initially founded in 2015 as a virtual center, is addressing urgent challenges in infectious medicine with the aim of individualized prognosis and diagnosis of infectious diseases, enabling tailored prevention and optimized personalized therapy for the benefit of the individual patient *(see also chapter "CiiM" in the section "HZI's Sites" of this Research Report)*. The construction costs are covered by the federal government, the state of Lower Saxony, the Helmholtz Association and HZI.

"The COVID-19 pandemic has just shown us how important infection research and personalized medicine are - and that research findings need to be transferred more quickly from bench to bedside," said Lower Saxony's Science Minister Falko Mohrs in his speech at the ceremony. "The life sciences are among the most important drivers of innovation, especially in the metropolitan region of Hannover-Braunschweig-Göttingen-Wolfsburg, and promise significant improvements in diagnosis and therapy. The new research building in the Medical Park will give the interdisciplinary research groups of CiiM the opportunity to realize their vision of better individual patient care."

"By using state-of-the-art molecular, imaging and data-based technologies, research is being conducted at CiiM to understand the individual course of infectious diseases much more precisely than before, in order to be able to offer tailored treatments for individual patients or groups of patients in the future," said Dirk Heinz, then Scientific Director of HZI.

Michael Manns, President of MHH, added: "The CiiM research building is another documentation of the strategic partnership between MHH and HZI in Braunschweig. Personalized medicine is becoming increasingly important

> **"CIIM HAS INTERNATIONAL MODEL AND FLAGSHIP CHARACTER.**

for many areas of medicine in order to provide the individual patient with the optimal therapy in terms of effectiveness, tolerability and costs. CiiM has international model and flagship character for personalized infection medicine."

During the groundbreaking ceremony, moderated by the CiiM directors Yang Li and Markus Cornberg, a time-capsule was buried, which contained current impressions of the event as well as good wishes from the guests and future users of the CiiM.

Once completed, the CiiM building will allow patient data and samples to be systematically stored, processed and analyzed with state-of-the-art technologies under one roof. For example, the scientists are looking for individual characteristics that influence severity of disease. Here, the aim is to identify new biomarkers that can be used to tailor therapy. These could help defining who needs to be treated particularly quickly, how long treatment should last and what happens to patients who do not respond well to treatment. This individualized approach will help to reduce the burden of disease, improve the quality of life of those affected and reduce the healthcare costs caused by infections. CiiM will thus combine the internationally unique expertise from clinical practice, research and data science in a transdisciplinary workflow that focuses on the individual infection patient and their best possible treatment.

Laying of the foundation stone for the Center for Individualized Infection Medicine (CiiM). Second from left: Falko Mohrs, Lower Saxony's Minister for Science and Culture; second from right: Veronika von Messling, Chairperson of HZI's Supervisory Board. © Karin Kaiser | MHH

Appreciation for infection research in Lower Saxony: The state's Minister President Stephan Weil (right) was welcomed at HZI by its Scientific Director, Dirk Heinz. © HZI | Verena Meier

SCIENCE FOR THE PUBLIC

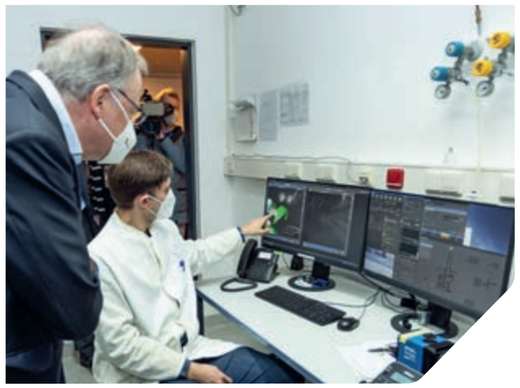
HIGHLIGHTS OF THE YEARS 2022 AND 2023

Politicians Visiting HZI

In 2022/23, several politicians visited HZI and its off-campus sites. For instance, the Minister President of Lower Saxony, Stephan Weil, visited the center on 4th February 2022. The visit focused on challenges and innovative approaches, especially in combating the SARS-CoV-2 pandemic, and the future development of infection research in Lower Saxony. Weil thanked all HZI employees for their efforts during the COVID-19 pandemic. Braunschweigs new mayor, Thorsten Kornblum, came to the Science Campus on May 6th, 2022 together with the Head of Department for Culture and Science, Anja Hesse. He described HZI as a "lighthouse visible from afar" and congratulated on its important contribution to combatting infectious diseases.

Collecting information about epidemics: German Federal Minister Bettina Stark-Watzinger (second from right and image below). © HZI | Verena Meier

On 28th July 2022 the Federal Minister for Education and Research, Bettina Stark-Watzinger talked to HZI scientists in order to find out more about pandemic preparedness, including those for Corona in autumn 2022, and the surveillance system "SORMAS" at HZI and DZIF.



Discussion with scientists: Stephan Weil in a Strutural Biology lab. © HZI | Verena Meier

© HZI | Verena Meier

Falko Mohrs, since November 2022 Minister for Science and Culture of Lower Saxony, visited HZI on 7th July the following year and was introduced to the research activities of the center at the Braunschweig campus with a focus on microbiota and drug research. Apart from special visits, numerous politicians also took part in events and ceremonies at HZI, for instance the 20th anniversary of the Biotechnological Student Laboratory BioS in June 2022 (see below), or the handover ceremony of Scientific Management on 4th December 2023, which was attended by Lower Saxony's Minister President Stephan Weil, among others.

HZI Director Josef Penninger greeting State Minister Falko Mohrs. © HZI | Verena Meier

State Minister Falko Mohrs talking to HZI staff. © HZI | Verena Meier

Public Outreach

A total of around 200 visitors in 2022 and more than 230 visitors in 2023 came to the Braunschweig campus of HZI. Some examples are the Braunschweig Rotary Club, a group of former GBF scientists, the Ministry of Finance of Lower Saxony and the DFK/Association for Specialists and Executives.

HZI organised and took part in several outreach events, such as the Readers' Forum of the Braunschweiger Zeitung (BZ) on 25.03.2022 which was moderated by Henning Noske (BZ), together with HZI scientists Melanie Brinkmann and Dirk Heinz as well as Dirk Brockmann from the Humboldt University, Berlin. They explained the pandemic situation in a panel discussion and answered questions from the audience.

A ceremony to mark the 20th anniversary of the BioS/Biotechnologisches Schülerlabor (Biotechnological Student Laboratory) took place on 09.06.2022 at HZI (see page 53).

Björn Thümler, then Lower Saxony's Minister of Science and Culture, and Grant Hendrik Tonne, Lower Saxony's Minister of Education, took part in the event, as did Braunschweig's mayor, Thorsten Kornblum, and the heads of the participating institutions. A group of school students from the IGS Peine was also present.

Both in 2022 (May 13th) and 2023 (May 10th), HZI participated in the "Salon der Wissenschaft", an event organised by the Haus der Wissenschaft to inform the public. In a relaxed dialog format, a direct exchange between citizens and researchers was made possible at an evening event. Participants from HZI in 2022 included Carsten Peukert, Department of Chemical Biology, and Miriam Große, Department Microbial Drugs; and in 2023: Miriam Große und Janyn Heisig (Vaccinology).

@ HZI | Rolf Rosenstock

Sound of Science:

HZI's Public Relations department started a podcast series in winter 2023. Experts like epidemiologist Berit Lange (photograph left) explain their research and its benefit for society to interested listeners on a regular basis.

Soil sampling in search of novel drugs: The project MICROBELIX, initiated by HZI's Saarbrücken branch, HIPS.
© HIPS | Daniel Krug

HANDS-ON RESEARCH FOR EVERYONE

CITIZEN SCIENCE PROJECTS AT HZI

Though scientific research often requires sophisticated equipment and high safety standards, there are also occasions where the broad public can contribute to obtain meaningful insights for researchers.

In recent years, many research institutes have developed forms of participative research. At HZI, as well, scientists increasingly involve citizens in projects where the collection of data from a large number of independent sources is helpful and feasible. These Citizen Science projects not only provide additional data for scientists – they also help to refine the broad public's understanding of how science works.

MICROBELIX: Microbial biodiversity in soil

As part of the Citizen Science hands-on campaign "MICROBELIX", citizens are collecting soil samples in regions throughout Germany with an expected high biodiversity. From these samples, previously unknown microbial strains are then isolated at the HZI site HIPS in Saarbrücken and tested for the production of bioactive natural products as a source for novel antibiotics.

The project, which initially was named "The Microbial Treasure Chest", was represented with an exhibit at the hands-on exhibition on the MS Wissenschaft in 2022. Subsequently, it became the collaborative project MICROBELIX, jointly launched in spring 2023 by researchers from HIPS and the Naturlandstiftung Saar (NLS). Together, both institutions set out to compete in the citizen science contest "Auf die Plätze! Citizen Science in deiner Stadt" and claimed one of the three winning places with over 2,000 votes from the public, as well as a 50,000 € prize.

Until the end of the school year 2023/24, students in the 9th and 10th grades will be introduced to topics such as biodiversity, climate change, infections and antimicrobial resistance in twelve units of the elective subject ecology. They also learn basic methods of molecular and microbiology, which they can use to conduct their own experiments with the support of the scientists.

In the CiFly citizen science project, flies are used as collectors of DNA from the environment in order to map biodiversity and possible zoonotic pathogens and their resistance in relation to various environmental influences.

CiFly is part of the One Health region of Western Pomerania, which is supported by the Federal Ministry of Education and Research as part of the "T!Raum - TransferRäume für die Zukunft von Regionen" initiative led by the University of Greifswald.

"CiFly": Flies help determine species diversity

In a recently launched project, school students from the Humboldt-Gymnasium in Greifswald and scientists from the HZI site HIOH jointly investigate biodiversity and pathogens with the help of flies.

Flycatchers for science: The HIOH project "CiFly".
Photos: Svea-Marie Essen, © HIOH

Air Quality and Health Data: SMARAGD / PIA

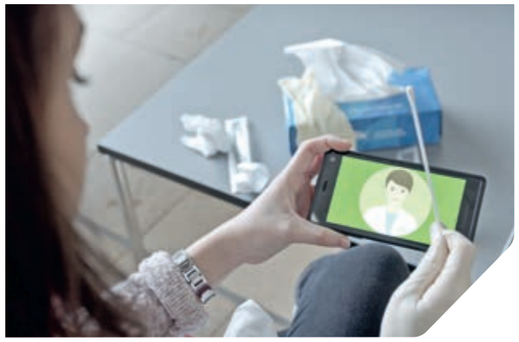
What influence does local pollution in German city centers have on acute respiratory infections? The SMARAGD project (short for: "Sensors for Measuring Aerosols and ReActive Gases to Deduce health effects") is addressing this question as part of a Citizen Science feasibility study in Cologne. The project involves experts from the Forschungszentrum Jülich (FZJ) and citizens of the city of Cologne.

The pollutants are recorded using mobile sensors; the focus here is on particulate matter, nitrogen oxides, ozone and carbon monoxide.

The technical core of SMARAGD is PIA (Prospective Monitoring and Management-App), a free and open source (FOSS) eResearch system developed by HZI researchers (https://helmholtz.software/software/pia). Hence, PIA is freely available. In SMARAGD, participants use PIA to report on their state of health and possible associated factors.

Patients can collect their own health data with the app PIA developed at HZI.

istockphoto.com © PeopleImages



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HIGHLIGHT PUBLICATIONS

Fungal spores (Laccaria) © HZI Mathias Müsken

A UNIQUE CLASS OF CAS NUCLEASES SHUTS DOWN INFECTED BACTERIA THROUGH EXTENSIVE DNA DESTRUCTION

CHASE BEISEL
HEAD OF DEPARTMENT SYNTHETIC RNA BIOLOGY

CRISPR-Cas defenses protect bacteria and archaea by recognizing sequences of foreign nucleic acids. This recognition is then followed by an immune response that either destroys the infection or shuts down the infected cells. Our group recently discovered a CRISPR-Cas nuclease called Cas12a2, which imparts immunity in a distinctive way—by indiscriminately degrading DNA within the infected cells upon detecting RNA of the infection.

In a recent study [1], we identified a single-effector CRISPR nuclease called Cas12a2 that imbues bacteria with a unique defense mechanism against genetic intruders (Figure 1). Unlike the closely related Cas12a, which cuts DNA at the target site dictated by the CRISPR RNA (crRNA) (Figure 2), Cas12a2 targets RNA, initiating a process that indiscriminately destroys RNA and DNA within the cell (Figure 3). This mechanism effectively stops the spread of infection by sacrificing the infected cell. Our findings mark the first observation of a single-effector CRISPR system utilizing RNA to activate a DNA-destruction response.

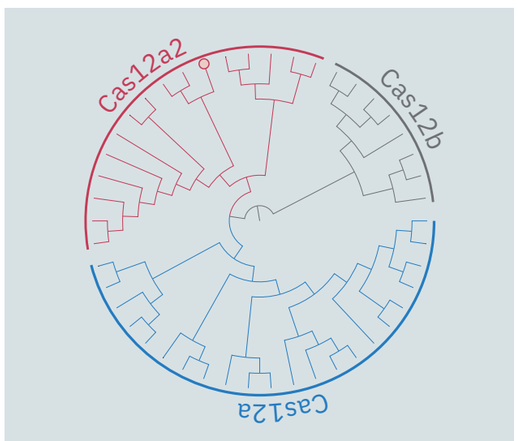

Figure 1: Phylogeny of the RNA-targeting Cas12a2 orthologs in relationship to the DNA-targeting Cas12a and Cas12b nucleases. The location of SuCas12a2 from *Sulvuricurvum sp* characterized in this study is marked with a circle. From Dmytrenko et al., Nature (2023) © CC BY 4.0

Cas12a2 displayed a remarkably flexible approach to RNA targeting, showing tolerance for mismatches between crRNA and the target, and the ability to recognize a broad spectrum of non-self protospacer flanking sequences (PFS). This flexibility characterizes Cas12a2 as a formidable defense even against rapidly evolving infections.

Upon detecting RNA from the infection, Cas12a2 goes on to destroy DNA in the cell, which we observed in the induction of the SOS response and the reduction of DNA contents within the infected bacteria. This process leads to growth arrest, as the bacteria attempt to repair the damage, or even cell death. Such a response effectively stops the spread of the infection, sacrificing the infected cell to protect the community.

In a companion publication [2], our collaborators showed that Cas12a2 undergoes massive structural changes upon binding to its RNA target, exposing a catalytic cleft in the nuclease capable of shredding any encountered nucleic acid—be it RNA, single-stranded DNA, or double-stranded DNA. This work also explored ways to mutate Cas12a2 to alter the type of nucleic acid that the nuclease degrades after recognizing its RNA target.

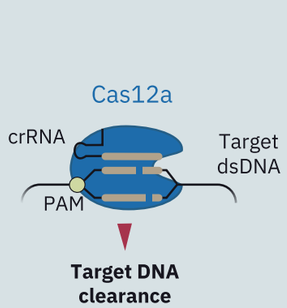

Figure 2: The known model of Cas12a immunity. PAM (yellow circle) marks the non-self protospacer adjacent motif (equivalent to PFS in RNA). The thick brown lines designate the complementary sequences in the CRISPR RNA (crRNA) and the DNA target. The conserved hairpin of the repeat within the crRNA is shown in black.

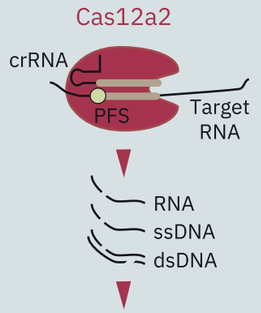

Figure 3: Our proposed model of Cas12a2 immunity and its effect on the cell. PFS (yellow circle) marks a protospacer flanking sequence (equivalent to PAM in DNA) required for target recognition and essential in preventing self-immunity. The thick brown lines designate the complementary sequences in the CRISPR RNA (crRNA) and the RNA target. The conserved hairpin of the repeat within the crRNA is shown in black.

The unique capabilities of Cas12a2 present promising opportunities for biotechnological applications, especially in the development of new diagnostic tools capable of directly detecting RNA from viruses or other pathogens. This potential establishes Cas12a2 as a valuable asset for research and technology development, enhancing our understanding of microbial defense mechanisms and creating new possibilities for medical and biotechnological innovations.

[1] Dmytrenko O, Neumann GC, Hallmark T, Keiser DJ, Crowley VM, Vialetto E, Mougiakos I, Wandera KG, Domgaard H, Weber J, Gaudin T, Metcalf J, Gray BN, Begemann MB, Jackson RN, Beisel CL (2023)
Cas12a2 elicits abortive infection through RNA-triggered destruction of dsDNA
Nature doi:10.1038/s41586-022-05559-3

[2] Bravo JPK, Hallmark T, Naegle B, Beisel CL, Jackson RN, Taylor DW (2023)
RNA targeting unleashes indiscriminate nuclease activity of CRISPR-Cas12a2
Nature doi:10.1038/s41586-022-05560-w

UNDERSTANDING THE SARS-COV-2 SHIFTY GENETIC ELEMENTS

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NEVA CALISKAN | HEAD OF RESEARCH GROUP RECODING MECHANISMS IN INFECTIONS
REDMOND SMYTH | HEAD OF RESEARCH GROUP GENOME ARCHITECTURE AND EVOLUTION OF RNA VIRUSES

The translation of viral ribonucleic acids (RNAs) is often driven by non-canonical events. These are encoded in the viral genome so that viruses can take control of the cellular translation machinery. One of these non-canonical translation events is programmed ribosomal frameshifting. It causes the translating ribosome to jump back or forward by one or more nucleotides into another reading frame, enabling viral replicative and structural proteins to be produced. Recently, Caliskan and Smyth teams have deciphered the structural changes in this process in SARS Coronavirus-2 using state-of-the-art technologies. Their findings could contribute to the discovery of new therapeutic targets.

Translation is an essential process in every living cell and crucial for protein production. Viruses have developed a spectrum of non-canonical events for each step of translation, allowing them to efficiently influence cellular protein synthesis. This is also the case with SARS-CoV-2: The virus employs ribosomal frameshifting to regulate the expression of its replicative enzymes. The success of this process depends on whether specific parts – frameshifting stimuli – are present within the viral RNA. One of these parts is a stable structure that essentially halts the ribosome and forces it into an alternative reading frame. The prevailing hypothesis for the pandemic virus SARS-CoV-2 suggests that this ribosomal obstacle is a pseudoknot structure with a stable RNA fold. Recent attempts by scientists to detect this pseudoknot structure in studies of the full virus genome, however, have failed. This apparent inconsistency in the literature has caught our attention.

