RESEARCH CENTER FOR INFECTIOUS DISEASES

ZENTRUM FÜR INFEKTIONSFORSCHUNG

SCIENTIFIC REPORT 2018-2019

WISSENSCHAFTLICHER BERICHT 2018-2019

Julius-Maximilians-
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WURZBURG

ZINF
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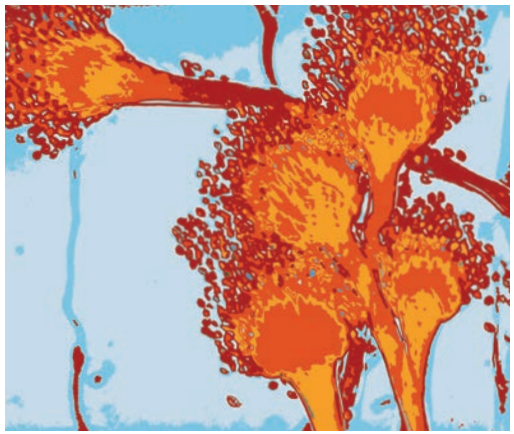
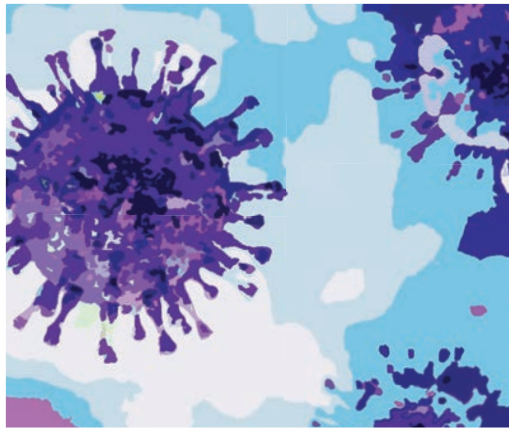




SCIENTIFIC REPORT 2018-2019

RESEARCH CENTER FOR INFECTIOUS DISEASES (ZINF)

ZINF NUMBERS

2018-2019

ABOUT THE ZINF

The Research Center for Infectious Diseases (ZINF) is a **MULTI-DISCIPLINARY NETWORK** of researchers in Würzburg addressing molecular principles of host-pathogen interactions. It brings together experts from **MICROBIOLOGY, PARASITOLOGY, VIROLOGY, IMMUNOLOGY, CHEMISTRY,** and **CLINICAL PRACTICE** and facilitates cross-faculty communication, initiation of joint research activities, as well as recruitment of extramural funding.

Founded in 1993 with financial support from the Federal Ministry of Research and Technology and afterwards the Bavarian State Ministry for Research and Art, the ZINF represents the **OLDEST ACADEMIC INSTITUTION** in Germany devoted to interdisciplinary research on infectious diseases. With 35 professors in infection biology, infectious diseases research is a key area of biomedical research at the Julius Maximilians University of Würzburg (JMU). The ZINF greatly benefits from strong interactions across faculties, clinics, and research institutions outside the JMU.

A core component of the ZINF has been its **YOUNG INVESTIGATOR GROUP** program that offers a unique entry for young researchers into their own scientific career. Research of the independent ZINF junior groups covered in the period of this report focuses on organoids as new infection models, high-throughput technologies to study the mode of action of antibiotic combinations, regulatory RNA molecules in anaerobic pathogens and in the microbiome, structural biology of mycobacteria, as well as the role of the microbiota in fungal infections.

The ZINF is a central scientific facility of the JMU Würzburg and has evolved into an internationally recognized and accredited institution.

CONTENT

ZINF SCIENTIFIC REPORT 2018-2019

1. GENERAL REMARKS

1.1 Speaker's Report / Bericht der Sprecherin 10
1.2 Structure of the ZINF 14
1.3 Events surrounding the ZINF 16

2. YOUNG INVESTIGATOR GROUPS OF THE ZINF

Sina Bartfeld - Organoids as Host Models 22
Ana Rita Brochado - Systems Biology of Antibiotic Action 24
Franziska Faber - RNA Biology of *Clostridioides difficile* 26
Sebastian Geibel - Structural Biology of Mycobacteria 28
Christian Perez - Regulatory Networks in Pathogenesis 30

3. MEMBERS OF THE ZINF

3.1 INSTITUTE OF MOLECULAR INFECTION BIOLOGY 34
Jörg Vogel - RNA Biology 36
Cynthia Sharma - Deep Sequencing Approaches to Pathogenesis 37
Heidrun Moll - Infection Immunology 38
Joachim Morschhäuser - Mycology 39
Knut Ohlsen - Gram-positive Cocci 40
Alexander Westermann - Host-Pathogen-Microbiota Interactions 41
Wilma Ziebuhr - Nosocomial Infections by Staphylococci 42

3.2 INSTITUTE FOR HYGIENE AND MICROBIOLOGY 44
Matthias Frosch - Molecular Surveillance of Invasive Bacterial Infections 46
Oliver Kurzai - Medical Microbiology and Mycology 47
Klaus Brehm - Helminth Infections 48
Christoph Schoen - Molecular Diagnostics and Functional Genomics of Human Pathogenic Bacteria 49
Alexandra Schubert-Unkmeir - Host-Pathogen Interactions 50
Ulrich Vogel - Infection Epidemiology of *Neisseria meningitidis* and Hospital Infection Control 51

3.3 INSTITUTE FOR VIROLOGY AND IMMUNOBIOLOGY – DEPARTMENT OF VIROLOGY 52
Lars Dölken - Systems Biology of Herpesvirus Infections 54
Florian Erhard - Computational Systems Virology 55
Jürgen Schneider-Schaulies - Morbillivirus Pathogenesis 56
Sibylle Schneider-Schaulies - Viral Immunomodulation 57

3.4 INSTITUTE FOR VIROLOGY AND IMMUNOBIOLOGY – DEPARTMENT OF IMMUNOLOGY 58
Wolfgang Kastenmüller - Leukocyte Dynamics 60
Niklas Beyersdorf - T Cell Biology 61
Thomas Herrmann - Immunogenetics 62
Manfred Lutz - Immune Regulation 63

3.5 DEPARTMENT OF MICROBIOLOGY, THEODOR BOVERI INSTITUTE, BIOCENTER 64
Thomas Rudel - Infection Biology of Bacteria 66
Martin Fraunholz - Cellular Microbiology 67
Roy Gross - Pertussis 68
Vera Kozjak-Pavlovic - Bacterial Invasion and Intracellular Survival 69

3.6 DEPARTMENT OF INTERNAL MEDICINE II 70
Hermann Einsele - Interaction of *Aspergillus fumigatus* with Human Natural Killer Cells and Dendritic Cells 72
Andreas Beilhack - Experimental Stem Cell Transplantation 73
Hartwig Klinker - Division of Infectious Diseases 74
Jürgen Löffler - Immunity against *Aspergillus* spp. 75

3.7 INSTITUTE OF SYSTEMS IMMUNOLOGY 76
Georg Gasteiger - Tissue Immunity 78
Mercedes Gomez de Agüero - Host-Microbial Interactions 79
Martin Vaeth - Metabolism and Immune Cell Signalling 80

3.8 HELMHOLTZ INSTITUTE FOR RNA-BASED INFECTION RESEARCH 82
Lars Barquist - Integrative Informatics for Infection Biology 84
Chase Beisel - RNA Synthetic Biology 85
Neva Caliskan - Recoding Mechanisms in Infections 86
Mathias Munschauer - Decoding RNA-Protein Interactomes of Regulatory RNA in Infection 87
Antoine-Emmanuel Saliba - Single-cell Analysis 88
Redmond Smyth - Genome Architecture and Evolution of RNA Viruses 89

3.9 ZINF MEMBER ASSOCIATED WITH OTHER INSTITUTES 90
Thomas Dandekar - Bioinformatics 92
Markus Engstler - Molecular and Physical Parasitology 93
Ulrike Holzgrabe - Medicinal Chemistry 94
Caroline Kisker - Structure-based Drug Design 95
Marco Metzger - Human 3D Tissue Models to Study Host-Pathogen Interactions in Infectious Research 96
Jürgen Seibel - Chemistry of Living Systems 97
August Stich - Tropical Medicine 98

4. RESEARCH PROGRAMS

4.1 DFG Collaborative Research Center (CRC) / SFB Transregio 34 102
4.2 DFG Collaborative Research Center (CRC) / SFB Transregio 124 102
4.3 DFG Research Unit 1680 103
4.4 DFG Research Unit 2123 103
4.5 DFG Research Unit 2830 104
4.6 DFG Priority Program SPP 1617 105
4.7 DFG Priority Program SPP 1656 105
4.8 DFG Priority Program SPP 1726 105
4.9 DFG Priority Program SPP 1784 106
4.10 DFG Priority Program SPP 1937 106
4.11 DFG Priority Program SPP 2002 106
4.12 DFG Priority Program SPP 2141 107
4.13 DFG German-African Cooperation Projects in Infectiology 107
4.14 BMBF #1Health-Prevent 108
4.15 BMBF InfectControl 2020 108
4.16 BMBF Target Validation for Pharmaceutical Drug Development 109
4.17 BMBF iMIP 110

4. RESEARCH PROGRAMS

4.18 European Research Area Networks (ERA-Net) 110
4.19 International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) 113
4.20 IBD-Labnet Coordination of Activities for Laboratory Surveillance of Invasive Bacterial Diseases 113
4.21 Wellcome Trust Strategic Award 114
4.22 Else Kröner Center for Advanced Medical & Medical Humanitarian Studies Würzburg – Mwanza/Tanzania 114
4.23 Bavarian Research Network bayresq.net 114

5. INFRASTRUCTURE

5.1 NRL for Meningococci and *Haemophilus influenzae* 118
5.2 The Consulting Laboratory for Echinococcosis 118
5.3 German Center for Infection Research (DZIF) 119
5.4 Interdisciplinary Center for Clinical Research (IZKF) 119
5.5 Core Unit Systems Medicine 121

6. TRAINING THE NEXT GENERATION

6.1 Graduate School of Life Sciences (GSLS) 124
6.2 DFG Research Training Group (Graduiertenkolleg GRK 2157) 3D Infect 125
6.3 DFG Research Training Group (Graduiertenkolleg GRK 2243) UBI 126
6.4 DFG Research Training Group (Graduiertenkolleg GRK 2581) SPHINGOINF 127

7. APPENDIX

7.1 ZINF Young Investigator Group Leaders Alumni 130
7.2 Meetings and Workshops (co)organized by ZINF Members 132
7.3 Seminars and Colloquia 134
7.4 Funding 140
7.5 Publications 148
7.6 Directory of People Associated with the ZINF 170

1

GENERAL REMARKS

1.1 SPEAKER'S REPORT

2018-2019

Dear readers,

Infectious diseases remain one of the central challenges for science and medicine in the 21st century. The ongoing global SARS-CoV-2 pandemic has clearly shown that the fight against infectious diseases is of particular social, political, and economic importance. The global challenges of a rising threat of zoonotic pathogens such as coronaviruses or emerging antimicrobial resistances that threaten the effective treatment of infections require a collective effort of scientists from all disciplines, developing and integrating new technologies and innovative strategies to study infection processes and develop novel therapeutics and vaccines.

In this report, we provide an overview about the 2018-2019 research activities and achievements of the Research Center for Infectious Diseases (ZINF) of the Julius-Maximilians-University (JMU) in Würzburg. To date, the ZINF network comprises 50 principal investigators from three faculties (Medicine, Biology, and Chemistry & Pharmacy), the Helmholtz Institute for RNA-based Infection Research (HIRI), and the Max-Planck-Research Groups on Systems Immunology. Research of ZINF members focuses on molecular principles of host-pathogen interactions of diverse bacterial, fungal, eukaryotic, and viral pathogens, the host immune response, the role of RNA in infections, and the development of new infection models or anti-infectives.

To fight the SARS-CoV-2 pandemic, researchers all over the world, including many ZINF members, have pooled their skills and resources to understand the epidemiology and pathobiology of this virus, develop a vaccine or novel diagnostics, and aid the people suffering from COVID-19. As they are not covered in the report period, some examples of the ongoing Corona research activities in Würzburg are listed here. The Department of Virology headed by Lars Dölken has greatly increased their capacities for SARS-CoV-2 diagnostics, and, together with the University Hospital (UKW), Oliver Kurzai and Ulrich Vogel (Institute for Hygiene and Microbiology) have established a Corona testing facility. Within the InfectControl network, Oliver Kurzai and colleagues from the Department of Pediatrics (UKW) initiated the BMBF (Federal Ministry of Education and Research)-funded Würzburg "Wü-KiTa-CoV" Corona kindergarten study that investigates the still unclear extent of viral spreading among young children. Several ZINF members are part of the BMBF-funded "Organo-Strat" network (coordinated by the Charité Berlin) addressing the type and extent of organ-specific disease development during SARS-CoV-2 infection, or the Bavarian FOR-COVID network (co-coordinator Jörg Vogel) on new ways to prevent infections, vaccination and treatment options, and a better understanding of the origin and development of COVID-19. Emmanuel Saliba (HIRI) joined forces with researchers in Berlin and Bonn and recently published a study in *Cell* employing single cell analyses to decipher differences in systemic immune responses during mild and severe COVID-19. Mathias Munschauer, Jörg Vogel, and colleagues have been charting a global interaction atlas of the SARS-CoV-2 RNA and the human host proteome (*Nature Microbiology, in press*). Within the GRK2157 3D Infect, new projects on SARS-CoV-2 have been launched, and, together with the lab of Chase Beisel, my group has been developing a CRISPR/Cas-based diagnostic method that can distinguish different respiratory viruses including SARS-CoV-2.

With the establishment of the ZINF in 1993 by Volker ter Meulen, Werner Goebel, and colleagues, and supported by the Federal Ministry of Research and Technology and afterwards the Bavarian Government, Würzburg gained a central scientific institution dedicated to cross-faculty research on infectious diseases. It developed into an internationally renowned center under the long term leaderships of the former ZINF speakers Jörg Hacker and Jörg Vogel. Jointly with the Institute of Molecular Infection Biology (IMIB), the ZINF celebrated its 25th birthday in 2018 together with national and international guests, friends, and colleagues at an anniversary symposium (p. 16-17). Speakers included Alfred Forchel (President of JMU), Marion Schäfer Blake (Majoress of Würzburg), ZINF scientific advisory board members Tone Tønjum (Oslo) and Eric Pamer (Chicago), ZINF Alumnus Daniel Lopez (Madrid), Jörg Vogel (Director of IMIB/HIRI), and Jörg Hacker (President of the National Academy Leopoldina). The 2018 Robert Koch Gold Medal Awardee Staffan Normark gave a Robert Koch Lecture and the current ZINF young investigators presented their ongoing and future research.

A central component of the ZINF has been its young investigator group (YIG) program, which was pioneering in promotion of independent junior groups at German universities. The success of the ZINF YIG program has also contributed to the recruitment of additional young scientists from all over the world to Würzburg through highly competitive funding sources. In 2018-2019, the ZINF young investigators Sina Bartfeld (ZINF, Organoids as new infection models), Christian Pérez (ZINF/IZKF, Role of the microbiota in fungal infections), and Sebastian Geibel (Elite Network Bavaria, Structural biology of mycobacteria), were joined by two new group leaders. In 2018, Franziska Faber started as head of a new ZINF YIG on RNA biology and pathogenesis of *Clostridioides difficile*, expanding the range of studied pathogens in Würzburg to anaerobic species. And in a joint venture, the ZINF and the Biocenter recruited Ana Rita Brochado, who started her lab in 2019 on high-throughput technologies to study systems biology of antibiotic actions. Recently, she was awarded a prestigious Emmy Noether research fellowship by the German Research Foundation (DFG). With the recruitment of these two new YIGs, the ZINF continues to be exceptionally successful in the promotion of female scientists, with 3 out of 5 current YIG leaders, and 7 out of 17 alumni, being female scientists.

The interdisciplinary environment of the ZINF enables YIG leaders to perform high impact research, as reflected by several seminal papers published in 2018-2019. For example, ZINF Alumnus Nicolai Siegel (since 2017 LMU Munich) reported in *Nature* the global mapping of the 3D genome architecture and its impact on antigenic variation of trypanosomes, which was performed by his group in Würzburg. This study also included the first scRNA-seq analysis of trypanosomes, which his lab set up jointly with the Saliba group. In 2019, the group of Sebastian Geibel reported the cryo-electron microscopy resolution of the structure of the core complex of the type VII secretion system from mycobacteria in *Nature*. The success of the ZINF is also reflected by professorship offers to current ZINF YIG leaders and by the 17 ZINF YIG Alumni holding national or international professorships or group leader positions. Most recently, we congratulate Sina Bartfeld on an offer for a Full Professor (W3) position as well as Christian Pérez on his new position as Associate Professor at UTHealth and wish him a great start in Houston.

Supported by an international scientific advisory board (SAB) of leading scientists, the ZINF has evolved into an internationally recognized and accredited institution. We would like to express our deepest gratitude to the members of our SAB and were delighted to welcome Melanie Blokesch (EPFL, Lausanne) and Jay Hinton (University of Liverpool) as new members in 2019. Moreover, we congratulate former ZINF YIG alumna and SAB member Katja Becker on her recent election as the new, and first female, DFG president (start: 2020) and wish her all the best for her new role in leading the German Research Foundation.

The past two years have been exceedingly rewarding and the achievements and research excellence of several ZINF members were recognized by awards, honors, and appointments in 2018/2019. These include multiple highly competitive and prestigious ERC (European Research Council) Grants: an Advanced Grant to Thomas Rudel, Consolidator Grants to Wolfgang Kastenmüller and Chase Beisel, a Proof-Of-Concept Grant to Lars Dölken and Florian Erhard, and most recently, a 2020 Starting Grant to Neva Caliskan. Furthermore, Franziska Faber (2018 Young Investigator Award) and Oliver Kurzai (2020 Main Research Award) received awards from the German Society for Hygiene and Microbiology (DGHM). ZINF members Hermann Einsele and Jörg Vogel were again listed by Thomson Reuters as "Highly Cited Researcher" in 2018-2020. In 2019, Ulrike Holzgrabe received the Bavarian Order of Merit (Bayerischer Verdienstorden), Manfred Lutz the Research Prize of the Vogel Foundation, and Jörg Vogel the Feldberg Prize of the Feldberg Foundation, respectively. Medical Faculty Dean Matthias Frosch was elected as the new President of the "Medizinischer Fakultätentag" in 2019, and Jörg Vogel will start as the new President of the European Academy of Microbiology in January 2021.

ZINF members also initiated or participated in innovative scientific networks on infectious diseases (p. 102-115). This includes, for example, the new DFG Research Unit 2830 "Advanced concepts in cellular immune control of Cytomegalovirus" (coordinator Lars Dölken) and the Research Training Group 2581 "Metabolism, topology, and compartmentalization of membrane proximal lipid and signaling components in infection" (coordinator Jürgen Seibel). The GRK 2157 3D Infect (coordinator Thomas Rudel) was successfully evaluated and will be funded for another 4.5 years. Matthias Frosch and Oliver Kurzai initiated the "Else-Kröner-Fresenius-Center for Advanced Medical & Medical Humanitarian Studies Würzburg-Mwanza/Tanzania". Several ZINF members are part of the recently established Bavarian research network *bayresq.net* on "New strategies against multi-resistant pathogens by means of digital networking". In their *Rbiotics* consortium, Jörg Vogel, Franziska Faber, and Lars Barquist develop new programmable RNA-based antibiotics against multi-resistant pathogens. Ana Rita Brochado and myself together with Christian Müller (Munich) will employ high-throughput approaches to decipher stress pathways involved in antibiotics resistance and virulence of pathogens in our *StressRegNet* consortium.

Besides the organization of several conferences and symposia by ZINF members, we were happy to welcome many international scientists and guest speakers at our colloquia and seminar series in Würzburg (p. 132-139). Earlier in 2020, the Faculty of Biology awarded an honorary doctorate to the renowned infection biologist and vaccinologist Rino Rappuoli (Siena). Peter Fineran from the University of Otago in New Zealand received a Research Fellowship for Experienced Researchers from the Alexander von Humboldt Foundation to visit the labs of Chase Beisel and mine in 2019. We look forward to hosting him again in 2021/2022 to continue our joint work on the regulation of bacterial CRISPR-Cas immune systems.

Although the SARS-CoV-2 pandemic is currently in focus, many additional infectious diseases remain huge social and medical challenges with a particular threat by the emergence of antibiotics resistant or even completely novel pathogens, including viruses. Moreover, the importance of fundamental research is highlighted not least by the 2020 Nobel Prize in Chemistry to Emmanuelle Charpentier and Jennifer Doudna for the development of a novel CRISPR-Cas based genome editing method. Intriguingly, the Cas9 "DNA scissors" were identified in the human pathogen *Streptococcus pyogenes*, underscoring the requirement for continuous basic research on infectious diseases besides finding novel ways to treat them. The ZINF provides an ideal network to join these tasks and I am looking forward to the next years of its infectious disease research activities. High-throughput and single cell sequencing, as well as novel imaging technologies will provide new insights into complex host-pathogen interactions with unprecedented resolution. Artificial intelligence approaches will pave the way to analyze and interpret large datasets in the fight against infectious diseases.

Finally, I would like to thank all ZINF members for fruitful collaborations, their contributions to this report and to the success of the ZINF. And I would like to thank the University of Würzburg and the Bavarian Government for their continued support of the ZINF.

CYNTHIA SHARMA
Spokesperson ZINF

Würzburg, November 2020

BERICHT DER SPRECHERIN

2018-2019

Liebe Leserinnen, liebe Leser,

Infektionskrankheiten sind auch im 21. Jahrhundert eine der zentralen Herausforderungen in Wissenschaft und Medizin. Insbesondere die aktuelle SARS-CoV-2 Pandemie hat verdeutlicht, wie essentiell die Bekämpfung von Infektionskrankheiten für Gesellschaft, Politik und Wirtschaft ist. Die globale Herausforderung einer zunehmenden Gefährdung durch zoonotische Krankheitserreger wie Coronaviren oder die Verbreitung von antimikrobiellen Resistenzen erfordert eine interdisziplinäre Zusammenarbeit von Wissenschaftlern, um neue Technologien und Strategien zur Erforschung von Infektionskrankheiten, sowie neue Therapeutika und Impfstoffe zu entwickeln.

Dieser wissenschaftliche Bericht gibt einen Überblick über die Forschung des Zentrums für Infektionsforschung (ZINF) der Julius-Maximilians-Universität (JMU) Würzburg in 2018-2019. Das ZINF ist ein interdisziplinäres Netzwerk, das aktuell 50 Mitglieder aus drei Fakultäten (Medizin, Biologie, Chemie & Pharmazie) sowie vom Helmholtz Institut für RNA-basierte Infektionsforschung (HIRI) und der Max-Planck-Forschungsgruppe Systemimmunologie zählt. Die Mitglieder forschen an molekularen Grundlagen von Wirt-Pathogen-Interaktionen diverser Krankheitserreger (Bakterien, Pilze, Eukaryoten, Viren), der Immunantwort des Wirts, der Rolle von RNA in Infektionen, sowie der Entwicklung neuer Infektionsmodelle oder Antiinfektiva.

Im Kampf gegen die SARS-CoV-2 Pandemie, dem sich zahlreiche Mitglieder des ZINF angeschlossen haben, arbeiten Forscher weltweit daran, die Ausbreitung und Pathogenese dieses Virus zu verstehen und einen neuen Impfstoff, Diagnostika oder Therapien zu entwickeln. In Würzburg hat z.B. das Institut für Virologie unter Leitung von Lars Dölken seine Kapazitäten für die SARS-CoV-2 Diagnostik stark erweitert und Oliver Kurzai und Ulrich Vogel (Institut für Hygiene und Mikrobiologie) haben gemeinsam mit dem Universitätsklinikum (UKW) ein Corona Testzentrum errichtet. Im Rahmen des InfectControl-Netzwerks initiierten Oliver Kurzai und Kollegen der Kinderklinik die vom BMBF (Bundesministerium für Bildung und Forschung) geförderte Würzburger „Wü-KiTa-CoV" Corona-Kindergartenstudie, die das noch unklare Ausmaß der Virusausbreitung bei Kindern untersucht. Mehrere ZINF-Mitglieder sind Teil von SARS-CoV-2-Forschungsverbünden wie z.B. dem BMBF-geförderten „Organo-Strat" Netzwerk (koordiniert durch die Charité Berlin), das sich mit Art und Ausmaß der organspezifischen Krankheitsentstehung einer SARS-CoV-2 Infektion befasst, oder dem bayerischen FOR-COVID Netzwerk (Co-Koordinator Jörg Vogel), das neue Wege der Infektionsprävention entwickeln, sowie die Entstehung und Entwicklung von COVID-19 besser verstehen möchte. Emmanuel Saliba (HIRI) und Kollegen aus Berlin und Bonn publizierten vor kurzem eine Studie in *Cell*, in der sie mittels Einzelzellanalysen Unterschiede in der systemischen Immunantwort bei milden und schweren COVID-19 Verläufen entschlüsselten. Mathias Munschauer, Jörg Vogel und Kollegen haben eine globale Kartierung von Komplexen zwischen der SARS-CoV-2 RNA und Proteinen des menschlichen Wirts erstellt (*Nature Microbiology*, *in press*). Auch im Rahmen des GRK 2157 3D-Infekt wurden neue Projekte zu SARS-CoV-2 gestartet und die Labore von Chase Beisel und mir haben gemeinsam eine CRISPR/Cas-basierte Diagnosemethode zur Unterscheidung diverser respiratorischer Viren, darunter SARS-CoV-2, entwickelt.

2018 konnte das ZINF auf ein Vierteljahrhundert erfolgreicher Infektionsforschung zurückblicken. Von Volker ter Meulen, Werner Goebel und Kollegen 1993 gegründet, wurde das ZINF zunächst finanziell durch das Bundesministerium für Forschung und Technologie und später durch die JMU und das Bayerische Staatsministerium gefördert. Damit erhielt Würzburg eine zentrale wissenschaftliche Einrichtung, die sich fakultätsübergreifend der Erforschung von Infektionskrankheiten widmet und sich unter der langjährigen Leitung der früheren ZINF-Sprecher Jörg Hacker und Jörg Vogel zu einem international angesehenen Zentrum entwickelt hat. Gemeinsam mit dem Institut für Molekulare Infektionsbiologie (IMIB) feierte das ZINF 2018 seinen 25. Geburtstag mit nationalen und internationalen Gästen, Freunden und Kollegen im Rahmen eines Jubiläumssymposiums (S. 16-17). Zu den Referenten gehörten Alfred Forchel (Präsident der JMU), die Würzburger Bürgermeisterin Marion Schäfer Blake, die Mitglieder des wissenschaftlichen Beirats Tone Tønjum (Oslo) und Eric Pamer (Chicago), der ehemalige ZINF-Nachwuchsgruppenleiter Daniel Lopez (Madrid), Jörg Vogel (Direktor des IMIB/HIRI) und Jörg Hacker (Präsident der Nationalen Akademie Leopoldina). Staffan Normark, Preisträger der Robert-Koch-Goldmedaille 2018, hielt die Robert-Koch-Vorlesung und die derzeitigen ZINF Nachwuchsgruppenleiter stellten ihre laufende und zukünftige Forschung vor.

Ein zentraler Bestandteil des ZINF ist das Nachwuchsprogramm (Young Investigator Group Program, YIG), das wegweisend für die Förderung unabhängiger Juniorgruppen an deutschen Universitäten war. Der Erfolg des Nachwuchsprogramms trägt auch dazu bei, dass junge Wissenschaftler aus der ganzen Welt über Forschungsgelder aus kompetitiven Verfahren nach Würzburg geholt werden konnten. 2018-2019 kamen zu den Gruppen von Sina Bartfeld (ZINF, Organoide als neue Infektionsmodelle), Christian Pérez (ZINF/IZKF, Rolle der Mikrobiota bei Pilzinfektionen) und Sebastian Geibel (Elitenetzwerk Bayern, Strukturbiologie von Mykobakterien), zwei neue ZINF YIGs hinzu. Franziska Faber startete 2018 ihre Gruppe zur RNA-Biologie und Pathogenese von *Clostridioides difficile*, wodurch das Würzburger Forschungsrepertoire um anaerobe Spezies erweitert wurde. Gemeinsam mit dem Biozentrum hat das ZINF 2019 Ana Rita Brochado für Würzburg gewinnen können. Ihr Labor untersucht die Systembiologie von Antibiotika-Wechselwirkungen mittels Hochdurchsatztechnologien und Ana Rita wurde vor kurzem durch ein prestigeträchtiges Emmy-Noether-Forschungsstipendium der Deutschen Forschungsgemeinschaft (DFG) ausgezeichnet. Mit diesen beiden neuen YIGs ist das ZINF weiterhin außerordentlich erfolgreich in der Förderung von Frauen in der Wissenschaft: die Leitungen von 3 von 5 derzeitigen und 7 von 17 ehemaligen YIGs sind weiblich.

Das interdisziplinäre Umfeld des ZINF ermöglicht es den YIGs hochkarätige Forschung zu betreiben, was sich in mehreren 2018-2019 veröffentlichten bahnbrechenden Arbeiten widerspiegelt. Zum Beispiel publizierte die Gruppe des ehemaligen ZINF Alumnus Nicolai Siegel (seit 2017 LMU München) in *Nature* ihre Arbeiten aus Würzburg zur globalen Kartierung der 3D Genomarchitektur von Trypanosomen und deren Einfluss auf die Antigenvariation, sowie die erste scRNA-seq Analyse dieser Pathogene (Kollaboration mit AG Saliba). Ebenfalls in *Nature* erschienen die Arbeiten von Sebastian Geibel zur kryoelektronenmikroskopischen Strukturauflösung vom zentralen Komplex des Typ VII-Sekretionssystems von Mykobakterien. Der Erfolg des ZINF spiegelt sich auch in Rufen auf Professorenstellen an die aktuellen YIG Leiter/innen, sowie in den nationalen und internationalen Professuren oder Gruppenleiterpositionen, welche die 17 ZINF Alumni innehaben, wieder. Als jüngste Beispiele möchten wir Sina Bartfeld zu einem Ruf auf eine W3-Professur sowie Christian Pérez zu seiner neuen Position als Associate Professor an der UTHealth in Houston gratulieren.

Der Erfolg und die Sichtbarkeit des ZINF wurde wegweisend durch unseren internationalen wissenschaftlichen Beirat bestehend aus führenden Wissenschaftler/innen begleitet und unterstützt. Bei unseren Beiratsmitgliedern möchten wir uns ganz herzlich bedanken und wir freuen uns, seit 2019 Melanie Blokesch (EPFL, Lausanne) und Jay Hinton (Universität Liverpool) als neue Mitglieder begrüßen zu dürfen. Zudem gratulieren wir der ehemaligen ZINF Nachwuchsgruppenleiterin und Beiratsmitglied Katja Becker zu ihrer Wahl zur ersten Präsidentin der Deutschen Forschungsgemeinschaft und wünschen ihr alles Gute für ihre neue Rolle an der DFG-Spitze seit 2020.

Auch 2018-2019 erhielten mehrere ZINF Mitglieder eine Reihe renommierter Preise und Ehrungen oder wurden auf wichtige Positionen ernannt. Dazu zählen mehrere prestigeträchtige ERC (European Research Council)-Grants: Thomas Rudel erhielt einen Advanced Grant, Wolfgang Kastenmüller und Chase Beisel erhielten Consolidator Grants, Lars Dölken und Florian Erhard einen Proof-Of-Concept Grant, und jüngst erhielt Neva Caliskan einen Starting Grant (2020). Die Deutsche Gesellschaft für Hygiene und Mikrobiologie zeichnete Franziska Faber (Nachwuchspreis 2018) und Oliver Kurzai (Hauptpreis 2020) aus. Hermann Einsele und Jörg Vogel wurden erneut von Thomson Reuters als „Highly Cited Researcher" (2018-2020) gelistet. 2019 erhielten Ulrike Holzgrabe den Bayerischen Verdienstorden, Manfred Lutz den Forschungspreis der Vogel-Stiftung und Jörg Vogel den Feldberg-Preis. Matthias Frosch wurde 2019 zum neuen Präsidenten des Medizinischen Fakultätentages gewählt und Jörg Vogel wird im Januar 2021 die Präsidentschaft der Europäischen Akademie für Mikrobiologie antreten.

ZINF-Mitglieder initiierten oder wirkten zudem in innovativen Forschungsnetzwerken zu Infektionskrankheiten mit (S. 102-115). Dazu gehören beispielsweise die neue DFG Forschungsgruppe 2830 „Advanced concepts in cellular immune control of Cytomegalovirus" (Sprecher Lars Dölken) und das Graduiertenkolleg 2581 „Metabolism, topology, and compartmentalization of membrane proximal lipid and signaling components in infection" (Sprecher Jürgen Seibel). Das GRK 2157 3D-Infekt (Sprecher Thomas Rudel) wurde erfolgreich evaluiert und wird für weitere 4,5 Jahre gefördert. Matthias Frosch und Oliver Kurzai initiierten das „Else-Kröner-Fresenius-Center for Advanced Medical & Medical Humanitarian Studies Würzburg-Mwanza/Tansania". Mehrere ZINF Mitglieder sind Teil des neu gegründeten bayerischen Forschungsnetzwerks *bayresq.net* zum Thema „Neue Strategien gegen multiresistente Krankheitserreger mittels digitaler Vernetzung". In ihrem *Rbiotics*-Konsortium entwickeln Jörg Vogel, Franziska Faber und Lars Barquist neue programmierbare RNA-basierte Antibiotika. Ana Rita Brochado und ich werden zusammen mit Christian Müller (München) in unserem *StressRegNet*-Konsortium Hochdurchsatzansätze zur Entschlüsselung von Stress-antworten, die an der Antibiotikaresistenz und Virulenz von Krankheitserregern beteiligt sind, einsetzen.

Mehrere Konferenzen und Symposien wurden von ZINF Mitgliedern organisiert und wir durften viele internationale Wissenschaftler und Gastredner bei unseren Kolloquien und Seminaren begrüßen (S. 132-139). Anfang 2020 verlieh die Fakultät für Biologie die Ehrendoktorwürde an den renommierten Infektionsbiologen und Vakkzinologen Rino Rappuoli (Siena). Professor Peter Fineran (Universität von Otago, Neuseeland) erhielt ein Forschungsstipendium der Alexander von Humboldt Stiftung, um 2019 das HIRI/IMIB zu besuchen und in den Laboren von Chase Beisel und mir an der Regulation von bakteriellen CRISPR-Cas Immunsystemen zu forschen. Wir freuen uns ihn 2021/2022 wieder bei uns begrüßen zu dürfen.

Obwohl die SARS-CoV-2 Pandemie derzeit im Mittelpunkt des Forschungsinteresses steht, bleiben Infektionskrankheiten generell und im Speziellen das Auftreten von antibiotikaresistenten oder neuartigen Krankheitserregern eine enorme soziale und medizinische Herausforderung. Die Bedeutung der Grundlagenforschung wird nicht zuletzt durch den kürzlich an Emmanuelle Charpentier und Jennifer Doudna verliehenen 2020 Chemie-Nobelpreis für die Entwicklung einer auf CRISPR-Cas basierten Genom-Editiermethode unterstrichen. Die Entdeckung der Cas9-"DNA-Schere" im Humanpathogen *Streptococcus pyogenes* verdeutlicht, dass neben der translationalen Forschung die Grundlagenforschung im Bereich der Infektionskrankheiten unerlässlich ist. Das ZINF bietet ein exzellentes, interdisziplinäres Forschungsnetzwerk, um sich diesen Aufgaben zu widmen, und ich freue mich auf die weiteren Aktivitäten des ZINF im Bereich der Infektionsforschung in den nächsten Jahren. Hochdurchsatz- und Einzelzell-Sequenzierung in Kombination mit neuen bildgebenden Verfahren werden neue Einblicke mit noch nie dagewesener Auflösung über komplexe Wirt-Pathogen-Interaktionen liefern. Insbesondere der Einsatz künstlicher Intelligenz wird den Weg zur Analyse und Interpretation großer Datensätze im Kampf gegen Infektionskrankheiten ebnen.

Abschließend möchte ich allen ZINF Mitgliedern für die hervorragende Zusammenarbeit, ihre Beiträge zu diesem Bericht sowie zum Erfolg des ZINF danken. Auch möchte ich der Universität Würzburg und dem Bayerischen Staatsministerium für ihre kontinuierliche Unterstützung des ZINF danken.

CYNTHIA SHARMA
Sprecherin des ZINF

Würzburg, November 2020

1.2 STRUCTURE OF THE ZINF

2018-2019

The ZINF consists of five internal and nine associated institutions spread across the Faculty of Medicine including the University Hospital, the Faculty of Biology, as well as the Faculty of Chemistry and Pharmacy. The Research Center is supported by an international scientific advisory board of leading scientists.

EXECUTIVE COMMITTEE MEMBERS

CYNTHIA SHARMA
Spokesperson (since 2018)
Institute of Molecular Infection Biology
Chair of Molecular Infection Biology II

WOLFGANG KASTENMÜLLER
Institute for Virology and Immunobiology
Chair of Immunology

LARS DÖLKEN
Institute for Virology and Immunobiology
Chair of Virology

OLIVER KURZAI
Institute for Hygiene and Microbiology
Chair of Medical Microbiology & Mycology

HERMANN EINSELE
Department of Internal Medicine II - ZIM
Chair of Internal Medicine II

THOMAS RUDEL
Department of Microbiology, Biocenter
Chair of Microbiology

MATTHIAS FROSCH
Institute for Hygiene and Microbiology
Chair of Hygiene and Microbiology

JÖRG VOGEL
Institute of Molecular Infection Biology
Chair of Molecular Infection Biology I

SCIENTIFIC ADVISORY BOARD MEMBERS

MICHAEL GILMORE
Chair of the SAB (since 2013)
Boston, US

DAVID HOLDEN
(since 2013)
London, GB

KATJA BECKER
(2016 - 2019)
Bonn, DE

ERIC PAMER
(since 2016)
Chicago, US

MELANIE BLOKESCH
(since 2019)
Lausanne, CH

GISELA STORZ
(since 2013)
Bethesda, US

JAY HINTON
(since 2019)
Liverpool, GB

TONE TØNJUM
(since 2013)
Oslo, NO

1.3 EVENTS SURROUNDING THE ZINF

CELEBRATING A QUARTER CENTURY OF THE ZINF

NOVEMBER 14TH, 2018

In 2018, together with the Institute of Molecular Infection Biology (IMIB), the Research Center for Infectious Diseases (ZINF) celebrated its 25th anniversary. The celebrations included a one-day scientific symposium that allowed for exchanges between current and former ZINF members, ZINF scientific advisory board members, friends, colleagues, and alumni of the Young Investigator Program.

With the establishment of the ZINF in 1993 by Professors Volker ter Meulen, Werner Goebel, Jörg Hacker, and colleagues, Würzburg gained a central, cross-faculty scientific institution dedicated to the interdisciplinary research of infectious diseases. 25 years after its foundation, the ZINF counts 50 principal investigators as members.

The anniversary symposium was an opportunity to reflect upon the accomplishments of the ZINF, get to know the research of the current five young investigator group leaders, and discuss the future of molecular infection biology research at both the JMU Würzburg and the international research community. The participants enjoyed the Robert Koch Lecture given by the 2018 Robert Koch Gold Medal Awardee Professor Staffan Normark as well as greetings and scientific presentations by national and international guests. In addition, Dr. Dennis Kopecko and Prof. Dirk Haller gave farewell lectures in honor of Dr. Tobias Ölschläger's retirement from the IMIB.

Former and current speakers of the ZINF (left to right: Jörg Hacker, Jörg Vogel, and Cynthia Sharma).

Dennis Kopecko and Tobias Ölschläger.

Klaus Toyka, Werner Goebel, and Martin Röllinghoff (left to right).

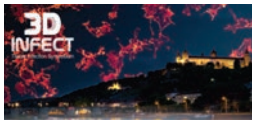
Daniel Lopez, Cynthia Sharma, Tone Tønjum, Marion Schäfer-Blake, Jörg Vogel, Alfred Forchel, and Jörg Hacker (left to right).

3D TISSUE INFECTION SYMPOSIUM

APRIL 5TH - 7TH, 2019

The 3D Tissue Infection Symposium provided a platform to bring together early stage researchers as well as experienced scientists from academia and pharmaceutical industry working on 3D human tissue cultures. The three-day symposium included talks by distinguished national and international speakers as well as talks and poster presentations by the graduate students of the GRK 2157 3D Infect. All participants enjoyed the lively scientific discussions about the advantages of using complex 3D human tissue models to study host-pathogen interactions.

The 3D Tissue Infection Symposium was organized by the PhD students of the DFG-funded GRK 2157. Images: David Kessie and Motaharehsadat Heydarian.



CEREMONY TO THE 80TH BIRTHDAY OF WERNER GOEBEL

OCTOBER 3RD, 2019

Colleagues and friends celebrated the 80th birthday of Professor Werner Goebel, a pioneer in the field of medical microbiology and a co-founder of the ZINF. As the first Chair of Microbiology at the University of Würzburg, he was among the key scientists that initially identified disease-causing factors in bacteria. Professor Goebel is also a passionate and distinguished pianist, who often performes at ceremonial acts at the University of Würzburg.

HONORARY DOCTORATE FOR RINO RAPPUOLI

JANUARY 31ST, 2020

Professor Rino Rappouli from Siena (Italy) is one of the most renowned researchers in infection biology and development of vaccines worldwide. To pay tribute to his extraordinary scientific achievements, he was awarded an Honorary Doctorate degree by the Faculty of Biology at the University of Würzburg in a ceremonial act.

President of the Leopoldina Jörg Hacker, Roy Gross, Dean of Biology Charlotte Förster, Honorary Doctor Awardee Rino Rappouli, University President Alfred Forchel (left to right). Images: Rudi Merkl

2

ZINF YOUNG INVESTIGATORS

SINA BARTFELD - ZINF

ANA RITA BROCHADO - ZINF/BIOCENTER

FRANZISKA FABER - ZINF

SEBASTIAN GEIBEL - ELITE NETWORK BAVARIA

J. CHRISTIAN PÉREZ - ZINF/IZKF

ORGANOIDS AS HOST MODELS

DR. SINA BARTFELD
Research Center for Infectious Diseases

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SELECTED PUBLICATIONS

Kayisoglu O, Weiss F, Niklas C, Pierotti I, Pompaiah M, Wallaschek N, Germer CT, Wiegering A, **Bartfeld S** (2020) *Location-specific cell identity rather than exposure to GI microbiota defines many innate immune signalling cascades in the gut epithelium.*
Gut gutjnl-2019-319919
(Epub ahead of print)

Stanifer ML, Muenchau S, Pervolaraki K, Kanaya T, Mukenhirn M, Albrecht D, Odendall C, Kagan J, **Bartfeld S**, Ohno H, Boulant S (2020) *Asymmetric distribution of TLR3 leads to a polarized immune response in human intestinal epithelial cells.*
Nature Microbiology 5(1):181-191

Wallaschek N, Niklas C, Pompaiah M, Wiegering A, Germer CT, Kricher S, Brändlein S, Maurus K, Rosenwald A, Yan HHN, Leung SY, **Bartfeld S** (2019) *Establishing pure cancer organoid cultures: identification, selection and verification of cancer phenotypes and genotypes.*
Journal of Molecular Biology 431(15): 2884-2893

Bartfeld S (2016) *Modeling infectious diseases and host-microbe interactions in gastrointestinal organoids.*
Developmental Biology 420(2):262–27

RESEARCH INTERESTS

The group studies host-pathogen interactions in the gastrointestinal tract using human stem cell-derived organoids as host models. We are particularly interested in the innate immune response and gastric pathogens, such as *Helicobacter pylori* and Epstein Barr Virus, and their contribution to gastric carcinogenesis.

The gastrointestinal tract is lined by a single-layered epithelium that renews itself every five days. The stem cells required for this constant regeneration reside in the epithelium itself, between the differentiated cells. The pathways that govern gastric stem cell identity and differentiation need to be tightly controlled, because if the delicate balance guarding healthy homeostasis is disturbed, cancer can arise. In the stomach, infections by pathogens, such as the carcinogenic bacterium *H. pylori*, and the resulting inflammation play a central role in cancer development.

In the past decade, advances in the field of stem cell biology have opened new avenues for medical research: a culture system has been developed that allows theoretically endless culture of primary cells from virtually any patient. In this approach, epithelial stem cells are isolated from the respective organ, placed in an extracellular matrix and supplemented with an organ-specific cocktail of growth factors and inhibitors. The stem cells subsequently divide and grow into three-dimensional mini-versions of the organ, from which they have been generated, and are thus called “organoids”. Organoids have been grown from the human small intestine, colon, stomach, and many other organs. For infection biology, organoids are a very promising new model system, because for the first time, the effect of infection on primary cells, including stem cells, can be studied.

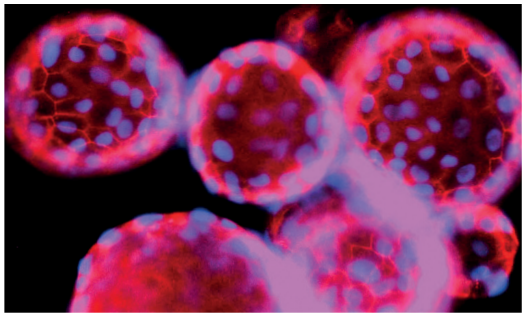

Figure 1: 3D human organoids. Red: Occludin. Blue: Nuclei.
Image by Carolin Niklas.

HIGHLIGHTS & OUTLOOK

We aim to further establish organoids as a standard *in-vitro* model for infection research. Human gastro-intestinal organoids self-organize into 3D cystic structures with a central lumen flanked by a single-layered, polarized epithelium, therefore they closely resemble the *in-vivo* situation. Each organoid harbors stem cells as well as differentiated cells next to each other, ideally organized in specific domains within one organoid, such as an intestinal villus-like domain and an intestinal crypt-like domain. The tissue identity is conserved in the adult stem cells: organoids generated from gastric tissue harbor gastric cell lineages (such as gland mucous cells and pit mucous cells) and organoids generated from intestinal tissue harbor intestinal cell lineages (such as enterocytes and goblet cells). Analyzing a new biobank of 42 organoids of the gastrointestinal tract, we recently found that this

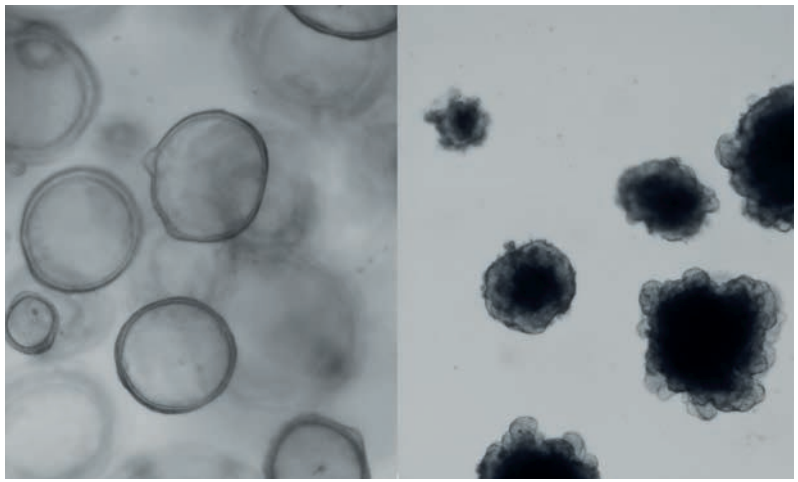

Figure 2: Human gastric organoids generated from healthy tissue (left) or cancer tissue (right).
Image by Nina Wallaschek.

cellular identity also extends to the innate immune signaling cascades of the epithelial cells: gastric cells express very specific and other innate immune receptors than small intestinal cells or cells of the colon. This organization of the innate immune sensors along the cephalocaudal axis is at least in part developmentally programmed in the stem cells, independent of contact to the gastrointestinal flora.

For infection, we use microinjection of bacteria into the organoids or infection of two-dimensional layers of cells grown from organoids. When organoids are infected with *H. pylori*, lineages of the glands mount a strong inflammatory response, while lineages of the pit react only marginally. Currently, it is unclear why specific cell types mount a different response to the infection. In cell lines and 2D layers of cells grown from organoids, the bacterium employs its type IV secretion system to inject not only the bacterial protein CagA, but also a bacterial sugar, D-*glycero*-β-D-*manno*-heptose-1,7-bisphosphate (βHBP). This can trigger the innate immune response in the host cell. An RNAi based genome-wide screen has identified ALPK1 and TIFA as crucial signaling components involved in this activation. NF-κB activation through the ALPK1-TIFA-axis is independent on CagA protein translocation, indicating that CagA translocation and HBP delivery into host cells are distinct features of the infection.

Organoids cannot only be grown from healthy tissue, but also from cancer tissue. The analysis of paired organoids from healthy and tumor tissue from the same patient has demonstrated that the patient-specific organoid’s drug response can be associated with its mutational status. This supports the conclusion that organoids not only faithfully represent the healthy epithelium, but also recapitulate the hallmarks of disease and are useful models for drug development and testing.

We will continue to combine organoid technology with system-wide approaches such as RNA-seq and targeted approaches such as CRISPR-Cas-mediated knockout to better understand host-pathogen interactions. We expect that this will provide new insights into the pathogenic changes in the host cell induced by infection. Also, as organoids can be established from virtually any patient, a comparison of host reactions from a broad range of patient-derived organoids will enable the identification of patient-specific responses and possible risk factors for cancer development. This will hopefully help to delineate the steps in infection-associated carcinogenesis and eventually provide new strategies for therapies.

SYSTEMS BIOLOGY OF ANTIBIOTIC ACTION

DR. ANA RITA BROCHADO

Emmy Noether group leader, Research Center for Infectious Diseases
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SELECTED PUBLICATIONS

Domenech A, **Brochado AR**, Sender V, Hentrich K, Henriques-Normark B, Typas A and Veening JW (2020) *Proton Motive Force Disruptors Block Bacterial Competence and Horizontal Gene Transfer.*
Cell Host & Microbe 27(4):544-555

Brochado AR, Telzerow A, Bobonis J, Banzhaf M, Mateus A, Selkrig J, Huth E, Bassler S, Zamarreño Beas J, Zietek M, Ng N, Foerster S, Ezraty B, Py B, Barras F, Savitski MM, Bork P, Göttig S and Typas A (2018) *Species-specific activity of antibacterial drug combinations.*
Nature 559(7713):259-263

Maier L, Pruteanu M, Kuhn M, Zeller G, Telzerow A, Anderson EE, **Brochado AR**, Fernandez KC, Dose H, Mori H, Patil KR, Bork P, Typas A (2018) *Extensive impact of non-antibiotic drugs on human gut bacteria.*
Nature 555(7698):623-628

AWARDS

DFG Emmy Noether Fellowship for junior group leaders on the topic: *Deciphering molecular mechanisms of bacterial cell death and persistence using antibiotic combination* (2019-2025)

RESEARCH INTERESTS

The discovery of antibiotics during the first half of the 20th century enabled efficient control of otherwise deadly bacterial infections. Since then, several antibiotic classes targeting essential processes in bacteria made it to highly successful clinical applications. Nonetheless, rapid development and widespread antibiotic resistance seriously compromises antibiotic effectiveness, and pan-resistant strains that resist all available antibiotics have been reported in the last few years. Following recent reports by the World Health Organization (WHO), Gram-negative bacteria including numerous Enterobacteriaceae and *Pseudomonas aeruginosa* are of special concern, due to the naturally low permeability of their cell envelope.

Synergistic antibiotic combinations offer an alternative strategy for overcoming the current lack of effective antibiotics in the short-term. However, the molecular mechanisms underlying drug combinations are largely unknown, which impairs rational design of antimicrobial combination therapies, and imposes an exhaustive and laborious testing.

Our group investigates molecular mechanisms of drug combinations across pathogenic Gram-negative bacteria. We focus on the Enterobacteriaceae model organisms *Escherichia coli* and *Salmonella enterica* serovar Typhimurium, as well as on the priority pathogen *P. aeruginosa*. We develop novel high-throughput approaches, and apply them in tandem with reverse genetics and computational biology tools to derive general principles driving drug interactions in bacteria.

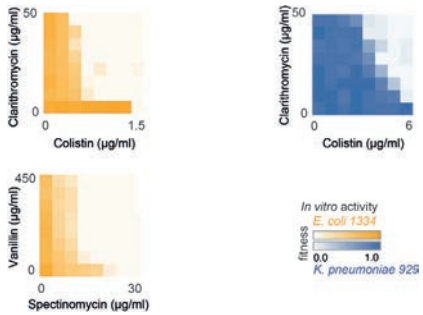

Figure 1: Synergistic drug combinations to overcome antibiotic resistance.
Image from Brochado *et al.*, 2018, Nature.

HIGHLIGHTS & OUTLOOK

Efficient synergistic combinations have been shown to counteract resistance mechanisms and to bypass membrane permeability limitations in Gram-negatives. Drug combinations are synergistic if the combined inhibition effect is stronger than the expected additivity, and antagonistic if it is weaker. In a close analogy to genetic interactions (or epistasis), synergy and antagonism are generally referred to as "drug interactions" and reflect functional interactions between the cellular processes triggered by the individual drugs. This renders drug combinations a prime tool to probe molecular mechanism and cellular complexity, in addition to their explicit clinical potential.

In a pioneer study, I profiled >17,000 drug interactions across three Gram-negative species, including prominent pathogens. One of the most striking findings from this study is that synergy and antagonism are incredibly species-specific, even across closely related species. On one hand this is a surprising observation, since antibiotic targets are typically conserved across bacteria. On the other hand, their species-specificity brings across drug combinations as prime candidates for narrow-spectrum treatments, where the pathogen is primarily targeted and commensals are spared. Which mechanisms explain the observed species-specificity is completely unexplored to date, and is thereby a central topic of the Emmy Noether project that we just started in the lab. We apply comparative reverse genetics approaches using mutant libraries of different pathogens to tackle this question. We focus on deciphering molecular mechanisms of synergistic combinations especially potent against difficult-to-treat pathogens, such as *P. aeruginosa.* Preliminary results point to multi-factorial mechanisms, not only involving the antibiotic target, but also other far less intuitive cellular processes. Progressing molecular work will further elucidate the mechanism of synergy and provide a breakthrough towards designing species-specific treatments.

