HZI HELMHOLTZ Centre for Infection Research

Project overview

	Project title	Supervisor	Group	Location
1	Deciphering the molecular mechanisms underlying IRGQ recognition of misfolded MHC-I molecules and its impact on antigen presentation	Lina Herhaus	IMSI (Immune Signaling)	HZI
2	Illuminating Complexes at the Interface between Phages and Bacterial Pathogens	Milan Gerovac	CPIC (Complexes in Phage-infected Cells)	HZI
3	Towards an atlas of antibody recombination scars for the personalized assessment of immunocompetence and DNA repair	Kathrin de la Rosa	PERI (Personalised Immunotherapy)	CiiM
4	Molecular decision points that determine cancer tissue colonization by Fusobacterium nucleatum	Jörg Vogel	RABI (RNA Biology of Bacterial Infections)	HIRI
5	Regulation of host protein synthesis by jumbo phage proteins	Jörg Vogel	RABI (RNA Biology of Bacterial Infections)	HIRI
6	Programmable RNA antibiotics	Jörg Vogel	RABI (RNA Biology of Bacterial Infections)	HIRI
7	Genetic Mechanisms of Severe Respiratory Syncytial Virus Infections	Thomas Pietschmann	EVIR (Experimental Virology)	TWINCORE
8	Virus-like-particle production, modification and purification	Maren Schubert	Virus-like-particle based technologies	HZI
9	Biomolecular Condensates in Viral Pathogenesis and Drug Discovery	Christiane Iserman	Biomolecular Condensates in Infection	HZI
10	Dissecting the Functional Genetic Landscape of Host-Virus Interactions in Reservoir and Spillover Hosts	Max Kellner	VICO (Laboratory for Virus-host co-evolution)	HZI
11	High-Throughput Screens for Host-Virus Interactions	Jan Schlegel	BioCodeLab (Biological Codes of Pathogens)	HZI
12	Diagnosing the microbiome – Characterizing biomarkers to allow the identification of patients with high risk for MDR-E infections	Till Strowig	MIKI (Mikrobielle Immunregulation)	HZI
13	Genome Mining of Myxobacteria with Systematic Heterologous Expression of Biosynthetic Gene Clusters	Rolf Müller	MINS (Microbial Natural Products)	HIPS
14	Cell-based drug delivery to control bacterial infections	Dagmar Wirth	MSYS (Model Systems for Infection and Immunity)	HZI
15	Synthesis and characterization of drug conjugates with smart linkers targeting Pseudomonas aeruginosa	Mark Brönstrup	CBIO (Chemical Biology)	HZI
16	New host factor of Hepatitis D Virus in hepatocytes	Arnaud Carpentier	EVIR (Experimental Virology)	TWINCORE

HZI HELMHOLTZ Centre for Infection Research

Joint Call for Doctoral Researchers - Project 1

Supervisor	Lina Herhaus
Location	Braunschweig, HZI Campus
Name of working group	IMSI (Immune Signaling)
Title of the project	Deciphering the molecular mechanisms underlying IRGQ recognition of misfolded MHC-I molecules and its impact on antigen presentation
Webpage link	https://www.helmholtz-hzi.de/en/research/research-groups/details/immune-signaling/

Summary (approx. 300 words)

This PhD project investigates the molecular mechanisms by which IRGQ, a cytosolic protein, identifies misfolded MHC-I molecules for autophagy-mediated degradation and its subsequent impact on antigen presentation. MHC-I molecules are critical for immune surveillance, as they present peptides to cytotoxic T cells to detect pathogen-infected or tumor cells. However, the processes targeting misfolded MHC-I for degradation remain poorly understood. IRGQ is recruited to the endoplasmic reticulum (ER), where it interacts with misfolded MHC-I molecules. These defective molecules expose their C-terminal tails to the cytosol, signaling their misfolded state. Preliminary data suggest that ubiquitylation of these tails enhances IRGQ interaction, particularly upon autophagy induction. Mass spectrometry will be used to identify key post-translational modifications (PTMs) on IRGQ critical for this interaction. The project will also characterize the IRGQ-MHC-I degradation complex, focusing on ubiquitin-binding proteins and MARCH family E3 ligases. A CRISPR-Cas9 screen will complement these studies to identify relevant E3 ligases involved in this process. The project will further assess IRGQ's role in shaping the MHC-I peptidome using mass spectrometry-based immunopeptidomics in wild-type (WT) and IRGQ knockout (KO) cells. Pathogen-derived and self-peptides will be classified using computational tools. Additionally, the role of IRGQ in preventing accumulation of unloaded MHC-I molecules and its effect on T cell activation will be evaluated through T cell assays. This PhD project aims to uncover the dual role of IRGQ in maintaining MHC-I integrity and modulating immune responses, offering insights into its potential influence on pathogen immunity and tumor surveillance.

Project related publication(s)

Herhaus, L.*#, Gestal-Mato, U.#, Eapen, V. V., Macinkovic, I., Bailey, H. J., Prieto Garcia, C., Misra, M., Jacomin, A. C., Ammanath, A. V., Covarrubias-Pinto, A., Michaelis, J., Bagaric, I., Zöllner, J., Bhaskara, R.M., Bündgen, G., Husnjak, K., Vollrath, J., Gikandi, A., Ribicic, S., Langer, J., Bopp, T., Weigert, A., Mancias, J., Harper, J.W., and Dikic, I.*(2024). IRGQ-mediated autophagy in MHC-I quality control promotes tumor immune evasion. Cell. https://doi.org/10.1016/J.CELL.2024.09.048.