In our study, we focused on the part of the viral RNA stimulating ribosomal frameshifting. Using cutting-edge technologies such as optical single-molecule optical tweezers, our team examined several viral frameshift RNA variants differing in length, or contain mutations. This allowed the team to analyze the folding behavior of RNA structures in real time at high resolution. In addition to these structural insights, frameshifting efficiency was determined for each RNA variant, thus linking RNA structure and function. Furthermore, our team investigated same RNA structures using a chemical method in a parallel approach. In addition to these structural insights, frameshifting efficiency was determined for each RNA variant, thus linking RNA stucture and function.

Our study reveals that a dynamic interplay of RNA structures determines the efficiency of ribosomal frameshifting – and thus viral replication. The results show that the postulated pseudoknot structure is essential. However, it was found that this particular structure likely only temporarily forms during translation. In contrast, an alternative dominant structure consisting of multiple hairpin helices inhibits the formation of pseudoknots. As the ribosome translates the viral genomic RNA, it must successively unfold the subsequent RNA structures. When translating the dominant helix

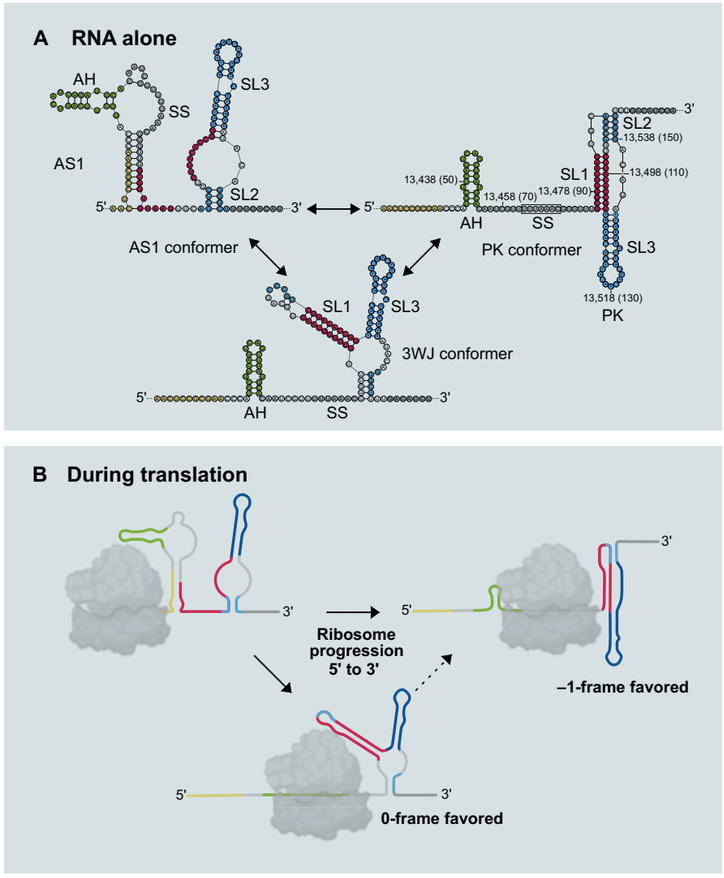

Figure: Proposed model of frameshift site conformational transitions as a translation regulatory switch. (**A**) SARS-CoV-2 RNA alone can transition between the AS1, canonical pseudoknot (PK) and the three-way junction (3WJ). (**B**) In cells, the viral RNA undergoes translation, replication/transcription or virion packaging depending on its localization and phase of infection. During translation, as the ribosome progresses, the AS1 conformer would be unwound by the helicase activity of the ribosome, which allow the formation of either the frameshift stimulatory PK or the three-way junction. As translation progresses, the three-way junction may also fold into the PK. Adapted from Pekarek et al. Nucleic Acids Res. 25: 728-743 (2023) © CC BY 4.0

form, the part of the RNA region becomes available at a certain point in time for the formation of a pseudoknot, which then rapidly forms.

The first author of the study explains “Multiple RNA structures collaborate in SARS-CoV-2 to finely tune gene expression. A change in the way the frameshifting RNA pairs with adjacent regions of the RNA can affect the formation of different structures and thus the ability of viruses to replicate in our cells.”

Frameshifting stimuli in viral RNAs are evolutionarily highly conserved. This makes them an attractive target for the development of new therapeutics that are robust against resistances. Understanding the structures of the target RNA in detail is therefore very important. So far, most attempts to discover new therapeutic targets have focused on the pseudoknot structure. Although this structure is crucial in the frameshifting process, our study suggests that it may not be an optimal target for therapeutics, as the pseudoknot is very short-lived. Instead, shifting the focus to alternative structures could promise a better hit rate.

Pekarek L, Zimmer MM, Gribling-Burrer AS, Buck S, Smyth R, Caliskan N (2023)
Cis-mediated interactions of the SARS-CoV-2 frameshift RNA alter its conformations and affect function
Nucleic Acids Res. doi: 10.1093/nar/gkac1184

A NEW CLASS OF VACCINES

© Verena Meier

LUKA ČIČIN-ŠAIN | HEAD OF DEPARTMENT VIRAL IMMUNOLOGY

Cytomegaloviruses (CMV) are herpesviruses that naturally induce unparalleled immune responses, which may be exploited for vaccine development. On the paradigmatic preclinical model, scientists from the Viral Immunology Department at HZI showed that CMV vectors elicit non-waning antibody responses upon a single immunization dose of mice. Mice lacking B-lymphocytes were poorly protected by the MCMV vaccine vector, demonstrating that antibodies are required for the immune protection against viral challenge. In wild type mice, proteins from SARS-CoV-2 or influenza virus expressed by a recombinant mouse CMV vector elicited neutralizing antibody responses that over time improved in neutralizing capacity and binding avidity. This opens the door for the development of CMV based vaccines inducing lasting immunity upon a single-immunization.

The strongest adaptive immune response in clinical medicine is induced by the human cytomegalovirus (HCMV). It has been proposed that harnessing this extraordinary immune response may allow to utilize these viruses as vaccine vectors. Cytomegaloviruses vectors eliciting protective T cell immune responses have been in the focus of the international community, but less was known about their ability to stimulate antibody responses. HZI scientists, in collaboration with national and international partners showed that CMVs are equally efficient at eliciting humoral immune responses that neutralize viral particles and protect the host from infections and disease. Humoral immunity depends on B-lymphocytes, which upon activation secrete antibodies that recognize viral particles outside of cells and neutralize their ability to bind to cells and infect them.

A team comprising several HZI research groups, partners from the German Primate Research Centre, as well as international partners from Israel and Croatia showed in a preclinical model that cytomegaloviruses elicit potent and lasting antibody responses against viral antigens. The groups introduced genes coding for the hemagglutinin antigen of influenza A virus (IAV) or the spike antigen of SARS-CoV-2, the virus causing COVID-19, into the genome of the mouse

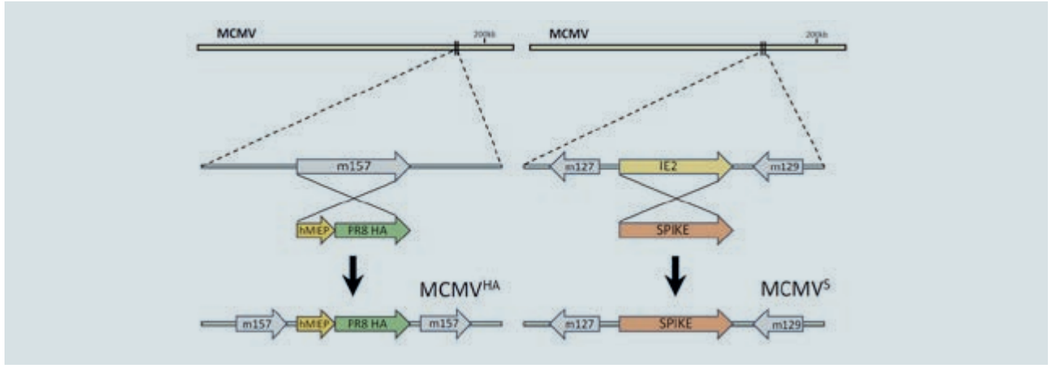

Figure 1: Schematic images of recombinant MCMV vector genomes. The HA gene of IAV PR8 was inserted along with the hMIEP in the m157 locus, while the SARS-CoV-2 spike ORF was inserted in place. Adapted from Kim et al. Cell. Mol. Immunol. 19: 234-244 (2022) © CC BY 4.0

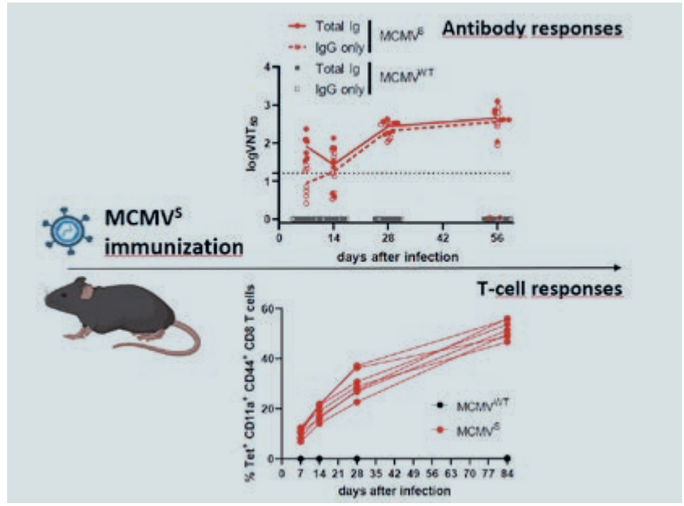

Figure 2: Mice were immunized with MCMV^S and blood immune responses were monitored for up to 3 months. Serum titers exhibiting 50% of maximal virus neutralization (VNT^{50}) and the percentage of Antigen specific CD8 T cells are shown on y-axes. Note that VNT^{50} titers are shown as log[10] values. Adapted from Kim et al. Cell. Mol. Immunol. 19: 234-244 (2022) © CC BY 4.0

cytomegaloviruses (MCMV) using recombinant DNA technology (Figure 1). MCMV is an orthologue of HCMV with highly similar infection dynamics and immunogenicity in mice and is commonly used to model immune responses to HCMV.

MCMVs expressing the IAV hemagglutinin induced strong and lasting humoral immune response, which protected mice against lethal challenge with the same virus. Similarly, a recombinant MCMV expressing the spike protein of the SARS-CoV-2 induced antibody responses that neutralized SARS-CoV-2 and expanding T cell responses (Figure 2). Remarkably, the antiviral affect persisted over time upon a single immunization, showing no signs of waning. This feature was in stark contrast to any other commercially available or experimental vaccine against SARS-CoV-2. A detailed analysis of serum antibody responses to the Spike antigen revealed that the avidity of binding increased over time, which would be consistent with continuous somatic hypermutation in latently infected mice.

Mice immunized with the IAV Hemagglutinin antigen were protected against challenge with a lethal dose of influenza virus and showed a reduction in virus titres over at least five orders of magnitude. To demonstrate that protection was due to antibody responses and not to T-lymphocytes, additional experiments were performed in genetically modified mice lacking all B-cells due to a developmental block, but maintaining T cells (JHT mice). In these mice the protection against disease and death provided by the MCMV vaccine vector was severely impaired, while infectious virus remained detectable in the lungs.

Taken together, the data argue that MCMV vaccine vectors elicit protective immune responses by inducing both arms of the adaptive immune response and a single immunization is sufficient to provide very lasting immunity. Therefore, this vaccine formulation provides unique advantages over any other approved vector. While the development of this vector for clinical applications still faces numerous hurdles, its potential is very strong and requires focused effort.

Kim Y, Zheng X, Eschke K, Chaudhry MZ, Bertoglio F, Tomić A, Krmpotić A, Hoffmann M, Bar-On Y, Boehme J, Bruder D, Ebensen T, Brunotte L, Ludwig S, Messerle M, Guzman C, Mandelboim O, Hust M, Pöhlmann S, Jonjić S, Čičin-Šain L (2022)
MCMV-based vaccine vectors expressing full-length viral proteins provide long-term humoral immune protection upon a single-shot vaccination
Cell. Mol. Immunol. doi: 10.1038/s41423-021-00814-5.

GLOBAL RNA INTERACTOMES REVEAL HOW SMALL RNA MOLECULES REGULATE SPORE FORMATION

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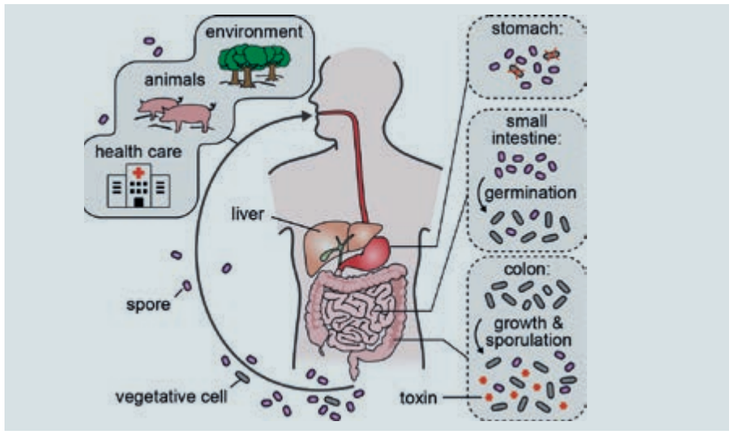
HEAD OF RESEARCH GROUP RNA BIOLOGY OF GRAM-POSITIVE BACTERIA

To survive adverse conditions, some bacteria produce a distinct cell type called endospores that exhibit minimal metabolic activity and intrinsic resistance to a range of environmental stressors. In the obligate anaerobic pathogen *Clostridioides difficile*, these endospores are the major infectious vehicle mediating host transmission, as well as intestinal survival of antibiotic therapy thereby contributing to significant rates of recurrent infections (Fig. 1). Spore formation is a trade-off because the vegetative mother cell dies in the process. Hence, initiation of spore morphogenesis is tightly controlled and presents an attractive target for therapeutic intervention. Our work has revealed small regulatory RNAs as central regulators of sporulation, which identifies RNA-based antisense technologies as potential novel approaches to block spore formation.

The process of spore formation can be described by several morphological stages whose formation is accomplished through compartmentalized transcription programs that are coordinated via sporulation-specific sigma factors (Fig. 2). The key transcriptional regulator that initiates spore gene expression is Spo0A. Interestingly, while the developmental stages of spore formation are largely conserved, many of the regulators that control the activity of Spo0A appear to be missing or to differ in their function in *C. difficile*. This might reflect a niche-specific adaptation to the intestinal environment and suggests the existence of previously overlooked regulatory mechanisms governing sporulation initiation in *C. difficile*.



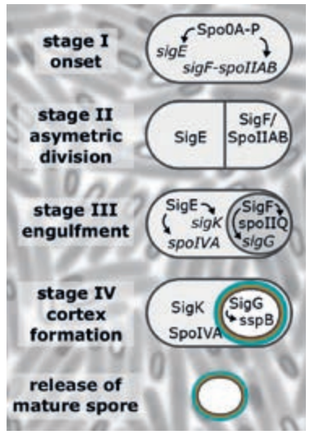


Figure 1, left: The infection cycle of *Clostridioides difficile*.
Figure 2, right: Morphological stages of spore formation. Transcription programs are coordinated via 4 sporulation-specific sigma factors SigE, SigF, SigG and SigK. Each sigma factor activates a set of transcription factors and other regulators of spore formation. The mature spore is released into the environment. Adapted from Fuchs et al. EMBO J. 42(12): e112858 (2023) © CC BY 4.0

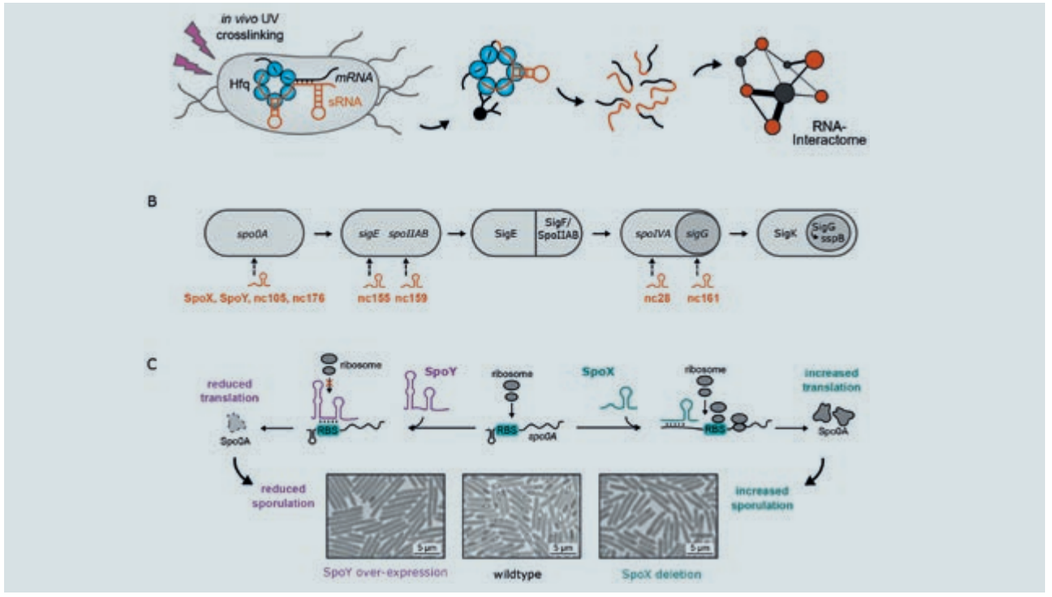


Figure 3: RIL-seq guided identification of small RNAs that regulate spore formation. **(A)** RIL-seq workflow. **(B)** Schematic overview of sporulation cascade. Regulators that were found in chimeras with sRNAs are shown. Corresponding sRNAs are highlighted in orange. **(C)** Model of sRNAs-mediated regulation of sporulation. Adapted from Fuchs et al. EMBO J. 42(12): e112858 (2023) ©CC BY 4.0

Small regulatory RNAs (sRNAs) have been identified as central hubs in the regulation of bacterial virulence and stress responses in many bacterial pathogens but have remained largely unexplored in *C. difficile*. Here, we determined the potential role of sRNAs as regulators of spore formation by adopting *RNA interaction by ligation and sequencing* (RIL-seq) (Fig. 3A).