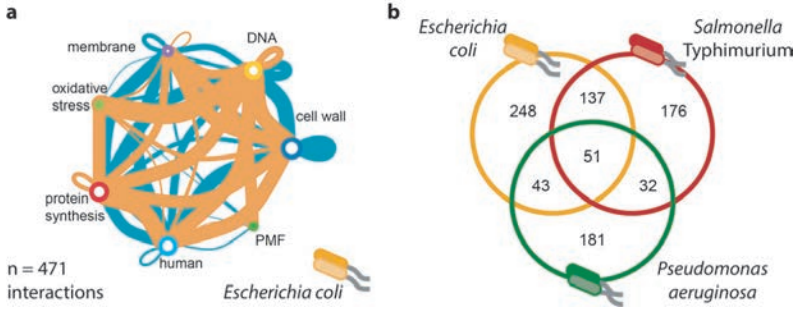

Figure 2: Drug interactions in bacteria: (a) drug interaction network in *E. coli* and (b) species-specificity of drug interactions.
Image from Brochado *et al.*, 2018, Nature.

An intriguing feature of drug interactions is a high prevalence of antagonism over synergy – meaning that bacterial cells can more often effectively make use of one drug to undermine the other rather than the opposite. We have previously shown that, for at least 50% of antagonistic combinations, the effective intracellular antibiotic concentration decreases upon addition of a second compound. Perhaps this is not totally unexpected for Gram-negatives, and it clearly suggests that drug transport could strongly drive the outcome of drug combinations. There are several mechanisms involving classical stress response pathways that bacteria can employ to enable such cross-protection, namely activation of major efflux pumps such as AcrAB-TolC. However, the regulatory triggers for such responses are widely unknown, especially in the context of drug combinations. This topic bridges ongoing and upcoming projects in our lab in a future collaboration with Prof. Dr. Cynthia Sharma (IMIB). In particular, we plan to deploy unique high-throughput technology to decipher key regulatory responses controlling drug activity in different pathogens.

Evidence of complex drug action in bacteria is greatly increasing, especially considering drug action towards bacterial cell death. Nowadays it is widely acknowledged that cell death by antibiotics likely results from multiple factors. Yet, investigating such factors in detail remains very challenging. A major focus of my Emmy Noether project is on deepening our understanding of the mode of action of antibiotic combinations leading to cell death, and large-scale drug combination assays are excellent tools to probe such complex cellular responses. We already started establishing high-throughput methods to test how drug combinations impact bacterial cell death in Gram-negative pathogens. This study will reveal general principles of cell death-based synergy and antagonism, and how they hold across different bacteria.

RNA BIOLOGY OF CLOSTRIDIOIDES DIFFICILE

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SELECTED PUBLICATIONS

Fuchs M, Lamm-Schmidt V, Ponath F, Jenniches L, Barquist L, Vogel J, **Faber F** (2020) *An RNA-centric global view of Clostridioides difficile reveals broad activity of Hfq in a clinically important Gram-positive bacterium.* **bioRxiv** doi: 10.1101/2020.08.10.244764

Faber F, Thiennimitr P, Spiga L, Byndloss MX, Litvak Y, Lawhon S, Andrews-Polymenis HL, Winter SE, Bäumler AJ (2017) *Respiration of microbiota-derived 1,2-propanediol drives Salmonella expansion during colitis.* **PLoS Pathogens** 13(1):e1006129

Faber F, Tran L, Byndloss MX, Lopez CA, Velazquez EM, Kerrinnes T, Nuccio SP, Wangdi T, Fiehn O, Tsolis RM, Bäumler AJ (2016) *Host-mediated sugar oxidation promotes post-antibiotic pathogen expansion.* **Nature** 534(7609):697-699
Selected for Nature Milestones in the Human Microbiota Research

AWARDS

Young Investigator Prize (Förderpreis) of the German Society for Hygiene and Microbiology, DGHM (2018)

RESEARCH INTERESTS

My research group is taking an RNA-centric approach to address riboregulation of gene expression in *Clostridioides difficile* as well as the clinical need for narrow-spectrum antibiotics for the treatment of infections with *C. difficile*. We aim to understand the molecular underpinnings of virulence regulation in *C. difficile* with a strong focus on small regulatory RNAs (sRNAs) and will leverage this knowledge for the development of species-specific RNA-based therapeutics directed against *C. difficile*.

C. difficile is currently the leading cause of antibiotic-associated diarrhea, as infection with *C. difficile* results in asymptomatic colonization in healthy individuals but can lead to widespread and potentially lethal pathologies after antibiotic treatment. Previous research has strongly focused on transcriptional regulation of *C. difficile* sporulation, toxin production, and central energy metabolism. However, the role of riboregulation during *C. difficile* infection is less well understood compared to other enteric pathogens such as *Salmonella*. In addition, *C. difficile* is thus far the only Gram-positive species in which the RNA chaperone Hfq has a large impact on gene expression and bacterial physiology such as sporulation, which is a crucial pathogenic feature of this bacterium enabling transmission between hosts.

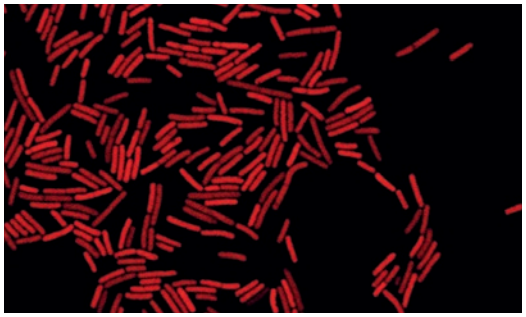

Figure 1: Confocal microscopy image showing *Clostridioides difficile* 630 expressing mCherryOPT (Ransom *et al.*, 2015) under the control of the *cwp2* promoter. Image by Franziska Faber.

HIGHLIGHTS & OUTLOOK

We are identifying sRNA candidates as well as cognate RNA-binding proteins (RBPs) to characterize their role in gene regulation with a focus on virulence pathways. To date, only one RBP, Hfq, has been shown to be functional and not a single sRNA has been mechanistically characterized in *C. difficile*. Utilizing state of the art methods of bacterial RNA biology, we have generated high-resolution RNA maps to define transcriptome architecture and build a global atlas of transcriptional and post-transcriptional control in *C. difficile*. Combined with Hfq pull-down approaches, this has revealed a broad RNA-binding activity for Hfq and led to the identification of potential regulated target genes involved in sporulation. Moreover, to identify functional RNA-protein complexes, we have applied Grad-seq to predict complexes of RNA and protein in *C. difficile*. Our work on *C. difficile* establishes a rich resource for researchers interested in this species, but also for bacterial RNA biology in general as the obtained in-gradient distributions provide also evidence for novel types of Hfq-RNA interactions. In addition, we have identified a novel RNA-binding protein with global RNA-binding activity in *C. difficile.* Current and future projects will investigate the implications of RNA-based regulation for *C. difficile* virulence.

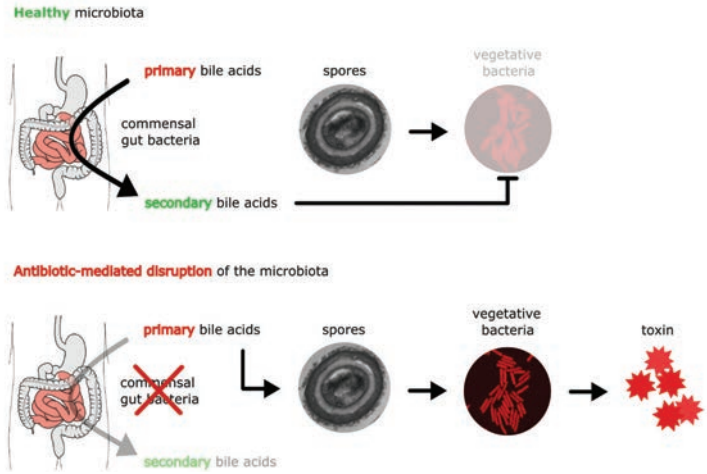

Figure 2: The impact of antibiotic-induced disruption of the microbiota on *C. difficile* gut colonization and pathogenesis.

Infections with *C. difficile* are inherently difficult to treat with conventional broad-spectrum antibiotics because accompanying disruption of the microbiota generates an environment that is permissive for *C. difficile* growth. This poses an urgent need for treatment strategies that are narrow-spectrum or at best specifically targeting *C. difficile*. RNA-based antimicrobials, including peptide nucleic acids (PNAs), are an attractive technology for species-specific antibiotics, because they inhibit essential genes on the RNA level through sequence-specific binding to the targeted mRNA. Proof-of-concept for this approach has already been demonstrated in Gram-negative (*e.g. Escherichia coli*, *Salmonella enterica*) and Gram-positive (*e.g. Listeria monocytogenes*) species. Mechanistic insights from our studies on RNA-based gene regulation will inform the design strategies for PNA candidates. Initial work in our lab has identified a peptide-PNA candidate targeting the essential gene *rpoB* that inhibits *C. difficile* growth and establishes proof-of-concept for this approach. To identify effective and species-specific PNA targets mediating bacterial inhibition, we are collaborating with Lars Barquist (HIRI) and Jörg Vogel (IMIB/HIRI) to investigate the effects of PNAs on multiple pathogenic bacteria and computationally predict optimal target sequences through machine learning approaches.

To investigate regulatory mechanisms governing host-pathogen interactions during infection with *C. difficile*, we aim to employ advanced cell culture models to recreate the human large intestine, a mostly anaerobic environment in which *C. difficile* can thrive. Using a polarized Transwell model of colonic cells under micro-aerobic conditions, we can perform *in-vitro C. difficile* infections over a course of 48 hours allowing the concomitant assessment of bacterial growth, toxin production, and sporulation, as well as associated host responses in a time-resolved manner. We will apply this model to compare host-pathogen interactions of different clinical strains with varying pathogenic potential. Further, in collaboration with the research group of Alexander Westermann (HIRI) and Marco Metzger (Tissue Engineering and Regenerative Medicine, University Hospital and Fraunhofer IGB, Würzburg), we are currently establishing a host model based on human primary cells that aims to recapitulate the *in-vivo* situation. This includes an anaerobic milieu, 3D structures reflecting colonic crypts, and a mucus layer. In the long term, we will investigate infections in the presence of selected members of the microbiota that were shown to impact *C. difficile* gut colonization. Through combination of dual RNA-seq and bacteriological and immunohistological methods, these studies will provide insights into the relevant cellular host processes targeted by the pathogen or the bacterial niche co-inhabitants.

STRUCTURAL BIOLOGY OF MYCOBACTERIA

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SELECTED PUBLICATIONS

Mietrach N, Damián-Aparicio D, Mielich-Süss B, Lopez D, **Geibel S** (2020) *Substrate Interaction with the EssC Coupling Protein of the Type VIIb Secretion System.*
Journal of Bacteriology 202(7): e00646-19

Famelis N, Rivera-Calzada A, Degliesposti G, Wingender M, Mietrach N, Skehel JM, Fernandez-Leiro R, Böttcher B, Schlosser A, Llorca O, **Geibel S** (2019) *Architecture of the mycobacterial type VII secretion system.*
Nature 576(7786):321-325

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Cell 171(6):1354-1367.e20

Mielich-Süss B, Wagner RM, Mietrach N, Hertlein T, Marincola G, Ohlsen K, **Geibel S**, Lopez D (2017) *Flotillin scaffold activity contributes to type VII secretion system assembly in Staphylococcus aureus.*
PLoS Pathogens 13(11):e1006728

RESEARCH INTERESTS

Pathogenic bacteria such as *Mycobacterium tuberculosis* or *Staphylococcus aureus* have evolved sophisticated nanomachines embedded in the bacterial cell envelope to orchestrate the secretion of virulence factors, which play important roles in pathogenesis. The group is interested in understanding the molecular mechanisms of type VII secretion systems (T7SSs) using an interdisciplinary approach combining structural (cryo-EM, X-ray crystallography) with biochemical methods. A better structural and mechanistic understanding of these systems will aid the design of novel antimicrobial strategies targeting mycobacteria, methicillin-resistant *S. aureus* (MRSA), and other pathogens that depend on T7SSs for host infections.

Tuberculosis is a highly infectious disease that is caused by various strains of mycobacteria. According to recent figures from the World Health Organization (WHO), it accounts for 1.5 million deaths every year.

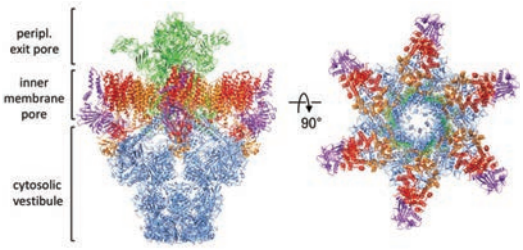

Figure 1: Model of the type VII secretion system. Left: side view of the ESX-3 nanomachine. Right: top view of the central membrane pore; the green periplasmic exit pore was cut away for clarity.

In *M. tuberculosis*, three homologous T7SSs (ESX-1, ESX-3, ESX-5) play central roles in its immune evasion strategy and mediate the uptake of essential nutrients. The group investigates ESX-3, which is essential to pathogen growth in response to iron-limiting conditions suggesting a role for ESX-3 in counteracting host defense mechanisms that restrict iron availability. Moreover, ESX-3 effector proteins have been implicated in mycobacterial evasion of phagocytosis and suppression of T-helper cell activation. The ESX-3 secretion machinery is therefore an attractive new target for antimicrobial strategies against an essential, intrinsic bacterial process involved in metal homeostasis, as well as promoting host clearance by restoring the immune response. However, neither the ESX-3 secretion mechanism nor the mechanism linking the secreted ESX-3 effector proteins to iron import, is currently understood.

In parallel, the group is pursuing the structural and functional investigation of the T7SSb found in pathogenic staphylococci such as the methicillin-resistant strain *S. aureus* USA300 (MRSA). *S. aureus* is the leading cause of bacteremia, endocarditis, osteomyelitis, as well as skin, soft tissue, pulmonary, and device-related infections. Effector proteins secreted by the T7SSb promote bacterial abscess formation and persistent infections in murine infection models. The T7SSb is distantly related to mycobacterial ESX systems through (i) a subset of secreted proteins belonging to the ESX virulence factor family and (ii) a motor ATPase of the FtsK/SpoIIIE ATPase family suggesting that both systems use similar substrate targeting mechanisms. Unlike in diderm mycobacteria, secreted proteins pass a monoderm cell wall in *S. aureus* indicating a different architecture of ESX systems and the

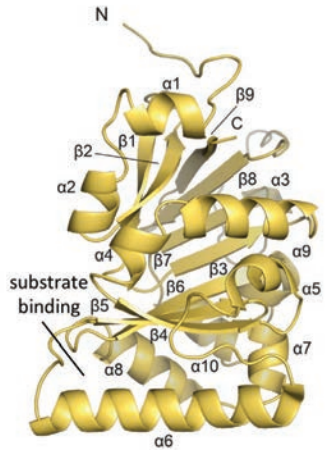

Figure 2: Crystal structure of the T7SSb substrate recognition domain.

T7SSb. To date, substrate recognition and secretion of ESS effector proteins are poorly understood due to the lack of structural information on the membrane embedded secretion machine and its interaction with substrates.

HIGHLIGHTS & OUTLOOK

To gain insights into the mycobacterial T7SS mechanism, the group has reconstituted a stable core complex of the ESX-3 secretion machine that contains four out of five membrane proteins (Figure 1) and determined its three-dimensional structure using single particle cryo-electron microscopy (cryo-EM) taking advantage of the recently established state-of-the-art electron microscopy facility at the University of Würzburg (Rudolf Virchow Center for Experimental Biomedicine).

The cryo-EM structure resolved for the first time all protein components in the ESX-3 complex and provided unprecedented insights into the architecture of mycobacterial type VII secretion machines (Famelis *et al.*, 2019, Nature). Using secretion assays in combination with mutagenesis studies, the group defined structural elements required for transport and derived a general model for the type VII-mediated effector protein transport. The ESX-3 complex spans the inner mycobacterial membrane and translocates effector proteins from the cytoplasm into the periplasmic space, from where further transport across the outer mycobacterial membrane occurs by a yet unknown mechanism. A cytosolic vestibule-like structure constitutes 24 loosely packed ATPase domains, which create the mechanical motion for substrate secretion by cycling through conformational states of ATP binding and ATP hydrolysis.

The investigation of the T7SSb led to the identification and crystallization of an essential extracellular domain of this system (Mietrach *et al.*, 2019, Acta Cryst F). The group is pursuing its structural determination by X-ray crystallography and has also taken first steps towards the reconstitution and structure determination of the membrane embedded secretion machine by cryo-EM (Miehlich-Süss *et al.*, 2017, PLoS Pathog). The group has determined the high-resolution structure of a substrate recognition domain of the T7SSb. A secretion assay as a functional readout of the T7SSb was established and used to characterize essential amino acids in the substrate binding pocket (Figure 2). Furthermore, we discovered a previously unknown second substrate binding site on the T7SSb secretion machine (Mietrach *et al.*, 2020, J Bacteriol). The crystal structure of the substrate recognition domain provides the structural basis for rational drug design/fragment-based screens to block substrate binding to this recognition domain. These compounds could serve as novel non-bactericidal antibiotics that target the T7SSb and thereby restore the host immune response.

REGULATORY NETWORKS IN PATHOGENESIS

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SELECTED PUBLICATIONS

Moreno-Velásquez SD, Tint SH, del Olmo Toledo V, Torsin S, De S, **Pérez JC** (2020) *The regulatory proteins Rtg1/3 govern sphingolipid homeostasis in the human associated yeast Candida albicans.* **Cell Reports** 30(3):620-629

del Olmo Toledo V, Puccinelli R, Fordyce PM, **Pérez JC** (2018) *Diversification of DNA binding specificities enabled SREBP transcription regulators to expand the repertoire of cellular functions that they govern in fungi.* **PLoS Genetics** 14(12):e1007884

Meir J, Hartman E, Eckstein MT, Guiducci E, Kirchner F, Rosenwald A, LeibundGut-Landmann S, **Pérez JC** (2018) *Identification of Candida albicans regulatory genes governing mucosal infection.* **Cellular Microbiology** 20(8):e12841

Böhm L, Torsin S, Tint SH, Eckstein MT, Ludwig T, **Pérez JC** (2017) *The yeast form of the fungus Candida albicans promotes persistence in the gut of gnotobiotic mice.* **PLoS Pathogens** 13(10):e1006699

RESEARCH INTERESTS

The group studies the regulatory circuitry that enables the human commensal and opportunistic fungal pathogen, *Candida albicans*, to colonize different niches in the human body. *C. albicans* serves as a model system to gain insights into the general strategies employed by members of the microbiota to proliferate as harmless commensals and how some of these microbes become life-threatening pathogens.

The human body harbors a large variety of non-bacterial microbes. Research on this non-bacterial flora, however, has lagged behind compared to prokaryotes. Fungi, in particular, remain underrepresented in microbiota studies. This is despite the fact that fungi play major roles in microbial community stability and human disease. Fungi infect billions of people every year and cause diseases that kill millions of individuals creating a burden on society similar to tuberculosis and malaria. Yet, the contribution of fungi to the global burden of disease is largely unrecognized. *C. albicans* is the most prominent fungal species residing in humans. While *C. albicans* can thrive in multiple niches within the human body (*e.g.* mouth, skin, gastrointestinal and genitourinary tracts), it most frequently dwells in the gut. The majority of healthy adults carry *C. albicans* as part of their normal gut microbiota. In addition to being a human commensal, *C. albicans* is a common cause of fastidious mucosal disease in otherwise healthy people. It is also the major cause of life-threatening fungal infections. In European countries, the incidence of invasive candidiasis is around 10 cases per 100,000 inhabitants and 1.09 cases per 1,000 hospital admissions. The mortality associated with these infections approaches 40%, underscoring the need for novel therapeutics to treat and prevent this disease.

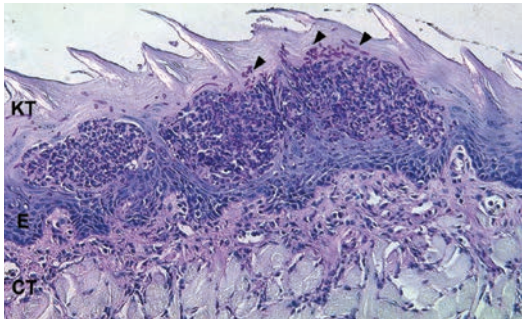

Figure 1: *C. albicans* (black triangles) penetrating mouse oral mucosa.
KT, keratinized tissue; E, epithelium; CT, connective tissue.

HIGHLIGHTS & OUTLOOK

We have looked at the interplay between the fungus *C. albicans* and the oral mucosa. Specifically, we screened a collection of *C. albicans* deletion strains in a mouse model of oral infection. To our knowledge, this is the first report of a genetic screen in an animal model of mucosal candidiasis. Through detailed analyses of the infected mucosae and the host response to wildtype and in one of the identified *Candida* mutants, we revealed a regulatory gene that explicitly governs persistence of the fungus in the oral cavity and fitness during vaginal infections. Our study thus opened the door to the unbiased and systematic discovery of fungal determinants contributing to mucosal disease. We also found that there was a minimal overlap in "hits" between the oral candidiasis screen and comparable screens that we had previously conducted in mouse models of intestinal colonization and disseminated infection. This finding highlights the distinct features of the *C. albicans*-host interplay in the oral cavity.

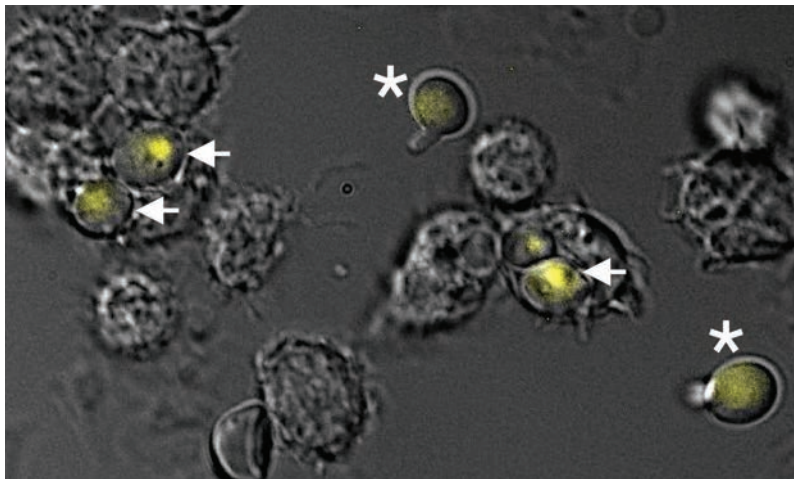

Figure 2: *C. albicans* engulfed by human neutrophils.
YFP reporter localizes to fungal nuclei upon engulfment (arrows). Asterisks denote free fungal cells.

We have also investigated the overall role of two regulatory proteins that *C. albicans* needs to successfully colonize the mammalian host. While these regulators had previously been linked to nitrogen metabolism in model yeasts, we recently reported that in *C. albicans* - a close relative of the model yeast *Saccharomyces cerevisiae* - the regulators' main function is connected to lipid biology. Our study provided the first systematic and quantitative examination of the whole *C. albicans* lipidome. We believe this dataset will become a key resource for researchers interested in lipids and will pave the way for the exploration of this major class of molecules in the context of host-pathogen interactions. Starting with a comprehensive survey of metabolites and lipids, and through extensive characterization of the inner workings of the regulators in *C. albicans*, we discovered a mechanism whereby sphingolipid homeostasis is linked to nutrient sensing in this organism. This work implicates sphingolipids, a class of molecules that is starting to receive a lot of attention in cell and molecular biology, in *C. albicans* pathogenesis.

Finally, we have examined a group of transcription regulators that had expanded in the lineage giving rise to *C. albicans*. While in most eukaryotes this family of regulators governs lipid biosynthesis, the three copies in *C. albicans* have acquired different functions, some of which contribute to the ability of *C. albicans* to reside in the human host and cause disease. We found that, despite a conserved overall structure, several members of the family exhibited substantially different DNA-binding specificities: some proteins bound non-palindromic DNA sequences whereas others bound a palindromic motif. Ancestral protein reconstruction experiments indicated that the likely family ancestor could bind both the non-palindromic as well as the palindromic DNA sequence. The different DNA-binding specificities observed in extant members of the family reflect, therefore, the partition of the ancestor's DNA-binding profile rather than the acquisition of a novel trait. This study provides a singular example of the origins of fungal transcription factors associated with the regulation of pathogenesis traits.

We are incorporating high resolution fluorescence microscopy to our studies of uncharacterized *C. albicans* transcription regulators. A major focus now is the gut of gnotobiotic mice, which we co-colonize with the fungus, individual gut bacteria, and defined microbial communities. We expect that these studies reveal novel aspects of the biology of *C. albicans* in the mammalian intestine.

3

MEMBERS OF THE ZINF

INSTITUTE OF MOLECULAR INFECTION BIOLOGY

INSTITUTE FOR HYGIENE AND MICROBIOLOGY

INSTITUTE FOR VIROLOGY AND IMMUNOBIOLOGY,
DEPARTMENT OF VIROLOGY

INSTITUTE FOR VIROLOGY AND IMMUNOBIOLOGY,
DEPARTMENT OF IMMUNOLOGY

DEPARTMENT OF MICROBIOLOGY,
THEODOR BOVERI INSTITUTE, BIOCENTER

DEPARTMENT OF INTERNAL MEDICINE II

INSTITUTE OF SYSTEMS IMMUNOLOGY

HELMHOLTZ INSTITUTE FOR
RNA-BASED INFECTION RESEARCH

ZINF MEMBERS ASSOCIATED WITH OTHER INSTITUTES

Image: University of Würzburg

3.1
INSTITUTE OF MOLECULAR INFECTION BIOLOGY

JÖRG VOGEL

CYNTHIA SHARMA

HEIDRUN MOLL

JOACHIM MORSCHHÄUSER

KNUT OHLSEN

ALEXANDER WESTERMANN

WILMA ZIEBUHR

The Institute of Molecular Infection Biology (IMIB) was founded in 1993 together with the Research Center for Infectious Diseases (ZINF) and is an interdisciplinary research institution within the Medical Faculty of the University of Würzburg, with strong ties to the Faculty of Biology. Prof. Dr. Jörg Vogel has been the director of IMIB and Chair of Molecular Infection Biology since 2009. In 2017, Prof. Dr. Cynthia Sharma was appointed as Chair of the newly established Department of Molecular Infection Biology II.

Members of the Institute investigate fundamental biological processes and molecular mechanisms, with a focus on pathogens and infectious diseases. Research at the IMIB involves the study of bacteria, viruses, parasites, and fungi, as well as their eukaryotic hosts and the interaction with the microbiome. Research activities range from prokaryotic and eukaryotic cell biology and immunology to fundamental aspects of gene regulation and RNA biology, as well as the development of novel 3D infection models. Furthermore, the Institute is home to the groups of the prestigious ZINF Young Investigator program.

RNA BIOLOGY

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SELECTED PUBLICATIONS

Imdahl F, Vafadarnejad E, Homberger C, Saliba AE, **Vogel J** (2020) *Single-cell RNA-seq reports growth condition-specific global transcriptomes of individual bacteria.*
Nature Microbiology 5(10):1202-1206

Stapels DAC, Hill PWS, Westermann AJ, Fisher RA, Thurston TL, Saliba AE, Blommestein I, **Vogel J**, Helaine S (2018) *Salmonella persisters undermine host immune defenses during antibiotic treatment.*
Science 362(6419):1156-1160

Saliba AE, Li L, Westermann AJ, Appenzeller S, Stapels DAC, Schulte LN, Helaine S, **Vogel J** (2017) *Single cell RNA-seq ties macrophage polarization to growth rate of intracellular Salmonella.*
Nature Microbiology 2:16206

AWARDS

Feldberg Prize – Feldberg Foundation for Anglo-German scientific exchange (2019)

RESEARCH INTERESTS

Non-coding RNAs play important regulatory roles in all domains of life. The group aims to understand the role of ncRNAs and RNA-binding proteins (RBPs) in the context of bacterial infections, with the goal to use this knowledge for targeted manipulation of the human microbiota. The current four main areas of research in the Vogel lab are: i) discovery of novel functional RNAs in microbes, which includes work on the cancer-associated bug *Fusobacterium nucleatum*; ii) characterization of and screens for bacterial RNA-binding proteins; iii) new RNA-seq methods for infection biology, including single-cell RNA-seq of eukaryotic and bacterial cells; iv) antisense oligonucleotide (ASO)-based antibiotics for precision editing of the human microbiome and complex microbial communities.

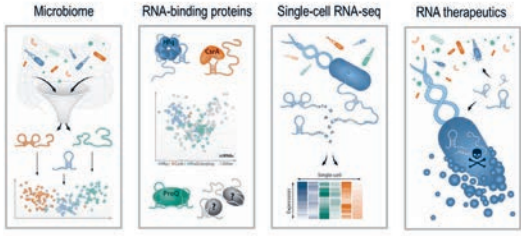
HIGHLIGHTS & OUTLOOK

Highlights of functional RNA studies were the successful characterization in *Salmonella* of new 3' end-derived small regulatory RNAs, *e.g.*, SdhX and NarS. These studies bolstered our previous findings that 3'UTRs of mRNAs constitute a rich source of regulatory small RNAs; similar sRNAs are now being reported in many different bacterial species. We also made much progress on the characterization of new RBPs, with a focus on ProQ and FinO domain proteins. Using a UV CLIP-seq approach in *Salmonella*, we provided evidence that ProQ is truly a global RBP that appears to recognize its many cellular RNA targets by a structural code (rather than primary sequence) that remains to be cracked. In addition, we defined pathways including virulence control in which ProQ-mediated gene regulation plays an important role.

RNA-seq remains a core technology in the lab. A clear highlight in the 2018-2019 period was our joint publication in *Science* with Sophie Helaine, in which we used our previously developed dual RNA-seq technology to study intracellular persister forms of *Salmonella*. Contrary to expectation, we found that these seemingly "dormant" bacteria maintain metabolism and secrete virulence factors to actively manipulate their host cells.

On new RNA-centric technologies for infection biology, we are now working hard to make single-cell RNA-seq a standard technique for the analysis of microbes.

On the applied side, we have started a new program on "programmable antibiotics" in the form of RNA-directed ASOs. Our goal is to make ASOs truly species-specific. To this end, we are putting together an interdisciplinary program, integrating diverse expertise from RNA biology, microbiology, immunology, single-cell biology, and pharmacy.



The four main areas of research in the Vogel lab.

DEEP SEQUENCING APPROACHES TO PATHOGENESIS

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SELECTED PUBLICATIONS

Eisenbart SK*, Alzheimer M*, Pernitzsch SR, Dietrich S, Stahl S, **Sharma CM** (2020) *A repeat-associated small RNA controls the major virulence factors of Helicobacter pylori.*
Molecular Cell in press, doi: 10.1016/j.molcel.2020.09.009

Alzheimer M, Svensson SL, König F, Schweinlin M, Metzger M, Walles H, **Sharma CM** (2020) *A three-dimensional intestinal tissue model reveals factors and small regulatory RNAs important for colonization with Campylobacter jejuni.*
PLoS Pathogens 16(2):e1008304

Dugar G, Leenay RT, Eisenbart SK, Bischler T, Aul BU, Beisel CL#, **Sharma CM#** (2018) *CRISPR RNA-dependent binding and cleavage of endogenous RNAs by the Campylobacter jejuni Cas9.*
Molecular Cell 69(5):893-905.e7
(DGHM Paper of the Month Award)

Dugar G, Svensson SL, Bischler T, Wäldchen S, Reinhardt R, Sauer M, **Sharma CM** (2016) *The CsrA-FliW network controls polar localization of the dual-function flagellin mRNA in Campylobacter jejuni.*
Nature Communications 7:11667

RESEARCH INTERESTS

Our research focuses on mechanisms of gene regulation in the gastric pathogen *Helicobacter pylori* and the related foodborne pathogen *Campylobacter jejuni*. We are especially interested in post-transcriptional regulation during stress response and virulence by small regulatory RNAs (sRNAs) and associated RNA-binding proteins (RBPs). We have been employing diverse deep sequencing approaches for global transcriptome and translatome analysis as well as to study RNA-protein complexes and have also been developing new approaches to globally capture RBPs. Using three-dimensional (3D) infection models based on tissue engineering, we are investigating the roles of sRNAs and RBPs in virulence of these widespread human pathogens.

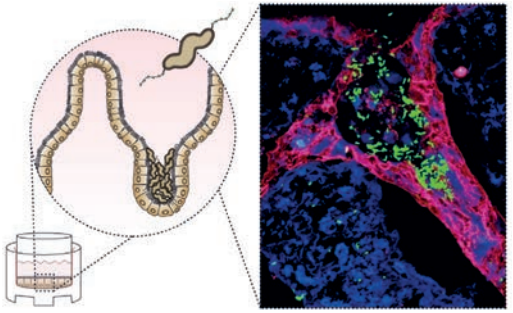
HIGHLIGHTS & OUTLOOK

Using genomics, biochemical, molecular biology, and genetics approaches, we are elucidating the roles and molecular mechanisms of sRNAs and RBPs of *H. pylori* and *C. jejuni*. Besides new mechanisms of riboregulation, we have identified several virulence-associated sRNAs, such as *H. pylori* sRNAs that can impact pathogenesis by controlling chemotaxis or LPS biogenesis genes, or even act as central regulators of major virulence factors.

Using our 3D intestinal tissue model, we have demonstrated a role in colonization for a *C. jejuni* sRNA, which represses a gene involved in flagellin modification. Based on Tn-seq and dual RNA-seq applied during infection of the 3D model, we have been identifying additional factors important for host-pathogen interactions.

Using co-IP combined with RNA-seq (RIP-seq) in *C. jejuni*, we have identified many flagellar mRNAs bound to the RBP CsrA, which, together with its protein antagonist FliW, regulates localization of the flagellin mRNA to the cell poles. While CRISPR-Cas9 nucleases are well known to cleave DNA, RIP-seq of *C. jejuni* Cas9 revealed that it can bind and cleave endogenous RNAs in a crRNA-guided manner. We also showed that RNA targeting by CjCas9 is programmable *in vitro*, thereby providing new technological opportunities. We are now further studying the potential impact of Cas9 on endogenous gene regulation.

Using ribosome profiling we have been analyzing bacterial translatomes and have identified many new small proteins of ≤100 aa in *C. jejuni* and *H. pylori*, which we are now characterizing. For example, we have uncovered a small protein essential for motility, which is crucial for virulence of *C. jejuni*. Overall, a better understanding of the underlying molecular mechanisms of virulence gene regulation and stress response will provide new targets for antimicrobial strategies.



Schematic and confocal image of *C. jejuni* accumulating in the crypt of a tissue-engineered 3D intestinal infection model. Nuclei (blue), adherens junctions (magenta), *C. jejuni* (green). Alzheimer *et al*., 2020.

INFECTION IMMUNOLOGY

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SELECTED PUBLICATIONS

Firdessa R, Good L, Amstalden MC, Chindera K, Kamaruzzaman NF, Schultheis M, Röger B, Hecht N, Oelschlaeger TA, Meinel L, Lühmann T, **Moll H** (2015) *Pathogen- and host-directed antileishmanial effects mediated by polyhexanide (PHMB).* **PLoS Neglected Tropical Diseases** 9(10):e0004041

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Schwarz T, Remer KA, Nahrendorf W, Masic A, Siewe L, Müller W, Roers A, **Moll H** (2013) *T Cell-Derived IL-10 Determines Leishmaniasis Disease Outcome and Is Suppressed by a Dendritic Cell Based Vaccine.* **PLoS Pathogens** 9(6):e1003476

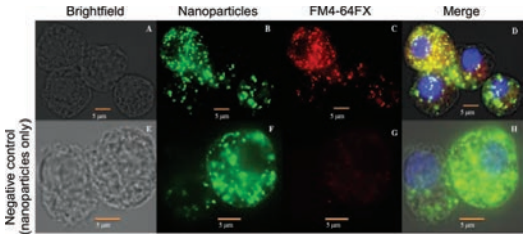
RESEARCH INTERESTS

Leishmaniasis is a neglected tropical disease with more than 1.3 million new cases and 30,000 deaths per year worldwide. Climate change allows the sand fly and the parasite to spread from the South, where the disease is already endemic, to more northern regions. Unsatisfactory anti-leishmanial treatment options stress the importance of developing inexpensive, effective, and rapid therapies against leishmaniasis.

HIGHLIGHTS & OUTLOOK

We have shown that successful parasitism requires *Leishmania* to survive and proliferate in their host cells, predominantly macrophages and dendritic cells (DC), and we understand that this ultimately blocks the production of the Th1-inducing cytokine IL-12. Both CD8+ and CD4+ T cell populations contain antigen-experienced cells that do not respond to antigen but also do not undergo apoptosis. Hence, T-cell exhaustion during leishmaniasis may have considerable negative impact on the efficacy of vaccination and the chemotherapeutic strategies. Our collaboration partners have demonstrated an exhausted T-cell status mediated by significantly elevated surface expression of co-inhibitory molecules (PD-1/PD-L1) in patients with chronic leishmaniasis. Blockade of the PD-1 ligand thus may promote the rescue of CD4+ and CD8+ T cell functions and induced the clearance of parasites. Ethical issues make the direct study of lesional lymphocyte function in patients challenging, therefore we propose studies with check-point inhibitors in the murine infection model.

Standard of care therapies (miltefosine, amphotericin B, antimonies) in use against leishmaniasis lead to a similar curative outcome independent of their mechanisms of drug action, and the data of a platinum-derivative used to cure mice from leishmaniasis indicated a strong partition of the immune system. This compares to chemotherapy of tumors, where selected therapeutics (cyclophosphamide, doxorubicin, oxaliplatin, mitoxantrone, patupilone) elicit immunogenic cell death, a tumor-specific CD8-driven immune response associated with the induction of DC, Calreticulin, HSP90, and a release of ATP and HMGB1. We suggest to establish immunogenic cell death (ICD)-enhancing strategies in combination with new *Leishmania*-targeted drugs. Inhibitors of the parasite proteins CK1.2, HSP90/HSP83 may have a better therapeutic window compared to today's repositioned old cancer drugs and in addition to an ICD-enhancing strategy may support long lasting anti-parasite immunity.



Fluorescence microscopy images of BMDMs after 30 minutes of incubation with 20 nm nanoparticles (green) showing co-localization with the endosomal marker FM4-64FX (red).

MYCOLOGY

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SELECTED PUBLICATIONS

Mayr EM*, Ramírez-Zavala B* , Krüger I, **Morschhäuser J** (2020) *A Zinc Cluster Transcription Factor Contributes to the Intrinsic Fluconazole Resistance of Candida auris.* **mSphere** 5(2):e00279-20

Mottola A, **Morschhäuser J** (2019) *An intragenic recombination event generates a Snf4-independent form of the essential protein kinase Snf1 in Candida albicans.* **mSphere** 4(3):e00352-19

Popp C, Ramírez-Zavala B, Schwanfelder S, Krüger I, **Morschhäuser J** (2019) *Evolution of fluconazole-resistant Candida albicans strains by drug-induced mating competence and parasexual recombination.* **mBio** 10(1):e02740-1

(DGHM Paper of the Month Award)

Ramírez-Zavala B, Manz H, Englert F, Rogers PD, **Morschhäuser J** (2018) *A hyperactive form of the zinc cluster transcription factor Stb5 causes YOR1 overexpression and beauvericin resistance in Candida albicans.* **Antimicrobial Agents and Chemotherapy** 62(12):e01655-18

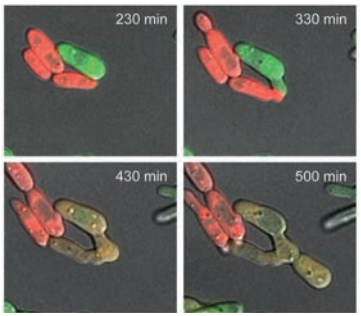
RESEARCH INTERESTS

The yeast *Candida albicans* is a harmless commensal in most healthy people, but it can also cause mucosal as well as life-threatening systemic infections. Our group studies the regulation of virulence traits, the role of metabolic adaptation in pathogenicity, and the evolution of drug resistance in *C. albicans* to better understand how this important fungal pathogen adapts to different niches and altered environmental conditions during colonization and infection.

HIGHLIGHTS & OUTLOOK

C. albicans can develop resistance to the antimycotic drug fluconazole, which inhibits ergosterol biosynthesis and is widely used to treat fungal infections. Besides mutations in the drug target enzyme, activating mutations in transcription factors that result in the constitutive overexpression of genes encoding ergosterol biosynthesis enzymes and multidrug efflux pumps are a frequent cause of resistance. Highly resistant clinical isolates usually contain a combination of these resistance mechanisms and are homozygous for the mutated alleles, which further increases drug resistance. To understand how such strains evolve, we used a set of isogenic strains that were heterozygous for different fluconazole resistance mutations and thus displayed moderately increased drug resistance. When these strains were propagated in the presence of fluconazole, they rapidly evolved further increased resistance by loss of heterozygosity for the mutated alleles. This was often accompanied by homozygosity at the mating type locus (*MTL*), which allowed the cells to switch to the mating-competent opaque morphology. Opaque cells with different resistance mutations mated with each other to produce tetraploid cells that contained genetic material from both parents. The mating products reassorted their merged genomes and, under selective pressure by the drug, generated progeny cells that retained the advantageous mutated alleles while returning to the diploid state. Therefore, fluconazole treatment not only selects for resistance mutations but also promotes genomic alterations that confer mating competence, which allows the cells to exchange individually acquired resistance mechanisms and generate highly drug-resistant progeny.

We are currently using libraries of activated transcription factors and protein kinase deletion mutants, which are central components of signaling pathways, to study the regulatory networks controlling morphogenesis, metabolic adaptation, and other virulence traits of *C. albicans*.



Mating of *C. albicans* cells with different fluconazole resistance mutations (labeled green and red), generating recombinant progeny cells (yellow).

GRAM-POSITIVE COCCI

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SELECTED PUBLICATIONS

Fan SH, Ebner P, Reichert S, Hertlein T, Zabel S, Lankapalli AK, Nieselt K, **Ohlsen K**, Götz F (2019) *MpsAB is important for Staphylococcus aureus virulence and growth at atmospheric CO_2 levels.*
Nature Communications 10(1):3627

Hilgeroth A, Yasrebi K, Suzen S, Hertlein T, **Ohlsen K**, Lalk M (2019) *Antibacterial Evaluation of Novel Substituted Cycloheptaindoles in Staphylococcus & Enterococcus Strains.*
Medical Chemistry 15(8):833-83

Seethaler M, Hertlein T, Wecklein B, Ymeraj A, **Ohlsen K**, Lalk M, Hilgeroth A (2019) *Novel Small-molecule Antibacterials against Gram-positive Pathogens of Staphylococcus and Enterococcus Species.*
Antibiotics 8(4):210

Jarick M, Bertsche U, Stahl M, Schultz D, Methling K, Lalk M, Stigloher C, Steger M, Schlosser A, **Ohlsen K** (2018) *The serine/threonine kinase Stk and the phosphatase Stp regulate cell wall synthesis in Staphylococcus aureus.*
Scientific Reports 8(1):1369

RESEARCH INTERESTS

Gram-positive pathogens are the leading cause of hospital-acquired infections. Our main research interest is the development of novel strategies against multiresistant staphylococci and enterococci and application of *in-vivo* models to study virulence mechanisms and efficacy of novel antibacterials. In particular, we have a track record in animal models, evaluation of antibacterials, determining the mode of action of antibacterial compounds, and the molecular biology of *Staphylococcus aureus*. Current projects particularly focus on novel targets for antibiotics, regulation of resistance and virulence, and gene expression analysis during infection.

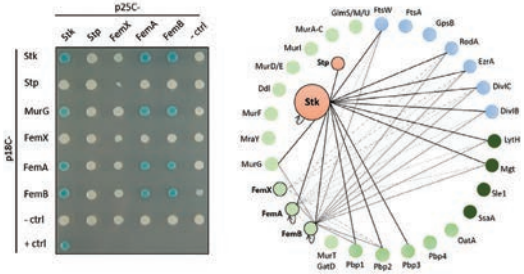
HIGHLIGHTS & OUTLOOK

Recently, we developed, together with cooperation partners, novel antibacterial compounds targeting bacterial pyruvate kinase for clinical application by comprehensive structure-activity relationship analysis of novel trisindolyl cycloalkanes. First lead compounds could be identified with promising activities similar to used antibiotics of last resort *in vitro*.

We are also interested in the regulation of cellular functions by eukaryotic-like serine/threonine kinases and phosphatases. To understand the cellular role of these enzymes, designated Stk and Stp, in *S. aureus* we have elucidated the interaction partners of Stk and Stp and defined their function in cell wall biosynthesis. We have found that post-translational modifications of cell wall synthesizing enzymes are important to ensure the efficiency and accuracy of the cell wall synthesis machinery in *S. aureus* (see Figure).

Carbon dioxide (CO_2) has a growth promoting effect in various bacteria, including *S. aureus*. We characterized the role of the inorganic carbon transporter MpsA *in vivo*. In a pneumonia model, bacteria lacking MpsA had a reduced chance to survive in the lung but not in other organs such as kidneys or liver. This suggests that MpsA is essential for *S. aureus* to establish an infection of the lung at higher CO_2 levels.

In the future, we are interested in analyzing expression of bacterial and host genes during *S. aureus* infections by applying dual RNA-seq methodology. In addition, we are investigating the regulation of resistance against bisquaternary bisnaphthalimides by a small RNA. Finally, we have started to use humanized mice to study the role of human specific virulence mechanisms of *S. aureus* in a mouse model.



Interaction network of Ser/Thr kinase Stk and phosphatase Stp based on the analysis of bacterial two-hybrid studies.

HOST-PATHOGEN-MICROBIOTA INTERACTIONS

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SELECTED PUBLICATIONS

Ryan D, Jenniches L, Reichardt S, Barquist L, **Westermann AJ** (2020) *A high-resolution transcriptome map identifies small RNA regulation of metabolism in the gut microbe Bacteroides thetaiotaomicron.*
Nature Communications 11(1):3557

Stapels DAC, Hill PWS, **Westermann AJ**, Fisher R, Thurston TL, Saliba A-E, Blommestein I, Vogel J, Helaine S (2018) *Salmonella persisters undermine host immune defences during antibiotic treatment.*
Science 362(6419):1156-1160

Westermann AJ, Förstner KU, Amman F, Barquist L, Chao Y, Schulte LN, Müller L, Reinhardt R, Stadler PF, Vogel J (2016) *Dual RNA-seq unveils noncoding RNA functions in Salmonella-host interplay.*
Nature 529(7587):496-501

AWARDS

Short-Term Fellowship Award by the European Molecular Biology Organization (EMBO, 2018)

RESEARCH INTERESTS

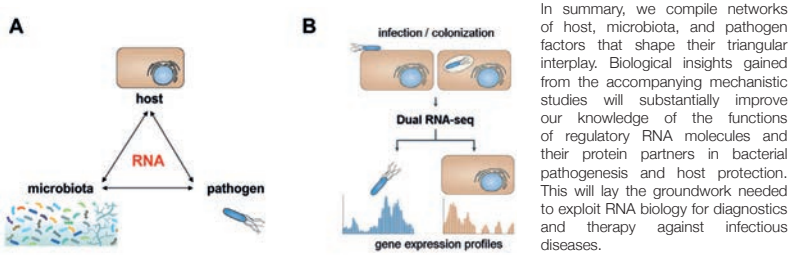
Bacterial infections of mammalian hosts are arguably highly complex biological processes. How do enteric bacterial pathogens promote infection and what defense mechanisms do they have to overcome in order to colonize the gut? What molecular mechanisms manifest the protective role of the intestinal microbiota against pathogenic attack? And what is the role of non-coding RNAs and RNA-binding proteins in these interactions? These and related questions are addressed in our group. Using cutting-edge RNA-seq-based techniques in combination with mechanistic studies, our research centers on the identification and functional characterization of RNA-mediated processes during bacterial colonization of the human gut.

HIGHLIGHTS & OUTLOOK

Pathogenic bacteria do not interact with their host in isolation, but in the presence of the protective bacteria collectively referred to as the microbiota. Thus, to combat infections we may not necessarily have to inhibit the pathogen directly, but we may instead foster competing commensals. By advancing multi-organism RNA-seq approaches (*e.g.* metatranscriptomics, dual and triple RNA-seq), we analyze the dynamic interplay of the host and its microbiota with invading pathogens.

The anaerobic *Bacteroides thetaiotaomicron* represents one of the most prevalent members of the gut microbiota and emerged as the model bacterium for functional microbiota research. By compiling a high-resolution transcriptome annotation for this microbiota member ('ThetaBase': https://bacteroides.helmholtz-hzi.de/), we recently identified hundreds of novel non-coding RNAs. In the absence of homologs for known global RNA-binding proteins such as Hfq or ProQ, we investigate the mechanistic aspects of sRNA activity in *Bacteroides*. Combining multiplexed CRISPR-based sRNA knockdown with advanced three-dimensional primary models of the human colon, we aim at identifying sRNAs employed by *B. thetaiotaomicron* to colonize its host niche and protect it against enteric pathogens.

In summary, we compile networks of host, microbiota, and pathogen factors that shape their triangular interplay. Biological insights gained from the accompanying mechanistic studies will substantially improve our knowledge of the functions of regulatory RNA molecules and their protein partners in bacterial pathogenesis and host protection. This will lay the groundwork needed to exploit RNA biology for diagnostics and therapy against infectious diseases.



An RNA-centric view of host-pathogen-commensal interactions. RNA-mediated processes shape host-microbe interactions (A) and can be studied by dual RNA-seq (B).

NOSOCOMIAL INFECTIONS BY STAPHYLOCOCCI

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SELECTED PUBLICATIONS

Schoenfelder SMK, Lange C, Prakash SA, Marincola G, Lerch MF, Wencker FDR, Förstner KU, Sharma CM, **Ziebuhr W** (2019) *The small non-coding RNA RsaE influences extracellular matrix composition in Staphylococcus epidermidis biofilm communities.* **PLoS Pathogens** 15(3):e1007618

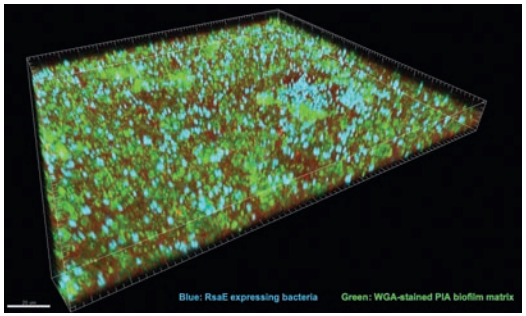
Lerch MF, Schoenfelder SMK, Marincola G, Wencker FDR, Eckart M, Förstner KU, Sharma CM, Thormann KM, Kucklick M, Engelmann S, **Ziebuhr W** (2019) *A non-coding RNA from the intercellular adhesion (ica) locus of Staphylococcus epidermidis controls polysaccharide intercellular adhesion (PIA)-mediated biofilm formation.* **Molecular Microbiology** 111(6):1571-1591

Marincola G, Wencker FDR, **Ziebuhr W** (2019) *The Many Facets of the Small Non-coding RNA RsaE (RoxS) in Metabolic Niche Adaptation of Gram-Positive Bacteria.* **Journal of Molecular Biology** 431(23): 4684-4698

Heilmann C, **Ziebuhr W**, Becker K (2019) *Are coagulase-negative staphylococci virulent?* **Clinical Microbiology and Infection** 2(9):1071-1080

RESEARCH INTERESTS

Our work aims at understanding the lifestyle of staphylococci as major opportunistic and nosocomial pathogens. Current projects focus on RNA-mediated regulation of virulence (*i.e.* biofilm formation) and metabolism in these Gram-positive bacteria. Regarding the latter, we intensively study control of *de novo* methionine biosynthesis by T-box riboswitches. We also have a long-standing interest in staphylococcal antibiotic resistance (ABR). Here, we are engaged in One Health aspects of staphylococcal epidemiology by analyzing ABR profiles of staphylococci from industrialised animal husbandry in Germany. Recently, we extended these analyses, in a joint project with colleagues from South Africa, Kenya, and Egypt, to various geographic regions in Africa. Finally, we support colleagues from chemistry and pharmacy in their efforts to identify novel lead compounds with anti-staphylococcal growth as well as biofilm activity.



CLSM image of RsaE expression in a *S. epidermidis* biofilm (cyan; P_{rsaE}-*cfp* reporter fusion). PIA matrix is stained with WGA-AlexaFluor488® (green).

HIGHLIGHTS & OUTLOOK

Life in biofilms is widespread in nature and is also a typical hallmark of nosocomial staphylococci. Biofilms functionally resemble multicellular organisms in terms of heterogeneous gene expression patterns. In a changing environment, heterogeneity is likely to facilitate persistence and survival of the population as a whole, but may also support division of labor within biofilms. Recently, we identified in *Staphylococcus epidermidis* a species-specific sRNA (*i.e.* IcaZ), which is indispensable for polysaccharide intercellular adhesin (PIA)-mediated biofilm formation in this organism. Also, we studied RsaE (synonym RoxS), which is a highly conserved sRNA in bacteria of the Bacillales order. We found that RsaE is heterogeneously expressed in *S. epidermidis* biofilms, where it influences extracellular biofilm matrix composition. RsaE seems to represent a potent riboregulator of central carbon metabolism and energy balance with many molecular RsaE/RoxS functions and targets being shared across Gram-positive species. These findings assign RsaE/RoxS a prominent role in the adaptation of Gram-positive bacteria to environments with varying nutrient availabilities.

Our future work will focus on the molecular details of IcaZ and RsaE functions in staphylococcal biofilms, including their role in metabolic niche diversification and programmed bacterial lysis. Moreover, we will validate T-box riboswitches as novel antibacterial targets by using RNA-mediated methionine biosynthesis control in staphylococci as a tool and proof of principle.

Image: Hilde Merkert

3.2
INSTITUTE FOR HYGIENE AND MICROBIOLOGY

MATTHIAS FROSCH

OLIVER KURZAI

KLAUS BREHM

CHRISTOPH SCHOEN

ALEXANDRA SCHUBERT-UNKMEIR

ULRICH VOGEL

The Institute for Hygiene and Microbiology (IHM) is part of the Medical Faculty at the University of Würzburg and subdivided into two departments. The Department of Hygiene and Microbiology is headed by Prof. Dr. Matthias Frosch since 1996. Prof. Dr. Oliver Kurzai was appointed as head of the newly established Department of Medical Microbiology and Mycology at the IHM in 2017.

The IHM provides diagnostics for infectious diseases caused by bacteria, viruses, fungi, and parasites, and advises clinicians on the treatment and prevention of these diseases. Research activities within the IHM focus on the molecular mechanisms involved in the pathogenesis of various infectious diseases. The Institute leads the European Centre for Disease Control and Prevention (ECDC) program "Coordination of activities for laboratory surveillance of Invasive Bacterial Diseases IBD-labnet". This program is dedicated to monitoring invasive infections caused by *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* throughout Europe.

The IHM also hosts the National Reference Laboratories for meningococci and *Haemophilus influenzae* (NRZMHI) and the Consiliary Laboratory for echinococcosis. In addition, the Chair of Medical Microbiology and Mycology at the IHM heads the National Reference Center for Invasive Fungal Infections (NRZMyk) located at the Hans Knöll Institute in Jena.