HZI HELMHOLTZ Centre for Infection Research

Joint Call for Doctoral Researchers - Project 2

Supervisor	Milan Gerovac
Location	Braunschweig, HZI Campus
Name of working group	CPIC (Complexes in Phage-infected Cells)
Title of the project	Illuminating Complexes at the Interface between Phages and Bacterial Pathogens
Webpage link	https://www.helmholtz-hzi.de/en/research/research-groups/details/complexes-in-phage-infected-cells/

Summary (approx. 300 words)

Jumbo phages encode for hundreds of factors with unknown functions likely involved in host-takeover. Our goal is to identify key players and enzymes that can be translated into biotechnological or medical applications. We are focusing on factors that target the gene expression machinery and modulate the stress response. In addition, we aim to study phage biology under near-native conditions such as biofilms. Bacteriophages need to take over the host gene expression machinery in order to replicate. This has to happen immediately after infection, also to overcome anti-phage defence systems. A general understanding of phage mechanisms for immediate targeting of host transcription and translation processes is lacking. We use integrative high-throughput approaches to identify phage-encoded proteins that target the gene expression machinery of Pseudomonas aeruginosa and other pathogens immediately upon infection with ΦKZ-like jumbo phages. By integrating biochemical, genetic and structural analyses, we characterise the molecular mechanisms of host takeover. We see large phage genomes as an untapped discovery space for proteins that modulate the host gene expression machinery and represent novel tools for medical applications and avenues to treat drug-resistant pathogens in antimicrobial crisis.

Project related publication(s)

Gerovac et al. 2024 bioRxiv, Putzeys et al. 2024 Current Opinion in Microbiology, Gerovac et al. 2024 Nature Microbiology

Joint Call for Doctoral Researchers - Project 3

Supervisor	Kathrin de la Rosa
Location	Hannover, CiiM
Name of working group	PERI (Personalised Immunotherapy)
Title of the project	Towards an atlas of antibody recombination scars for the personalized assessment of immunocompetence and DNA repair
Webpage link	https://www.helmholtz-hzi.de/en/research/research-groups/details/personalised-immunotherapy/

Summary (approx. 300 words)

Objectives: Diversification of the immune repertoire relies on a potent DNA-repair machinery. DNA-repair defects can not only cause immunodeficiencies, but also developmental disorders, or predispose to cancer. The group developed a novel methodology to assess, at high throughput, the quality of DNA repair by profiling genomic scars generated during class switch recombination (CSR). Here, it is aimed to generate a knockout library of >40 DNA repair factors and compare class switch repair outcomes with CRISPR/Cas9 repair in human primary B cells and published datasets of non-B cells. Furthermore, the project aims at assessing the potential of the method as an indicator of infectious disease susceptibility and disease management in existing patient cohorts of the Hannover Medical School (MHH). Expected Results: By comparing physiological (CSR) and artificial (Cas9) DNA-break repair in human cells, this project will clarify whether B cells serve as a universal marker to assess DNA repair outcomes. Specifically, it will provide an atlas of sequence architectures of repaired CSR- versus Cas9-mediated DNA breaks in B cells and their genetic dependencies. In addition, it will be clarified whether the tool can be used as a biomarker for prevention and treatment of infectious diseases.

Project related publication(s)

(1) Lebedin, M., M. Foglierini, S. Khorkova, C. V. García, C. Ratswohl, A. N. Davydov, M. A. Turchaninova, C. Daubenberger, D. M. Chudakov, A. Lanzavecchia, and K. de la Rosa. 2022. Different classes of genomic inserts contribute to human antibody diversity. Proc National Acad Sci 119: e2205470119. DOI: 10.1073/pnas.2205470119. PMID: 36037353. Open Access (2) Pieper, K.*, J. Tan*, L. Piccoli*, M. Foglierini, S. Barbieri, Y. Chen, C. Silacci-Fregni, T. Wolf, D. Jarrossay, M. Anderle, A. Abdi, F. M. Ndungu, O. K. Doumbo, B. Traore, T. M. Tran, S. Jongo, I. Zenklusen, P. D. Crompton, C. Daubenberger, P. C. Bull, F. Sallusto, and A. Lanzavecchia. 2017. Public antibodies to malaria antigens generated by two LAIR1 insertion modalities. Nature 548: 597–601. DOI: 10.1038/nature23670. PMID: 28847005;
(3) Patent application 14115 P 6581 EP

HZI HELMHOLTZ Centre for Infection Research

Joint Call for Doctoral Researchers - Project 4

Supervisor	Jörg Vogel
Location	Würzburg, HIRI
Name of working group	RABI (RNA Biology of Bacterial Infections)
Title of the project	Molecular decision points that determine cancer tissue colonization by Fusobacterium nucleatum
Webpage link	https://www.helmholtz-hzi.de/en/research/research-groups/details/rna-biology-of-bacterial-infections/

Summary (approx. 300 words)

Fusobacteria, long known as abundant oral microbes, have recently garnered broad attention when they were found to colonize tumors elsewhere in the body. Clinical and epidemiological research has now firmly linked fusobacteria to enhanced tumor progression, chemoresistance and poor prognosis of several human cancers and suggested that their removal from tumor sites could benefit cancer therapy. However, sustained systemic antibiotic administration is not a valid treatment option due to severe side-effects. To interfere with tumor colonization in a more directed manner, it is essential to understand the molecular decisions in the host during the process of fusobacterial colonization of the tumor environment. The central hypothesis of this project is that the discovery of molecular factors that underlie tumor colonization by Fusobacterium nucleatum will yield selective strategies to rid tumors of fusobacteria, while sparing a patient's protective microbiota. Therefore, we seek to unravel the molecular mechanisms that allow F. nucleatum to colonize colon cancer tissue and to understand how local environments are manipulated as host cells respond to fusobacteria at these sites. Key to our approach is the introduction of RNA-centric technologies to assay bacterial and host gene activities during initial fusobacterial colonization of tumor cells in vitro and within the complex tumor environment. We aim to identify key molecular decision points during cancer tissue colonization by F. nucleatum to define targets for intervention.

