RESEARCH CENTER FOR INFECTIOUS DISEASES

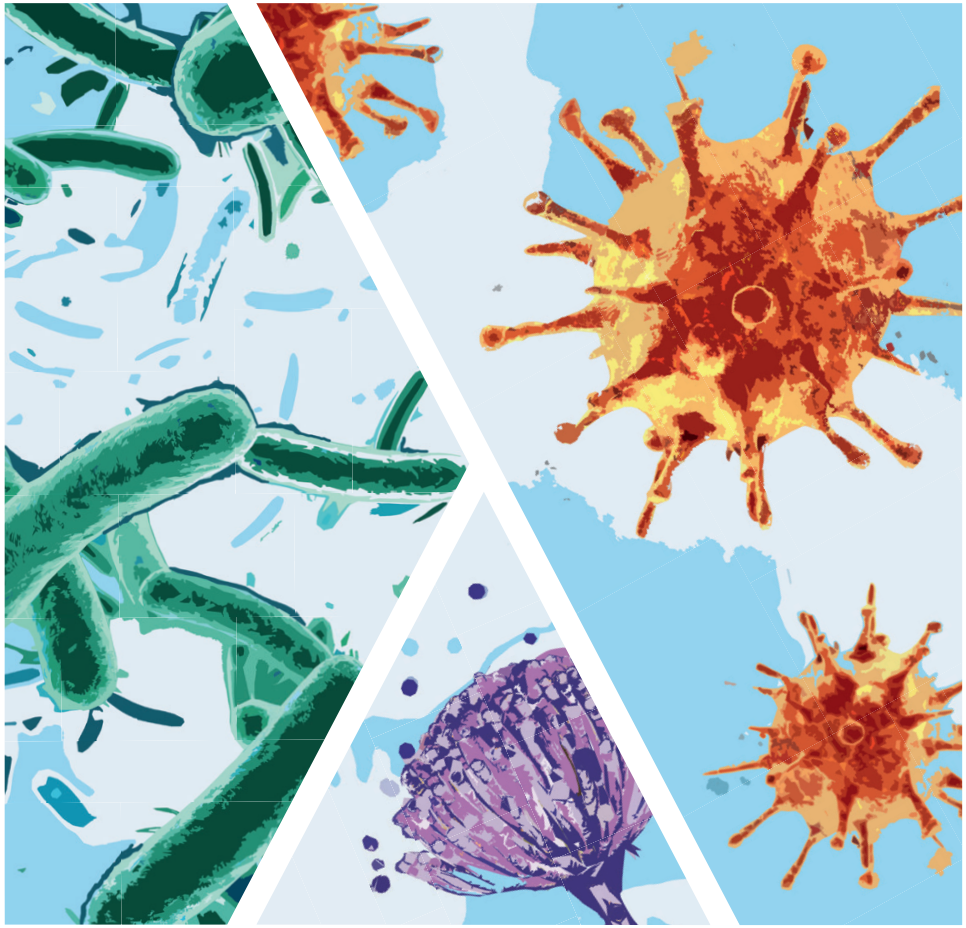
ZENTRUM FÜR INFEKTIONSFORSCHUNG

SCIENTIFIC REPORT 2020-2022

WISSENSCHAFTLICHER BERICHT 2020-2022

Julius-Maximilians-
UNIVERSITÄT
WÜRZBURG

ZINF
IMIB



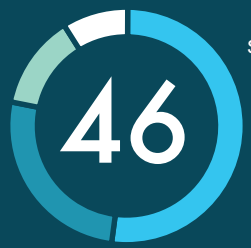
SCIENTIFIC REPORT 2020-2022

RESEARCH CENTER FOR INFECTIOUS DISEASES (ZINF)

ZINF NUMBERS

2020-2022

52 SCIENTIFIC MEMBERS OF THE RESEARCH CENTER FROM 16 INTERNAL & ASSOCIATED INSTITUTES AND DEPARTMENTS INCLUDING 6 YOUNG INVESTIGATORS



PATHOGENS STUDIED AT THE ZINF

- Bacteria
- Viruses
- Parasites
- Fungi

17 ZINF YOUNG INVESTIGATOR GROUP ALUMNI

115 MEETINGS, WORKSHOPS, & SEMINARS (CO)ORGANIZED BY ZINF MEMBERS

725 HIGH IMPACT PUBLICATIONS IN SCIENTIFIC JOURNALS

27 NATIONAL & INTERNATIONAL RESEARCH NETWORKS INVOLVING ZINF MEMBERS

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-Universität 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 the promotion of **YOUNG SCIENTISTS** and offering them a unique entry 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.

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1

GENERAL REMARKS

1.1 SPEAKER'S REPORT

2020-2022

Dear readers,

This year, the Research Center for Infectious Diseases (ZINF) of the Julius-Maximilians-Universität (JMU) in Würzburg celebrates its 30th anniversary. Founded in 1993 by Volker ter Meulen, Werner Goebel, and colleagues, the ZINF matured under the long-term leaderships of its former speakers Jörg Hacker and Jörg Vogel into a premier scientific institution for cross-faculty research on infectious diseases in Germany. In this Scientific Report, we provide you with a summary of the scientific achievements at the ZINF in 2020-2022 and an overview of the milestones that paved the way for the ZINF to become an internationally renowned center (p. 16-17).

To date, the ZINF counts 52 PIs from three different JMU faculties (Medicine, Biology, Chemistry & Pharmacy), as well as the Helmholtz Institute for RNA-based Infection Research (HIRI) and the Max-Planck-Research Groups on Systems Immunology (WüSi) in Würzburg. ZINF members study the underlying molecular principles of host-pathogen interactions for diverse bacterial, fungal, eukaryotic, and viral pathogens, as well as the host response. A key strength and unique focus of the ZINF is the investigation of the role of RNA molecules in infections, which we combine with the development of new infection models to drive the development of novel anti-infectives as well as RNA-based technologies and therapies.

In the last three years, ZINF members initiated or participated in diverse innovative scientific networks on infectious diseases (p. 108-122). One of the biggest successes was the recent approval of the new DFG (German Research Foundation)-funded Collaborative Research Center (CRC) 1583 *DECIDE - Decisions in infectious diseases* (speaker Thomas Rudel). 22 ZINF PIs participate in *DECIDE* and will collaborate on identifying host-specific molecular determinants that control the course of infections. Moreover, a second funding phase was approved for the DFG Research Unit 2830 on *Advanced cellular immune control of cytomegalovirus* (speaker Lars Dölken). In 2020, Oliver Kurzai and Matthias Frosch initiated the new *Else Kröner Center for Advanced Medical & Humanitarian Studies Würzburg-Mwanza/Tanzania*. Funded by the Elite Network Bavaria, a new graduate program *RNAmed - Future leaders in RNA-based Medicine* (speaker Jörg Vogel) started at the end of 2022 to train young scientists in the emerging area of RNA-based therapeutics and diagnostics. The ZINF was also strengthened by new infrastructures. In 2019, the *German Center for intersectoral control of neglected tropical diseases* (DZVT) was established with Markus Engstler as a founding member. To explore infections and other diseases at the level of individual cells, the *Single-Cell Center Würzburg* (speaker Jörg Vogel) took off in 2021 as a joint initiative of the HIRI, JMU, University Hospital Würzburg (UKW), WüSi, and the Fraunhofer Translational Center for Regenerative Therapies (TLZ-RT) with start-up funding by the Bavarian State Ministry of Economic Affairs, Regional Development and Energy. It is complemented by the new DFG-funded core facility *MICROSEQ - Centre for Microbial Single-Cell RNA-seq* (led by Jörg Vogel) to also enable single-cell RNA-sequencing of bacteria.

Since the start of the COVID-19 pandemic, ZINF members actively participated in the fight against SARS-CoV-2. For example, the *Wü-KiTa-CoV* coronavirus kindergarten study initiated by Oliver Kurzai and colleagues studied the viral spreading among young children. Within the Bavarian research consortium *FOR-COVID* and the BMBF (Federal Ministry of Education and Research)-funded *Organo-Strat* network, ZINF members explored the mechanisms of SARS-CoV-2 infection. The Saliba group has made great strides to understand the pathomechanism of COVID-19 in the blood and in the lung at the single-cell level with two collaborative studies together with researchers in Berlin published in *Cell* in 2020 and 2021. Mathias Munschauer, Jörg Vogel, and colleagues have described the first global atlas of direct interactions between the SARS-CoV-2 viral RNA and human host proteins (*Nature Microbiology*, 2021). In a joint effort of the lab of Chase Beisel (HIRI) and my group at the IMIB (Institute of Molecular Infection Biology), supported by Oliver Kurzai and Christoph Schoen at the Institute of Hygiene and Microbiology, we have developed a novel, multiplexable CRISPR/Cas9-based RNA diagnostics platform (LEOPARD) that can detect different viral variants in just one test. This technology arose via basic microbiology research in a food-borne pathogen and was accelerated by the strong synergistic expertise in Würzburg. Our resulting joint study published in *Science* in 2021 was selected as a winner in the category Life Sciences of the 2021 *Falling Walls Science Breakthroughs of the Year*.

In 2020-2022, ZINF welcomed three new members: Cindrilla Chumduri investigates the crosstalk of infections and carcinogenesis, Bhupesh Prusty focuses on human herpesvirus, and as head of the newly established Department of Translational Pediatrics at the UKW, Dorothee Viemann explores the maturation and host defense by the innate immune system of children. The ZINF family was greatly saddened by the loss of a long-term member, esteemed colleague and friend Ulrich Vogel on October 4th, 2022 (see Obituary on p. 53). Ulrich was a world-renowned expert in molecular biology and epidemiology of *Neisseria meningitidis* and was instrumental in the successful handling of the COVID-19 pandemic at the UKW. He will be infinitely missed both as a colleague as well as a scientist.

An important, central component of the ZINF has always been the promotion of young investigator groups (YIG) (p. 24-35). In May 2022, the ZINF welcomed a new BMBF-funded YIG on infectious diseases research that is headed by Carmen Aguilar. Her group focuses on developing innovative host-directed approaches to tackle recurrent urinary tract infections caused by increasingly antibiotic-resistant uropathogenic *E. coli*. Like many former YIG alumni, several ZINF YIGs moved on to leading national and international positions. Sina Bartfeld was assigned Chair of Medical Biotechnology at the Technical University Berlin in September 2021. Sebastian Geibel and Christian Pérez became Associate Professors at the University of Leiden (Netherlands) and UTHealth Houston's McGovern Medical School (USA), respectively. Moreover, we congratulate Ana-Rita Brochado on her recent acceptance of a W1 tenure track W3 professorship at the University of Tübingen.

The success of our YIG programme is not the least due to the invaluable input and feedback by our international scientific advisory board (SAB). We would like to express the deepest gratitude to our SAB members Michael Gilmore (Harvard Medical School, USA), David Holden (Imperial College London, UK), Gisela Storz (National Institute of Child Health and Human Development, USA), Tone Tønjum (Oslo University Hospital, Norway), Melanie Blokesch (Swiss Federal Institute of Technology, Switzerland), and Jay Hinton (University of Liverpool, UK).

Despite several hurdles posed by the COVID-19 pandemic, ZINF members were recognized by awards, honors, and appointments in 2020-2023. These include multiple highly competitive and prestigious *ERC (European Research Council) Grants*: A 2020 Starting Grant to Neva Caliskan, 2022 Starting Grants to Mathias Munschauer and Alexander Westermann, as well as 2022 Consolidator Grants to Lars Dölken and myself. IMIB and HIRI director Jörg Vogel was elected to the Bavarian Academy of Sciences and Humanities in March 2023 and is president of the European Academy of Microbiology since 2021. Neva Caliskan received the *2021 Science Award* from the ZONTA Club Würzburg and was recently elected to the Board of Directors of the RNA Society. Hermann Einsele and Jörg Vogel were again listed by Thomson Reuters as *Highly Cited Researchers* in 2020-2022. In 2021, Ana-Rita Brochado received the *Röntgenpreis* of the University of Würzburg, Antoine-Emmanuel Saliba an *EMBO Young Investigator Award*, Ulrike Holzgrabe was awarded the *Elsa Ullmann Medal* by the German Pharmaceutical Society, Oliver Kurzai received the *2020 Research Award* of the DGHM (German Association for Microbiology and Hygiene), and Chase Beisel and myself were honored to receive the *2022 Pettenkofer Award*. In 2022, the *Bavarian Order of Merit* was awarded to Hermann Einsele and Markus Engstler received the *Memento Research Prize*. The JMU Würzburg appointed Emmanuel Saliba as W2 professor for "Single Cell Biology" in 2023. Franziska Faber became a Junior Professor at JMU with affiliations of her group to the HIRI. She has recently accepted an offer for a W2 professorship in "Microbial Interactions" at JMU and Alexander Westerman will join the JMU Biocenter as associate professor in "Microbiology".

In May 2022, the HIRI celebrated its fifth birthday with an anniversary symposium at the Würzburg Residenz. Friends, colleagues, and guests, such as the President of the Bavarian State Parliament Ilse Aigner and Dirk Heinz, the former Scientific Director of the HZI in Braunschweig, congratulated the HIRI and its director Jörg Vogel on their achievements. In July 2023, the HIRI will welcome guests from politics and academia for the ceremonial groundbreaking of its own building. In November 2022, the JMU Medical Faculty honored Dirk Heinz with an honorary doctorate at its "Dies academicus" for his breakthroughs in structural biology and infection research. We also congratulate former ZINF speaker Jörg Hacker on the *2022 Robert Koch Medal in Gold*, honoring his outstanding services to science over more than 40 years.