MOLECULAR SURVEILLANCE OF INVASIVE BACTERIAL INFECTIONS

PROF. MATTHIAS FROSCH

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SELECTED PUBLICATIONS

Moremi N, Claus H, Rutta L, **Frosch M**, Vogel U, Mshana SE (2018) *High carriage rate of extended-spectrum beta-lactamase-producing Enterobacteriaceae among patients admitted for surgery in Tanzanian hospitals with a low rate of endogenous surgical site infections.*
Journal of Hospital Infection 100(1): 47-53

Frosch M (2018) *Significance of the doctorate in scientific medical education.*
Bundesgesundheitsblatt für Gesundheitsforschung & Gesundheitsschutz 61(2):141-147

Klughammer J, Dittrich M, Blom J, Mitesser V, Vogel U, **Frosch M**, Goesmann A, Müller T, Schoen C (2017) *Comparative Genome Sequencing Reveals Within-Host Genetic Changes in Neisseria meningitidis during Invasive Disease.*
PLoS One 12(1):e0169892

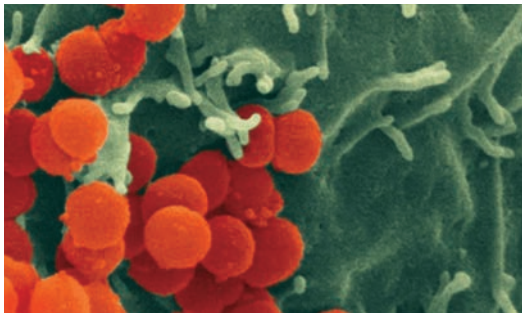
Lam TT, Claus H, **Frosch M**, Vogel U (2016) *Analysis of non-typeable Haemophilus influenzae in invasive disease reveals lack of the capsule locus.*
Clinical Microbiology and Infection 22(1):63.e7-8

RESEARCH INTERESTS

The diversity of bacterial isolates within a species is the focus of research activities at the Department of Hygiene and Microbiology. There is increasing evidence that this diversity of pathogenic bacteria is key to understanding the complex interplay between pathogen and host and the correlations between certain bacterial finetypes and the clinical presentation, progression and outcome of infectious diseases. *Neisseria meningitidis*, the meningococcus, is a paradigm of a commensal and pathogenic bacterium, many variants of which colonize the human nasopharynx. However, only a relatively small number of these variants, known as hypervirulent and hyperinvasive types, are associated with severe invasive and often lethal disease. Several groups at the Institute for Hygiene and Microbiology (IHM) focus on deciphering the basis for virulence, analyzing the complex interaction of commensal and virulent meningococci with the human host and developing tools for their identification and typing. The reports of the ZINF members Ulrich Vogel, Alexandra Schubert-Unkmeir, and Christoph Schoen, working at the IHM, illustrate these research projects in more detail.

HIGHLIGHTS & OUTLOOK

Transnational collaborations between European Reference laboratories for meningococci, *Haemophilus influenzae*, and *Streptococcus pneumoniae* have been further promoted on behalf of the ECDC (European Centre for Disease Prevention and Control). Within this framework, a laboratory network (IBD-labnet) comprised of all Reference Laboratories on *Neisseria meningitidis*, *Haemophilus influenzae*, and *Streptococcus pneumoniae* in the EU Member States is coordinated by the IHM and aims to harmonize laboratory surveillance of invasive bacterial diseases. The goal is to improve laboratory capacities to accurately characterize these invasive bacterial isolates. To fulfill this task, the IHM assists the participating National Reference Laboratories to continuously improve laboratory performance with respect to the identification and characterization of *Neisseria meningitidis*, *Haemophilus influenzae*, and *Streptococcus pneumoniae*, as well as the implementation of new techniques for routine diagnosis and typing. In this regard, the IHM is supporting the ECDC's strategy and roadmap for the integration of molecular typing into laboratory surveillance. Special emphasis lies on the establishment of standards and surveillance systems enabling the EU wide use of whole genome sequencing as the method of choice for typing of meningococcal bacteria.



Microvilli formation induced in human brain endothelial cells upon contact with *Neisseria meningitidis*.

MEDICAL MICROBIOLOGY AND MYCOLOGY

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SELECTED PUBLICATIONS

von Lilienfeld-Toal M, Wagener J, Einsele H, Cornely OA, **Kurzai O** (2019) *Invasive Fungal Infection.*
Deutsches Ärzteblatt International 116(16):271-278

Wagner L, Stielow JB, de Hoog GS, Bensch K, Schwartze VU, Voigt K, Alastruey-Izquierdo A, **Kurzai O**, Walther G (2019) *A new species concept for the clinically relevant Mucor circinelloides complex.*
Persoonia doi: 10.3767/persoonia.2020.44.03

Geißel B, Loiko V, Klugherz I, Zhu Z, Wagener N, **Kurzai O**, van den Hondel CAMJJ, Wagener J (2018) *Azole-induced cell wall carbohydrate patches kill Aspergillus fumigatus.*
Nature Communications 9(1):3098

AWARDS

Main Research Award of the German Society for Hygiene and Microbiology, DGHM (2020)

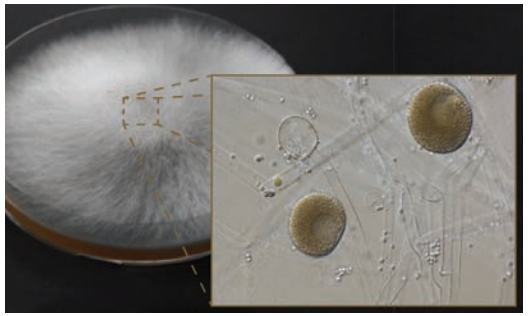
RESEARCH INTERESTS

Invasive fungal infections in Europe are mainly caused by yeasts in the genus *Candida* and filamentous *Aspergillus* species. They primarily affect a growing number of immunocompromised patients and are associated with high mortality. Clinical management of fungal diseases is complex due to a growing variety of fungal pathogens that include rare and new species and the development of antifungal drug resistance in some established pathogenic fungi. We investigate the interaction between fungal pathogens and the human host to elucidate virulence traits as well as relevant effector patterns in the host immune response. Within the National Reference Center for Invasive Fungal Infections (NRZMyk), we directly apply our findings and expertise through diagnostic tests and consiliary advice in clinical settings.

HIGHLIGHTS & OUTLOOK

Candida spp. are a major cause of bloodstream infections. Using a human whole blood infection model, we study host-pathogen interactions during candidemia. Bioinformatic modeling allows us to determine rates of fungal killing by different immune cell populations as well as immune escape of *C. albicans*. Resolving the taxonomy of pathogenic fungi is important to understand the evolution of virulence. We revisited the taxonomy of the clinically relevant *Mucor circinelloides* complex using molecular and phenotypic traits. This resulted in the description of 14 discrete species, including five novel taxa. Importantly, these species showed clear differences in their antifungal susceptibility profiles.

Whereas susceptibility profiles of *Mucor* spp. are largely determined by primary resistance, azole resistance in *Aspergillus fumigatus* is an acquired phenotype. We could show that azoles initially act fungistatically on *A. fumigatus*. This is mechanistically separate from their succeeding fungicidal effect, which is triggered by synthesis of cell wall carbohydrate patches that penetrate the plasma membrane and kill the fungus. Our insights into resistance mechanisms and fungal taxonomy are applied to patient care in the NRZMyk, hosted at the Hans-Knöll-Institute in Jena (Head Prof. Dr. Oliver Kurzai).



The *Mucor circinelloides* complex consists of 14 discrete species.

HELMINTH INFECTIONS

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SELECTED PUBLICATIONS

Pérez MG, Spiliotis M, Rego N, Macchiaroli N, Kamenetzky L, Holroyd N,Cucher M, **Brehm K***, Rosenzvit MC* (2019) *Deciphering the role of miR-71 in Echinococcus multilocularis early development in vitro.*
PLoS Neglected Tropical Diseases 13:e0007932

Herz M and **Brehm K** (2019) *Evidence for densovirus integrations into tapeworm genomes.*
Parasites & Vectors 12(1):560

Förster S, Koziol U, Schäfer T, Duvoisin R, Cailliau K, Vanderstraete M, Dissous C, **Brehm K** (2019) *The role of fibroblast growth factor signalling in Echinococcus multilocularis development and host-parasite interaction.*
PLoS Neglected Tropical Diseases 13(3):e0006959

Montagne J, Preza M, Castillo E, **Brehm K**, Koziol U (2019) *Divergent Axin and GSK-3 paralogs in the beta-catenin destruction complexes of tapeworms.*
Development Genes and Evolution 229(4):89-102

RESEARCH INTERESTS

Parasitic flatworms (cestodes and trematodes) are a major cause of human disease worldwide. The group investigates host-parasite interaction mechanisms and parasite development using the cestode model system *Echinococcus multilocularis*. The metacestode larval stage of this tapeworm causes the lethal disease alveolar echinococcosis (AE) through extensive cancer-like growth within the host liver, accompanied by suppression of the host immune system. AE treatment causes enormous problems since only few cases are amenable to surgical treatment and the majority of patients have to undergo life-long chemotherapy. The group previously showed that parasite growth is decisively driven by totipotent somatic stem cells, and the proliferation dynamics of this cell population is at the focus of our research interests. The group also extensively studies parasite genomics/transcriptomics and engages in the development of forward genetic methodology for flatworm parasites. Finally, immune-modulatory activities of the *Echinococcus* metacestode stage and the development of novel chemotherapeutics against the disease are investigated.

HIGHLIGHTS & OUTLOOK

The group has developed numerous tools for studying molecular host-parasite interactions and parasite development, including *in-vitro* cultivation systems for *Echinococcus* larvae and stem cells. Furthermore, the group completed a whole genome/transcriptome sequencing project for *E. multilocularis*. Recently, the group discovered molecular developmental mechanisms explaining cancer-like growth behavior of the *E. multilocularis* metacestode, which is achieved by modulation of the anterior-posterior body axis of the invading larvae. This is (1) controlled by parasite Wnt signaling, but (2) also modified by host hormones and cytokines such as insulin, FGF, and EGF. Very recently, the group established that the parasite stem cell population is inherently resistant to currently used chemotherapeutics (*e.g.* benzimidazoles) and that secreted parasite cytokines of the TGF-b family actively induce immunosuppressive T-cells during an infection. These data explain, for the first time, why current AE chemotherapy is parasitostatic only, and how immunosuppression of the host is achieved.

Ongoing studies focus on the establishment of transgene techniques in the parasite (*e.g.* by CRISPR/Cas9), on the influence of the host immune response on body axis modification in parasite larvae, and on the development of novel chemotherapeutics targeting the parasite's kinome.

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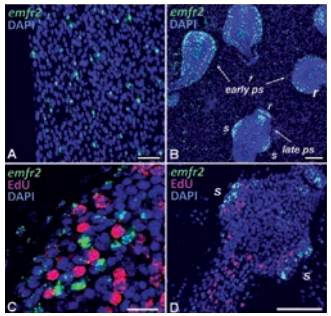

Whole mount *in situ* hybridization analysis of *E. multilocularis* FGF receptor (Emfr2) expression in metacestode vesicles (A) with developing protoscoleces (B,C) and mature protoscolex (D).

MOLECULAR DIAGNOSTICS AND FUNCTIONAL GENOMICS OF HUMAN PATHOGENIC BACTERIA

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SELECTED PUBLICATIONS

Heidrich N, Hagmann A, Bauriedl S, Vogel J, **Schoen C** (2019) *The CRISPR/Cas system in Neisseria meningitidis affects bacterial adhesion to human nasopharyngeal epithelial cells.*
RNA Biology 16(4):390-396

Liese JG, **Schoen C**, van der Linden M, Lehmann L, Goettler D, Keller S, Maier A, Segerer F, Rose MA, Streng A (2019) *Changes in the incidence and bacterial aetiology of paediatric parapneumonic pleural effusions/empyema in Germany, 2010-2017: a nationwide surveillance study.*
Clinical Microbiology and Infection 25(7):857-864

Heidrich N, Bauriedl AS, Barquist L, Li L, **Schoen C***, Vogel J* (2017) *The primary transcriptome of Neisseria meningitidis and its interaction with the RNA chaperone Hfq.*
Nucleic Acids Research 45(10):6147-67

Harrison, O. B., **Schoen C**, Retchless AC, Wang X, Jolley KA, Bray JE, Maiden MCJ (2017) *Neisseria genomics: current status and future perspectives.*
Pathogens and Diseases 75(6):ftx060

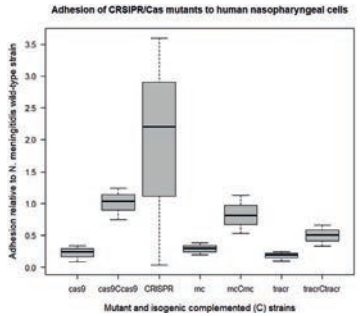
RESEARCH INTERESTS

The application of molecular techniques enables the rapid detection of pathogenic microorganisms and provides a better understanding of the genetic basis of their pathogenicity. Accordingly, as an academic diagnostic laboratory, we provide molecular diagnostic services in numerous collaborative research projects with scientific as well as clinical partners within the ZINF and beyond. We further use genomics and transcriptomics to understand the genomic basis for commensal and invasive behavior in human-adapted pathogens.

HIGHLIGHTS & OUTLOOK

Parapneumonic pleural effusions/empyema (PPE/PE) are severe complications of community-acquired pneumonia. In collaboration with the Department of Pediatrics, University Hospital of Würzburg, we investigated the bacterial etiology and incidence of pediatric PPE/PE in Germany after the introduction of universal pneumococcal conjugate vaccine (PCV) immunization for infants. In 488 of the 1,447 children with PPE/PE (34%) 541 bacteria (>40 species) were detected by 16S rDNA-PCR and/or conventional culture, most frequently *Streptococcus pneumoniae* (41%), *Streptococcus pyogenes* (19%), and *Staphylococcus aureus*. Incidence of *S. pneumoniae* PPE/PE decreased from 3.5 (95%CI 2.5-4.6) per million children in 2010/11 to 1.5 (95%CI 0.9-2.4) in 2013/14 (p 0.002), followed by a re-increase to 2.2 (95%CI 1.5-3.2) by 2016/17 (p 0.205). These data show that cases of pediatric PPE/PE were still caused mainly by *S. pneumoniae* despite widespread PCV immunization and, increasingly, also by *S. pyogenes*.

Neisseria meningitidis is a prime example of another human-adapted commensal pathogen, which is the leading cause of sepsis and epidemic meningitis worldwide. In a previous genome-wide study, we found an association of its type II-C CRISPR/Cas system with carriage and thus, less invasive lineages. We further showed that *cas9* deletion strains are impaired in the adhesion to human nasopharyngeal cells, which constitutes a central step in the pathogenesis of invasive meningococcal disease. Transcriptome sequencing and RIP-seq analyses performed in close collaboration with the group of Prof. Dr. Jörg Vogel (IMIB/HIRI) further showed that meningococcal Cas9 does not directly bind to or affect the expression of surface adhesins but rather exerts its effect on cell adhesion in an indirect manner. Consequently, these findings provide first evidence that the meningococcal CRISPR/Cas system exerts novel functions beyond its established role in defense against foreign DNA.



Deletion of Cas9, RNase III (*rnc*), and tracrRNA, but not of CRISPR-RNAs impairs adhesion to human nasopharyngeal cells *in vitro* (Heidrich *et al.*, 2019, Methods in Molecular Biology 1969:33-49).

HOST-PATHOGEN INTERACTIONS

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SELECTED PUBLICATIONS

Martins Gomes SF, Westermann AJ, Sauerwein T, Hertlein T, Förstner KU, Ohlsen K, Metzger M, Shusta EV, Kim BJ, Appelt-Menzel A, **Schubert-Unkmeir A** (2019) *Induced Pluripotent Stem Cell-Derived Brain Endothelial Cells as a Cellular Model to Study Neisseria meningitidis Infection.* **Frontiers in Microbiology** 10:1181

Peters S, Schlegel J, Becam J, Avota E, Sauer M, **Schubert-Unkmeir A** (2019) *Neisseria meningitidis Type IV Pili Trigger Ca^{2+}-Dependent Lysosomal Trafficking of the Acid Sphingomyelinase To Enhance Surface Ceramide Levels.* **Infection and Immunity** 87(8):e00410-19

Schlegel J, Peters S, Doose S, **Schubert-Unkmeir A**, Sauer M (2019) *Super-Resolution Microscopy Reveals Local Accumulation of Plasma Membrane Gangliosides at Neisseria meningitidis Invasion Sites.* **Frontiers in Cell and Developmental Biology** 7:194

Burgert A, Schlegel J, Becam J, Doose S, Bieberich E, **Schubert-Unkmeir A**, Sauer M (2017) *Characterization of Plasma Membrane Ceramides by Super-Resolution Microscopy.* **Angewandte Chemie International Edition** 56(22):6131-6135

RESEARCH INTERESTS

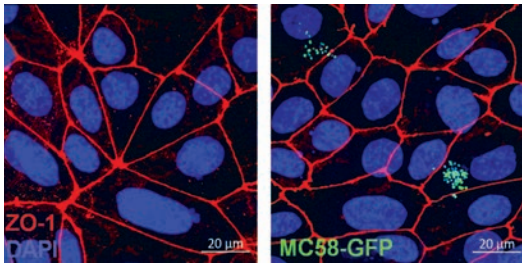
The group is interested in understanding the strategies used by *Neisseria meningitidis* to colonize the brain vasculature and to cross the blood-cerebrospinal fluid barrier (B-CSFB). To reveal these strategies, we use tissue culture-based cell models including brain endothelial cells (BECs) and a wide spectrum of innovative molecular, biochemical, and cell biological methods.

Preliminary data from our group have revealed that *N. meningitidis* is capable of activating the enzyme acid sphingomyelinase (ASM) in BECs to modulate ASM-generated ceramide levels in the membrane of ECs. Ceramide molecules associate into large-membrane platforms (CRPs), which serve as platforms for the concentration of signaling components, their assembly into higher-order complexes, and the transmission of signals across the plasma membrane.

HIGHLIGHTS & OUTLOOK

Based on our initial observation, we have begun an in-depth analysis of the role of the ASM-ceramide system and involved signaling pathways. During the last two years, we have shown that the interaction of the type IV pili of *N. meningitidis* with BECs contributes to a transient activation of ASM followed by ceramide release in BECs. By using *d*STORM (with Prof. Dr. M. Sauer, Biocenter Würzburg), we showed that exposure of pilus-enriched fractions to BECs increased the overall number of CRPs with a size of 80 nm in the plasma membrane. Within the newly funded GRK 2581, we aim to analyze the role of sphingosine 1 phosphate (S1P) and S1P1-2 during the inflammatory response and the modulation of barrier permeability and integrity.

We have also initiated a study to implement iPSC-derived BECs as a novel cellular model for *N. meningitidis* infection in close collaboration with Dr. A. Appelt-Menzel/PD Dr. M. Metzger (LS TERM Würzburg) within the GRK 2157. BECs were differentiated from iPSCs according to previously described methods. *N. meningitidis* was found to directly disrupt the TJ proteins ZO-1, Occludin, and Claudin-5. In accordance with TJ loss, a sharp loss in TEER, and an increase in NaF permeability could be shown. Notably, bacterial transmigration correlated with junctional disruption. In addition, RNA-Seq data analyses of infected iPSC-BECs were established (with Jun. Prof. Dr. A. Westermann, IMIB/HIRI) providing expression data of *N. meningitidis*-responsive host genes. In the future, we will develop a multicellular *in-vitro* model of the B-CSFB and implement co-culture models of human primary meningeal cells and BECs as well as an *in-vitro* circulatory 2D *N. meningitidis*-BEC interaction model.



Confocal microscopy images of iPSC-BECs seeded onto ibidi slides infected with GFP-expressing *Neisseria meningitidis* strain MC58. Image from Martins Gomes *et al.*, 2019, Frontiers in Microbiology.

INFECTION EPIDEMIOLOGY OF NEISSERIA MENINGITIDIS AND HOSPITAL INFECTION CONTROL

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SELECTED PUBLICATIONS

Krone M, Lâm TT, Claus H, **Vogel U** (2020) *Recurrent invasive meningococcal infections - quantifying the risk, Germany, 2002 to 2018.* **Eurosurveillance** 25

Krone M, Lâm TT, **Vogel U**, Claus H (2020) *Susceptibility of invasive Neisseria meningitidis strains isolated in Germany to azithromycin, an alternative agent for post-exposure prophylaxis.* **Journal of Antimicrobial Chemotherapy** 75(4):984-987

Krone M, *et al.*, **Vogel U**, Borrow R (2019) *Increase of invasive meningococcal serogroup W disease in Europe, 2013 to 2017.* **Eurosurveillance** 24

Moremi N, Claus H, Rutta L, Frosch M, **Vogel U**, Mshana SE (2018) *High carriage rate of extended-spectrum beta-lactamase-producing Enterobacteriaceae among patients admitted for surgery in Tanzanian hospitals with a low rate of endogenous surgical site infections.* **Journal of Hospital Infection** 100(1):47-53

RESEARCH INTERESTS

Neisseria meningitidis as well as *Haemophilus influenzae* are commensal pathogens of the human host. The group conducts infection epidemiology projects within the framework of the National Reference Laboratory for meningococci and *Haemophilus influenzae* (NRZMHi).

The infection control team of the University Hospital in Würzburg led by Prof. Ulrich Vogel is involved in infection control projects.

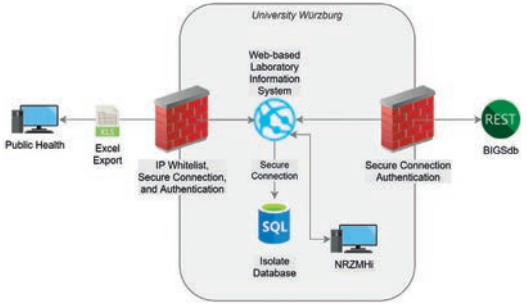
HIGHLIGHTS & OUTLOOK

In collaboration with various partners, the National Reference Laboratory for meningococci and *H. influenzae* published work on various aspects of diagnostics, spread of invasive isolates, vaccines, and carriage.

Hospital infection control projects focused on surveillance in Tanzania in collaboration with Nyambura Moremi. The infection control laboratory contributed to a paper on the impact of sterilization on bioink components in collaboration with the Chair for Drug Formulation and Delivery.

The reference laboratory since 2019 types all strains by genome-based methods in collaboration with the Core Unit Systems Medicine. Cluster algorithms will be refined by reevaluating previously described outbreaks. A new database released by our group will be further developed. It will support data exchange with the ECDC (Stockholm) and the PubMLST database (Oxford).

The infection control team will focus its scientific activity on the management of COVID-19 in hospitals, utilizing data accumulated during the first wave of the pandemic. Manuscripts are currently in preparation on patient admission screening and outbreak control in a nursing home.



Structure of the meningococcal laboratory surveillance database at the reference laboratory for meningococci. Image by Markus Reinhardt.

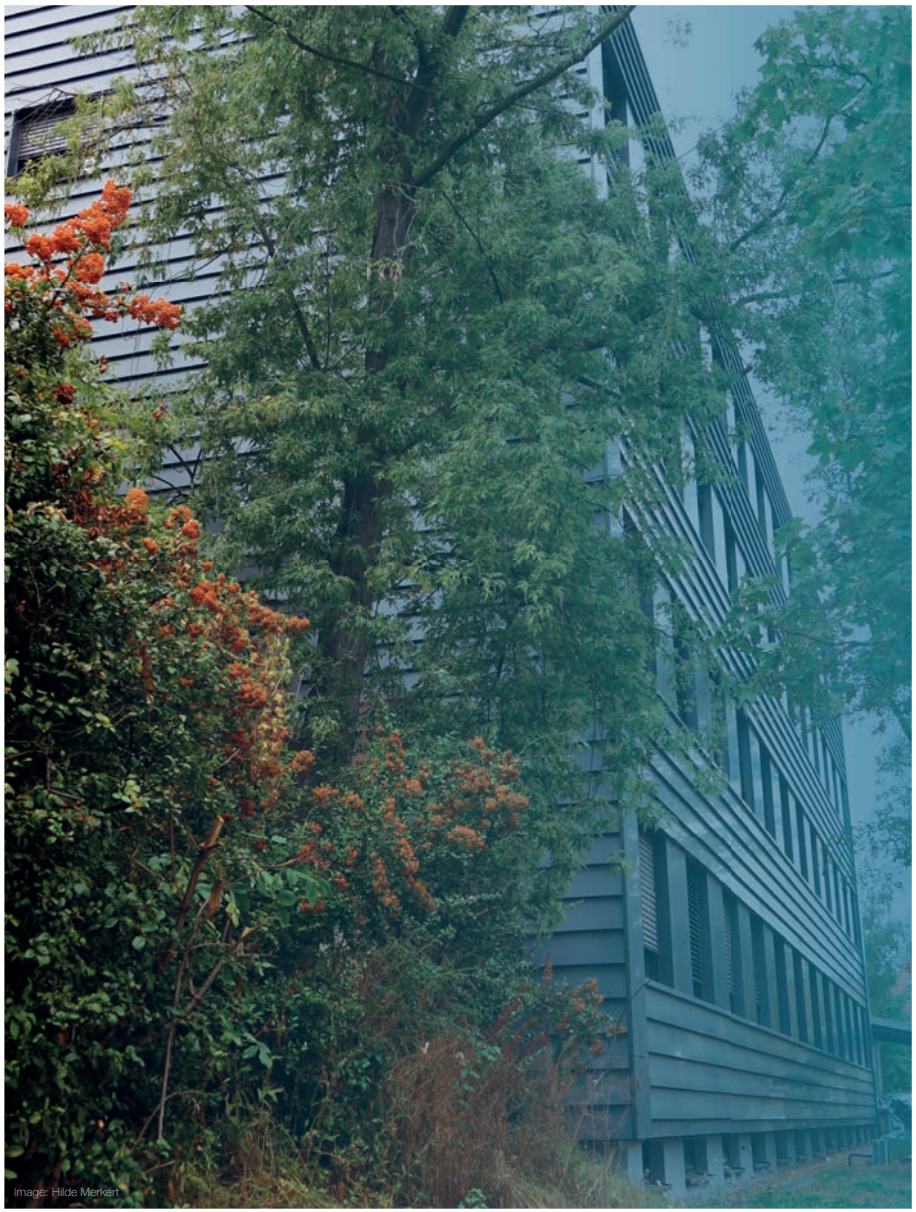


Image: Hilde Merkert

3.3
INSTITUTE FOR VIROLOGY AND IMMUNOBIOLOGY – DEPARTMENT OF VIROLOGY

LARS DÖLKEN

FLORIAN ERHARD

JÜRGEN SCHNEIDER-SCHAULIES

SIBYLLE SCHNEIDER-SCHAULIES

The Institute for Virology and Immunobiology is part of the Medical Faculty at the University of Würzburg. Prof. Dr. Lars Dölken has held the Chair of Virology since 2015.

Virology-focused research at the Institute centers on analyzing the regulatory principles involved in viral replication and gene expression. In addition, researchers are investigating the pathogenesis of several viruses and are elucidating the molecular basis for the occurrence of resistance to antiviral compounds. Research is also being conducted into the development of viral vectors to be used for gene therapy. The Institute also provides virus diagnostics to the University Clinics.

SYSTEMS BIOLOGY OF HERPESVIRUS INFECTIONS

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SELECTED PUBLICATIONS

Whisnant AW, Jürges CS, Hennig T, Wyler E, Prusty B, Rutkowski AJ, L'hernault A, Djakovic L, Göbel M, Döring K, Menegatti J, Antrobus R, Matheson NJ, Künzig FWH, Mastrobuoni G, Bielow C, Kempa S, Liang C, Dandekar T, Zimmer R, Landthaler M, Grässer F, Lehner PJ, Friedel CC, Erhard F*, **Dölken L*** (2020) *Integrative functional genomics decodes herpes simplex virus 1.*
Nature Communications 11(1):2038

Erhard F, Baptista MAP, Krammer T, Hennig T, Lange M, Arampatzi P, Jürges CS, Theis FJ, Saliba AE, **Dölken L** (2019) *scSLAM-seq reveals core features of transcription dynamics in single cells.*
Nature 571(7765):419-423.

Erhard F, Halenius A, Zimmermann C, L'Hernault A, Kowalewski DJ, Weekes MP, Stevanovic S, Zimmer R, **Dölken L** (2018) *Improved Ribo-seq enables identification of cryptic translation events.*
Nature Methods 15(5):363-366

Baptista MAP, **Dölken L** (2018) *RNA dynamics revealed by metabolic RNA labeling and biochemical nucleoside conversions.*
Nature Methods 15(3):171-172

RESEARCH INTERESTS

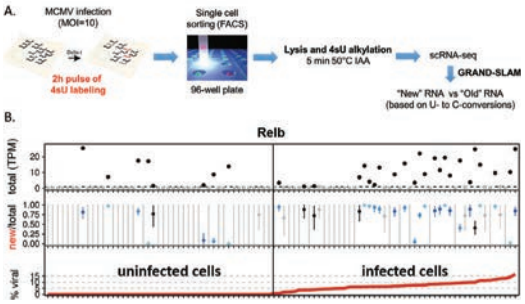
Herpesviruses cause a broad spectrum of diseases ranging from the common cold sore to cancer. Our group employs systems biology approaches combined with virus reverse genetics systems to study viral host cell modulation and immune evasion. Herpes simplex virus 1 (HSV-1) is the causative agent of common cold sores but is also responsible for life-threatening encephalitis. During productive infection, HSV-1 installs a profound shut-off of host gene expression. Our group studies the underlying molecular mechanisms. A second focus is on cytomegaloviruses (CMV). Human CMV (HCMV) is an important pathogen in immunosuppressed patients and responsible for congenital infections in about 1 of 1,000 newborns. The murine CMV (MCMV) animal model recapitulates many features of CMV biology. Our group studies the function and immunological role of non-canonical CMV gene products including upstream open reading frames (uORFs) and microRNAs.

HIGHLIGHTS & OUTLOOK

Using an integrative multiomics approach, we identified hundreds of novel viral transcripts and ORFs of HSV-1, HCMV, and MCMV. Many of these represent so-called short ORFs (sORFs). Large-scale validation of cellular sORFs was achieved by MHC-I ligandome analyses. This revealed that sORFs encode a novel class of stress-responsive antigens, which represent poor substrates for cross-presentation due to their inherent instability but are nevertheless efficiently presented via MHC-I. In the frame of our DFG-funded research unit FOR 2830, we aim to elucidate the functional role of CMV uORFs in immunological control and viral evasion thereof.

Recently, we made the surprising observation that HSV-1 triggers widespread disruption of transcription termination of cellular but not viral genes. In collaboration with Yongsheng Shi from Irvine, USA, we found that the viral master regulator ICP27 both disrupts cellular and rescues viral transcription termination by interacting with the cellular CPSF complex.

In collaboration with Florian Erhard (Institute for Virology and Immunobiology) and Emmanuel Saliba (Helmholtz Institute for RNA-based Infection Research), we developed single cell SLAM-seq (scSLAM-seq). Employing metabolic RNA labeling and chemical nucleotide conversions, this enables the differentiation of newly transcribed RNA from pre-existing RNA in individual cells thereby recording transcriptional activity for thousands of genes. scSLAM-seq provides a temporal dimension to single cell expression profiles and enables dose-response analysis at single cell level.



(A) Workflow of scSLAM-seq. (B) Example of MCMV-induced gene expression.

COMPUTATIONAL SYSTEMS VIROLOGY

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SELECTED PUBLICATIONS

Whisnant AW, Jürges CS, Hennig T, Wyler E, Prusty B, Rutkowski AJ, L'hernault A, Djakovic L, Göbel M, Döring K, Menegatti J, Antrobus R, Matheson NJ, Künzig FWH, Mastrobuoni G, Bielow C, Kempa S, Liang C, Dandekar T, Zimmer R, Landthaler M, Grässer F, Lehner PJ, Friedel CC, **Erhard F***, Dölken L* (2020) *Integrative functional genomics decodes herpes simplex virus 1.*
Nature Communications 11(1):2038

Erhard F, Baptista MAP, Krammer T, Hennig T, Lange M, Arampatzi P, Jürges CS, Theis FJ, Saliba AE, Dölken L (2019) *scSLAM-seq reveals core features of transcription dynamics in single cells.*
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Erhard F, Halenius A, Zimmermann C, L'Hernault A, Kowalewski DJ, Weekes MP, Stevanovic S, Zimmer R, Dölken L (2018) *Improved Ribo-seq enables identification of cryptic translation events.*
Nature Methods 15(5):363-366

Jürges C, Dölken L, **Erhard F** (2018) *Dissecting newly transcribed and old RNA using GRAND-SLAM.*
Bioinformatics 34(13):i218-i226

RESEARCH INTERESTS

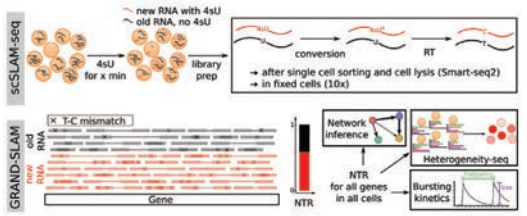
We develop computational and statistical methods and tools for analyzing "omics" data. By applying these approaches in various herpesvirus models we study the mechanisms by which viruses take over or modulate their host cells and evade immune responses. Key technologies such as next generation sequencing and mass spectrometry offer countless opportunities in systems biology. To take advantage of these, we work on innovative experimental approaches in collaboration with groups inside and outside of the ZINF and combine these with specifically tailored computational analysis methods. We also focus on the integrative analysis of "multi-omics" data. We believe that technological advances and integrative approaches will pave the way towards understanding complex systems such as virus infection.

HIGHLIGHTS & OUTLOOK

Metabolic RNA labeling with nucleotide conversion provides elegant means to analyze the temporal dynamics of RNA on a large-scale. We developed the first method (GRAND-SLAM) that can compute truly quantitative temporal estimates from such experiments by statistical modeling. Together with the Dölken and Saliba labs, we then developed single-cell SLAM-seq (scSLAM-seq). In contrast to standard scRNA-seq, this new technique resolves fast, dynamic changes of gene expression as *e.g.* induced by virus infection with unprecedented detail in single cells and directly visualizes transcriptional bursting. By effectively measuring every cell at two time points, we can infer functional genetic interactions by modeling transcriptional activity of individual cells in response to a perturbation based on their pre-perturbation expression heterogeneity. This approach, called Heterogeneity sequencing, will enable us to study pro- and antiviral factors for various viruses.

Based on our methods PRICE (high-resolution analysis of ribosome profiling data) and Peptide-PRISM (proteogenomic identification of MHC-I ligands), we uncovered cryptic peptides, which are translated from mostly short and so far unknown ORFs, and constitute up to 15% of the peptides presented by MHC-I. These are now tested immunologically (with the Schlosser and Schilling labs for tumor peptides, and within FOR 2830 for viral peptides).

Furthermore, we used a large collection of omics data sets to compile and validate the most comprehensive annotation of a large DNA virus (herpes simplex virus 1; with the Dölken lab). A similar annotation for the human and murine cytomegalovirus genomes is a major goal of our FOR 2830 project.



The conversion of 4sU incorporated into new RNA results in characteristic mismatches. New and old RNA can be quantified in single cells for thousands of genes.

MORBILLIVIRUS PATHOGENESIS

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SELECTED PUBLICATIONS

Grafen A, Schumacher F, Chithelen J, Kleuser B, Beyersdorf N, **Schneider-Schaulies J** (2019) *Use of Acid Ceramidase and Sphingosine Kinase Inhibitors as Antiviral Compounds Against Measles Virus Infection of Lymphocytes in vitro.*
Frontiers in Cell and Developmental Biology 7:218

Hollmann C, Wiese T, Dennstädt F, Fink J, **Schneider-Schaulies J**, Beyersdorf N (2019) *Translational Approaches Targeting Ceramide Generation from Sphingomyelin in T Cells to Modulate Immunity in Humans.*
Frontiers in Immunology 10:2363

Tiwarekar V, Fehrholz M, **Schneider-Schaulies J** (2019) *KDELR2 Competes with Measles Virus Envelope Proteins for Cellular Chaperones Reducing Their Chaperone-Mediated Cell Surface Transport.*
Viruses 11(1):27

Tiwarekar V, Wohlfahrt J, Fehrholz M, Scholz CJ, Kneitz S, **Schneider-Schaulies J** (2018) *APOBEC3G-Regulated Host Factors Interfere with Measles Virus Replication: Role of REDD1 and Mammalian TORC1 Inhibition.*
Journal of Virology 92(17):e00835-18

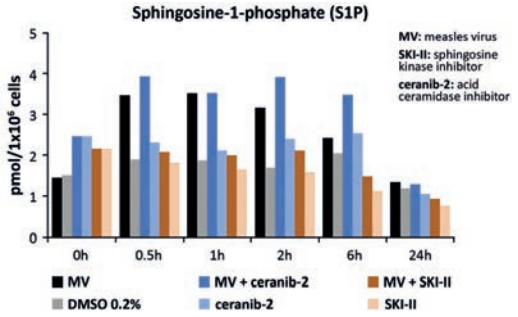
RESEARCH INTERESTS

Measles, caused by a negative-stranded RNA virus of the genus morbillivirus, family Paramyxoviridae, is not a simple children's disease, but can cause a number of complications such as transient immunosuppression, life-threatening diarrhea, pneumonia, blindness, and various forms of encephalitis. Due to these complications more than 100,000 children worldwide still die every year due to acute measles infections. In addition, after the acute infection of predominantly very young children, the virus may persist for longer times in the host. After an average 6 to 12 years of persistence, measles virus (MV) may replicate and spread through the brain and cause the lethal disease subacute sclerosing panencephalitis (SSPE).

Vaccination against measles not only protects against the acute disease, but also from SSPE. However, due to socioeconomic problems, vaccination is not sufficiently applied in many countries. An antiviral therapy is urgently needed.

HIGHLIGHTS & OUTLOOK

We are using cultures of primary human peripheral blood mononuclear cells (PBMCs) and human NTera-2 pluripotent stem cells differentiated to neurons (NT2-N cells) as model systems for MV infections of lymphocytes and neurons. Thereby, persistently infected postmitotic NT2-N cells are used as model for SSPE. We test a number of inhibitors of cellular functions (host factors) and viral activities to find optimal ways to inhibit viral replication. Recently, we characterized parts of the cellular sphingolipid metabolism required for viral replication as a potential target for antiviral therapy in PBMC. Inhibitors of the acid ceramidase and the sphingosine kinase 1 and 2 reduced viral titers in PBMC by approximately 1 log (90%). Furthermore, a number of inhibitors are being used to optimize inhibition of viral replication in persistently MV-infected differentiated NT2-N cells.



Increase of S1P concentrations in primary human PBMCs after infection with MV and inhibition of this by SKI-II, but not by ceranib-2. Grafen *et al.*, 2019, Frontiers in Cell and Developmental Biology.

VIRAL IMMUNOMODULATION

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SELECTED PUBLICATIONS

Derakhshani S, Kurz A, Japtok L, Schumacher F, Pilgram L, Steinke M, Kleuser B, Sauer M, **Schneider-Schaulies S**, Avota E (2019) *Measles Virus Infection Fosters Dendritic Cell Motility in a 3D Environment to Enhance Transmission to Target Cells in the Respiratory Epithelium.*
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Avota E, de Lira MN, **Schneider-Schaulies S** (2019) *Sphingomyelin Breakdown in T Cells: Role of Membrane Compartmentalization in T Cell Signaling and Interference by a Pathogen.*
Frontiers in Cell and Developmental Biology 7:152

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Frontiers in Immunology 9:815

Collenburg L, Beyersdorf N, Wiese T, Arenz C, Saied E, Becker-Flegler A, **Schneider-Schaulies S**, Avota E (2017) *The activity of the neutral sphingomyelinase is important in T cell recruitment and directional migration.*
Frontiers in Immunology 8:1007

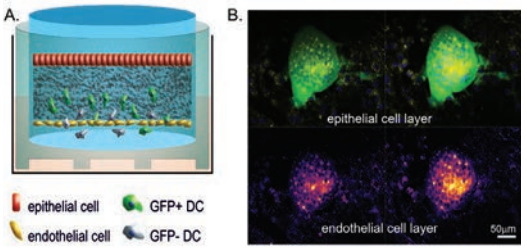
RESEARCH INTERESTS

Viruses can modulate the activity of host immune cells to facilitate their survival, replication, and spread. Measles virus (MV) induces a general immunosuppression, which dampens virus-specific immune responses and favors the establishment of secondary or chronic infections. It also exploits antigen-presenting cells for trafficking early and late in infection. The group aims at defining mechanisms underlying these processes with special emphasis on virally induced dynamic repatterning of membrane lipid and protein complexes in T cells or dendritic cells.

HIGHLIGHTS & OUTLOOK

Dynamic membrane changes induced by MV interactions with the T cell surface were found to account for MV-induced T cell silencing. As major membrane components, sphingomyelin and its metabolite ceramide regulate segregation of receptors and their associated signalosomes into membrane micro-domains and thereby, cellular signaling. MV interaction with T cells induced neutral sphingomyelinase (NSM) activity, and this essentially accounted for the observed inhibition of actin cytoskeletal dynamics. Indicating that NSM generally acts to dampen T cell responses, its ablation accelerated early activation in co-stimulated T cells, which we recently assigned to elevated metabolic activity in the absence of this enzyme. Strikingly, NSM proved to be of crucial importance in supporting polarization, dynamics, and stability of microtubules and thereby, sustainment of T cell receptor signaling, as well as T cell directional motility. Sphingolipid compartmentalization and trafficking in T cells are currently directly studied using functional analogues suitable for click reactions with Jürgen Seibel (Organic Chemistry, Würzburg) and Markus Sauer (Biophysics, Würzburg). In a complex 3D respiratory tract model established by us (collaboration with Maria Steinke, TERM, Würzburg), another sphingolipid, sphingosine-1-phosphate, produced upon MV infection, substantially contributed to enhanced polarization and motility of infected dendritic cells (DCs) and thereby viral transmission to epithelial cells.

Current and future experiments focus on the identification and functional characterization of up- and downstream effectors in MV-induced NSM2 activation as well as their spatiotemporal regulation. These are being performed in collaboration with partnering groups within the GRK 2581 (granted early in 2020) and involve systems biology, signaling, biochemical, and high resolution.



(A) MV infected (GFP+) DCs switch to fast, ameboid migration in a 3D respiratory tract model, and transmit MV to endo- and epithelial cells (B).

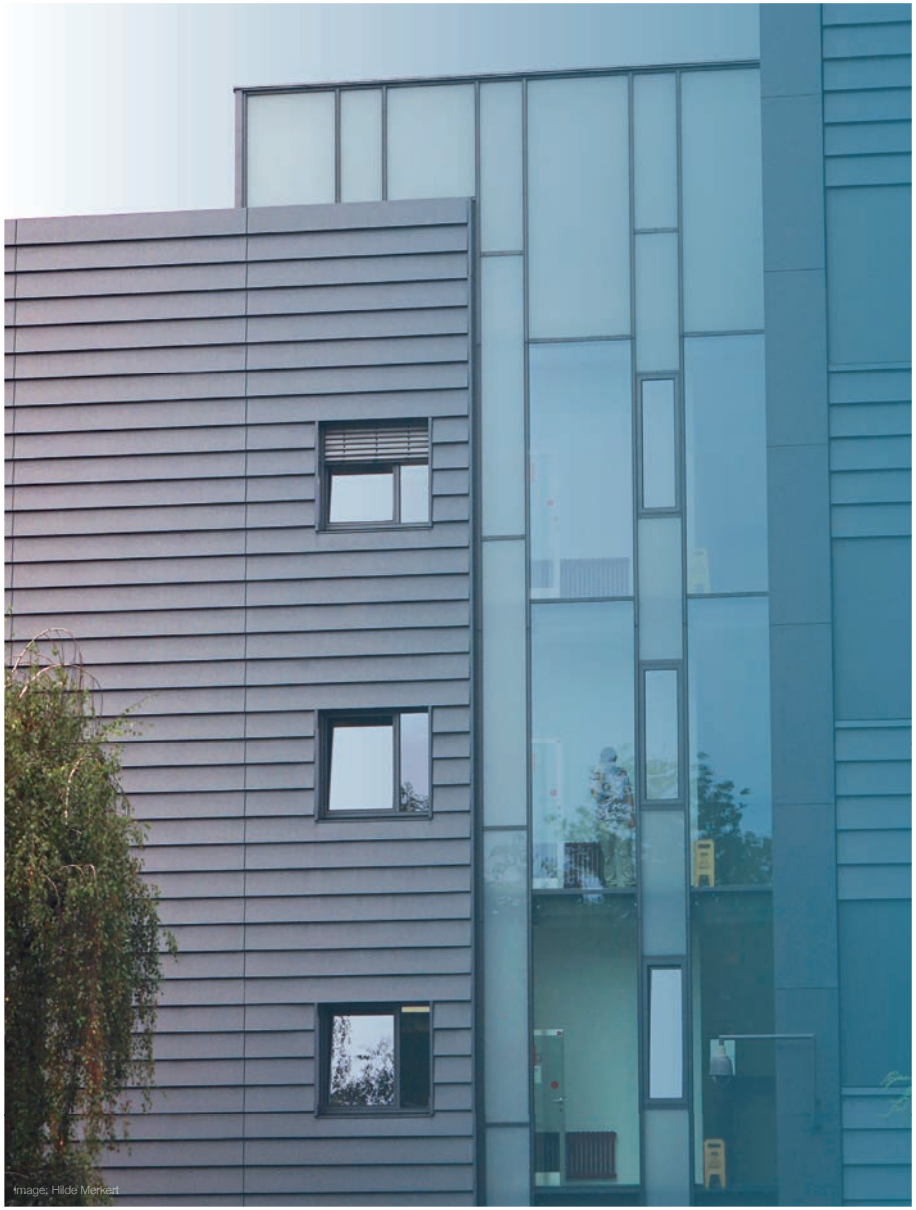


Image: Hilde Merkert

3.4

INSTITUTE FOR VIROLOGY AND IMMUNOBIOLOGY – DEPARTMENT OF IMMUNOLOGY

WOLFGANG KASTENMÜLLER

NIKLAS BEYERSDORF

THOMAS HERRMANN

MANFRED LUTZ

The Institute for Virology and Immunobiology is part of the Medical Faculty at the University of Würzburg. Prof. Dr. Wolfgang Kastenmüller is the Acting Director of the Department of Immunology.

The research interests of the individual groups focus on a broad spectrum of basic and applied immunological topics. Many of the results from basic research are translated into preclinical therapy models for infections, allergies, autoimmune diseases, transplant rejection, and graft-versus-host disease. The Institute also provides diagnostic services for autoantibodies for the University Clinics.

LEUKOCYTE DYNAMICS

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SELECTED PUBLICATIONS

Ataide MA, Komander K, Knöpper K, Peters AE, Wu H, Eickhoff S, Gogishvili T, Weber J, Grafen A, Kallies A, Garbi N, Einsele H, Hudecek M, Gasteiger G, Hölzel M , Vaeth M, **Kastenmüller W** (2020) *BATF3 programs CD8 T cell memory.*
Nature Immunology (accepted).

Welz M, Eickhoff S, Abdullah Z, Trebicka J, Gartlan KH, Spicer JA, Demetris AJ, Akhlaghi H, Anton M, Manske K, Zehn D, Nieswandt B, Kurts C, Trapani JA, Knolle P, Wohlleber D, **Kastenmüller W** (2018) *Perforin inhibition protects from lethal endothelial damage during fulminant viral hepatitis.*
Nature Communications 9(1):4805

Bedoui S, Gebhardt T, Gasteiger G, **Kastenmüller W** (2016) *Parallels and differences between innate and adaptive lymphocytes.*
Nature Immunology 17(5):490-494

AWARDS

ERC Consolidator Grant on the topic: *Spatiotemporal regulation of T-cell Priming* (2018)

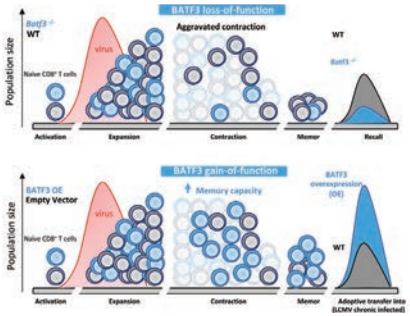
RESEARCH INTERESTS

A central aspect of the cellular elements of the immune system is their capacity to rapidly migrate between and within organs. The group aims to understand the mechanistic basis of leukocyte migration and how the interaction between cells is orchestrated in order to mount an effective immune response. For example, they aim to understand how, when, and where CD8 T cells are activated and with which dendritic cell types they communicate in order to generate an adaptive immune response in the context of an acute or chronic viral infection. They use these insights to improve immunotherapy and to engineer T cells to optimize their capacity to fight cancer.

Besides studying the cellular interactions that culminate into a protective immune response, we are also interested to investigate the dynamic behavior and interaction of cells that regulate immunity like Treg cells. More recently, we are investigating the function and migratory behavior of so-called invariant T cells and studying their ability to protect the host against bacterial infections such as *Staphylococcus aureus*.

HIGHLIGHTS & OUTLOOK

In one of our recent unpublished studies, we found that the AP-1 family transcription factor BATF3 regulates the quality of memory CD8 T cells in a cell intrinsic manner in the context of infections. In contrast to known factors involved in CD8 T cell memory formation such as TCF7, BATF3 is only transiently expressed after T cell activation but has long-lasting effects on T cell survival and persistence. In this regard, the effects of BATF3 are reminiscent of the role of CD4 help for cytotoxic CD8 T cells that similarly programs the quality of the ensuing memory population. Beyond this, we are particularly excited about the effects of BATF3 overexpression in CD8 T cells, because it enhances cellular fitness and longevity without affecting CD8 T cell differentiation or functionality. BATF3 does so by optimizing CD8 T cell metabolism and the expression patterns of cytokine and costimulatory receptors. Due to these changes, BATF3 overexpressing CD8 T cells outcompeted control populations in the context of acute and chronic viral infections. We further demonstrate that BATF3 optimizes CD8 T cell stemness and longevity not only in murine, but importantly also in human, CD8 T cells. Therefore, our results identify the AP-1 transcription factor family member BATF3 as a promising candidate to optimize the T cell quality for immunotherapy against cancer in humans.



The AP-1 family transcription factor BATF3 programs CD8 T cell memory.

T CELL BIOLOGY

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SELECTED PUBLICATIONS

Grafen A, Schumacher F, Chithelen J, Kleuser B, **Beyersdorf N**, Schneider-Schaulies J (2019) *Use of Acid Ceramidase and Sphingosine Kinase Inhibitors as Antiviral Compounds Against Measles Virus Infection of Lymphocytes in vitro.*
Frontiers in Cell and Developmental Biology 7:218

Dasari P, Koleci N, Shopova IA, Wartenberg D, **Beyersdorf N**, Dietrich S, Sahagún-Ruiz A, Figge MT, Skerka C, Brakhage AA, Zipfel PF (2019) *Enolase From Aspergillus fumigatus Is a Moonlighting Protein That Binds the Human Plasma Complement Proteins Factor H, FHL-1, C4BP, and Plasminogen.*
Frontiers in Immunology 10:2573

Langenhorst D, Haack S, Göb S, Uri A, Lühder F, Vanhove B, Hünig T, **Beyersdorf N** (2018) *CD28 Co-stimulation of T Helper 1 Cells Enhances Cytokine Release In Vivo.*
Frontiers in Immunology 9:1060

Schneider-Schaulies J, **Beyersdorf N** (2018) *CD4+ Foxp3+ regulatory T cell-mediated immunomodulation by anti-depressants inhibiting acid sphingomyelinase.*
Biological Chemistry 399(10):1175-82

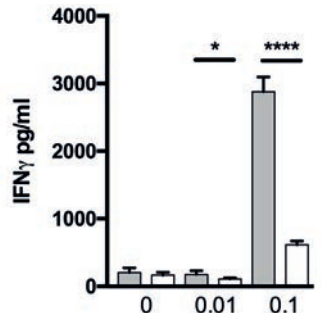
RESEARCH INTERESTS

Innate and adaptive immunity interact to provide the host with a highly efficient defense against pathogenic microorganisms. T cells crucially contribute to adaptive immunity and further orchestrate the immune response as a whole. Apart from providing immunity against microbial pathogens, T cells also play an important role in fighting cancer. Therefore, our group has a long-standing interest in cell surface receptor-mediated T cell activation and how T cell responses can be harnessed for therapeutic purposes.

HIGHLIGHTS & OUTLOOK

During the first year of life infants are very susceptible towards so-called 'childhood diseases' such as measles. Unfortunately, in some children the measles virus persists in the brain after the acute infection, which may lead to a lethal form of encephalitis called Subacute Sclerosing Panencephalitis (SSPE), for which there currently is no curative treatments. Prof. Jürgen Schneider-Schaulies' and our group could, however, recently show that modulators of sphingolipid metabolism are capable of inhibiting measles virus replication in cell culture, while not interfering with the activation and differentiation of protective T cells. These findings may, thus, lay the basis for future novel treatments of chronic measles virus infection, and possibly other viral infections, of the brain.

After an acute viral or bacterial infection, immunological memory arises protecting the host upon re-infection with the same pathogen. In the protection against intracellular pathogens, so-called CD4+ T helper 1 (Th1) cells producing the cytokine interferon γ (IFN γ) are key. Until recently it has, however, been unclear how much their re-activation after secondary contact with the pathogen depends on sensing 'danger'. With our recent observation that secondary stimulation of Th1 cells heavily depends on co-stimulation via the CD28 receptor on the T cell surface, we could show that sensing 'danger' is essential for their re-activation. The continued dependence of Th1 cells on CD28 co-stimulation reduces the risk of unwanted immune responses and opens novel possibilities for immunomodulatory interventions.



IFN γ secretion by OVA-specific CD4+ T helper 1 (Th1) cells (grey) is reduced upon CD28 inhibition (white). Published in Langenhorst *et al.*, 2018, Frontiers in Immunology.