Project related publication(s)

Ponath F et al. 2022 PNAS doi: 10.1073/pnas.2201460119

Ponath F et al. 2021 Nature Microbiology doi: 10.1038/s41564-021-00927-7

Parhi L et al. 2020 Nature Communications doi: 10.1038/s41467-020-16967-2

Joint Call for Doctoral Researchers - Project 5

Supervisor	Jörg Vogel
Location	Würzburg, HIRI
Name of working group	RABI (RNA Biology of Bacterial Infections)
Title of the project	Regulation of host protein synthesis by jumbo phage proteins
Webpage link	https://www.helmholtz-hzi.de/en/research/research-groups/details/rna-biology-of-bacterial-infections/

Summary (approx. 300 words)

Phages with large genomes and complex lifestyles represent exciting opportunities to discover new molecular factors and principles of host manipulation. Most of the proteins encoded by these phage genomes have no matches in the current sequence databases. For example, the 280-kB genome of ΦKZ, a jumbo bacteriophage that infects Pseudomonads, possesses >369 annotated open reading frames but only a small fraction of the encoded proteins has a known function. This promises a vast untapped discovery space for proteins with specialized functions, e.g., in the modulation of the host gene expression machinery. We have recently published an integrative high-throughput approach called Grad-seq to uncover phage-encoded proteins that target the gene expression machinery of Pseudomonas aeruginosa upon infection with ΦKZ. Strikingly, we found many phage proteins that form or associate with large protein complexes in the host, e.g. the RNA polymerase or ribosomes. Through biochemical, genetic, and structural analyses, we identified the abundant and conserved phage factor ΦKZ014 and showed that it targets the large ribosomal subunit near the 5S ribosomal RNA. ΦKZ014 is among the earliest ΦKZ proteins expressed after infection and remains bound to ribosomes during the entire translation cycle. We have also identified specific Pseudomonas strains in which ΦKZ014 is essential for productive phage replication. These strains lend themselves as genetic systems for the functional dissection of ΦKZ014. In this project, we aim to characterize the molecular mechanisms employed by ΦKZ to manipulate the host translation machinery and to promote viral replication. In addition, we aim to identify the anti-phage defence system that is bypassed by ΦKZ014, which will allow us to establish a new link between translation and bacterial immunity.

Project related publication(s)

Gerovac M et al. 2024 Nature Microbiology (doi: 10.1038/s41564-024-01616-x)

Gerovac M et al. 2021 mBio (DOI: 10.1128/mBio.03454-20)

HZI HELMHOLTZ Centre for Infection Research

Joint Call for Doctoral Researchers - Project 6

Supervisor	Jörg Vogel
Location	Würzburg, HIRI
Name of working group	RABI (RNA Biology of Bacterial Infections)
Title of the project	Programmable RNA antibiotics
Webpage link	https://www.helmholtz-hzi.de/en/research/research-groups/details/rna-biology-of-bacterial-infections/

Summary (approx. 300 words)

Antisense technologies have the potential to form a foundation for the development of a new generation of antibiotics. Upon delivery into the bacterial cell, short antisense oligonucleotides (ASOs) or mimics thereof can directly modulate bacterial gene expression, for example, by suppressing mRNA translation of an essential target protein. The programmable nature of ASOs, which is based on simple base-pairing rules, allows rational and specific drug design and opens myriad applications including the rapid development of ASOs that can kill emerging pathogens, sensitize drug-resistant strains, or block expression of key virulence factors all while sparing the native microbiome. However, despite ample proof-of-concept for efficacy against a diverse range of bacterial pathogens in vitro and in vivo, ASOs are yet to advance to the point of drug approval. In the Vogel lab, we offer many different projects for new applications of such “asobiotics” that go beyond the mere killing of pathogens, for example, interfering with undesired activities of commensals and even targeting the natural enemies of microbes, that is, bacteriophages (in the context of phage therapy). This way, we are addressing the growing antimicrobial resistance crisis and providing solutions for the analysis of genetically intractable microbes.

Project related publication(s)

doi: 10.1093/nar/gkac362, doi: 10.1093/nar/gkab242, DOI: 10.1261/rna.080347.124, https://www.biorxiv.org/content/10.1101/2024.07.31.605949v1, doi: 10.1261/rna.079969.124, doi: 10.1261/rna.079263.122

Joint Call for Doctoral Researchers - Project 7

Supervisor	Thomas Pietschmann
Location	Hannover, TWINCORE
Name of working group	EVIR (Experimental Virology)
Title of the project	Genetic Mechanisms of Severe Respiratory Syncytial Virus Infections
Webpage link	https://twincore.de/labs/pietschmann-lab

Summary (approx. 300 words)

Respiratory syncytial virus (RSV) is a major cause of severe respiratory disease in newborns and older adults, posing a global health challenge. Building on our extensive experience and international collaborations, we have established a unique cohort of children who suffered severe RSV infections. Using advanced computational genomics, we identified key gene candidates and genetic variants associated with disease severity. In this project, you will unravel the mechanisms by which one of these factors influences RSV infection and disease outcomes. Employing state-of-the-art approaches—CRISPR-Cas9 perturbation, primary human lung cell models, and single-cell transcriptomics—you will explore how genetic variants affect viral biology, inflammation, and cellular pathways. This work not only advances our understanding of RSV pathophysiology but also lays the foundation for novel diagnostics. Join our dynamic and international research team to work at the interface of basic and applied science, leveraging cutting-edge technologies in a collaborative environment to make meaningful scientific discoveries.