After a two-year in-person break due to the COVID-19 pandemic, we are thrilled to switch back from virtual seminars to in-house meetings and are happy to again welcome international scientists at our colloquia and seminar series here in Würzburg (p. 144-149). Moreover, we are looking forward to the international *CRISPR 2023* conference and the inter-academy meeting *Microbiology 2023* that will be hosted at the IMIB/ZINF/HIRI in June and September 2023, respectively. We were also happy to welcome Peter Fineran (University of Otago, NZ) for a second research stay at the IMIB/HIRI in 2021/2022 as part of his *Research Fellowship for Experienced Researchers* from the Alexander von Humboldt Foundation and congratulate him on his election as fellow of the SCIAS (Siebold-Collegium Institute for Advanced Studies) at JMU Würzburg.

Fundamental research on infectious diseases remains our biggest asset to tackle current challenges, such as the rise in antibiotic resistant bacteria. Understanding the heterogeneity of infection processes at the single-cell level as well as the role of RNA molecules as regulators, guides, scaffolds, signaling molecules, or ligands in pathogens and their hosts will help to address such issues. The ZINF provides an ideal research network to tackle these tasks. Its international visibility, the unique expertise of many ZINF members on the various aspects of RNA and infections, together with the development of new high-throughput and single-cell approaches, novel imaging technologies and the use of artificial intelligence approaches will provide new insights into complex host-pathogen interactions with unprecedented resolution. These fundamental insights will also enable new tools and therapies, including the emerging nucleic-acid based technologies and therapies. Towards such future scientific directions, ZINF members are also actively involved in proposals for new Clusters of Excellence within the current excellence strategy of the German federal and state governments.

Last but not least, I would like to thank the JMU Würzburg and the Bavarian Government for their support of the ZINF as well as the ZINF members for their contributions to this report and to the success of the ZINF. I look forward to the next years of collaborative research!

CYNTHIA SHARMA
Spokesperson ZINF

Würzburg, June 2023

BERICHT DER SPRECHERIN

2020-2022

Liebe Leserinnen, liebe Leser,

dieses Jahr feiert das Zentrum für Infektionsforschung (ZINF) der Julius-Maximilians-Universität (JMU) Würzburg sein 30-jähriges Bestehen. Gegründet 1993 von Volker ter Meulen, Werner Goebel und Kollegen, entwickelte sich das ZINF unter der langjährigen Leitung seiner früheren Sprecher Jörg Hacker und Jörg Vogel zu einer der führenden wissenschaftlichen Einrichtungen für fakultätsübergreifende Infektionsforschung in Deutschland. In diesem Bericht möchten wir Ihnen eine Zusammenfassung der wissenschaftlichen Leistungen der Jahre 2020-2022 sowie einen Überblick über die Meilensteine geben, welche das ZINF zu einem international renommierten Zentrum gemacht haben (S. 16-17).

Das ZINF umfasst derzeit 52 Forschende aus drei Fakultäten der JMU (Medizin, Biologie, Chemie und Pharmazie) sowie dem Helmholtz-Institut für RNA-basierte Infektionsforschung (HIRI) und den Max-Planck-Forschungsgruppen für Systemimmunologie (WüSi) in Würzburg. ZINF-Mitglieder erforschen molekulare Grundlagen von Wirt-Pathogen-Interaktionen für pathogene Bakterien, Pilze, Viren und eukaryotische Erreger sowie die Wirt-Immunantwort. Hier ist besonders die Untersuchung von RNA-Molekülen bei Infektionen ein Schwerpunkt, den wir mit dem Aufbau neuer Infektionsmodelle kombinieren, um somit die Entwicklung neuer Antiinfektiva und RNA-basierter Technologien und Therapien voranzutreiben.

In den letzten drei Jahren haben ZINF-Mitglieder verschiedene wissenschaftliche Netzwerke zu Infektionskrankheiten initiiert oder sich daran beteiligt (S. 108-122). Einer der größten Erfolge ist die Bewilligung des neuen, von der Deutschen Forschungsgemeinschaft (DFG) geförderten Sonderforschungsbereichs (SFB) 1583 *DECIDE - Entscheidungsprozesse bei Infektionskrankheiten* (Sprecher Thomas Rudel) in 2022. 22 an *DECIDE* beteiligte ZINF-Mitglieder werden an der Identifizierung wirts-spezifischer molekularer Faktoren arbeiten, die den Infektionsverlauf bestimmen. Des Weiteren wurde eine zweite Förderphase für die DFG-Forschergruppe 2830 zum Thema *Fortschrittliche Konzepte in der zellulären Immunkontrolle von Zytomegalieviren* (Sprecher Lars Dölken) bewilligt. Oliver Kurzai und Matthias Frosch initiierten 2020 das neue *Else Kröner Center for Advanced Medical & Humanitarian Studies Würzburg-Mwanza/Tanzania*. Gefördert durch das Elitenetzwerk Bayern startete Ende 2022 ein neues Graduiertenprogramm *RNAmed - Future leaders in RNA-based Medicine* (Sprecher Jörg Vogel) zur Ausbildung von Nachwuchswissenschaftlerinnen und -wissenschaftlern in dem aufstrebenden Bereich der RNA-basierten Medizin. Das ZINF wurde auch durch neue Infrastrukturen gestärkt. Durch Mitbegründung von Markus Engstler wurde 2019 das *Deutsche Zentrum für die sektorübergreifende Bekämpfung vernachlässigter Tropenkrankheiten* (DZVT) eingerichtet. Um Infektionen und andere Krankheiten auf Einzelzellebene zu erforschen, startete 2021 das *Single-Cell-Center Würzburg* (Sprecher Jörg Vogel) als gemeinsame Initiative des HIRI, der JMU, dem Universitätsklinikum Würzburg (UKW), dem WüSi und dem Fraunhofer Translationszentrum für Regenerative Therapien (TLZ-RT) mit einer Anschubfinanzierung durch das Bayerische Staatsministerium für Wirtschaft, Landesentwicklung und Energie. Es wird ergänzt durch das neue DFG-Gerätezentrum *MICROSEQ - Zentrum für mikrobielle Einzelzell-RNA-seq* (Leitung: Jörg Vogel), welches sich auf Einzelzell-RNA-Sequenzierung von Bakterien fokussiert.

Seit Beginn der COVID-19-Pandemie beteiligten sich ZINF-Mitglieder aktiv an der Überwachung und Bekämpfung von SARS-CoV-2. Beispielsweise untersuchte die von Oliver Kurzai und Kollegen initiierte *Wü-KiTa-CoV* Coronavirus-Kindergartenstudie die Virusausbreitung bei Kleinkindern. Im Rahmen des bayerischen Forschungskonsortiums *FOR-COVID* und des vom Bundesministerium für Bildung und Forschung (BMBF) geförderten Netzwerks *Organo-Strat* untersuchten ZINF-Mitglieder die Mechanismen der SARS-CoV-2 Infektion. Die Saliba-Gruppe hat große Fortschritte zum Verständnis des Pathomechanismus von COVID-19 im Blut und in der Lunge auf Einzelzellebene gemacht. Diese neuen Erkenntnisse wurden zusammen mit Forschergruppen aus Berlin in zwei Studien 2020 und 2021 in *Cell* veröffentlicht. Mathias Munschauer, Jörg Vogel und Kollegen haben den ersten globalen Atlas der direkten Interaktionen der SARS-CoV-2 RNA mit menschlichen Wirtsproteine beschrieben (*Nature Microbiology*, 2021). Gemeinsam haben das Labor von Chase Beisel (HIRI) und meine Gruppe am IMIB (Institut für Molekulare Infektionsbiologie) mit Unterstützung von Oliver Kurzai und Christoph Schoen am Institut für Hygiene und Mikrobiologie eine multiplex-fähige CRISPR/Cas9-basierte Diagnostiktechnologie (LEOPARD) entwickelt, die virale Varianten in nur einem Test nachweisen kann. Diese Technologie basiert auf Erkenntnissen der mikrobiologischen Grundlagenforschung an einem Lebensmittelkeim und wurde durch die starke synergetische Expertise in Würzburg beschleunigt. Unsere daraus resultierende gemeinsame wissenschaftliche Studie in *Science* (2021) wurde als Gewinner in der Kategorie Life Sciences für die 2021 *Falling Walls Science Breakthroughs of the Year* ausgewählt.

In 2020-2022 begrüßte das ZINF drei neue Mitglieder: Cindrilla Chumduri erforscht das Zusammenspiel von Infektionen und Krebsentstehung, Bhupesh Prusty beschäftigt sich mit humanen Herpesviren, und Dorothee Viemann erforscht als Leiterin der neu gegründeten Abteilung Translationale Pädiatrie am UKW das angeborene Immunsystem von Kindern. Das ZINF trauert um sein langjähriges Mitglied, den geschätzten Kollegen Ulrich Vogel, der am 4. Oktober 2022 verstorben ist (Nachruf S. 53). Ulrich war ein weltweit anerkannter Experte auf dem Gebiet der Molekularbiologie und Epidemiologie von *Neisseria meningitidis* und war maßgeblich an der erfolgreichen Bewältigung der COVID-19-Pandemie am UKW beteiligt. Er wird sowohl als Kollege als auch als Wissenschaftler sehr fehlen.

Ein zentraler Bestandteil des ZINF war immer die Förderung von unabhängigen Nachwuchsgruppen (NWG) (S. 24-35). Im Mai 2022 rekrutierte das ZINF eine neue, vom BMBF geförderte NWG in der Infektionsforschung, die von Carmen Aguilar geleitet wird. Ihre Gruppe konzentriert sich auf die Entwicklung innovativer, wirts-basierter Ansätze zur Bekämpfung wiederkehrender Harnwegsinfekte verursacht durch antibiotikaresistente uropathogene *E. coli*. Wie viele ehemalige NWGs am ZINF haben auch mehrere der aktuellen ZINF-Gruppenleiterinnen und -leiter führende nationale und internationale Positionen angenommen. Sina Bartfeld wurde im September 2021 auf den Lehrstuhl für Medizinische Biotechnologie an der Technischen Universität Berlin berufen. Sebastian Geibel und Christian Pérez wurden Associate Professors an der Universität Leiden (Niederlande) bzw. der McGovern Medical School der UTHealth Houston (USA). Außerdem gratulieren wir Ana-Rita Brochado zu ihrem kürzlich erfolgten Ruf auf eine W1-Professur mit Tenure Track auf W3 an der Universität Tübingen.

Der Erfolg des Nachwuchsgruppenprogramms ist nicht zuletzt auf das äußerst wertvolle Feedback unseres internationalen wissenschaftlichen Beirats (SAB) zurückzuführen. Wir möchten unseren SAB-Mitgliedern Michael Gilmore (Harvard Medical School, USA), David Holden (Imperial College London, UK), Gisela Storz (National Institute of Child Health and Human Development, USA), Tone Tønjum (Oslo University Hospital, Norwegen), Melanie Blokesch (Swiss Federal Institute of Technology, Schweiz) und Jay Hinton (University of Liverpool, UK) sehr herzlich für ihren Einsatz danken.

Trotz einiger Hürden während der COVID-19 Pandemie konnten 2020-2023 zahlreiche wissenschaftliche Erfolge verzeichnet werden und ZINF-Mitglieder wurden mit Preisen und Rufen ausgezeichnet. Dazu gehören mehrere hoch kompetitive und prestigeträchtige *ERC (European Research Council) Grants*: Ein Starting Grant für Neva Caliskan in 2020, 2022 Starting Grants für Mathias Munschauer und Alexander Westermann sowie 2022 Consolidator Grants für Lars Dölken und mich. Jörg Vogel wurde im März 2023 in die Bayerische Akademie der Wissenschaften gewählt und ist seit 2021 Präsident der Europäischen Akademie für Mikrobiologie. Neva Caliskan erhielt den *Wissenschaftspreis 2021* des ZONTA Clubs Würzburg und wurde kürzlich in den Vorstand der RNA Society gewählt. Hermann Einsele und Jörg Vogel wurden 2020-2022 erneut von Thomson Reuters als *Highly Cited Researchers* gelistet. 2021 erhielt Ana-Rita Brochado den *Röntgenpreis* der JMU, Antoine-Emmanuel Saliba einen *EMBO Young Investigator Award*, Ulrike Holzgrabe wurde mit der *Elsa-Ullmann-Medaille* der Deutschen Pharmazeutischen Gesellschaft ausgezeichnet, Oliver Kurzai erhielt 2020 den *DGHM (Deutsche Gesellschaft für Mikrobiologie und Hygiene) Hauptpreis*, und Chase Beisel und mir war es eine große Ehre den *Pettenkofer-Preis 2022* zu erhalten. Der *Bayerische Verdienstorden* wurde 2022 an Hermann Einsele verliehen und Markus Engstler erhielt den *Memento-Forschungspreis*. 2023 hat die JMU Emmanuel Saliba zum W2-Professor für „Single Cell Biology“ ernannt. Franziska Faber wurde Juniorprofessorin an der JMU mit Angliederung ihrer Gruppe an das HIRI. Vor Kurzem hat sie einen Ruf auf eine W2-Professur für „Mikrobielle Interaktionen“ an der JMU angenommen, und Alexander Westermann wird dem JMU-Biozentrum als W2-Professor für „Mikrobiologie“ beitreten.

Im Mai 2022 feierte das HIRI seinen 5. Geburtstag mit einem Jubiläumssymposium in der Würzburger Residenz. Freunde, Kollegen und Gäste, wie z.B. die Präsidentin des Bayerischen Landtags Ilse Aigner und Dirk Heinz, der ehemalige wissenschaftliche Leiter des HZI in Braunschweig, gratulierten dem HIRI und seinem Direktor Jörg Vogel zu den Erfolgen. Im Juli 2023 wird das HIRI Gäste aus Politik und Wissenschaft zum feierlichen Spatenstich seines Neubaus begrüßen. Im November 2022 ehrte die Medizinische Fakultät der JMU Dirk Heinz mit der Ehrendoktorwürde beim „Dies academicus“ für seine bahnbrechenden Arbeiten in der Strukturbiologie und Infektionsforschung. Wir gratulieren auch dem ehemaligen ZINF-Sprecher Jörg Hacker zur *Robert-Koch-Medaille 2022 in Gold*, mit der seine herausragenden Verdienste um die Wissenschaft in mehr als 40 Jahren gewürdigt wurden.