IMMUNOGENETICS

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SELECTED PUBLICATIONS

Fichtner AS, Karunakaran MM, Gu S, Boughter CT, Borowska MT, Starick L, Nohren A, Gobel TW, Adams EJ, **Herrmann T** (2020) *Alpaca (Vicugna pacos), the first nonprimate species with a phosphoantigen-reactive Vγ9Vδ2 T cell subset.* **PNAS** 117(12):6697-6707

Karunakaran MM, Willcox CR, Salim M, Paletta D, Fichtner AS, Noll A, Starick L, Nöhren A, Begley CR, Berwick KA, Chaleil RAG, Pitard V, Déchanet-Merville J, Bates PA, Kimmel B, Knowles TJ, Kunzmann V, Walter L, Jeeves M, Mohammed F, Willcox BE, **Herrmann T** (2020) *Butyrophilin-2A1 Directly Binds Germline-Encoded Regions of the Vgamma9Vdelta2 TCR and Is Essential for Phosphoantigen Sensing.* **Immunity** 52(3):487-498.e6

Fichtner AS, Karunakaran MM, Starick L, Truman RW, **Herrmann T** (2018) *The Armadillo (Dasypus novemcinctus): A Witness but Not a Functional Example for the Emergence of the Butyrophilin 3/Vγ9Vδ2 System in Placental Mammals.* **Frontiers in Immunology** 9:265

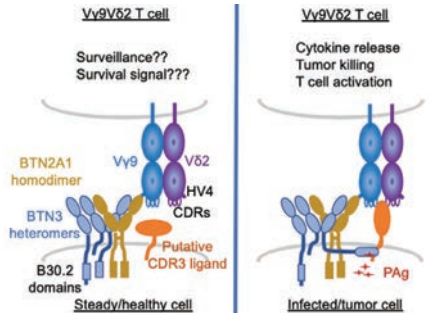
RESEARCH INTERESTS

Vγ9Vδ2 T cells are effectors with anti-microbial and anti-tumor activity. Their eponymous Vγ9Vδ2 T-cell antigen-receptor recognizes phosphoantigens (PAg) sensing tumor or host cells. The PAg (E)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate (HMBPP) is found in many eubacteria and in apicomplexa such as *Plasmodium* spp. and leads to expansion of Vγ9Vδ2 T cells in infections. The ubiquitous but very weak PAg isopentenyl pyrophosphate (IPP) is increased in tumors, especially after administration of aminobisphosphonates (*e.g.* zoledronate) and triggers anti-tumor activity. We aim to understand the molecular basis of recognition of PAgs in infections and to harness the anti-tumor effector potential of Vγ9Vδ2 T cells.

HIGHLIGHTS & OUTLOOK

A key player in Vγ9Vδ2 T cell-activation is the cell surface molecule butyrophilin BTN3A1. Its extracellular domain is very similar to members of the B7 family (*e.g.* CD80/86). Binding of PAgs to the intracellular B30.2 domain of BTN3A1 leads to a conformational change of the entire molecule, and finally to Vγ9Vδ2 T-cell activation by the BTN3A1-expressing cell. This requires cooperation with the BTN3A1 paralogues BTN3A2 and BTN3A3. Until recently, Vγ9Vδ2 T cells were found only in primates. We identified and characterized key genes of PAg-recognition (Vγ9, Vδ2, and BTN3) and their products in other mammalian species (Fichtner *et al.,* 2018) and newly generated reagents allowed us to identify the alpaca (*Vicugna pacos*) as the first non-primate species with functional Vγ9Vδ2 T cells. Interestingly, alpaca possess only one BTN3, which merges the functions of the three human BTN3s (Fichtner *et al.*, 2020).

We also identified the human BTN2A1 molecule as a new player in PAg-presentation by screening human-rodent radiation hybrids for their capacity of PAg-presentation (Karunakaran *et al.*, 2020). In cooperation with the Willcox group in Birmingham, UK, BTN2A1 binding was shown to the Vγ9 gene product and the V-domain of BTN3A1. BTN2A1 and BTN3A1 transferred the capacity of PAg presentation to rodent cells and is aimed to be used for creation of a transgenic mouse model for PAg-reactive Vγ9Vδ2 T cells, which so far can only be studied in primates. The study of the molecular basis of interaction between the butyrophilins and of ligands binding to the Vγ9Vδ2 TCR will also be continued.



Vγ9δ T cell activation: BTN2A1 binds to Vγ9 and PAg binding to BTN3A1 induces a conformation of the BTN-complex, exposing an unknown ligand(s) to the CDR3s of Vγ9Vδ TCR. Hermann *et al.*, 2020, Cells.

IMMUNE REGULATION

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SELECTED PUBLICATIONS

John V, Kotze LA, Ribechini E, Walzl G, Du Plessis N, **Lutz MB** (2019) *Caveolin-1 Controls Vesicular TLR2 Expression, p38 Signaling and T Cell Suppression in BCG Infected Murine Monocytic Myeloid-Derived Suppressor Cells.* **Frontiers in Immunology** 10:2826

Ribechini E, Eckert I, Beilhack A, Du Plessis N, Walzl G, Schleicher U, Ritter U, **Lutz MB** (2019) *Heat-killed Mycobacterium tuberculosis prime-boost vaccination induces myeloid-derived suppressor cells with spleen dendritic cell-killing capability.* **JCI Insight** 5(13):128664

Vendelova E, Ashour D, Blank P, Erhard F, Saliba AE, Kalinke U, **Lutz MB** (2018) *Tolerogenic Transcriptional Signatures of Steady-State and Pathogen-Induced Dendritic Cells.* **Frontiers in Immunology** 9:333

AWARDS

Research Grant and Award of the Vogel-Stiftung Dr. Eckernkamp (2019)

RESEARCH INTERESTS

Infective microbes have developed a number of strategies to avoid elimination by the host's immune system such as activation of immune tolerance mechanisms. We are investigating how different pathogens manipulate dendritic cells (DCs) and myeloid-derived suppressor cells (MDSCs).

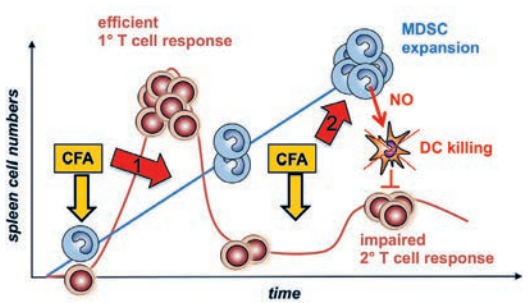
HIGHLIGHTS & OUTLOOK

While the functional role of MDSCs has been widely described, their hematopoietic origin is largely unclear. We have described that the signaling cascades via GM-CSF and subsequent signals through IRF-1/IFN-γR and AKT/mTOR are molecular requirements for the conversion of human or mouse conventional monocytes into monocytic MDSCs. This indicates that, instead of a specific MDSC precursor, transcriptional and translational changes induced in monocytes are sufficient to generate monocytic MDSCs.

As the interaction of MDSCs with mycobacteria is not well studied, we investigated the uptake, signaling, and suppressor function of live *Mycobacterium bovis* Bacille-Calmette-Guérin (BCG) in murine MDSCs and the specific role of caveolin-1 (Cav-1) in this process. Cav-1 organizes the surface Toll-like receptors-2 and -4 (TLR2, TLR4) that are important for mycobacterial recognition. Using gene-deficient MDSCs we found that (i) Cav-1 is dispensable for the internalization of BCG, (ii) vesicular TLR2 signaling in M-MDSCs is a major signaling pathway induced by BCG, (iii) vesicular TLR2 signals are controlled by Cav-1, (iv) vesicular TLR2/Cav-1 signaling is required for T cell suppressor functions.

In the search for an efficient tuberculosis (TB) vaccine, we had previously found that TB patients show elevated levels of MDSCs in their blood circulation and thus hypothesized that mycobacterial vaccines may also induce MDSCs that counteract the vaccine-induced T cell immune response. Our data indicate that repeated vaccination with *Mycobacterium tuberculosis* (Mtb) emulsified in oil (Complete Freund's Adjuvant) induces MDSCs. As a novel mechanism of suppression, we identified the killing of DCs in the spleen that indirectly suppresses T cell responses against Mtb (see Figure).

We will further investigate the interaction of mycobacteria with MDSCs and their induction by anti-TB vaccines. We will also study the detailed interaction of MDSCs with T cells by testing new MDSC markers for functional suppressor activity as well as their *in-vivo* homing potential to understand the anatomical strategy of MDSC-mediated immune suppression in whole organisms.



Repeated *Mycobacterium tuberculosis* (Mtb) vaccinations (CFA) induce myeloid-derived suppressor cells (MDSC) that suppress T cell responses by killing dendritic cells (DC).

Image: Daderot, Wikipedia

3.5

DEPARTMENT OF MICROBIOLOGY, THEODOR BOVERI INSTITUTE, BIOCENTER

THOMAS RUDEL

MARTIN FRAUNHOLZ

ROY GROSS

VERA KOZJAK-PAVLOVIC

The Department of Microbiology is part of the Faculty of Biology at the University of Würzburg. Prof. Dr. Thomas Rudel has chaired the department since 2008.

The research activities at the Department center on the pathogenicity mechanisms of different microorganisms, including the manipulation of various signaling cascades, non-coding RNAs, and cellular processes such as the cell death pathways in the host. In this context, infection biology of obligate intracellular bacteria such as *Chlamydia* spp. is a major focus. Groups are also investigating the molecular basis of disseminating gonococcal infections and the host cell death induced by *Staphylococcus aureus*, as well as the intracellular lifestyle of this bacterium. In addition, there is also great interest in understanding the role of (co-)infections in the onset of ovarian cancer and the signaling pathways involved, as well as the development and application of new 3D infection models.

INFECTION BIOLOGY OF BACTERIA

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SELECTED PUBLICATIONS

Rajeeve K, Das S, Prusty BK, **Rudel T** (2018) *Chlamydia trachomatis paralyses neutrophils to evade the host innate immune response.*
Nature Microbiology 3(7):824-835

Chowdhury SR, Reimer A, Sharan M, Kozjak-Pavlovic V, Eulalio A, Prusty BK, Fraunholz M, Karunakaran K, **Rudel T** (2017) *Chlamydia preserves the mitochondrial network necessary for replication via microRNA-dependent inhibition of fission.*
Journal of Cell Biology 216(4):1071-1089

Fischer A, Harrison KS, Ramirez Y, Auer D, Chowdhury SR, Prusty BK, Sauer F, Dimond Z, Kisker C, Scott Hefty P, **Rudel T** (2017) *Chlamydia trachomatis-containing vacuole serves as deubiquitination platform to stabilize Mcl-1 and to interfere with host defense.*
eLife 6:e21465

AWARDS

ERC Advanced Grant on the topic: *Neutrophil – Chlamydia Interactions at the Crossroad of Adaptation and Defence* (2019)

RESEARCH INTERESTS

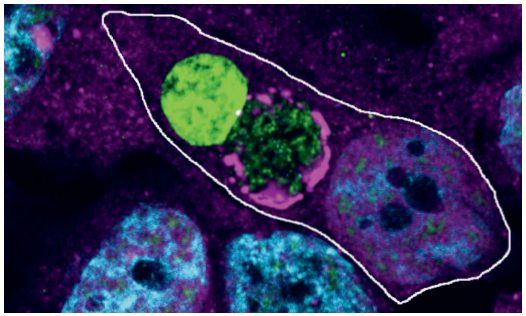
The group investigates pathogenicity mechanisms of the major human pathogens *Chlamydia*, *Neisseria gonorrhoeae*, and *Staphylococcus aureus*. Furthermore, there is a focus on bacterial and viral co-infections and their impact on human diseases such as cancer.

During infection, bacterial pathogens can dramatically alter host cell function to overcome innate and acquired immune responses and to inhabit their preferred niches. Research is divided into three major areas: (1) infection biology of obligate intracellular bacteria (*Chlamydia, Simkania*), (2) bacterial factors required for dissemination and adaptation as well as the host cell response to *Neisseria gonorrhoeae*, and (3) cell biology of *Staphylococcus aureus* infection, particularly the induction of host cell death.

HIGHLIGHTS & OUTLOOK

Chlamydia trachomatis, an obligate intracellular human pathogen, is a major cause of sexually transmitted diseases. Infections often occur without symptoms, a feature that has been attributed to the ability of the pathogen to evade the host immune response. We could show that *C. trachomatis* paralyses the host immune system by preventing the activation of polymorphic nuclear leukocytes (PMNs). PMNs infected with *Chlamydia* fail to produce neutrophil extracellular traps and the bacteria are able to survive in PMNs for extended periods of time. We have identified the secreted chlamydial protease-like activating factor (CPAF) as an effector mediating the evasion of the innate immune response since CPAF-deficient *Chlamydia* activate PMNs and are subsequently efficiently killed. CPAF suppresses the oxidative burst and interferes with chemical-mediated activation of neutrophils. We identified formyl peptide receptor 2 (FPR2) as a target of CPAF. FPR2 is cleaved by CPAF and released from the surface of PMNs.

We will continue to investigate various pathogenicity mechanisms of different bacteria. With respect to obligate intracellular bacteria, metabolic adaptation to the host cell intracellular environment will be of particular interest. Furthermore, we will continue to pursue the molecular basis of disseminating gonococcal infections and host cell death induced by *S. aureus* infection. In addition, it is our goal to understand the significance of infections in the emergence and progression of cancer. Therefore, we aim to investigate the contribution of *Chlamydia* infections to the onset of ovarian cancer and the signaling pathways involved using suitable *in-vitro* and *in-vivo* models for malignant transformation.



Co-infection of *Chlamydia* wildtype (green, no ubiquitin) and a deubiquitinase mutant (strong ubiquitination of inclusion in pink) in the same host cell.

CELLULAR MICROBIOLOGY

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SELECTED PUBLICATIONS

Horn J, Klepsch M, Manger M, Wolz C, Rudel T, **Fraunholz M** (2018) Long *Noncoding RNA SSR42 Controls Staphylococcus aureus Alpha-Toxin Transcription in Response to Environmental Stimuli.*
Journal of Bacteriology 200(22): e00252

Das S, Lindemann C, Young BC, Muller J, Österreich B, Ternette N, Winkler AC, Paprotka K, Reinhardt R, Förstner KU, Allen E, Flaxman A, Yamaguchi Y, Rollier CS, van Diemen P, Blättner S, Remmele CW, Selle M, Dittrich M, Mueller T, Vogel J, Ohlsen K, Crook DW, Massey R, Wilson DJ, Rudel R, Wyllie DH, **Fraunholz M** (2016) *Natural mutations in a Staphylococcus aureus virulence regulator attenuate cytotoxicity but permit bacteremia and abscess formation.*
PNAS 113(22):E3101-10

Blättner S, Das S, Paprotka K, Eilers U, Krischke M, Kretschmer D, Remmele CW, Dittrich M, Müller T, Schuelein-Voelk C, Hertlein T, Mueller MJ, Huettel B, Reinhardt R, Ohlsen K, Rudel T, **Fraunholz M** (2016) *Staphylococcus aureus Exploits a Non-ribosomal Cyclic Dipeptide to Modulate Survival within Epithelial Cells and Phagocytes.*
PLoS Pathogens 12(9):e1005857

RESEARCH INTERESTS

Staphylococcus aureus is taken up by phagocytic cells of the human immune system but is also readily internalized by cells such as endothelial or epithelial cells. Cytotoxic *S. aureus* strains are able to escape phagosomal vesicles, replicate in the cytoplasm, and kill the host cells from within. The involved bacterial effectors and host factors as well as the underlying molecular mechanisms are largely unknown.

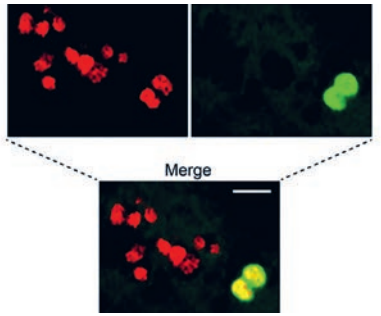
The research group focuses on the identification of bacterial virulence factors involved in phagosomal escape and cytotoxicity as well as host factors that support the intracellular survival of *S. aureus*.

HIGHLIGHTS & OUTLOOK

By infecting fluorescent phagosomal escape reporter cell lines with *S. aureus* mutants, we identified several bacterial genes involved in phagosomal escape of the pathogen. Among others, we identified a non-ribosomal peptide synthase (NRPS) involved in the process. The *S. aureus* NRPS and its cyclized dipeptide products enhance *S. aureus* phagosomal escape, thereby contributing to epithelial and immune cell death.

To identify virulence factors involved in *S. aureus*-induced virulence on a genome-wide scale, we conducted unbiased transposon mutant pool screens *in vitro* and *in vivo*. By transposon insertion site deep sequencing, we not only identified a role for the NRPS in *S. aureus* infections, but also identified the involvement of the transcriptional regulator Rsp in *S. aureus* intracellular cytotoxicity. Mutants in *rsp* had reduced cytotoxicity and were avirulent in mouse lung infections. Identification of the transcription factor regulon established the long non-coding RNA SSR42 as the main Rsp effector. Mutants within the genes for Rsp or SSR42 lost their hemolytic and cytotoxic phenotypes. Most interestingly, *S. aureus rsp* mutants can be recovered from bacteremia isolates in patients with nasal *S. aureus* carriage. This demonstrates that during human nasal carriage, *S. aureus* is able to acquire mutations within the *rsp* locus, which can influence the invasiveness of the pathogen.

Our results indicate a fine-tuned host-pathogen interplay for intracellular *S. aureus* involving the uptake of the bacteria, their host-cell dependent phagosomal escape, growth within the cells, and cytolysis of the infected host cells. We currently conduct time-resolved infection experiments to characterize molecular mechanisms and timing of the involved processes in both host and pathogen.



A fluorescent escape reporter (green) is recruited to intracellular *S. aureus* (red) upon phagosomal escape of the bacteria. Scale bar: 5 µm.

PERTUSSIS

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SELECTED PUBLICATIONS

Kupper M, Stigloher C, Feldhaar H, **Gross R** (2016) *Distribution of the obligate endosymbiont Blochmannia floridanus and expression analysis of putative immune genes in ovaries of the carpenter ant Camponotus floridanus.* **Arthropod Structure & Development** 45(5):475-487

Bibova I, Hot D, Keidel K, Amman F, Slupek S, Cerney O, **Gross R**, Vecerek B (2015) *Transcriptional profiling of Bordetella pertussis reveals requirement of RNA chaperone Hfq for Type III secretion system functionality.* **RNA Biology** 12(2):175-85

Gupta SK, Kupper M, Ratzka C, Feldhaar H, Vilcinskas A, **Gross R**, Dandekar T, Förster F (2015) *Scrutinizing the immune defence inventory of Camponotus floridanus applying total transcriptome sequencing.* **BMC Genomics** 16(1):540

Steinke M, **Gross R**, Walles H, Gangnus R, Schütze K, Walles T (2014) *An engineered 3D human airway mucosa model based on an SIS scaffold.* **Biomaterials** 35(26):7355-62

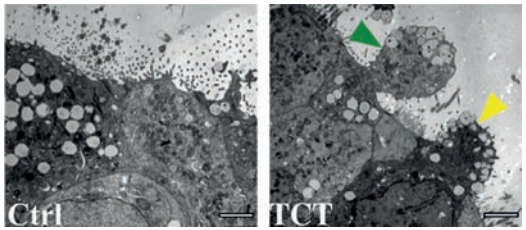
RESEARCH INTERESTS

Bordetella pertussis is the obligate human pathogen that causes whooping cough. The disease is highly contagious and, despite the presence of effective vaccines, it still is a major cause of disease and a large number of deaths worldwide. In the past twenty years new types of acellular vaccines were introduced replacing quite reactogenic whole cell vaccines. Since then, there has been the reemergence of pertussis even in countries with good vaccination coverage. Thus, it is pertinent to characterize the virulence mechanisms of this obligate human pathogen in appropriate test systems most closely resembling the natural situation. For this purpose, we developed 3D tracheal models from primary human cells (hTBMs) and use these models to study and re-evaluate the relevance of *B. pertussis* virulence factors. These factors include several adhesins and toxins including the tracheal cytotoxin (TCT), which is a spontaneously released low molecular weight compound of the cell wall. In animal models such as hamster tracheal explants, TCT was shown to cause massive tissue destruction. Accordingly, we started to investigate the activities of this toxin in human tissue model systems to further evaluate its role during infection in humans.

HIGHLIGHTS & OUTLOOK

During the first phase of the project, the methods to reproducibly generate 3D tracheal models from primary human cells were improved. The effects of purified TCT on the models was then investigated and compared with previously published results mainly obtained in animal models. Briefly, in the 3D models the toxin caused massive tissue destruction including blebbing of epithelial cells. This phenomenon correlated with the induction of NO production and stimulation of inflammatory cytokines, confirming previous results obtained with hamster tracheal explants, thus providing strong evidence for the importance of this toxin for pathogenesis in humans as well.

Currently, preparative work is being carried out to investigate the host cell response to bacterial infection by RNA-seq analysis and, in particular, by single-cell RNA-seq, which is challenging since *B. pertussis* is an extracellular pathogen and classical cell sorting of infected cells is not easily possible. Depending on the results of the RNA-seq analysis, further experiments will be performed with the 3D infection models, including the use of *B. pertussis* strains with mutations in various virulence genes and the determination of the role of apparently relevant signaling pathways of the host during *B. pertussis* infection.



TEM showing blebbing of denuded ciliated cells (green arrowhead) and nonciliated cell (yellow arrowhead) in hTBMs before (left) and after intoxication with TCT (right). Scale bars: 2 µm.

BACTERIAL INVASION AND INTRACELLULAR SURVIVAL

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SELECTED PUBLICATIONS

Kunz TC, Götz R, Gao S, Sauer M, **Kozjak-Pavlovic V** (2020) *Using expansion microscopy to visualize and characterize the morphology of mitochondrial cristae.* **Frontiers in Cell and Developmental Biology** 8:617

Heydarian M, Yang T, Schweinlin M, Steinke M, Walles H, Rudel T, **Kozjak-Pavlovic V** (2019) *Biomimetic Human Tissue Model for Long-Term Study of Neisseria gonorrhoeae Infection.* **Frontiers in Microbiology** 10:1740

Chowdhury SR, Reimer A, Sharan M, **Kozjak-Pavlovic V**, Eulalio A, Prusty BK, Fraunholz M, Karunakaran K, Rudel T (2017) *Chlamydia preserves the mitochondrial network necessary for replication via microRNA-dependent inhibition of fission.* **Journal of Cell Biology** 216(4):1071-1089

Reimer A, Seufert F, Weiwad M, Ebert J, Bzdyl NM, Kahler CM, Sarkar-Tyson M, Holzgrabe U, Rudel T, **Kozjak-Pavlovic V** (2016) *Inhibitors of macrophage infectivity potentiator-like PPIases affect neisserial and chlamydial pathogenicity.* **International Journal of Antimicrobial Agents** 48(4):401-408

RESEARCH INTERESTS

We investigate bacterial and cellular factors involved in the interaction of *Neisseria gonorrhoeae* with epithelial and immune cells of the host. For this, we have developed three-dimensional models of relevant tissues. In addition, we are interested in the role of mitochondria and sphingolipids in infection, focusing on the intracellular pathogen *Simkania negevensis*.

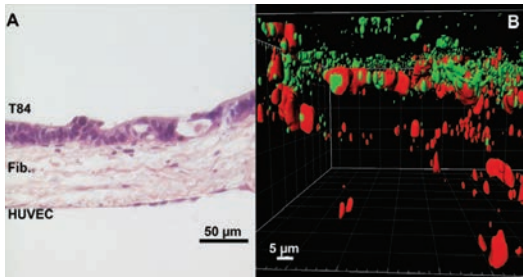
N. gonorrhoeae is an obligate human pathogen that causes gonorrhea. The bacteria depend on pili for initial adhesion, Opa proteins for invasion, and $PorB_{IA}$ porin for dissemination. Neutrophils are the first responders during gonococcal infection. However, *N. gonorrhoeae* can survive the neutrophil attack, using them as a Trojan horse for spreading from the primary infection site.

S. negevensis is a *Chlamydia*-related obligate intracellular pathogen connected to pulmonary infections. The *S. negevensis* vacuole forms close contacts with the endoplasmic reticulum and mitochondria and depends on host cell lipids for development, which is why these bacteria are a good model for researching the interplay between cell organelles and pathogenic microorganisms.

HIGHLIGHTS & OUTLOOK

We have identified novel cellular and bacterial factors important for *N. gonorrhoeae* attachment to, invasion, and survival in epithelial cells and neutrophils. We have generated 3D tissue models using endometrial, mesothelial, colon, and urethral epithelial cell lines, and improved them by addition of endothelial cells and neutrophils. We established endometrial organoid culture as the source of primary cells. We also studied the role of mitochondria during infection with *S. negevensis*, which connected to our work on proteins crucial for mitochondrial morphology and cristae maintenance.

Our aims are to use advanced 3D tissue models in a bioreactor setup to study interaction of bacteria with cell surface, bacterial transmigration, and, after addition of neutrophils, the fate of gonococci upon contact with cells of the immune system. We are developing imaging procedures, which will allow us to study infection processes in greater depth. These include application of expansion microscopy and lipid staining using click chemistry. The connection between mitochondria, sphingolipids, and *S. negevensis*, as well as mitochondrial biogenesis in the context of infection remain in our focus. Further on, the cellular exit of *S. negevensis* and the importance of cell death manipulation in this process represent one of the new directions in our research.



Advanced 3D tissue models in H&E (A) and fluorescence (B) staining. Neutrophils (red) interact with gonococci (green) at the tissue surface.

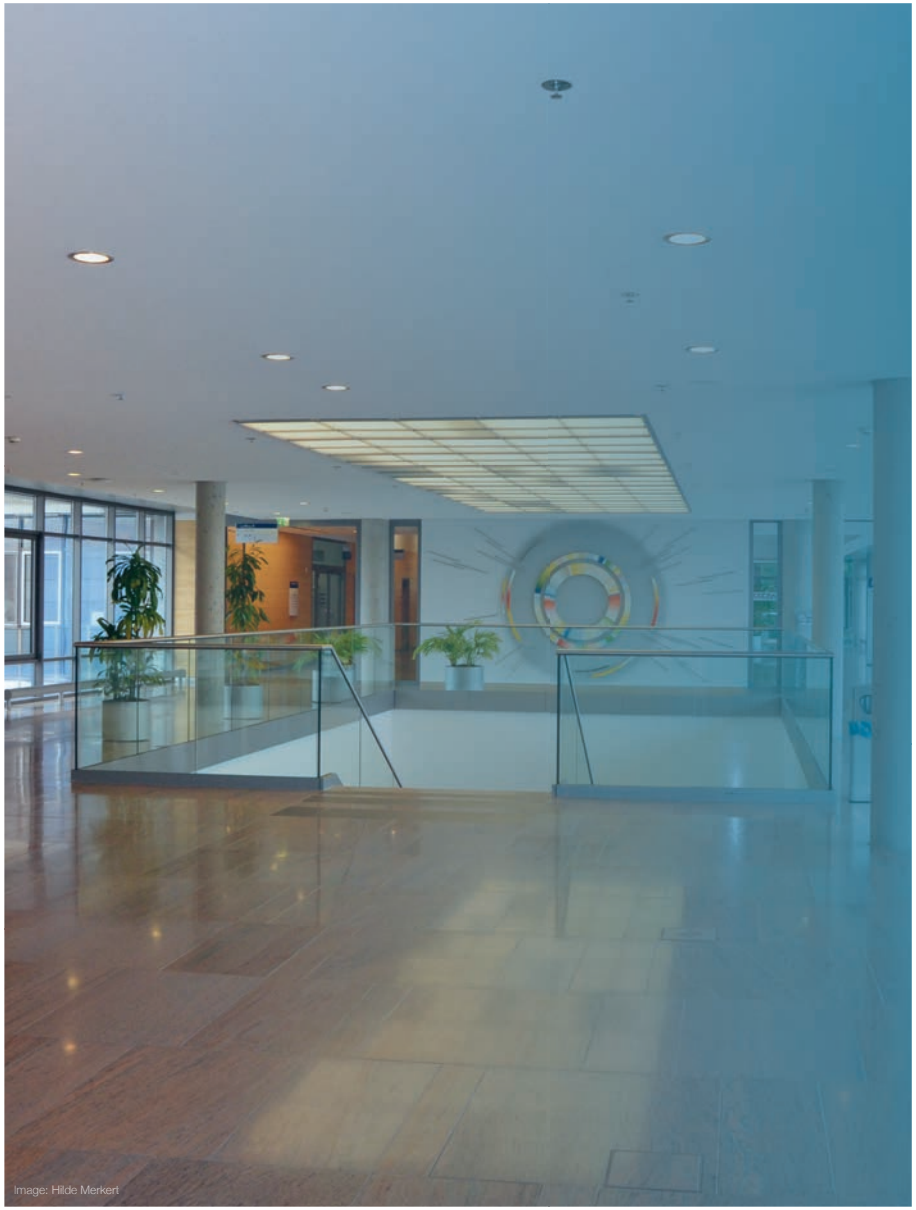


Image: Hilde Merkert

3.6
DEPARTMENT OF INTERNAL MEDICINE II

HERMANN EINSELE

ANDREAS BEILHACK

HARTWIG KLINKER

JÜRGEN LÖFFLER

The Department of Internal Medicine II at the University Hospital is part of the Medical Faculty of the University of Würzburg. Since 2004, it has been under the directorship of Prof. Dr. Hermann Einsele.

The department contains six research divisions, which include Hematology and Medical Oncology, Infectious Diseases, Gastroenterology, Hepatology, Clinical Immunology, and Psychosomatics. Excellent conditions for clinical research, teaching, and patient care exist due to close interdisciplinary interactions with the Center of Internal Medicine and Center of Operative Medicine.

It contains a new and state-of-the-art stem cell transplantation unit and the University Hospital Würzburg runs the second largest stem cell transplantation program in Germany, and implements many novel strategies. The division of Infectious Diseases has been certified as one of the first Centers of Infectology in Germany. The clinical focuses of the division are HIV infections, chronic viral hepatitis, and opportunistic infections in immunocompromised patients.

INTERACTION OF ASPERGILLUS FUMIGATUS WITH HUMAN NATURAL KILLER CELLS AND DENDRITIC CELLS

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SELECTED PUBLICATIONS

Einsele H, Ljungman P, Boeckh M (2020) *How I treat CMV reactivation after allogeneic hematopoietic stem cell transplantation.*
Blood 135(19):1619-1629.

Marty F, Ljungman P, Chemaly R, Maertens J, Dadwal S, Duarte R, Haider S, Ullmann A, Katayama Y, Brown J, Mullane K, Boeckh M, Blumberg E, **Einsele H**, Snydman D, Kanda Y, DiNubile M, Teal V, Wan H, Murata Y, Kartsonis N, Leavitt R (2017) *Cytomegalovirus Prophylaxis with Letermovir in Hematopoietic-Cell Transplantation.*
New England Journal of Medicine 377(25):2433-2444

Neuenhahn M, Albrecht J, Odendahl M, Schlott F, Dössinger G, Schiemann M, Lakshmipathi S, Martin K, Bunjes D, Harsdorf S, Weissinger EM, Menzel H, Verbeek M, Uharek L, Kröger N, Wagner E, Kobbe G, Schroeder T, Schmitt M, Held G, Herr W, Germeroth L, Bonig H, Tonn T, **Einsele H**, Busch DH, Grigoleit GU (2017) *Transfer of minimally manipulated CMV-specific T cells from stem cell or third-party donors to treat CMV infection after allo-HSCT.*
Leukemia 31(10):2161-2171

RESEARCH INTERESTS

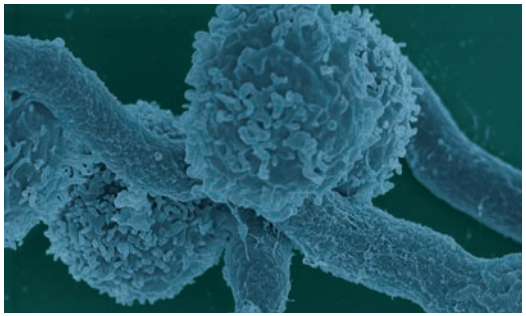
I) *Aspergillus fumigatus* is a saprophytic fungus ubiquitously present in the environment that is one of the most important fungal pathogens causing severe invasive disease in immunocompromised patients. Inhaled conidia are internalized by airway epithelial cells or pulmonary macrophages before undergoing germination and hyphal growth, leading to invasive aspergillosis. The lack of reliable diagnostic tools and effective treatments result in mortality rates of 40-90% in high-risk populations.

II) Despite improved and novel antiviral drug therapies, HCMV infection in immunocompromised patients remains associated with severe clinical complications and mortality due to HCMV-specific immune responses, especially mediated by T and NK cells. Thus, adoptive transfer of HCMV-directed donor-derived T and NK cells as well as vaccination strategies of donor and/or recipient are increasingly attractive therapeutic approaches to improve HCMV-directed immune reconstitution post-transplant. Despite the identification of several immunodominant HCMV-peptides that have been shown to induce T cell responses in alloSCT patients, we are still unable to reliably predict if a patient will develop HCMV reactivation or will need a long-lasting antiviral chemotherapy due to an insufficient HCMV-directed immune control.

HIGHLIGHTS & OUTLOOK

I) Within the CRC/Transregio 124, we aim to combine state-of-the-art research in mycology and immunology to gain novel insights into the pathophysiology of invasive mycoses to improve diagnosis and treatment. Together with members of the ZINF and research groups from Jena, we will utilize high-throughput approaches to characterize infection-relevant networks of *A. fumigatus* and host cells. To elucidate regulatory circuits in both the pathogen and the host, the groups are systematically investigating the pathogen itself and its interaction with single cell types (*e.g.* epithelial or DC), complex infection and mouse models, and clinical samples using functional genomics. In the next years we aim to provide new insights into the pathogenicity of *A. fumigatus* and identify diagnostic biomarkers and potential targets for new antimycotic approaches.

II) We aim to better identify patients at risk for HCMV disease and to improve the selection of HCMV-directed T and NK cells for adoptive transfer and of HCMV-derived peptides for vaccination strategies. Here, we will study the reconstitution of antiviral T and NK cell responses in alloSCT patients, the respective stem cell donor, and healthy donors using novel sets of HCMV epitopes. We aim to optimize immune monitoring, prediction of HCMV-related complications, and improve adoptive T cell therapies.



Aspergillus fumigatus hyphae and activated human natural killer (NK) cells.

EXPERIMENTAL STEM CELL TRANSPLANTATION

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SELECTED PUBLICATIONS

Ribechini E, Eckert I, **Beilhack A**, Plessis N, Walzl G, Schleicher U, Ritter U, Lutz MB (2019) *Heat-killed Mycobacterium tuberculosis prime-boost vaccination induces myeloid-derived suppressor cells with spleen dendritic cell-killing capability.*
JCI Insight 5(13):128664

Wertheimer T, Velardi E, Tsai J, Cooper K, Xiao S, Kloss CC, Ottmüller KJ, Mokhtari Z, Brede C, deRoos P, Kinsella S, Palikuqi B, Ginsberg M, Young LF, Kreines F, Lieberman SR, Lazrak A, Guo P, Malard F, Smith OM, Shono Y, Jenq RR, Hanash AM, Nolan DJ, Butler JM, **Beilhack A**, Manley NR, Rafii S, Dudakov JA, van den Brink MRM (2018) *Production of BMP4 by endothelial cells is crucial for endogenous thymic regeneration.*
Science Immunology 3(19):eaal2736

Chopra M, Biehl M, Steinfatt T, Brandl A, *et al.*, **Beilhack A** (2016) *Exogenous TNFR2 activation protects from acute GvHD by induction of host Treg expansion.*
Journal of Experimental Medicine 213(9):1881–1900

AWARDS

Award of the foundation Forschung Hilft! (2019)

RESEARCH INTERESTS

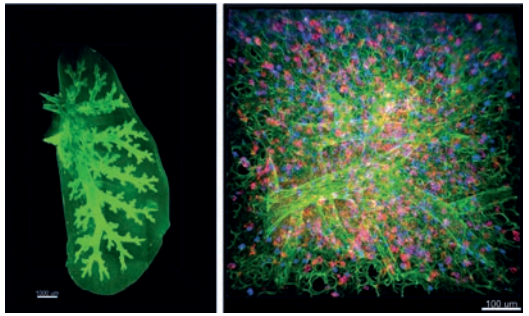
Employing and advancing state-of-the-art methods and following an interdisciplinary research approach, the Beilhack lab aims to develop the next generation of immunotherapy and immunodiagnostics for inflammatory diseases, infections, and cancer.

The fungus *Aspergillus fumigatus* can cause life-threatening fungal infections after allogeneic hematopoietic cell transplantation or in other situations when the immune system is perturbed. Imbalances of local or systemic immune defense mechanisms or disruption of cellular barriers can result in invasive pulmonary aspergillosis. Clearance of these infections depends on innate and adaptive immune effector cells. By modulating the immune system, we are analyzing the changes in interaction patterns and their effect on the outcome of fungal infections. We aim to elucidate the interplay of host and pathogen under *in vivo* conditions to develop novel strategies to improve disease outcome.

HIGHLIGHTS & OUTLOOK

In the past decade, we have been developing microscopy and imaging techniques to investigate complex immune processes *in vivo*. Besides non-invasive imaging of luminescent *A. fumigatus* infection *in vivo*, we have developed a high-resolution multicolor light-sheet fluorescence microscopy (LSFM) technique to monitor complex immune responses in intact organs of mice or in biopsies from patients. Generating a plane of light to section through biological specimens, LSFM can acquire multicolor images at speeds 100 to 1,000 times faster than *e.g.* confocal microscopy. This method has the advantage of being able to visualize and quantify single cell interactions within their intact three-dimensional tissue environment. Recently, we employed LSFM to uncover the time-resolved progression and spatial distribution of *A. fumigatus* during infection and the dynamics of immune cell recruitment in different scenarios of immunosuppression.

As members of the Collaborative Research Center TRR124 FungiNet, we are investigating dynamic immune-pathogen interactions in mouse models *in vivo*. As members of the DFG GRK 2157 3D Infect, we combine microscopy techniques and organ-on-a-chip models. Currently, we are exploring how cytokine networks fine-tune host defense mechanisms within the local tissue environment and regulate tissue-resident immune cell subsets. Currently we are expanding our endeavor to an invertebrate model (*Bombyx mori*) to investigate host-pathogen interactions and novel antifungal strategies. Combining basic research with our close ties to the clinics we aim at improving diagnostics and therapeutic options for patients suffering from chronic opportunistic infections.



Light-sheet fluorescence microscopy to reveal host-pathogen interactions (mouse lung, left; detail right).

DIVISION OF INFECTIOUS DISEASES

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SELECTED PUBLICATIONS

Yuen MF, Schiefke I, Yoon JH, Ahn SH, Heo J, Kim JH, Chan HLY, Yoon KT, **Klinker H**, *et al.* (2019) *RNA Interference Therapy with ARC-520 Results in Prolonged HBsAg Response in Patients with Chronic Hepatitis B Infection.* **Hepatology** doi: 10.1002/hep.31008

Knop V, Hofmann WP, Buggisch P, **Klinker H**, Mauss S, Günther R, Hinrichsen H, Hüppe D, Pfeiffer-Vornkahl H, Simon KG, Berg T, Manns MP, Friedrich-Rust M (2019) *Estimation of liver fibrosis by noncommercial serum markers in comparison with transient elastography in patients with chronic hepatitis C virus infection receiving direct-acting antiviral treatment.* **Journal of Viral Hepatitis** 26(2):224-30

Schultheiß M, Kling S, Lenker U, von Bibra M, Rosenkranz B, **Klinker H** (2018) *Lopinavir serum concentrations of critically ill infants: a pharmacokinetic investigation in South Africa.* **Medical Microbiology & Immunology** 207(5-6):339-343

AWARDS

"Top Mediziner" in Germany for infectious diseases in the ranking of the "Focus" magazine (2019 & 2020)

RESEARCH INTERESTS

The group uses laboratory and clinical-based approaches to investigate innovative anti-infective strategies in the fields of HIV infection, chronic hepatitis B and C, as well as opportunistic infections in immunocompromised hosts. The pharmacokinetic analysis center focuses on the detection and quantification of different antiviral and antifungal agents.

The section of Infectious Diseases is a clinical center within the German Liver Foundation. Since 2005, the study-center has participated in the world-wide study-network for strategical HIV-studies INSIGHT (International Network for Strategic Initiatives in Global HIV Trials) sponsored by the National Institutes of Health in the USA (see http://www.insighttrials.org).

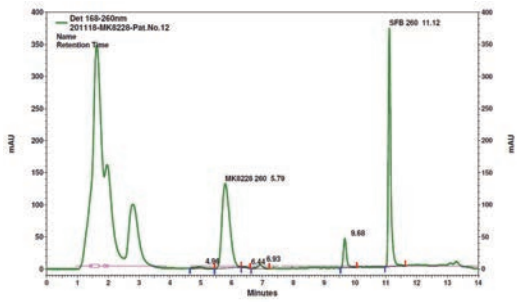
HIGHLIGHTS & OUTLOOK

The laboratory specializes in developing and implementing methods for evaluating pharmacokinetics and therapeutic drug monitoring of virostatic and antifungal agents. One major focus is the pharmacokinetic evaluation of HIV protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI) during antiretroviral therapy in patients with HIV infection. New methods are currently being developed for the determination of bictegravir and doravirin concentrations. Many clinical studies were performed in the field of chronic hepatitis B and C.

The antifungal triazoles voriconazole and posaconazole are broadly used for either treatment or prophylaxis of invasive fungal infections. Voriconazole is metabolized by the CYP P450-system, while posaconazole inhibits the cytochrome P450 enzymes. For pharmacokinetic studies, we have developed a combined HPLC-assay for the determination of serum concentrations of both triazoles.

Letermovir is a new antiviral drug approved for prophylaxis of CMV disease in CMV-positive adults receiving an allogeneic hematopoietic stem cell transplant. Being a substrate of the hepatic uptake transporter OATP1B1/3, coadministration of OATP inhibitors and genetic variabilities lead to clinically relevant changes in drug exposure. As the first group we could establish a high performance liquid chromatography (HPLC) assay for determination of letermovir concentration and evaluated letermovir serum concentrations in different clinical settings (Dr. Nora Isberner).

The determination of plasma concentrations of antiviral and antifungal drugs will provide insights into the individual pharmacokinetics of antiviral treatments in different patient groups and will contribute to improving the efficacy and safety of long-term treatment.



HPLC run of the determination of letermovir (MK8228, concentration 4.731 ng/ml).
SFB = sorafenib = internal standard.

IMMUNITY AGAINST ASPERGILLUS SPP.

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SELECTED PUBLICATIONS

Zoran T, Weber M, Springer J, White L, Bauer J, Schober A, Löffler C, Seelbinder B, Hünniger K, Kurzai O, Scherag A, Schäuble S, Morton O, Einsele H, Linde J, **Löffler J** (2019) *Treatment with etanercept and low monocyte concentration contribute to the risk of invasive aspergillosis in patients post allogeneic stem cell transplantation.* **Scientific Reports** 9(1):17231

Löffler J, Ebel F (2018) ***Size matters - how the immune system deals with fungal hyphae.*** **Microbes & Infection** 20(9-10):521-25

Ziegler S, Weiss E, Schmitt A, Schlegel J, Burgert A, Terpitz U, Sauer M, Moretta L, Sivori S, Leonhardt I, Kurzai O, Einsele H, **Löffler J** (2017) *CD56 Is a Pathogen Recognition Receptor on Human Natural Killer Cells.* **Scientific Reports** 7(1):6138

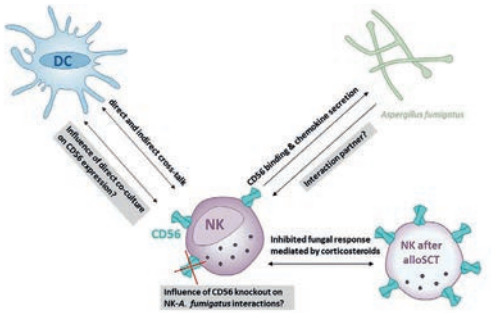
Hellmann A, Lother J, Wurster S, Lutz M, Schmitt A, Morton O, Eyrich M, Czakai K, Einsele H, **Löffler J** (2017) *Human and murine innate immune cell populations display common and distinct response patterns during their in vitro interaction with the pathogenic mould Aspergillus fumigatus.* **Frontiers in Immunology** 8:1716

RESEARCH INTERESTS

Aspergillus fumigatus (AF) is a major cause of morbidity and mortality in immunocompromised patients. Cells of the innate immune system recognize the fungus and its different morphologies by distinct pattern recognition receptors (PRRs), which induce cell specific as well as general defense mechanisms. The most important cells of the innate immune system are alveolar macrophages, granulocytes, natural killer (NK) cells, as well as dendritic cells (DC). Our group aims to better understand the interaction of AF with the innate and adaptive immune system, and with other pathogens and to characterize genetic susceptibility to the fungus.

HIGHLIGHTS & OUTLOOK

The research of my group focuses on immune recognition of AF, patients' genetic susceptibility to this fungus, and the molecular diagnosis of invasive fungal infections. We have revealed TLR2-, TLR4-, and dectin-1-dependent activation of DCs by the fungus. Furthermore, we have shown that NK cells interact with and recognize AF via the NK cell receptor CD56, which results in the release of Th1-like cytokines and fungal killing. Using live cell imaging and dStorm microscopy, we have revealed that DCs are key players in the activation of NK cells and that this activation is mediated by the C-type lectin dectin-1. Recently, our group has performed extensive studies on the role of chimeric antigen receptors (CAR) for antigens of AF on NK cells and T cells. We will continue to functionally characterize PBMC and NK cells isolated from patients after allogeneic SCT during their *ex vivo* interaction with fungal pathogens. Another major research interest is the genetic susceptibility of patients to AF infections. Genotyping of a large DNA bank identified SNPs that are potentially associated with the occurrence of *Aspergillus* infections. In parallel, we study the interaction of AF with other pathogens of the lung, focusing on CMV. Using dual RNA-seq, and optionally in addition a viral pathogen, with subsequent siRNA knockdown of selected target genes, we aim to define specific immune-relevant pathways involved in aspergillosis. Our future studies will investigate the role of CD56 as immune receptor on NK cells using CRISPR-Cas technology. We will also strive to better understand the pathophysiology of *Mucorales* infections. Recently, we have led several clinical studies on the diagnosis of fungal infections, and we are active leading contributors to the standardization of *Aspergillus* and *Mucorales* diagnosis worldwide (I am the head of the Fungal PCR Initiative Steering Committee). Overall, our aim is to develop patient-specific risk profiles and individual management strategies for patients suffering from AF infection.



Summary of the current research projects with a focus on NK cell – *Aspergillus* interaction analyses.

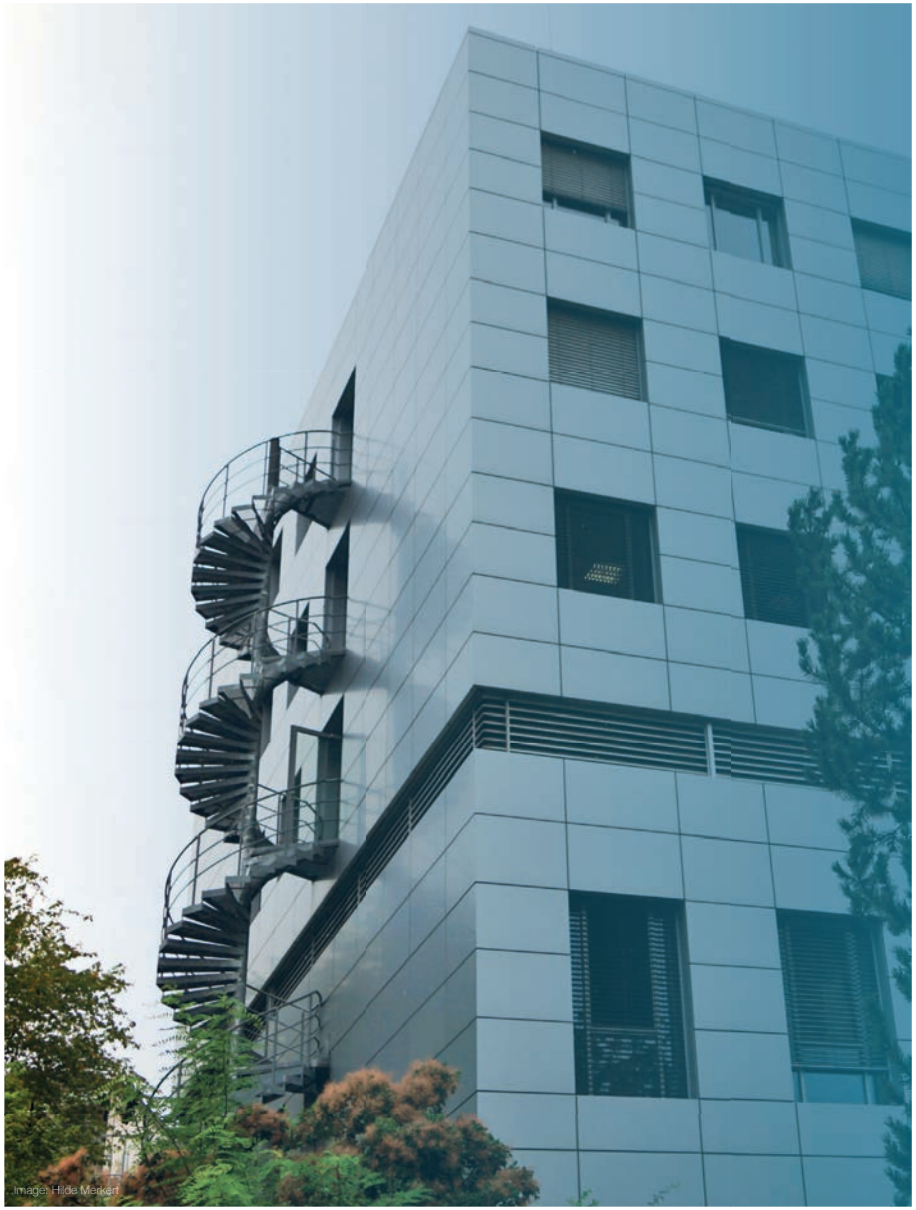
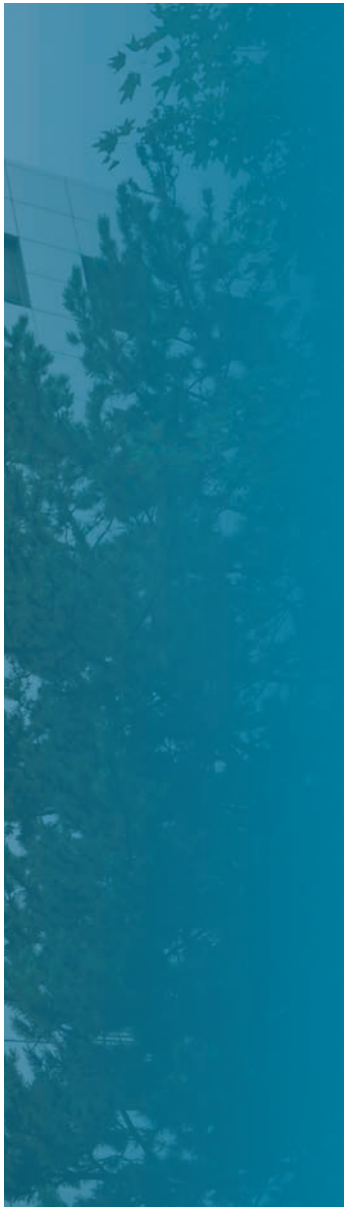


Image: Hilde Merkert



3.7
INSTITUTE OF SYSTEMS IMMUNOLOGY

GEORG GASTEIGER

MERCEDES GOMEZ DE AGÜERO

MARTIN VAETH

The Institute of Systems Immunology was founded in a collaborative effort between the Max Planck Society and the University of Würzburg and is located on the Medical Campus. With the cooperation agreement signed in 2013, the Institute began its research in 2017 with the appointments of Prof. Dr. Wolfgang Kastenmüller and Prof. Dr. Georg Gasteiger as Chairs of the newly founded Departments of Systems Immunology and Systems Immunology II, respectively, at the University of Würzburg.

Research at the Institute pursues a holistic approach to study the immune system and its interactions with the organism as a whole. One focal area is the protection that the immune system can provide against pathogens or cancer cells. Diseases triggered by the immune system such as multiple sclerosis or rheumatism are another research focus.

In particular, the Institute focuses on where and how cells of the immune system interact to achieve an effective immune response or to prevent inflammatory disease processes. Researchers at the Institute of Systems Immunology are developing new genetic tools that allow for the visualization of a wide variety of specific cell types to test their function. The ultimate goal is to understand the basic principles for a successful immune response against infectious agents and tumors and to use them therapeutically.

TISSUE IMMUNITY

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SELECTED PUBLICATIONS

Zeis P, Lian M, Fan X, Herman JS, Hernandez DC, Gentek R, Elias S, *et al.*, **Gasteiger G** (2020) *In situ maturation and tissue adaptation of type 2 innate lymphoid cell progenitors.*
Immunity (accepted)

Straub T, Freudenberg MA, Schleicher U, Bogdan C, **Gasteiger G**, Pircher H (2018) *Bacterial coinfection restrains antiviral CD8 T-cell response via LPS-induced inhibitory NK cells.*
Nature Communications 9(1):4117

Muschaweckh A, Buchholz VR, Fellenzer A, *et al.*, **Gasteiger G** (2016) *Antigen-dependent competition shapes the local repertoire of tissue-resident memory CD8+ T cells.*
Journal of Experimental Medicine 213(13):3075-3086

Bedoui S, Gebhardt T, **Gasteiger G**, Kastenmüller W (2016) *Parallels and differences between innate and adaptive lymphocytes.*
Nature Immunology 17(5):490-4

Gasteiger G, Fan D, Dikyi S, Lee SY, Rudensky AY (2015) *Tissue residency of innate lymphoid cells in lymphoid and non-lymphoid organs.*
Science 350(6263):981-5

RESEARCH INTERESTS

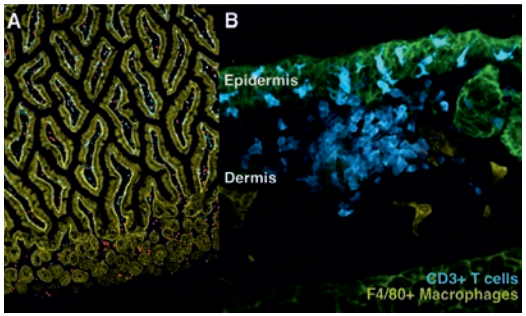
In addition to mobile cells of the immune system that migrate through our body, most anatomical compartments are populated by resident immune cells that act as local sentinels and contribute to homeostasis, repair, and function of their host tissue. Understanding the development, regulation, and function of these cells is therefore relevant for a broad range of physiological and pathological conditions. We are investigating how innate and adaptive lymphocytes adjust to specific tissue environments and how they function as part of local immune cell networks. Our aim is to understand the context-dependent physiological and pathological functions of resident lymphocytes for immune homeostasis as well as infectious and inflammatory diseases.

HIGHLIGHTS & OUTLOOK

Our previous work revealed that currently known subsets of innate lymphoid cells (ILCs) are locally maintained as tissue-resident cells in all examined lymphoid and non-lymphoid organs. We have now identified tissue-associated ILC progenitors that enable the local differentiation, tissue-specific imprinting, and specialization of ILCs. In collaboration with ZINF research groups, we are currently investigating how these mechanisms determine local host-pathogen interactions in tissue-specific microenvironments.