Project related publication(s)

1: Sake SM, Zhang X, Rajak MK, Urbanek-Quaing M, Carpentier A, Gunesch AP,Grethe C, Matthaei A, Rückert J, Galloux M, Larcher T, Le Goffic R, Hontonnou F,Chatterjee AK, Johnson K, Morwood K, Rox K, Elgaher WAM, Huang J, Wetzke M,Hansen G, Fischer N, Eléouët JF, Rameix-Welti MA, Hirsch AKH, Herold E, EmptingM, Lauber C, Schulz TF, Krey T, Haid S, Pietschmann T. Drug repurposing screenidentifies lonafarnib as respiratory syncytial virus fusion protein inhibitor.Nat Commun. 2024 Feb 8;15(1):1173. doi: 10.1038/s41467-024-45241-y. PMID:38332002; PMCID: PMC10853176.2: Sake SM, Kosch C, Blockus S, Haid S, Gunesch AP, Zhang X, Friesland M,Trummer SB, Grethe C, Kühnel A, Rückert J, Duprex WP, Huang J, Rameix-Welti MA,Empting M, Fischer N, Hirsch AKH, Schulz TF, Pietschmann T. RespiratorySyncytial Virus Two-Step Infection Screen Reveals Inhibitors of Early and LateLife Cycle Stages. Antimicrob Agents Chemother. 2022 Dec 20;66(12):e0103222.doi: 10.1128/aac.01032-22. Epub 2022 Nov 8. PMID: 36346232; PMCID: PMC9765014.3: Wetzke M, Funken D, Lange M, Bejo L, Haid S, Monteiro JGT, Schütz K, HappleC, Schulz TF, Seidenberg J, Pietschmann T, Hansen G. IRIS: Infection withRespIratory Syncytial Virus in infants-a prospective observational cohort study.BMC Pulm Med. 2022 Mar 15;22(1):88. doi: 10.1186/s12890-022-01842-1. PMID:35291998; PMCID: PMC8922907.4: Risso-Ballester J, Galloux M, Cao J, Le Goffic R, Hontonnou F, Jobart-MalfaitA, Desquesnes A, Sake SM, Haid S, Du M, Zhang X, Zhang H, Wang Z, Rincheval V,Zhang Y, Pietschmann T, Eléouët JF, Rameix-Welti MA, Altmeyer R. A condensate-hardening drug blocks RSV replication in vivo. Nature. 2021Jul;595(7868):596-599. doi: 10.1038/s41586-021-03703-z. Epub 2021 Jul 7. PMID:34234347.5: Jo WK, Schadenhofer A, Habierski A, Kaiser FK, Saletti G, Ganzenmueller T,Hage E, Haid S, Pietschmann T, Hansen G, Schulz TF, Rimmelzwaan GF, OsterhausADME, Ludlow M. Reverse genetics systems for contemporary isolates ofrespiratory syncytial virus enable rapid evaluation of antibody escape mutants.Proc Natl Acad Sci U S A. 2021 Apr 6;118(14):e2026558118. doi:10.1073/pnas.2026558118. PMID: 33811145; PMCID: PMC8040649.

HZI HELMHOLTZ Centre for Infection Research

Joint Call for Doctoral Researchers - Project 8

Supervisor	Maren Schubert
Location	Braunschweig, HZI Campus
Name of working group	Virus-like-particle based technologies
Title of the project	Virus-like-particle production, modification and purification
Webpage link	https://www.tu-braunschweig.de/bbt/team/dr-maren-schubert

Summary (approx. 300 words)

Virus-like-particles (VLP) are generated as the result of expression of a single or co-expression of several viral structural proteins. They can resemble the complete three-dimensional surface of any desired virus without containing viral genetic information, rendering them non-infectious and thereby safe. VLPs can be very diversly utilized as drug carriers, to develop and evaluate drugs, in vaccine development, and as commercial vaccines (e.g. Cervix). Consequently, they are an important research tool to achieve a faster response to new viruses and virus variants to prepare against the next pandemic. Different expression systems can be used to produce VLPs but insect cells in combination with the Baculovirus Expression Vector System (BEVS) are most often employed due to the achieved high yields. This technology-focused PhD project can be divided in three main objectives: First, the baculovirus-free production of different VLPs in insect cells using plasmid-based expression as well as by establishing a novel stable expression system. Hereby, several disadvantages of BEVS like parallel baculovirus protein and particle production will be avoided while still obtaining high VLP yields. Second, the design and expression of different modified VLPs for very diverse applications: As efficient drug carrier, to present membrane proteins for drug development as well as adapted and tailored vaccine vectors. Last, to set up an efficient purification pipeline to obtain pure VLP material required for the applications. Design and construction of expression vectors, cell culture techniques, high-throughput cell-based assays, detailed characterization of the VLPs (ELISA, Nano-Tracking-Analysis, cytometer analysis, western blot etc.) and advanced purification processes will be standard methods in this PhD project. Furthermore, close cooperations with other groups at the HZI will ensure to bring the developed recombinant VLPs into applications.