Nach einer zweijährigen Pause aufgrund von COVID-19 freuen wir uns wieder internationale Gäste bei unseren Kolloquien und Seminarreihen in Würzburg begrüßen zu dürfen (S. 144-149). Mit großer Vorfreude blicken wir auch auf die internationale *CRISPR 2023* Konferenz sowie die Akademien übergreifende Tagung *Microbiology 2023*, die im Juni bzw. September 2023 am IMIB/ZINF/HIRI stattfinden werden. Desweiteren haben wir uns gefreut Peter Fineran (University of Otago, NZ) im Rahmen seines Forschungsstipendiums der Alexander von Humboldt-Stiftung 2021/2022 zu einem zweiten Forschungsaufenthalt am IMIB/HIRI begrüßen zu dürfen und gratulieren ihm zur Aufnahme als SCIAS (Siebold-Collegium Institute for Advanced Studies)-Fellow an der JMU Würzburg.

Grundlagenforschung zu Infektionskrankheiten ist eines der wichtigsten Elemente, um aktuelle gesellschaftliche Herausforderungen wie vermehrte Antibiotikaresistenzen zu bewältigen. Ein besseres Verständnis der zellulären Heterogenität von Infektionsprozessen sowie der Rolle von RNA-Molekülen als Regulatoren, Leit- und Signalmoleküle, Gerüste oder Liganden in Pathogenen und ihren Wirten wird dazu beitragen, solche Fragen zu klären. Das ZINF bietet ein ideales, interdisziplinäres Forschungsnetzwerk, um diese Aufgaben zu bewältigen. Das einzigartige Fachwissen vieler ZINF-Mitglieder zu verschiedenen Aspekten von RNA und Infektionen, zusammen mit der Entwicklung neuer Hochdurchsatz- und Einzelzellansätze, neuartiger Bildgebungsverfahren und dem Einsatz von künstlicher Intelligenz werden neue Einblicke in komplexe Wirt-Pathogen-Interaktionen mit noch nie dagewesener Auflösung ermöglichen. Diese grundlegenden Erkenntnisse werden auch zur Entwicklung neuer Ansätze und Therapien beitragen, einschließlich der neuen Nukleinsäure-basierten Technologien und Medizin. Im Hinblick auf solche hochaktuellen wissenschaftlichen Forschungsbereiche sind die Mitglieder des ZINF auch aktiv an Anträgen für neue Exzellenzcluster im Rahmen der laufenden Exzellenzstrategie des Bundes und der Länder beteiligt.

Nicht zuletzt möchte ich der JMU Würzburg und der Bayerischen Staatsregierung für ihre Unterstützung des ZINF sowie den ZINF-Mitgliedern für ihre Beiträge zu diesem Bericht und zum Erfolg des ZINF danken. Ich freue mich auf die nächsten Jahre gemeinsamer Forschung!

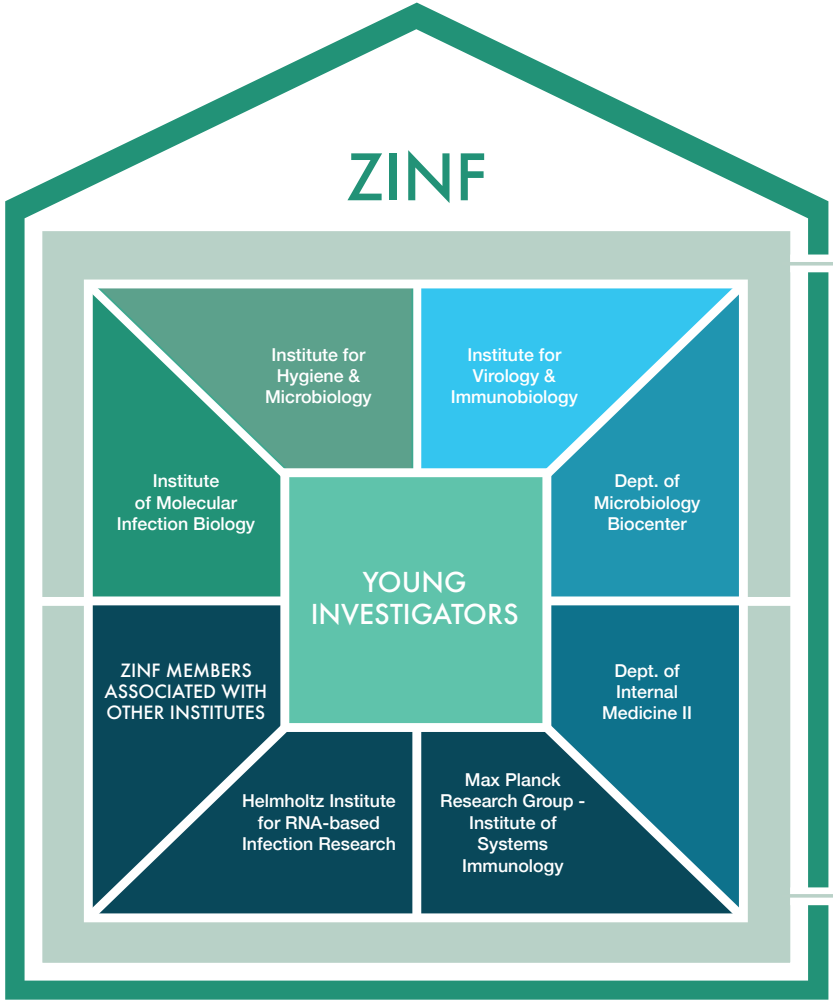
CYNTHIA SHARMA
Sprecherin des ZINF

Würzburg, Juni 2023

1.2 STRUCTURE OF THE ZINF

2020-2022

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.



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1.3 LOOKING BACK – 30 YEARS OF ZINF

1993-2023

Pathogenic microorganisms including bacteria, viruses, and fungi, pose an increasing threat to human health. Thirty years ago, a burgeoning interest in the molecular factors and principles behind human infections led the University of Würzburg (JMU) to take an interdisciplinary approach to become a leader in infectious disease research. Enabled by generous funding from the Federal Ministry of Research and Technology, JMU started a successful young investigator group (YIG) program, which together with research groups at the JMU, led to the foundation of a Research Center for Infectious Diseases (ZINF) in 1993. In recognition for its contribution to the Würzburg research landscape, the ZINF became a central scientific facility of the JMU in 2009.

Founders of the ZINF: Jörg Hacker, Volker ter Meulen and Werner Goebel (left to right).

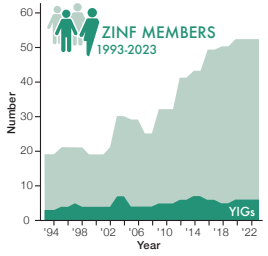
The ZINF was founded by JMU Professors Volker ter Meulen, Jörg Hacker, and Werner Goebel, whose scientific foresight led them to conclude that strong infectious disease research needed a cross-faculty center integrating diverse scientific disciplines. The initial federal funding of the ZINF was stepwise replaced by financial support by the Bavarian Government and the JMU. Funding for ZINF YIGs also drew heavily on prestigious external programs, such as the Elite Network Bavaria (ENB), the Emmy Noether program of the German Research Council (DFG), the Bundesministerium für Bildung and Forschung (BMBF), or the Interdisciplinary Center for Clinical Research (IZKF).

Spring 1994 saw the first ZINF groups move into the former Chemistry buildings at Röntgenring 11, near the main station. Around the same time, Volker ter Meulen, Jörg Hacker, and the founder of the University's Rudolf Virchow Centre (RVZ) initiated the reconstruction of the former surgery department on JMU's Medical Campus in Grombühl. In September 2009, the Institute of Molecular Infection Biology (IMIB), ZINF, and RVZ moved into their new home: a 9,000-m² research building offering generous space for laboratories, offices, and teaching, and even a lecture hall that seats 400 people. This building now also temporarily hosts the Helmholtz Institute for RNA-based Infection Research (HIRI).

The IMIB/ZINF moved from the Campus Röntgenring to the Medical Campus in Grombühl, where the old surgical department was transformed into a state-of-the-art research center. It is currently home to more than 300 scientists from all over the world affiliated with the IMIB/ZINF, RVZ and HIRI. © H. Merkert

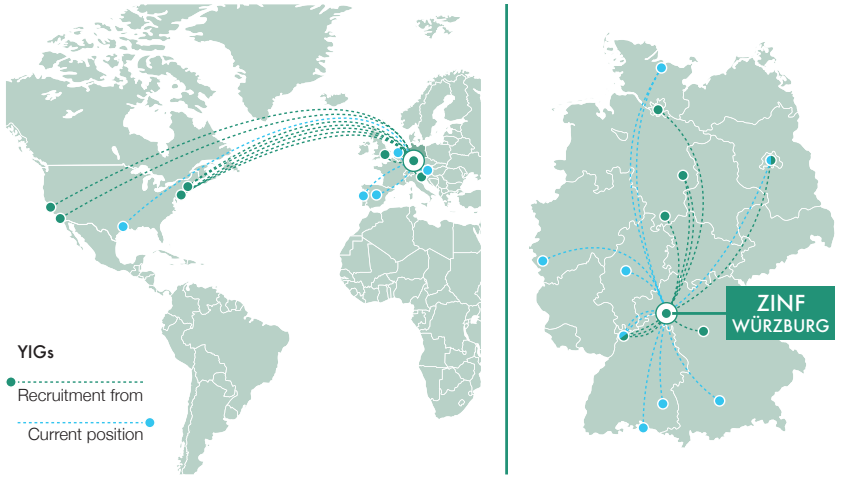
Ever since its foundation, members of the ZINF have established and been involved in diverse research consortia and networks dedicated to infectious diseases research. In 1984, Volker ter Meulen secured the collaborative research centre (CRC) 165 *Gene Expression in Vertebrates* for Würzburg, which contributed greatly to the initial development of the ZINF. Two further CRCs demonstrate the importance of the ZINF, with members leading more than half the funded projects: CRC 479 on *Pathogen variation and host response in infectious diseases* (Prof. Thomas Hünig, 1998-2009) and CRC 630 on *Agents against infectious diseases* (Prof. Gerhard Bringmann, 2003-2015). Most recently, JMU has been awarded CRC 1583 *DECIDE* (Prof. Thomas Rudel) to unravel and exploit molecular decision points in host-pathogen interactions as a new basis for anti-infective therapy. Almost every project of *DECIDE* is led or co-coordinated by a ZINF member. Many more collaborative networks and scientific initiatives have contributed to the research profile of the JMU and the ZINF demonstrating their successful synergistic research environment.

One of the most prominent features of the ZINF has always been its strong focus on promoting young scientists. In 1999, Jörg Hacker and colleagues established the DFG international research training group (RTG) 587 on *Gene regulation in and by pathogens*, which subsequently developed into the graduate program section *Infectious Diseases Research* of the Graduate School of Life Sciences (GSLS). To train a new generation of infection biologists, members of the ZINF are at the forefront of integrating novel and cutting-edge methodologies into the field of infection biology. This is impressively demonstrated in the RTG 2157 *3D Infect* (speaker Thomas Rudel), which focuses on the development and application of human 3D infection models based on organoid and tissue engineering technologies. Support for young scientists is additionally evidenced in the many institutions, programs, additional RTGs, and organizations associated with the ZINF.



Starting with Jörg Vogel's arrival in 2009 as the successor of Jörg Hacker as IMIB director, the JMU made several strategic recruitments to strengthen the area of RNA research and in particular its role in infectious diseases in Würzburg. These recruitments and the international visibility of the ZINF allowed Würzburg to successfully apply for the establishment of the University's first federally funded institute, the HIRI, in 2016. This institute, which is a partnership with the Helmholtz Centre for Infection Research in Braunschweig, is the first institution of its kind in the world to combine research on RNA with infection biology. Recent additions to the research landscape of Würzburg and the ZINF also included a Max Planck Research Group on Systems Immunology on the Grombühl Campus in 2017.

To this day, the ZINF continues to be a platform for young investigators offering both the physical infrastructure and mentoring support needed to establish a successful career in infection biology. The prestigious YIG program of the ZINF (1993-2020) was not only able to recruit outstanding scientists from all over the world (e.g., Netherlands, United Kingdom, Italy, USA) but many ZINF Alumni also moved on to leading international positions. Under the leadership of former and current ZINF speakers (V. ter Meulen: 1993-2003; J. Hacker: 2003-2009; M. Frosch: 2009-2011; J. Vogel: 2011-2018; C. Sharma: since 2018) the ZINF has grown into an internationally renowned research center. Through cutting-edge technological developments, e.g., in the field of single-cell analysis, research within the ZINF continues to break new ground. An increasing focus is to not only understand, but to also combat the threat posed by pathogenic microorganisms. In particular, understanding the role of RNA in infections has vast potential, with opportunities to exploit these molecules as diagnostics or drugs, an approach urgently needed to combat the rising threat of antibiotic resistant bacteria. Through its interdisciplinary expertise, the ZINF and its members continue to advance the knowledge on infectious diseases and open up new avenues for research and biotechnology.



1.4 EVENTS SURROUNDING THE ZINF

ZONTA SCIENCE AWARD

OCTOBER 13TH, 2021

Neva Caliskan, a junior group leader at the Helmholtz Institute for RNA-based Infection Research (HIRI), received the 2021 Science Award from the ZONTA Club Würzburg.