We are also investigating local mechanisms for the "selection" or fine-tuning of a tissue- and site-specific repertoire of resident memory cells that can optimally recognize antigens present in discernible regions or niches within a given tissue. Such mechanisms may be critical to generate local pools of resident memory T cells that can control pathogens persisting in defined anatomical regions, and to strategically position T cells with specificity for regionally distinct heterogeneous microbial communities.

In our quest to understand the development and maintenance of the "functional architecture" of local networks of tissue lymphocytes, we are employing genetic mouse models, experimental models of inflammatory diseases, tumors, and infection, as well as single-cell genomics and advanced imaging. In different projects we study the skin, lung, female reproductive tract, liver and salivary gland, which all represent clinically relevant infection niches.



Local frontline defense: T cells (blue) and ILC2 (red) lining the intestinal epithelium (A). Tissue-resident memory T cells in the skin (B).

HOST-MICROBIAL INTERACTIONS

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SELECTED PUBLICATIONS

Mooser C, **Gomez de Agüero M**, Ganal-Vonarburg SC (2018) *Standardization in host-microbiota interaction studies: challenges, gnotobiology as a tool, and perspective.*
Current Opinion Microbiology 44:50-60

Macpherson AJ, **Gomez de Agüero M**, Ganal-Vonarburg SC (2017) *How nutrition and the maternal microbiota shape the neonatal immune system.*
Nature Reviews Immunology 17(8): 508-517

Hacini-Rachinel F, **Gomez de Agüero M**, Kanjarawi R, Moro-Sibilot L, Le Luduec JB, Macari C, Boschetti G, Bardel E, Langella P, Dubois B, Kaiserlian D (2017) *Intestinal dendritic cell licensing through Toll-like receptor 4 is required for oral tolerance in allergic contact dermatitis.*
Journal of Allergy and Clinical Immunology 141(1):163-170

Gomez de Agüero M*, Ganal-Vonarburg S*, Uchimira Y, Fuhrer T, Rupp S, Steinert A, Hapfelmeier S, Sauer U, McCoy KD*, Macperson AJ* (2016) *Neonatal innate immune development driven by the maternal microbiota.*
Science 351(6279):1296

RESEARCH INTERESTS

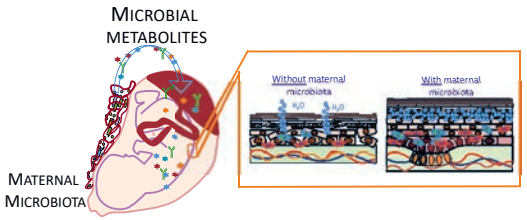
Mammalians harbor trillions of millions of microorganisms, including bacteria, fungi, protozoa, archaea, and viruses, which collectively form the commensal microbiota providing the host with essential vitamins, energy, and pathogen exclusion. It is now largely accepted that mammalian immunity is profoundly stimulated by exposure to microbiota and/or their molecular metabolites. Recently, several studies have defined a critical window early in life for the microbiota to shape the immune system. Our previous work revealed the pivotal role played by microbiota during pregnancy on the development of the immune system. Indeed, maternal microbiota metabolites cross the placenta and shape the offspring intestinal immunity to prepare the newborn for the challenges that occur from birth.

In the passage from the protected maternal uterus to the external environment full of challenges, the skin barrier plays a key role. The outer layer of the skin, the epidermis, concentrates most of the cutaneous barrier function. With a quasi-exclusive uterine development, it is largely accepted that the ontogeny and differentiation of the skin would occur independently of the microbiota and is genetically programmed. We aim to revise the genetic preprograming dogma of the development of the skin and investigate the relative contribution of microbiota to the proper development of the neonatal skin barrier.

HIGHLIGHTS & OUTLOOK

We use a sophisticated gnotobiotic research model based on an auxotrophic *Escherichia coli* strain for exclusive gestational colonization with sterile offspring. Flow cytometry, histology, scRNA sequencing, and metabolic analysis of the pre- and postnatal skin allowed us to show that maternal microbiota shapes the development of the skin. Maternal microbiota regulates gene expression of epidermal stem cells. The differentiation of the keratinocytes to a more mature or specialized stage is impaired in the absence of maternal microbial cells. In addition, maternal microbiota modulates the recruitment and maturation of epidermal immune cells, such as Langerhans cells. Finally, the permeability barrier and wound healing in neonates is enhanced by gestational colonization.

We currently focus our research on in-depth investigation of the mechanisms underlying the development of the skin, the early and late consequences of being born with a deficient skin barrier, and the strategies for acute restoration. Our studies will contribute to a better understanding of the development of the skin, the largest organ of the body.



Maternal microbial derived metabolites shape embryonic skin development positively impacting on the barrier function of the neonates.

METABOLISM AND IMMUNE CELL SIGNALLING

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SELECTED PUBLICATIONS

Kahlfuss S, Kaufmann U, Concepcion AR, Noyer L, Raphael D, **Vaeth M**, Yang J. Pancholi P, Maus M, Muller J, Kozhaya L, Khodadadi-Jqmayran, Sun Z, Shaw P, Unutmaz D, Stathopulos PB, Feist C, Cameron SB, Turvey SE, Feske S (2020) *STIM1-mediated calcium influx controls antifungal immunity and the metabolic function of non-pathogenic Th17 cells.*
EMBO Molecular Medicine 12(8): e11592

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Trends in Immunology S1471-4906 (20)30149-6

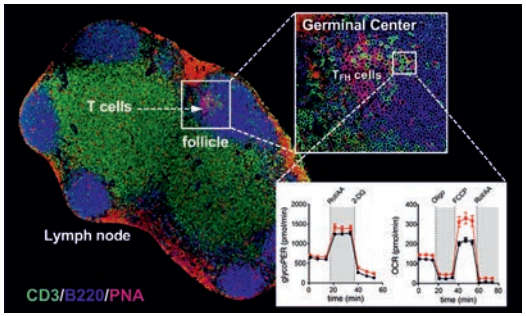
Vaeth M, Wang YH, Eckstein M, Yang J, Silverman GJ, Lacruz RS, Kannan K, Feske S (2019) *Tissue resident and follicular Treg cell differentiation is regulated by CRAC channels.*
Nature Communications 10(1):1183

Vaeth M, Feske S (2018) *NFAT control of immune function: New Frontiers for an Abiding Trooper.*
F1000 Research 7:260

RESEARCH INTERESTS

A major challenge for the immune system is the discrimination between 'self' tissue and 'non-self' antigens that are associated with infectious pathogens or malignant cells to prevent the destruction of the body's own healthy tissues. Immunological tolerance is the fine but flexible balance between immunity to infection and the prevention of autoimmunity, dysregulation of which can result in severe immunological pathologies.

Our laboratory investigates the underlying molecular principles of immunological tolerance focusing on the metabolic programming of immune cells in the context of viral infection and immune tolerance. Over the last decades, it became clear that 'immunometabolism' is not solely important to provide energy required for the proliferation and effector function of lymphocytes, but also controls gene expression and epigenetic programming of different immune cells. A deeper understanding of these metabolic regulatory circuits promises new therapeutic avenues to treat immune-related pathologies, such as persistent infections.



T follicular helper (T_{FH}) cells migrate into B cell follicles and undergo metabolic changes after interaction with germinal center (GC) B cells.

HIGHLIGHTS & OUTLOOK

Lymphocytes are critical mediators of adaptive immune responses to pathogens and provide long-term protection by the formation of immunological memory. The research in our laboratory investigates the metabolic control of lymphocyte differentiation, function, and memory formation in different tissue environments. We showed recently that cell cycle entry, clonal expansion, and the effector differentiation of virus-specific T cells depends critically on calcium (Ca^{2+}). Ca^{2+} signals induce a metabolic switch in naïve T cells and change their metabolic phenotype from a quiescent to a high-rate anabolic state that is characterized by elevated aerobic glycolysis and mitochondrial metabolism. This metabolic re-programming of naïve T cells is critical for the clonal expansion of antigen-specific lymphocytes and controls the formation of memory T cells. Glucose metabolism plays a central role in both the activation and differentiation of T cells, but elevated glycolysis can also promote functional exhaustion of lymphocytes and curtail efficient anti-viral immunity. Based on our original observation that glucose metabolism is a central regulator of both T cell-mediated immunity and tolerance, we aim to further dissect the underlying molecular, transcriptional and epigenetic consequences of elevated glucose metabolism and investigate if metabolic programming of lymphocytes is a feasible strategy to optimize T cell-mediated immunity to pathogens and malignant diseases.

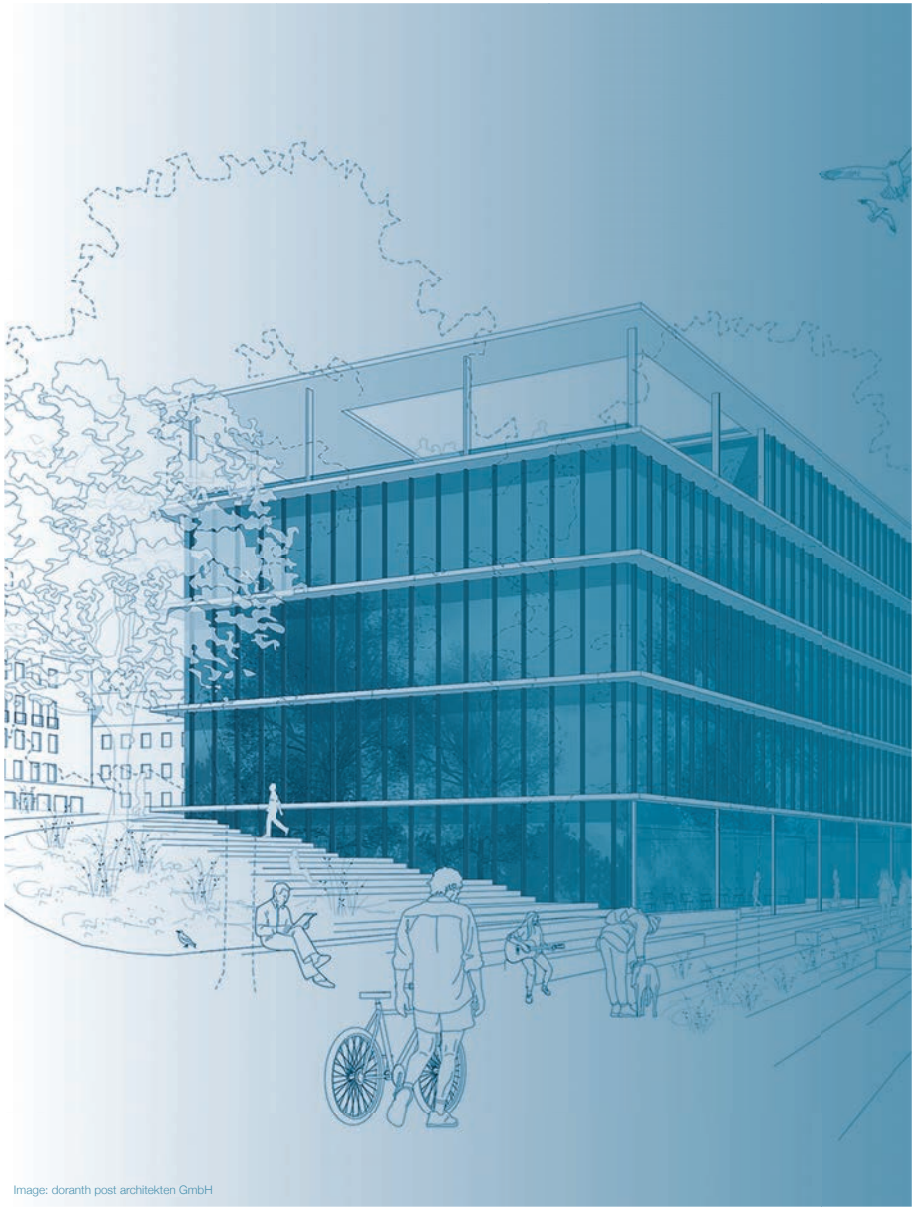


Image: doranth post architekten GmbH

3.8
HELMHOLTZ INSTITUTE FOR RNA-BASED INFECTION RESEARCH

LARS BARQUIST

CHASE BEISEL

NEVA CALISKAN

MATHIAS MUNSCHAUER

ANTOINE-EMMANUEL SALIBA

REDMOND SMYTH

The Helmholtz Institute for RNA-based Infection Research (HIRI) was established in May 2017 in a joint effort by the Helmholtz Centre for Infection Research (HZI) in Braunschweig and the University of Würzburg. Located on the Würzburg Medical Campus, the HIRI is the first research institution worldwide to fully focus on the role of RNA in infection processes. As a federal Institute, the HIRI pioneers an integrative approach to exploit the vast potential of RNA as a diagnostic, a drug, and a therapeutic target for new strategies to combat infectious diseases.

Lead by Acting Director Jörg Vogel, the HIRI focuses on four central research areas: basic research on bacterial pathogens, on viruses, and on the host immune response provides a comprehensive understanding of the role of RNA in infections. These three general areas are complemented by applied research on RNA delivery for diagnostic and therapeutic purposes.

The synergy between HIRI research groups and the infection research and translational competences at the University of Würzburg as well as at the HZI Braunschweig creates unique opportunities to effectively convert knowledge based on fundamental research into applications to establish novel therapeutic and diagnostic strategies for the treatment of infectious diseases.

INTEGRATIVE INFORMATICS FOR INFECTION BIOLOGY

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SELECTED PUBLICATIONS

Mika-Gospodorz B, Giengkam S, Westermann AJ, Wongsantichon J, Kion-Crosby W, Chuenklin S, Wang LC, *et al.*, Vogel J, **Barquist L**#, Salje J# (2020) *Dual RNA-seq of Orientia tsutsugamushi informs on host-pathogen interactions for this neglected intracellular human pathogen.* **Nature Communications** doi: 10.1038/s41467-020-17094-8

Ryan D, Jenniches L, Reichardt S, **Barquist L**, Westermann AJ (2020) *A high-resolution transcriptome map identifies small RNA regulation of metabolism in the gut microbe Bacteroides thetaiotaomicron.* **Nature Communications** doi: 10.1038/s41467-020-17348-5

Wheeler NE, Gardner PP, **Barquist L** (2018) *Machine learning identifies signatures of host adaptation in the bacterial pathogen Salmonella enterica.* **PLoS Genetics** 14(5):e1007333

Barquist L, Mayho M, Cummins C, Cain AK, Boinett CJ, Page AJ, Langridge GC, Quail MA, Keane JA, Parkhill J (2016) *The TraDIS toolkit: sequencing and analysis for dense transposon mutant libraries.* **Bioinformatics** 32(7):1109-1111

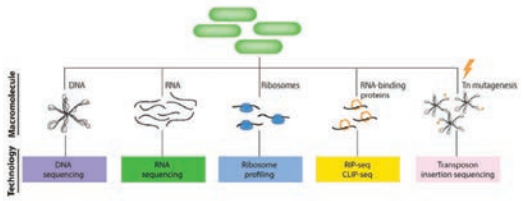
RESEARCH INTERESTS

The group, established in 2018, uses data science technologies, including visualization, machine learning, and statistical modelling, to extract biological insight from high-throughput genomic and post-genomic data. We use these technologies to understand the effects of RNA-based regulation in bacteria and non-coding RNA's role in host-pathogen interactions as well as pathogen evolution.

There is now a growing cottage industry centered on harnessing classical molecular biological techniques to high-throughput sequencing to take advantage of the scaling properties of this technology. These methods can provide insight into a wide variety of cellular processes, for instance transcription, translation, RNA-binding protein interactions, or fitness effects. However, they also often rely on complex treatments and experimental designs that introduce substantial complications in interpreting and integrating the resulting data. As a result, the critical bottleneck in moving from hypothesis to result is increasingly not in data generation, but in data analysis. We use the bacterial pathogen *Salmonella enterica* as a model system for the development of systems approaches leveraging these technologies to gain insight into virulence processes.

HIGHLIGHTS & OUTLOOK

Our work focuses on developing data analysis and interpretation approaches for functional genomics data at the intersection of RNA and infection. These include both machine learning and statistical approaches. Using classical machine learning methods, we have been developing new approaches for predicting CRISPRi guide efficiency from genome-wide essentiality screens to separate guide effects that can be controlled in design from differences in depletion due to features of targeted transcripts. We have also been investigating hierarchical Bayesian statistical approaches to the analysis of complex sequencing-based experiments. This approach allows us to separate experimental effects of interest from confounding factors. We have been applying this approach to study global changes in RNA stability in the absence of major RNA-binding proteins, and to understanding the genetic interactions of these proteins and small RNAs during infection using transposon insertion sequencing. Finally, we also have an interest in data integration and visualization and have been developing interactive platforms that allow the user to integrate and explore heterogeneous functional genomics data.



High-throughput methods for characterization of the bacterial transcriptome, spanning applications from transcript discovery to inferring function.

RNA SYNTHETIC BIOLOGY

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SELECTED PUBLICATIONS

Liao C, Ttofali F, Slotkowski RA, Denny SR, Cecil TD, Leenay RT, Keung AJ, **Beisel CL** (2019) *Modular one-pot assembly of CRISPR arrays enables library generation and reveals factors influencing crRNA biogenesis.* **Nature Communications** 10(1):2948

Marshall R, Maxwell CS, Collins SP, Jacobsen T, Luo ML, Begemann MB, Gray BN, January E, Singer A, He Y, **Beisel CL***, Noireaux V* (2018) *Rapid and Scalable Characterization of CRISPR Technologies Using an E. coli Cell-Free Transcription-Translation System.* **Molecular Cell** 69(5):146-157

Leenay RT, Maksimchuk KR, Slotkowski RA, Agrawal RN, Gomaa AA, Briner AE, Barrangou R, **Beisel CL** (2016) *Identifying and visualizing functional PAM diversity across CRISPR-Cas systems.* **Molecular Cell** 62(1):137-147

AWARDS

ERC Consolidator Award (2019)

D. I. C. Wang Young Investigator Award, Biotechnology & Bioengineering Journal (2018)

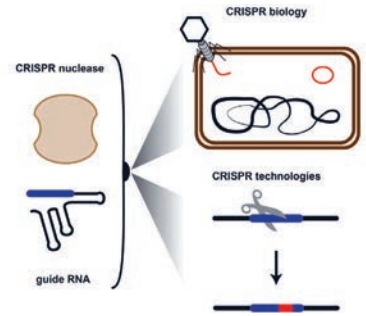
RESEARCH INTERESTS

CRISPR-Cas systems comprise RNA-guided immune systems that have formed the basis for revolutionary genome-editing technologies. The group aims to understand the functional diversity of these immune systems in prokaryotes and how they can be further exploited to advance the study, diagnosis, and treatment of infectious diseases in humans. Within this broad focus, the group seeks to explore the expanse of CRISPR-Cas systems found in nature in order to understand their functional diversity and their potential toward different application areas. Furthermore, the group aims to exploit the resulting insights to develop a new generation of CRISPR technologies with an eye toward understanding, identifying, and eradicating bacterial pathogens.

HIGHLIGHTS & OUTLOOK

Towards understanding CRISPR-Cas systems, we have devised a series of experimental methodologies to identify protospacer-adjacent motifs (PAMs) flanking a target sequence. Towards exploiting CRISPR-Cas systems, we first demonstrated that these systems could be harnessed as antimicrobial agents and have been actively developing delivery vehicles based on engineered bacteriophages. Finally, we have established several collaborations to elucidate the functional domains within guide RNAs and to develop DNA-based delivery vehicles for CRISPR ribonucleoprotein complexes into mammalian cells. In total, these efforts have established the versatility of CRISPR-Cas systems and laid a foundation for future efforts to exploit these systems for addressing infectious disease. In the next few years, we aim to extend our prior efforts to advance the characterization of CRISPR-Cas systems and how these systems can be exploited to probe the genetics of bacterial pathogens and generate programmable-spectrum antimicrobials effective against multi-drug resistant bacteria.

Separately, the group is advancing gene-editing capabilities in bacteria. For instance, we have an ongoing collaboration with Chr. Hansen, a starter-culture company in Denmark, developing CRISPR-based tools to probe the genetic features of lactobacilli probiotics. The group is also advancing the same tools to perform combinatorial, genome-wide screens to quickly uncover genetic features linked to the infection cycle and pathogenesis. We are also advancing CRISPR-based antimicrobials by evaluating which of the diverse CRISPR nucleases yield the most potent antimicrobial activity and how to best generate bacteriophage-based delivery vehicles. These efforts are being extended from laboratory strains of *Escherichia coli* to important pathogens such as *Klebsiella* and *Shigella* and could yield much-needed alternatives to antimicrobials.



The Beisel group works at the interface of CRISPR biology and technologies.

RECODING MECHANISMS IN INFECTIONS

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SELECTED PUBLICATIONS

Bock LV*, **Caliskan N***, Korniy N, Peske F, Rodnina MV, Grubmüller H (2019) *Thermodynamic control of -1 programmed ribosomal frameshifting.* **Nature Communications** 10(1):4598

Matsumoto S, **Caliskan N**, Rodnina MV, Murata A, Nakatani K (2018) *Small synthetic molecule-stabilized RNA pseudoknot as an activator for -1 ribosomal frameshifting.* **Nucleic Acids Research** 46(16):8079-8089

Caliskan N, Wohlgemuth I, Korniy N, Pearson M, Peske F, Rodnina MV (2017) *Conditional switch between frameshifting regimes upon translation of dnaX mRNA.* **Molecular Cell** 66(4):558-567

AWARDS

ERC Starting Grant on the topic: *Real-time analysis of ribosomal frameshifting and its impact on immunity and disease* (2020)

Young Leaders in Science Training Program Award from the Schering Foundation, Germany (2018)

RESEARCH INTERESTS

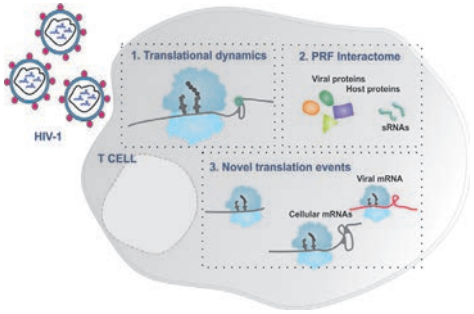
RNA viruses like influenza and coronavirus spread around the world every year with the risk of pandemics. Other RNA viruses like HIV are no longer fatal for the developed world, yet are chronic diseases with no real cure. A striking feature of these viruses is that their mRNAs contain specific signals that direct a portion of translating ribosomes to move into an alternative –1 reading frame. Frameshifting is a well-conserved translational recoding event and is critical for the virulence and pathogenicity of RNA viruses. In addition to *cis*-acting RNA elements, it is suggested that there are numerous cellular factors and small RNAs involved in the regulation of frameshifting. However, how these interactions work during translation elongation remains elusive.

Our objectives are 1) Understanding the interplay between RNA and RNA-binding elements in reprogramming translation; 2) Discovering unconventional translation events in host cellular genes upon HIV-1 infection, sequencing of ribosome protected fragments at different stages of infection to monitor *in vivo* translation profiles; 3) Understanding how cellular sRNAs and proteins regulate the efficiency of translational recoding, which can have essential roles in immune regulation and infection; 4) Exploiting the structural dynamics of frameshifting secondary structures in the presence of *trans*-factors; 5) Screening small molecules for targeting HIV and SARS-CoV-2 frameshift sites.

HIGHLIGHTS & OUTLOOK

Understanding the mechanisms by which pathogens exploit the host translation machinery is highly relevant in an era where viral outbreaks are increasing. So far,

- Using pulldown and proteomics, we identified several cellular proteins, which upon overexpression decrease frameshifting rates on viral mRNAs significantly. We currently characterize these factors by loss/gain of function and infection assays.
- Using cutting-edge confocal assisted optical tweezers, we discovered that the binding of the *trans*-acting viral protein 2A leads to the stabilization of the wild type cardiovirus frameshift RNA structure.
- We have established infection assays and cell culture conditions to globally study host cell translation in T-cells, as well as successfully prepared RNA and Ribo-seq libraries from HIV-1 infected cells.
- We identified small molecule interaction partners of frameshift RNAs, which can modulate the efficiency of recoding on the SARS-CoV-2 mRNA. This can be a promising therapeutic strategy to interfere with viral replication.



Overview of Caliskan lab projects: 1) translational dynamics, 2) regulation of recoding, and 3) high-throughput approaches to identify novel recoding events.

DECODING RNA-PROTEIN INTERACTOMES OF REGULATORY RNA IN INFECTION

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SELECTED PUBLICATIONS

Schmidt N, Lareau C, Keshishian H, Ganskih S, Schneider C, Hennig T, Melanson R, Werner S, Wei Y, Zimmer M, Ade J, Kirschner L, Zielinski S, Dölken L, Lander ES, Caliskan N, Fischer U, Vogel J, Carr S, Bodem J, **Munschauer M** (2020) *The SARS-CoV-2 RNA-protein interactome in infected human cells.* **Nature Microbiology** *in press*

Munschauer M, Nguyen CT, Sirokman K, Hartigan CR, Hogstrom L, Engreitz JM, Fulco CP, Subramanian V, Chen J, Ulirch JC, Schenone M, Guttman M, Carr SA, Lander ES (2018) *The NORAD lncRNA assembles a topoisomerase complex critical for genome stability.* **Nature** 561(7721):132-136.

Khajuria RK, **Munschauer M**, Ulirsch JC, Fiorini C, Ludwig LS, McFarland SK, Abdulhay NJ, Specht H, Keshishian H, Mani DR, Jovanovic M, Ellis SR, Fulco CP, Engreitz JM, Schütz S, *et al.* (2018) *Ribosome Levels Selectively Regulate Translation and Lineage Commitment in Human Hematopoiesis.* **Cell** 173(1):90-103.e19

AWARDS

Helmholtz Young Investigator Award (2018)

RESEARCH INTERESTS

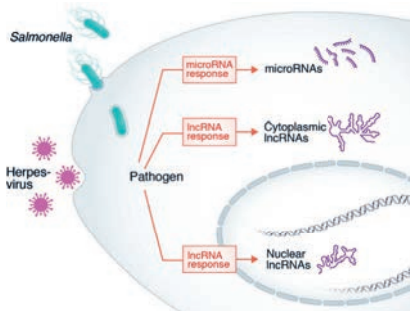
To effectively combat pathogens, host cells need to be able to rapidly adjust their gene expression programs and mount an effective host response. In addition to messenger RNA (mRNA), thousands of so-called long non-coding RNAs (lncRNAs) are actively transcribed and specifically regulated as a result of bacterial or viral infections. While lncRNAs resemble their protein-coding counterparts in length, splicing structure, and biochemical properties, they do not serve as templates for protein synthesis. Hence, their physiological functions and biochemical mechanisms are challenging to dissect, and in many cases remain poorly understood.

The Munschauer group aims to decipher the genetic code controlling lncRNA function by obtaining a quantitative understanding of their molecular interactions and decoding the sequence features or structural elements that mediate these interactions. We seek to elucidate the composition of lncRNA complexes and aim to identify biochemical interactions that enable lncRNA functions.

HIGHLIGHTS & OUTLOOK

With the recent introduction of RNA antisense purification and mass spectrometry (RAP-MS), it is now possible to obtain an unbiased and quantitative picture of the human proteome that directly binds to almost any RNA of interest in intact cells. Using this approach, we have recently shown that lncRNAs can modulate proteins and control their ability to assemble higher-order ribonucleoprotein complexes (Munschauer *et al.*, 2018, Nature). This mode of regulation is frequently referred to as 'riboregulation' and our group is particularly interested in broadly exploring this concept in the context of infection biology.

Beyond lncRNAs, the Munschauer lab is taking a strong interest in viral pathogens, particularly RNA viruses. We aim at understanding their direct interactions with the host cell proteome in order to identify host dependency factors and characterize underlying modes of regulation. In this context, we have recently started to systematically identify the compendium of proteins bound to the genomic RNAs of several positive-sense RNA viruses. To this end, our group is developing and applying cutting-edge technologies to characterize direct interactions of individual RNA species with proteins at high resolution and in a quantitative manner. Ultimately, we hope to utilize insights into the mechanisms of RNA function in order to improve our understanding and ability to treat infectious disease.



The mammalian non-coding RNA response to bacterial or viral infections.
Adapted from Munschauer and Vogel, 2018, EMBO Journal.

SINGLE-CELL ANALYSIS

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SELECTED PUBLICATIONS

Imdahl F*, Vafadarnejad E*, Homberger C, **Saliba AE#**, Vogel J# (2020) *Single-cell RNA-sequencing reports growth-condition-specific global transcriptomes of individual bacteria.*
Nature Microbiology *in press*

Schulte-Schrepping J*, Reusch N*, Paclik D*, Baßler K*, *et al.*, Schultze JL#, Aschenbrenner AC#, Li Y#, Nattermann J#, Sawitzki B#, **Saliba AE#**, Sander LE#, Deutsche COVID-19 OMICS Initiative (DeCOI) (2020) *Severe COVID-19 is marked by a dysregulated myeloid cell compartment.*
Cell S0092-8674(20)30992-2

Erhard F#, Baptista MAP, Krammer T, Hennig T, Lange M, *et al.*, **Saliba AE#**, Dölken L# (2019) *scSLAM-seq reveals core features of transcription dynamics in single cells.*

AWARDS

Circulation Research Best Manuscript Award (2018)

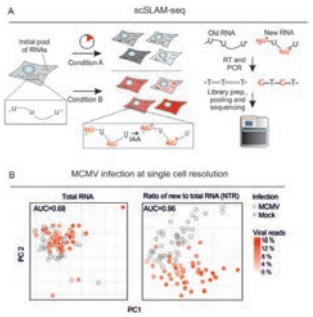
RESEARCH INTERESTS

The ability of pathogens to subvert host cells for survival or replication is in part due to their astonishing capacity to adopt different lifestyles. Characterizing and understanding infected cells at single-cell level resolution using genome-wide transcriptome analysis, in combination with *in vivo* models and tissue engineering, are a powerful approach to understand the heterogeneity inherent to the infection process. These approaches also have the potential to decipher the host-pathogen microenvironment and ultimately resolve the impact of individual infection foci on the disease progression with unprecedented resolution. By studying *Salmonella* Typhimurium and respiratory viruses as model pathogens, we develop quantitative methods based on single-cell transcriptomics to track the physiological features of every individual pathogen in space and time in association with its host and to reconstitute the three-dimensional environment of infection foci.

HIGHLIGHTS & OUTLOOK

In the context of infection, we have pioneered the use of scRNA-seq to investigate heterogeneity in the response of macrophages to *Salmonella*, focusing on bacteria with different growth status including non-replicating 'persisters' that have been linked to recurrent infections. We have revealed a spectrum of functional host response states to growing and non-growing bacteria; specifically, we have discovered that macrophages containing growing bacteria become anti-inflammatory cells. Our data support the emerging idea that bacteria use host genome plasticity to subvert infected cells. These discoveries have fostered novel research directions to integrate scRNA-seq with time series and spatial reconstitution of infection foci. In order to capture time-dependent processes at the single cell level, we developed RNA metabolic approaches (coined scSLAM-seq) to reveal the earliest transcriptomic changes at the first encounter between host and pathogen.

In addition, increasing the sensitivity of scRNA-seq enables us to capture and describe the transcriptome of individual bacterial cells. Such an approach will enable us to also reveal the various fates of pathogens in different infection foci as well as intercellular variability within communities. Yet, the overarching goal will be to interpret these data within the original spatial context of the tissue using imaging-based approaches.



scSLAM-seq captures transcriptional dynamics in infected cells. MCMV, mouse cytomegalovirus; 4sU, 4-thiouridine; IAA, iodoacetamide.

GENOME ARCHITECTURE AND EVOLUTION OF RNA VIRUSES

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SELECTED PUBLICATIONS

Smyth RP, Smith MR, Jousset A-C, Despons L, Laumond G, Decoville T, Cattenoz P, Moog C, Jossinet F, Mougel M, Paillart J-C, von Kleist M & Marquet R (2018) *In cell mutational interference mapping experiment (in cell MIME) identifies the 5' polyadenylation signal as a dual regulator of HIV-1 genomic RNA production and packaging.*
Nucleic Acids Research 46(9):559, doi:10.3389

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Frontiers in Immunology 9:559

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Frontiers in Immunology 9:2097

Mailler E, Bernacchi S, Marquet R, Paillart J-C, Vivet-Boudou V, **Smyth RP** (2016) *The life-cycle of the HIV-1 gag–RNA complex.*
Viruses 8(9):258-267

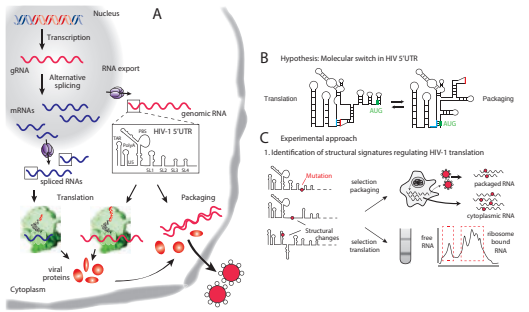
RESEARCH INTERESTS

We study RNA viruses, such as HIV-1, influenza, and SARS-CoV-2, using an RNA-centric approach that focuses on the folding of the RNA genome into complex 3D structures. These RNA structures play key roles in viral replication, pathogenesis, and evolution. On the one hand, we investigate the interaction of these functional RNA structures with proteins, small molecules, or other nucleic acids to identify novel antiviral targets. On the other hand, we study genome architecture in viral particles to better understand molecular mechanisms of viral evolution.

HIGHLIGHTS & OUTLOOK

Using high-throughput mutational and functional profiling, we have discovered a novel RNA motif that regulates the translation of the HIV-1 genome. Our analysis revealed that HIV-1 does not regulate translation of its genome via the 3'UTR, but rather through a short sequence motif within the 5'UTR. We hypothesize that this motif binds a *trans*-cellular or viral factor that could eventually be targeted in antiretroviral therapy. Beyond HIV-1, we are interested in discovering the general principles underlying the regulation of translation by RNA structure. To this end, we have recently repurposed a next generation sequencing technology to perform a parallel analysis of the kinetics of translation initiation. In these experiments, we transcribe and tether RNA to an Illumina flowcell in a way that couples sequencing information to a functional readout. With this system, we will study the role of RNA structure, protein-RNA interactions, and ribosome associated factors on the rate of translation initiation of millions of molecules in parallel.

To better understand the role of RNA dynamics and RNA conformational switches during viral replication, we are also pioneering the analysis of viral RNA structure at the single molecule level using nanopore technology. Finally, to understand the role of higher order RNA structure on viral replication and evolution we have established a new methodology called RNA-RNA-seq. Using the human ribosome and influenza virus as model systems, we have shown that RNA-RNA-seq can identify *cis* and *trans* RNA-RNA interactions in cellular contexts. By combining RNA-RNA-seq with state-of-the-art imaging technologies we are identifying molecular restrictions to influenza evolution by reassortment. Our long-term goal is to better understand the emergence of novel viral strains, such as how potentially pandemic influenza arises from genetic reassortment in pigs or birds.



(A) HIV-1 genomic RNA is packaged into viruses and translated into proteins. (B) Proposed RNA structural switches. (C) Experimental approach.

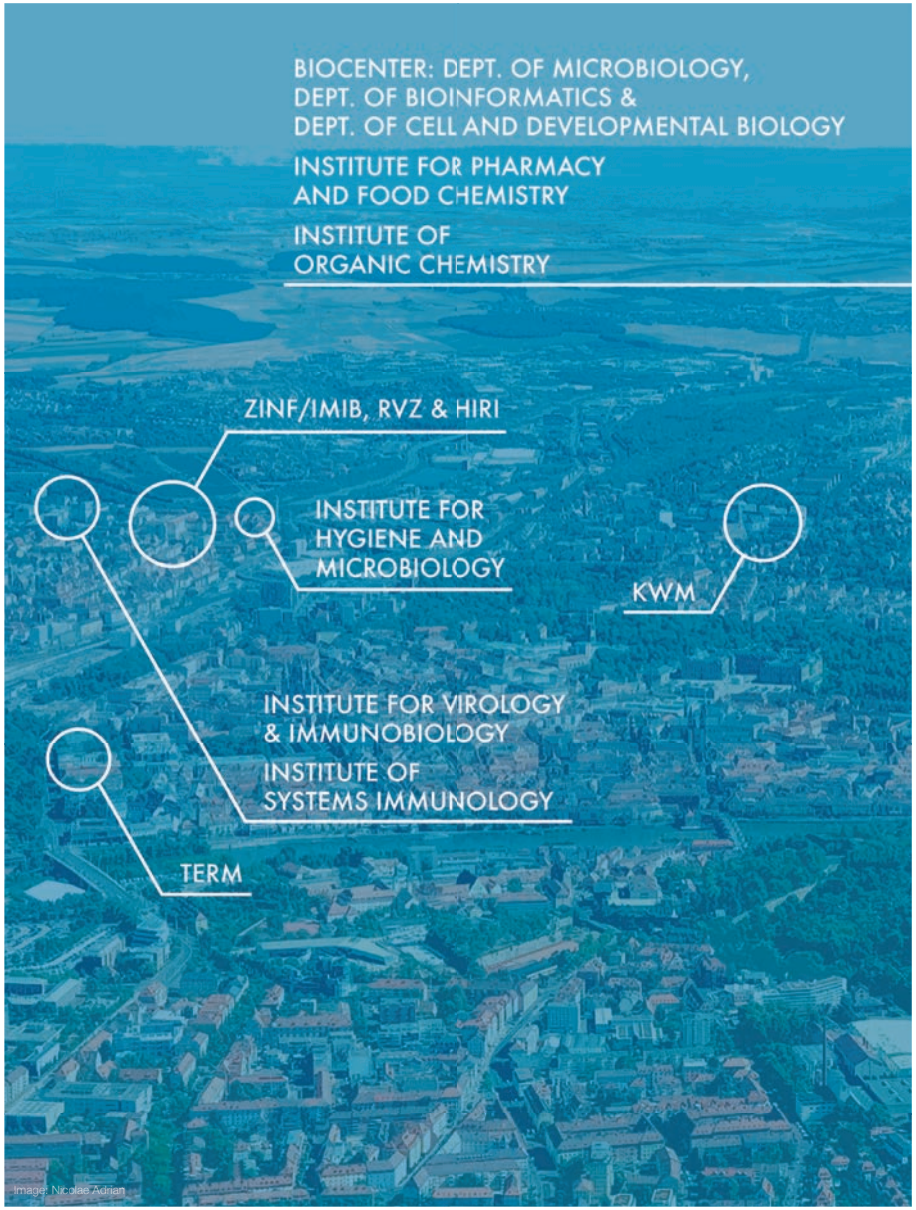


Image: Nicolae Adrian

3.9
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SELECTED PUBLICATIONS

Yang M, Rajeeve K, Rudel T, **Dandekar T** (2019) *Comprehensive Flux Modeling of Chlamydia trachomatis Proteome and qRT-PCR Data Indicate Biphasic Metabolic Differences Between Elementary Bodies and Reticulate Bodies During Infection.*
Frontiers in Microbiology 10:2350

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Bioengineered 10(1):190-196

Srivastava M, Bencurova E, Gupta SK, Weiss E, Löffler J, **Dandekar T** (2019) *Aspergillus fumigatus Challenged by Human Dendritic Cells: Metabolic and Regulatory Pathway Responses Testify a Tight Battle.*
Frontiers in Cellular and Infection Microbiology 9:168

Naseem M, Bencurova E, **Dandekar T** (2018) *The Cytokinin-Activating LOG-Family Proteins Are Not Lysine Decarboxylases.*
Trends in Biochemical Sciences 43(4):232-236

RESEARCH INTERESTS

A variety of approaches model host-pathogen interactions, from individual molecules to metabolic pathways, as well as systems biology, modelling regulatory networks and the dynamics of complex biological systems. Hereby, we follow a generic approach as we are interested in various infection models including different hosts such as animals or plants as well as different infectious agents from fungi to bacteria and viridae. To fulfill our goals, we are furthermore developing new algorithms to model regulatory and metabolic networks as well as generating different and specific biological models of metabolism and regulation in different infection processes.

HIGHLIGHTS & OUTLOOK

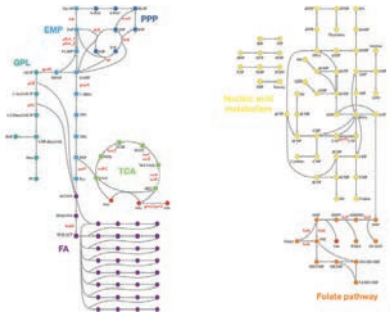
Regarding plant immunity, we found that the LOG enzyme is not a lysine decarboxylase but an important mediator of cytokinin hormonal responses during infection.

We modelled *Chlamydia* flux and metabolism during their biphasic infection course, elementary bodies, and reticulate bodies. Comprehensive Flux Modeling of the *Chlamydia trachomatis* life cycle was based on selected proteome data by elementary mode analysis and calculation of mode strengths. Validation involved qRT-PCR data on various enzymes (Yang *et al*., 2019). With the Kurzai group, we looked at *Candida auris* outbreaks in Germany and could unequivocally prove that infections came from different strains and were not the result of intrahospital transmission. With the Löffler group, we studied how *Aspergillus fumigatus* is challenged by human dendritic cells. There is a tight battle between fungus (growth pathways, redox protection) and the dendritic cells (immune response pathways supported by lipid metabolism, Srivastava *et al*., 2019).

We analyzed antifungal drug and vaccine targets by computer modeling. In collaboration with the Hans Knöll Institute, we analyzed in conidia-containing phagolysosomes processes governing immune evasion.

Oncolytic virus efficiency was predicted by antigen profiling analysis and fitted Boolean models (Cecil *et al*., 2019). Fecal short chain fatty acids (SCFAs) and SCFA-producing bacteria in gut microbiome of human NAFLD are implied in systemic T-cell activation and advanced disease, a new IZKF-funded collaboration with a focus on the mycobiome.

Infections are complex multiparametric processes. To be accessible, omics data are critical so that bioinformatics can shed a light on them analyzing changes in metabolism and regulatory networks and the tight interaction of attack, response, and defense between host and pathogen.



Overview of the central metabolism of *Chlamydia* spp. Image adapted from Yang *et al.*, 2019, Frontiers in Microbiology.

MOLECULAR AND PHYSICAL PARASITOLOGY

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Trends in Parasitology 34(12):1056-1067

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Nature Microbiology 2(11):1523-1532

Bargul JL, Jung J, McOdimba FA, Omogo CO, Adung'a VO, Kruger T, Masiga DK, **Engstler M** (2016) *Species-Specific Adaptations of Trypanosome Morphology and Motility to the Mammalian Host.*
PLoS Pathogens 12(2):e1005448

RESEARCH INTERESTS

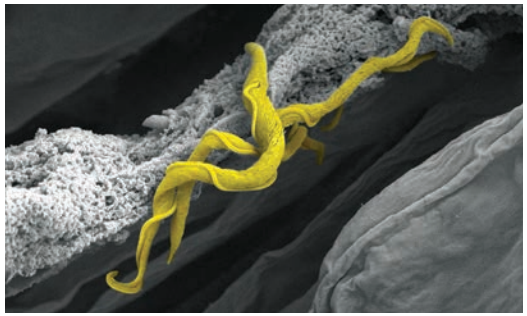
Motion is a hallmark of life. We study motion on very different scales, from molecules to organelles to cells and beyond. Our model system is the African trypanosome, a deadly blood parasite, which is perfect for the analysis of motion on different scales. Throughout their complex life cycle, they are constantly in motion: the cyclical path between their insect vector (tsetse fly) and human host demands dramatic cell biological changes to constantly adapt to these varying environments. At all times, trypanosomes are covered with a dense coat of variant surface glycoproteins (VSG), encoded by VSG genes that are subjected to antigenic variation. In order to stay functional during the cell division cycle, the VSG coat has to maintain its density and fluidity. This process requires very accurate control of membrane and protein trafficking, making trypanosomes ideal models for studying the motion of vesicles and organelles.

HIGHLIGHTS & OUTLOOK

In the framework of the Physics DFG SPP 1726 "Microswimmers", we are looking at the amazing diversity of trypanosome morphotypes in the tsetse fly. Using advanced fluorescence light sheet microscopy, we have described the topology inside the tsetse fly with unprecedented precision. High-end imaging of transgenic parasites, supported by advanced mathematical modelling, allowed us to track individual cells in very large swarms and will help to understand the biological meaning behind the dramatic transitions between solitary and collective motion patterns, principles that can also be translated to other systems, such as microbial biofilms.

In addition, our work on trypanosome development challenges the dogma that life cycle progression to the quiescent stumpy stage requires a quorum sensing factor. Instead, we found that this developmental transition can also occur stochastically, during antigenic variation.

We will intensify our studies on the molecular and genetic control of trypanosome development and using a biophysical approach of single-molecule analyses of VSGs on living parasites and in defined systems, we will provide insights into the dynamics of the trypanosome surface coat. We will continue our analysis of trypanosomes as versatile eukaryotic microswimmers. One focus will be on the tsetse fly parasites, the other on the dissemination and annidation of different trypanosome species in their vertebrate hosts. For this, we have established human skin tissue models that are naturally infected with trypanosomes by tsetse flies.



African trypanosomes (yellow) undertake a weeks-long journey through the transmitting tsetse fly, which is marked by fascinating adaptations to dramatically changing microenvironments.

MEDICINAL CHEMISTRY

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SELECTED PUBLICATIONS

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Seufert F, Kuhn M, Hein M, Weiwad M, Vivoli M, Norville IH, Sarkar-Tyson M, Marshall LE, Schweimer K, Bruhn H, Rosch P, Harmer NJ, Sotriffer CA, **Holzgrabe U** (2016) *Development, synthesis and structure-activity-relationships of inhibitors of the macrophage infectivity potentiator (Mip) proteins of L. pneumophila and B. pseudomallei.* **Bioorganic and Medicinal Chemistry** 24(21):5134-5147

AWARDS

Bayerischer Verdienstorden (2019)

RESEARCH INTERESTS

New anti-infective drugs, especially against protozoa such as malaria, trypanosoma, and leishmania, as well as Gram-negative bacteria, are urgently needed due to the fact that many currently available drugs have significant adverse effects in addition to increasing levels of resistance. The latter is especially true for Gram-negative bacteria, such as *Pseudomonas, Klebsiella, Chlamydia,* and *Neisseria*. Blocking the entry of the bacteria, their invasion and their dissemination in the host by targeting virulence factors represent promising strategies to fight infections. Most Gram-negative bacteria express "macrophage infectivity potentiator" (Mip) proteins that are involved in these processes and thus a promising target.

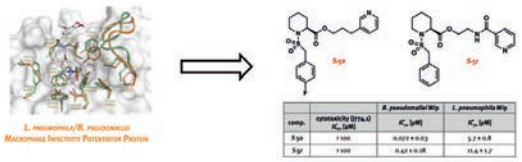
However, for tropical diseases like malaria, sleeping sickness, and Chagas disease the situation is even worse because of the lack of effective drugs. The group develops and optimizes new anti-infectives, especially by means of structure- and ligand-based drug design.

HIGHLIGHTS & OUTLOOK

Since Mip has been proven to be a lethal target in a wide range of Gram-negative bacteria, we have established a library of highly active inhibitors of BpMips and LpMips by applying structure-based design in collaboration with D. Begley and P. Myler (Seattle), I. Norville (Exeter), as well as T. Inglis and M. Sarkar-Tyson (Perth). Those inhibitors were also able to inhibit a plethora of the Mip peptidyl-proline-isomerase (PPIase) from *Francisella tularensis, Yersinia pestis, Coxiella burnetii,* and *Klebsiella pneumoniae,* as well as from *Chlamydia trachomatis, Neisseria meningitidis* & *gonorrhoeae*, and *Leishmania tropica*. Since *Trypanosoma cruzi* are also equipped with a Mip protein, we are going to address this enzyme within a consortium of researchers financed by the BMBF (iMIP). The aim of these studies is not only to find potent inhibitors, being useful in the therapy of an infection, but also to fully understand the Mip role in the different organisms.

Bisnaphthalimides were found to be active against staphylococci. Interestingly, nitro-substituted compounds produced a red color in multi-resistant staphylococci. In collaboration with K. Ohlsen (Würzburg), the color changes could be attributed to a reduction of the nitro group by a reductase that is overexpressed in resistant bacteria, revealing a new mechanism of resistance.

Furthermore, we are interested to find new anti-infective substances in the plant kingdom and to optimize quinolone amides for treatment of trypanosomiasis.



Structure-based design of Mip inhibitors for the treatment of infections by *Legionella* and *Burkholderia*.

STRUCTURE-BASED DRUG DESIGN

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Ramirez YA, Adler TB, Altmann E, Klemm T, Tiesmeyer C, Sauer F, Kathman SG, Statsyuk AV, Sotriffer C, **Kisker C** (2018) *Structural Basis of Substrate Recognition and Covalent Inhibition of Cdu1 from Chlamydia trachomatis.* **ChemMedChem** 13(19): 2014-2023

Giroud M, Dietzel U, Anselm L, Banner D, Kuglstatter A, Benz J, Blanc JB, Gaufreteau D, Liu H, Lin X, Stich A, Kuhn B, Schuler F, Kaiser M, Brun R, Schirmeister T, **Kisker C**, Diederich F, Haap W (2018) *Repurposing a Library of Human Cathepsin L Ligands: Identification of Macrocyclic Lactams as Potent Rhodesain and Trypanosoma brucei Inhibitors.* **J Med Chem** 61(8):3350-3369

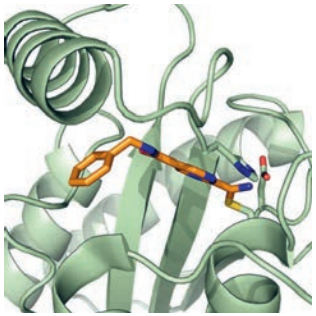
RESEARCH INTERESTS

The continuous emergence of widespread antibiotic resistances in pathogenic bacteria poses a serious risk for current healthcare systems and new approaches for the treatment of infectious diseases are urgently required. The obligate intracellular bacterium *Chlamydia trachomatis* is the most frequently diagnosed sexually transmitted disease pathogen worldwide, and causes more than 100 million new cases annually. Our approach focuses on the inhibition of the chlamydial deubiquitinases ChlaDub1 & ChlaDub2 with the aim to establish new tools for the treatment of *Chlamydia* infections.

HIGHLIGHTS & OUTLOOK

The secretion of dedicated deubiquitinases by obligate intracellular bacteria plays an intriguing role in the evasion of the host cell immune response during an infection. Several key components of the cellular immune response, *e.g.* the NF-kappa-B inhibitor alpha (IκBα) and the anti-apoptotic member of the Bcl-2 family Mcl-1, have been described as targets of the chlamydial deubiquitinases ChlaDub1 & ChlaDub2, thus clearly emphasizing the importance of these proteins to chlamydial pathogenicity, which is further supported by apparent growth deficits in ChlaDub1-deficient *C. trachomatis* strains. Encouraged by these results, we pursue the development of specific ChlaDub inhibitors for anti-chlamydial therapy.

Based on a so-called target hopping approach, pre-existing compounds from Novartis, designed to specifically target the evolutionary related Adenain protease, were screened for their inhibitory potential against ChlaDub1. Out of seven tested Adenain inhibitors, two displayed crossreactivity towards ChlaDub1 with dissociation constants in the micromolar range. Despite their moderate affinity, we succeeded to solve crystal structures of ChlaDub1 covalently modified by the two compounds. These structures provide the basis to proceed with a structure-aided drug design approach. Combining docking algorithms with molecular dynamic simulations, we built upon the cyano-pyrimidine backbones of our two lead structures, generating a library of more specific ChlaDub inhibitors. This approach proved to be successful, as the most promising candidate, termed HJR108, displayed a 10-fold increase in affinity towards ChlaDub1 compared to its precursors. Several additional cycles of structure-based drug design will be required to obtain an inhibitor with sufficient affinity and substrate specificity towards ChlaDub1 & ChlaDub2.



Close-up view of the ChlaDub1 active site. The inhibitor is covalently linked to the catalytically active Cys345 via its cyano-pyrimidine based warhead.

HUMAN 3D TISSUE MODELS TO STUDY HOST-PATHOGEN INTERACTIONS IN INFECTIOUS RESEARCH

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SELECTED PUBLICATIONS

Alzheimer M, Svensson SL, König F, Schweinlin M, **Metzger M**, Walles H, Sharma CM (2020) *A Three-Dimensional Intestinal Tissue Model Reveals Factors and Small Regulatory RNAs Important for Colonization With Campylobacter jejuni.*
PLoS Pathogens 16(2):e1008304

Schulte LN, Schweinlin M, Westermann AJ, Janga H, Santos SC, Appenzeller S, Walles H, Vogel J, **Metzger M** (2020) *An Advanced Human Intestinal Coculture Model Reveals Compartmentalized Host and Pathogen Strategies During Salmonella Infection.*
mBio 11(1):e03348-19

Martins Gomes SF, Westermann AJ, Sauerwein T, Hertlein T, Förstner KU, Ohlsen K, **Metzger M**, Shusta EV, Kim BJ, Appelt-Menzel A, Schubert-Unkmeir A (2019) *Induced Pluripotent Stem Cell-Derived Brain Endothelial Cells as a Cellular Model to Study Neisseria meningitidis Infection.*
Frontiers in Microbiology 10:1181

Kress S, Baur J, Otto C, Burkard N, Braspenning J, Walles H, Nickel J, **Metzger M** (2018) *Evaluation of a Miniaturized Biologically Vascularized Scaffold in vitro and in vivo.*
Scientific Reports 8(1):4719

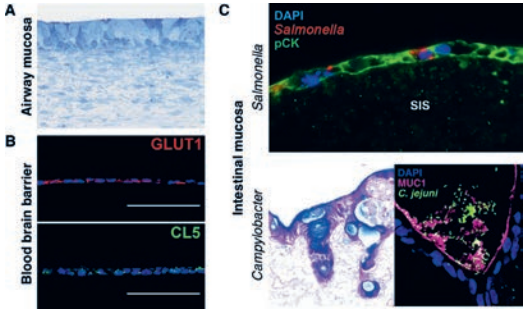
RESEARCH INTERESTS

A major obstacle in infection biology is the limited ability to recapitulate human disease trajectories in traditional cell culture and animal models, which impedes the translation of basic research into clinics. Our research interest is to apply state-of-the-art tissue engineering techniques, including the use of novel biomaterials, dynamic culture, and co-culture settings, allowing the study of the underlying cellular and molecular mechanisms involved in distinct infectious diseases. Of particular interest are models representing human barrier organs such as the gastrointestinal tract, blood-brain barrier, the respiratory tract, and the skin, which pose the main contact surface for pathogenic microbes.