Project related publication(s)

Jaron, M., Lehky, M., Zarà, M., Zaydowicz, C.N., Lak, A., Ballmann, R., Heine, P.A., Wenzel, E.V., Schneider, K.-T., Bertoglio, F., Kempter, S., Köster, R.W., Barbieri, S.S., Van den Heuvel, J., Hust, M., Dübel, S., & Schubert, M. (2022). Baculovirus-free SARS-CoV-2 Virus Like Particle Production in Insect Cells for Rapid Neutralization Assessment. Viruses 14: 2087

Lampinen, V., Gröhn, S., Lehmler, N., Jartti, M., Hytönen, V.P., Schubert, M.* & Hankaniemi, M.M.* (2024). Production of norovirus-, rotavirus-, and enterovirus-like particles in insect cells is simplified by plasmid-based expression. Scientific Reports 14:14874

Joint Call for Doctoral Researchers - Project 9

Supervisor	Christiane Iserman
Location	Braunschweig, HZI Campus
Name of working group	Biomolecular Condensates
Title of the project	Biomolecular Condensates in Viral Pathogenesis and Drug Discovery
Webpage link	https://scholar.google.com/citations?hl=en&user=rUCSsmAAAAAJ

Summary (approx. 300 words)

Do you want to know how viruses employ biomolecular condensates to infect their hosts? Would you like to hunt for drugs targeting viruses? Do you like to work with a creative and collaborative approach and study a physicochemical principle that can be applied to drug discovery?
The focus of the Iserman group is to investigate the role of biomolecular condensates in pathogen-host interactions, with a long-term goal of developing innovative antiviral inhibitors. Condensates, comprising biological polymers like nucleic acids and proteins, form concentrated droplets within cells through a process known as demixing. Recent studies emphasize their importance in viral replication, capsid assembly, packaging, and immune evasion. While host cells use condensates as part of their defense, viruses often exploit or deactivate these structures to facilitate infection. The central them of the lab is to combine fundamental research in biomolecular condensates with drug discovery. We combine advanced imaging, biochemical, and innovative organoid techniques to study fundamental principles of host-viral interactions. Once a drug target is identified, we employ high-throughput and automation techniques for compound screening in close collaboration with chemists at HZI. We are looking to recruit an experimental doctoral candidate to join our team. Excitement for collaborative and innovative research is a must and previous experience in virology a bonus.

Project related publication(s)

HZI HELMHOLTZ Centre for Infection Research

Joint Call for Doctoral Researchers - Project 10

Supervisor	Max Kellner
Location	Braunschweig, HZI Campus
Name of working group	VICO (Laboratory for Virus-host co-evolution)
Title of the project	Dissecting the Functional Genetic Landscape of Host-Virus Interactions in Reservoir and Spillover Hosts
Webpage link	https://scholar.google.com/citations?user=GK3pJMwAAAAJ&hl=en

Summary (approx. 300 words)

Reservoir animals play a crucial role in the ecology and transmission of zoonotic viruses, some of which can cross the species barrier through spillover infections [1]. Zoonotic virus spillovers pose a significant threat to global health and have historically led to pandemics or epidemic outbreaks in both humans and animals. Unlike spillover hosts, natural reservoirs often do not exhibit signs of disease following natural or experimental infection. Bats serve as important natural hosts and are confirmed or suspected reservoirs for several highly pathogenic human viruses of pandemic concern, including Filoviruses (Ebola, Marburg), Coronaviruses (MERS and SARS-related), and Paramyxoviruses (Nipah and Hendra) [2]. The genetic basis of disease resilience in bats—and reservoir species in general—remains poorly understood but may result from long-term co-evolutionary adaptations between viruses and their hosts.The newly established junior research group VICO (Laboratory for Virus-host co-evolution), based at the HZI in Braunschweig, focuses on the functional genetic landscape of host-virus interactions in disease-resilient hosts, with a particular emphasis on bats and innate immune responses at mucosal surfaces. The prospective PhD candidate will employ cutting-edge molecular and cellular techniques to investigate these interactions in both natural reservoir and spillover hosts [3]. Using novel organoid models and innovate approaches to assess and manipulate host-virus interactions, the project aims to unravel the regulation of antiviral responses in these mammals and how viruses evade them. Through cross-species experiments, the research strives to identify critical species-specific differences that may contribute to divergent disease outcomes. This work will provide a foundation for understanding the unique relationship between reservoirs and viruses, explaining pathogen virulence in spillover hosts, and uncovering new avenues for antiviral therapies. The PhD candidate will thrive in an international and collaborative research environment, benefiting from hands-on training in advanced cell biology, genetic perturbation, and bioinformatics. The interdisciplinary nature of the newly established group offers opportunities to engage in large-scale research efforts spanning virology, ecology, and medicine, providing a broad scientific perspective and involvement in ground-breaking research.

Project related publication(s)

[1] Pathways to zoonotic spillover; Nature Reviews Microbiology, volume 15, pages 502–510 (2017)[2] Lessons from the host defences of bats, a unique viral reservoir; Nature volume 589, pages 363–370 (2021)[3] Reconstructing bat antiviral immunity using epithelial organoids, bioRxiv, doi: 10.1101/2024.04.05.588241 (2024)

Joint Call for Doctoral Researchers - Project 11

Supervisor	Jan Schlegel
Location	Braunschweig, HZI Campus
Name of working group	Biological Codes of Pathogens - BioCodeLab
Title of the project	High-Throughput Screens for Host-Virus Interactions
Webpage link	https://scholar.google.com/citations?user=O5mIupkAAAAJ&hl=en&oi=ao

Summary (approx. 300 words)

The interdisciplinary junior research group "BioCodeLab" focuses on developing tools to identify and decipher biological codes of pathogens. While we have profound knowledge and technologies to shed light on pathogens' genomes, we are still in the dark with respect to many other biological codes, such as the glycan and membrane code. However, these codes not only carry valuable information about the pathogen's origin but also influence its function. These codes cannot be directly delineated by the pathogens' genetic information but are rather shaped by their complex interactions with the host and environment. Our mission is to identify these codes at single-pathogen resolution to obtain further insights about their past, present and future. We will apply this knowledge to develop innovative strategies to improve viral therapeutics and pandemic preparedness tools. To do so, the BioCodeLab follows an interdisciplinary approach at the intersection of biology, chemistry and physics. The fast identification of molecular players involved in host-virus interactions is key for pandemic preparedness and the development of therapeutic interventions. However, several roadblocks impede the development of a swift and robust pipeline: the complexity & dynamics of host-virus crosstalk, the plenitude of involved biomolecules, the small size of viruses. Therefore, our team is looking for a highly motivated PhD student to develop robust screening platforms with the capacity to control and reconstitute cellular complexity to extract quantitative binding and fusion parameters of viruses at an unmatched speed and versatility. We are seeking a self-driven interdisciplinary doctoral student with a keen interest in technology development at the intersection of biophysics and virus infection research.