Neva Caliskan and HIRI director Jörg Vogel. Photo: © HIRI/Tim Schnyder

Left to right: ZONTA laureates C. Morbach (DZHI), N. Caliskan (HIRI/JMU), A. Nowak-Król (JMU) and President of the ZONTA Club Würzburg C. Martin. Photo: © HIRI/Tim Schnyder

HIRI'S FIFTH ANNIVERSARY

MAY 10TH, 2022

With about 200 guests, supporters, and collaboration partners, the Helmholtz Institute for RNA-based Infection Research (HIRI) celebrated its fifth birthday at the Residenz in Würzburg. The HIRI was founded in 2017 in a joint venture of JMU and the Helmholtz Centre for Infection Research (HZI) Braunschweig. Research at HIRI focuses on fundamental and translational aspects of RNA molecules during bacterial and viral infections, making it the first research institution of its kind worldwide.

Managing director of the HIRI Prof. Dr. Jörg Vogel. Photo: © HIRI/Mario Schmitt

From left to right: Dirk Heinz, Paul Pauli, Ilse Aigner, Jörg Vogel, Alice Hohn, Ulrike Wolf, Elisabeth Gerndt and Uwe Klug. Photos (including those shown below): © HIRI/Mario Schmitt

SPHINGOINF SYMPOSIUM

SEPTEMBER 20TH - 22TH, 2022

The international symposium "Sphingolipids in Infection 2022" took place in the Juliusspital Zehntscheune in Würzburg and was organised by the students of the GRK 2581 (speaker: J. Seibel). The symposium aimed to integrate scientists from diverse backgrounds to drive innovation towards sphingolipid-based research.

GASB6 CONFERENCE

SEPTEMBER 21ST - 23RD, 2022

The 6th annual conference of the German Association for Synthetic Biology (GASB) took place at the IMIB/ZINF building and was organized by Chase Beisel, HIRI. The GASB6 conference hosted outstanding speakers as well as poster sessions.

PETTENKOFER PRIZE

OCTOBER 6TH, 2022

Cynthia Sharma (IMIB) and Chase Beisel (HIRI) were awarded the 2022 Pettenkofer Prize in a festive ceremony at the New Town Hall in Munich. The foundation recognized their innovative CRISPR-Cas9-based diagnostic platform "LEOPARD".

Left: Oliver Keppler, Cynthia Sharma and Chase Beisel (l.t.r.). Right: Pettenkofer Prize ceremony at the New Town Hall in Munich. Photos: © Ingrid Grossmann

PHD RETREAT OF THE IMIB/ZINF & HIRI

OCTOBER 13TH - 14TH, 2022

PhD students of the IMIB/ZINF and the HIRI organized a retreat in Bayreuth filled with two-days of talks, poster presentations, scientific exchange, as well as an open disussion about sustainability in science.

PhD students and PIs of the IMIB/ZINF and HIRI sharing two days of science in Bayreuth. Photos: © HIRI/Katharina Wandera.

RETREAT OF THE GRK 2157 3D INFECT

OCTOBER 19TH - 21ST, 2022

For the 6th time, PhD students and PIs of the GRK 2157 "3D Infect" met at their annual retreat to discuss the newest developments for 3D tissue models to study microbial infections by human pathogens. The three day retreat in Berlin included talks by PIs and PhD students, poster sessions, as well as visits to the biotechnology companies TissUse and Cellbricks.

Sina Bartfeld at the GRK poster session.

Pleasant get-together after an exciting conference day. Photos: © GRK 2157

HONORARY DOCTORATE FOR DIRK HEINZ

NOVEMBER 8TH, 2022

Professor Dirk Heinz has made outstanding contributions to the scientific community in the fields of structural biology and infection research and was one of the key drivers in establishing the HIRI. The Medical Faculty of the University of Würzburg paid tribute to his extraordinary achievements, and awarded Prof. Heinz an Honorary Doctorate at its "Dies academicus".

Left to right: Professors Pauli (JMU President), Heinz (Scientific Director of the HZI), and Frosch (Dean of Medicine, JMU). Photo: © Angie Wolf/University Hospital Würzburg

Professors Dirk Heinz, Cynthia Sharma and Lars Dölken (l.t.r.). Photo: © Angie Wolf/UKW

SYMPOSIUM "BIOFABRICATION MEETS INFECTION"

NOVEMBER 24TH - 25TH, 2022

The TRR 225 (Biofab)/GRK 2157 (3D Infect) symposium "Biofabrication meets Infection" took place at the IMIB/ZINF and focused primarily on complex tissue models and biofabrication. The meeting hosted international high-profile speakers. Over two days, the scientific program enabled an exchange between researchers working in the fields of biofabrication, tissue model development, and infection research to identify synergies and boost new research ideas and cooperations.

Organizers (left) and participants (right) of the symposium "Biofarbrication meets Infection". Photos: © GRK 2157 & TRR 225

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ZINF YOUNG INVESTIGATORS

CARMEN AGUILAR - ZINF/BMBF

SINA BARTFELD - ZINF

ANA RITA BROCHADO - ZINF/BIOCENTER

FRANZISKA FABER - ZINF/HIRI

SEBASTIAN GEIBEL - ELITE NETWORK BAVARIA

J. CHRISTIAN PÉREZ - ZINF/IZKF

HOST PATHWAYS IN URINARY TRACT INFECTIONS

DR. CARMEN AGUILAR

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SELECTED PUBLICATIONS

Aguilar C*, Pauzuolis M*, Pompaiah M, Vafadarnejad E, Arampatzi P, Fischer M, Narres D, *et al.*, Saliba A-E, Bartfeld S (2022) *Helicobacter pylori shows tropism to gastric differentiated pit cells dependent on urea chemotaxis.*
Nature Communications 13(1):5878
*equally contributing authors

Aguilar C, Costa S, Maudet C, Vivek-Ananth RP, Zaldívar-López S, Garrido JJ, Samal A, Mano M, Eulalio A (2021) *Reprogramming of microRNA expression via E2F1 downregulation promotes Salmonella infection both in infected and bystander cells.*
Nature Communications 12(1):3392

Aguilar C, Alves da Silva M, Saraiva M, Neyazi M, Olsson IAS, Bartfeld S (2021) *Organoids as host models for infection biology - a review of methods.*
Experimental & Molecular Medicine 53(10):1471-1482

Aguilar C*, Cruz AR*, Rodrigues Lopes I, Maudet C, Sunkavalli U, Silva RJ, Sharan M, Lisowski C, Zaldívar-López S, Garrido JJ, Giacca M, Mano M, Eulalio A (2020) *Functional screenings reveal different requirements for host microRNAs in Salmonella and Shigella infection.*
Nature Microbiology 5(1):192-205
*equally contributing authors

RESEARCH INTERESTS

Urinary tract infections (UTIs) caused by Gram-negative uropathogenic *Escherichia coli* (UPEC) are among the most common infections worldwide. One in two women will suffer a UTI at least once in their life. Despite effective antibiotic treatment, more than 50% of patients will experience recurrence within a year, suggesting that treatment is less than ideal.

Continuous antibiotic prophylaxis with extended courses of low-dose antibiotic therapy is often the only available treatment for recurrent UTIs. This is associated with increased frequency of antimicrobial resistance. Up to now, most of the anti-infective research has been focused on combating the bacterial side. Yet, whether a person is susceptible to infection by UPEC is also decided by host factors, and while bacterial factors have been studied extensively, host factors have been sorely neglected. A better understanding of host mechanisms will help to develop new strategies to combat recurrent UTIs.

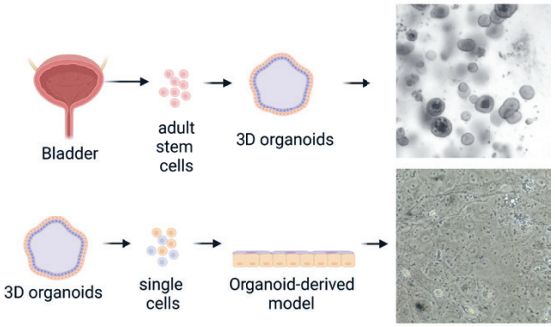

Figure 1: Generation of ASC-derived bladder organoids and organoid-derived models. Figure was created with the help of BioRender.

My research group studies the interplay between UPEC and the urinary tract epithelium from a host perspective. We use adult stem cell derived-organoids and organoid-based models to closely mimic the natural infection site. These models will then be utilized to identify and functionally characterize specific host factors and/or pathways controlling the outcome of the infection. In addition, we will also focus on those that are involved in UPEC persistence to potentially exploit them as novel therapeutic drug targets. Overall, my group will address this urgent medical challenge by gaining a deeper understanding of signalling pathways involved in UPEC pathogenesis to develop novel host-based approaches to treat UTIs.

HIGHLIGHTS & OUTLOOK

The vast majority of UTIs occur in the urinary bladder. The bladder epithelium consists of a transitional epithelium with multiple layers of three distinct cell types: a basal layer of progenitor cells, multiple layers of intermediate transitional cells, and a single layer of superficial differentiated umbrella cells facing the bladder lumen. To investigate host molecular mechanisms controlling UPEC infection that could be translated into new therapies, we need to use *in-vitro* models that closely mimic the human site of infection.

Adult stem cell-derived organoids provide an excellent model for infection biology and translational studies since they are able to differentiate and self-organize similar to as they do *in vivo*. These organoids are generated from adult stem cells present in the bladder epithelium and can be used as a source of expandable primary cells to establish other *in-vitro* models, such as more advanced tissue-engineered models. Using bladder organoids, we

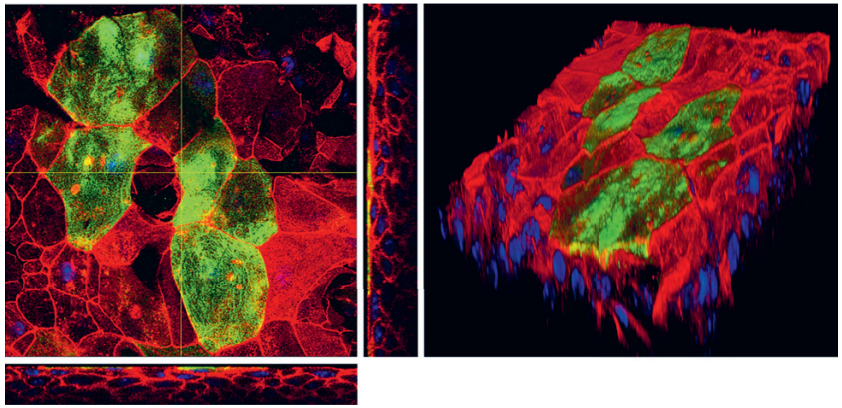

Figure 2: Confocal orthogonal view of the bladder organoid-derived model showing superficial umbrella-like cells. Nuclei (blue), actin (red), uroplakin 3a (green).

are currently developing organoid-derived models containing all three distinct urothelial cell subtypes. The use of these model systems will provide us with a powerful tool to discover relevant factors involved in UPEC infection of the bladder epithelium in the coming years.

MicroRNAs (miRNAs) are a class of genome-encoded small regulatory RNAs that play a major role in the post-transcriptional control of eukaryotic gene expression, by repressing target transcripts containing complementary binding sites. They are a class of RNA molecules with well-established functions in physiological and pathological host processes. In addition, they are now increasingly recognized as an integral part of the host immune response to fight infections by either promoting or inhibiting the bacterial infection. MiRNAs can regulate infections by modulating virtually any host function, including the immune response, cell cycle, cell death, and autophagy.

Yet, the regulation of miRNAs in the human bladder epithelium upon UPEC infection and its use to treat infection has not been addressed. We will use miRNome profiling and gain/loss-of-function approaches to analyze miRNA regulation upon UPEC infection and to identify miRNAs with modulatory effect in the infection. The functional characterization of selected miRNAs, their targets, and downstream molecular pathways is expected to lead to the characterization of previously unappreciated pathways relevant for UPEC infection.

Given the complexity of the crosstalk between bacteria and host during the infection, it is likely that cellular heterogeneity will play a role in the formation of persisters in the epithelium. Ascertaining such heterogeneity using a single cell RNA-sequencing (scRNA-seq) approach allows detailed profiling of the whole transcriptome of individual cells, providing a unique signature for each one. Since the presence of UPEC persisters is directly related to the development of recurrent episodes of UTIs, a deeper understanding of the mechanisms involved is necessary to combat this issue. For example, the specific requirements of the target cell type allowing UPEC persistence have so far not been described. Applying scRNA-seq technology on the UPEC-infected organoid-derived models, we plan to identify new host cell receptors and/or intracellular factors that are required for UPEC to infect and persist in the urothelium. Based on this knowledge, new therapeutic approaches could be designed to target host pathways to prevent and/or eliminate bacterial persisters.

Overall, we aim to obtain a better understanding of the host pathways controlling UPEC infection in the bladder. This will contribute to the development of new therapeutic strategies to defeat recurrent UTIs and antibiotic-resistant UPEC to advance the fight against AMR.

ORGANOIDS AS HOST MODELS

PROF. SINA BARTFELD
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SELECTED PUBLICATIONS

Aguilar C, Pauzuolis M, Pompaiah M, Vafadarnejad E, Arampatzi P, Fischer M, Narres D, *et al.*, Saliba A-E*, **Bartfeld S***
(2022) *Helicobacter pylori shows tropism to gastric differentiated pit cells dependent on urea chemotaxis.*
Nature Communications 13(1):5878
*corresponding authors

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PLoS Pathogens 17(2):e1009210

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Asymmetric distribution of TLR3 leads to a polarized immune response in human intestinal epithelial cells.
Nature Microbiology 5(1):181-191

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.