HIGHLIGHTS & OUTLOOK

Our 3D intestinal tissue model was used to study human enteric infections at a level of detail that is not achieved by conventional two-dimensional monocultures. Our model comprises epithelial and endothelial layers, a decellularized intestinal matrix scaffold, and immune cells. Upon *Salmonella* infection, the model mimics human gastroenteritis, in that it restricts the pathogen to the epithelial compartment, an advantage over existing mouse models. Application of dual transcriptome sequencing to the *Salmonella*-infected model revealed the communication of epithelial, endothelial, monocytic, and natural killer cells among each other and with the pathogen (cooperation with Prof. Jörg Vogel, Würzburg). Our results suggest that *Salmonella* uses its type III secretion systems to manipulate STAT3-dependent inflammatory responses locally in the epithelium without accompanying alterations in the endothelial compartment. Our approach promises to reveal further human-specific infection strategies employed by *Salmonella* (Fig. Panel C) and other gastrointestinal pathogens such as *Helicobacter pylori* and *Campylobacter jejuni* (cooperation with Prof. Cynthia Sharma, Würzburg; Fig. Panel C).

Other research highlights comprise our iPSC-derived human blood-brain-barrier (BBB) model to study infection pathways of *Neisseria meningitidis* (cooperation with Prof. Alexandra Schubert-Unkmeir, Würzburg; Fig. Panel B), which causes diseases such as meningitis and sepsis. Our primary human upper airway tissue models were used to study interactions with *Bordetella pertussis* (cooperation with Prof. Roy Gross, Würzburg; Fig. Panel A). After infection, we observed severe epithelial damage, such as cellular extrusions and impaired barrier integrity. Currently this model is also used in re-purposing compound screens with respect to the current COVID-19 pandemic.



3D *in vitro* models of (A) human airway mucosa, (B) iPSC-derived BBB, and (C) the human gut. Images by M. Steinke (A), A. Appelt-Menzel (B), M. Schweinlin (C, *Salmonella*), M. Alzheimer (C, *Campylobacter*)

CHEMISTRY IN LIVING SYSTEMS

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SELECTED PUBLICATIONS

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Chemical Science 9(24):5312-5321

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Scientific Reports 7(1):17627

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ChemBioChem 18(15):1477-1481

RESEARCH INTERESTS

Our research interests center around the exploding field of glycosciences, sphingolipids, and natural products including the development of chemical and enzymatic syntheses, biocatalysis, protein engineering, and drug delivery. Our motivations arise from the challenge of understanding fundamental molecular mechanisms of life and direct them.

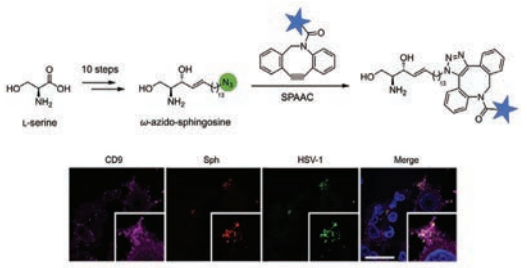
HIGHLIGHTS & OUTLOOK

Sphingolipids in infectious diseases: Because sphingolipids are major components of membranes, sphingolipid biosynthesis and metabolism and availability of their signaling inert or bioactive species substantially affect the biophysical properties of membranes and the subcellular redistribution of receptors and signaling complexes.

This may essentially regulate pathogen uptake and handling at a cellular and organismic level as well as survival and activity of immune cells. We aim to identify and validate targets for novel anti-infective strategies targeting infectious diseases at the level of modulation of sphingolipid metabolism. As a long-term perspective, rationally defined synthetic sphingolipid analogues or metabolizing enzymes will be evaluated for therapeutic options in different infectious disease models.

Metabolic labeling of cell surfaces and in cells was established in order to study and characterize cell signaling and cell-cell interactions to examine inflammation and infection processes. Carbohydrates and sphingolipids, which were modified by introducing an azide or alkyne group passed the natural sphingolipid and carbohydrate biosynthetic pathways and were incorporated into the post-translational glycan patterns of proteins and sphingolipid metabolism.

Chemical bioorthogonal posttranslational protein modification & inhibitor design: Site directed mutagenesis has been used to reshape proteins in their function. We investigate bioorthogonal chemical tyrosine modification via the Ene-reaction which seems to be an attractive strategy especially for tailoring the scaffold of enzymes while extending the canon of natural amino acids. In addition to the protein modification we also follow ligand/inhibitor design of proteins. One example is galectins, a protein family that has recently become a promising source of cancer research, such as galectin-1, which sits on the surface of all human cells; on tumor cells, however, it occurs in enormous quantities, making it an interesting target for diagnostics and therapy. Complex sugar molecules specifically binding to the tumor protein Galectin-1 are designed, which could help to recognize tumors at an early stage and to combat them in a targeted manner.



Functional sphingolipids visualized in herpes infection.

TROPICAL MEDICINE

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SELECTED PUBLICATIONS

Giroud M, Dietzel U, Anselm L, Banner D, Kuglstatter A, Benz J, Blanc JB, Gaufreteau D, Liu H, Lin X, **Stich A**, *et al.* (2018) *Repurposing a Library of Human Cathepsin L Ligands: Identification of Macrocyclic Lactams as Potent Rhodesain and Trypanosoma brucei Inhibitors.*
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RESEARCH INTERESTS

Tropical Medicine is a multisectorial field that comprises of travel medicine, diagnosis, and treatment of diseases in hot climates, rare infections, migrant health, as well as the provision of medical care in resource-limited regions. It goes far beyond infectious diseases, also providing the link to the new research areas of *Global* and *Planetary Health*.

Two percent of returning travelers seek medical care for symptoms connected with the exposure to tropical diseases such as malaria or dengue fever, parasite infections (*e.g. Giardia intestinalis*), or skin conditions (*e.g.* Larva migrans cutanea, staphylococcal pyodermia or erysipelas). In the area of migrant health, German clinicians are often faced with unfamiliar diseases such as leprosy, intestinal helminths, sickle cell disease, familial Mediterranean fever, or extrapulmonary tuberculosis, some of which are difficult to diagnose and require specialized expertise for which Würzburg has one of the leading centers in Germany.

Patient care during the 2019 Ebola outbreak in DRC.

HIGHLIGHTS & OUTLOOK

As part of the daily clinical routines, our department has managed the diagnosis and care of patients with rare infectious diseases like tularaemia, histoplasmosis, or echinococcosis. We were directly involved in the control of the second largest Ebola outbreak in history, which took place in the Democratic Republic of Congo. In Colombia we are involved in an EKFS-founded project to combat Chagas Disease in indigenous populations. Our work on migrant health in Germany is developing a comprehensive approach to improve medical care for asylum seekers and to provide their access to health care as a basic human right. In this context we developed a tool to improve compliance and treatment outcome in migrant patients with tuberculosis.

During the next years we will intensify our cooperation with African partners especially in Tanzania, with a strong focus on schistosomiasis and other parasitic diseases. Together with the Würzburg-based German Leprosy and Tuberculosis Relief Association, the world's largest leprosy relief organization, and other partners we founded the *German Center for Multisectorial Fight Against Neglected Tropical Diseases* (DZVT). Our priority in the next years will be to establish a focal point for training, exchange, and networking in the field of Global Health.

4

RESEARCH PROGRAMS

4 RESEARCH PROGRAMS

CURRENT RESEARCH PROGRAMS OF ZINF MEMBERS

4.1

DFG COLLABORATIVE RESEARCH CENTER (CRC) / SFB TRANSREGIO 34

PATHOPHYSIOLOGY OF STAPHYLOCOCCI IN THE POST-GENOME ERA

Staphylococcus aureus is a leading cause of bacterial infection in hospitals worldwide. This microbe is a prominent example of the current antibiotic resistance crisis, one of the major threats to health in the 21st century. However, *S. aureus* is also a fascinating model organism to study host-pathogen interactions. Humans are exposed to these bacteria often within the first hours of life. These encounters have a multi-faceted outcome, ranging from symptomless colonization and mild skin infections to life threatening disease. Despite extensive efforts in the field, we still lack an effective vaccine to protect from *S. aureus*. The bacterium is equipped with an impressive assortment of fitness and virulence factors, including a wide variety of immune evasive compounds. Intricate regulation networks enable it to withstand hostile environmental conditions, such as nutrient limitation, oxidative stress, or anaerobic conditions. In recent years, *S. aureus* has also been recognized as a facultative intracellular pathogen that can persist inside endothelial and epithelial cells and establish a chronic infection.

The SFB Transregio 34 (Würzburg, Greifswald, Tübingen, Münster) addresses multiple dimensions and complexities of this topic by an interdisciplinary approach using new methodology. It brings together bacteriological and immunological expertise with quantitative biomolecular analytics, structural biology, genomics, bioinformatics, hematology, and imaging. In the postgenomic era, the availability of whole-genome sequences of *S. aureus* and its human host has paved the way for comprehensive analysis of transcription profiles, proteins, and metabolites. It is now possible to obtain biological fingerprints of bacteria and host with unprecedented detail. This opens avenues for a new quality in the understanding of cell physiology, pathophysiology, and infection biology. The CRC/TRR 34 focuses on host-pathogen interaction during *S. aureus* colonization and infection, progressing from cell culture systems of increasing complexity to animal models of infection, and studies with human subjects.

Projects involving ZINF members:

A02 KNUT OHLSEN
(Institute of Molecular Infection Biology)
Phosphoproteomic analysis of *Staphylococcus aureus:* Functional characterization of kinases and identification of their substrates

Z03 *In vivo* imaging of *Staphylococcus aureus* infections

A08 THOMAS DANDEKAR
(Dept. of Bioinformatics)
A systems biology perspective of metabolic and regulatory adaptation of *Staphylococcus aureus* to infection-related conditions

INFZ01 An integrated view of adaptation of *Staphylococcus aureus*

B04 WILMA ZIEBUHR
(Institute of Molecular Infection Biology)
Regulation of methionine metabolism in staphylococci: Impact on fitness and virulence

C06 JÖRG VOGEL
(Institute of Molecular Infection Biology)
Post-invasion events in *Staphylococcus aureus* infected host cells – A combined transcriptomics / proteomics *in vivo* approach

C11 MARTIN FRAUNHOLZ & THOMAS RUDEL
(Dept. of Microbiology)
Host cell death induced by *Staphylococcus aureus* and its linkage to phagosomal escape

4.2

DFG COLLABORATIVE RESEARCH CENTER (CRC) / SFB TRANSREGIO 124

PATHOGENIC FUNGI & THEIR HUMAN HOST: NETWORKS OF INTERACTION - FUNGINET

The incidence of invasive mycoses due to opportunistic fungal pathogens has increased significantly over the past two decades. This increase in infections is associated with excessive morbidity and mortality and is directly related to a growing number of patients at risk of developing serious fungal infections. Despite this, the current diagnosis of life-threatening fungal infections remains difficult and is often too late. There are only limited options for therapies, which are often ineffective. The yeast *Candida albicans* and the filamentous fungus *Aspergillus fumigatus* are by far the most important causes of life-threatening invasive mycoses in Europe. Both fungi have developed multiple sophisticated, specific, and unique pathogenicity mechanisms, many of which are not well understood.

This CRC/TRR 124 brings together researchers from the Friedrich Schiller University and Hans Knöll Institute in Jena and the ZINF in Würzburg to obtain comprehensive insights into the medically important fungi *C. albicans* and *A. fumigatus* and their interactions with the human host. The aims of the CRC/TRR 124 are to identify pathogenic determinants specific for each fungus and investigate the roles of epithelial barriers, the mechanisms of innate immunity, and potential contributions of the adaptive immune system to the pathogenesis of fungal infections. These will help to elucidate the complex mechanisms of fungal infections and identify common principles of their pathogenesis. The insights gained from these studies will be applied to develop new therapeutic approaches. To obtain a comprehensive description and understanding of complex invasive fungal infections, a systems biological approach will be taken to complement studies of fungal pathobiology and the response of the immune system. Systems biology will help to reveal the structure and dynamics of molecular and cellular cause-effect relations within these pathogenic interactions. The vision of systems biology is the generation of a virtual infection model that enables the prediction of the consequences of changing parameters, such as reduced activity of certain immune effector cells or receptors for the infection. A detailed knowledge of the infection biology of *A. fumigatus* and *C. albicans* and the immune response mechanisms will provide the basis for better diagnosis and therapy of systemic infections. Due to the involvement of two very active clinical departments, a sufficient number of samples will be available for analysis and greatly contribute to fulfilling the potential of developing the basic science (bench) to the patient (bedside).

Projects involving ZINF members:

A02 HERMANN EINSELE & JÜRGEN LÖFFLER
(Dept. of Internal Medicine II)
Interaction of *Aspergillus fumigatus* with human natural killer cells, dendritic cells, and human alveolar epithelia

A03 ANDREAS BEILHACK
(Dept. of Internal Medicine II)
In vivo analysis of temporal and spatial disease progression and immune cell recruitment during invasive *Aspergillus fumigatus* and *Candida albicans* infections

B01 THOMAS DANDEKAR
(Dept. of Bioinformatics)
Modelling interactions between the host and fungal pathogens by combining metabolic pathway analysis and evolutionary game theory

B02 Interaction networks of signaling molecules and pathways between the pathogenic fungi *Aspergillus fumigatus* and *Candida albicans* and their human host

C01 CHRISTIAN PÉREZ
(ZINF and IZKF)
Molecular characterization of *Candida albicans* mucosal colonization, infection, and translocation

C02 JOACHIM MORSCHHÄUSER
(Institute of Molecular Infection Biology)
Regulation of *Candida albicans* virulence traits by protein kinases

C03 OLIVER KURZAI
(Institute for Hygiene and Microbiology)
Intrinsic modulation of neutrophil antifungal activity against *Candida albicans*

C06 NIKLAS BEYERSDORF
(Institute for Virology and Immunobiology)
Secreted fungal proteins in immune evasion and pathogenicity

4.3

DFG RESEARCH UNIT 1680

UNRAVELLING THE PROKARYOTIC IMMUNE SYSTEM

The CRISPR-Cas system (CRISPR: clustered regularly interspaced short palindromic repeats, Cas: CRISPR-associated) is an adaptive and heritable resistance mechanism against foreign genetic elements. It consists of clusters of repetitive chromosomal DNA in which short palindromic DNA repeats are separated by short spacers, the latter being sequences derived from the invader. Key players of this prokaryotic immune system are the CRISPR RNAs and Cas proteins, the latter of which show a remarkable degree of diversity and belong to approximately 45 different protein families. For most of these proteins their functional roles are unclear.

The major goal of the DFG Research Unit 1680 is to unravel the CRISPR-Cas system in bacteria and archaea. While it has some conserved features in prokaryotes, bioinformatics analyses suggest the presence of certain protein components in cyanobacteria and some chloroflexi, which otherwise occur exclusively in archaea. Despite the progress made in understanding CRISPR function, the structure and function of its key components remain unknown. The novel approach of this Research Unit is to take seven different bacterial and archaeal organisms to define the common main features of the CRISPR system and to unravel the species-specific unique subsystems using a comparative approach with the help of mass spectrometry, crystallography, and bioinformatics.

Projects involving ZINF members:

B02 JÖRG VOGEL
(Institute of Molecular Infection Biology)
Alternative functions of the CRISPR-associated endonuclease Cas9

4.4

DFG RESEARCH UNIT 2123

SPHINGOLIPID DYNAMICS IN INFECTION CONTROL

Lipid ordered membrane microdomains enriched for sphingomyelin and sterols are believed to serve as platforms for the compartmentalization of membrane-associated proteins such as receptors and membrane-proximal signaling components in regulating processes involved in cytoskeletal dynamics. As major membrane components, sphingolipids and their ceramide metabolites play a key role in the dynamics of activated membrane microdomains.

These are implicated in steps decisive for the interaction of a host cell with pathogens such as attachment, entry, intracellular trafficking, compartmentalization, and regulation of cell autonomous defense. Because immune responses can also be regulated at the level of sphingolipid dynamics, this pathway most likely controls elements in the pathogenesis of infectious diseases where pathogen uptake, spread, and dissemination are counteracted by host autonomous, innate, and adaptive immune responses.

The ultimate goal of the Research Unit 2123 is the identification of novel targets and the development of tools for (immuno)therapeutic interventions. Core topics of this consortium are the regulatory role of sphingolipid dynamics at the host and pathogen level by addressing (1) adhesion, activation, differentiation, and effector functions of T cells at a molecular and cellular level as well as in experimental infection models, and (2) pathogen adhesion/invasion, trafficking, and modulation of host cell functions essential in the control of bacterial pathogens. The research unit combines expertise in the infection biology of medically important pathogens such as measles virus (MV), *Neisseria meningitidis*, *Neisseria gonorrhoeae*, and *Mycobacterium tuberculosis*, with sphingolipid biology in infectious viral and bacterial disease pathogenesis, as well as T cell biology, immunotherapy, and macrophage biology. The Research Unit 2123 benefits from a technical platform providing highly advanced, novel approaches for spatial resolution of sphingolipids to achieve its vision to translate major finding into clinical application.

Projects involving ZINF members:

P01 SIBYLLE SCHNEIDER-SCHAULIES
(Institute for Virology and Immunobiology)
Sphingomyelinase activation in T cells: Implications for T cell activation and paralysis and Central Coordination Project

P02 NIKLAS BEYERSDORF & JÜRGEN SCHNEIDER-SCHAULIES
(Institute for Virology and Immunobiology)
Role of sphingolipids in the regulation of anti-viral T cell responses

P03 ALEXANDRA SCHUBERT-UNKMEIR
(Institute for Hygiene and Microbiology)
Analysis of the functional relevance of sphingomyelinases and ceramide in meningococcal pathogenesis

P04 THOMAS RUDEL
(Dept. of Microbiology)
Sphingolipids in gonococcal infection

P06 MARTIN FRAUNHOLZ
(Dept. of Microbiology)
Role of the acid sphingomyelinase/ceramide system in lung edema induced by *Staphylococcus aureus* toxin

P07 JÜRGEN SEIBEL
(Institute of Organic Chemistry)
Coating of endotracheal tubes with sphingosine to prevent bacterial growth and ventilator associated pneumonia

Z01 JÜRGEN SEIBEL
(Institute of Organic Chemistry)
Sphingolipid metabolic pathways in infection control by the use of chemically synthesized modified sphingolipids and in the era of sphingolipidomics

4.5
DFG RESEARCH UNIT 2830
ADVANCED CONCEPTS IN CELLULAR IMMUNE CONTROL OF CYTOMEGALOVIRUS

The human cytomegalovirus (HCMV) persistently infects the majority of the world's population. Its clinical relevance and socioeconomic impact is large, but commonly underappreciated. While HCMV infection of healthy individuals is usually subclinical, life-threatening HCMV disease is frequent among the immunocompromised. In particular, hematopoietic stem cell or solid organ transplant recipients suffer from HCMV-induced pneumonia, colitis, retinitis, or graft rejection followed by transplant failure. An even larger social burden stems from congenital HCMV infection. Moreover, HCMV persistence is associated with cardiovascular disease in the elderly and immunosenescence, indicating that insidious HCMV disorders affect a large swath of the general population. While antiviral drugs against HCMV are in clinical use, their benefit is limited by serious adverse effects and the development of drug resistance. While a vaccine against HCMV is still not available, substantial efforts are thus being undertaken to generate and explore an HCMV-based vaccine platform.

The central aim of this Research Unit is to close major gaps in knowledge about the immunological function of CMV gene products and their role in host immune system-pathogen interaction. In particular, the consortium aims to understand the molecular interactions of CMV-infected antigen-presenting cells (APCs) with cytotoxic T cell (CTLs) and natural killer (NK) cells at the molecular, cellular, and organism level. Studies in the murine cytomegalovirus (MCMV) animal model revealed many fundamental aspects of this interaction that were subsequently confirmed for HCMV. These include, but are not restricted to, (i) the efficient subversion of CD8 T cell and NK cell responses by viral immune evasins, (ii) the continuous expansion of CMV-specific CD8 T cells (memory inflation) over time, (iii) the intensive interplay between activating and inhibitory NK cell receptors in virus control that shape a host's susceptibility to CMV infection, and (iv) the generation of 'memory-like' NK cells that show features of adaptive immunity. By bringing together findings from various experimental systems, the Research Unit aims to map big pictures of CMV pathogenesis, evasion strategies, and immunity. In addition, the integration of clinical groups will enable key findings of the Research Unit to immediately impact diagnostic procedures, risk stratification, and immunotherapies executed at the University Hospitals in Würzburg and Freiburg as well as at the Hannover Medical School (MHH).

Projects involving ZINF members:

P01 LARS DÖLKEN & FLORIAN ERHARD
(Dept. of Virology)
Integrative analyses of CMV translatomes and MHC-I ligandomes

P09 HERMANN EINSELE
(Dept. of Internal Medicine II)
Personalized medicine – Risk stratification and prevention of HCMV-related disease in transplant patients based on MHC-I ligandomes

4.6
DFG PRIORITY PROGRAM SPP 1617
PHENOTYPIC HETEROGENEITY AND SOCIOBIOLOGY OF BACTERIAL POPULATIONS

The DFG-funded Priority Program SPP 1617 brings together microbiologists from all fields of bacteriology (*e.g.*, infection biology, terrestrial microbiology, biotechnology, *etc.*) with theoreticians from the mathematical and physical sciences. In a combined interdisciplinary effort, SPP 1617 aims at a deeper understanding of the complexity of bacterial populations and the theoretical modelling and prediction of their diversity. The focal point of this research is the generation of phenotypic variation in bacterial communities, the evolutionary mechanisms that give rise to genotypes expressing diverse phenotypes, as well as the biological significance of the processes. Individual projects cover cell-cell communication and the production of common goods, the division of labor, as well as bet-hedging strategies in bacteria of medical, biotechnological and ecological interest.

Projects involving ZINF members:

WILMA ZIEBUHR
(Institute of Molecular Infection Biology)
Heterogeneous gene expression, metabolic variability, and differentiation in *Staphylococcus epidermidis* biofilms

4.7
DFG PRIORITY PROGRAM SPP 1656
INTESTINAL MICROBIOTA - A MICROBIAL ECOSYSTEM AT THE EDGE BETWEEN IMMUNE HOMEOSTASIS & INFLAMMATION

The gut provides an explicitly large and dynamic interface towards the luminal microbiota, and tissue homeostasis is achieved by a compartmentalized immune system. The goal of the SPP 1656 is to achieve a functional understanding of microbe-host interactions in health and disease, beyond rapidly emerging knowledge of largely descriptive compositional and metagenomic analyses. Fundamental research will help to identify factors that shape the bi-directional interaction between microbiota and host under physiologic and pathologic conditions, specifically aiming to understand the transition of immune homeostasis towards inflammatory pathologies. This includes (1) the interaction between the intestinal microbiota and the mucosal immune system at early life stages and in response to diet and host genotypes, (2) microbe-host interactions in the pathophysiological transition from immune homeostasis to infectious and chronic inflammatory disorders, and (3) the establishment of mechanistic concepts for pre-clinical efficacy and risk evaluation of probiotic intervention and fecal transplantation in infectious and chronic inflammatory disorders. Moreover, the SPP 1656 aims to develop infrastructural networks such as a one-core center for the generation of novel germ-free models and three outposts for specific experimental applications. In addition, the SPP 1656 will strengthen two core centers for metagenomic and metabolite analysis with a strong emphasis on the transfer of standardized methodologies and protocols for sample processing and data analysis.

Projects involving ZINF members:

CHRISTIAN PÉREZ
(ZINF and IZKF)
Genetic circuits underlying fungal-bacterial interactions in the mammalian intestine

4.8
DFG PRIORITY PROGRAM SPP 1726
MICROSWIMMERS - FROM SINGLE PARTICLE MOTION TO COLLECTIVE BEHAVIOR

Locomotion and transport of microorganisms in fluids is an essential aspect of life. Searching for food, orientation toward light, spreading of progeny, and the formation of colonies require locomotion, for which microorganisms such as bacteria, algae, and sperm exploit flagella for propulsion. However, swimming at the microscale occurs at low Reynolds numbers, where fluid friction and viscosity dominate inertia. This requires swimming strategies that differ from those used in the macroscopic world in *e.g.* propulsion mechanism, energy supply, and regulation in response to external stimuli. Understanding these mechanisms at the molecular level opens avenues for control of biological systema and the design of artificial nanomachines.

The aim of the SPP 1726 is to coherently combine research activities on microswimmers in biology, biophysics, theoretical and experimental soft matter physics, and simulation sciences. Advanced experimental techniques, new nanotechnological tools, soft-matter chemistry and physics, and novel simulation approaches promise deeper insights into the underlying physical and bio-chemical processes and provide the tools to design and construct new artificial microswimmers. Accordingly, the major focus of the priority program is (1) the understanding of biological microswimmers, (2) the design and understanding of artificial microswimmers, and (3) the cooperative behavior and "swarming" of ensembles of microswimmers.

Projects involving ZINF members:

MARKUS ENGSTLER
(Dept. of Cell and Developmental Biology)
From solitary swimmers to swarms and back: trypanosomes on their journey through the tsetse fly

4.9

DFG PRIORITY PROGRAM SPP 1784

CHEMICAL BIOLOGY OF NATIVE NUCLEIC ACID MODIFICATIONS

Natural covalent nucleic acid modifications form a new hidden layer of information in the genetic code beyond the classical four-letter alphabet. The Priority Program SPP 1784 was established to unravel this code. A network of researchers with backgrounds in chemical biology, structural biology, enzymology, and bioinformatics aims to gain a deeper insight into where, how, and why native nucleic acid modifications occur and how they influence cellular processes. Modifications, as defined in the program, are specifically introduced into the nucleic acid by cognate enzymes, and do not include chemical lesions, DNA or RNA damage inflicted by light, reactive oxygen species, chemicals, and the like. SPP participants address current challenges in the detection, localization, recognition, and function of naturally occurring modifications in RNA and DNA. These goals are further supported by a bundle of measures including provisions for central network funds for analytical methods crucial to the field, in particular deep sequencing and LC-MS.

Projects involving ZINF members:

CYNTHIA SHARMA
(Institute of Molecular Infection Biology)
Identification and functional characterization of pseudouridine in mRNAs and non-coding RNAs of the bacterial human pathogen *Campylobacter jejuni*

JÖRG VOGEL
(Institute of Molecular Infection Biology)
Discovery and characterization of RNA modifications in a bacterial model pathogen

4.10

DFG PRIORITY PROGRAM SPP 1937

INNATE LYMPHOID CELLS

The most recently discovered family of innate immune cells are innate lymphoid cells (ILCs), which contribute to the maintenance of tissue homeostasis, the tolerance to food or commensal bacteria, and the immune responses to pathogens. The SPP 1937 aims to establish an interdisciplinary research program that comprehensively investigates ILCs in mouse models and humans by providing novel insights into ILCs as guardians of tissue homeostasis and repair, in the defense against infections, and in the pathogenesis of inflammation-driven diseases. These lines of research will identify previously unappreciated functions of the immune system and will pave the way for the development of new treatment strategies in inflammation. Research on ILCs has a strong interdisciplinary trajectory far beyond immunology because it develops at the interface between the immune system and the biology of organ development as well as tissue homeostasis and repair. The SPP 1937 aims to (1) understand the signals and molecular mechanisms controlling ILC fate decisions and effector functions, (2) determine how ILCs can discriminate between "self" and "non-self", (3) understand the role of ILCs in organ homeostasis and tissue renewal, and (4) analyze the contribution of ILCs for immunity to infections and in the pathogenesis of inflammation-driven diseases.

Projects involving ZINF members:

GEORG GASTEIGER
(Institute of Systems Immunology)
Tissue-niches and cellular interactions of mouse and human ILCs at single-cell resolution

4.11

DFG PRIORITY PROGRAM SPP 2002

SMALL PROTEINS IN PROKARYOTES, AN UNEXPLORED WORLD

Prokaryotes are highly abundant and diverse organisms living in all ecological niches. They have broad impact on the environment and our health and are crucial for biotechnology and the food industry. To fully understand their versatile lifestyles and exploit their metabolic capacities, knowledge about their biochemical repertoires and regulatory processes is required. Modern genomics and transcriptomics technologies have discovered a wealth of hidden small genes containing short open reading frames (sORFs) in many prokaryotic genomes. These sORFs encode small proteins of <50 amino acids in length and are typically missed by automated gene predictions. Preliminary studies have shown that these small proteins impact cellular processes such as energy generation, transport, virulence, symbiosis, sporulation, and photosynthesis. They often localize to membranes and can modulate the activity of larger protein complexes. These initial findings notwithstanding, the full repertoire and function of this cellular small proteome, which comprises potentially hundreds of small proteins in any given prokaryote, remains to be uncovered.

The Priority Program SPP 2002 aims to unravel this emerging major class of prokaryotic gene products in order to examine the full repertoire, functions, and functional importance of prokaryotic small proteins. With the overall goal to identify the composition and characterize the function(s) of the prokaryotic small proteome this Priority Program exclusively focuses on ribosomally synthesized small proteins in prokaryotes. To achieve these goals, the SPP fosters an interdisciplinary cooperation of researchers in microbiology, infection biology, plant physiology, chemistry, biochemistry, genetics, genomics, as well as applied bioinformatics.

Projects involving ZINF members:

CYNTHIA SHARMA
(Institute of Molecular Infection Biology)
Exploring small proteins in the foodborne pathogen *Campylobacter jejuni*
and Central Project Z2: Ribosome Profiling & Bioinformatics

JÖRG VOGEL
(Institute of Molecular Infection Biology)
Functions of small proteins regulated during *Salmonella* infection

4.12

DFG PRIORITY PROGRAM SPP 2141

MUCH MORE THAN DEFENSE: THE MULTIPLE FUNCTIONS AND FACETS OF CRISPR-CAS

One of the most exciting breakthroughs in biology in the past decade has been the discovery of the CRISPR-Cas system. Initially identified as a prokaryotic RNA-based defense system, it is now known that genome defense is just one of many functions of this molecular machine. Thus, the prevailing view of CRISPR-Cas as a defense system is too narrow as other important cellular processes can be carried out by the CRISPR-Cas system, such as virulence regulation, DNA repair, and the regulation of group behavior. In some cases, CRISPR-Cas systems may even have completely lost their immune-related functions. At this time, we have barely begun to understand the full biological potential of this system. The newly revealed functions of the CRISPR-Cas system promise exciting biological discoveries and surprising insights into the new activities and will open several novel avenues of research. Thus far, the new CRISPR-Cas functions have primarily been discovered fortuitously and systematic approaches to detect new functions are lacking.

The SPP 2141 aims to find new CRISPR-Cas functions beyond defense using a systematic coordinated approach with 21 research groups. A team of scientists from different disciplines, such as microbiology, genetics, medical microbiology, biochemistry, biophysics, bioinformatics, ecology, structural biology, molecular dynamics, single-molecule localization microscopy, and single-molecule biochemistry, makes this program truly interdisciplinary. The two major goals of the SPP 2141 are: (1) The identification and investigation of new CRISPR-Cas functions beyond genome defense using model representatives of archaea and bacteria, and (2) the elucidation of the molecular mechanisms underlying these novel functions using state-of-the-art methods. The program is supplemented by a public outreach module to communicate the science of CRISPR-Cas to society in a comprehensible manner and to facilitate the discussion of controversial issues with the public, such as for human genome editing applications.

Projects involving ZINF members:

CHASE BEISEL
(Helmholtz Institute for RNA-based Infection Research)
Functional characterization of extensively self-targeting CRISPR-Cas systems in the bacterial plant pathogen *Xanthomonas albilineans*

CHRISTOPH SCHOEN
(Institute for Hygiene and Microbiology)
The CRISPR/Cas system in *Neisseria meningitidis* and its potential role in host cell adhesion

CYNTHIA SHARMA
(Institute of Molecular Infection Biology)
Mechanisms and functions of endogenous RNA-targeting by CRISPR-Cas9 in *Campylobacter jejuni*

4.13

DFG GERMAN-AFRICAN COOPERATION PROJECTS IN INFECTIOLOGY

SHARE - STAPHYLOCOCCI IN AFRICA: RESISTANCE & EPIDEMIOLOGY

The DFG German-African Cooperation program funds joint research projects between scientists in Germany and Africa investigating infectious diseases with a focus on neglected infectious diseases, and their social and economic implications. In its recent global surveillance report, the WHO has identified antimicrobial resistance (AMR) of human pathogens as a serious problem that threatens the achievements of modern medicine. AMR strikes all countries worldwide, but in contrast to industrialized regions, there is a major gap in knowledge about the magnitude of the problem in countries with limited resources. For the African region, the WHO identified a lack of data particularly on antibacterial resistance (ABR) for many common and serious conditions, such as meningitis, pneumonia and bloodstream infections. Also, ABR is no longer exclusively a problem in human health, but is also an issue in veterinary medicine, agriculture, food safety and in the environment. The term 'One Health' was recently coined to reflect this holistic approach to the problem. In this project, we will focus on ABR and its molecular mechanisms in staphylococci in three African regions (North, East, and South) by adopting the One Health approach. Staphylococci are some of the most common human pathogens. They cause a wide range of clinical manifestations, but also occur as harmless skin commensals in humans as well as in animals, and some species transiently survive in the environment. Staphylococci readily acquire many different resistance genes, and methicillin-resistant *Staphylococcus aureus* (MRSA) and coagulase-negative staphylococci (MR-CoNS) are among the most common causes of healthcare-associated infections worldwide. However, MRSA and MR-CoNS also occur outside of medical facilities and are detectable in the community, in animal husbandries, as well as in the environment. The occurrence of the same resistance genes in CoNS and

S. aureus suggests ongoing genetic exchange between MRSA and other staphylococci, and CoNS may serve as a reservoir of resistance genes for *S. aureus*. The suggested research aims to develop a comprehensive insight into the molecular epidemiology and molecular resistance mechanisms present in staphylococci in Africa. In the ShARE program, medical microbiologists from Egypt, Kenya and South Africa work together with molecular infection biologists from Germany to determine the MRSA and MR-CoNS clonal lineages currently circulating in healthcare settings, livestock and the community in the three African regions. The project particularly focuses on elucidating the molecular mechanisms and genetic basis of resistance against novel and last resort antibiotics, as well as on the identification of factors that drive ABR expression and transfer into MRSA.

Projects involving ZINF members:

WILMA ZIEBUHR
(Institute of Molecular Infection Biology)
Molecular epidemiology and antimicrobial resistance mechanisms in staphylococci from various geographic regions in Africa

4.14

BMBF #1HEALTH-PREVENT

ONE HEALTH INTERVENTIONS TO PREVENT ZOONOTIC SPREAD OF ANTIMICROBIAL MULTIDRUG-RESISTANT BACTERIAL MICROORGANISMS

#1Health-PREVENT aims to implement suitable intervention measures to prevent the zoonotic spread of bacterial multidrug resistant microorganisms (MDRO) in agriculture, human, and veterinary medicine as well as in the environment. Pursuing a truly One Health approach, the consortium fosters interdisciplinary collaboration by joining partners from veterinary and human medical microbiology, molecular microbiology, as well as from public health and agriculture. #1Health-PREVENT will answer open epidemiological questions related to zoonotic MDRO spread. Furthermore, the program will challenge novel intervention measures for their efficacy and practical feasibility to limit zoonotic MDRO dissemination.

Coagulase-negative staphylococci (CoNS) from livestock and livestock environments were recently found to be extensively drug-resistant by carrying novel antimicrobial resistance (AMR) genes and displaying uncommon phenotypic AMR, including resistance against last resort antibiotics. Little is known about the impact of these low-grade pathogens and their transmission to directly exposed humans. Also, their role in the ecological niche as putative links between the general environmental AMR gene pool and host-colonizing as well as pathogenic bacteria is poorly understood. In this project, we will fill knowledge gaps concerning the epidemiology of AMR-CoNS among livestock-exposed individuals and test several intervention measures (*i.e.* use of probiotic bacteria, alternative housing conditions of animals) for their efficacy to reduce the AMR burden in farm environments. The overarching goal of the project is to interfere with the emergence of pathogenic MDROs at an early stage and to prevent their dissemination to humans, including transmission into hospitals.

Projects involving ZINF members:

WILMA ZIEBUHR
(Institute of Molecular Infection Biology)
Reducing the AMR burden in farm environments: Impact on human commensals and zoonotic pathogens

4.15

BMBF INFECTCONTROL 2020

A rapidly increasing threat is arising from new or resistant pathogens and their growing global circulation. This threat is further afflicted with a drastic lack of (new) effective drugs as well as insufficient preventive and diagnostic possibilities. There is also a great demand for awareness and information, especially regarding patients and specialists in health care professions. InfectControl 2020 (Speaker: Axel Brakhage, Jena, Scientific Manager: Oliver Kurzai) is a consortium of representatives from enterprises and academia that jointly aims to develop solutions to these problems on a national and global level. Proposals are being developed within the scope of the funding program "Zwanzig20 – Partnerschaft für Innovation" headed by the Federal Ministry for Education and Research (BMBF). With InfectControl 2020, a highly innovative research alliance has been established that aims to develop and commercially implement new strategies for the early recognition, the control, and successful approaches to fight infectious diseases.

Projects involving ZINF members:

4.15.1 FUNGAL INFECTIONS AND AZOLE RESISTANCE (FINAR & FINAR 2.0)

OLIVER KURZAI (coordination)
(Institute for Hygiene and Microbiology)

Mold fungi cause life-threatening infections in immunocompromised patients and high costs. Similar to avian species, invasive mycoses are among the most common diseases. Despite an increasing number of cases, diagnostic possibilities are still inadequate. Moreover, resistance to important antimycotics has recently emerged. A possible cause for this is the widespread use of similar substances in plant protection. In contrast to bacterial antibiotic resistance, however, the spread of resistance in fungi still seems avoidable. Within the framework of FINAR, decisive preliminary work has been carried out, which for the first time allows a systematic analysis of the development of resistant *A. fumigatus* strains in the environment. At the same time, the cooperation between the academic partners and Biotype Diagnostic within the framework of FINAR will result in the availability of a test prototype of a diagnostic kit, which, in addition to the molecular detection of *A. fumigatus*, will also allow for the detection of the most important resistance mutations. A first patent for this method has been applied for. Based on these results, FINAR 2.0 aims to develop and test strategic measures in agriculture to contain the emergence of resistance as well as to further optimize and to multicenter evaluate of the test prototype in a network of diagnostic laboratories.

4.15.2 TRANSSECTORAL RESEARCH PLATFORM (TRP)

OLIVER KURZAI
(Institute for Hygiene and Microbiology)

The Transsectoral Research Platform (TRP) aims to strengthen the cooperation of more than 30 partners of InfectControl 2020 and to educate excellent young researchers by carrying out transdisciplinary research projects. Facing the growing challenges of infectious diseases requires the joined forces of multiple disciplines and to cooperate at excellent scientific standards. In an interdisciplinary cooperation between genetics and infection biology, the TRP will for the first time identify genetic polymorphisms that influence an immune response to infectious agents. The occurrence of genetic polymorphisms means that the gene in question can vary from patient to patient and thus, different gene products may be formed in patients, which have an effect on the immune response. This research area is groundbreaking for closer cooperation between genetics and infection biology and provides data sets that can be used in cooperation with other partners - including industry - to develop individualized therapeutic approaches.

4.15.3 RAI STUDENTS

OLIVER KURZAI
(Institute for Hygiene and Microbiology)

Medical students are tomorrows' prescribers and specifically addressed in RAI Students. In an interdisciplinary team, we develop new teaching tools and education modules to educate future MDs with regard to rational antibiotic use in infections (RAI). We aim to convey the problems of non-rational antibiotic use and communication as well as decision making skills that are required for rational decisions in antibiotic treatment.

4.15.4 ART4FUN

Antigen reactive T cells for the diagnosis and therapy of fungal-associated diseases in risk patients

HERMANN EINSELE & JÜRGEN LÖFFLER
(Dept. of Internal Medicine II)

Aspergillus fumigatus and other fungi cause life-threatening infections in the immunocomromised or allergic reactions in patients including those with cystic fibrosis, asthma, and chronic obstructive pulmonary disease. The actual degree of fungal-associated pathologies is not entirely clear because fungi are part of our daily environment, making conclusive microbiological detection difficult. Accordingly, current therapies are often non-specific and delayed, and diagnostic methods are currently not routine. Members of the consortium have developed an immune cell-based approach, antigen reactive T cell enrichment (ARTE), which allows the host-pathogen status to be precisely determined and used for diagnosis. ART4Fun integrates host-pathogen status and clinical epidemiology and veterinary data for an overarching diagnostic and risk assessment of fungal lung pathologies and to develop new therapies and prevention strategies. This project involves the engineering of *Aspergillus* specific T cells and their evaluation both *in vitro* and in an *in vivo* mouse model of invasive aspergillosis using advanced *in vivo* imaging techniques. Clinical samples from patients with invasive aspergillosis will be acquired and made available to other consortium members.

4.16

BMBF TARGET VALIDATION FOR PHARMACEUTICAL DRUG DEVELOPMENT

The steady increase in nosocomial infections and antibiotic resistance threatens our health worldwide. The sharp decline in newly approved drugs, particularly in the area of anti-infectives, represents a great challenge for the global health system. Thus, it is urgently necessary to develop new, innovative medicines. In the development of new active substances, the choice of target molecule against which the medication is directed is of particular importance, as this defines the effect of the corresponding therapy. In this program, new targets will be validated, serving as structures for the development of new drugs.

Projects involving ZINF members:

PyrBac: Validation of pyruvate kinase as a novel metabolic target to combat antibiotic resistant bacteria

KNUT OHLSEN
(Institute of Molecular Infection Biology)

The PyrBac project aims to develop novel active substances against resistant bacteria for antibiotic therapy. The target of the new substances, pyruvate kinase (PK), is a key enzyme of bacterial metabolism not captured by conventional antibiotics. PK has recently been identified as a possible target for the development of new antibiotics. It is an essential metabolic enzyme that catalyzes the last and irreversible step of glycolysis. Due to its essentiality and close networking with other metabolic pathways, PK has a very low mutation rate, which makes it a promising target for antimicrobial therapy. Structural differences between the human isoenzymes and bacterial pyruvate kinases provide the opportunity to develop selective inhibitors of this enzyme, which might be new antibiotics for the control of multidrug-resistant strains. First, various substance classes already recognized as suitable are chemically modified and their antimicrobial activity is determined. The most active substances are then physico-chemically characterized and pharmacological and toxicological properties are examined. At the same time, a sensitive detection system is established to detect the substances in the organism. The early application of industrial

standards is intended to ensure that the results are quickly transferred to further development together with the pharmaceutical industry. The project is therefore pursuing a highly innovative approach to laying the foundations for new treatment options for infections caused by antibiotic-resistant bacteria.

TRANsACT: T-box riboswitches as novel antibacterial targets: Validation of RNA-mediated methionine biosynthesis control in staphylococci as tool and proof of principle

WILMA ZIEBUHR & KNUT OHLSEN
(Institute of Molecular Infection Biology)

Current development of novel antibacterial drugs is significantly hampered by a shortage of validated drug targets. The TRANsACT project focuses on T-box riboswitches (TBRS) as novel target structures against a broad range of important Gram-positive human pathogens such as multiresistant staphylococci and enterococci, *Clostridium difficile*, pneumococci, and mycobacteria. TBRS represent unique bacterial RNA transcription control platforms that interact with tRNAs as ligands to regulate downstream gene expression. They are widespread among Gram-positive bacteria, where they control many essential pathways involved in amino acid and tRNA metabolism. Importantly, TBRS are prokaryote-specific and have no counterpart in eukaryotes, rendering these structures highly selective antibacterial targets. The aim of the project is to define the structural constraints of TBRS functions as targets for future antibacterial compound binding. We employ a staphylococcal methionyl-tRNA-specific TBRS (met-TBRS) as a structure model, and use met-TBRS-mediated control of methionine biosynthesis of *S. aureus* as convenient conditional system to study TBRS functions in living bacterial cells as well as in animal infection models. The project builds on comprehensive molecular and functional data, already demonstrating that TBRS impairment can indeed abolish bacterial growth. TRANsACT will move the project from basic research to application by generating robust target validation data and tools that can immediately be used for future compound screening and preclinical drug development endeavors.

4.17

BMBF iMIP

DEVELOPMENT OF NON-IMMUNOSUPPRESSIVE FK506 ANALOGS AS MACROPHAGE INFECTIVITY POTENTIATOR (MIP) INHIBITORS FOR THE TREATMENT OF LEGIONELLA PNEUMOPHILA, BURKHOLDERIA PSEUDOMALLEI, AND TRYPANOSOMA CRUZI INFECTIONS

Gram-negative, pathogenic bacteria such as *Legionella* or *Burkholderia* and eukaryotic parasites such as *Trypanosoma cruzi* are responsible for serious infectious diseases such as Legionnaires' disease or Chagas disease. The pathogens use the evolutionary conserved virulence factor "Macrophage Infectivity Potentiator" (MIP) for tissue invasion and infection of human host cells. The natural substances FK506 and rapamycin bind and inhibit MIPs, but at the same time have an immunosuppressive effect. In their initial form, the natural substances are unsuitable for the treatment of infectious diseases, since suppression of the human immune system must be avoided when treating bacteria.

The aim of this BMBF project is to develop non-immunosuppressive FK506 analogues as drug-like MIP inhibitors for the treatment of MIP-dependent pathogens. For this purpose, derivatives of FK506 will be synthesized, which preferentially bind to the MIP proteins of *Legionella pneumophila*, *Burkholderia pseudomallei*, and *Trypanosoma cruzi*. The MIP inhibitors will be improved step by step by chemical modifications, which will be supported by structural information gained in the project. If successful, promising substances can be generated with which MIPs can be blocked in meaningful cell and animal models. This should create promising starting points for new anti-infective substances.

Projects involving ZINF members:

ULRIKE HOLZGRABE
(Institute for Pharmacy and Food Chemistry)
Development of MIP inhibitors of the FK506 type for the treatment of *Trypanosoma cruzi* infections

4.18

EUROPEAN RESEARCH AREA NETWORKS (ERA-NET)

The aim of ERA-NET is to promote greater coordination and joint calls for proposals for national and regional research funding programs in strategically important thematic areas of European research and innovation. To this end, research funding organizations and program managers from EU member states and associated states pool financial and human resources for the development of joint activities. This supports and improves the advancement, efficiency, and effectiveness of European research.

4.18.1 INFECT-ERA

Infectious diseases cause tens of thousands of deaths each year in Europe. Despite all the measures taken to address infectious diseases, different factors have contributed to recent challenges: (1) the threat of emerging pathogens, (2) mass migration, global travelers, and growth of congested urban slums, (3) mis- and overuse of antibiotics, and (4) co-infection with at least two pathogens. Through this initiative, ERA-NET partners aim to understand all basic aspects of complex human infection biology questions that are not limited to specific pathogens, such as co-infection, the crosstalk between host and pathogens, as well as the relationship between microbial environment and infection. The ERA-NET consortium funds high quality and cutting-edge transnational and translational research bringing together basic, applied, technology-driven, and clinical research approaches to a broad variety of topics regarding infectious diseases.

Networks involving ZINF members:

AspMetNet: Systematic identification of antifungal drug targets by a metabolic network approach

THOMAS DANDEKAR
(Dept. of Bioinformatics)

Fungal infections pose an increasing threat to the immuno-compromised and limitations in antifungal therapy arise from non-specific symptoms of infection, poor diagnostics, and few options for treatment. Current antifungal drugs interfere with the fungal cell wall or plasma membrane but show limited efficacy, severe side effects, or pathogen resistance. Despite their promise to serve as highly specific antifungal targets, fungal metabolic pathways have been widely neglected. Because *Aspergillus*, the causative agent of aspergillosis, apparently lacks specific virulence factors, its general characteristics such as growth and tissue penetration strongly correlate with the outcome of infection of a susceptible host. This relies strictly on nutrient acquisition and metabolic turnover and therefore makes biosynthetic pathways a prime target in antimycotic therapy. The basic concept of this consortium is to explore the metabolism of the pathogenic species *A. fumigatus* on a comprehensive scale. Emerging from transcriptome profiling data, metabolic network reconstruction will serve to identify fungal-specific biosynthetic pathways and key reactions. Predictions for unique enzymes will result in a candidate list of genes, the inactivation of which is likely to result in an auxotrophic phenotype based on conditional essentiality of the biosynthetic reaction. Phenotypic and molecular characterization of these genes will culminate in virulence studies to test infectivity in established animal models of aspergillosis. Based on the resulting data collections, the metabolic network model will be refined in an iterative manner to yield further candidates. Essentially, this systematically applied metabolic network approach will yield novel antifungal drug targets based on the metabolism of *A. fumigatus* that will serve as candidates for therapeutic intervention to fight fungal infections.

CampyRNA: Combining high-throughput and single-cell analyses to study RNA regulators important in the early steps of *Campylobacter* infection

CYNTHIA SHARMA & ANA EULALIO
(Institute of Molecular Infection Biology & ZINF Alumna, present address: Center for Neuroscience and Cell Biology, University of Coimbra)

Bacterial infections entail an active interplay between the virulence factors of a pathogen and the host response. Non-coding RNAs (ncRNAs), including small, regulatory RNAs in bacteria and host microRNAs, are increasingly recognized as important posttranscriptional gene expression regulators during infection. This consortium uses *Campylobacter jejuni*, currently the most common cause of bacterial food poisoning, as a model organism to study the role of host and pathogen ncRNAs during the early steps of infection, specifically the adhesion to and invasion of epithelial cells. To obtain a comprehensive overview of the host and pathogen ncRNAs expressed during infection and how they control pathogenesis, this consortium combines several high-throughput approaches with single-cell microscopy techniques. The project will shed light on new virulence regulators of *C. jejuni*, which could constitute targets for novel antimicrobial strategies. In addition, the new approaches developed in this project will be applicable for the study of additional human pathogens. Cynthia Sharma is the coordinator of this junior consortium.

CINOCA: Co-infection as a cause of ovarian cancer

THOMAS RUDEL
(Dept. of Microbiology)

The clinical impact of bacteria-virus co-infections and the subsequent chronic infections are both poorly understood, partly due to the difficulty in drawing conclusive etiological links years after the infection. This transnational network aims to investigate the contribution of chronic co-infections with human herpes viruses (HHVs) and the intracellular bacterium *Chlamydia trachomatis* (Ctr) to the onset of ovarian cancers. Recent epidemiological studies suggest a strong association of ovarian cancers with both agents and only to a minor extent with human papillomavirus, a known etiologic agent of cervical cancer. An important paradigm shift in recent years now firmly assigns the origin of ovarian cancer to the epithelial lining of the Fallopian tube (FT), a prime meeting site for chronic, often asymptomatic infections by both HHVs and Ctr. Thus, accumulating evidence warrants a careful analysis of the molecular events by which these pathogens synergize in establishing their infectious niche and co-operatively promote malignant transformation. This consortium consists of leading European laboratories in the areas of HHVs and *Chlamydia* research and two highly committed clinical and SME partners. Together with a clinical partner, who has generated an organoid model of human FT cells, *in vitro* studies will be performed. This novel infection model will provide the basis for in-depth genomic and epigenomic analyses that will allow tracing the infection-driven events of host cell transformation on a genomic scale. In concert, this consortium will illuminate the molecular mechanisms by which HHVs and Ctr jointly reprogram human epithelial cells, providing the basis for malignant transformation.

eDEVILLI: Early Determinants of DNA-Virus Lytic or Latent Infection

LARS DÖLKEN
(Dept. of Virology)

Severe disease caused by herpes viruses typically does not surface during the initial infection of the otherwise healthy host, but rather when the virus reactivates from latency in immunocompromised individuals, such as organ transplant recipients and AIDS patients. Understanding the mechanisms that contain viral infection and push the virus into latency immediately upon infection may enable their use for life-saving preventive and therapeutic measures. The eDEVILLI consortium focuses on the characterization of the molecular mechanisms that define whether a DNA virus infection will result in latency

or in lytic infection. By combining a systems biology approach with cutting edge genetic manipulation of both the host cell and the virus, we will define the host and the viral factors that bind to viral genomes immediately upon infection and shape the decision whether an incoming virus will trigger the lytic cycle, or if it will remain latent.

The Nice Bug: Commensalism versus disease – Asymptomatic carriage or urosepsis

JÖRG VOGEL
(Institute of Molecular Infection Biology)

The symbiotic relationship between commensals and their hosts is made possible by a lack of virulence and immune activation. Commensals also actively modify the host environment. Through exquisite molecular mechanisms, they perturb host gene expression, especially pathways which enhance persistence and reduce pathology. This project examines a novel strategy to use the protective potential of commensals to prevent recurrent urinary tract infection (UTI). Asymptomatic bacteriuria (ABU) is a commensal-like state, which protects the urinary tract against super-infections by more virulent strains. We will establish ABU in UTI-prone patients by inoculating them with the strain *E. coli* 83972. Therapeutic efficacy of this approach has already been demonstrated in placebo-controlled studies. Genomic, transcriptomic and proteomic tools may now be applied to analyze the molecular basis of commensalism and protection in human hosts.

4.18.2 ERANET-LAC

ERANet-LAC is a Network of the European Union (EU) and with Latin America and Caribbean Countries (LAC) on Joint Innovation and Research Activities with the aim to disseminate, support, and contribute to bi-regional research and innovation activities. An EU-LAC platform for funding agencies will serve as an information and communication platform and offer substantial guidelines as well as online working spaces to facilitate and enhance the development of future concrete joint initiatives.

Networks involving ZINF members:

Development of New Diagnostic and Treatment Options for Helminthic Neglected Diseases

KLAUS BREHM
(Institute for Hygiene and Microbiology)

The project aims to develop new therapeutic and diagnostic tools to contribute to the control of neglected diseases caused by helminth parasites, such as cystic (CE) and alveolar (AE) echinococcosis. Due to the scarcity of available anthelmintic drugs and the possible emergence of resistance, the discovery of new anthelmintic drugs is mandatory. The assembled international and interdisciplinary team has characterized a number of molecules that may play important roles in nutrient acquisition, attenuation of the host's immune response, and development of these parasites, and has also developed *in vitro* and *in vivo* models as well as studied epidemiological and clinical aspects of these diseases. A new approach based on distinct biological and metabolic aspects of parasitic helminths will consider in particular parasite-specific lipid binding proteins and microRNAs. As these molecules are unique to the pathogens, they fulfill the main requirement for good selective therapeutic targets. Assessment of their cellular expression will help to prioritize targets that are widely expressed, including in the key stem cell population. The uniqueness/divergence of several miRNAs and their ability to be detected in biological fluids also makes them potential new specific biomarkers. Ultrasound studies and sera collection from human populations affected by CE will be performed in order to include the potentially new biomarkers in the stage specific approach according to WHO-IWGE (Informal Working Group on Echinococcosis). In addition, US surveys will provide a rapid impact on the health system of the rural populations involved in the study. The evaluation of specific parasite molecules as new therapeutic/diagnosis targets using bioinformatics, molecular biology, biochemistry, and biophysical methods will be integrated with relevant clinical and epidemiological information. The expected outcome of the project is the development of new compounds that bind and inhibit essential and unique molecules of these parasites, as well as to find new detection tools, thereby improving the status of both treatment and early diagnosis of these complex and neglected diseases.