Our analysis identified manifold sRNA interactions with mRNAs coding for regulators of distinct morphological sporulation stages (Fig. 3B). Most interestingly, the *spo0A* mRNA was bound by several sRNAs, identifying it as a central target of sRNA regulation. Using genetic and biochemical approaches, we could demonstrate a relationship between *spo0A* regulation by two of these sRNAs, SpoY and SpoX, and the formation of spores. By binding to distinct sequences in the 5' untranslated region of the *spo0A* mRNA, SpoY and SpoX have opposing effects on spo0A transcript stability and translation which leads to corresponding changes in Spo0A protein levels and sporulation frequencies (Fig. 3C). Moreover, each sRNA had a distinct target regulon beyond spo0A, that suggested a global impact on the infection process. In fact, we showed that *C. difficile* strains lacking SpoX or SpoY were significantly impaired in their general ability to colonize the gut of antibiotic-treated mice.

Our study has revealed a rich post-transcriptional layer in the regulation of spore formation. Many of the identified sRNAs show distinct expression profiles which hints at their role in fine-tuning sporulation initiation in response to environmental signals. Understanding the biological impact of these sRNA-target interactions could be leveraged to develop strategies with the potential to specifically inhibit spore formation.

Fuchs M, Lamm-Schmidt V, Lenče T, Sulzer J, Bublitz A, Wackenreuter J, Gerovac M, Strowig T, Faber F. (2023)
A network of small RNAs regulates sporulation initiation in *Clostridioides difficile*
EMBO J. doi: 10.15252/embj.2022112858

LASB INHIBITORS FOR THE TREATMENT OF *PSEUDOMONAS AERUGINOSA* LUNG INFECTIONS

© Oliver Dietze

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HEAD OF DEPARTMENT DRUG DESIGN AND OPTIMISATION

Infections caused by the Gram-negative pathogen *Pseudomonas aeruginosa* pose an escalating global threat to human health. Conventional antibiotic therapy is hindered by the rapid development of resistance, underscoring the pressing need for innovative treatment strategies. In this study, we present an unconventional method to counter *P. aeruginosa*-related infections by targeting its primary virulence factor, the elastase LasB. LasB is an extracellular protease that degrades elastin and collagen in human tissue, thereby facilitating tissue penetration. Additionally, the degradation of components of the host immune system contributes to immune evasion. Hence, inhibiting LasB proves to be a promising strategy. In our publication, the interdisciplinary team succeeded in developing a new class of LasB-inhibiting phosphonates. These compounds performed excellently in a series of *in vitro* and *ex vivo* assays and also showed promising performance in a murine *in vivo* lung infection model.

In previous studies, we have successfully developed highly active LasB inhibitors; however, they exhibited a drawback – their zinc-binding thiol group was chemically unstable. To address this issue, we have designed derivatives incorporating alternative zinc-binding groups (ZBGs) (Figure 1A).

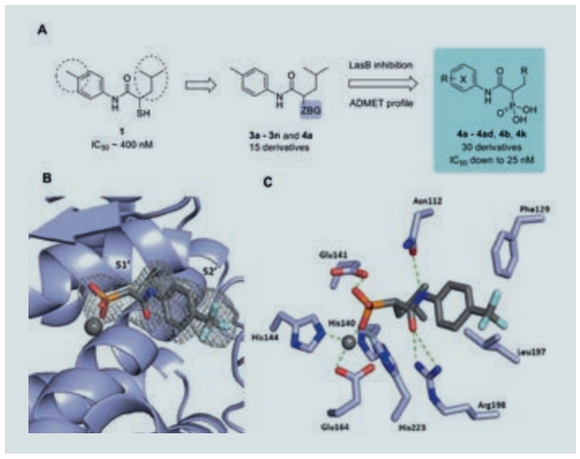

Figure 1: Optimization of phosphonate derivatives and co-crystallization of **4b** with LasB. (A) Optimization of **1** leading to derivatives with nanomolar (nM) IC_{50} values against LasB. Compounds **4b** and **4k** turned out to be the most active phosphonates with IC_{50} values of ~25 nM. (B) Cartoon representation of LasB (slate) in complex with **4b** (gray), with the S1' and S2' binding-sites of the enzyme occupied by the compound highlighted. The gray isomesh represents a polder map of **4b** contoured at 3 σ. (C) Schematic 2-D representation of LasB-**4b** interactions. Hydrogen bonds are displayed in dotted green lines, while all other residues exhibit hydrophobic interactions with the ligand. The active site zinc cation is shown as gray sphere in (B) and (C). Adapted from Konstantinovic et al. ACS Cent. Sci. doi: 10.1021/acscentsci. 3c01102 © CCBY 4.0

Compounds with phosphonic acid as the ZBG displayed a remarkable increase in activity compared to the initial thiol **1.** Moreover, these phosphonates were characterized by an outstanding *in vitro* ADMET profile (no cytotoxicity, good solubility and high chemical and metabolic stability).

To understand the binding mode of phosphonic acids, we co-crystallized the most active compound **4b** with LasB. As shown in Figures 1B&C, the phosphonate group binds to the zinc cation that is located in the active site of LasB. Compared to thiol **1**, **4b** forms additional interactions with the enzyme, accounting for the enhanced activity.

Subsequent experiments uncovered LasB-related toxicity against human lung cells (in 2D and 3D cell culture models). Interestingly, this toxicity was reduced by inhibitors **4a** and **4b**. In parallel, experiments in a *Galleria mellonella* larvae model revealed, that LasB-related toxicity was reduced when the larvae were treated with **4b**. This effect was particularly pronounced and showed synergistic effects when **4b** was combined with tobramycin.

Further promising findings were that our compounds could inhibit LasB in the nanomolar range even in the presence of pulmonary surfactant, which has the potential to inactivate anti-infectives. Regarding their selectivity, we were pleased to find that the compounds did not inhibit human off-targets and were untoxic against human cells and zebrafish embryos. These systematically generated data regarding *in vitro* activity and ADMET properties enabled us to rationally select the best phosphonate for subsequent *in vivo* studies.

In mouse pharmacokinetics studies, phosphonic acids **4a** and **4b** were found at high levels in the epithelial lining fluid (ELF) after intratracheal administration. Interestingly, their concentrations were significantly above the half-maximal inhibitory concentrations (IC_{50}) values, which underlines their therapeutic potential. Also, a subsequent nebulization study on 4b revealed high initial ELF and lung levels, maintaining a moderate range for 24 h and 8 h, respectively.

We then examined whether these promising data would also result in the substances being active in a murine lung infection model. Remarkably, the combination of levofloxacin and **4b** exhibited a synergistic effect, significantly reducing bacterial burden below stasis (Figure 2A). A direct proof that this therapeutic effect was a result of LasB inhibition, is the finding that the LasB protein levels in blood, indicative of dissemination, showed notable reduction even with the LasB inhibitor alone (Fig. 2B). While the vehicle control demonstrates the protease's tissue-destroying properties, allowing it to cross the lung barrier and become systemic, LasB inhibition prevents this, indicating a significantly desirable reduction in bacterial dissemination through the lung epithelium. With these results, we are confident that we have made a major contribution to the development of innovative, non-traditional anti-infectives which, when administered together with a standard antibiotic, could bring added value for patients. In order to achieve this goal, we would like to enhance the available effects using further optimized LasB inhibitors. In addition, selected substances have already shown high levels in the lung after intravenous administration in follow-up studies, which opens up possibilities for the treatment of further indications, such as hospital-acquired and ventilator-associated pneumonia.

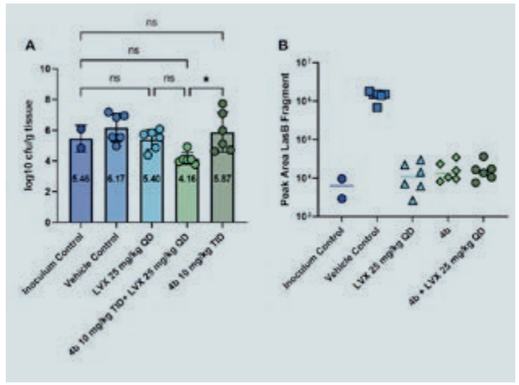

Figure 2: Pharmacodynamic Studies in Mice Infected with *Pseudomonas aeruginosa* DSM-1117. (A) Bacterial growth in lung tissue. Inoculum control – number of colony-forming units (cfu) in the lungs 15 min after infection; all other lungs were taken after 24 h; vehicle control – mice treated with the vehicle; LVX 25 mg/kg QD – mice treated with LVX; **4b** 10 mg/kg TID + LVX 25 mg/kg QD – mice treated with both **4b** and LVX; **4b** 10 mg/kg TID – mice treated with **4b**. (B) LasB levels in blood, based on same treatment groups as in (A). QD, once per day; TID, three times per day; LVX, levofloxacin. From Konstantinovic et al. ACS Cent. Sci. doi: 10.1021/acscentsci. 3c01102 © CCBY 4.0

Konstantinovic J, Kany AM, Alhayek A, Abdelsamie AS, Sikandar A, Voos K, Yao Y, Andreas A, Shafiei R, Loretz B, Schönauer E, Bals R, Brandstetter H, Hartmann RW, Ducho C, Lehr CM, Beisswenger C, Müller R, Rox K, Haupenthal J, Hirsch AKH (2023)
Inhibitors of the Elastase LasB for the Treatment of Pseudomonas aeruginosa Lung Infections
ACS Cent. Sci. doi: 10.1021/acscentsci.3c01102

LINKING DYNAMIC INFECTION MODELS TO LARGE-SCALE ADAPTIVE EPIDEMIC PANELS

© Verena Meier

BERIT LANGE | ACTING HEAD OF DEPARTMENT EPIDEMIOLOGY

During the SARS-CoV-2 pandemic several crucial infectious disease epidemiology infrastructures needed for epidemic preparedness were lacking in Germany. One of them is an adaptive epidemic panel to monitor the spread of the infection and use this information directly for dynamic projections. The clinical epidemiology group at HZI is leading the adaptive population-based cohort MuSPAD (multilocal and serial prevalence study of antibodies against (respiratory) infectious diseases in Germany). This initiative has laid the foundation for the newly established epidemic panel, which is strengthened by the parallel build-up of methodological capacity with large modelling platforms and networks.

MuSPAD has recruited more than 34.000 participants in eight German regions. With innovative digital and diagnostic tools like the prospective monitoring and management app PIA and multiplex serology assays, and by linking with other clinical and population-based cohorts like NAKO, MuSPAD can swiftly and systematically evaluate the frequency, dynamics, burden, and complications of various infectious diseases in the population (Figure 1). Additionally, modelling capacity has been strengthened through modelling platforms (www.respinow.de) and networks (www.monid.net) in Germany by the Epidemiology Team at HZI and have been linked to this population cohort.

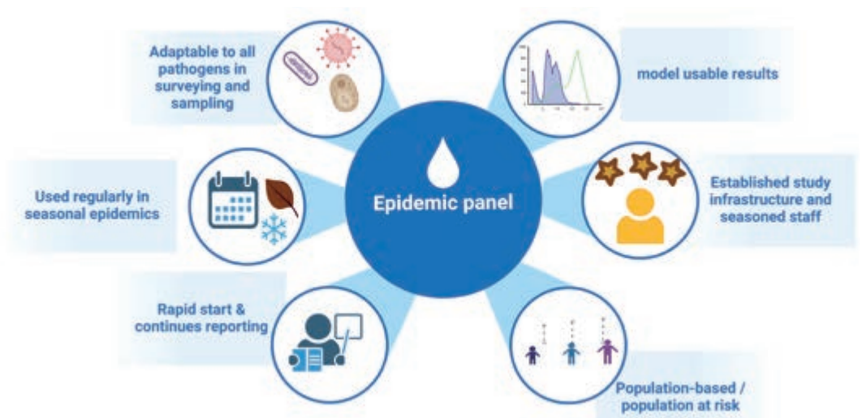

Figure 1: General characteristics of an epidemic panel from Lange, B. *et al.* Zenodo. doi: 10.5281/zenodo.11202400

In Rodiah *et al.* a diverse team from multiple centers developed a detailed infection model over different age groups. This model can account for underreported infections in specific population groups using data from studies like MuSPAD. This was then used to improve understanding of the contribution of different population groups to the incidence of infection during different phases of the SARS-CoV-2 pandemic (Figure 2). Taking age and phase-specific underreporting into account, the modelling study demonstrated that contacts of younger adults and teenagers contributed more than expected to infections during the first three waves of the pandemic in Germany. The work also presented a modelling analysis from the transition of the SARS-CoV-2 Delta to the Omicron wave in early 2022 that showcases that only this type of age-specific model was able to adequately predict the trajectory of hospital incidences for adults and children. Such projections represent crucial information during an epidemic and should ideally be available in real-time. Therefore, the development of such modelling and its link to population studies is important in order to better target measures to specific population groups for infectious diseases.

Subsequent work using this combined approach has shown that MusPAD is able to very rapidly provide model-usable estimates, for complex immune correlates of SARS-CoV-2, for RSV and for HCV. Currently HZI is the only institution in Germany able to provide both scenario-modelling estimates for RSV seasons as well as regular forecasting updates in the new German-wide forecasting hub for respiratory infections (www.respinowhub.de). This is particularly important with population-scale RSV prevention strategies expected to be rolled out in Germany from the 24/25 season.

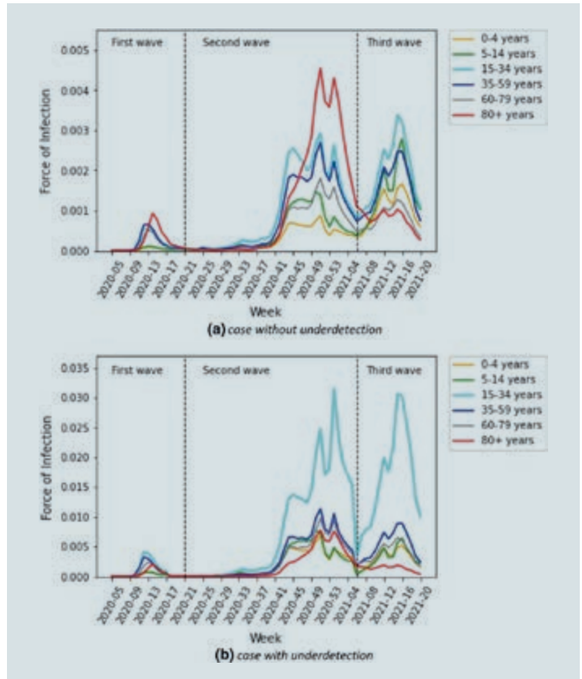

Figure 2: Force of infection for different age groups dependent on not including (a) or including (b) estimates of underdetection from population-based studies. From Rodiah et al. Eur J Epidemiol 38: 39-58 (2023) © CC BY 4.0

Rodiah I, Vanella P, Kuhlmann A, Jaeger VK, Harries M, Krause G, Karch A, Bock W, Lange B. (2023)
Age-specific contribution of contacts to transmission of SARS-CoV-2 in Germany
Eur J Epidemiol. doi: 10.1007/ s10654-022-00938-6.

DISTINCT INNATE IMMUNE MEMORY PROGRAMS UNVEILED BY SINGLE-CELL ANALYSIS

© Tom Figiel

YANG LI | HEAD OF DEPARTMENT OF COMPUTATIONAL BIOLOGY FOR INDIVIDUALIZED MEDICINE

Research in the past decade has highlighted the broad benefits of innate immune memory (known as trained immunity, TI) for host defense. However, it has also suggested potentially detrimental outcomes in immune-mediated and chronic inflammatory diseases. In this study, we demonstrate cellular transcriptional programs in response to four different inducers of trained immunity in monocyte populations at single-cell resolution.

In 1921, the development of the live-attenuated Bacillus Calmette-Guérin (BCG) vaccine was a significant breakthrough in the fight against tuberculosis. Notably, epidemiological investigations have unveiled an interesting aspect of BCG vaccination, namely, its potential to confer protection against all-cause mortality in children. Following BCG vaccination for weeks to months, monocyte activity is enhanced, characterized by increased production of pro-inflammatory cytokines upon subsequent challenges with the homologous or heterologous pathogens. This biological process is termed as trained immunity (TI), describing the acquired nonspecific memory in innate immune cells. Metabolic reprogramming has shown to be involved in TI in monocytes, facilitating a faster and greater activation of gene expression upon re-stimulation. However, the potential heterogeneity in the transcriptional responses of innate immune cells involved in TI in a certain individual has not been studied to the best of our knowledge. For instance, do all monocytes show similar gene expression profiles upon the induction of TI or is there heterogeneity across cells? Does the induction of TI by different stimuli result in distinct transcriptional programs?