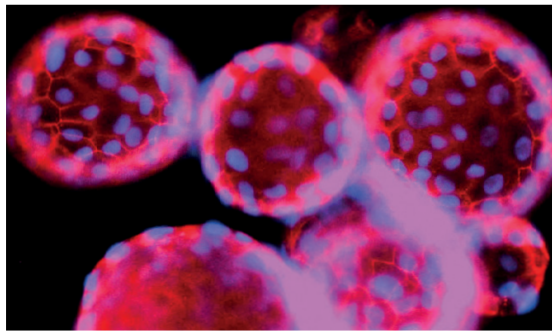

Figure 1: 3D human organoids. Red: Occludin. Blue: Nuclei.
Image by Carolin Niklas.

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 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.

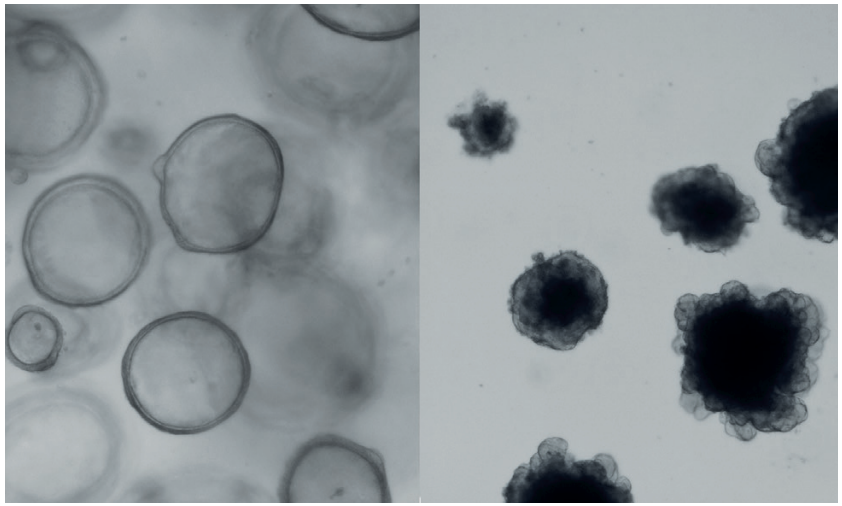

Figure 2: Human gastric organoids generated from healthy tissue (left) or cancer tissue (right).
Image by Nina Wallaschek.

Epstein-Barr virus (EBV) is best known for infection of B cells, in which it usually establishes an asymptomatic lifelong infection, but is also associated with the development of multiple B cell lymphomas. EBV also infects epithelial cells and is etiologically linked with at least 8% of gastric cancer (EBVaGC). While B cell entry and lymphomagenesis is relatively well understood, the sequence of events leading to EBVaGC remains enigmatic. Recently, ephrin receptor A2 (EPHA2) was proposed as the epithelial cell receptor on human cancer cell lines. However, EBV does not infect healthy adult stem cell-derived gastric organoids, despite presence of EPHA2 mRNA and protein. In matched pairs of normal and cancer-derived organoids from the same patient, EBV only infected the cancer organoids. While there was no clear pattern of differential expression between normal and cancer organoids for EPHA2 at the RNA and protein level, the subcellular location of the protein differed markedly. Confocal microscopy showed EPHA2 localization at the cell-cell junctions in primary cells, but not in cancer cell lines. Furthermore, histologic analysis of patient tissue revealed the absence of EBV in healthy epithelium and presence of EBV in epithelial cells from inflamed tissue. These data suggest that the EPHA2 receptor is not accessible to EBV on healthy gastric epithelial cells with intact cell-cell contacts, but either this or another, yet to be identified receptor may become accessible following cellular changes induced by inflammation or transformation, rendering changes in the cellular architecture an essential prerequisite to EBV infection.

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

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Emmy Noether group leader, Research Center for Infectious Diseases
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AWARDS

Röntgenpreis, University of Würzburg (2021)

Hector Research Career Development Award, Hector Fellow Academy (2020)

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.

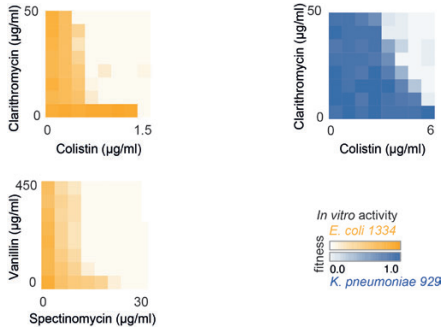

Figure 1: Synergistic drug combinations to overcome antibiotic resistance.
Image from Brochado *et al.*, 2018, Nature.

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 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.

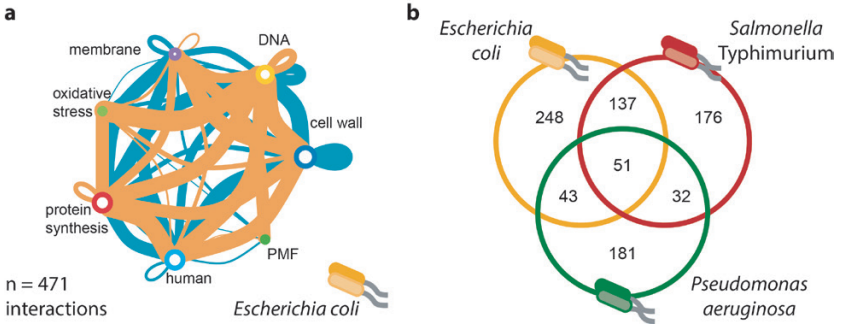

Figure 2: Drug interactions in bacteria: (a) drug interaction network in *E. coli* and (b) species-specificity of drug interactions.
Image from Brochado *et al.*, 2018, Nature.

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 collaboration with Prof. Dr. Cynthia Sharma (IMIB). In particular, we are deploying 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 GRAM-POSITIVE BACTERIA

JUN. PROF. FRANZISKA FABER

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SELECTED PUBLICATIONS

Fuchs M, Lamm-Schmidt V, Sulzer J, Ponath F, Jenniches L, Kirk JA, Fagan RP, Barquist L, Vogel J, **Faber F** (2021) *An RNA-centric global view of Clostridioides difficile reveals broad activity of Hfq in a clinically important gram-positive bacterium*.
PNAS 118(25):e2103579118

Lamm-Schmidt V, Fuchs M, Sulzer J, Gerovac M, Hör J, Dersch P, Vogel J, **Faber F** (2021) *Grad-seq identifies KhpB as a global RNA-binding protein in Clostridioides difficile that regulates toxin production*.
microLife uqab004

Ponath F, Tawk C, Zhu Y, Barquist L, **Faber F**, Vogel J (2021) *RNA landscape of the emerging cancer-associated microbe Fusobacterium nucleatum*.
Nature Microbiology 6(8):1007-1020

Tiffany CR, Lee JY, Rogers AWL, Olsan EE, Morales P, **Faber F#**, Bäumler A# (2021) *The metabolic footprint of Clostridia and Erysipelotrichia reveals their role in depleting sugar alcohols in the cecum*.
Microbiome 9(1):174
#corresponding authors

RESEARCH INTERESTS

In my research group we are interested in the mechanisms of post-transcriptional gene regulation that are mediated by small regulatory RNAs and their cognate RNA-binding proteins (RBPs). We study these processes in gram-positive pathogens to understand the molecular mechanisms that fine-tune stress responses and the expression of virulence factors.

The current focus in my lab is the obligate anaerobic bacterium *Clostridioides difficile*, which is an enteric pathogen of humans and animals. *C. difficile* is the leading cause of antibiotic-associated diarrhea, and causes mild to severe forms of colitis that can be lethal. Antibiotic-induced dysbiosis, and the associated changes in the intestinal metabolome render a host susceptible to *C. difficile* infections (CDI). Moreover, failure of microbial recovery after successful treatment of a primary *C. difficile* infection with conventional antibiotics are associated with high recurrence/ relapse rates of up to 20%.

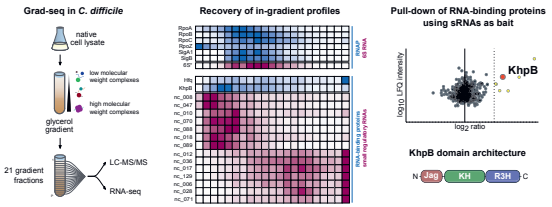

Figure 1: Grad-seq guided identification of RNA-binding proteins in *C. difficile*.

Due to this antibiotic dilemma, *C. difficile* research is strongly focused on understanding the microbiota-pathogen interplay during CDI to develop a rational design of microbial cocktails that facilitate microbiota recovery and re-instate colonization resistance against *C. difficile*. In our group, we are taking an RNA-centric approach by characterizing the molecular underpinnings of gene regulation by sRNAs and their cognate RBPs to leverage this knowledge for the development of species-specific RNA-based therapeutics directed against *C. difficile*.

HIGHLIGHTS & OUTLOOK

Using state of the art methods of bacterial RNA biology, we have generated high-resolution RNA maps to define the transcriptome architecture and to build a global atlas of non-coding transcriptional and post-transcriptional regulators in *C. difficile*. Furthermore, gradient centrifugation of native cell lysates combined with RNA-seq and mass spectrometry of individual gradient fractions (Grad-seq) has led to the identification of a previously uncharacterized protein, called KhpB, that belongs to a broadly conserved family of RBPs. Using co-immunoprecipitation of both Hfq and KhpB in combination with RNA-seq revealed that both proteins are globally acting RBPs in *C. difficile*. Our work has established a rich resource for researchers interested in this species, but also for bacterial RNA biology in general.

Current projects are investigating the implications of RNA-based regulation for *C. difficile* virulence. For example, our functional characterization of KhpB has revealed that it has pleiotropic functions in the cell, which comprise the regulation of cell elongation as well as the production of its central

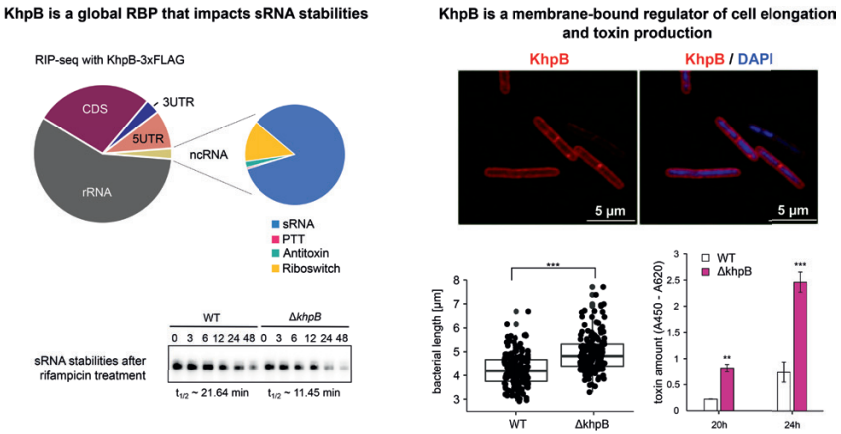

Figure 2: KhpB is a global RBP that regulates cell elongation and toxin production.

virulence factor, the clostridial toxin. We are now investigating how these seemingly unrelated cellular processes are functionally connected by KhpB. Furthermore, our transcriptome-based annotation of sRNAs has revealed two novel sRNAs that regulate the translation of the mRNA encoding for the master regulator of sporulation Spo0A. In this project, we are currently investigating the impact of this post-transcriptional regulation on the production of *C. difficile* spores. A better understanding of the spore formation process is particularly important because successful CDI treatment is complicated by the persistence of spores that are resistant against antibiotics.

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*. Antisense oligomers (ASOs), including peptide nucleic acids (PNAs), are an attractive technology for species-specific antibiotics, because they can inhibit essential genes on the RNA level through sequence-specific binding to the targeted mRNA. Mechanistic insights from our studies on RNA-based gene regulation will inform the design strategies for PNA candidates. The most common strategy to deliver these ASOs into the bacterial cytoplasm is their conjugation to cell penetrating peptides. However, our recent research revealed that this strategy is inefficient in *C. difficile*. Therefore, we are currently exploring alternative delivery strategies that include the complexation of ASOs with cationic amphiphilic bolaamphiphiles (or bolalipids).

To investigate regulatory mechanisms governing host colonization by *C. difficile*, we employ advanced cell culture models to simulate the mostly anaerobic environment of the human large intestinal tract. Using a polarized Transwell model of colonic cells that produces an adherent mucus layer, we can perform *in-vitro C. difficile* infections under micro-aerobic conditions allowing the concomitant assessment of bacterial growth, toxin production, and sporulation, as well as associated host responses in a time-resolved manner. We observe robust colonization of the mucus layer that is promoted by the production of clostridial toxins. 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

Rivera-Calzada A, Famelis N, Llorca O, **Geibel S** (2021) *Type VII secretion systems: structure, functions and transport models.* **Nature Reviews Microbiology** 19(9): 567-584

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

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. 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

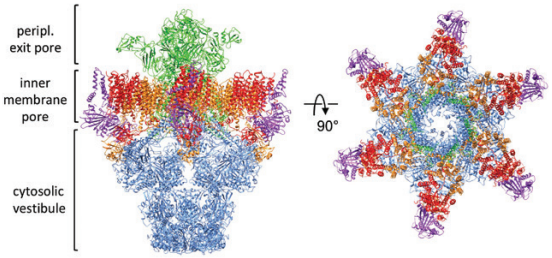

Figure 1: Model of the type VII secretion system. Left: side view of the ESX-3 nanomachine. Right: top view of the central membrane pore; the green periplasmic exit pore was cut away for clarity.