Project related publication(s)

(1) Schlegel, J.; Porebski, B.; Andronico, L.; Hanke, L.; Edwards, S.; Brismar, H.; Murrell, B.; McInerney, G. M.; Fernandez-Capetillo, O.; Sezgin, E. A Multiparametric and High-Throughput Platform for Host–Virus Binding Screens. Nano Lett. 2023, 23 (9), 3701–3707. https://doi.org/10.1021/acs.nanolett.2c04884. (2) Sych, T.; Schlegel, J.; Barriga, H. M. G.; Ojansivu, M.; Hanke, L.; Weber, F.; Beklem Bostancioglu, R.; Ezzat, K.; Stangl, H.; Plochberger, B.; Laurencikiene, J.; El Andaloussi, S.; Fürth, D.; Stevens, M. M.; Sezgin, E. High-Throughput Measurement of the Content and Properties of Nano-Sized Bioparticles with Single-Particle Profiler. Nat Biotechnol 2024, 42 (4), 587–590. https://doi.org/10.1038/s41587-023-01825-5.

HZI HELMHOLTZ Centre for Infection Research

Joint Call for Doctoral Researchers - Project 12

Supervisor	Till Strowig
Location	Braunschweig, HZI Campus
Name of working group	MIKI (Microbial Immune Regulation)
Title of the project	Diagnosing the microbiome – Characterizing biomarkers to allow the identification of patients with high risk for MDR-E infections
Webpage link	https://www.helmholtz-hzi.de/en/research/research-groups/details/microbial-immune-regulation/

Summary (approx. 300 words)

Are you passionate about microbiology and eager to explore the complex interactions between the human microbiome and infectious diseases? Join our research team in unraveling how microbial communities in the gastrointestinal (GI) tract protect against infections and prevent colonization by multi-drug resistant (MDR) bacteria.

The human gut microbiome plays a crucial role in defending against community-acquired (CA) infections through a process known as colonization resistance (CR). However, factors such as antibiotic use, underlying diseases, and reduced microbial diversity can weaken this defense, creating an environment where harmful pathogens thrive. While recent research has shed light on the mechanisms behind CR, we still lack the ability to accurately predict an individual's resistance to MDR bacteria based on microbiome composition alone.

- In this PhD project, you will:
  Investigate microbial biomarkers linked to high MDR-E colonization levels in the gut
- Utilize human-derived samples, in vitro culture systems, and in vivo mouse models to explore the risk of systemic infections.
- Collaborate with leading researchers at HZI and other German institutions, working at the forefront of microbiome research.

We seek a highly motivated PhD candidate with:
A strong background in microbiology.
Experience (or strong interest) in microbiome research, molecular biology, and NGS data analysis.
Willingness to work with gnotobiotic mouse models.

If you're excited about tackling some of the biggest challenges in microbiome research and infectious disease prevention, we encourage you to apply!

Project related publication(s)

Almási E, Eisenhard L, Osbelt L, Lesker TE, Vetter AC, Knischewski N, Bielecka AA, Gronow A, Muthukumarasamy U, Wende M, Tawk C, Neumann-Schaal M, Brönstrup M, Strowig T. Klebsiella oxytoca facilitates microbiome recovery via antibiotic degradation and restores colonization resistance in a diet-dependent manner, Nat Commun. 2025 Jan 9. PMID: 39789003

Osbelt L, d. H. Almási E, Wende M, …, Flieger A, Schlüter D, Müller R, Erhardt M, Zechner EL, Strowig T, Klebsiella oxytoca inhibits Salmonella infection through multiple microbiota-context-dependent mechanisms. Nat Micro. 2024 Jun 11., PMID38862602

Osbelt L, Wende M, Almási É, Derksen E, … , Fischer T, Schlüter D, Strowig T. Klebsiella oxytoca causes colonization resistance against multidrug-resistant K. pneumoniae in the gut via cooperative carbohydrate competition. Cell Host Microbe. 2021 Nov 10;29(11):1663-1679.e7. Epub 2021 Oct 4. PMID: 34610293.

Joint Call for Doctoral Researchers - Project 13

Supervisor	Rolf Müller
Location	Saarbrücken, HIPS
Name of working group	MINS (Microbial Natural Products)
Title of the project	Genome Mining of Myxobacteria with Systematic Heterologous Expression of Biosynthetic Gene Clusters
Webpage link	https://www.helmholtz-hips.de/en/mins

Summary (approx. 300 words)