To answer these questions, we trained monocytes in vitro by 4 different stimuli and generated single-cell RNA sequencing (scRNA-seq) dataset (Figure 1). Monocytes/macrophages were re-clustered after being trained and we identified three subpopulations, including MCI (genes encoding chemokines

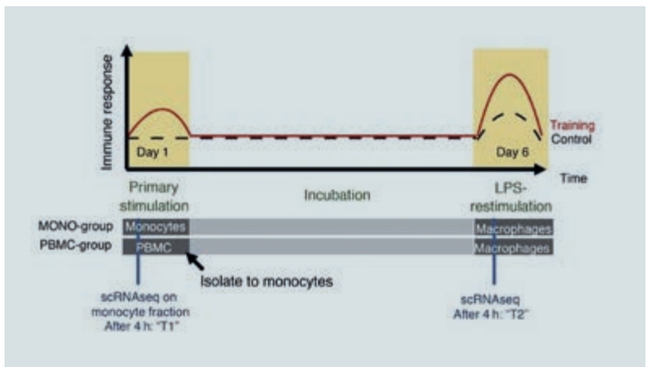

Figure 1: Study design. Monocytes (M-MONO) and PBMCs (M-PBMC) were isolated and incubated in vitro with culture medium (RPMI, negative control), β-glucan (BG), uric acid (UA), oxidized low-density lipoprotein (ox-LDL), and muramyl dipeptide (MDP) for 24 hours. After a 4-hour stimulation, cells were isolated for scRNA-seq (T1). On day 6, cells were restimulated with LPS for 4 hours and then isolated for scRNA-seq (T2). M-MONO, monocytes trained in the absence of lymphocytes; M-PBMC, monocytes trained in the presence of lymphocytes. From Zhang et al. J Clin Invest. 132: e147719 (2022) © CC BY 4.0

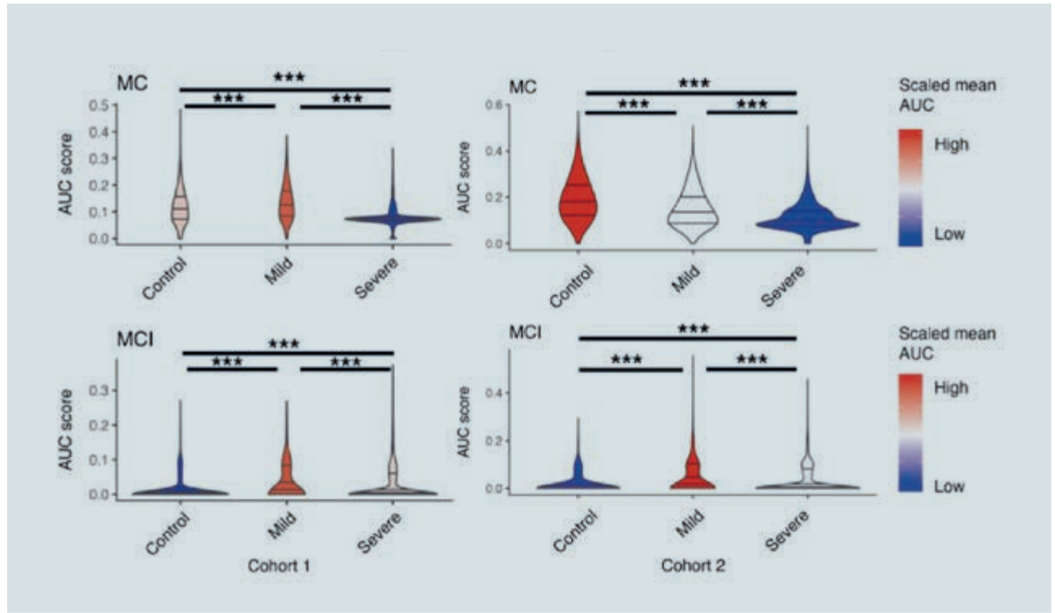

Figure 2: Our findings indicate that both identified subpopulations of trained cells could play important roles in these conditions, highlighting the importance of TI programs in mediating pathogenetic mechanisms in infections and inflammatory diseases, and suggesting therapeutic and/or prevention implications that need to be investigated in further studies. From Zhang et al. J Clin Invest. 132: e147719 (2022) © CCBY 4.0

and proinflammatory cytokines), MC (enhanced expression of chemokines only), and NT (nontrained cells). To our best knowledge, the present study is the first to describe cellular heterogeneity of TI at the single-cell-transcriptome level.

Another crucial aspect to explore is whether the intercellular interactions in blood and tissues influence the TI process. We observed a significantly higher percentage of MC subpopulations in samples from the monocytes in the presence (M-PBMC) group, indicating that T cell presence during TI induction amplifies the process. This is reflected by the higher expression of genes encoding CXCL9-11 chemokines in the monocytes trained in the presence of lymphocytes (in the PBMC model), compared with the purified monocytes.

These findings of MCI and MC subpopulations offer potential insights into immunotherapeutic applications to human diseases. Therefore, we extended our investigation to infectious diseases and/or autoimmune diseases and observed genes around GWAS risk loci of ulcerative colitis (UC) patients significantly enriched in differentially expressed genes (DEGs) detected in MCI/MC subpopulations. These genes again formed distinct subgroups, upregulated in either MCI or MC. In monocytes from COVID-19 patients, we found significantly higher MC and MCI signatures in mild patients compared with severe patients (Wilcoxon's test, $P < 2.2 \times 10{-}16$; Figure 2), which again demonstrated that severe patients have suppressed TI signatures.

Zhang B, Moorlag SJ, Dominguez-Andres J, Bulut Ö, Kilic G, Liu Z, van Crevel R, Xu CJ, Joosten LA, Netea MG, Li Y. (2022)
Single-cell RNA sequencing reveals induction of distinct trained-immunity programs in human monocytes.
J Clin Invest. doi: 10.1172/JCI147719

CRITICAL ASSESSMENT OF METAGENOME INTERPRETATION: THE SECOND ROUND OF CHALLENGES

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ALICE C. McHARDY | HEAD OF DEPARTMENT
COMPUTATIONAL BIOLOGY OF INFECTION RESEARCH

Metagenomics — the study of the collective genomes of microorganisms from environmental samples — provides fundamental insights into the structures and functions of microbial communities. Computational processing is key for the interpretation of metagenomes, but a lack of consensus about benchmarking complicates performance assessment. The Critical Assessment of Metagenome Interpretation (CAMI) initiative brings together the metagenomics research community to facilitate the benchmarking of computational methods, the establishment of standards, and good practices. To promote involvement of labs around the world, CAMI organizes challenges, in which participants are invited to download novel metagenomic datasets and submit the results of applying their methods to these data. In our study, we describe the results of the second round of challenges (CAMI II), benchmarking state-of-the-art methods using metrics and procedures agreed upon by the community. The results identify challenges and guide researchers in selecting methods for analyses.

Our planet is inhabited by an enormous number of microbial organisms that live together in communities, which range from simple to highly complex in terms of the number of different taxa, on every accessible surface. Metagenomics allows us to also study community members that are difficult to obtain in pure culture. This has created new opportunities to study microbial communities and explore environments and applications, such as rapid pathogen detection from clinical samples. To process the large amounts of emerging metagenomic data, computational methods have been developed. However, for researchers to be able to choose the most suitable ones for their research, a comprehensive and continuous benchmarking is needed. CAMI, the Initiative for the Critical Assessment of Metagenome Interpretation, is a community-driven effort addressing this need, by offering comprehensive benchmarking challenges on datasets representing common experimental settings, data generation techniques and environments in microbiome research.

For the second round of challenges (CAMI II), we created and offered metagenome datasets representing a range of different environments; a marine environment, a plant-associated environment — including fungal and host plant genome sequences — and a high-strain-diversity environment that we called ‘strain madness’. Specific challenges were provided for metagenome assembly software, genome and taxonomic binners, and taxonomic profilers. Further, clinical pathogen diagnostics from metagenomics data is a highly relevant translational problem requiring computational processing. Therefore, we offered a metagenome dataset of a blood sample from a patient with hemorrhagic fever for participants to identify pathogens and to indicate those likely to cause the symptoms described in a case report.

Overall, participants submitted ~5,000 sets of results from 76 programs and their versions. Analysis of the results identified computationally efficient and well-performing software with regards to key measures, with a substantial performance improvement compared to software assessed in the first CAMI challenge. For metagenome assembly, long-read sequences proved particularly valuable for difficult-to-assemble regions such as 16S rRNA genes. Overall assembly quality was shown to depend on preprocessing, genome coverage and the presence of closely related strains (Figure 1a). Most metagenome assembly software did not resolve individual strains, in some cases intentionally. For taxonomic profilers and binners, several methods consistently ranked highly across performance measures (Figures 1b and 2). In every method category, methods capable of processing the entire datasets within minutes to a few hours were available (Figure 1c). For the clinical pathogen challenge, ten manually curated, hence not reproducible results were received. The number of identified taxa per result varied considerably. Four submissions identified the pathogen, with three attributing it as the causal one.

CAMI II will provide guidance for researchers choosing appropriate analysis software and suggest relevant research areas for method developers, such as the taxonomic assignment and profiling of Archaea, viruses and taxa at low bacterial ranks, as well as achieving reproducibility for causal pathogen detection from clinical samples. Metagenomics has great potential for clinical pathogen diagnostics and treatment; however, further assessments are needed, and there are more hurdles to overcome before its clinical application.

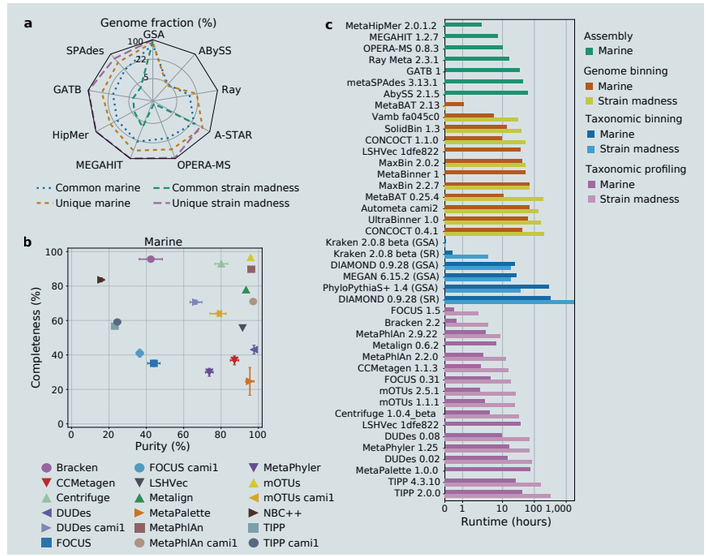

Figure 1: CAMI II results for two of five assessed method categories and method runtimes. **a**, Fraction of genomes covered by assembled contigs, for unique genomes (no other genome with ≥95% average nucleotide identity in the dataset) and common genomes. Labeled around the plot are the methods, with GSA (gold standard assembly) denoting the best possible performance achievable by a method. **b**, Purity versus completeness of taxonomic profiles for the marine dataset at the genus taxonomic rank. **c**, Method runtimes in log scale for all assessed categories.
From Meyer et al. Nature Methods 19: 429–440 (2022) © CC BY 4.0

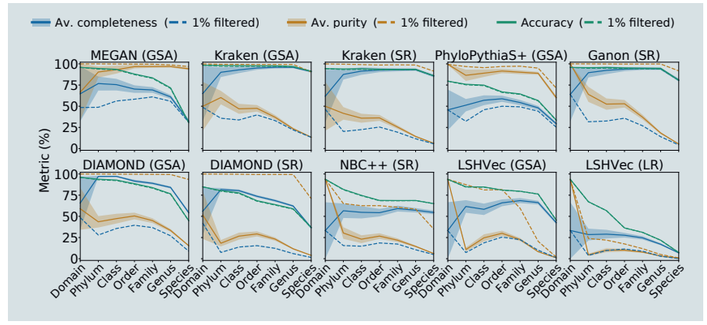

Figure 2: Taxonomic binning performance across ranks for the marine dataset. Metrics were computed over unfiltered (solid lines) and 1%-filtered (that is, without the 1% smallest bins in base pairs, dashed lines) predicted bins of short reads (SR), long reads (LR) and contigs of the gold standard assembly (GSA). Shaded bands show the standard error across bins.
From Meyer et al. Nature Methods 19: 429–440 (2022) © CC BY 4.0

Meyer F, Fritz A, Deng ZL, Koslicki D, Lesker TR, Gurevich A, Robertson G, … , Häußler S, Khaledi A, Maechler F, Mesny F, Radutoiu S, Schulze-Lefert P, Smit N, Strowig T, Bremges A, Sczyrba A, McHardy AC. (2022)
Critical Assessment of Metagenome Interpretation: the second round of challenges
Nat Methods doi: 10.1038/s41592-022-01431-4.

CHLOROTONILS: TWO BUGS WITH ONE STONE

ROLF MÜLLER | HEAD OF DEPARTMENT MICROBIAL NATURAL PRODUCTS

The global rise of antimicrobial resistance is one of the most pressing issues of our time. In order to ensure that effective antibiotics will still be available in the future, there is an urgent need to discover antimicrobial compounds with novel structures and mechanisms of action for the development of new drugs against infectious diseases. One of the most important sources of such novel drug scaffolds are natural products derived from microorganisms. These often highly potent substances are produced by bacteria or fungi to gain an advantage over competing microbes in their natural environment (e.g. the soil). However, before these molecules can be used to combat pathogenic bacteria in humans, they must be optimized for this application in usually lengthy processes to ensure sufficient efficacy and exclude side effects as far as possible. We have optimized an antimicrobial natural product that is active against infections with both, the hospital acquired MRSA (methicillin-resistant *Staphylococcus aureus*) pathogen and the malaria causing parasite, for preclinical research and future potential application in humans (Figure 1).

Chlorotonils were described for the first time in 2007 from the soil bacterium *Sorangium cellulosum* by researchers of the HZI. In addition to being highly effective against the malaria pathogen *Plasmodium falciparum*, chlorotonils also show very good activity against Gram-positive bacteria such as the hospital acquired pathogen *Staphylococcus aureus* - also known as MRSA. Despite the promising antimicrobial activity of chlorotonils, their use in the clinic was considered unlikely until recently because the known derivatives were poorly soluble. We have therefore set ourselves the task of specifically improving the physicochemical properties of the natural substance class in order to make the potent chlorotonils accessible for early preclinical development.

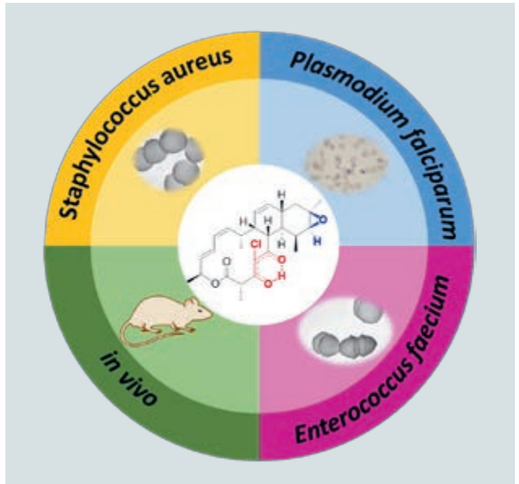

Figure 1: Structure and activity of the new drug candidate.
© HIPS/Walter Hofer

Although chlorotonil can be produced by chemical synthesis, the production of the natural product by this route is very time-consuming and cost-intensive, and yields are low. We found that the natural substance can be produced on a large scale by its natural producer *S. cellulosum* via fermentation. We used the molecules isolated in this way as a starting point for the production of new derivatives that do not occur in nature. During so-called semisynthesis, specific parts of the molecule were chemically modified in order to improve physicochemical properties while maintaining the excellent activity.

After the successful synthesis of 25 chlorotonil derivatives and extensive *in vitro* studies, we were able to identify a molecule with very good solubility that, in addition to good activity against *P. falciparum*, was also highly active against a number of multi-resistant bacteria. To prove that the newly developed molecule is also active in living organisms, the drug candidate was tested in a mouse infection model with *S. aureus*. Here, administration of the improved chlorotonil derivative actually reduced the bacterial load of the infected animals up to ten thousand-fold (Figure 2).

Another advantage of the compound scaffold apart from their resistance-breaking properties is that we were unable to observe resistance formation in our experiments. This gives hope that the active ingredient can be used for a longer time before resistant pathogens emerge in the clinical setting.

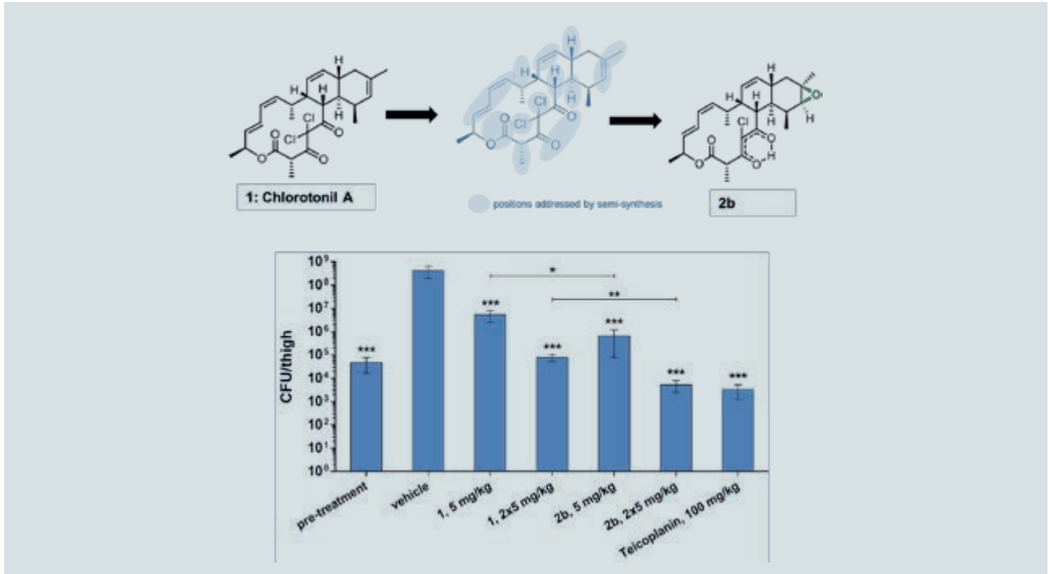

Figure 2: Optimization of Chlorotonil A (**1**) to provide derivative **2b** (upper) that shows in vivo efficacy in a neutropenic mouse model of S. aureus thigh infection (lower). Adapted from Hofer et al. Angew. Chem. Int. Ed., 61, e202202816, (2022) © CC BY 4.0

Hofer W, Oueis E, Fayad AA, Deschner F, Andreas A, de Carvalho LP, Hüttel S, Bernecker S, Pätzold L, Morgenstern B, Zaburannyi N, Bischoff M, Stadler M, Held J, Herrmann J, Müller R. (2022)
Regio- and Stereoselective Epoxidation and Acidic Epoxide Opening of Antibacterial and Antiplasmodial Chlorotonils Yield Highly Potent Derivatives
Angew Chem Int Ed Engl.: doi: 10.1002/anie.202202816

HOW SARS-COV-2 INITIATES VIRAL RNA SYNTHESIS

© private

MATHIAS MUNSCHAUER
HEAD OF RESEARCH GROUP LNCRNA AND INFECTION BIOLOGY

During infection of a host cell, pathogenic RNA viruses produce different types of RNAs with distinct functions. For SARS-CoV-2 this includes full-length copies of the RNA genome as well as subgenomic RNAs in both positive- and negative-sense orientation. The present study dissects the intracellular interaction profiles of these functionally distinct viral RNA species and identifies a human protein that selectively recognizes the negative-sense RNA of SARS-CoV-2. Surprisingly, the study further uncovers that SARS-CoV-2 utilizes the viral protein NSP9 to initiate viral RNA production and that this priming mechanism is regulated by SND1, explaining why SND1 is required for effective viral RNA synthesis. Together, this work describes a fundamentally novel insight into the RNA synthesis mechanism utilized by SARS-CoV-2 and uncovers an unsuspected host dependency of this process.