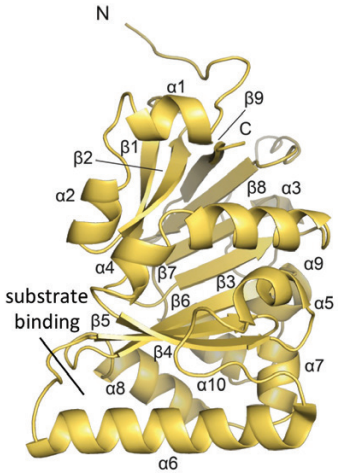

Figure 2: Crystal structure of the T7SSb substrate recognition domain.

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 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

DR. J. CHRISTIAN PÉREZ

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SELECTED PUBLICATIONS

Reuter-Weissenberger P, Meir J, **Pérez JC** (2021) *A Fungal Transcription Regulator of Vacuolar Function Modulates Candida albicans Interactions with Host Epithelial Cells.* **mBio** 12(6):e0302021

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

Eckstein MT, Moreno-Velásquez SD, **Pérez JC** (2020) *Gut Bacteria Shape Intestinal Microhabitats Occupied by the Fungus Candida albicans.* **Current Biology** 30(23):4799-4807.e4

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.

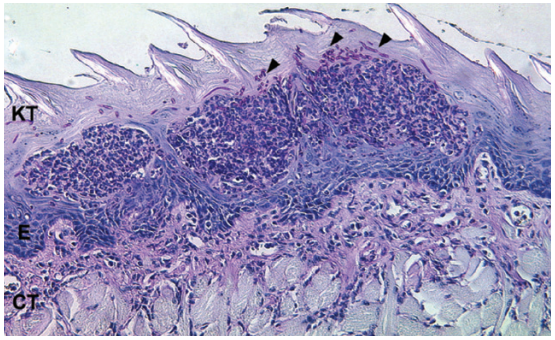

Figure 1: *C. albicans* (black triangles) penetrating mouse oral mucosa.
KT, keratinized tissue; E, epithelium; CT, connective tissue.

HIGHLIGHTS & OUTLOOK

We have investigated the 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.

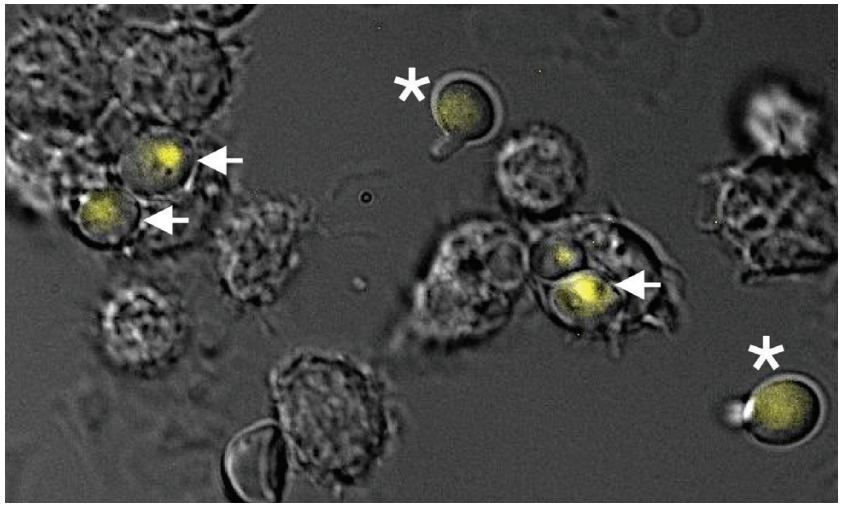

Figure 2: *C. albicans* engulfed by human neutrophils.
YFP reporter localizes to fungal nuclei upon engulfment (arrows). Asterisks denote free fungal cells.

We also examined how the spatial distribution of a human commensal fungus across the mammalian intestine is shaped by individual gut bacterial species. Imaging studies had revealed that the microbes that compose the gut microbiota do not randomly distribute across the intestine but rather display intriguing patterns of spatial structuring. This finding had generated a great deal of excitement in the microbiota field because it was suggestive of relationships and interdependencies among microbial taxa. Still missing, however, were experimental studies that looked at defined sets of microbes in the gut with the goal of learning what drove their spatial organization. Our study sought to fill this void. By imaging the gut of gnotobiotic mice inoculated with individual or mixed gut commensals (the fungus *C. albicans* and the bacteria *Bacteroides thetaiotaomicron* or *Lactobacillus reuteri*), we reported three key observations. First, we demonstrated that *B. thetaiotaomicron*, a saccharolytic bacterial species, is necessary and sufficient to elicit the formation of an outer mucus layer in the murine intestine. Second, we established that *C. albicans*, the most prominent fungus residing in the human gut, localizes to the interior of a *B. thetaiotaomicron*-promoted outer mucus layer. And, third, we showed that Bacteroides-processed mucin – as opposed to intact mucin – can better fuel the growth of *C. albicans*.

Finally, we have dissected the molecular function of a previously undescribed *C. albicans* gene which contributes to fungal colonization in the oral cavity and gastrointestinal tract. We combined full-genome molecular biology approaches (ChIP-Seq and RNA-Seq) and extensive cell biology experiments to reveal that this gene linked to colonization of murine mucosal surfaces encodes a transcription regulator of vacuolar function. We demonstrated that *C. albicans* attachment to epithelial cells is modulated by this transcription regulator through a mechanism that depends on the status of the fungal vacuole. To our knowledge, it is the first report implicating this organelle in shaping *Candida* interactions with host epithelial cells. Our findings, therefore, suggest that fungal vacuole physiology regulation is intrinsically linked to, and shapes to a significant extent, the physical interactions that *Candida* cells establish with mammalian mucosal surfaces.

3

MEMBERS OF THE ZINF

Image: University of Würzburg

3.1 INSTITUTE OF MOLECULAR INFECTION BIOLOGY

JÖRG VOGEL

CYNTHIA SHARMA

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 since 2009 and Chair of Molecular Infection Biology I. 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, 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

PROF. JÖRG VOGEL

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SELECTED PUBLICATIONS

Ponath F, Tawk C, Zhu Y, Barquist L, Faber F, **Vogel J** (2021) *RNA landscape of the emerging cancer-associated microbe Fusobacterium nucleatum.* **Nature Microbiology** 6(8):1007-1020

Hör J, Garriss G, Di Giorgio S, Hack LM, Vanselow JT, Förstner KU, Schlosser A, Henriques-Normark B, **Vogel J** (2020) *Grad-seq in a Gram-positive bacterium reveals exonucleolytic sRNA activation in competence control.* **EMBO Journal** 39(9):e103852

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

AWARDS

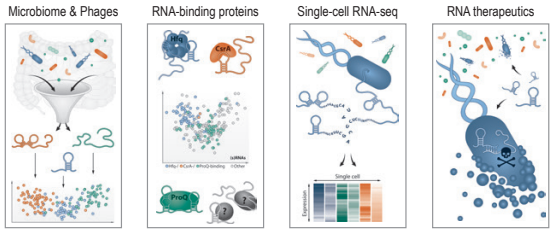
Highly Cited Researcher 2022
(continuously since 2015)

RESEARCH INTERESTS

Non-coding RNAs are crucial regulators in all domains of life. We study the role of ncRNAs and RNA-binding proteins (RBPs) in the context of bacterial infections to target the human microbiota. The main areas of the Vogel lab are: i) discovery of functional RNAs in microbes and phages, including the cancer-associated *Fusobacterium nucleatum*; ii) characterization of novel bacterial RBPs; iii) new RNA-seq methods for infection biology, like single-cell RNA-seq of eukaryotic and bacterial cells; iv) antisense oligomers-based antibiotics for precision editing of the human flora and complex microbial communities.

HIGHLIGHTS & OUTLOOK

A Vogel-lab highlight was the generation of a pneumococci RNA/protein complexome resource with the description of a specific exonuclease as a new actor in the competence for DNA uptake and virulence. We developed RNase-sensitive gradient fractionation combined with mass spec (GradR) to predict novel RBPs for intestinal flora and an online tool to compare visualization of sedimentation profiles of differential gradient-based tools. As a new project, we explore the interplay between phages and their host bacteria using dual Grad-seq to study how a phage infection alters host complexes. We focused on RNA-protein complexes that either pass the genetic message to protein production or exert regulatory functions themselves; for the latter, we identified regulatory RNAs in the phage. A better understanding of the molecular targets of phages in host cells can build the foundation for new molecular tools for microbiome modulation. A main contribution to understanding the biology of cancer-related commensals is our in-depth description of the transcriptome of *F. nucleatum*, a member of the oral microflora. We developed much-needed genetic tools and combined RNA-seq to begin to uncover regulatory RNA networks letting *F. nucleatum* to adapt to diverse niches in the human body. In the field of RNA-seq methods, we pioneered true single-cell global transcriptomics of bacteria. To this end, we improved a poly(A)-independent single-cell RNA-seq protocol to comprehensively detect growth-dependent gene expression patterns in individual bacteria across all RNA classes and genomic regions. We have moved „programmable antibiotics“ further toward application. We improved the understanding of how antisense peptide nucleic acid (PNA) inhibits mRNAs of essential genes. This is the key to programmable PNA-based species-specific antibiotics with high potency and predictable antibacterial activity. Also, we established a unified experimental framework for future development and evaluation of antimicrobial antisense oligomers for precision editing of the microbiota.



The four main areas of research in the Vogel lab.

DEEP SEQUENCING APPROACHES TO PATHOGENESIS

PROF. CYNTHIA SHARMA

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SELECTED PUBLICATIONS

Jiao C, Sharma S, Dugar G, Peeck NL, Bischler T, Wimmer F, Yu Y, Barquist L, Schoen C, Kurzai O, **Sharma CM**[#], Beisel CL[#] (2021) *Noncanonical crRNAs derived from host transcripts enable multiplexable RNA detection by Cas9.* **Science** 372(6545):941-948

(Winner in the category Life Sciences, Falling Walls Science Breakthroughs of the Year 2021) #corresponding authors

Pernitzsch SR, Alzheimer M, Bremer BU, Robbe-Saule M, De Reuse H, **Sharma CM** (2021) *Small RNA mediated gradual control of lipopolysaccharide biosynthesis affects antibiotic resistance in Helicobacter pylori.* **Nature Communications** 12(1):4433

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** 80(2):210-226.e7

AWARDS

Pettenkofer Prize (2022)

ERC Consolidator Grant 2022: *Exploring the expanding universe of RNA-binding proteins in bacteria* (bacRBP)

RESEARCH INTERESTS

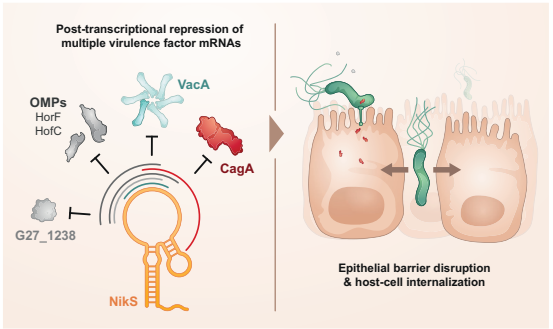
Our research centers around mechanisms of gene regulation that control stress responses and virulence in the gastric pathogen *Helicobacter pylori* and the foodborne pathogen *Campylobacter jejuni*. We focus on post-transcriptional regulation by small regulatory RNAs (sRNAs) and RNA-binding proteins (RBPs). In addition to analyzing transcriptomes/translatomes and RNA-protein complexes by deep sequencing methods, we also develop approaches to globally capture RBPs. Using 3D tissue-engineered infection models, we are investigating the roles of sRNAs, RBPs, and small proteins in virulence of these human pathogens.

HIGHLIGHTS & OUTLOOK

Via genomics, biochemical, molecular biology, and genetics approaches, we are elucidating the roles and mechanisms of bacterial sRNAs and RBPs. We discovered, e.g., that NikS sRNA acts as a central regulator of major virulence factors and impacts pathogenesis of *H. pylori*. Our research also revealed unexpected connections of sRNAs to length-variable repeats: *H. pylori* RepG sRNA gradually modulates expression of genes involved in chemotaxis and surface structures that are important for host colonization and antibiotics sensitivity. In *C. jejuni*, we found that a virulence-associated sRNA pair CJnc180/190 is processed in a complex pathway, highlighting a role for RNase III in sRNA biogenesis. Furthermore, CJnc180 is a cis-acting antagonist of CJnc190, adding cis-encoded RNAs to the expanding diversity of RNA antagonists. Our research on the CRISPR-Cas immune system in *C. jejuni* revealed a new type of guide RNAs derived from host RNAs for the Cas9 nuclease. Together with the Beisel lab, we translated this unexpected discovery into a new multiplexable diagnostic platform called LEOPARD.

Our ERC-CoG project explores the so far largely uncharted universe of bacterial RBPs, using our newly developed method for RBP capture in bacteria, called CoCAP. Our pilot screens in *C. jejuni* and *Salmonella* captured both known RBPs as well as new RBP candidates. These include many unconventional RBPs lacking a known RNA-binding domain and with often already defined functions in the cell, e.g., in metabolism or cell division. We are now exploring the mechanisms and functional consequences of their interaction with RNA.

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



The small RNA NikS acts as a central regulator of virulence genes in the gastric pathogen *Helicobacter pylori* (Figure adapted from Eisenbart *et al.*, 2020).