4.18.3 ERA-NET JPI-EC-AMR

Antibiotic resistance is a global problem and is considered by the World Health Organization as one of the three greatest threats to human health for the next decades. The European Joint Programming Initiative on Antimicrobial Resistance (JPIAMR), a global collaborative platform engaging 28 member nations, has been established to curb antibiotic resistance with a One Health approach.

The aim of the ERA-Net Cofund JPI-EC-AMR is to unravel the complex dynamics of selection and transmission of antimicrobial resistance in a multidisciplinary approach to identify and characterize the determinants that contribute to the spread of resistance at genetic, bacterial, animal, human, societal, and environmental levels. JPI-EC-AMR will provide a better, quantitative understanding of drug-resistant bacteria in animals, food, and the environment, and to what extent they contribute to the burden of antibiotic-resistant infections in humans. Research in this area is crucial in order to provide the robust scientific evidence needed to make informed decisions regarding interventions and policy measures in hospital, community, and agricultural settings.

Networks involving ZINF members:

CRISPRattack: Advancing CRISPR antimicrobials to combat the bacterial pathogen *Klebsiella pneumoniae*

CHASE BEISEL
(Helmholtz Institute for RNA-based Infection Research)

The increasing incidence of multidrug-resistant bacterial infections and the trickling pipeline of novel antibiotic classes demand a new generation of antimicrobials. One promising avenue has been the development of antimicrobials based on CRISPR-Cas immune systems. These systems can be programmed to specifically and efficiently eliminate cells harboring multi-drug resistance genes without impinging on resident microbiota. However, CRISPR antimicrobials remain to be advanced from a few proof-of-principle demonstrations to established therapeutics that can effectively combat the most pressing pathogens. The aim of CRISPRattack is to advance this antimicrobial platform to selectively kill *Klebsiella pneumoniae*, a major cause of multi-drug resistant, nosocomial infections worldwide. A series of experimental approaches will identify the most active CRISPR nucleases and DNA target sites for programmed killing, engineer bacteriophage delivery vehicles that can efficiently deliver CRISPR to a large fraction of clinical isolates, and evaluate the efficacy of the most promising therapeutic candidates in mouse infection models. Once demonstrated, the resulting optimized CRISPR antimicrobials will represent a large leap forward for the development of novel antimicrobials against *Klebsiella*, and they will provide a framework to develop similar antimicrobials against other high-priority pathogens associated with multidrug resistance.

4.19
INTERNATIONAL NETWORK FOR STRATEGIC INITIATIVES IN GLOBAL HIV TRIALS (INSIGHT)

The mission of the National Institutes of Health (NIH) sponsored INSIGHT network is to develop strategies for the optimization of treatment (antiretroviral therapies (ART), immunomodulatory therapies, and interventions to prevent and treat complications of HIV and ART) in order to prolong disease-free survival in a demographically, geographically, and socio-economically diverse population of individuals infected with HIV. In order to carry out this mission, the research agenda will be pursued through:

- Large randomized trials with morbidity and mortality outcomes, preceded, where appropriate, by vanguard (smaller, pilot) studies to refine design parameters;
- Studies relevant to both resource-abundant and resource-constrained countries;
- Studies directed at minimizing the adverse effects of long-term treatment, while maximizing treatment benefits;
- Substudies conducted as part of larger trials;
- Studies designed to allow for co-enrolment, so that multiple major research questions can be addressed in the cohorts under follow-up;
- Carefully planned epidemiological analyses, including nested case-control studies that take advantage of a large cross study database and associated specimen repositories; and
- Linkages with other networks, in order to maximize efficiency and research productivity.

During this seven-year funding cycle, INSIGHT will conduct seven major clinical trials, three of which are underway, and three vanguard trials at approximately 400 sites in 37 countries. Each of the trials will have carefully planned substudies that add value to the experimental design of the parent protocols. These substudies will investigate mechanistic questions and evaluate the experimental interventions for important secondary outcomes in a cost-effective way. Two of the trials will be preceded by intermediate-size vanguard studies to refine protocols for larger scale investigation, *e.g.*, to estimate parameters for sample size or to more precisely define the study arms.

Projects involving ZINF members:

HARTWIG KLINKER
(Dept. of Internal Medicine II)
Strategic Timing of AntiRetroviral Treatment (START)

4.20
IBD-LABNET COORDINATION OF ACTIVITIES FOR LABORATORY SURVEILLANCE OF INVASIVE BACTERIAL DISEASES

Accurate laboratory surveillance of *Neisseria meningitidis*, *Haemophilus influenzae*, and *Streptococcus pneumoniae* is pivotal for public health management of invasive bacterial disease (IBD). In light of this, the European Center for Disease Prevention and Control (ECDC) has funded the IBD laboratory network (IBD-labnet) since September 2008 within the framework of the program "*Laboratory surveillance and external quality assurance of invasive bacterial diseases in EU*" and, since October 2011, the follow-up program "*Coordination of Activities for Laboratory Surveillance of Invasive Bacteria Diseases*". Both projects were coordinated by Matthias Frosch (until 2018) and Ulrich Vogel (from 2019 until 2020) from the Institute for Hygiene and Microbiology, who were assisted by Gabriele Gerlach. The project aimed to enhance laboratory capacity, to harmonise the use of methods, and to ensure the quality of typing data.

IBD-labnet performed surveys to map expertise regarding identification and characterisation of invasive pathogens and to analyse training needs. The network organised External Quality Assurances (EQAs) in collaboration with UK NEQAS (United Kingdom National External Quality Assessment Service). Continuing education has been offered through the organisation of targeted training workshops, especially with respect to the implementation of molecular typing methods and the analysis of whole genome sequence (WGS) data. IBD-labnet organised summits with representatives of all National Reference Laboratories to evaluate the capacities and current practices in application of WGS for IBD surveillance. A representative European Meningococcal Strain Collection (EMSC) with 799 invasive isolates from 16 participating countries was established as a basis for the creation of the EMSC Genomic Library to support an integrated surveillance of disease-associated genotypes in Europe (Bratcher *et al.*, 2018 Euro Surveill). The network, which has now completed its mission, fostered collaboration within the member states, helped to develop laboratory capacity in economically weaker regions of the EU,

supported the extended use of whole genome sequencing for typing in Europe, and assisted the ECDC in its efforts to define strategies for European molecular surveillance.

4.21

WELLCOME TRUST STRATEGIC AWARD

FLATWORM FUNCTIONAL GENOMICS INITIATIVE

Parasitic flatworms cause some of the most chronic infectious diseases on our planet. The Flatworm Functional Genomics Initiative develops game-changing research tools for the study and manipulation of parasitic flatworm species responsible for the devastating diseases echinococcosis (hydatid disease) and schistosomiasis (bilharzia). The initiative will develop transformative functional genomics reagents and make them readily available to the academic research community through well-curated North American and European repositories. Specifically, they will use expertise in molecular biology, cell biology, and parasitology to create transgenic lines of parasitic flatworms, as well as primary and immortal cell lines derived from these pathogens. These reagents will enable helminthologists to keep pace with other more tractable areas of infectious disease biology and more effectively contribute to the control of parasites responsible for chronic human and animal diseases. FUGI is available online at www.sanger.ac.uk/collaboration/flatworm-function-genomics-initiative-fugi/.

Projects involving ZINF members:

KLAUS BREHM
(Institute for Hygiene and Microbiology)
Functional genomics in *Echinococcus multilocularis*

4.22

ELSE KRÖNER CENTER FOR ADVANCED MEDICAL & MEDICAL HUMANITARIAN STUDIES WÜRZBURG – MWANZA/TANZANIA

To improve the medical care in the region around Mwanza, which is Würzburg's partner city in Tanzania, the "Else Kröner-Fresenius-Center for Advanced Medical & Medical Humanitarian Studies Würzburg – Mwanza" was founded in the beginning of 2020. This research and healthcare center will bring together and strengthen the already existing medical and scientific activities of the Julius-Maximilians-University (JMU), the University Hospital (UKW), the Medical Mission Institute (MI), and the German Leprosy and Tuberculosis Relief Association (DAHW) in collaboration with the Catholic University of Health and Allied Sciences and the Bugando Medical Center in Mwanza in a coordinated and sustainable manner. The proposed medical-humanitarian development cooperation can build on a longstanding interdisciplinary collaboration of the involved partners. In the coming five years, the education and vocational training of medical specialists and students will be expanded within the scope of exchange programs and the development of a joint study program within public health. Additionally, the medical specialization in both places and a close collaboration within clinical research will be expedited. The newly established center will also focus on an improved medical care of the population in the hospital in Mwanza as well as an improved community healthcare in the area around Lake Victoria. Emphasis will be placed on the development of a multi-approach program to fight schistosomiasis, a parasitic disease which is widespread in the lake zone and associated with high morbidity rates.

Projects involving ZINF members:

MATTHIAS FROSCH (project management) &
OLIVER KURZAI (scientific coordination)
(Institute for Hygiene and Microbiology)

4.23

BAVARIAN RESEARCH NETWORK BAYRESQ.NET

NEW STRATEGIES AGAINST MULTI-RESISTANT PATHOGENS BY MEANS OF DIGITAL NETWORKING

According to the WHO, antimicrobial resistance currently poses the greatest long-term threat to human health and wellbeing. Many research efforts worldwide are focusing on this issue. The Bavarian research network bayresq.net builds on novel approaches within basic research to address and counteract the development and spread of resistance in infectious pathogens. The central idea of the program is in gaining a deeper understanding of the processes, which take place during infection/colonization as well as the interactions between pathogen and host. To achieve this understanding, a common approach based on the systematic use of modern data networks among the bayresq.net projects should enable all users to take immediate advantage of recently collected data.

Through the projects of this research network, Bavaria will be strengthened both in the area of life sciences as well as data management. At the same time, the groundwork for the development of improved medical care for future generations is being set. During the last few years, the Bavarian state government has been able to continuously improve the framework and conditions for the research landscape in Bavaria and thereby generated optimal conditions for innovative and novel research fields. The area of molecular biology, in particular, has managed to rapidly react to international trends as well as pick up and advance specific key topics relevant to the scientific community. The research network bayresq.net provides the opportunity to create important conditions for coping with future challenges within and beyond the borders of Bavaria by sustaining and stimulating basic research in areas such as immunology, the microbiome, and infectious diseases.

Networks involving ZINF members:

StressRegNet: Identifying stressor-regulator pairs involved in bacterial stress response, virulence, and antibiotic sensitivity using high-throughput approaches and machine learning

CYNTHIA SHARMA & ANA RITA BROCHADO
(Institute of Molecular Infection Biology, ZINF/Dept. of Microbiology)

Pathogens are constantly exposed to numerous environmental cues, which can originate from their host, the microbiome, as well as from food, antibiotics, and other drugs. Pathogens employ diverse strategies to adapt to these continuously changing environments, mostly through transcriptional or post-transcriptional gene expression control. Besides proteins that act as global stress regulators at the transcriptional level, small regulatory RNAs (sRNAs) are important players that control stress response and virulence at the post-transcriptional level. In addition to regulation of virulence genes or metabolism during host colonization, there is an increasing number of examples where sRNAs can impact antibiotic resistance and tolerance. However, the external cues that trigger many molecular pathways and regulators are still largely elusive, as well as how these regulatory cascades impact bacterial virulence and sensitivity to antibiotics.

Using high-throughput approaches, the StressRegNet consortium aims to explore, which chemical signals (stressors) trigger pathways responsible for controlling bacterial adaptation to the host and to antibiotics in the two major human pathogens *Salmonella* and *Campylobacter*. Identifying such stressors will help unravel the extent of cross-talk (epistasis) between different sensing and adaptation mechanisms in bacteria, and expose unknown bacterial "Achilles heels", such as virulence or antibiotic sensitivity pathways, as targets for novel therapeutic intervention.

The StressRegNet project combines bacterial genetics, high-throughput screening, and machine learning approaches to obtain a general picture of chemical stimuli that trigger bacterial stress responses mediated by sRNAs and/or global regulators. To this end, transcriptional reporter libraries of stress-related regulatory sRNAs in *Salmonella* and *Campylobacter* will be profiled for their activity upon exposure to >3,000 host-related small molecules. Subsequently, the development of machine-learning techniques will allow us to decipher the implications of these pathways for bacterial sensitivity to antimicrobials. The interdisciplinary approach of the StressRegNet consortium enables this unique chemical genomics approach and the strong interactions between wet-lab scientists and mathematicians will advance infection biology research through digitalization.

Rbiotics: A Digital Approach to Novel RNA Antibiotics for Health and Disease

JÖRG VOGEL, FRANZISKA FABER, & LARS BARQUIST
(Institute of Molecular Infection Biology, ZINF, Helmholtz Institute for RNA-based Infection Research)

Conventional antibiotics generally work against a broad spectrum of bacterial pathogens. This promotes the development of antibiotic resistance and damages our protective microbiota, which can have unwanted effects on our health. New antibiotics are therefore needed that can directly target individual pathogens, leaving beneficial bacteria unharmed. In a multidisciplinary approach, the Rbiotics project is studying antibiotics based on RNA-like molecules, so-called peptide nucleic acids (PNAs) that bind to messenger RNA through complementary base pairing and can inhibit the production of proteins. Such RNA antibiotics can be modified through simple chemical means to achieve effectiveness against emerging pathogens and can be used to specifically attack individual bacterial strains.

Using high-throughput processes and machine learning, Rbiotics will create a digital platform that will enable researchers to specifically design drug molecules against a variety of dangerous pathogens. PNAs have already been confirmed to be effective in preclinical studies, but there are many open questions, for instance about the rules for programming such RNA antibiotics, mechanisms of resistance development, and possible toxicity to host cells and non-targeted members of the microbiome. We are pursuing a combination of transcriptome analysis and machine learning to understand the effects of PNAs on bacterial pathogens and to identify effective PNA candidates.

The goal of the Rbiotics project is to establish effective PNA candidates for important clinical pathogens by characterizing the molecular basis of PNA activity and resistance development through the systematic analysis of high-throughput data. The knowledge gained from these studies will form the basis for future logical design of RNA antibiotics to use against multi-drug resistant pathogens and for editing the microbiome. The development of programmable antibiotics will have major implications for the treatment of bacterial infections: as only the particular strain targeted is affected, issues of resistance development in other bacteria can be avoided. Additionally, this approach will avoid harming our natural commensal bacteria. This strategy could also be used to target specific functions of bacteria, for instance so that resistant bacteria become sensitive to conventional antibiotics, or pathogens no longer express toxins. Since certain bacterial pathogens are also associated with tumorigenesis, RNA antibiotics could also be of interest for cancer treatment or prophylaxis in the future.

5

INFRASTRUCTURE

5 INFRASTRUCTURE

2018-2019

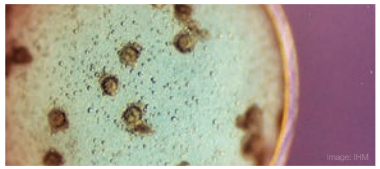
5.1
NRL FOR MENINGOCOCCI AND HAEMOPHILUS INFLUENZAE

The National Reference Laboratory (NRL) for meningococci and *Haemophilus influenzae* is hosted at the Institute for Hygiene and Microbiology at the University of Würzburg and is headed by Ulrich Vogel. The NRL has been commissioned by the Robert Koch Institute (RKI) to conduct representative laboratory surveillance of invasive meningococcal disease and invasive infections caused by *Haemophilus influenzae* in Germany, in close collaboration with the RKI. The NRL data are regularly matched with statutory notification data to achieve comprehensive datasets, which are also reported to the European Centre for Diseases Prevention and Control (ECDC). The NRL advises laboratories and public health authorities with respect to diagnosis, epidemiology, and prevention of meningococcal disease. It also collaborates with international networks, *e.g.* ECDC IBD-labnet and the European Meningococcal Disease Society (EMGM). The NRL annually processes 800 samples from patients with invasive bacterial infections. Key parameters assessed include serogroup or serotype, clonal finetype, and antibiotic resistance. Since 2019, whole genome sequencing has been applied for typing of meningococci. All sequences are available at PubMLST. Culture-independent analysis by sensitive PCR assays and DNA sequencing is performed on 100-150 samples per annum. The reference laboratory further conducts serological investigation of vaccine responses.

Annual reports for both infectious agents are available at **www.nrzmhi.de**.

A geographic information system can be accessed at **www.episcangis.org**.

5.2
THE CONSULTING LABORATORY FOR ECHINOCOCCOSIS



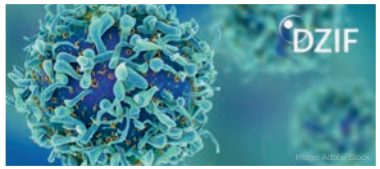
The Robert Koch Institute appoints the consulting laboratory for echinococcosis in Germany every second year for consultation, quality management, and development of diagnostic procedures. The Institute for Hygiene and Microbiology has been hosting the consulting laboratory for echinococcosis since 1997. The consulting laboratory is an assigned set point laboratory for interlaboratory comparison tests. It is also involved in the preparation and updating of quality standards for microbiological diagnostic procedures (MIQ). The consulting laboratory offers information regarding the prevention and epidemiology of different types of echinococcosis as well as on their diagnosis, differential diagnosis, and therapy. Moreover, detection of antibodies against *Echinococcus multilocularis* and *E. granulosus* in human sera is also offered by the consulting laboratory in addition to microscopy of cyst aspirates, sputa, other liquid samples, as well as solid tissue obtained at surgery for echinococcal structures. The consulting laboratory also provides parasitological analysis of stained and covered microscopic slides for echinococcal structures and differentiation of the parasite. After consultation with the treating physician, the consulting laboratory can provide detection of echinococcal DNA by PCR.

There is a close connection of the consulting laboratory and the research group of Klaus Brehm at the Institute for Hygiene and Microbiology, who investigates the host parasite relationship of alveolar echinococcosis.

The consulting laboratory for echinococcus is available online at **www.echinococcus.de**.

5.3
GERMAN CENTER FOR INFECTION RESEARCH (DZIF)

PROPHYLACTIC APPLICATION OF ESCALATING DOSES OF DONOR-DERIVED CENTRAL MEMORY T-LYMPHOCYTES AFTER ALLOGENEIC HEMATOPOETIC PROGENITOR CELL TRANSPLANTATION TO PREVENT INFECTIOUS COMPLICATIONS: A PROSPECTIVE, FIRST IN MAN, OPEN PHASE I/IIA CLINICAL TRIAL



In this multicenter clinical study, Hermann Einsele and Götz Ulrich Grigoleit (Dept. of Internal Medicine II) cooperate with clinicians from Munich, Tübingen, and Hannover to improve allogeneic hematopoietic progenitor cell transplantation (alloHPCT). AlloHPCT is a potentially curative treatment option for hematological malignancies. During the last decade, acute myeloid leukemia (AML) has become a major indication for alloHPCT. However, the survival of transplanted AML patients is substantially limited – in particular in older patients – by graft versus host disease (GVHD). *In vitro* T cell depletion can minimize the risk for GVHD, but leads to infectious complications with various opportunistic pathogens. Central memory T cells (Tcm) have been described to contribute most efficiently to rapid immune reconstitution after adoptive T cell transfer with a comparatively low risk for GVHD induction. In addition, it was recently demonstrated in pre-clinical mouse models as well as first clinical trials that adoptive immunotherapy of very few numbers of antigen-specific T cell purified under minimally manipulating conditions (without any *in vitro* cell culture) can be sufficient for effective and long-lasting immune reconstitution. In this trial, Tcm will be purified by a recently available serial positive selection technology (Fab Streptamer-Technology) and their safety will be tested in a phase I/IIa clinical trial in AML patients undergoing allo HPCT of an HLA-matched, *in vitro* T cell-depleted graft.

For further information please visit **www.dzif.de.**

5.4
INTERDISCIPLINARY CENTER FOR CLINICAL RESEARCH (IZKF)

The IZKF Würzburg organizes the Medical Faculty's internal research funding, aiming to strengthen clinical research by funding interdisciplinary cooperation between clinicians and scientists. Peer-reviewed application procedures and a transparent fund management are prerequisites for the IZKF's internal research management. It is steered by three governance boards, which comprise the general assembly (meeting of all IZKF members), the executive board that is responsible for the coordination of all programs and the funding decisions, as well as the external scientific advisory board that accompanies the Center's activities and is involved in the evaluation of project proposals. The IZKF's main research areas are represented in the IZKF Project Grants. The aim of this topic-focused funding is to align the Faculty's existing scientific priorities and to explore and enhance new topics. A close collaboration between clinical and basic research is required to receive funding by the IZKF. After up to three years of IZKF funding, the projects should be transferred to external third-party funds. The IZKF invites proposals every 18 months and receives an average of 30-35 project proposals with each call. Usually, 10-12 projects receive funding. In 2019, the IZKF supported 31 projects in 6 project areas with the participation of 25 clinical departments and institutes.

Projects involving ZINF members:

A303 MANFRED LUTZ
(Institute for Virology and Immunobiology)
Role of the immune system in the pathogenesis of Parkinson's Disease

A401 OLIVER KURZAI & THOMAS DANDEKAR
(Institute for Hygiene and Microbiology, Dept. of Bioinformatics)
The role of the intestinal mycobiome in the pathogenesis of the non-alcoholic fatty liver disease (NAFLD)

A408 MANFRED LUTZ
(Institute for Virology and Immunobiology)
Induction of memory type regulatory T cells in allergen immunotherapy

B343 LARS DÖLKEN
(Institute for Virology and Immunobiology)
Merkel cell carcinoma: model systems for carcinogenesis and therapy of a virus-induced tumor

B369 ANDREAS BEILHACK
(Dept. of Internal Medicine II)
Pharmacological destabilization of tumor ECM to increase the effectiveness of immunotherapeutics

The IZKF also funds Clinician scientists, who represent an indispensable link between basic sciences, clinical research, and patient care. Since both healthcare and research are increasingly complex and demanding areas, the IZKF and the Medical Faculty have decided to take complementary as well as new paths in career support of young physicians by establishing a rotation PLUS programme, a returnee programme, and a Clinician Scientist programme. The third key instrument of the IZKF funding is to support the research infrastructure at the Medical Faculty. This includes, in particular, the implementation of Core Facilities at the IZKF, in which important methods, techniques, or special services for (clinical) research are bundled, enhanced, and offered as a service.

The IZKF supported the following Core Facilities in the reporting period:

- Core Unit Systems Medicine: nucleic acid sequencing, bioinformatics, and single-cell analysis. **www.med-uni-wuerzburg.de/cu/sysmed**
- Interdisciplinary Bank of Biomaterials and Data Würzburg (ibdw, established in 2011 as one of five national BMBF-funded biobanks; sub-area tissue): safe storage of biomaterials (Contact: Prof. Dr. Roland Jahns, Prof. Dr. Andreas Rosenwald **www.ukw.de/interdisziplinaere-einrichtungen/interdisziplinaere-biomaterial-und-datenbank-wuerzburg**
- Service Unit for Confocal Microscopy and Flow Cytometry-based cell sorting: application of fluorescence techniques, *e.g.*, systems introduction, support and consulting on experimental designs, and optional data analysis (Contact: Prof. Dr. Andreas Beilhack, Prof. Dr. Wolfgang Kastenmüller). **www.virologie.uni-wuerzburg.de/service/imaging**
- Interdisciplinary Unit for Personalized Oncology/ Precision Oncology (IUPO): a platform for patient-oriented analyses for all kinds of tumors to further develop the field of personalized tumor therapy by combining scientific and clinical expertise (Contact: Prof. Dr. Ralf Bargou, Prof. Dr. Svenja Meierjohann, Prof. Dr. Andreas Rosenwald).

For further information please visit the IZKF website at **www.med.uni-wuerzburg.de/izkf.**

TWINSIGHT

Under the umbrella of the IZKF, an Integrative Clinician Scientist College (ICSC) intends to provide a uniform and joint platform for all clinician-scientist programs or individual funding schemes in the Faculty of Medicine. One of these funding themes is the newly established Else Kröner-Forschungskolleg for Translational Twinning in Systems Immunology and High-throughput Technology (TWINSIGHT), which is funded by the Else Kröner-Fresenius-Foundation and coordinated by professors Bastian Schilling and Matthias Goebeler (Department of Dermatology, Venerology, and Allergology). With several ZINF members as co-applicants (Florian Erhard, Wolfgang Kastenmüller, and Cynthia Sharma), there is also a close scientific-methodological and structural link to the ZINF. The TWINSIGHT Clinician Scientist College aims to join forces to address the problem of an ever-increasing workload in medicine and the fast pace of technological development leading to an increasing separation of health care and basic sciences. The program is embedded within the ICSC Würzburg and enables clinical tandem teams of physicians in an early career stage to approach their own research project by learning and using systems immunological methods and pioneering technologies. It also provides a broad complementary curriculum to train and prepare clinician scientists for a career in university medicine.

The TWINSIGHT College supports physicians working on innovative projects using systematic approaches in the fields of (1) tumour immunology and immunotherapy, (2) inflammatory and autoimmune diseases, (3) metabolic and cardiovascular immunology, or (4) infection immunology. The common goal of the projects is to decipher pathophysiologically relevant immunological processes of such diseases and to improve their therapies on the basis of mechanistic risk or benefit-based patient stratification, or to define patient groups on a molecular level that have either no or very great benefit from approved therapies. In addition, support is provided for projects that develop and analyze relevant preclinical or *in silico* models from clinical questions.

For further information please visit **www.med.uni-wuerzburg.de/izkf/integrative-clinician-scientist-college-wuerzburg/else-kroener-forschungskolleg-twinsight.**

5.5 CORE UNIT SYSTEMS MEDICINE

Next-generation sequencing technologies have revolutionized the scientific landscape and have become ubiquitous and essential tools across all areas of research, allowing holistic insights into biological systems. To address the ever-growing demand for generation, analysis, and interpretation of such data, the Core Unit Systems Medicine (CU SysMed) was launched in 2013 by a joint venture of the Medical Faculty of the University of Würzburg and the Interdisciplinary Center for Clinical Research (IZKF) of the University Hospital Würzburg and is located at the Institute of Molecular Infection Biology. The CU SysMed is a central institution that provides services and expertise to researchers at the University and the University Hospital in Würzburg as well as external groups by developing, applying, and analyzing a broad range of high-throughput deep sequencing technologies. These include, for example, mammalian exome sequencing, bacterial and viral genome sequencing, transcriptome sequencing (mRNA, ncRNA, total RNA), in addition to special sequencing techniques such as dual RNA-seq to analyze the transcriptome of host and pathogen in parallel, as well as CLIP-seq, RIP-seq, and Grad-seq to study RNA-protein complexes. In collaboration with the Helmholtz Institute for RNA-based Infection Research (HIRI), a particular focus of the CU SysMed was placed on the development and application of single-cell RNA sequencing (scRNA-seq) techniques to address the heterogenous effect of a pathogen during infection on different cell types on a singular cell level rather than a whole cell population. The team of the CU SysMed profits from a strong alliance between wet-lab scientists and bioinformaticians as well as close collaborations with the local research groups and, consulted by a steering committee, it will continue to expand its portfolio of high-throughput methods based on requests of the local research community.

For further information please visit the website of the CU SysMed at **www.med.uni-wuerzburg.de/cu/sysmed.**

6

TRAINING THE NEXT GENERATION OF INFECTION BIOLOGISTS

6 TRAINING THE NEXT GENERATION OF INFECTION BIOLOGISTS

6.1

GRADUATE SCHOOL OF LIFE SCIENCES (GSLS)

Graduate School Life Sciences

In 2006, the University of Würzburg launched the Graduate School of Life Sciences (GSLS), which was initiated by a common effort of the faculties of Biology, Medicine, Chemistry and Pharmacy, Physics, and Human Sciences. It offers a highly interdisciplinary work and study environment for doctoral researchers and ensures common graduation standards and rules for doctoral researchers. This consists of training that goes beyond mere scientific expertise and education of doctoral projects and includes, for example, general lectures and seminars, methods and transferable skills courses, as well as annual retreats. The GSLS was funded by the "German Universities Excellence Initiative" of the Federal and State Governments for more than 13 years. Now, the State of Bavaria and the University of Würzburg are strongly committed to support the GSLS to assure its sustainability for the next seven years. The GSLS is the largest graduate school at the University of Würzburg.

Within the framework of the graduate school, affiliated research institutions are grouped together based on related research activities and currently form the five "Research Sections" of the GSLS: Biomedicine, Clinical Sciences, Infection and Immunity, Integrative Biology, and Neuroscience. The GSLS also houses doctoral researchers of collaborative research programs such as the DFG-funded collaborative research centers and Transregios, research training groups, and clinical research groups, as well as other collaborative programs funded by the Federal Ministry of Education and Research (BMBF), the European Union, and other sources. Currently, more than 300 research groups are affiliated with the GSLS, and this combined expertise is reflected in more than 500 concurrent doctoral researchers, over 190 medical doctoral researchers, and the ever-rising number of more than 600 graduates. The dedicated team of the GSLS, under direction of Dr. Gabriele Blum-Oehler, is working passionately to provide a structured doctoral research training for all graduate students in their care.

Key training elements in the Graduate School are (1) a thesis committee of three principal investigators instead of a single supervisor, (2) a panel of training activities, from which an individual program is tailored to each doctoral researcher, (3) the active participation of doctoral researchers in courses and seminars, and (4) a set of requirements to warrant a common quality standard.

Mentoring System
Each doctoral researcher has an individual thesis committee, which meets with the doctoral researcher on an annual basis to monitor progress and adjust research and training activities. Additionally, the doctoral researchers report the status of their project within their research groups and programs to exchange ideas and obtain feedback within their peer-group.

Training activities
The training activities comprise a minimum of 4-6 hours per week and consist of seminars, journal clubs, program seminars, methods courses and transferable skills workshops, as well as retreats and international conferences.

Common Graduation Commission
The participating faculties form a common graduation commission within the respective graduate school. The commission is responsible for the conferral of all doctoral degrees within the graduate school. This enforces common standards across disciplines and fosters interdisciplinary cooperation in graduate training.

SECTION INFECTION AND IMMUNITY

Section Speakers:
PROF. DR. GEORG GASTEIGER
(Institute of Systems Immunology)

PROF. DR. JOACHIM MORSCHHÄUSER
(Institute of Molecular Infection Biology)

One of the major focal points of the University of Würzburg is reflected in the GSLS section "Infection and Immunity", a highly interdisciplinary and internationally recognized core research area of the university. Within the graduate school, almost 80 principal investigators across more than 20 research centers, institutes, clinics, and departments as well as additional institutions outside the university are associated with this scientific section. Research in this section covers a broad range of topics such as host-pathogen interactions, genome research in pathogenic microbes, non-coding RNAs in infections, RNA-based mechanisms during host-pathogen interactions, identification and characterization of novel anti-infectives, molecular processes of immune response in various host organisms, mechanisms of tumorigenic processes induced by microbes, and new concepts in immune therapy, as well as infection models. By comprehensively covering such an extensive range of topics, the GSLS guarantees the broadest possible training for doctoral researchers yet provides a focus on common and converging mechanisms centering around infectious disease research.

6.2

DFG RESEARCH TRAINING GROUP (GRADUIERTENKOLLEG GRK 2157) 3D INFECT

3D TISSUE MODELS FOR STUDYING MICROBIAL INFECTIONS BY HUMAN PATHOGENS

3D Infect GRK 2157 Research Training Group www.uni-wuerzburg.de/grk2157

Infectious diseases are still one of the main causes of mortality of man. A clear limitation of studying human pathogens is the lack of a relevant infection model. This is particularly true for human pathogens for which no animal reservoir is known. Since simple cell lines, cell culture systems, or animals are highly artificial models for human pathogens, the GRK 2157 aims to develop and apply novel human three-dimensional (3D) infection models based on engineered human tissues. The objective is to elucidate the molecular and mechanistic basis for interactions between host and microbes in natural infections with the long-term goal to develop new anti-infective strategies.

The main entrance routes for human pathogens are the skin as well as the respiratory, gastrointestinal, and urogenital tract. Engineered 3D human tissues of these entry routes are utilized for infection experiments with selected human-specific microbes (*Chlamydia, Neisseria, Campylobacter, Bordetella, Salmonella, Trypanosoma*, and measles virus). The GRK 2157 will establish vascularized tissue models to address bacterial dissemination, such as seen in gonococcal infection, whereas models for secondary barriers including human endothelia, 3D human blood brain barrier or dynamic DC/T cell interactions will be developed with groups working with microbes causing meningitis or encephalitis (meningococci, trypanosomes, and measles virus). Natural tissues consist of more than one cell type, and individual cells may behave differently from cells within monolayers and may even be metabolically reprogrammed in response to pathogen encounter. These predispositions not only require the investigation of microbes during interactions with complex tissue, but also the exploration of the response of individual host cells to the infection. The challenges of performing molecular analysis in such complex infection models will be met by applying the latest next-generation and high-throughput technology such as bioimaging (*e.g.* super-resolution fluorescence imaging, dSTORM) and Raman Spectroscopy, as well as single- and multi-cell next-generation RNA- and DNA-sequencing. In addition, the identification of infection-induced signaling pathways will likely yield new targets for the development of therapeutic strategies to protect from or combat bacterial, parasite and viral infections. All students work on interdisciplinary scientific projects. To provide them with a sound intellectual foundation the thesis committee develops an individual education program for students during their graduate training. This will result in a tailored, broad, and comprehensive education of each student.

Spokesperson of the GRK 2157:
PROF. DR. THOMAS RUDEL
(Dept. of Microbiology)

Projects involving ZINF members:

01 ANDREAS BEILHACK
(IZKF, Dept. of Internal Medicine II)
Host-pathogen interactions revealed by 3D high-resolution microscopy

02 THOMAS RUDEL & THOMAS DANDEKAR
(Dept. of Microbiology, Dept. of Bioinformatics)
Host factors required for the initiation and propagation of *Chlamydia trachomatis* infections

03 THOMAS RUDEL & VERA KOZJAK-PAVLOVIC
(Dept. of Microbiology)
Bacterial and host cell factors important for the invasion and dissemination of *Neisseria gonorrhoeae*

04 ALEXANDRA SCHUBERT-UNKMEIR
(Institute for Hygiene and Microbiology)
Meningococcal ligands and molecular targets required for adhesion and penetration of the blood-cerebrospinal fluid barrier under shear stress

05 CYNTHIA SHARMA
(Institute of Molecular Infection Biology)
Virulence factors and regulators required during *Campylobacter jejuni* infections

06 ROY GROSS
(Dept. of Microbiology)
Characterization of host cell responses after *Bordetella pertussis* infection using 2D and 3D *in vitro* airway test systems

07 SIBYLLE SCHNEIDER SCHAULIES
(Institute for Virology and Immunobiology)
Membrane and protein microdomains governing measles virus transmission at entry and exit interface

08 JÖRG VOGEL & MARCO METZGER
(Institute of Molecular Infection Biology, Dept. of Tissue Engineering and Regenerative Medicine)
Establishing a human intestinal tissue model to study host and pathogen determinants that restrict *Salmonella enterica* infection

09 MARKUS ENGSTLER
(Dept. of Cell and Developmental Biology)
Development of tsetse fly-transmitted African trypanosomes in human skin tissue models

10 SINA BARTFELD
(Research Center for Infectious Diseases)
Analysis of the innate immune response of gastrointestinal epithelium in 3D organoids

6.3
DFG RESEARCH TRAINING GROUP (GRADUIERTENKOLLEG GRK 2243) UBI

UNDERSTANDING UBIQUITYLATION: FROM MOLECULAR MECHANISMS TO DISEASE

The posttranslational modification of proteins by ubiquitin („ubiquitylation") has taken center stage in eukaryotic cell biology. Ubiquitylation triggers the degradation of damaged proteins, cell cycle regulators, transcription factors, and metabolic enzymes by the 26S proteasome. It serves as a versatile mark in many non-proteolytic processes such as DNA damage repair, receptor signaling and endocytosis. Given the multifaceted cellular functions of protein ubiquitylation, it is not surprising that abnormalities of the ubiquitin system causally contribute to the pathogenesis of a multitude of diseases including cancer, neurodegenerative disorders, and infectious diseases. In many cases, however, neither the precise function of the affected ubiquitin system component in healthy individuals, nor details of the pathogenesis following its impairment, is known. These limited mechanistic insights constitute an obstacle to the design of efficient therapeutic strategies and emphasize the requirement for continued efforts in basic research.

The research program of the GRK 2243 is focused on uncovering molecular mechanisms underlying the cellular functions of key enzymes at all levels of the ubiquitin system: the E1, E2 and E3 enzymes that mediate the ubiquitylation of specific target proteins; the de-ubiquitylating enzymes (DUBs) that control, counteract and edit target protein ubiquitylation; and the ATPase p97 (also known as Cdc48 and VCP), an abundant and essential regulator for the turnover of ubiquitylated target proteins. The elucidation of molecular mechanisms and physiological functions of these enzymes will guide the subsequent exploration of their dysfunction in ubiquitin-related diseases and the identification of small-molecule inhibitors as potential lead compounds for future therapeutic approaches.

The research program comprises 15 individual research projects in four core research areas:

A. Mechanism and regulation of ubiquitylation enzymes
The catalytic cascade of E1, E2, and E3 enzymes forms the heart of the ubiquitin system. Research area A is focused on the characterization of the structures, catalytic activities, and regulatory mechanisms of these ubiquitylation enzymes.

B. Mechanism and substrate recognition of de-ubiquitylating enzymes
DUBs have now received full recognition, both as antagonists and as modulators of ubiquitin chain formation. Research area B is focused on the structural and functional characterization of DUBs that play critical roles in cancer and infectious diseases.

C. Mechanisms of transcriptional control by (de-)ubiquitylating enzymes
Target protein ubiquitylation and de-ubiquitylation play numerous roles in transcription. Research area C focuses on the control of transcription through the ubiquitylation state of two important groups of transcription factors, Myc family members and SREBPs (sterol regulatory element-binding proteins), which are central regulators of cell growth and lipid metabolism, respectively.

D. Mechanism of p97 function in health and disease
The ATPase p97 is essential for various pathways of the ubiquitin system, because it releases ubiquitylated substrates for subsequent proteasomal degradation or non-proteolytic fates. Research area D is focused on the elucidation of the molecular mechanism of p97 function, its control by regulatory cofactors, its mutational impairment in neurodegenerative diseases, and its manipulation by small molecule inhibitors.

Spokesperson of the GRK 2243:
PROF. DR. ALEXANDER BUCHBERGER
(Dept. of Biochemistry)

Projects involving ZINF members:

B1 CAROLINE KISKER
(Rudolf Virchow Center for Integrative and Translational Bioimaging (RVZ))
Structural and functional analysis of the Fbw7-Usp28 complex

B3 CAROLINE KISKER & THOMAS RUDEL
(RVZ, Dept. of Microbiology)
Mechanism of substrate recognition by chlamydial DUBs

B4 THOMAS RUDEL & CAROLINE KISKER
(Dept. of Microbiology, RVZ)
Function of chlamydial DUBs during infection

6.4
DFG RESEARCH TRAINING GROUP (GRADUIERTENKOLLEG GRK 2581) SPHINGOINF

METABOLISM, TOPOLOGY, AND COMPARTMENTALIZATION OF MEMBRANE PROXIMAL LIPID AND SIGNALING COMPONENTS IN INFECTION

In spite of the availability of preventive strategies, infectious diseases continue to be a major threat worldwide. Therefore, there is a demand for continuous development of anti-infective or immuno-therapeutic strategies, in particular for conditions where conventional interventive means are not available, prohibited, or fail. To control infectious diseases, novel interventive strategies should therefore effectively modulate:

1. innate and adaptive immune responses and/or
2. tissue and cell compartment-specific autonomous metabolic parameters, all of which operate to limit (or in some instances also promote) both pathogen spread and tissue damage.

Common denominators of these cellular processes are dynamic alterations in membrane metabolism. This efficiently defines compartmentalization of the repertoire of host and immune cell receptors, associated signaling pathways, cytoskeletal dynamics, and effector mechanisms. Because sphingolipids are major components of membranes, sphingolipid biosynthesis and metabolism and availability of their signaling inert or bioactive species substantially affects the biophysical properties of membranes and the subcellular redistribution of receptors and signaling complexes. This may essentially regulate pathogen uptake and handling at a cellular and organismic level as well as survival and activity of immune cells, where they shape the magnitude and quality of the individual cellular compartments acting to control a given pathogen. Targeted intervention of sphingolipid turnover has proven to be a successful strategy in inflammation, but its potential as a target in controlling infectious diseases at the level of metabolism and immune controls requires further definition.

Therefore, the GRK 2581 aims to identify and validate targets for novel anti-infective or immunotherapeutic strategies targeting infectious diseases at the level of modulation of sphingolipid metabolism. As a long-term perspective, rationally defined synthetic sphingolipid analogues or metabolizing enzymes will be evaluated for therapeutic options in respective models of infectious diseases. These ambitious goals demand multidisciplinary training of a new generation of young scientists trained within the GRK 2581 that will be capable of integrating and implementing cutting edge basic and clinical infectiology, immunology, high-end microscopy, bio- and organic chemistry, as well as lipid and protein analytics and their bioinformatic processing.

Spokesperson of the GRK 2581:
PROF. DR. JÜRGEN SEIBEL
(Institute of Organic Chemistry)

Projects involving ZINF members:

01 LARS DÖLKEN, NIKLAS BEYERSDORFER & SIBYLLE SCHNEIDER-SCHAULIES
(Institute for Virology and Immunobiology)
The NSM2 as virus effector: targets, topology and functional consequences in T cells

03 NIKLAS BEYERSDORFER & WOLFGANG KASTENMÜLLER
(Institute for Virology and Immunobiology, Institute of Systems Immunology)
Sphingolipids balancing CD4+ Foxp3+ regulatory and effector T cell responses in chronic viral infections

04 ALEXANDRA SCHUBERT-UNKMEIR
(Institute for Hygiene and Microbiology)
Role of Sphingosine-1-phosphate and S1P1-3 receptors in the pathophysiology of meningococcal meningitis

05 OLIVER KURZAI
(Institute for Hygiene and Microbiology)
The role of sphingolipids in innate immune recognition of *Candida albicans*

06 MARTIN FRAUNHOLZ
(Dept. of Microbiology)
Determining the role of sphingomyelinases in *S. aureus* phagocytosis

07 THOMAS RUDEL
(Dept. of Microbiology)
Sphingolipid trafficking and function in Chlamydiales infection

08 VERA KOZJAK-PAVLOVIC
(Dept. of Microbiology)
Mitochondrial sphingolipids and their role in infection

09 JÜRGEN SEIBEL
(Institute of Organic Chemistry)
Sphingolipid metabolic pathways in infection control by the use of chemically synthesized modified sphingolipids and in the era of sphingolipidomics

7
APPENDIX

ZINF YOUNG INVESTIGATOR GROUP LEADERS ALUMNI

MEETINGS AND WORKSHOPS (CO)ORGANIZED BY ZINF MEMBERS

SEMINARS AND COLLOQUIA

FUNDING

PUBLICATIONS

DIRECTORY OF PEOPLE ASSOCIATED WITH THE ZINF

7.1 ZINF YOUNG INVESTIGATOR GROUP LEADERS ALUMNI

Since the founding of the Research Center for Infectious Diseases, many former Young Investigator group leaders have been appointed to highly competitive positions at various universities and industrial companies.

HEIDRUN MOLL

Current position:
C3-Professorship at the University of Würzburg, Institute of Molecular Infection Biology (IMIB)

Research at the ZINF:
1993 - 1998
Pathogenicity of *Leishmania*

MICHAEL LANZER

Current position:
C4-Professorship at the University of Heidelberg, University Hospital Heidelberg, Center for Infectious Diseases, Parasitology Unit

Research at the ZINF:
1994 - 1999
Pathogenicity of human malaria parasites

JOACHIM REIDL

Current position:
Professorship at the University of Graz, Institute of Molecular Biosciences

Research at the ZINF:
1996 - 2003
Virulence of Gram-negative bacteria

JOACHIM MORSCHHÄUSER

Current position:
C3-Professorship at the University of Würzburg, Institute of Molecular Infection Biology (IMIB)

Research at the ZINF:
1997 - 2000
Pathogenicity of *Candida*

KATJA BECKER

Current position:
C4-Professorship at the University of Gießen, since 2020 President of the German Research Foundation, Deutsche Forschungsgemeinschaft

Research at the ZINF:
1999 - 2000
Malarial parasites as targets for the development of antiparasitic drugs

KLAUS ERB

Current position:
Project Manager, Boehringer Ingelheim Pharma GmbH & Co. KG, Dept. of Cancer Immunology & Immune-modulation, Adj. Prof. at the University of Würzburg

Research at the ZINF:
1999 - 2004
Immunology of intracellular pathogens and allergic disorders

MATTHIAS LEIPPE

Current position:
C4-Professorship at the University of Kiel, Institute of Zoology

Research at the ZINF:
2001 - 2003
Molecular parasitology

CHRISTOF HAUCK

Current position:
W3-Professorship at the University of Konstanz, Cell Biology

Research at the ZINF:
2001 - 2006
Pathogen-host communication

SVEN HAMMERSCHMIDT

Current position:
W3-Professorship at the University of Greifswald, Interfaculty Institute of Genetics and Functional Genomics

Research at the ZINF:
2003 - 2007
Pathogenicity of *Streptococcus pneumoniae*

UTE HENTSCHEL HUMEIDA

Current position:
W3-Professorship at the University of Kiel and the GEOMAR Helmholtz Centre for Ocean Research Kiel, Marine Symbioses Research Unit

Research at the ZINF:
2004 - 2008
Novel antiinfectives

GABRIELE PRADEL

Current position:
W2-Professorship at the RWTH Aachen University, Cellular and Applied Infection Biology

Research at the ZINF:
2005 - 2011
Malaria: Transmission blocking strategies

ANN-KRISTIN MÜLLER

Current position:
Group Leader at the University Hospital Heidelberg, Center for Infectious Diseases, Parasitology Unit, Project Manager at BioRN Network e.V.

Research at the ZINF:
2007 - 2008
Biology of rodent malaria parasites

SVEN KRAPPMANN

Current position:
W2-Professorship at the University Hospital Erlangen, Institute of Microbiology, Clinical Microbiology, Immunology and Hygiene

Research at the ZINF:
2007 - 2012
Aspects of *Aspergillus fumigatus* pathogenicity

DANIEL LOPEZ

Current position:
Tenured Scientist Group Leader, Spanish National Research Council (CSIC), Spanish National Centre for Biotechnology (CNB), Dept. of Microbial Biotechnology

Research at the ZINF:
2010 - 2015
Bacterial cell differentiation

CYNTHIA SHARMA

Current position:
W3-Professorship at the University of Würzburg, Institute of Molecular Infection Biology (IMIB), Chair of Molecular Infection Biology II

Research at the ZINF:
2010 - 2016
Deep sequencing approaches to pathogenesis

ANA EULALIO

Current position:
Principal Investigator at the University of Coimbra, Center for Neuroscience and Cell Biology (CNC)

Research at the ZINF:
2012 - 2017
Host RNA metabolism

NICOLAI SIEGEL

Current position:
W2-Professorship at the Ludwig-Maximilians-Universität München, Biomedical Center Munich (BMC), Experimental Parasitology

Research at the ZINF:
2012 - 2017
Trypanosoma gene regulation

7.2 MEETINGS AND WORKSHOPS (CO)ORGANIZED BY ZINF MEMBERS

MEETINGS AND WORKSHOPS 2018-2019

Please note that for meetings and workshops organised by multiple people, only ZINF members are listed.

RNA Biology Course
Chase Beisel, Neva Caliskan
Würzburg, 9 - 13 December 2019

RNA and Infection Science Slam
Neva Caliskan
Würzburg, 25 November 2019

Science Communication Workshop
Neva Caliskan
Würzburg, 14 - 15 November 2019

EMBO Workshop "The impact of bacterial infections on human cancer"
Thomas Rudel
Berlin, 26 - 29 October 2019

EMBO Symposium "The Non-Coding Genome"
Jörg Vogel
EMBL Heidelberg, 16 - 19 October 2019

8th International Summer School Infection Biology 2019
Thomas Dandekar
Würzburg, 23 - 27 September 2019

AIChE 3rd International Conference on CRISPR Technologies
Chase Beisel, Jörg Vogel
Würzburg, 16 - 18 September 2019

22nd International Symposium on Signal Transduction at the Blood-Brain Barriers
Marco Metzger
Würzburg, 11 - 13 September 2019

Else-Kröner-Symposium "Translational Immunology – From Target To Therapy VI"
Andreas Beilhack
Würzburg, 27 - 29 June 2019

9th Würzburg Meningococci- and *Haemophilus influenzae*-Workshop: Meningo meets TB
Ulrich Vogel
Würzburg, 25 June 2019

15th EMGM Congress 2019
Ulrich Vogel
Lisbon (Portugal), 27 - 30 May 2019

Joint Meeting TR124 "FungiNet" & Invasive Mycoses in Haematological Malignancies XIII (IMIHM XIII)
Hermann Einsele, Oliver Kurzai, Jürgen Löffler
Würzburg, 27 - 28 May 2019

Infection & Immunity Short Course, co-organized by HIRI and IMIB
Franziska Faber, Emmanuel Saliba, Alexander Westermann
Würzburg, 8 - 10 May 2019

Cold Spring Harbor Asia Conference "Bacterial Infection & Host Defense"
Jörg Vogel
Suzhou (China), 8 - 12 April 2019

3D Tissue Infection Symposium
Thomas Rudel
Würzburg, 5 - 7 April 2019

Workshop "Single-cell Biology of Infection"
Emmanuel Saliba, Jörg Vogel
Würzburg, 28 March 2019

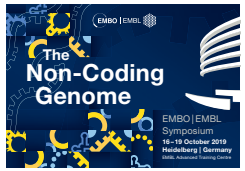
Frontiers in Medicinal Chemistry 2019 – Joint conference of the Gesellschaft Deutscher Chemiker and the Deutschen Pharmazeutischen Gesellschaft
Ulrike Holzgrabe
Würzburg, 24 - 27 March 2019

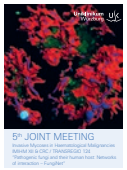
Cell-free TXTL Workshop intended for SPP 2141 students
Chase Beisel
Würzburg, 11 - 13 February 2019

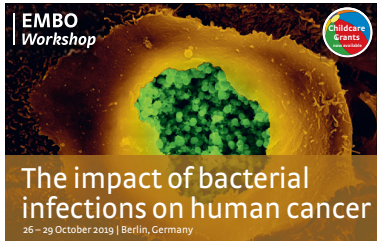
Update chronische Virushepatitis 2019
Hartwig Klinker
Würzburg, 30 January 2019

Workshop for the Initiation and Development of Biotechnological Strategies in Glycoscience
Jürgen Seibel
Würzburg, 23 - 24 January 2019

Workshop & Hands-on Training "RNA-seq data analysis" for the students of the GRK 2157, 3D Infect
Emmanuel Saliba, Cynthia Sharma, Alexander Westermann
Würzburg, 13 - 14 December 2018







RNA Biology Course
Chase Beisel, Neva Caliskan
Würzburg, 26 - 28 November 2018

ZINF 25th Anniversary Symposium
Cynthia Sharma
Würzburg, 14 November 2018

4th qNMR Summit 2018
Ulrike Holzgrabe
Würzburg, 10 - 11 October 2018

7th International Summer School Infection Biology 2018
Thomas Dandekar
Würzburg, 17 - 21 September 2018

Joint Meeting TR124 "FungiNet" & Invasive Mycoses in Haematological Malignancies XII (IMIHM XII)
Hermann Einsele, Oliver Kurzai, Jürgen Löffler
Würzburg, 26 - 27 June 2018

Symposium der Fachgruppen "Mikrobielle Pathogenität" (DGHM/VAAM) und "Gastrointestinale Infektionen" (DGHM) 2018
Cynthia Sharma
Bad Urach, 20 - 22 June 2018

Else-Kröner-Symposium "Translational Immunology – From Target To Therapy V"
Andreas Beilhack
Würzburg, 12 - 13 April 2018

28th Annual Meeting of the German Society for Parasitology
Markus Engstler
Berlin, 21 - 24 March 2018

Carbohydrate Biocatalysis Symposium
Jürgen Seibel
Cuernavaca (Mexico), 18 March 2018

Immunology Training Course for the students of the GRK 2157, 3D Infect
Andreas Beilhack
Würzburg, 12 - 14 March 2018

28th Annual Meeting of the German Society of Virology (GFV) 2018
Lars Dölken
Würzburg, 14 - 17 March 2018

DGHM 2018 Fachgruppenmeeting Microbial Pathogenesis (MPAT)
Alexandra Schubert-Unkmeir
Bochum, 19 - 21 February 2018

Joint DAAD – ShARE Meeting "Staphylococci and Antimicrobial Resistance Management"
Wilma Ziebuhr
Würzburg, 7 - 9 February 2018

Update chronische Virushepatitis 2018
Hartwig Klinker
Würzburg, 31 January 2018

7.3 SEMINARS AND COLLOQUIA

SEMINARS & COLLOQUIA 2018-2019

MICROBIOLOGY COLLOQUIUM

17 December 2019
Ilse Jacobsen, University of Jena
Pathogenesis of candidiasis: The impact of bacteria and fungal virulence factors

03 December 2019
Philippe Bouloc, Institute for Integrative Biology of the Cell (I2BC), Paris, FR
Competition experiments reveal *S. aureus* regulatory RNAs that cope with antibiotic and iron stresses

19 November 2019
Fabrizia Stavru, Institut Pasteur, Paris, FR
Mitochondria and intracellular bacteria: how close can you get?