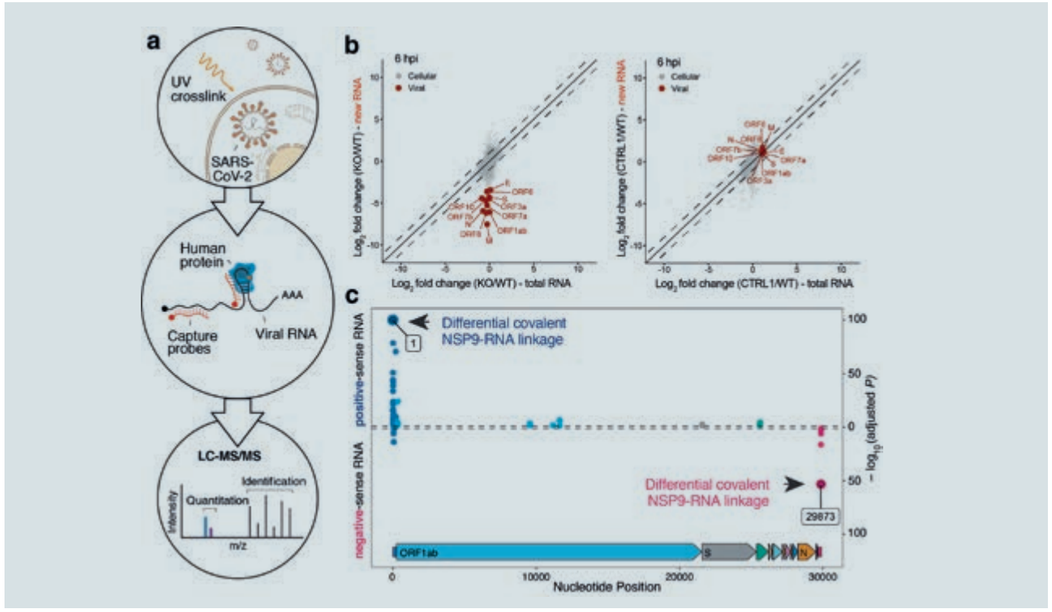

Figure 1, above: SARS-CoV-2 RNA-protein interactions and their relevance for viral RNA synthesis **a**, Outline of RNA antisense purification workflow to identify proteins bound to SARS-CoV-2 genomic RNA and subgenomic mRNA. SARS-CoV-2 infected cells are subjected to UV-crosslinking to stabilize RNA-protein interactions. Viral RNAs are purified using antisense probes targeting sequence regions in genomic and subgenomic viral RNAs. **b**, Effect of SND1 depletion on newly synthesized viral RNA levels, quantified by SLAM-seq analysis at 6 h post infection (hpi). Average log_2 fold changes in total RNA (x axis) and newly synthesized RNA (y axis) are shown for SND1 KO and CTRL cells, relative to WT cells (n = 2 independent infections). **c**, SND1-dependent changes in covalent NSP9-RNA linkages across the SARS-CoV-2 genome in positive and negative-sense RNA. Adapted from Schmidt et al. Cell 186: 4834–4850 (2023) © CC BY 4.0

Interactions between RNA replication products of pathogenic RNA viruses and the proteome of the host cell can determine the activation of host response pathways and influence viral RNA biogenesis and replication mechanisms. The present study examines for the first time how the interaction signatures of functionally distinct viral RNAs, namely the SARS-CoV-2 RNA genome and its subgenomic mRNAs differ in infected human cells. Focusing on factors with a binding preference for subgenomic RNAs, the study reports that the human protein SND1 selectively recognizes the negative-sense RNA of SARS-CoV-2. Prior to this work, our knowledge about the interactions of negative-sense SARS-CoV-2 RNA was severely limited due to its low intracellular abundance and the high degree of secondary structure. Depletion of the negative-sense RNA binder SND1 results in a dramatic loss of nascent viral RNA production and a reduced size of the replication organelle formed in infected human cells. A detailed characterization of SND1 binding partners in infected cells revealed an intriguing interaction between SND1 and several non-structural viral proteins (NSPs) involved in establishing RNA synthesis capabilities in infected cells. Of particular interest was a direct interaction between SND1 and NSP9. The authors could show that NSP9 is covalently linked to the 5' ends of both positive and negative-sense viral RNAs. Since the covalent linkage occurs at the exact nucleotide were viral RNA synthesis initiates, these findings implicate NSP9 in priming of viral RNA synthesis. Unexpectedly, depletion of the host protein SND1 led to a remodeling of NSP9 occupancy at initiation sites and impacted formation of the covalent linkage between NSP9 and viral RNA, which may explain why SND1 depleted cells display a strong reduction in viral RNA synthesis.

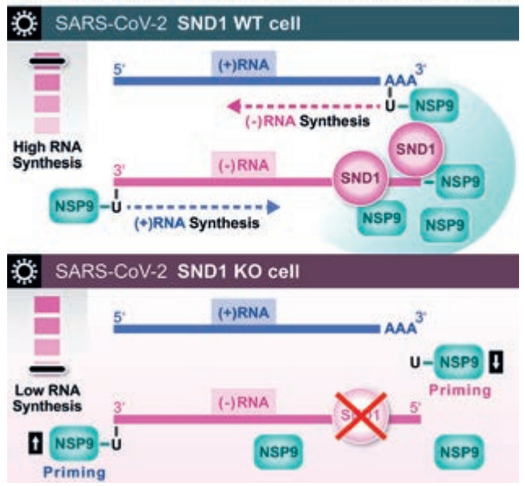

Figure 2, left: Model illustrating effect of SND1 on SARS-CoV-2 priming and RNA synthesis. Loss of SND1 leads to impaired recruitment of NSP9 to viral RNA and altered priming of viral RNA synthesis. From Schmidt et al. Cell 186: 4834–4850 (2023) © CC BY 4.0

The present study identifies a previously overlooked protein priming mechanism that initiates viral RNA production in SARS-CoV-2 infected cells and also uncovers that this mechanism is regulated by the host RNA-binding protein SND1. These are fundamental insights into the RNA synthesis mechanism of SARS-CoV-2 and provide valuable starting points for the rational design of novel antivirals, for instance by targeting the interaction between SND1 and NSP9 with small molecule inhibitors.

Schmidt N, Ganskih S, Wei Y, Gabel A, Zielinski S, Keshishian H, Lareau CA, Zimmermann L, Makroczyova J, Pearce C, Krey K, Hennig T, Stegmaier S, Moyon L, Horlacher M, Werner S, Aydin J, Olguin-Nava M, Potabattula R, Kibe A, Dölken L, Smyth RP, Caliskan N, Marsico A, Krempl C, Bodem J, Pichlmair A, Carr SA, Chlanda P, Erhard F, Munschauer M. (2023)
SND1 binds SARS-CoV-2 negative-sense RNA and promotes viral RNA synthesis through NSP9
Cell doi: 10.1016/j.cell.2023.09.002

ISG15 DEFICIENCY – FROM GENETIC DEFECT TO EXPERIMENTAL TREATMENTS

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FRANK PESSLER
HEAD OF RESEARCH GROUP BIOMARKERS FOR INFECTIOUS DISEASES

ISG15 deficiency is a recently discovered congenital disorder. It belongs to the family of so-called auto-inflammatory disorders, which means that affected children develop symptoms from ongoing uncontrolled inflammation. We were asked to help in the diagnosis of two siblings with recurring fevers and skin ulcerations of unknown etiology. We found that the children were homozygous for a loss-of-function mutation in the ISG15 gene. This easily explained the fevers, as ISG15 is a well-known inhibitor of interferon responses. However, using a 3D skin model, we unexpectedly found that ISG15 is in addition important for formation and integrity of the skin epithelium and that an experimental treatment consisting of TGFβ, doxycycline, and ruxolitinib normalized the abnormalities seen in this model.

Rheumatologic disorders were believed to be due to autoimmunity such as autoantibodies or self-reactive T cells. But in the early 2000's a new disease concept came up: in autoinflammatory disorders, there is no evidence of autoimmunity, but affected children nonetheless present with recurrent fevers and other manifestations of chronic inflammation such as skin rash, seizures, arthritis, pneumonitis, hepatitis, and so on. The study presented here was initiated by the disease of a two-year old boy who had been suffering from recurrent, cosmetically disfiguring skin ulcers since 6 months of age (Figure 1). A biopsy of a lesion revealed that this was a small vessel vasculitis. The same family had another baby, who developed identical lesions around 6 months of age. This sounded like a genetically determined condition, and we obtained blood samples from the whole family. Whole exome sequencing revealed that the affected children were homozygous for a loss-of-function mutation in the *ISG15* gene: a nonsense codon led to a truncated protein lacking the functional domain (Figure 2). ISG15 is a major negative regulator of interferon responses, and the loss of this inhibitor likely causes ongoing inflammation in children with ISG15 deficiency due to chronically overactive interferon signaling. But we reasoned that it took more than inflammation to cause these severe skin lesions. In collaboration with colleagues at the Department of Dermatology of MHH a 3D model of skin epithelium based on wild-type and *ISG15*$^{-/-}$ fibroblasts and keratinocytes was developed. We found that the *ISG15*$^{-/-}$ models had a much looser architecture (Figure 3) and fewer desmosomes and that *ISG15*$^{-/-}$ fibroblasts were defective in migration. All of these could be, at least partially, corrected with an experimental concoction of TGFβ, doxycycline, and the Jak1/2 inhibitor ruxolitinib, an inhibitor of interferon signaling. Subsequently, it was found that *ISG15*$^{-/-}$ macrophages were hyperinflammatory and had a major defect in mitochondrial energy generation and redox balance, which could be normalized by treatment with ruxolitinib. Thus, elucidating the genetic basis of the clinical manifestations of these children allowed us to uncover previously unrecognized cardinal functions of ISG15 and to suggest treatments for this rare disorder. Jak1/2 inhibitors such as ruxolitinib have since become the standard of care for ISG15 deficiency.

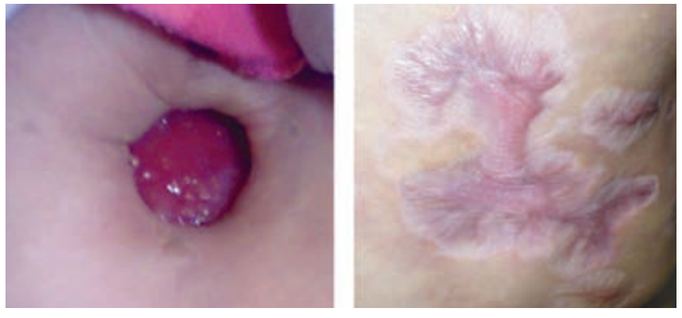

Figure 1: Skin lesions seen in one of the affected children. The lesions present as ulcerations of varying depth and heal with scar formation. Malik et al. J Clin Invest. 132: e931 (2022) © CC BY 4.0

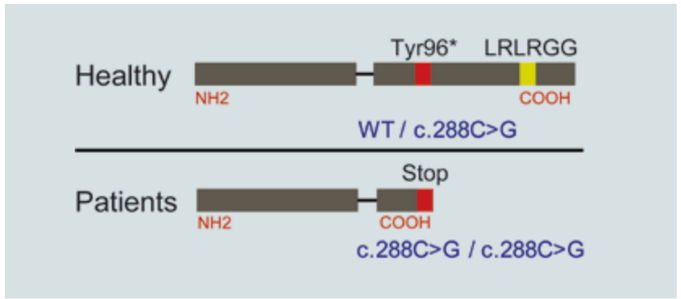

Figure 2: The *ISG15* gene encodes a protein with a ubiquitin-like functional domain containing a critical LRLRGG motif, which is required for interactions with target proteins. The affected children are homozygous for a stop codon that leads to synthesis of a truncated ISG15 protein lacking the functional domain. Unaffected family members were heterozygous for this mutation. Malik et al. J Clin Invest. 132: e931 (2022) © CC BY 4.0

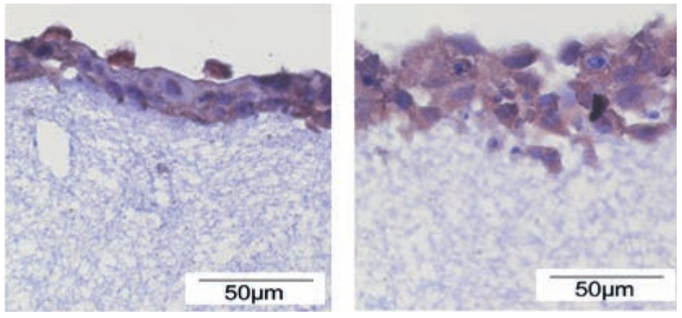

Figure 3: 3D model of epidermis formation based on fibroblasts and keratinocytes grown on a collagen matrix. A compact epidermis forms with wild-type cells, whereas a loose arrangement forms with *ISG15*$^{-/-}$ cells. Malik et al. J Clin Invest. 132: e931 (2022) © CC BY 4.0

Malik MNH, Waqas SF, Zeitvogel J, Cheng J, Geffers R, Gouda ZA, Elsaman AM, Radwan AR, Schefzyk M, Braubach P, Auber B, Olmer R, Müsken M, Roesner LM, Gerold G, Schuchardt S, Merkert S, Martin U, Meissner F, Werfel T, Pessler F. (2022)
Congenital deficiency reveals critical role of ISG15 in skin homeostasis
J Clin Invest.: doi: 10.1172/JCI141573.

CHLOROTONIL A PRESERVES COLONIZATION RESISTANCE AND PREVENTS RELAPSING *CLOSTRIDIOIDES DIFFICILE* INFECTION

© Verena Meier

TILL STROWIG
HEAD OF DEPARTMENT MICROBIAL IMMUNE REGULATION

Clostridioides difficile is a spore-forming, anaerobic, intestinal pathogen. It is the leading cause of hospital-associated diarrhea. In general, treatment of _Clostridioides difficile_ infections (CDIs) is challenging due to high relapse rates. In this case, antibiotics are both the main treatment and the major risk factor for infection. It is worrying that resistance to several antibiotics is continuing to spread. Interestingly, the natural product chlorotonil A (ChA) can inhibit disease and prevents recurrent CDIs (rCDIs). In contrast to vancomycin, it affects the murine and porcine microbiota to a lesser extent and is linked to faster recovery of the microbiota after CDI. Additionally, ChA accumulates in the spores of _C. difficile_ and therefore inhibits its outgrowth.

CDI remains a major healthcare problem since the antibiotics currently used to treat it, like vancomycin and metronidazole, sustain a functionally impaired microbiota, which is in itself a risk factor for developing CDI. In combination with the persistence of endospores, this results in high rates of recurrent infections occurring in approximately 20% of all patients. Consequently, there is an urgent need for new antibiotics against *C. difficile* with little impact on colonization resistance to ensure proper treatment and reduce the risk of recurrent infections or other adverse effects caused by a damaged microbiota. In our study that was conducted with colleagues at the Friedrich-Loeffler-Institute, the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), Greifswald University, and the Leibniz Institute DSMZ - German Collection of Microorganisms and Cell Cultures GmbH, we characterized the effect and activity of the antimicrobial compound chlorotonil A (ChA) that has been isolated by researchers at the HIPS from the myxobacterium *Sorangium cellulosum* (Figure 1). Since the antibacterial activity of ChA and its derivate ChB1-Epo2 is restricted to Gram-positive pathogens, we assumed that chlorotonils are good candidates to clear CDI more effectively and less damaging than vancomycin. Firstly, we confirmed the antimicrobial activity of the chlorotonils against *C. difficile* by screening a panel of clinical *C. difficile* strains, including ones resistant against metronidazole, vancomycin, or fidaxomicin, in standardized growth assays. Next, we assessed the potential of chlorotonils for treating CDIs by using a well-established murine infection model and could show that ChA successfully antagonizes established CDIs and prevents relapsing infection. In additional experiments, we were able to show that ChA treatment has a lower impact on the intestinal metabolome compared to vancomycin and clindamycin and exhibits less harmful effects on commensal bacteria. In terms of rCDI, we tested the effect of the chlorotonils on the outgrowth of *C. difficile* spores into vegetative cells and could show that vancomycin and metronidazole failed to inhibit spore outgrowth, whereas ChA and to a lesser degree ChB1-Epo2 were able to inhibit spore outgrowth (Figure 2). Finally, our findings show that ChA is a promising candidate for the successful treatment of CDI due to its capacity to both antagonize an established CDI and prevent relapses.

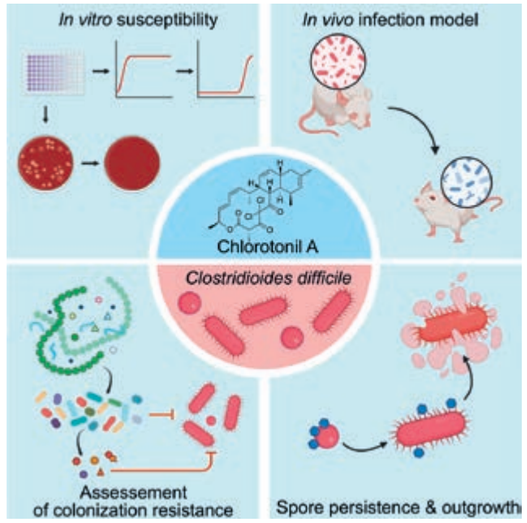

Figure 1: Chlorotonil A interferes with the lifestyle of *Clostridioides difficile* and preserves colonization resistance. From Bublitz et al. Cell Host Microbe 31: 734–750 (2023) © CC BY 4.0

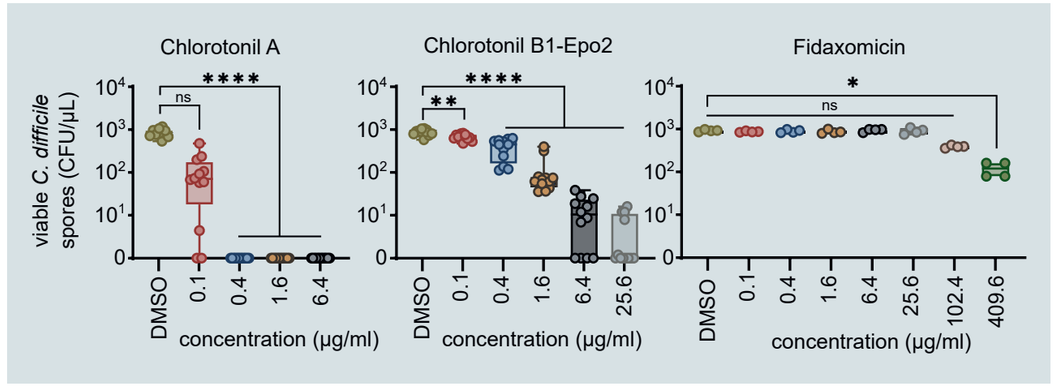

Figure 2: Chlorotonil A accumulates in the spore and inhibits outgrowth. Concentration-dependent inhibition of *C. difficile* spore outgrowth after incubation with ChA, ChB1-Epo2 and fidaxomicin determined by CFU count on plate. Concentrations above 6.4 µg/mL exceed the aqueous solubility of ChA and were therefore left out. Adapted from Bublitz et al. Cell Host Microbe 31: 734–750 (2023) © CC BY 4.0

Bublitz A, Brauer M, Wagner S, Hofer W, Müsken M, Deschner F, Lesker TR , Neumann-Schaal M, Paul L-S, Nübel U, Bartel J, Kany AM, Zühlke D, Bernecker S, Jansen R, Sievers S, Riedel K, Herrmann J, Müller R, Fuchs TM, Strowig T (2023)
The natural product chlorotonil A preserves colonization resistance and prevents relapsing Clostridioides difficile infection
Cell Host Microbe doi.org/10.1016/j.chom.2023.04.003

HZI'S SITES

Pseudomonas aeruginosa biofilm (c) HZI Mathias Müsken

© HZI | Verena Meier

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THERESIA STRADAL
SPOKESPERSON FOR THE HZI CAMPUS BRAUNSCHWEIG

TIME OF CHANGE

THE HZI FOUNDATION CAMPUS IN BRAUNSCHWEIG

Originally the only HZI location on the site and premises of the former Gesellschaft für Biotechnologische Forschung (GBF), HZI's foundation campus on the "Science Campus Braunschweig Süd" covers many essential aspects of modern infection research. High-level fundamental research is pursued and novel concepts for combatting infectious diseases are jointly developed and implemented.