MYCOLOGY

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SELECTED PUBLICATIONS

Ramírez-Zavala B, Krüger I, Dunker C, Jacobsen ID, **MorschhäuserJ** (2022) *The protein kinase Ire1 has a Hac1-independent essential role in iron uptake and virulence of Candida albicans.*
PLoS Pathogens 18(2):e1010283

Ramírez-Zavala B, Mottola A, Krüger I, **Morschhäuser J** (2021) *A suppressor mutation in the β-subunit Kis1 restores functionality of the SNF1 complex in Candida albicans snf4Δ mutants.*
mSphere 6(6):e0092921

Mottola A, Ramírez-Zavala B, Hünniger K, Kurzai O, **Morschhäuser J** (2021) *The zinc cluster transcription factor Czf1 regulates cell wall architecture and integrity in Candida albicans.*
Molecular Microbiology 116(2):483-497

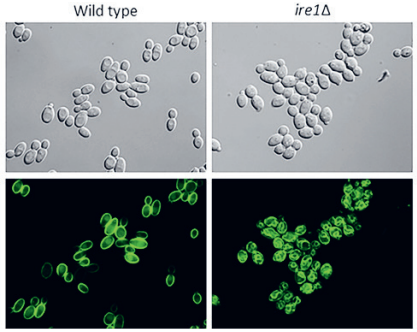
Mottola A, Schwanfelder S and **Morschhäuser J** (2020) *Generation of viable Candida albicans mutants lacking the „essential" protein kinase Snf1 by inducible gene deletion.*
mSphere 5(4):e00805-20

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

Microbial pathogens must cope with severely restricted iron availability in mammalian hosts to invade and establish themselves within infected tissues. To uncover signaling pathways that are involved in the adaptation of *C. albicans* to iron limitation, we generated a comprehensive protein kinase deletion mutant library of a wild-type strain. Screening of this library revealed that the protein kinase Ire1, which has a conserved role in the response of eukaryotic cells to endoplasmic reticulum (ER) stress, is essential for growth of *C. albicans* under iron-limiting conditions. Ire1 was not necessary for the activity of the transcription factor Sef1, which regulates the response of the fungus to iron limitation, and Sef1 target genes that are induced by iron depletion were normally upregulated in *ire1*Δ mutants. Instead, Ire1 was required for proper localization of the high-affinity iron permease Ftr1 to the cell membrane. Intriguingly, iron limitation did not cause increased ER stress, and the transcription factor Hac1, which is activated by Ire1-mediated removal of the non-canonical intron in the *HAC1* mRNA, was dispensable for Ftr1 localization to the cell membrane and growth under iron-limiting conditions. Nevertheless, expression of a pre-spliced *HAC1* copy in *ire1*Δ mutants restored Ftr1 localization and rescued the growth defects of the mutants. Both *ire1*Δ and *hac1*Δ mutants were avirulent in a mouse model of systemic candidiasis, indicating that an appropriate response to ER stress is important for the virulence of *C. albicans*. However, the specific requirement of Ire1 for the functionality of the high-affinity iron permease Ftr1, a well-established virulence factor, even in the absence of ER stress uncovers a novel Hac1-independent essential role of Ire1 in iron acquisition and virulence of *C. albicans*. Our libraries of protein kinase deletion mutants and activated transcription factors are valuable tools to study the regulatory networks controlling virulence traits of *C. albicans*.



Subcellular localization of the high-affinity iron permease Ftr1 (GFP-tagged) in *C. albicans* wild-type cells and *ire1*Δ mutants.

GRAM-POSITIVE COCCI

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SELECTED PUBLICATIONS

Ibrahim ES, **Ohlsen K** (2022) *The Old Yellow Enzyme OfrA Fosters Staphylococcus aureus Survival via Affecting Thiol-Dependent Redox Homeostasis.*
Frontiers in Microbiology 13:888140

Liang C, Rios-Miguel AB, Jarick M, Neurgaonkar P, Girard M, François P, Schrenzel J, Ibrahim ES, **Ohlsen K***, Dandekar T* (2021) *Staphylococcus aureus transcriptome data and metabolic modelling investigate the interplay of Ser/Thr Kinase PknB, its phosphatase Stp, the glmR/yvcK Regulon and the cdaA operon for metabolic adaptation.*
Microorganisms 9(10):2148
*corresponding authors

Umstätter F, Domhan C, Hertlein T, **Ohlsen K**, Mühlberg E, Kleist C, Zimmermann S, Beijer B, Klika KD, Haberkorn U, Mier W, Uhl P (2020) *Vancomycin Resistance Is Overcome by Conjugation of Polycationic Peptides.*
Angewandte Chemie International Edition 59(23):8823-8827

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.

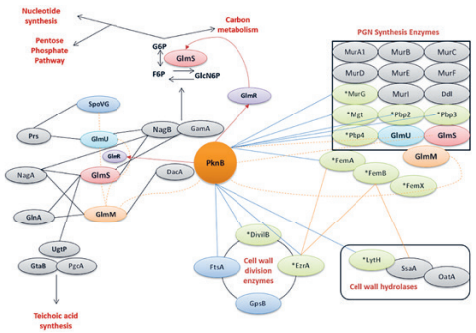
HIGHLIGHTS & OUTLOOK

Recently, we developed, together with cooperation partners, novel antibacterial compounds targeting bacterial cell wall synthesis for clinical application by comprehensive *in-vitro* and *in-vivo* analysis of novel peptide-linked antibiotics such as vancomycin. A first lead compound could be identified with better activities compared to used antibiotics of last resort *in vitro*. Moreover, we characterized the mode of action of novel bisindolyl-substituted cycloalkane indoles by pyruvate kinase inhibition assays. Two hit compounds were selected for comprehensive pharmacological studies within our preclinical development program.

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 PknB (Stk) and Stp, in *S. aureus* we have elucidated the transcriptome of mutated strains lacking PknB and Stp and modeled the data in metabolic flux networks. We have found that both the kinase and phosphatase are important factors in metabolic adaptation of *S. aureus* including the switch from glycolysis to gluconeogenesis and cell wall metabolism (see Figure).

In addition, we have established a humanized mouse model to study the role of virulence factors of *S. aureus* specifically targeting human immune cells.

In the future, we are interested in analyzing expression of bacterial and host genes during *S. aureus* infections by applying dual RNA-seq and single cell RNA-seq methodology. In addition, we are investigating the physiological function and regulation of a novel oxidoreductase belonging to the class of Old Yellow Enzymes (OYEs). This enzyme plays an essential role in stress response of *S. aureus* and is important for the survival of the pathogen after phagocytosis.



Interaction network of Ser/Thr kinase PknB based on metabolic flux analysis.

HOST-PATHOGEN-MICROBIOTA INTERACTIONS

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SELECTED PUBLICATIONS

Schuster EM, Epple MW, Glaser KM, Mihlan M, Lucht K, Zimmermann JA, Bremser A, Polyzou A, Obier N, Cabezas-Wallscheid N, Trompouki E, Ballabio A, Vogel J, Buescher JM, **Westermann AJ**, Rambold AS (2022) *TFEB induces mitochondrial itaconate synthesis to suppress bacterial growth in macrophages.*
Nature Metababolism 4(7):856-866

Westermann AJ#, Vogel J# (2021) *Cross-species RNA-seq for deciphering host-microbe interactions.*
Nature Reviews Genetics 22(6):361-378
#corresponding authors

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

AWARDS

ERC Starting Grant 2022: *Deciphering commensal-host-pathogen metabolic interactions to combat intestinal infections* (GUT-CHECK)

RESEARCH INTERESTS

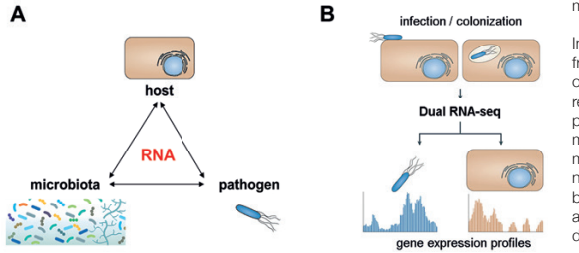
Our intestinal tract offers an attractive environment for both beneficial and pathogenic bacteria. The beneficial bacteria of our microbiota feast on undigested foods and provide numerous health benefits. Enteric pathogens see this environment as an entry point for infection. Both groups influence each other, creating a tripartite interaction with us, the host. Understanding the regulatory processes that decide on the outcome of these encounters represents an emerging research area to combat infectious diseases. While the field has focused on protein-mediated processes, our group investigates the role of RNA-centric mechanisms in controlling microbial interactions in the gut.

HIGHLIGHTS & OUTLOOK

The anaerobic Gram-negative bacterium *Bacteroides thetaiotaomicron* represents a predominant member of the human gut microbiota and emerged as the model bacterium for functional microbiota research. By compiling a high-resolution transcriptome annotation for this bacterium ('Theta-Base': https://bacteroides.helmholtz-hzi.de/), we recently identified hundreds of novel small regulatory RNAs (sRNAs), whose functional and mechanistic characterization represents one major focus of the group. For example, we pursue a unique, multi-pronged strategy to identify and understand *in vivo*-relevant *Bacteroides* sRNAs in a systematic manner. To this end, we combine cross-species RNA-seq approaches (metatranscriptomics, dual and triple RNA-seq) and multiplexed CRISPR-based sRNA knockdown with advanced human colon models.

Most known sRNAs do not operate in isolation, but depend on assisting RNA chaperones to fulfill their regulatory functions. In the absence of homologs of classical global RNA-binding proteins, we combine computational and experimental screens to search for alternative global RNA binders in *Bacteroides*. Recent findings from the lab, for instance, suggest a *Bacteroides* cold-shock protein as an RNA-binder and to contribute to bacterial colonization of the host mucous layer.

In summary, biological insights gained from these studies will improve our knowledge of the functions of regulatory RNA molecules and their protein partners in a predominant member of the human intestinal microbiota. This will lay the groundwork needed to exploit microbiota RNA biology for diagnostics and therapy against enteric infections and microbial disorders in our gut.



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

Marincola G, Jaschkowitz G, Kieninger AK, Wencker FDR, Fessler AT, Schwarz S, **Ziebuhr W** (2021) *Plasmid-Chromosome Crosstalk in Staphylococcus aureus: A Horizontally Acquired Transcription Regulator Controls Polysaccharide Intercellular Adhesin-Mediated Biofilm Formation.*
Frontiers in Cellular and Infection Microbiology 11:660702

Wencker FDR, Marincola G, Schoenfelder SMK, Maass S, Becher D, **Ziebuhr W** (2021) *Another layer of complexity in Staphylococcus aureus methionine biosynthesis control: unusual RNase III-driven T-box riboswitch cleavage determines met operon mRNA stability and decay.*
Nucleic Acids Research 49(4):2192-2212

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

RESEARCH INTERESTS

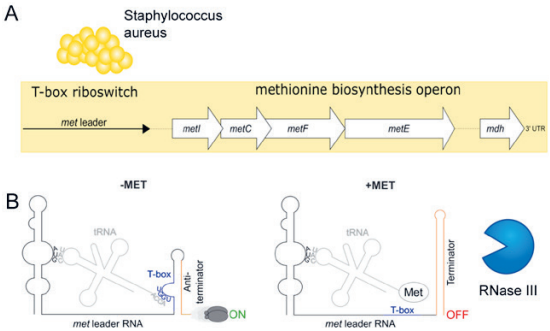
Our work aims at understanding the lifestyle of staphylococci as major opportunistic and nosocomial pathogens. Current projects focus on RNA-mediated regulation of biofilm formation and metabolism in these Gram-positive bacteria. We intensively study control of *de novo* methionine biosynthesis by T-box riboswitches.

We also have an interest in antibiotic resistance (ABR) mechanisms and their spread. Here, we are engaged in One Health aspects of staphylococcal epidemiology by analyzing ABR profiles of staphylococci from industrialised animal husbandry in Germany and Africa. Finally, we support colleagues from pharmacy in their efforts to identify novel lead compounds with anti-staphylococcal activity.

HIGHLIGHTS & OUTLOOK

N-formyl methionine is the universal N-terminal amino acid of prokaryotic proteins making methionine indispensable for bacterial growth. *Staphylococcus aureus* is capable of synthesising methionine *de novo* and therefore to sustain in niches where the amino acid is lacking. We established that expression of the *met* operon in *S. aureus* is controlled by a unique hierarchical control pathway involving a T-box riboswitch (TBRS) as regulatory centre piece. TBRS are widespread in Gram-positive bacteria where they control a number of (essential) genes engaged in amino acid metabolism. They represent transcription control systems that bind uncharged cognate tRNAs as effector molecules. The TBRS residing in the met leader RNA of the *S. aureus* met operon is exceptionally long, and by determining its secondary structure we identified a terminator helix that is target for RNase III. Cleavage by the enzyme releases the *met* leader from the *met* operon mRNA and initiates RNase J-mediated 5' to 3' degradation of the mRNA, with a longer lifespan of the transcript towards the 3'-end. As transcript destabilization is reflected by varying protein amounts, we hypothesize that RNA decay represents another level in the complex methionine biosynthesis control network to adjust protein amounts to current metabolic requirements.

Based on these results, our current and future work focuses on the exploitation of T-box riboswitches as novel antibacterial targets, using RNA-mediated methionine biosynthesis control as a tool and proof of principle.



Organization of the *S. aureus* met operon (A) and function of the MET-T-box riboswitch as transcription control system in response to tRNA charge (B). Wencker *et al.*, 2021, NAR.

Image: Hilde Merkert

3.2
INSTITUTE FOR HYGIENE AND MICROBIOLOGY

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. Since 2021, the Institute is headed by Prof. Dr. Oliver Kurzai, who was appointed Chair 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.