The demand for novel small-molecule drugs is on a continuous rise regarding the number of different pathologies, especially infectious diseases. Myxobacteria are a prolific source for secondary metabolites with diverse structures and intriguing biological activities. However, compared to the numbers of biosynthetic gene clusters (BGCs) predicted in the genomes of myxobacteria, the number of discovered myxobacterial compounds is still limited. To explore the underexploited biosynthetic potential of myxobacteria, promising strains have been whole-genome sequenced. All BGCs will be categorized into different groups based on criteria such as potential compound class, novelty, key biosynthetic genes, and BGC size, which will help us to prioritize BGCs for heterologous expression in well-studied host strains. The BGCs will first be assembled by various technologies including recombineering and gene synthesis. Different gene engineering and BGC transfer strategies will be employed to improve the success rate for BGC heterologous expression (e.g. promoter exchange or transcription regulator engineering). State-of-the-art analytic methods and instrumentation at HIPS will facilitate the discovery, isolation and structure elucidation of novel compounds from novel wild type and heterologous host strains. Promising compounds with unknown biosynthesis origin are constantly found, the biosynthetic pathways of isolated compounds will be elucidated by comprehensive in vivo and in vitro studies. Finally, the bioactivity of compounds against various pathogens and cancer cell lines will be tested and their mode-of-action will be analyzed. The PhD project(s) include the following topics:

1. Heterologous expression of BGCs from myxobacteria.
2. Isolation, purification, and structure elucidation of compounds produced from innovative myxobacteria previously uncultured and by heterologous expression.
3. Characterization of the biosynthetic pathways of compounds discovered in this study.
4. Bioactivity testing and mode-of-action analysis of compounds discovered in this study.

In summary, our final goal is to learn about new chemistry from nature and to produce novel compounds with improved activities based on the acquired knowledge.

Project related publication(s)

Autologous DNA mobilization and multiplication expedite natural products discovery from bacteria, Xie et al. (2024), Science;
Discovery of the Pendulisporaceae: An extremotolerant myxobacterial family with distinct sporulation behavior and prolific specialized metabolism, Garcia et al. (2024), Chem;
The Sandarazols are Cryptic and Structurally Unique Plasmid-Encoded Toxins from a Rare Myxobacterium, Panter et al. (2021), Angewandte Chemie;
Bacteria as genetically programmable producers of bioactive natural products, Hug et al. (2020), Nature Reviews Chemistry;
Production optimization and biosynthesis revision of corallopyronin A, a potent anti-filarial antibiotic, Pogorevc et al. (2019), Metabolic Engineering;

HZI HELMHOLTZ Centre for Infection Research

Joint Call for Doctoral Researchers - Project 14

Supervisor	Dagmar Wirth
Location	Braunschweig, HZI Campus
Name of working group	MSYS (Model Systems for Infection and Immunity)
Title of the project	Cell-based drug delivery to control bacterial infections
Webpage link	https://www.helmholtz-hzi.de/en/research/research-groups/details/model-systems-for-infection-and-immunity/

Summary (approx. 300 words)

The overall aim of this project is the controlled delivery of antibacterials to local infections (e.g. in the lung or on implants) by utilizing patient-derived cells. The project specifically focusses on macrophages due to their unique properties to efficiently take up drug-associated particles, and (b) to preferentially accumulate in infected tissues. Leveraging these features, macrophages will be exploited as dynamic carriers for drug-associated nanoparticles. Recently, we have explored various mechanisms to achieve precise, localized, and timely controlled drug release from these cellular carriers. We proved diagnostic ultrasound and alternating magnetic field (AMF)-induced local hyperthermia as clinically approved triggers for controlled drug release. Furthermore, in a complementary approach, we rewired infection-associated cellular signalling pathways for controlled induction of apoptosis, paving the way for autonomous drug release from nanoparticle-loaded cells. Based on these preliminary activities, the proposed project will focus on utilizing this strategy to combat local bacterial infection. Specifically, the efficiency and specificity of both externally and autonomously controlled drug release will be assessed in preclinical animal models, analysing key pharmacokinetic and pharmacodynamic parameters. In addition, the efficacy of the strategy in combating local infections associated with implants will be explored. To maximize therapeutic potential, it is foreseen to expand the scope of the project by incorporating multiplexed delivery of various antibacterial agents. This will allow to harness synergistic modes of actions, thereby minimizing the required drug concentrations. Additionally, the project foresees the implementation of synthetic expression circuits in macrophages for specifically modifying/adjusting cellular functions, thereby improving the carrier functions and/or the therapeutic capacity. Finally, the feasibility of releasing therapeutic factors from macrophages to support tissue regeneration will be assessed, aiming for a holistic approach that addresses both infection control and tissue healing.

Project related publication(s)

[1] O. Desai, M. Köster, D. Kloos, N. Lachmann, H. Hauser, A. Poortinga, D. Wirth, Ultrasound-triggered drug release in vivo from antibubble-loaded macrophages, Journal of controlled release, 378 (2024) 365-376. Doi 10.1016/j.jconrel.2024.12.007

[2] O. Desai, S. Kumar, M. Köster, S. Ullah, S. Sarker, V. Hagemann, M. Habib, N. Klaassen, S. Notter, C. Feldmann, N. Ehlert, H. Hauser, D. Wirth, Macrophages co-loaded with drug-associated and superparamagnetic nanoparticles for triggered drug release by alternating magnetic fields, Drug Deliv Transl Res, in press (2025). doi 10.1007/s13346-024-01774-9

[3] N. Gödecke, J. Riedel, S. Herrmann, S. Behme, U. Rand, T. Kubsch, L. Cicin-Sain, H. Hauser, M. Köster, D. Wirth, Synthetic rewiring and boosting type I interferon responses for visualization and counteracting viral infections, Nucleic Acids Research, 48 (2020) 11799–11811. Doi 10.1093/nar/gkaa961

[4] S. Ullah, K. Seidel, S. Turkkan, D.P. Warwas, T. Dubich, M. Rohde, H. Hauser, P. Behrens, A. Kirschning, M. Koster, D. Wirth, Macrophage entrapped silica coated superparamagnetic iron oxide particles for controlled drug release in a 3D cancer model, Journal of controlled release, 294 (2019) 327-336. doi: 10.1016/j.jconrel.2018.12.040.