The Braunschweig site comprises strong units for Structural Biology, Cell Biology, Immunology, Microbiology, Epidemiology and Vaccine Research. It is also the home of unique infrastructures including facilities for fermentative and total synthesis of natural compounds, a cutting-edge animal facility with some 300 different mouse strains, state-of-the-art biosafety level 1-3 (BSL1-3) laboratories, and units for imaging and omics technologies.

The change in HZI's leadership in 2023 has brought plans and concepts for considerable growth, particularly at the main site in Braunschweig. A significant expansion of research units as well as science support infrastructure, as outlined in the successful project applications "MICROSTAR" and "HUMAN" (*see Interview with Josef Penninger and Thomas Pietschmann in this report*), has been initiated and will fully materialize in the upcoming years.

Up to 20 new research units, including junior groups for young investigators, technology experts and clinician scientists will be established. A first call for applications has been issued late in 2023. The majority of the new groups and support units will be based in Braunschweig, where they interact with the established groups, the novel Director's synergy project (see below) and the other HZI sites.

In future, the Foundation Campus will focus on the central research topic of infection resilience. Thereby, it utilizes existing strengths, such as for instance epidemiological work on suitable interventions against the spread of pathogens or probiotic therapy to prevent colonization with resistant bacteria. Significant opportunities and new momentum in this field will be gained by integration of the new junior groups, technology experts and clinician scientists, who will join skillsets, expertise and network with established groups in Braunschweig and the other sites.

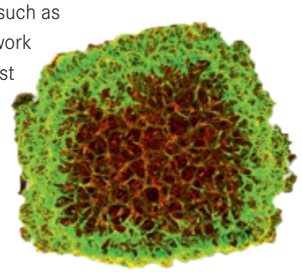


Figure 1: A blood vessel generated by the new organoid robot on campus. © HZI | Junseong Lee

The new departure is already materializing on campus, for example through the establishment of a new cultivation and pipetting robot for human organoids in the context of the Director's Synergy Project. Supported by artificial intelligence, this machine, which is unique in academic research in Europe, can grow and supply thousands of organoids simultaneously – with the highest quality and standardization. This means completely new framework conditions for human-oriented investigations into the pathophysiology of infections and validation of new intervention procedures to serve the entire HZI and our collaboration partners.

In addition, more than 15 thousand viral and bacterial effector genes are being cloned as part of the Director's Synergy Project, making them available for functional analyses in the research laboratories on the Braunschweig campus and beyond. The synergy project thus lays a new foundation for the discovery of weapons with which pathogens attack the infection resilience of humans. At the same time, this provides unique access to the tools with which microbes assert themselves in competition on our planet. In this way, the project opens vast grounds for collaborations and accesses a new arsenal of functions that we can use in the future to strengthen our resilience against infections.

The recent establishment of a new 200kV Cryo-electron microscope in the Department of Structural Biology, headed by Wulf Blankenfeldt, which is particularly suited for single particle measurements and electron diffraction is a key asset to visualize these microbial machines with atomic resolution.

Parallel to this in autumn 2023 a new HZI Seminar Series was initiated that caters for the interests and needs of the scientists in Braunschweig, but is also being transmitted to the other sites to maximize outreach. The lectures are a big success with high ranking speakers in the first quarter of 2024, namely Mattia Zampieri, University of Basel, Switzerland, Philipp Henneke, University Medical Center and Faculty of Medicine Freiburg, Jim Naismith, University of Oxford, UK.

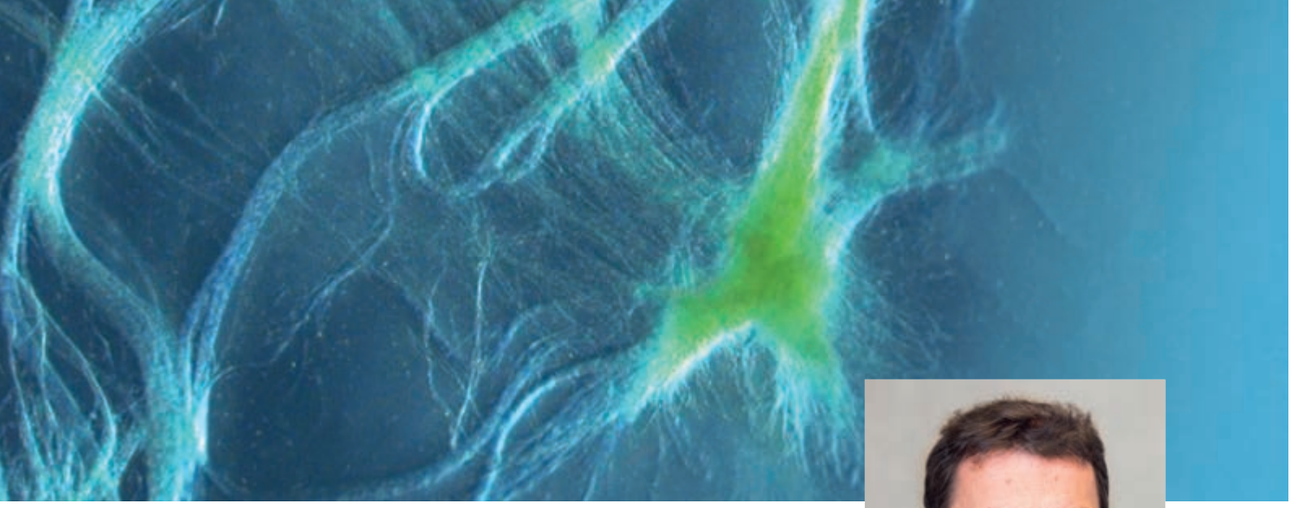
Powerful technology for new research avenues: The organoid cultivation robot on HZI's Braunschweig campus is unique in academic research in Europe. From left: HZI scientists Kenny Aina, Yadvir Singh, Kristin Metzdorf. © HZI

Early in 2023, Gerard Krause, head of the Department of Epidemiology, was appointed to a leading position at the WHO in Geneva and left HZI. Krause took over the "Global Infectious Disease Surveillance Unit" at the WHO. He was given a ceremonial farewell in February 2023. Berit Lange has taken over provisional management of the Department of Epidemiology as acting head. Lange was elected to the IAB of the DZIF in March 2023 and was appointed to the Standing Committee on Vaccination (STIKO) together with 19 experts from Germany in January 2024.

SCIENCE CAMPUS
Braunschweig-Süd

THE LIFE SCIENCE CAMPUS BRAUNSCHWEIG-SÜD

Together with neighboring institutes and other partners on HZI premises, the center has established the "Science Campus Braunschweig Süd", reflecting concentrated on-site collaborations in research, development and education. Regional partners in this integrated campus include TU-BS, DSMZ, Fraunhofer Institute for Toxicology and Experimental Medicine (Fraunhofer ITEM), the German Center for Infection Research (DZIF), the "BioS" lab for school students and a number of start-up companies.



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ROLF MÜLLER | SCIENTIFIC DIRECTOR OF HIPS

IN SEARCH OF NOVEL ANTI-INFECTIVE DRUGS

THE HELMHOLTZ INSTITUTE FOR PHARMACEUTICAL RESEARCH SAARLAND (HIPS)

HIPS was founded in 2009 as a branch institute of HZI in close collaboration with Saarland University (UdS). Its scientists conduct pharmaceutical research with a focus on antimicrobial resistance (AMR) and aim to develop novel bioactive compounds to combat antibiotic-resistant bacteria. To bring these molecules into application, HIPS collaborates closely with international partners from the pharmaceutical industry, as well as academic partners in a highly interdisciplinary setting. In the past two years, the institute started implementing the expansion process decided by federal and state governments in late 2020.

HIPS and UdS were able to apply the expansion funds to successfully attract a number of renowned researchers to the Saarbrücken campus and thus strengthen its focus on drug research. The newly appointed HIPS PIs are Tobias Gulder (Natural Products Biotechnology), Christine Beemelmanns (Anti-Infectives from Microbiota), Andreas Keller (Clinical Bioinformatics), Alexey Gurevich (Human-Microbe Systems Bioinformatics) and Martin Empting (Antiviral and Antivirulence Drugs), as well as the junior research group leader Kenan Bozhüyük (Synthetic Biology of Natural Products). Professors appointed to Saarland University who are affiliated with HIPS are Tanja Gulder (Natural Products Synthesis) and Andrea Volkamer (Data Driven Drug Design). Notably, all advertised positions could be filled with the prime candidates of the search, who often agreed to choose HIPS over offers to prestigious universities worldwide. Furthermore, HIPS was successful in keeping the bioinformatics professor Olga Kalinina (Drug Bioinformatics) on site, although she received several calls to other German universities.

HIPS HELMHOLTZ Institute for Pharmaceutical Research Saarland

To make room for the growing team of scientists, HIPS is undergoing spatial expansion in two phases. In the first construction phase, which began in September 2023, a new building will be set up in modular construction until early 2025. Preparations for the second phase have started in 2023 and will result in a second new building by 2029.

Interactions and collaboration with Saarland University have been further intensified, not only through joint appointments, but also through the research alliance "Pharmaceutical Research Saarland", which supported the successful acquisition of the "TALENTS" Graduate school funded by the EU-COFUND program. Here, over the course of five years, 15 international doctoral students will be trained at the interface of clinical medicine, microbiology and pharmaceutical science with a special focus on microbiome-modulating therapies. The Research Alliance enables the participating scientists to create synergies at the Saarbrücken/Homburg site and work on joint research projects in the field of pharmaceutical research. Given its success, the Research Alliance was extended for a second three-year term in 2022.

To rapidly advance the development of new pharmaceuticals, Saarland University and HIPS also agreed to bundle their expertise in the fields of drug research, computer science, and medicine as well as strengthen the interaction with the pharmaceutical and biotechnology industry at a national and international level. To this end, the "PharmaScienceHub" (PSH) was founded as a collaboration platform in 2023. The aim of the PSH is to streamline the interaction between all involved players and allow for strategic measures, such as targeted appointments. The opportunity to take part in PSH was a major selling point during the appointment of the aforementioned professors and PSH is a central element of the planned cluster of excellence "nextAID³ – Next Generation of AI-driven Drug Discovery and Development" at Saarland University. In February 2024, the German Research Foundation (DFG) invited Saarland University and its partners to submit a full proposal for nextAID³, for which Anna Hirsch acts as spokesperson. In order to successfully combine experimental and computer-aided research, an interdisciplinary team of over 40 researchers has joined forces for nextAID³.

HIPS acquired funding from strategically important partners in the field of AMR-research, including the Bill and Melinda Gates Foundation, CARB-X, INCATE and GoBio. Importantly, in early 2024, HIPS was invited to become a member of the TB Drug Alliance (TBDA), a partnership of leading institutions and pharmaceutical companies, which allows for access to experts and technologies that will join the HIPS in developing novel strategies against tuberculosis.

In late 2023, the German Federal Ministry of Education and Research (BMBF) decided to fund the establishment of a German-Ukrainian core of excellence to help discover new anti-infectives and make them available for medical purposes. The core of excellence, funded with 2.5 million euros, is to be located in the western Ukrainian city of Lviv – in collaboration with Saarland University and HIPS.

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JÖRG VOGEL | MANAGING DIRECTOR OF HIRI

LEARNING THE LANGUAGE OF RNA TO COMBAT INFECTION

THE HELMHOLTZ INSTITUTE FOR RNA-BASED INFECTION RESEARCH (HIRI)

The year 2022 marked the fifth anniversary of the Helmholtz Institute for RNA-based Infection Research (HIRI), established as a joint initiative between HZI and the Julius-Maximilians-Universität Würzburg (JMU). From its inception, the institute has been dedicated to harnessing the potential of ribonucleic acid (RNA) as a diagnostic, drug, and therapeutic target to design new strategies to combat infectious diseases and to edit the microbiome.

The HIRI combines RNA research with infection biology to (i) identify RNA-based mechanisms in virulence and host defense, (ii) understand infections at the single-cell level, and (iii) harness RNA in medical applications. Based on strong basic RNA research, the institute's long-term goal is to develop innovative therapeutic approaches to better diagnose and treat human infections. In 2022, the HIRI Scientific Advisory Board, chaired by Anna Pyle (Yale University), conducted its inaugural meeting during which the panel of 14 internationally renowned scientists received an overview of the institute's scientific activities.

Personnel

2022 saw the departure of Alice Hohn, Head of Administration, who was instrumental during HIRI's formative years. Throughout 2023, Tobias Kerrinnes served as interim Head of Administration. The institute has grown to 9 working groups and about 100 scientific, technical and administrative staff from 19 countries. The Helmholtz Young Investigator Group of Redmond Smyth successfully passed its scientific evaluation. Single-cell expert Emmanuel Saliba was appointed to a W2 professorship at the JMU Medical Faculty. Franziska Faber, who was associated to the HIRI in July 2022, and Alexander Westermann, were each appointed W2 professors in microbiology at the JMU. Mathias Munschauer accepted the Willy Robert Pitzer Professorship at Goethe University Frankfurt, and Lars Barquist assumed the position of an Assistant Professor at the University of Toronto.

Publications, funding and awards

Over the reporting period, research by HIRI scientists and affiliates resulted in more than 90 research papers, many in high-profile journals including *Nature* and *Cell*. In 2022, the Pettenkofer Prize was awarded to HIRI department head Chase Beisel and Cynthia Sharma (JMU) for the development of the CRISPR-Cas-based diagnostic platform LEOPARD. HIRI director Jörg Vogel was appointed committee member for the Gottfried Wilhelm Leibniz Program of the German Research Foundation (DFG). In 2023, he was elected a full member of the Bavarian Academy of Sciences and Humanities. HIRI group leader Neva Caliskan was elected to the Board of Directors of the RNA Society.

RNA*med* doctoral students met Nobel laureate Katalin Karikó (fourth from the right side) in Würzburg in July 2023 © HIRI

HIRI director Jörg Vogel at the HIRI anniversary ceremony.
© HIRI | Mario Schmitt

The Free State of Bavaria supported RNA research within the program "Excellence Networks and University Cooperations" (EVUK). In 2023, the DFG launched a new Collaborative Research Center "Decisions in Infectious Diseases" (DECIDE) with participation of HIRI research groups. The Helmholtz Association is supporting the commercialization of the LEOPARD technology with two grants. Helmholtz AI funded a project aiming to decipher viral RNA-host interactions with the help of artificial intelligence, spearheaded by HIRI group leader Mathias Munschauer and Annalisa Marsico from Helmholtz Munich.

Microbiologist Rotem Sorek received the Max Planck-Humboldt Research Award 2023 and will investigate key mechanisms of bacterial and human immune systems in collaboration with Jörg Vogel at HIRI and Veit Hornung at Ludwig-Maximilians-Universität (LMU) in Munich.

HIRI HELMHOLTZ Institute for RNA-based Infection Research

Training, teaching and networking

HIRI group leaders continued offering courses on "Infection & Immunity" and "RNA Biology," and organized workshops on science communication. The "RNA & Infection" graduate program, initiated in 2018, has expanded to 11 PhD students. Jörg Vogel coordinates a new graduate program RNA*med*, funded by the Elite Network of Bavaria that prepares students to enter the rapidly growing field of RNA-based medicine. In July 2023, RNA*med* doctoral students had the amazing opportunity to meet Nobel laureate Katalin Karikó.

After a pandemic hiatus, the "RNA Seminar" series resumed as the Würzburg Life Science Seminar, featuring many international and high-profile speakers. The HIRI co-hosted the international conference "CRISPR 2023" and helped organize the Interacademy Conference "Microbiology 2023". The first HIRI retreat took place in Tutzing in 2023.

Single-Cell Center

The Single-Cell Center Würzburg, established by HIRI and funded by the Free State of Bavaria, granted 67 seed grants to study diseases at the single-cell level since its foundation, with 20 of those grants awarded in 2022. In July 2023, HIRI group leader Emmanuel Saliba succeeded Jörg Vogel as spokesperson of the center.

New building

The groundbreaking ceremony for HIRI's new building on the Medical Campus Würzburg marked a milestone in 2023. Once completed, the building will enable the institute to permanently fulfill its research mission in Würzburg.

Ilse Aigner, President of the Bavarian State Parliament at the HIRI anniversary ceremony. © HIRI | Mario Schmitt

The HIOH team in January 2024, © HIOH | Andreas Sachse

© HIOH | JME

FABIAN LEENDERTZ | FOUNDING DIRECTOR OF HIOH

MILESTONES AND EXPANSION: THE EVOLVING LANDSCAPE OF HIOH

THE HELMHOLTZ INSTITUTE FOR ONE HEALTH (HIOH)

A One Health team

Since its establishment in November 2021, the Institute has grown considerably. HIOH currently employs over 60 people from 13 different nations (as of February 2024, see above). We were able to recruit Sébastien Calvignac-Spencer as head of the department *Pathogen Evolution* and Katharina Schaufler as head of the department *Ecology and Epidemiology of Antimicrobial Resistance* (see photographs below). The professorships were appointed by the University of Greifswald and the University Medicine, respectively. In addition, we welcomed Fee Zimmermann as head of the *One Health Surveillance* core unit and Jan Frederik Gogarten as head of the *Evolutionary Community Ecology* junior research group (Figure 1).