22 October 2019
Margherita Y. Turco, University of Cambridge, UK
Organoid systems to model the maternal-fetal interface of human pregnancy

16 July 2019
Sven Hammerschmidt, University of Greifswald
The infection dynamics of the pathobiont *Streptococcus pneumoniae*

02 July 2019
Richard Hayward, University of Cambridge, UK
Lessons in nuclear remodelling from *Chlamydia trachomatis*

18 June 2019
Jennifer Rohn, University College London, UK
The secret life of invasive bacteria: modelling chronic urinary tract infection with a novel human organoid platform

04 June 2019
Ana Rita Brochado, University of Würzburg
Deciphering antimicrobial drug interactions using high-throughput approaches

21 May 2019
Peter Redder, Centre of Integrative Biology (CBI) in Toulouse, FR
RNA decay in *Staphylococcus*: global scale and molecular detail

07 May 2019
Joseph Zackular, University of Pennsylvania, US
Pathogen-microbiota interactions during *Clostridium difficile* infection

29 January 2019
Robert Fagan, University of Sheffield, UK
Cracking a difficult crystal shell: dissecting S-layer structure and function

15 January 2019
Man-Wah Tan, Genentech, San Francisco, US
Inspired by Nature: Engineering natural products and antibodies to treat infections

20 November 2018
Gunnar Hansson, University of Gothenburg, SE
The MUC2 mucin and the inner mucus layer as an innate immune mechanism that inhibits inflammation and ulcerative colitis - similarities to chronic lung diseases

06 November 2018
John D. MacMicking, Yale University, US
Cell-autonomous immunity to infection: the art of self-defense

23 October 2018
Harry Low, Imperial College London, UK
Architecture of a bacterial type II secretion system

10 July 2018
Jörg Overmann, German Collection of Microorganisms and Cell Cultures (DSMZ), Braunschweig
Elucidating novel functions in microbial dark matter

26 June 2018
Bernhard Krismer, University of Tübingen
Bacterial way of life in the human nose - a story about *Staphylococcus aureus* and its competitors

12 June 2018
Caroline Genco, TUFTS University in Medford and Somerville, US
Distinct gonococcal gene signatures expressed during human mucosal infection in men & women

05 June 2018
Gilad Bachrach, Hebrew University of Jerusalem, IL
From tooth to tumor, cancer acceleration by *Fusobacterium nucleatum*. Did you floss today?

29 May 2018
Manuel Amieva, Stanford University, US
Should we be looking for the bacterial stem cell compartment? Lessons from *Helicobacter pylori*

15 May 2018
John D. MacMicking, Yale University, US
Cell-autonomous immunity to infection: the art of self-defense

17 April 2018
Mathias Hornef, University Hospital Aachen
The neonatal window of opportunity: age-dependent factors of enteric host-microbial homeostasis

06 February 2018
Rob Lavigne, KU Leuven, BE
Hijacking *Pseudomonas*: using phage to develop new antibacterial design strategies and biotechnological applications

30 January 2018
Karl Forchhammer, University of Tübingen
Prepared for awakening: the resuscitation program of a dormant *Cyanobacterium*

23 January 2018
Birgitta Henriques-Normark, Karolinska Institute, Stockholm, SE
Pneumococcal interactions with the host

16 January 2018
Dominique Sanglard, University of Lausanne, CH
A journey through fungal cell functions by antifungal drug resistance mechanisms

09 January 2018
Martin Simon, University of Saarland
Small RNA pathways in *Paramecium*: Environmental RNAi by bacterial RNA and non-Mendelian inheritance of gene expression patterns

RNA SEMINAR

10 December 2019
Sam Sternberg, Columbia University, US
Transposon-encoded CRISPR-Cas systems direct RNA-guided DNA integration

26 November 2019
Markus Landthaler, Max-Delbrück Center for Molecular Medicine in the Helmholtz Association, Berlin
Post-transcriptional regulation in cellular space and time

12 November 2019
Peter Fineran, University of Otago, NZ
CRISPR-Cas regulation and immune mechanisms

29 October 2019
Yang Li, Centre for Individualised Infection Medicine, Hannover
A big data approach for individualised infection medicine: translating genetic variation into immune function

15 October 2019
Gisela Storz, NIH, Bethesda, US
Redundancy in regulatory RNA networks

Anna Pyle, Yale University, US
Targeting the unique features of fungal RNA metabolism for a new generation of nontoxic drugs

23 July 2019
Mathias Munschauer, HIRI, Würzburg
Decoding the functions of long non-coding RNAs through their protein interactomes

09 July 2019
Daniel Wilson, University of Hamburg
Antimicrobial peptides as novel ribosome-targeting antibiotics

14 May 2019
Chris Hill, University of Cambridge, UK
Defining the "licence to cut": structural and functional insights from deconstructing the eukaryotic mRNA 3' end processing machinery

30 April 2019
Chris Ponting, University of Edinburgh, UK
Post-transcriptional regulation of mitochondrial activity by noncoding RNAs

05 February 2019
Noam Stern-Ginossar, Weizmann Institute of Science, Jerusalem, IL
Post-transcriptional control of host gene expression during viral infection

22 January 2019
Peter Nielsen, University of Copenhagen, DK
A future of genetic antibiotics – antibacterial properties of antisense peptide nucleic acids (PNA)-peptide conjugates

Thorsten Stafforst, University of Tübingen
Engineering tools for site-specific RNA manipulation

8 January 2019
Ciarán Condon, CNRS Paris, FR
Coupling of transfer RNA and ribsomal RNA maturation via stringent control

18 December 2018
Susan Carpenter, University of California, UC Santa Cruz, US
How do long non-coding RNAs contribute to inflammation?

11 December 2018
Simone Backes, University of Würzburg
The roles of small non-coding RNAs during virus infection

27 November 2018
Blake Wiedenheft, Montana State University, US
Evolutionary outcomes of CRISPR-anti-CRISPR conflict

13 November 2018
Demian Cazalla, University of Utah, US
Lessons from viruses: a novel function for Sm-class RNAs

30 October 2018
Renate König, Paul-Ehrlich-Institute, Langen
New insights into innate sensing and restriction of HIV-1

16 October 2018
Fabian Theis, Helmholtz Zentrum München
Machine learning in single cell genomics

03 July 2018
Tom Cooper, Baylor College of Medicine, Houston, US
Alternative splicing regulatory networks in development and their disruption in disease

19 June 2018
Barbara Treutlein, Max Planck Institute for Evolutionary Anthropology, Leipzig
Reconstructing human organ development using single-cell transcriptomics

22 May 2018
Lingling Chen, Shanghai Institute of Biochemistry and Cell Biology, CN
The diversity of long non-coding RNAs, their generation and function

08 May 2018
Helge Grosshans, Friedrich Miescher Institute for Biomedical Research, Basel, CH
Cell fate control through post-transcriptional regulation and oscillatory gene expression

24 April 2018
Claus-Dieter Kuhn, University of Bayreuth
The role of piRNAs in planarian regeneration

10 April 2018
Henrik Ørum, CiVi Biopharma, US
RNA therapeutics - the long road to success

ORGANOID CLUB

22 October 2019
Motaharehsadat Heydarian, University of Würzburg and Pargev Hovhannisyan, University of Würzburg
Organoids derived from female genital tract as infection models

02 October 2019
Marco Metzger, University Hospital Würzburg, Fraunhofer Institute for Silicate Research ISC, TERM
Intestinal organoids in preclinical research

Jason Spence, University of Michigan, US
A cellular atlas of the developing human intestinal stem cell niche

25 June 2019
Oliver Hartmann, University of Würzburg
Microscopy of organoids

25 June 2019
Matt Zilbauer, University of Cambridge, UK
Human intestinal epithelial organoids - tools to investigate epigenetics in health and Inflammatory Bowel Diseases.

18 June 2019
Elmar Wolf, University of Würzburg
Identifying MYC-associated oncogenic targets by genetic screens in complex systems

28 May 2019
Markus Diefenbacher, University of Würzburg
Targeting protein stability in cancer: mouse and organoid models

Mirjana Kessler, Charité University Medicine Berlin
Chronic *Chlamydia* infection organoid model & origins of tubal disease

Kai Kretzschmar, Hubrecht Institute, NL
Modelling epidermal stem cell expansion and differentiation in a dish

05 April 2019
Matthias Lutolf, EPFL, CH
Engineering next-generation intestinal organoids

13 March 2019
Sina Bartfeld, University of Würzburg
Infection, innate immune signaling and cancer in the gut

Henner Farin, University of Frankfurt
Stem cell-derived organoids as genetic models for signaling in the colon cancer microenvironment

VIROLOGY AND IMMUNOBIOLOGY SEMINAR

25 November 2019
Andreas Pichlmair, Technical University München
Intracellular organization of the innate immune response – and its disturbance by viruses

18 November 2019
Bernhard Nieswandt, RVZ Würzburg
Ischaemic stroke: a thrombo-inflammatory disease?

11 November 2019
Luka Cicin-Sain, HZI Braunschweig
The latency of CMV in balance with the host immune system

28 October 2019
Caspar Ohnmacht, Center of Allergy and Environment (ZAUM), TU and Helmholtz Zentrum München
Regulating the regulators: microbiome, Tregs and dendritic cells

18 July 2019
Ralf Bartenschlager, University Hospital Heidelberg
Flaviviridae - host cell interactions: A tale of proteins, lipids and RNA

15 July 2019
Steeve Boulant, University Hospital Heidelberg
Importance of type III interferon and cellular polarity on host/enteric pathogen interaction at intestinal epithelium

08 July 2019
Peter Murray, Max Planck Institute of Biochemistry Martinsried
Myeloid metabolism and immune control

01 July 2019
Melanie Brinkmann, Technical University Braunschweig
Meticulous and multifaceted: how herpesviruses fine tune the innate immune response

17 June 2019
Nicola Gagliani, Center for Internal Medicine, UKE Hamburg
CD4 T cell functional heterogeneity and plasticity: understanding immune homeostasis and its underlying mechanisms

27 May 2019
Thomas Pietschmann, Institute of Experimental Virology, Twincore Hannover
Genetic determinants of severe respiratory syncytial virus infection in infants

22 May 2019
Adam Grundhoff, Heinrich Pette Institute, Leibniz Institute for Experimental Virology Hamburg
Repressive chromatin states and herpesvirus latency establishment: Who is in the driving seat?

13 May 2019
Elisa Monzon-Casanova, Babraham Institute, University of Cambridge, UK
Essential roles for the RNA-binding proteins PTBPs during lymphocyte development and effector functions

06 May 2019
Percy Knolle, Technical University München
Metabolic activation of CD8 T cells in the liver causing tissue damage

28 January 2019
Friedemann Weber, JLU Giessen
Induction and suppression of the interferon response by segmented negative-sense RNA viruses

21 January 2019
Neva Caliskan, HIRI Würzburg
Translating viral and cellular frameshift genes one codon at a time

14 January 2019
Loretta Tuosto, Sapienza University Rom, IT
Human CD28 costimulatory molecule: pro-infammatory functions beyond a qualitative and quantitative support to TCR signals

17 December 2018
Susanne Stutte, LMU München
Type-1-interferon suppresses appetite, induces malnutrition and alters immune cell composition by interfering with the endocrine system

03 December 2018
Oliver Kurzai, University of Würzburg
From immune recognition of fungal pathogens towards personalized medicine

02 July 2018
Andreas Müller, Otto-von-Guericke University in Magdeburg
Dissecting *Leishmania major* proliferation and host cell tropism by novel *in vivo* biosensors

25 June 2018
Frank Kirchhoff, University Hospital Ulm
Relevance beyond HIV: novel antiretroviral restriction factors

22 June 2018
Sammy Bedoui, University of Melbourne, AU
Innate regulation of CD8 T cell immunity

04 June 2018
Andrew MacDonald, University of Manchester, UK
Dendritic cells and macrophages in promotion and regulation of type 2 inflammation

28 May 2018
Klaus Osterrieder, FU Berlin
(Bi) codon deoptimization in herpes- and influenza viruses: a way to new modified live virus vaccines?

07 May 2018
Jan Rohr, University Hospital Freiburg
T cell cooperativity shapes antigen-specific immune responses

23 April 2018
Simone Becattini, Sloan Kettering Institute, Memorial Sloan Kettering Cancer Center New York, US
Host-microbe symbiosis in the gut: a two-sided story

09 April 2018
Thomas Tüting, University Hospital for Dermatology and Venereology Magdeburg
Redirecting antiviral host defense against cancer

08 February 2019
Elvira Mass, University of Bonn
Is neurodegenerative disease a kind of cancer?

08 February 2018
Stephan Becker, Philipps University Marburg
Transcription and replication of filoviruses

29 January 2018
Stipan Jonjic, University of Rijeka, HR
Brain-resident memory CD8 T cells induced by congenital CMV infection prevent brain pathology and virus reactivation

15 January 2018
Wolfgang Schamel, Centre for Biological Signalling Studies (BIOSS), University of Freiburg
Mechanisms of abTCR and gdTCR activation: from signalling to new cancer immunotherapy concepts

OTHER SEMINARS

Only selected seminars of ZINF members or related to infectious diseases are listed.

INAUGURAL LECTURES

03 May 2019
Cynthia Sharma, Institute of Molecular Infection Biology (IMIB), Würzburg
Kleine RNAs in pathogenen Bakterien – mehr als nur vier Buchstaben

Oliver Kurzai, Institute for Hygiene and Microbiology (IHM), Würzburg
Das vergessene Königreich – wie Pilze unser Leben verändern

02 June 2018
Wolfgang Kastenmüller, Institute of Systems Immunology, Würzburg
Das Immunsystem in Raum und Zeit

Georg Gasteiger, Institute of Systems Immunology, Würzburg
Netzwerke geweberesidenter Immunzellen

BIOZENTRUMS-KOLLOQUIUM

27 November 2019
Christof Niehrs, Institute of Molecular Biology, Mainz
Decoding of regulatory R-loops

13 November 2019
Antonio Di Pietro, Department of Genetics, University of Córdoba, ES
Dynamics of host adaptation in the fungal pathogen *Fusarium oxysporum*

08 May 2019
Bernd Bukau, Center of Molecular Biology (ZMBH), University of Heidelberg
Folding and assembly of newly synthesized proteins revealed by ribosome profiling

14 November 2018
Dean W. Felsher, Standford School of Medicine, Stanford University, US
MYC oncogene is a master regulator of the immune response

24 October 2018
Georg Gasteiger, Institute of Systems Immunology, Würzburg
Local players in immunity: networks of tissue resident lymphocytes

06 June 2018
Anne Willis, MRC Toxicology Unit at the University of Cambridge, UK
Regulation of mRNA translation via control of elongation in health and disease states

31 January 2018
Stefan Raunser, Max Planck Institute of Molecular Physiology, Dortmund
The power of cryo-EM to elucidate biological mechanisms

PHYSICO MEDICA

11 December 2019
Chase Beisel, Helmholtz-Institute for RNA-based Infection Research (HIRI), Würzburg and Jörg Vogel, Institute of Molecular Infection Biology (IMIB) in Würzburg
Human Nature - Die CRISPR Revolution
Film mit anschließender Diskussion

11 December 2018
Thomas Cooper, Baylor College of Medicine, Houston, Texas, US
Investigation of myotonic dystrophy revealed a network of developmentally regulated alternative splicing, the disruption of which causes disease features

03 July 2018
Thomas Cooper, Baylor College of Medicine, Houston, Texas, US
Alternative splicing regulatory networks in development and their disruption in disease

7.4 FUNDING

FUNDING IN 2018-2019

BARTFELD, SINA

EU Horizon 2020: REMODEL – Research models in infection, cancer, and tissue regeneration: replacement and translation. Twinning Project with IBMC (Portugal), University of Utrecht (NL), University of Copenhagen (DK)

DFG GRK 2157: 3D Infect – 3D Tissue Models for Studying Microbial Infections by Human Pathogens (Project 10): Analysis of the innate immune response of gastrointestinal epithelium in 3D organoids

Käthe und Josef Klinz-Stiftung: Systemic Analysis of immunological barrier function in organoids from adult stem cells

BEILHACK, ANDREAS

DFG SFB/TRR 124: FungiNet – Pathogenic fungi and their human host: Networks of interaction (Project A03): *In vivo* analysis of temporal and spatial disease progression and immune cell recruitment during invasive *Aspergillus fumigatus* infection

DFG SFB/TRR 225: Biofab – From the fundamentals of biofabrication towards functional tissue models (Project B08): Time-resolved biophotonics approach cellular signaling, cell-matrix interactions and matrix remodeling mechanisms in biofabricated constructs

DFG GRK 2157: 3D Infect – 3D Tissue Models for Studying Microbial Infections by Human Pathogens (Project 01): Host-pathogen interactions revealed by 3D high resolution microscopy

IZKF (B-369): Pharmacological destabilization of tumor ECM to increase the effectiveness of immunotherapeutics

Deutsche José Carreras Leukämie-Stiftung (DJCLS 05R/2016): Separation of GvHD from GvL-effects by targeting the TWEAK/Fn14-system

Else-Kröner-Forschungskolleg for Interdisciplinary Translational Immunology (Coordinator), Else-Kröner-Fresenius-Stiftung (second funding period)

m^4 Award of the Bavarian Ministry of Economic Affairs and Media, Energy and Technology

Bayerische Forschungsstiftung (WP2TP3): FortiTher – Tumor diagnostics for individualized therapy

BEISEL, CHASE

DFG SPP 2141: Much more than defence – the multiple functions and facets of CRISPR-Cas (BE 6703/1-1): Functional characterization of extensively self-targeting CRISPR-Cas systems in the bacterial plant pathogen *Xanthomonas albilineans*

ERA-Net JPI-EC-AMR (01KI182): CRISPRattack – Advancing CRISPR antimicrobials to combat the bacterial pathogen *Klebsiella pneumoniae*

Benson Hill (Sponsored Research Agreement): Characterizing and enhancing the properties of the Cms1 nuclease

DARPA (Safe genes program HR0011-17-2-0042): Technologies to control, surveil, and counter genome-editing nucleases and gene drives

BEYERSDORF, NIKLAS

DFG SFB/TRR 124: FungiNet – Pathogenic fungi and their human host: Networks of interaction (Project C06): Role of secreted *Candida albicans* proteins in immune evasion and Pathogenicity

DFG FOR 2123: SphingoFOR – Sphingolipid dynamics in infection control (BE 4080/3-2): Role of sphingolipids in the regulation of anti-viral T cell responses

DFG (BE 4080/2-1): The role of CD28-mediated signals in programming and reprogramming of mouse and human memory and induced regulatory T cells

BMBF (031L0156C): *In-vitro* test methods to evaluate the efficacy of immunological therapies for malignant melanoma

IZKF (E-298): Therapeutic modulation of regulatory T cells in minipigs to improve wound healing and survival after myocardial infarction

BREHM, KLAUS

ERANet-LAC (ELAC2015/T080544): NDTND – Development of New Diagnostic and Treatment Options for Helminthic Neglected Diseases

Wellcome Trust Strategic Award (107475/Z/15/Z): FUGI – Flatworm Functional Genomics Initiative: Development of cestode functional genomics tools

Bayerische Forschungsstiftung (AZ-1341-18): KITE – Kinase inhibitors as therapeutic agents for echinococcosis

BROCHADO, ANA RITA

DFG Emmy Noether Grant: Deciphering molecular mechanisms of bacterial cell death and persistence using antibiotic combinations

CALISKAN, NEVA

RNA Society: RNA Salon-Würzburg

DANDEKAR, THOMAS

DFG SFB/TRR 34: Pathophysiology of Staphylococci in the Post-Genome-Era (Project A08): A systems biology perspective of metabolic and regulatory adaptation of *Staphylococcus aureus* to infection-related conditions

DFG SFB/TRR 34: Pathophysiology of Staphylococci in the Post-Genome-Era (Project Z01): An integrated view of adaptation of *Staphylococcus aureus*

DFG SFB/TRR 124: FungiNet – Pathogenic fungi and their human host: Networks of interaction (Project B01): Modelling interactions between the host and fungal pathogens by combining metabolic pathway analysis and evolutionary game theory

DFG SFB/TRR 124: FungiNet – Pathogenic fungi and their human host: Networks of interaction (Project B02): Interaction networks of signaling molecules and pathways between the pathogenic fungi Aspergillus fumigatus and *Candida albicans* and their human host

DFG GRK 2157: 3D Infect – 3D Tissue Models for Studying Microbial Infections by Human Pathogens (Project 02): Host factors required for the initiation and propagation of *Chlamydia trachomatis* infections

IZKF (A-401): NAFLD – The role of the intestinal mycobiome in the pathogenesis of the non-alcoholic fatty liver disease

StMWi HIRI Seed Grant #12: Functional host-pathogen transcriptomics of human macrophages and dendritic cells challenged with *Aspergillus fumigatus* and cytomegalovirus

DÖLKEN, LARS

ERC Consolidator Award: Herpesvirus Effectors of RNA Synthesis, Processing Export and Stability

Infect-ERA (ERA-Net), 2nd Call Consortium: eDEVILLI – Early Determinants of DNA-Virus Lytic or Latent Infection

DFG FOR 2830: Advanced Concepts in Cellular Immune Control of Cytomegalovirus (Speaker) (Project 01): Integrative analyses of CMV translatomes and MHC-I ligandomes

DFG (DO 1275/6-1): Functional analysis of downstream open chromatin induced in HSV-1 infection

DFG (DO 1275/10-1): Integrative analyses of CMV translatomes and MHC-I peptidomes

StMWi HIRI Seed Grants #9: Intrinsic host-cell defenses limiting cytomegalovirus transcription and translation in latency; #10: Establishment of Grad-seq to study RNA-protein interaction networks in human cells using the HSV-1 host shut-off model; #22: Heterogeneity of the host response to acute and chronic infection in primary myeloid cells

EINSELE, HERMANN

European Commission FP7: T-Control – Donor T Cells for Immune Control (Health-F4-2013-601722): Clinical trial for the treatment of infections and tumor relapse after allogeneic HSCT; Clinical trial for the treatment of acute steroid refractory GVHD after allogeneic HSCT

EU Horizon 2020: EURE-CART – European Endeavour for Chimeric Antigen Receptor Therapies

EU Horizon 2020: CARAMBA – SLAMF7-CAR T cells prepared by Sleeping Beauty gene-transfer for immunotherapy of multiple myeloma: a rare hematologic disease

DFG SFB/TRR 124: FungiNet – Pathogenic fungi and their human host: Networks of interaction (Project A02): Interaction of *Aspergillus fumigatus* with human natural killer cells, dendritic cells

DFG SFB/TRR 221: Modulation of graft-versus-host and graft-versus leukemia immune responses after allogeneic stem cell transplantation (Project A03): CAR-engineered T cells that augment the graft-versus-leukemia effect of allogeneic HSCT

DFG FOR 2830: Advanced Concepts in Cellular Immune Control of Cytomegalovirus (Project 09): Personalized medicine – Risk stratification and prevention of HCMV-related disease in transplant patients based on MHC-I-ligandomes

BMBF InfectControl 2020: Art4FUN – Antigen-reactive T cells for the diagnosis and therapy of fungal-associated diseases in high-risk patients

BMBF Verbundantrag: IMMUNOQUANT – Antibody- and T cell-based immunotherapy depending on antigen density and detection of tumor-associated antigens on solid tumors with dSTORM

Wilhelm-Sander-Stiftung (2020.017.1): Development and evaluation of human natural killer cells with synthetic antigen-specific receptors (CAR NK) and therapeutic antibodies for the add-on treatment of invasive fungal infections

StMWi HIRI Seed Grant #23: Genetic engineering of chimeric antigen receptor (CAR) T cells for immunotherapy in cancer and infection

ENGSTLER, MARKUS

DFG GRK 2157: 3D Infect – 3D Tissue Models for Studying Microbial Infections by Human Pathogens (Project 09): Development of tsetse fly-transmitted African trypanosomes in human skin tissue models

DFG SPP 1726: Microswimmers – From Single Particle Motion to Collective Behaviour (EN 305/4-3 and EN 305/8-1): From solitary swimmers to swarms and back: trypanosomes on their journey through the tsetse fly

DFG German-African Cooperation Projects in Infectiology (EN 305/5-1 and EN 305/7-1): Antibody clearance as virulence factor in African sleeping sickness

German-Israeli Foundation for Scientific Research and Development (GIF I-1473-416.13/2018): Effect of extracellular *Trypanosoma brucei* vesicles on collective and social parasite motility and development in the tsetse fly

ERHARD, FLORIAN

DFG FOR 2830: Advanced Concepts in Cellular Immune Control of Cytomegalovirus (Project 01): Integrative analyses of CMV translatomes and MHC-I ligandomes

StMWi HIRI Seed Grants #10: Establishment of GRAD-seq to study RNA-protein interaction networks in human cells using the HSV-1 host shut-off model; #22: Heterogeneity of the host response to acute and chronic infection in primary myeloid cells

FRAUNHOLZ, MARTIN

DFG SFB/TRR 34: Pathophysiology of Staphylococci in the Post-Genome-Era (Project C11): Host cell death induced by *Staphylococcus aureus* and its linkage to phagosomal escape

DFG FOR 2123: SphingoFOR – Sphingolipid dynamics in infection control (FR 1504/4-1): Role of the acid sphingomyelinase/ceramide system in lung edema induced by *Staphylococcus aureus* toxin

StMWi HIRI Seed Grant #7: Mode of action of the novel virulence regulatory RNA SSR42 during *Staphylococcus aureus*-induced osteomyelitis

FROSCH, MATTHIAS

EU/ECDC grant: Coordination of activities for laboratory surveillance of invasive bacterial diseases (*N. meningitidis, H. influenzae, and S. pneumoniae*) in Member States and EEA/EFTA countries

RKI Grant (1369-237): National Reference Laboratory for Meningococci and *Haemophilus influenzae*

RKI Grant (1369-378): Consiliary Laboratory for Echinococcosis

GASTEIGER, GEORG

ERC Starting Grant: Tissue-resident Lymphocytes – Development and Function in "real life" Contexts

DFG Emmy Noether Grant: Adaptive-innate lymphocyte crosstalk – mechanisms, functions, and consequences

DFG SPP 1937: Innate lymphoid cells (GA 2129/2-1): Tissue-niches and cellular interactions of mouse and human ILCs at single-cell resolution

GEIBEL, SEBASTIAN

Elitenetzwerk Bayern (N-BM-2013-246): Structural biology of mycobacterial secretion machines

GOMEZ DE AGÜERO, MERCEDES

Novartis Foundation for medical-biological Research

Ambizione Swiss National Funding

GROSS, ROY

DFG GRK 2157: 3D Infect – 3D Tissue Models for Studying Microbial Infections by Human Pathogens (Project 06): Characterization of host cell responses after *Bordetella pertussis* infection using 2D and 3D *in vitro* airway test systems

HERRMANN, THOMAS

DFG FOR 2799: Receiving and Translating Signals via the gamma-delta T Cell Receptor (HE 2346/8-1): Phylogeny and Function of Vγ9Vδ2 T cells – Human vs. Camelids

DFG (HE 2346/7-1): Vγ9Vδ2 T cells – Identification in non-primate species and analysis of molecular determinants of antigen-recognition

Wilhelm Sander-Stiftung (2013.907.2): Mechanistic basis for new strategies of γδ T cell-mediated immunotherapies against multiple myeloma

Deutsche Krebshilfe (70112079): Function and therapeutic relevance of chromosome 6 localized genes for recognition and elimination of tumor cells by human Vγ9Vδ2 T cells

HOLZGRABE, ULRIKE

BMBF iMIP Naturstoffmedizin: Development of non-immunosuppressive FK506 analogues as macrophage infectivity potentiator (MIP) inhibitors for the treatment of *Legionella pneumophila*, *Burkholderia pseudomallei*, and *Trypanosoma cruzi* infections (16GW0212): Development of MIP inhibitors of the FK506 type for the treatment of *Trypanosoma cruzi* infections

DMTC (Project 10.44): Pharmaceutical Development of Antivirulence Compounds Against BW Pathogens

Bayerische Forschungsstiftung (AZ 1204-16): Antibiotic-osmoprotective ionic liquids

Elitenetzwerk Bayern, Internationales Doktorandenkolleg: Receptor dynamics – Emerging Paradigm for Novel Drugs (Project): Development of pathway-specific dualsteric ligands and investigation into their mode of action

Bayern Innovativ (PBN-MED-1604-0009): Personalisierte Medizin für Menschen mit psychischen Erkrankungen

Leibniz-Gemeinschaft: PHARMSAFE – Development of a predictive solid state tool for improved pharmaceutical safety

KASTENMÜLLER, WOLFGANG

ERC Consolidator Grant: Spatiotemporal regulation of T-cell Priming

KISKER, CAROLINE

DFG GSC 106: GSLS – Excellence Initiative by the German federal and state governments

DFG GRK 2243: UBI – Understanding Ubiquitylation: From Molecular Mechanisms to Disease (Project B01): Structural and functional analysis of the Fbw7-Usp28 complex; (Project B03): Mechanism of substrate recognition by chlamydial DUBs

KLINKER, HARTWIG

NIH and BMBF (01 KG 0915): START – Strategic Timing of Antiretroviral Treatment

Hector-Stiftung (STIF-99): Individualized cancer therapy with kinase inhibitors using drug monitoring – optimization by minimally invasive at-home sampling

KOZJAK-PAVLOVIC, VERA

DFG GRK 2157: 3D Infect – 3D Tissue Models for Studying Microbial Infections by Human Pathogens (Project 03): Bacterial and host cell factors important for the invasion and dissemination of *Neisseria gonorrhoeae*

KURZAI, OLIVER

EU Horizon 2020: HDM-FUM – Host-Directed Medicine in Invasive Fungal Infections

DFG SFB/TRR 124: FungiNet – Pathogenic fungi and their human host: Networks of interaction (Project C03): Intrinsic modulation of neutrophil antifungal activity against *Candida albicans*

BMBF InfectControl 2020: FINAR & FINAR 2.0 – Fungal Infections and Azole Resistance

BMBF InfectControl 2020: RAI students – Rational use of antibiotics through information and communication: New target group - students of human medicine and pharmacy

BMBF InfectControl 2020: Transsectoral Research Platform (TFP) – Genome-wide identification of risk markers in the immune response against infections

BMBF InfectControl 2020: Innovationslabor Imaging

BMBF Center for Sepsis Control and Care CSCC: QUANTIM – Quantification of Innate Immune Function in Whole Blood Infection Assays

IZKF (A-401): NAFLD – The role of the intestinal mycobiome in the pathogenesis of the non-alcoholic fatty liver disease

BMG/RKI grant (1369-240): NRZMyk – Nationales Referenzzentrum für Invasive Pilzinfektionen

Else-Kröner-Fresenius-Stiftung: Else-Kröner-Fresenius-Center for Advanced Medical & Humanitarian Studies Würzburg - Mwanza

LÖFFLER, JÜRGEN

DFG SFB/TRR 124: FungiNet – Pathogenic fungi and their human host: Networks of interaction (Project A02): Interaction of *Aspergillus fumigatus* with human natural killer cells and dendritic cells

BMBF InfectControl 2020: Art4FUN – Antigen-reactive T cells for the diagnosis and therapy of fungal-associated diseases in high-risk patients

BMBF (BayBIO 1606-0003 - TbaselA): T cell-based monitoring for invasive *Aspergillus* in patients with haematological diseases

Wilhelm Sander-Stiftung (2015.083.1): Diagnostic strategies for cancer patients with respiratory fungal infections

StMWi HIRI Seed Grant #12: Functional host-pathogen transcriptomics of human macrophages and dendritic cells challenged with *Aspergillus fumigatus* and cytomegalovirus

LUTZ, MANFRED

DFG (LU 851/6-2): VLA-1-dependent migration patterns and functions of monocytic myeloid-derived suppressor cells (M-MSDC) during autoimmunity and infection

DFG (LU 851/14-1): Conversion of anergic non-regulatory into Foxp3-IL-10+ regulatory T cells by dendritic cells *in vivo*

IZKF (A-303): Role of the immune system in the pathogenesis of Parkinson's Disease

Wilhelm Sander-Stiftung (2013.60.1): Functional roles of direct and bystander release of IL-12 by dendritic cells for T cell activation and anti-tumor immunity

StMWi HIRI Seed Grant #22: Heterogeneity of the host response to acute and chronic infection in primary myeloid cells

METZGER, MARCO

EU-IMI (807015): IM2PACT – Investigating Mechanisms and Models Predictive of Accessibility of Therapeutics into the brain

DFG GRK 2157: 3D Infect – 3D Tissue Models for Studying Microbial Infections by Human Pathogens (Project 08): Establishing a human intestinal tissue model to study host and pathogen determinants that restrict *Salmonella enterica* infection

BMBF (031B0073B): KMUinnovativ – Establishment of human intestinal tissue models for preclinical high-throughput screening

BMBF-individualisierte Stammzelltherapien (01EK1608A): HiPSTAR – Establishment, validation, and standardization of individualized hiPS-based blood brain barrier models for Alzheimer's drug development and testing *in vitro*

AiF-ZIM (ZF4353102NK7): Development of a novel combination compound for the treatment of a decubitus wound and development of a decubitus skin model

Bayerische Forschungsstiftung: FORTiTher – Research association for tumor diagnostics for individualized therapy

StMWi: RoboMuk – Robotics-based production of personalized organoid test systems for *in vitro* testing of CFTR mutation-specific cystic fibrosis agents

StMWi HIRI Seed Grant #2: miR-mediated regulation of mucus producing intestinal cells during infection and inflammation

MORSCHHÄUSER, JOACHIM

DFG SFB/TRR 124: FungiNet – Pathogenic fungi and their human host: Networks of interaction (Project C02): Regulation of *Candida albicans* virulence traits by protein kinases

DFG (MO 846/6-2): Phenotypic switching and genomic alterations as host adaptation mechanisms of the opportunistic fungal pathogen *Candida albicans*

DFG (MO 846/7-2): Systematic functional analysis of the zinc cluster transcription factor family of the pathogenic yeast *Candida albicans* by artificial activation

NIH/NIAID: Novel Azole Resistance Mechanisms in *Candida albicans*

MUNSCHAUER, MATHIAS

Helmholtz Association (HGF) Young Investigator Program

OHLSEN, KNUT

DFG SFB/TRR 34: Pathophysiology of Staphylococci in the Post-Genome-Era (Project A02): Phosphoproteomic analysis of *Staphylococcus aureus*: Functional characterization of kinases and identification of their substrates; (Project Z03): *In vivo* imaging of *Staphylococcus aureus* infections

BMBF Health Research (GFTARV62): PyrBac – Target validation for pharmaceutical drug development: Validation of pyruvate kinase as novel metabolic target to combat antibiotic resistant bacteria

PÉREZ, CHRISTIAN

DFG SFB/TRR 124: FungiNet – Pathogenic fungi and their human host: Networks of interaction (Project C01): Molecular characterization of *Candida albicans* mucosal colonization, infection, and translocation

DFG SPP 1656: Intestinal Microbiota (PE 2371/3-1): Genetic circuits underlying fungal-bacterial interactions in the mammalian intestine

DFG (PE 2371/2-1): Mechanisms of host colonization by a eukaryotic member of the microbiota

RUDEL, THOMAS

ERC Advanced Grant: Neutrophil – *Chlamydia* Interactions at the Crossroad of Adaptation and Defence

DFG SFB/TRR 34: Pathophysiology of Staphylococci in the Post-Genome-Era (Project C11): *Staphylococcus aureus* induced host cell death mechanisms

DFG GRK 2157: 3D Infect – 3D Tissue Models for Studying Microbial Infections by Human Pathogens (Project 02): Host factors required for the initiation and propagation of *Chlamydia trachomatis* infections; (Project 03): Bacterial and host cell factors important for the invasion and dissemination of *Neisseria gonorrhoeae*

DFG GRK 2243: UBI – Understanding Ubiquitylation: From Molecular Mechanisms to Disease (Project B03): Mechanism of substrate recognition by chlamydial DUBs

DFG FOR 2123: SphingoFOR – Sphingolipid dynamics in infection control (RU 631/31-1): Sphingolipids in gonococcal infection

DFG (RU 631/12-1): Regulation of Expression of *opa* Genes of *Neisseria gonorrhoeae* by Antisense RNA

SALIBA, ANTOINE-EMMANUEL

DFG GE 539/14-1: Understanding the cellular inventory of pediatric kidney tumors

SIDACTION grant: A triple approach to study HIV-1, the infected host cells and opportunistic bacteria

StMWi HIRI Seed Grants #16: Single cell profiling of the immune response to influenza vaccination: proof of concept; #17: Impact of microbial colonization on stromal cells from gut-draining lymph nodes; #18: Cellular collaboration transfers competence for viral defense and quenches single-cell heterogeneity; #22: Heterogeneity of the host response to acute and chronic infection in primary myeloid cells

SCHNEIDER-SCHAULIES, JÜRGEN

DFG FOR 2123: SphingoFOR – Sphingolipid dynamics in infection control (SCHN 320/24-2): Role of sphingolipids in the regulation of anti-viral T cell responses

SCHNEIDER-SCHAULIES, SIBYLLE

DFG GRK 2157: 3D Infect – 3D Tissue Models for Studying Microbial Infections by Human Pathogens (Project 07): Membrane and protein microdomains governing measles virus transmission at entry and exit interface

DFG FOR 2123: SphingoFOR – Sphingolipid dynamics in infection control (SCHN 405/10-2): Sphingomyelinase activation in T cells: Implications for T cell activation and paralysis; (SCHN 405/11-2): Central project

SCHOEN, CHRISTOPH

DFG SPP 2141: Much more than defence – the multiple functions and facets of CRISPR-Cas (SCHO 1322/3-1): The CRISPR/Cas system in *Neisseria meningitidis* and its potential role in host cell adhesion

StMWi HIRI Seed Grant #8: The role of the RNA chaperone ProQ in riboregulation of meningococcal virulence

SCHUBERT-UNKMEIR, ALEXANDRA

DFG GRK 2157: 3D Infect – 3D Tissue Models for Studying Microbial Infections by Human Pathogens (Project 04): Meningococcal ligands and molecular targets required for adhesion and penetration of the blood-cerebrospinal fluid barrier under shear stress

DFG FOR 2123: SphingoFOR – Sphingolipid dynamics in infection control (SCHU 2394/2-2): Analysis of the functional relevance of sphingomyelinases and ceramide in meningococcal pathogenesis

BaCaTec (Bavaria California Technology Center): Blood brain barrier failure during bacterial and viral infections

SEIBEL, JÜRGEN

DFG SFB/TRR 225: Biofab – From the fundamentals of biofabrication towards functional tissue models (Project B05): Glycoengineering as a tool to control the behavior of mesenchymal stem cells in biofabrication processes

DFG FOR 2123: SphingoFOR – Sphingolipid dynamics in infection control (SE 1410/6-2): Central project, Sphingolipid metabolic pathways in infection control by the use of chemically synthesized modified sphingolipids and in the era of sphingolipidomics; (SE 1410/7-1): Coating of endotracheal tubes with sphingosine to prevent bacterial growth and ventilator-associated pneumonia

BMBF (01DN16034): Synthesis of tailored modular hybrid oligosaccharides

SHARMA, CYNTHIA

DFG GRK 2157: 3D Infect – 3D Tissue Models for Studying Microbial Infections by Human Pathogens (Project 05): Virulence factors and regulators required during *Campylobacter jejuni* infections

DFG SPP 1784: Chemical Biology of native Nucleic Acid Modifications (SH 580/4-1): Identification and characterization of pseudouridine in mRNAs and non-coding RNAs of the bacterial human pathogen *Campylobacter jejuni*

DFG SPP 2002: Small Proteins in Prokaryotes, an Unexplored World (SH 580/7-1): Central Project Z02, Ribosome Profiling and Bioinformatics; (SH 580/8-1): Exploring micro-proteins in the food-borne pathogen *Campylobacter jejuni*

DFG SPP 2141: Much more than defence – the multiple functions and facets of CRISPR-Cas (SH 580/9-1): Mechanisms and functions of endogenous RNA-targeting by CRISPR-Cas9 in *Campylobacter jejuni*

Infect-ERA (ERA-NET) 2nd Call Junior Consortium: CampyRNA - Combining high-throughput and single-cell analyses to study RNA regulators important for the early steps of *Campylobacter* infection

StMWi HIRI Seed Grants #6: Exploring RNA-Protein-Complexes in the gastric pathogen *Helicobacter pylori* using Grad-Seq; #24: Elucidation of the function of the tRNA modifying enzyme GidA as a potential global translational regulator in *Pseudomonas aeruginosa*

SMYTH, REDMOND

BMBF: Computational methods to decipher function-associated structure in long ncRNAs

STICH, AUGUST

Rexroth Foundation: Interdisciplinary Center for Research in Tropical Medicine

German Academic Exchange Service: Development of a triangular partnership Bugando - Stellenbosch - Würzburg in medical education and research

Else-Kröner-Fresenius-Stiftung: Control of Chagas and other parasitic diseases in Colombia

VOGEL, JÖRG

DFG SFB/TRR 34: Pathophysiology of Staphylococci in the Post-Genome-Era (Project C06): Post-invasion events in *Staphylococcus aureus* infected host cells – A combined transcriptomics/proteomics *in vivo* approach

DFG GRK 2157: 3D Infect – 3D Tissue Models for Studying Microbial Infections by Human Pathogens (Project 08): Establishing a human intestinal tissue model to study host and pathogen determinants that restrict *Salmonella enterica* infection

DFG FOR 1680: Unravelling the Prokaryotic Immune System (VO 875/7-2): Alternative functions of the CRISPR-associated endonuclease Cas9

DFG SPP 1784: Chemical Biology of native Nucleic Acid Modifications (VO 875/13-1): Discovery and characterization of RNA modifications in a bacterial model pathogen

DFG SPP 1935: Deciphering the mRNP code – RNA-bound determinants of post-transcriptional gene regulation (VO 875/17-2): Characterization of factors and mechanisms of starvation-induced control of TOP mRNA translation

DFG SPP 2002: Small Proteins in Prokaryotes, an Unexplored World (VO 875/20-1): Functions of µ-proteins regulated during *Salmonella* infection

DFG (VO 875/14-1): Exploring biogenesis and functions of 3'UTR-derived small regulatory RNAs

DFG (VO 875/19-1): Understanding PinT, a noncoding RNA timer of virulence gene expression

DFG (VO 875/18-1): Gottfried Wilhelm Leibniz Preis

Infect-ERA (ERA-NET) 2nd Call Consortium: The Nice Bug - Commensalism versus disease? Asymptomatic carriage or urosepsis

StMWi HIRI Seed Grants #1: Discovery of RNA regulators of the enteric pathogen *Clostridium difficile*; #3: Dynamic reprogramming of the transcriptional landscape of *Salmonella enterica* during gastrointestinal infection; #4: The role of RNA in antibiotic resistance and mode of action; #5: Dual RNA-seq to decipher the impact of preexisting influenza A virus infection on the transcriptional profile and virulence of *Streptococcus pneumoniae*; #7: Mode of action of the novel virulence regulatory RNA SSR42 during *Staphylococcus aureus*-induced osteomyelitis; #8: The role of the RNA chaperone ProQ in riboregulation of meningococcal virulence; #12: Functional host-pathogen transcriptomics of human macrophages and dendritic cells challenged with *Aspergillus fumigatus* and cytomegalovirus; #16: Single cell profiling of the immune response to influenza vaccination: proof of concept; #21: Modulation of microbiota by oral delivery of anti-sense oligonucleotides

VOGEL, ULRICH

IBD-labnet Coordination of Activities for Laboratory Surveillance of Invasive Bacterial Diseases: European Centre for Disease Control and Prevention, contract 4 ECD.9696 under framework contract ECDC 2016/001

RKI grant (1369-237): National Reference Laboratory for Meningococci and *Haemophilus influenzae*

WESTERMANN, ALEXANDER

SIDACTION Grant: A triple approach to study HIV-1, the infected host cells and opportunistic bacteria

StMWi HIRI Seed Grants #3: Dynamic reprogramming of the transcriptional landscape of *Salmonella enterica* during gastrointestinal infection; #5: Dual RNA-seq to decipher the impact of preexisting influenza A virus infection on the transcriptional profile and virulence of *Streptococcus pneumoniae*; #12: Functional host-pathogen transcriptomics of human macrophages and dendritic cells challenged with *Aspergillus fumigatus* and cytomegalovirus

ZIEBUHR, WILMA

DFG SFB/TRR 34: Pathophysiology of Staphylococci in the Post-Genome-Era (Project B4): Regulation of methionine metabolism in staphylococci: Impact on fitness and virulence

DFG SPP 1617: Phenotypic Heterogeneity and Sociobiology of Bacterial Populations (ZI 665/2-1): Heterogeneous gene expression, metabolic variability and differentiation in *Staphylococcus epidermidis* biofilms

DFG German-African Cooperation Projects in Infectiology: ShARE – Staphylococci in Africa: Resistance & Epidemiology (ZI 665/3-1): Molecular epidemiology and antimicrobial resistance mechanisms in staphylococci from various geographic regions in Africa

BMBF #1Health-PREVENT: One Health Interventions to Prevent Zoonotic Spread of Antimicrobial Multidrug-Resistant Bacterial Microorganisms (01KI1727E): Reducing the AMR burden in farm environments: Impact on human commensals and zoonotic pathogens

7.5 PUBLICATIONS

PUBLICATIONS IN 2018-2019 (listed in alphabetical order)

Please note that only publications of ZINF members that are relevant for infectious disease research are listed below.

BARQUIST, LARS

Cain AK, Boinett CJ, **Barquist L**, Dordel J, Fookes M, Mayho M, Ellington MJ, Goulding D, Pickard D, Wick RR, Holt KE, Parkhill J, Thomson NR (2018) *Morphological, genomic and transcriptomic responses of Klebsiella pneumoniae to the last-line antibiotic colistin.* **Scientific Reports** 8(1):9868

Holmqvist E, Li L, Bischler T, **Barquist L**, Vogel J (2018) *Global Maps of ProQ Binding In Vivo Reveal Target Recognition via RNA Structure and Stability Control at mRNA 3' Ends.* **Molecular Cell** 70(5):971-982.e6

Kingsley RA, Langridge G, Smith SE, Makendi C, Fookes M, Wileman TM, El Ghany MA, Keith Turner A, Dyson ZA, Sridhar S, Pickard D, Kay S, Feasey N, Wong V, **Barquist L**, Dougan G (2018) *Functional analysis of Salmonella Typhi adaptation to survival in water.* **Environmental Microbiology** 20(11):4079-4090

Nolan LM, Whitchurch CB, **Barquist L**, Katrib M, Boinett CJ, Mayho M, Goulding D, Charles IG, Filloux A, Parkhill J, Cain AK (2018) *A global genomic approach uncovers novel components for twitching motility-mediated biofilm expansion in Pseudomonas aeruginosa.* **Microbial Genomics** 4(11):e000229

Wheeler NE, Gardner PP, **Barquist L** (2018) *Machine learning identifies signatures of host adaptation in the bacterial pathogen Salmonella enterica.* **PLoS Genetics** 14(5):e1007333

Chihara K, Bischler T, **Barquist L**, Monzon VA, Noda N, Vogel J, Tsuneda S (2019) *Conditional Hfq Association with Small Noncoding RNAs in Pseudomonas aeruginosa Revealed through Comparative UV Cross-Linking Immunoprecipitation Followed by High-Throughput Sequencing.* **mSystems** 4(6):e00590-19

Jose BR, Gardner PP, **Barquist L** (2019) *Transcriptional noise and exaptation as sources for bacterial sRNAs.* **Biochemical Society Transactions** 47(2):527-539

Ondari EM, Klemm EJ, Msefula CL, El Ghany MA, Heath JN, Pickard DJ, **Barquist L**, Dougan G, Kingsley RA, MacLennan CA (2019) *Rapid transcriptional responses to serum exposure are associated with sensitivity and resistance to antibody-mediated complement killing in invasive Salmonella Typhimurium ST313.* **Wellcome Open Research** 4:74

BARTFELD, SINA

Renz H, Adkins BD, **Bartfeld S**, Blumberg RS, Farber DL, Garssen J, Ghazal P, Hackam DJ, Marsland BJ, McCoy KD, Penders J, Prinz I, Verhasselt V, von Mutius E, Weiser JN, Wesemann DR, Hornef MW (2018) *The neonatal window of opportunity-early priming for life.* **Journal of Allergy and Clinical Immunology** 141(4):1212-1214

Yan HHN, Siu HC, Law S, Ho SL, Yue SSK, Tsui WY, Chan D, Chan AS, Ma S, Lam KO, **Bartfeld S**, Man AHY, Lee BCH, Chan ASY, Wong JWH, Cheng PSW, Chan AKW, Zhang J, Shi J, Fan X, Kwong DLW, Mak TW, Yuen ST, Clevers H, Leung SY (2018) *A Comprehensive Human Gastric Cancer Organoid Biobank Captures Tumor Subtype Heterogeneity and Enables Therapeutic Screening.* **Cell Stem Cell** 23(6):882-897.e11

Wallaschek N, Niklas C, Pompaiah M, Wiegering A, Germer CT, Kircher S, Brändlein S, Maurus K, Rosenwald A, Yan HHN, Leung SY, **Bartfeld S** (2019) *Establishing Pure Cancer Organoid Cultures: Identification, Selection and Verification of Cancer Phenotypes and Genotypes.* **Journal Molecular Biology** 431(15):2884-2893

Stanifer ML, Mukenhirn M, Muenchau S, Pervolaraki K, Kanaya T, Albrecht D, Odendall C, Hielscher T, Haucke V, Kagan JC, **Bartfeld S**, Ohno H, Boulant S (2020) *Asymmetric distribution of TLR3 leads to a polarized immune response in human intestinal epithelial cells.* **Nature Microbiology** 5(1):181-191 (Epub 2019)

BEILHACK, ANDREAS

Hülsdünker J, Ottmüller KJ, Neeff HP, Koyama M, Gao Z, Thomas OS, Follo M, Al-Ahmad A, Prinz G, Duquesne S, Dierbach H, Kirschnek S, Lämmermann T, Blaser MJ, Fife BT, Blazar BR, **Beilhack A**, Hill GR, Häcker G, Zeiser R (2018) *Neutrophils provide cellular communication between ileum and mesenteric lymph nodes at graft-versus-host disease onset.* **Blood** 131(16):1858-1869

Jarick KJ, Mokhtari Z, Scheller L, Hartweg J, Thusek S, Le DD, Ranecky M, Shaikh H, Qureischi M, Heinze KG, **Beilhack A** (2018) *Photoconversion of Alloreactive T Cells in Murine Peyer's Patches During Acute Graft-Versus-Host Disease: Tracking the Homing Route of Highly Proliferative Cells In Vivo.* **Frontiers in Immunology** 9:1468

Rudelius M, Rosenfeldt MT, Leich E, Rauert-Wunderlich H, Solimando AG, **Beilhack A**, Ott G, Rosenwald A (2018) *Inhibition of focal adhesion kinase overcomes resistance of mantle cell lymphoma to ibrutinib in the bone marrow microenvironment.* **Haematologica** 103(1):116-125

Solimando AG, Brandl A, Mattenheimer K, Graf C, Ritz M, Ruckdeschel A, Stühmer T, Mokhtari Z, Rudelius M, Dotterweich J, Bittrich M, Desantis V, Ebert R, Trerotoli P, Frassanito MA, Rosenwald A, Vacca A, Einsele H, Jakob F, **Beilhack A** (2018) *JAM-A as a prognostic factor and new therapeutic target in multiple myeloma.* **Leukemia** 32(3):736-743

Ullrich E, Abendroth B, Rothamer J, Huber C, Büttner-Herold M, Buchele V, Vogler T, Longerich T, Zundler S, Völkl S, **Beilhack A**, Rose-John S, Wirtz S, Weber GF, Ghimire S, Kreutz M, Holler E, Mackensen A, Neurath MF, Hildner K (2018) *BATF-dependent IL-7RhiGM-CSF+ T cells control intestinal graft-versus-host disease.* **Journal of Clinical Investigation** 128(3):916-930

Wertheimer T, Velardi E, Tsai J, Cooper K, Xiao S, Kloss CC, Ottmüller KJ, Mokhtari Z, Brede C, deRoos P, Kinsella S, Palikuqi B, Ginsberg M, Young LF, Kreines F, Lieberman SR, Lazrak A, Guo P, Malard F, Smith OM, Shono Y, Jenq RR, Hanash AM, Nolan DJ, Butler JM, **Beilhack A**, Manley NR, Rafii S, Dudakov JA, van den Brink MRM (2018) *Production of BMP4 by endothelial cells is crucial for endogenous thymic regeneration.* **Science Immunology** 3(19):eaal2736

Medler J, Nelke J, Weisenberger D, Steinfatt T, Rothaug M, Berr S, Hünig T, **Beilhack A**, Wajant H (2019) *TNFRSF receptor-specific antibody fusion proteins with targeting controlled FcγR-independent agonistic activity.* **Cell Death & Disease** 10(3):224

Ribechini E, Eckert I, **Beilhack A**, Du Plessis N, Walzl G, Schleicher U, Ritter U, Lutz MB (2019) *Heat-killed Mycobacterium tuberculosis prime-boost vaccination induces myeloid-derived suppressor cells with spleen dendritic cell-killing capability.* **JCI Insight** 5(13):128664

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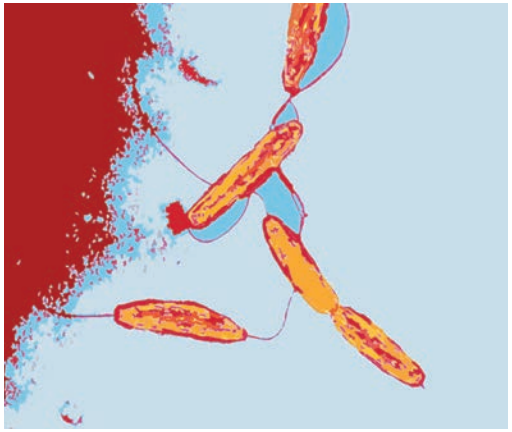

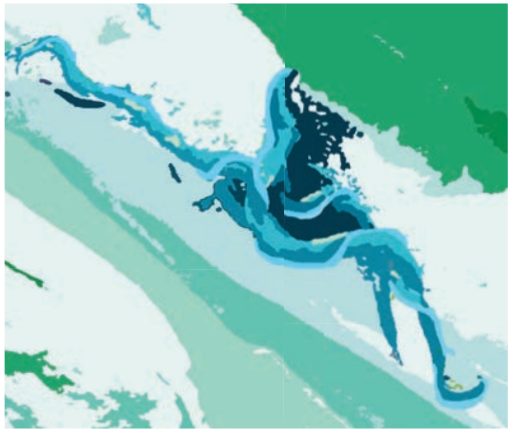

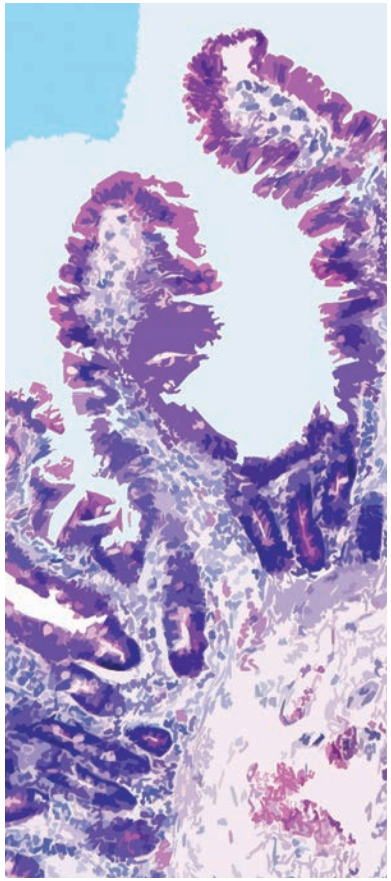

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