Joint Call for Doctoral Researchers - Project 15

Supervisor	Mark Brönstrup
Location	Braunschweig, HZI Campus
Name of working group	CBIO (Chemical Biology)
Title of the project	Synthesis and characterization of drug conjugates with smart linkers targeting Pseudomonas aeruginosa
Webpage link	https://www.helmholtz-hzi.de/en/research/research-groups/details/chemical-biology/

Summary (approx. 300 words)

The drug discovery program of the Department 'Chemical Biology' (CBIO) employs state-of-the-art chemical strategies to tackle infectious diseases. A great challenge in the development of new antibiotics is finding a way to penetrate the double membranes of Gram-negative bacteria, the group of bacteria that also contain many drug-resistant variants. We conduct structure–activity relationship (SAR) studies and medicinal chemistry campaigns on both natural products and synthetic compounds, producing potent novel derivatives with new modes of action, and good efficacy in vivo. A specific expertise of the group concerns the synthesis and characterization of multifunctional drug conjugates against multidrug-resistant bacteria; this is the Theme of the doctoral Thesis. Two proposals are ready to be started: A conjugate targeting Pseudomonas aeruginosa, using a high-affinity binder to Pseudomonas bacteria, is coupled to a potent antibiotic that is released by a smart linker. The linker is either activated by enzymes at the infection side, or chemically using an (unpublished) transition metal-catalysed reaction. Alternatively, we pursue a concept for antibacterial PROTACs that degrade cellular bacterial targets. This makes use of our toolbox built for antiviral PROTACs, although the mode of action on bacteria is different and widely unexplored so far. Both projects involve multistep chemical synthesis with natural product-derived, optimized antibiotics. Bioanalytical, microbiological and high resolution imaging work can be either done by the doctoral student or by collaborators in the context of our newly started ERC Synergy project 'AI4AMR'.

Project related publication(s)

- Shekhar A ,Di Lucrezia R, Jerye K, Korotkov VS,….Brönstrup M. Highly potent quinoxalinediones inhibit alpha-hemolysin and ameliorate lung infections by Staphylococcus aureus. Cell Host Microbe (2025), accepted in principle.
- Charoenpattarapreeda J, Tegge W, Xu C, Harmrolfs K, Hinkelmann B, Wullenkord H, Hotop SK, Beutling U, Rox K, Brönstrup M. A Targeted Click-to-Release Activation of the Last-Resort Antibiotic Colistin Reduces its Renal Cell Toxicity. Angew Chem Int Ed Engl. 2024;63(47):e202408360. doi: 10.1002/anie.202408360.
- Peukert C, Popat Gholap S, Green O, Pinkert L, van den Heuvel J, van Ham M, Shabat D, Brönstrup M. Enzyme-Activated, Chemiluminescent Siderophore-Dioxetane Probes Enable the Selective and Highly Sensitive Detection of Bacterial Pathogens. Angew Chem Int Ed Engl. 2022;61(25):e202201423. doi: 10.1002/anie.202201423.
- Tegge W, Guerra G, Höltke A, Schiller L, Beutling U, Harmrolfs K, Gröbe L, Wullenkord H, Xu C, Weich H, Brönstrup M. Selective Bacterial Targeting and Infection-Triggered Release of Antibiotic Colistin Conjugates. Angew Chem Int Ed Engl. 2021;60(33):17989-17997. doi: 10.1002/anie.202104921.

HZI HELMHOLTZ Centre for Infection Research

Joint Call for Doctoral Researchers - Project 16

Supervisor	Arnaud Carpentier
Location	Hannover, TWINCORE
Name of working group	Experimental Virology
Title of the project	New host factor of Hepatitis D Virus in hepatocytes
Webpage link	https://twincore.de/labs/pietschmann-lab

Summary (approx. 300 words)

Infection by the Hepatitis D Virus (HDV) is responsible for the most severe form of viral hepatitis. Despite the development of new antiviral strategies, there is no curative treatment yet, emphasizing the need to further study host pathogen interactions of the virus. We recently characterized the HDV infection of mature stem cell derived hepatocytes, also known as Hepatocyte-like cells (HLCs), using single cell RNA sequencing. We identified a dozen cellular genes statistically enriched within infected HLCs. The present project will focus on the deciphering of the role of these host genes during HDV infection. The PhD candidate will have the opportunity to work on both hepatic cell lines and stem cell derived hepatocytes, and will have access to state-of-the-art technics, from gene editing to confocal microscopy, transcriptomics and virological assays. The work is hosted by the Institute of Experimental Virology at Twincore (Hannover), thus benefiting from a great international and collaborative environment. Moreover, our contacts with the close-by Hannover Medical School (MHH) will allow translational collaborations. The work will improve our understanding of HDV infection mechanisms and lead the way to the development of new antiviral strategies.

Project related publication(s)

1. Carpentier A, Sheldon J, Vondran FWR, et al. Efficient acute and chronic infection of stem cell-derived hepatocytes by hepatitis C virus. Gut 2020;69:1659–1666.

2. Lange F, Garn J, Anagho HA, et al. Hepatitis D virus infection, innate immune response and antiviral treatments in stem cell-derived hepatocytes. Liver International 2023;43:2116–2129.

3. Carpentier A. Cell Culture Models for Hepatitis B and D Viruses Infection: Old Challenges, New Developments, and Future Strategies. Viruses 2024;16:716.

4. Frericks N, Klöhn M, Lange F, et al. Host-targeting antivirals for chronic viral infections of the liver.

Antiviral Research 2025;234:106062.

5. Lange F, Garn J, Brühn M, et al. Single cell analysis of HDV infected stem cell-derived hepatocytes reveals an IRF1 driven restriction of HDV infection. Journal of Hepatology; resubmitted after major revision.