Figure 1: The structure of HIOH with its three departments (in white), two core units (in blue) and one junior research group (in turquoise) and the appointed heads. (Created with BioRender.com)

Towards systematic longitudinal One Health monitoring

According to the One Health approach, the health of humans, animals and their environment needs to be considered as inextricably linked. Consequently, implementing this principle, the core of HIOH's research concept is the establishment of One Health surveillance efforts, i.e., health monitoring across the disciplines. Comprehensive longitudinal sample and data collection and analysis is conducted in two model regions: (1) the African tropics, as hotspots for the emergence of new zoonotic diseases, and (2) Mecklenburg-Western Pomerania, as a strongly agricultural area with a low population density. To strengthen research on emerging infections and antimicrobial resistance in our first model region, HIOH and the Robert Koch Institute have recently established a new training and research laboratory at the Centre Hôspitalier et Universitaire de Bouaké (CHU Bouaké, Côte d'Ivoire, see photograph below).

One Health research in both model regions is currently further strengthened through strategic funding in six selected joint projects, which enhance HIOH's close collaboration with partner institutions in Greifswald and with HZI. The projects, which aim at expanding One Health surveillance efforts such as human cohorts and wildlife disease monitoring in Sub-Saharan Africa as well as in the Northeast of Germany, were launched at a joint kick-off meeting in December 2023. A subsequent call for additional multilateral collaborative One Health projects was published.

Interdisciplinary networking and outreach

To anchor the One Health concept in Germany, the well-established former National Research Platform for Zoonoses, jointly funded by six federal ministries (BMBF, BMG, BMEL, BMUV, BMVg and BMZ), has recently been transformed into the *One Health Platform* (OHP). For the next five years, HIOH will manage one of the OHP's three offices, alongside those at the University of Münster and at the Friedrich-Loeffler-Institute. In particular, HIOH will be responsible for internationalizing and expanding the OHP research network into the fields of environmental and climate research.

In addition to many international projects, HIOH is currently engaging on a local scale, with non-scientific stakeholders in Mecklenburg-Western Pomerania by implementing a BMBF-funded citizen science project (CiFly).

Appointment of Sébastien Calvignac-Spencer by State Minister Bettina Martin. © Ministry of Science, Culture, Federal and European Affairs Mecklenburg-Vorpommern | Christian Moeller

HIOH HELMHOLTZ Institute for One Health

Appointment of Katharina Schaufler at the Ministry of Science, Culture, Federal and European Affairs Mecklenburg-Vorpommern | Christian Moeller

Publicly acknowledging his achievements and groundbreaking work in the field of zoonotic infectious disease research using the One Health concept, Fabian Leendertz, founding director at HIOH, was awarded the Hamburg Science Prize in November 2023. He will use the prize money of €100,000 for preparatory work on intercultural cooperation in One Health surveillance.

Logistical developments at HIOH

In the absence of a dedicated HIOH research building – which could, cautiously estimating, be expected to be completed by February 2027 – all laboratories and offices are currently located in temporary premises across the University campus. After successful assessment by the authorities, the laboratories in these temporary premises commenced operations in January 2023, allowing for the transfer of more than 180,000 samples to HIOH.

To support the construction of HIOH's new research building, the Ministry of Science, Culture, Federal and European Affairs Mecklenburg-Vorpommern has made a commitment to supply additional 15 million €. Bettina Martin, the Minister of Science, took the opportunity to announce the good news in person at HIOH.

Fabian Leendertz, director of HIOH, at the opening of a new training and research laboratory at the Centre Hôspitalier et Universitaire de Bouaké (CHU Bouaké, Côte d'Ivoire). Source: Grit Schubert | © RKI

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ULRICH KALINKE | EXECUTIVE DIRECTOR OF TWINCORE

15 YEARS OF TRANSLATIONAL INFECTION RESEARCH

THE TWINCORE CENTRE FOR EXPERIMENTAL AND CLINICAL INFECTION RESEARCH

At TWINCORE, multidisciplinary teams of clinician scientists, basic researchers and data scientists strive to channel new knowledge into clinical practice. In close collaboration with TWINCORE's founding institutions, HZI and Hannover Medical School (MHH), together with national and international partners, they study bacteria, viruses and the reactions of the immune system against these pathogens.

While the public attention to the SARS-CoV-2 pandemic was fading, it has remained an important topic for our research activities. Since February/March 2020, 23 projects in the fields of virology, immunology and bacteriology were launched together with HZI and MHH as well as with national and international partners. The projects aimed to investigate SARS-CoV-2, better understand the immune response in COVID-19 patients, develop models for research into the disease and develop new treatment and prevention options. In addition, a project on Long COVID was funded by the COVID-19 Research Network Lower Saxony (COFONI).

In September 2022, the 14th TWINCORE symposium was held together with the 13th VPM Days of Vakzine Projekt Management GmbH (now: Serum Life Science Europe GmbH) under the title "Lessons from the pandemic for future infection research". Presentations were also given by venture capitalists and multilateral financial institutions such as the European Investment Bank. To mark the anniversary of TWINCORE, our 15th Symposium with the theme "15 years of translational infection research" took place in September 2023.

TWINCORE has developed a recruitment strategy for the strategic filling of junior group leader positions. Positions for "clinician scientists" have been established at all career levels to develop research projects at the interface between clinics and fundamental research. On the other hand, the filling of junior research group leader positions with excellent basic scientists is being promoted.

In November 2023, Yannic Bartsch was appointed to a W1 junior professorship. He started working in his junior research group "Anti-viral Antibody Omics" in January 2023 and was awarded funding for a Helmholtz Young Investigator Group Leader position in April 2023.

Due to the ever-increasing importance of bioinformatics and the resulting exponential growth in data storage requirements and enhanced speed of data transfer, the focus was laid on upscaling storage capacity, computing power, data transfer speed and throughput. The move from fixed to flexible workplaces also led to reorganization of the necessary network infrastructure.

A transfer strategy was developed to identify projects with high transfer potential and lead them into exploitation. An external advisory board on exploitation matters has been established that met for the first time in August 2023.

TWINCORE developed a strategic focus on antibody research comprising projects by various research groups, which exchange protocols and share expertise. This research is part of the DZIF bridging topic "Antibody-based therapies". Here, a whole series of third-party funded projects totaling more than EUR 2 million were acquired and first patents were registered.

The "Lower Saxony International Summer Academy (LISA)" is largely funded by the RESIST Cluster of Excellence and receives support by the Ministry of Science and Culture of Lower Saxony (MWK) since 2023.

©TWINCORE

TRAIN Translationsallianz in Niedersachsen

TRANSLATION ALLIANCE IN LOWER SAXONY (TRAIN):

TWINCORE houses the office of the Translational Alliance in Lower Saxony TRAIN, which aims to join forces for translational activities in the Hannover-Braunschweig-Göttingen region. The alliance offers training programs by the TRAIN Academy and provides technological platforms in the field of OMICS technologies for translational research. Ulrich Kalinke is branch manager of TRAIN and spokesperson for the TRAIN Academy.

TRAIN operates in various fields. In the TRAIN Omics area, the focus is on networking among omics technology platforms at different institutions, making omics technologies more broadly available to the different partner institutions, and defining quality standards for these technologies. Moreover, TRAIN Omics is bringing partners together for new collaborative third party funded projects.

The TRAIN Academy provides further training for scientists. In October 2023, the kick-off event of the eighth class of the two-year continuing education program "Translational Research and Medicine: From Idea to Product" took place. The teaching events are mostly held in hybrid form to facilitate attendance of participants from the different partner locations.

Furthermore, the PhD program BIOMEDAS was initiated as part of TRAIN. It is aimed at offering a data science environment for PhD students who want to acquire broad expertise in data sciences and medical research. Coordinated by the CiiM/HZI, the first BIOMEDAS cohort started in 2020; up to and including 2023, the cohorts comprised a total of 27 PhD students.

In order to further expand cooperation in health research in the Hannover-Braunschweig-Göttingen region in the future, the Physikalisch-Technische Bundesanstalt (PTB) will join the TRAIN network and expand TRAIN's expertise in the attractive research field of biochemical measurement. With the help of PTB the theme of data quality assurance in the omics space will be addressed.

In addition, there are various approaches to develop the existing science triangle into an even more active and attractive transfer ecosystem so that exploitation will become an integral element of translational research in the future.

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YANG LI AND MARKUS CORNBERG | DIRECTORS CiiM

PRECISION MEDICINE: TAILORING INFECTIOUS DISEASE CARE TO INDIVIDUAL NEEDS

CENTRE FOR INDIVIDUALISED INFECTION MEDICINE (CiiM)

The Centre for Individualised Infection Medicine (CiiM), a joint initiative of HZI and MHH, aims to revolutionise medicine for infectious diseases in the direction of precision medicine. With the goal of individual prognosis, diagnosis and personalised prevention and therapy, CiiM seeks to pioneer data-based methods in this field and develop patient-oriented approaches.

Infectious diseases are complex on diverse levels. Susceptibility to infection, risk for severe courses, treatment success or potential for prophylaxis are all influenced by various factors including the affected patients themselves, their microbiota as well as the causing pathogens. However, personalised approaches in infectious diseases medicine remain underutilized. The CiiM seeks to address this gap by fostering interdisciplinary collaboration to tailor diagnosis, prevention, and treatment to individual patient needs (figure 1).

By integrating clinical data with modern high-throughput analytical methods utilizing innovative methods of data analysis and knowledge discovery in the field of Big Data and Artificial Intelligence, CiiM aims to generate insights facilitating evidence-based medicine. This interdisciplinary effort involves basic researchers, data scientists, technologists, life scientists and clinicians working closely together to analyse complex datasets and translate findings into clinical practice. Led by directors Yang Li and Markus Cornberg, supported by the

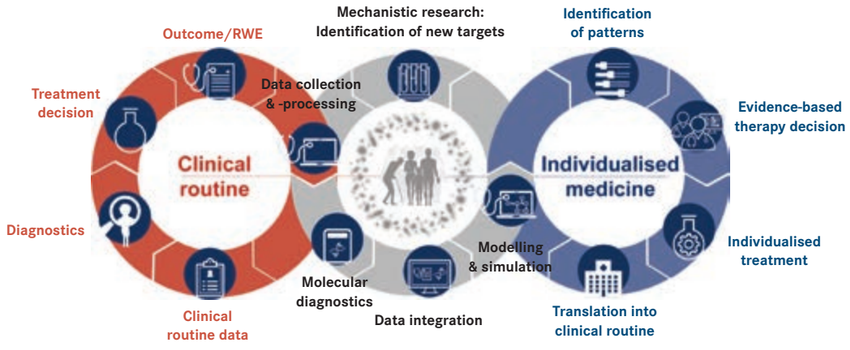

Figure 1: Planned CiiM Workflow © Debarry | CiiM

The planned CiiM building
© HDR_IMAGINA_Visual Collaboration

CiiM
CENTRE FOR INDIVIDUALISED INFECTION MEDICINE

CiiM coordinator Jennifer Debarry, CiiM with its groups and associated professors ensures close coordination between clinics, research, and data science.

The planned CiiM building will provide a conducive environment for collaboration and innovation. The groundbreaking ceremony took place in 2022. Since then, the construction site has been set up, earthworks and structural work have been completed and the timber construction work is currently underway. The building will be operational and ready for use in 2025.

The interdisciplinary CiiM team has seen continuous expansion in recent years (figure 2). Since 2022, the addition of the group "Clinical Bioinformatics" (led by Cheng-Jian Xu, MHH) has enriched CiiM with expertise in epigenetics. Furthermore, starting in 2024, the group "Personalised Immunotherapy" (led by Kathrin de la Rosa, HZI) will join, bringing expertise in B-cell and antibody omics. Additionally, the core team responsible for driving key administrative and strategic areas in close coordination with parent institutions has been strengthened.

At CiiM interdisciplinary networks are actively enhanced through various strategies. Ties with clinical departments at MHH have been strengthened through tandem projects in the KlinStrucMed program. International collaborations, including unique cohort development, are supported by CiiM fellows and through sabbaticals, such as Kumar Visvanathan from Melbourne, who joined CiiM from August to November 2023, and our first CiiM scholarship holder, Yin-Han Chou from Taiwan, who began her PhD in October 2023. Additionally, CiiM is involved in regional and overarching research structures like the COVID-19 Research Network Lower Saxony (COFONI) and the new Lower Saxony Research Centre for Artificial Intelligence and Causal Methods in Medicine (CAIMed). Currently, a CAIMed junior research group is being set-up at CiiM focusing on artificial intelligence and bioinformatics for the focus area infection medicine.

Establishing patient and population cohorts is vital for CiiM's work, e.g. leveraging omics and data analysis to identify biomarkers for targeted patient management, and has been significantly advanced in recent years. The groundwork for the "CiiM Entry Lab" is underway, encompassing ethical protocols, sample processing standards, and data management workflows. Alongside the health control cohort (*GesKo*), recruitment for a geriatric trauma cohort (smart) has been initiated in collaboration with the department of trauma surgery from MHH, aiming to enhance understanding of post-operative infections and develop tailored treatments. In collaboration with the RESIST cluster of excellence it is also planned to study infection susceptibility in older adults. Additionally, within the EU Horizon Project D-SOLVE, coordinated via CiiM, individual host responses to Hepatitis D Virus and its treatment are being investigated and three distinct cohorts are being established, including an Investigator Initiative Trial (IIT).

Figure 2: The CiiM Team © Debarry | CiiM

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DIETER JAHN
DIRECTOR OF THE SYSTEMS BIOLOGY CENTRE BRICS

BRICS: UNDERSTANDING HEALTH

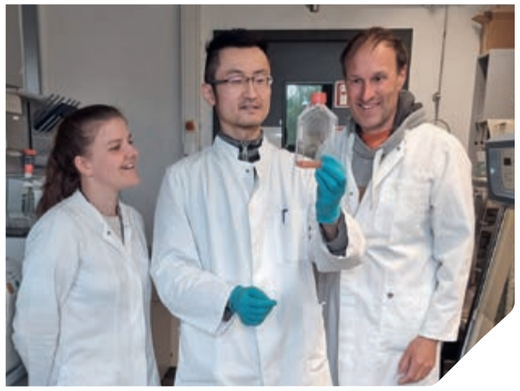
BRICS – BRAUNSCHWEIG INTEGRATED CENTRE FOR SYSTEMS BIOLOGY

BRICS is an interdisciplinary and internationally oriented research centre for systems biology aiming to understand health and fight disease. For this purpose, BRICS is part of the Core Research Area "Engineering for Health" at the Technische Universität Braunschweig (TU-BS). It is jointly operated by strong cooperation partners: TU-BS, HZI, the Leibniz Institute DSMZ – German Collection of Microorganisms and Cell Cultures GmbH and the National Metrology Institute Physikalisch Technische Bundesanstalt (PTB).

UNDERSTANDING HOST–PATHOGEN INTERACTIONS WITH SYSTEMS BIOLOGY

BRICS is interested in the molecular networks that keep biological systems in balance. One scientific focus is the host-pathogen interaction during an infection process. An infection induces a metabolic cross-talk between host cells and the pathogen. How metabolism is involved in disease progression and how metabolic intervention can be of advantage for disease outcome are of interest. In this context, scientists at BRICS use state-of-the-art methodology to record the highly complex metabolic networks holistically and model the underlying principles. With the help of bioinformatic methods, crucial factors can be identified that cause biological systems to become unbalanced – and thus lead to disease.

BRICS



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Mesaconic acid: BRICS research team discovers body's own anti-inflammatory substance

The immune system and its metabolic processes play a decisive role in health. A team of scientists around Karsten Hiller from BRICS has discovered an endogenous, anti-inflammatory substance: mesaconic acid. Mesaconic acid, which is secreted by immune cells, inhibits bacterial infection and inflammation. The BRICS researchers are currently investigating the underlying mechanism of the anti-inflammatory effect of mesaconic acid. In the future, this molecule could be used to develop drugs to combat excessive inflammatory reactions like septic shock resulting from blood poisoning. Further, autoimmune diseases such as psoriasis and inflammatory bowel disease (IBD) may become curable without the known side effects of anti-inflammatory drugs currently in use.

New junior professorship in the field of cellular metabolism

To strengthen the metabolism research, in February 2022, Thekla Cordes joined TU Braunschweig as a Junior Professor, heading the Cellular Metabolism group at BRICS. She came from the Salk Institute and the University of California in San Diego, USA. Her research focuses on understanding how metabolism impacts cellular functions and contributes to inflammatory metabolic diseases. Using techniques like mass spectrometry, Cordes and her team decipher metabolic changes occurring during infections and host-pathogen interactions. Her group is also integrated into HZI, where she heads the group "Cellular Metabolism in Infections (CMII)" at the department of chemical biology led by Mark Brönstrup, serving as a major link between HZI, TU Braunschweig, and BRICS. Her expertise also benefits metabolic research at BRICS, fostering collaboration with researchers from partner institutions, such as Karsten Hiller and Andre Wegner (TU Braunschweig), Gavin O'Connor (PTB), and Meina Neumann-Schaal (DSMZ).Thekla Cordes and her team exemplify how close interaction among BRICS partners synergizes to advance our understanding of health and disease.

© TU Braunschweig | Thekla Cordes

© CSSB

© CSSB

MICHAEL KOLBE
HEAD OF THE DEPARTMENT STRUCTURAL INFECTION BIOLOGY

POWERFUL LIGHT SOURCES FOR INFECTION RESEARCH

THE CENTRE FOR STRUCTURAL SYSTEMS BIOLOGY (CSSB)

The Centre for Structural Systems Biology (CSSB) in Hamburg is a joint effort and a scientific hub of nine partner institutions currently hosting twelve research groups located under one roof on the Science City Campus in Hamburg-Bahrenfeld. Three universities and six research institutes in Northern Germany formed a unique collaborative research alliance with a focus on molecular infection biology in this dedicated centre. Researchers at CSSB are currently investigating questions in cellular and molecular infection biology that explore the underlying mechanisms of viruses, bacteria, and parasites causing infectious diseases in humans.

The centre's four state-of-the-art technology platforms provide and develop cutting-edge technologies and help to foster collaborations within CSSB and across its partner institutions. The infrastructure at CSSB provides researchers with cutting-edge light sources and state-of-the-art technologies (e.g. imaging- and biophysical characterization), as well as personnel know-how, that include approaches of artificial intelligence, structural biology and multi-modal imaging, to investigate infection processes over different scales in time and resolution. HZI is represented at CSSB by the research group "Structural Infection Biology" (STIB), led by Michael Kolbe. The STIB group is working on the architecture and activity of virulence factors that facilitate the invasion of enteric pathogens, causing Shigellosis, Salmonellosis or systemic infections.

CSSB
Centre for Structural
Systems Biology

FACTS AND FIGURES

HEp-2 cells infected with four bacterial species © HZI Gabriella Molinari

ORGANIZATION CHART

HZI HELMHOLTZ Centre for Infection Research

Helmholtz Centre
for Infection Research GmbH
Inhoffenstraße 7
38124 Braunschweig

AR – Supervisory Board
MinDir'in Prof. Dr. V. von Messling (BMBF), **Chair**
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KD
Clinical Director
Prof. Dr. med. M. Cornberg

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GB
Equal Opportunity Commissioner
Katja Flaig

Helmholtz Program Infection Research

Topic 1: Bacterial and Viral Pathogens
Spokesperson: Prof. Dr. W. Blankenfeldt

Dep. **BIFO** – Computational Biology for Infection Research – *Prof. Dr. A. McHardy* – BRICS
Dep. **EEZD** – Ecology and Emergence of Zoonotic Diseases – *Prof. Dr. F. Leendertz* – HIOH
Dep. **PAEV** – Pathogen-Evolution – *Prof. Dr. Calvignac-Spencer* – HIOH
Dep. **GEAR** – Epidemiology and Ecology of Antimicrobial Resistance – *Prof. Dr. Katharina Schaufler* – HIOH
Dep. **EPID** – Epidemiology – *Dr. Berit Lange (temp. manager)*
Dep. **EVIR** – Experimental Virology – *Prof. Dr. T. Pietschmann (Deputy Director)* – TC
Dep. **MOST** – Molecular Structural Biology – *Prof. Dr. Dr. D. Heinz*
JRG **EVCO** – Evolutionary Community Ecology – *Dr. J. Gogarten* – HIOH

Dep. **MOBA** – Molecular Bacteriology – *Prof. Dr. S. Häußler*
RG **GMAK** – Genome Analytics – *Dr. R. Geffers*
Dep. **RABI** – RNA-Biology of Bacterial Infection – *Prof. Dr. J. Vogel* – HIRI
JRG **GARV** – Genome Architecture and Evolution of RNA-Viruses – *Prof. Dr. R. Smyth* – HIRI
RG **HOPI** – Host-Pathogen-Microbiota-Interactions – *Prof. Dr. A. Westermann* – HIRI
RG **IIIB** – Integrative Informatics for Infection Biology – *Prof. Dr. L. Barquist* – HIRI
JRG **LRIB** – LncRNA and Infection Biology – *Prof. Dr. M. Munschauer* – HIRI
RG **RANA** – RNA-Analysis Center – *Dr. A.-E. Saliba (Deputy)* – HIRI
RG **REMI** – Recoding Mechanisms in Infections – *Prof. Dr. N. Caliskan* – HIRI
RG **SIGA** – Single Cell Analysis – *Dr. A.-E. Saliba* – HIRI
Dep. **RSYN** – RNA Synthetic Biology – *Prof. Dr. C. Beisel* – HIRI

Dep. **SFPR** – Structure and Function of Proteins – *Prof. Dr. W. Blankenfeldt*
RG **CPRO** – Cellular Proteome Research – *Prof. Dr. L. Jänsch*
RG **MPRO** – Microbial Proteomics – *Prof. Dr. S. Engelmann*
RG **RPEX** – Recombinant Protein Expression – *Dr. J. van den Heuvel*
Dep. **STIB** – Structural Infection Biology – *Prof. Dr. M. Kolbe* – CSSB
Dep. **ZBIO** – Cell Biology – *Prof. Dr. T. Stradal*
RG **MZBI** – Molecular Cell Biology – *Prof. Dr. K. Rottner*
JRG **NIBI** – Nano Infection Biology – *Prof. Dr. C. Sieben*
RG **VIMM** – Virology and Innate Immunity – *Prof. Dr. M. Brinkmann*
RG **ZEIM** – Central Facility for Microscopy – *Dr. M. Müsken (Deputy)*

Topic 2: Immune Response and Interventions
Spokesperson: Prof. Dr. L. Cicin-Sain

Dep. **BIIM** – Computational Biology for Individualised Medicine – *Prof. Dr. Y. Li* – CiiM
Dep. **EXIM** – Experimental Immunology – *Prof. Dr. J. Hühn*
Dep. **EXPI** – Experimental Infection Research – *Prof. Dr. U. Kalinke* – TC
RG **BIOM** – Biomarkers in Infection and Immunity – *PD Dr. F. Pessler* – TC
RG **NIND** – Neuroinflammation and Neurodegeneration – *Prof. Dr. M. Korte*
JRG **AVAO** – Anti-viral antibody-omics – *Dr. Yannic Bartsch* – TC
Dep. **MIKI** – Microbial Immune Regulation – *Prof. Dr. T. Strowig*
RG **DINF** – Dynamics of respiratory infections – *Prof. Dr. H. Slevogt*

Dep. **VAC** – Vaccinology and Applied Microbiology – *Prof. Dr. C.A. Guzmán*
RG **MSYS** – Model Systems for Infection and Immunity – *Prof. Dr. D. Wirth*
Dep. **VIRI** – Viral Immunology – *Prof. Dr. L. Cicin-Sain*
RG **IMMI** – Innate Immunity and Infection – *Prof. Dr. A. Kröger*
RG **IREG** – Immune Regulation – *Prof. Dr. D. Bruder*
RG **VMED** – Core Facility of Comparative Medicine – *Dr. M. Greweling-Pils*
Dep. **SIMM** – Systems Immunology – *Prof. Dr. M. Meyer-Hermann* – BRICS

Topic 3: Anti-Infectives
Spokesperson: Prof. Dr. M. Brönstrup

Dep. **CBIO** – Chemical Biology – *Prof. Dr. M. Brönstrup*
RG **COPS** – Compound Profiling and Screening – *Prof. Dr. U. Bilitewski*
RG **MINP** – Microbial Interactions and Processes – *Prof. Dr. D. Pieper*
RG **CMII** – Cellular Metabolism in Infection – *Prof. Dr. T. Cordes* – BRICS
Dep. **DDEL** – Biological Barriers and Drug Delivery – *Prof. Dr. C.-M. Lehr* – HIPS
Dep. **DDOP** – Drug Design and Optimization – *Prof. Dr. A. Hirsch* – HIPS
AG **AVID** – Antiviral and Antivirulence Drugs – *Dr. M. Empting* – HIPS
RG **CBCH** – Chemical Biology of Carbohydrates – *Prof. Dr. A. Titz* – HIPS
Dep. **MICA** – Anti-infectives from Microbiota – *Prof. Dr. C. Beemelmanns* – HIPS
Dep. **NABI** – Natural Product Bio-technology – *Prof. Dr. T. Gulder* – HIPS

Dep. **MINS** – Microbial Natural Products – *Prof. Dr. R. Müller* – HIPS
RG **AMEG** – Actinobacteria Metabolic Engineering Group – *Prof. Dr. A. Luzhetskyy* – HIPS
JRG **GEMS** – Genome Mining for Secondary Metabolites – *Dr. Ch. Fu* – HIPS
RG **INI** – Infection Immunology – *Prof. Dr. E. Medina*
JRG **MANA** – Microbiota-Associated Natural Products – *Dr. J. Hegemann* – HIPS
JRG **SIMS** – Synthetic Biology of Microbial Natural Products – *Dr. J. Bozhüyük* – HIPS
Dep. **CLIB** – Clinical Bioinformatics – *Prof. Dr. A. Keller* – HIPS
RG **WIBI** – Drug-Bioinformatics – *Prof. Dr. O. Kalinina* – HIPS
RG **HMSB** – Human-Microbe Systems Bioinformatics – *Prof. Dr. A. Gurevich* – HIPS
Dep. **MWIS** – Microbial Drugs – *Prof. Dr. M. Stadler*

Locations | branch offices

HIPS, Helmholtz Institute for Pharmaceutical Research Saarland
Managing Director: Prof. Dr. Rolf Müller | Administrative Management: Dr. Stephanie Thomas

HIRI, Helmholtz Institute for RNA-based Infection Research, Würzburg
Managing Director: Prof. Dr. Jörg Vogel |
temp. Administrative Management: Dr. Tobias Kerrinnes

HIOH, Helmholtz Institute One Health, Greifswald
Managing Director: Prof. Dr. Fabian Leendertz|
Administrative Management: Dr. Till Suchsland

CiiM, CiiM, Centre for Individualised Infection Medicine
Managing Directors: Prof. Dr. Yang Li, Prof. Dr. med. Markus Cornberg

BRICS, Braunschweig Integrated Centre of Systems Biology

CSSB, Centre for Structural Systems Biology

TC, TWINCORE, Centre for Experimental and Clinical Infection Research GmbH
Scientific Director: Prof. Dr. Ulrich Kalinke |
Administrative Management: Dr. Albrecht Goez

Legend

Dep.: Department
RG: Research Group
JRG: Junior Research Group

Commissioners

DSB – Data Protection Commissioner – *H. Ohrdorf*
ISB – IT-Safety Officer – *H. Eggers*
Ombudsteam – *Dr. Th. Ebensen*
TSB – Animal Welfare Officer – *Dr. M. Greweling-Pils*
SBV – Representative Body for Disabled Employees – *H. Ohrdorf*

Departments

EM – Purchasing Department – *K. Maaß*
FC – Finance and Controlling – *Interimistic P. John (external)*
FMM - Funding Management DZIF – *Dr. V. Nagy*
JUR – Legal Affairs and Licences – *Dr. C. Kügler-Walkemeyer*
ORG – Organisation – *R. Lomberg* (Anti-Corruption Commissioner)
PA – Human Resources – *J. Schinkel (Deputy Director)*
PE – HR Development – *Dr. S. Kirchhoff*
BEM - Occupational Re-entry Management – *C. Körner*
RZ – Computer Centre – *Dr. J. Metge*
SU – Safety and Environmental Affairs – *Dr. S. Talay*
S3-Platform – *Dr. K. Schulze*
TB – Technical Services – *C. Köntges*

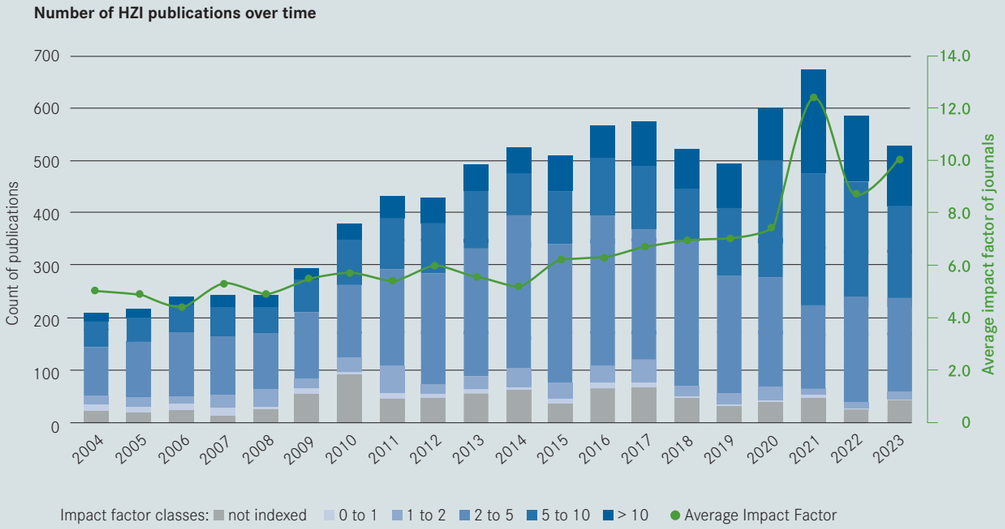
Staff Units

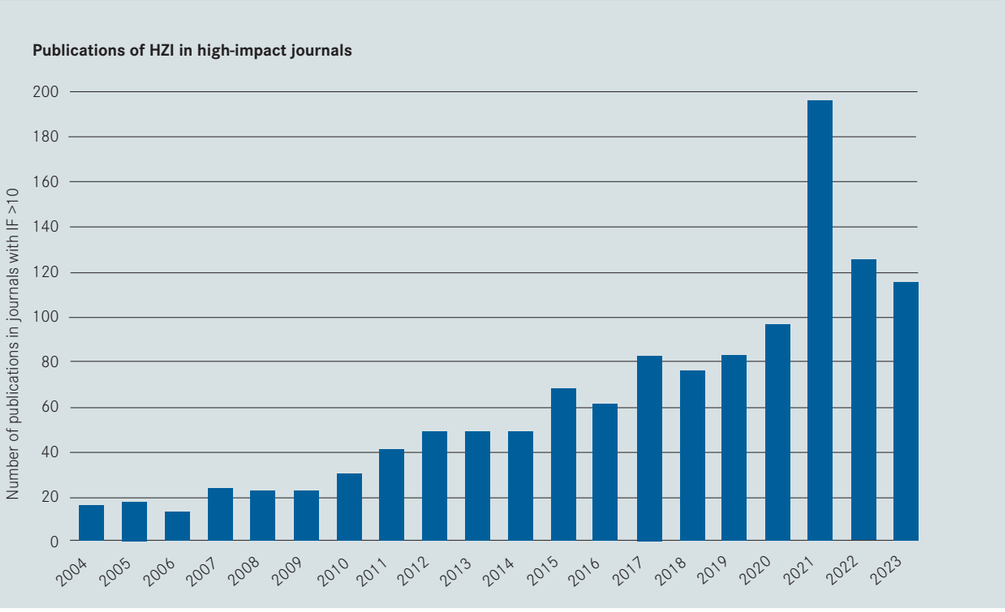
BIB – Library – *A. Talk*
FASI – Occupational Safety Specialist – *C. Strömpl*
IMM - Innovation Management – *Dr. St. Scherer* (Technology Transfer Commissioner) (Knowledge Transfer Commissioner)
DA – Third Party Funds Acquisition – *Dr. B. Gerstel*
PS – Patents – *D. Meseke*
IR – Internal Auditing – *C. Beth*
NH – Sustainability Management – *A.-K. Winkler-Hanns*
PuK – Press and Communication – *S. Thiele*
QM – Quality Management – *Dr. H. Kollmus*
VIT – Administration-IT – *H. Eggers*
WST – Scientific Strategy – *Dr. B. Grün*
SKO – Strategic Communication – *M. Braun*

Version: January 2024

PUBLICATIONS

In 2022 and 2023, HZI scientists published more than 1100 scientific articles, a high percentage of which appeared in high-ranking research journals (> 20 %).



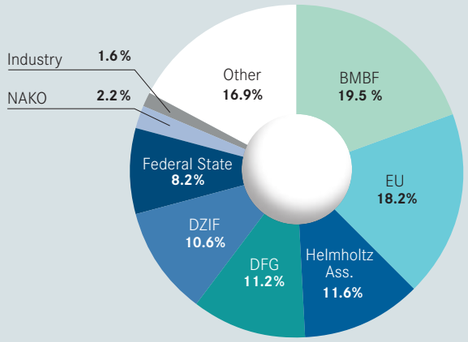


FINANCING

In 2023, the complete budget of HZI amounted to more than 117.8 Mio € including 36.9 Mio € of third-party funding. Most external funding came from national programs (> 80 %) and about 19.8 % were from EU programs and industry.

THIRD-PARTY FUNDING OF THE HZI 2023

Source	Spending (M€)
BMBF *(Federal Ministry of Education and Research)*	7.18
EU	6.71
Helmholtz Association	4.28
DFG	4.13
DZIF	3.90
Federal state	3.04
NAKO	0.83
Industry	0.58
Other	6.27
Sum (M€)	**36.92**



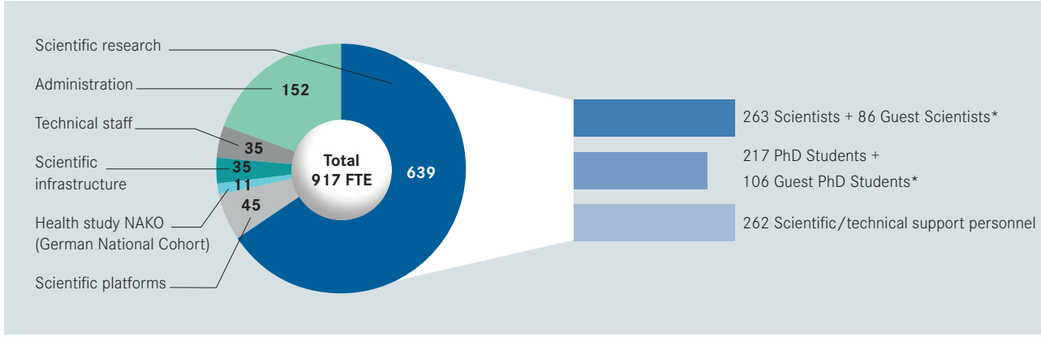
PARTICIPATION IN RELEVANT RESEARCH NETWORKS

The Center participated in 2023 in 51 DFG programs (including Clusters of Excellence and Collaborative Research Centers), 39 EU projects (including ERC Starting, Consolidator, and Proof-of-Concept Grants), and 60 BMBF/BMVi/SPRIND projects.

PATENTS, PROPERTY RIGHTS AND LICENSES

	2022	2023
Priority based applications	6	11
Total number of held property rights	279	333
Licence agreements to others	24	26
Licence proceeds (thousand €)	311	244

PERSONNEL



At the end of 2023, the HZI staff comprised 1069 full and part-time employees, corresponding to 917 Full-Time Equivalents (FTE). The majority of HZI personnel are scientific staff (695 FTE). *) In addition, 192 guest scientists contributed to many projects. They received their grants from third parties and are not included in the bar chart.

OFFICIAL BOARDS AND COMMITTEES OF HZI

(Status: End of 2023)

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SC	Prof. Dr. Marianne van der Sande	Institute of Tropical Medicine Antwerp	Antwerp | Belgium
SC	Prof. Dr. Paul Wilmes	Université du Luxembourg	Esch-sur-Alzette | Luxemburg

RESEARCH REPORT 2022/2023

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HEp-2 cells infected with four bacterial species (c) HZI Gabriella Molinari

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