MEDICAL MICROBIOLOGY AND MYCOLOGY

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SELECTED PUBLICATIONS

Barber AE, Sae-Ong T, Kang K, Seelbinder B, Li J, Walther G, Panagiotou G, **Kurzai O** (2021) *Aspergillus fumigatus pan-genome analysis identifies genetic variants associated with human infection*. **Nature Microbiology** 6(12):1526-1536

Aldejohann AM, Herz M, Martin R, Walther G, **Kurzai O** (2021) *Emergence of resistant Candida glabrata in Germany.* **JAC Antimicrobial Resistance** 3(3): dlab122

Wagner L, Stielow JB, de Hoog GS, Bensch K, Schwartze VU, Voigt K, Alastruey-Izquierdo A, **Kurzai O**, Walther G (2020) *A new species concept for the clinically relevant Mucor circinelloides complex*. **Persoonia** 44:67-97

AWARDS

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

RESEARCH INTERESTS

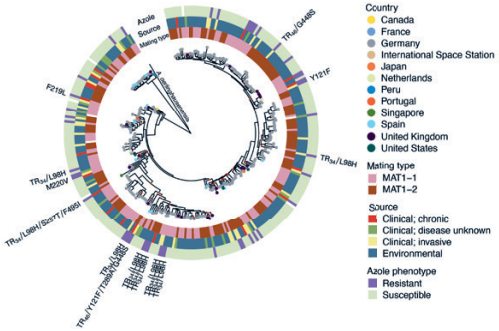
Invasive fungal infections in Europe are mainly caused by yeasts in the genus *Candida* and filamentous *Aspergillus* species. They primarily affect a growing number of immunocompromised patients and are associated with high mortality. Clinical management of fungal diseases is complex due to a growing 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

Aspergillus fumigatus is an important fungal pathogen, which causes more than 300,000 cases of invasive infections worldwide each year. In a large genome study, we analyzed a collection of 300 globally sampled genomes to define the pan-genome of *A. fumigatus*. Within this dataset we could unravel the genomic variation between clinical and environmental isolates and illuminate how genetic diversity contributes to virulence and antifungal drug resistance. Ultimately, these findings may point the way to possible new therapeutic approaches and an improved disease management.

Working towards a better management of invasive *Candida* infections, we performed susceptibility testing on *C. glabrata* isolates submitted to the NRZMyk (Head Prof. Dr. Oliver Kurzai). Almost half of the isolates tested for echinocandin susceptibility exhibited a resistant phenotype. However, for some isolates a distinct susceptible/resistant classification by the EUCAST breakpoint definition was not possible, prompting us to suggest the introduction of extended residual resistance testing in these cases. Additionally, some isolates exhibited a strong resistance phenotype without the presence of any target gene mutation, suggesting the presence of additional, yet unknown, resistance mechanisms.

By revisiting the taxonomy of the clinically relevant *Mucor circinelloides* complex, we could reveal a higher species diversity than described so far. The new species concept is based on the combination of multi-locus phylogeny and phenotypic studies and includes 14 discrete species, including five novel taxa. Importantly, these species showed clear differences in their antifungal susceptibility profiles.



Whole-genome phylogeny of environmental and clinical *A. fumigatus*.

HELMINTH INFECTIONS

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SELECTED PUBLICATIONS

Koike A, Becker F, Sennhenn P, Kim J, Zhang J, Hannus S, **Brehm K** (2022) *Targeting Echinococcus multilocularis PIM kinase for improving anti-parasitic chemotherapy.* **PLoS Neglected Tropical Diseases** 16(10):e0010483

Grimm J, Krickl J, Beck A, Nell J, Bergmann M, Tappe D, Grüner B, Barth TF, **Brehm K** (2021) *Establishing and evaluation of a polymerase chain reaction for the detection of Echinococcus multilocularis in human tissue.* **PLoS Neglected Tropical Diseases** 15(2):e0009155

Stoll K, Bergmann M, Spiliotis M, **Brehm K** (2021) *A MEKK1 - JNK mitogen activated kinase (MAPK) cascade module is active in Echinococcus multilocularis stem cells.* **PLoS Neglected Tropical Diseases** 15(12):e0010027

Nono JK, Lutz MB, **Brehm K** (2020) *Expansion of Host Regulatory T Cells by Secreted Products of the Tapeworm Echinococcus multilocularis.* **Frontiers in Immunology** 11:798

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.

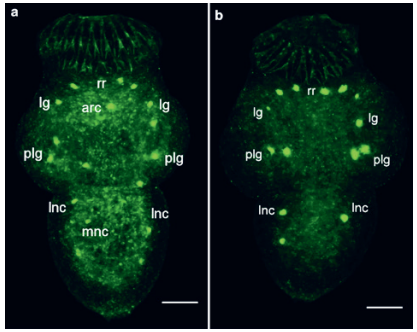
The group previously showed that parasite growth is decisively driven by totipotent somatic stem cells, and the proliferation dynamics of this cell population is at the focus of our research interests. The group also extensively studies parasite genomics/transcriptomics and engages in the development 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.



Whole mount *in situ* hybridization of *E. multilocularis* serotonin transporter sert (a) and tryptophane hydroxylase tph (b) expression in the protoscolex. Different ganglia of the nervous system are indicated.

MOLECULAR DIAGNOSTICS AND FUNCTIONAL GENOMICS OF HUMAN PATHOGENIC BACTERIA

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SELECTED PUBLICATIONS

Jiao C, Sharma S, Dugar G, Peeck NL, Bischler T, Wimmer F, Yu Y, Barquist L, **Schoen C**, Kurzai O, Sharma CM, Beisel CL (2021) *Noncanonical crRNAs derived from host transcripts enable multiplexable RNA detection by Cas9.* **Science** 372(6545):941-948

Bauriedl S, Gerovac M, Heidrich N, Bischler T, Barquist L, Vogel J, **Schoen C** (2020) *The minimal meningococcal ProQ protein has an intrinsic capacity for structure- based global RNA recognition.* **Nature Communications** 11(1):2823

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

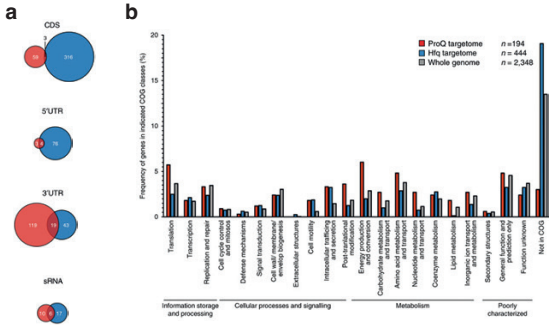
RESEARCH INTERESTS

The application of molecular techniques allows the rapid detection of pathogens 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. A special focus of our work in recent years is on the pathogenic role of small RNAs (sRNAs) and RNA-binding proteins (RBPs) in human-adapted pathogens.

HIGHLIGHTS & OUTLOOK

Neisseria meningitidis (Nm) is a human-adapted commensal pathogen and a worldwide leading cause of sepsis and epidemic meningitis. Its small genome of about 2 Mb encodes only a very limited number of RBPs like Hfq and ProQ. In contrast to the well-established role of Hfq, neither the physiological role nor possible *in vivo* RNA targets of ProQ have been investigated so far. Together with the group of Jörg Vogel (HIRI/IMIB) we used *in vivo* UV CLIP-seq and global gene expression profiling to draft a ProQ-RNA interaction landscape and analyse its functional overlap with the Hfq targetome. Surprisingly, we found that this comparatively small protein of about 120 amino acids is able to associate with 16 sRNAs and 166 mRNAs primarily at Rho-independent terminators (3'UTR in Figure a) and to affect the expression of more than 250 genes with diverse functions (Figure b). ProQ ensures that meningococci can better repair their DNA if damaged and it makes them resistant to oxidative stress. Both these factors contribute significantly to the bacteria's pathogenic properties (Bauriedl *et al.* 2020).

Another important class of RBPs is Cas9, which is a dual RNA-guided DNA endonuclease enzyme associated with the CRISPR system. CRISPR-Cas systems recognize foreign genetic material using CRISPR RNAs (crRNAs). In type II systems, a trans-activating crRNA (tracrRNA) hybridizes to crRNAs to drive their processing and utilization by Cas9. In collaboration with the groups of Cynthia Sharma (IMIB) and Chase Beisel (HIRI) we were involved in the development of a novel tracrRNA/Cas9-based molecular assay called LEOPARD. By engineering tracrRNA to function like crRNA guides, LEOPARD recognizes many target RNAs simultaneously and allows for the rapid multiplexed detection of pathogens. For example, LEOPARD allowed simultaneous detection of RNAs from different respiratory viruses in one test and distinguished SARS-CoV-2 and its variants with single-base resolution in patient samples (Jiao *et al.* 2021).



Comparison of binding locations (CDS, 5'UTR, 3'UTR, sRNA) (a) and functional profiles (b) for (m)RNAs that bind to ProQ (red) or Hfq (blue).

HOST-PATHOGEN INTERACTIONS

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PetersS,KaiserL,*et al.*,KleuserB,SeibelJ, **Schubert-Unkmeir A** (2021) *Click-correlative light and electron microscopy (click-AT-CLEM) for imaging and tracking azido- functionalized sphingolipids in bacteria.* **Scientific Reports** 11(1):4300

RESEARCH INTERESTS

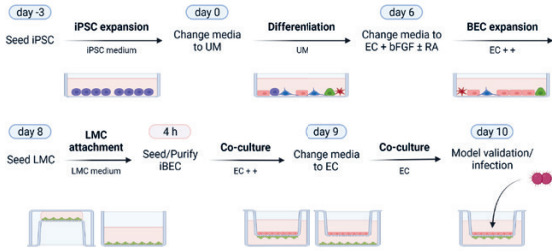
Neisseria meningitidis is a human-specific bacterium that can gain access to the central nervous system by crossing the meningeal blood-cerebrospinal fluid barrier (BCSFB). The group is interested in understanding the strategies used by *N. meningitidis* to colonize the brain vasculature and to cross this barrier. 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.

Recent work from our group showed that *N. meningitidis* can modulate the sphingolipid metabolism and hijack the sphingolipid balance in BECs to promote cellular adhesion as well as invasion. In addition, however, many of the naturally occurring and synthetic sphingolipids are also cytotoxic to cancer cells, and some are known to exert antibacterial activity against pathogenic microorganisms.

HIGHLIGHTS & OUTLOOK

We demonstrated that some sphingolipid metabolites may also serve as a first line of defense against *N. meningitidis* due to their antimicrobial activity. Based on our observation of growth-inhibiting effects of sphingolipid metabolites against *N. meningitidis*, we have begun to uncover the possible mechanism of their antimicrobial action. We were able to show that sphingolipids are incorporated into the outer membrane of the Gram-negative bacterium *N. meningitidis* and lead to its rupture. The development of azido-modified sphingolipids (developed by Prof. J. Seibel) provided us with drug candidates whose incorporation into bacteria could also be followed and visualized using correlative light and electron microscopy. The pre-embedding labeling used in this application allowed high-resolution localization of incorporated fluorescent labels throughout the ultrastructural background without labeling in the section (with Prof. C. Stigloher and Prof. M. Sauer).

Previous research on the interaction of *N. meningitidis* with the cerebral vasculature has mostly been performed with immortalized BECs that lack physiologically relevant barrier properties. We therefore continued our work within GRK 2157 and successfully developed an *in vitro* model of the meningeal BSCFB using pluripotent stem cell (iPSC)-derived BECs in co-culture with leptomeningeal cells from tumor biopsies. After validating the phenotype of the meningeal BCSFB (by TEER measurements, NaF permeability, and TEM), this model is now being used to study *N. meningitidis* infection.



Scheme of differentiation of iPSC-derived BECs and co-culture with leptomeningeal cells (Endres *et al.*, 2022, FBCNS).

INFECTION EPIDEMIOLOGY OF NEISSERIA MENINGITIDIS AND HOSPITAL INFECTION CONTROL

PROF. ULRICH VOGEL
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SELECTED PUBLICATIONS

Wagenhäuser I, Knies K, Rauschenberger V, Eisenmann M, McDonogh M, Petri N, Andres O, Flemming S, Gawlik M, Papsdorf M, Taurines R, Böhm H, Forster J, Weismann D, Weißbrich B, Dölken L, Liese J, Kurzai O, **Vogel U**, Krone M (2021) *Clinical performance evaluation of SARS-CoV-2 rapid antigen testing in point of care usage in comparison to RT-qPCR.* **EBioMedicine** 69:103455

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Krone M, Lâm TT, Claus H, **Vogel U** (2020) *Recurrent invasive meningococcal infections - quantifying the risk, Germany, 2002 to 2018.* **Euro Surveillance** 25(25):1900565

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

RESEARCH INTERESTS

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

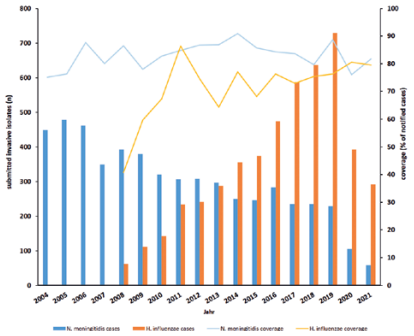
The infection control team of the University Hospital in Würzburg is involved in infection control projects, since 2020 also covering COVID-19.

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, and vaccines.

The reference laboratory since 2019 types all strains by genome-based methods in collaboration with the Core Unit Systems Medicine. A web-based database launched by our group on Jan 1, 2020, will be further developed. It will support data exchange with the RKI (Berlin), the ECDC (Stockholm), and the PubMLST database (Oxford).

The infection control team has focused its scientific activity on the management of COVID-19 in hospitals, utilizing data accumulated during the various waves of the pandemic.



Surveillance of invasive meningococcal and *H. influenzae* disease. Note the effects COVID-19 measures had on case numbers.

OBITUARY PROF. ULRICH VOGEL, MD 1964-2022:

A SCIENTIFIC MENTOR AND EXPERT IN INFECTION PREVENTION AND CONTROL

For copyright reasons, we refer you to the original version of this obituary published in Medical Microbiology and Immunology 2022 Nov 3:1-2. doi: 10.1007/s00430-022-00751-8.

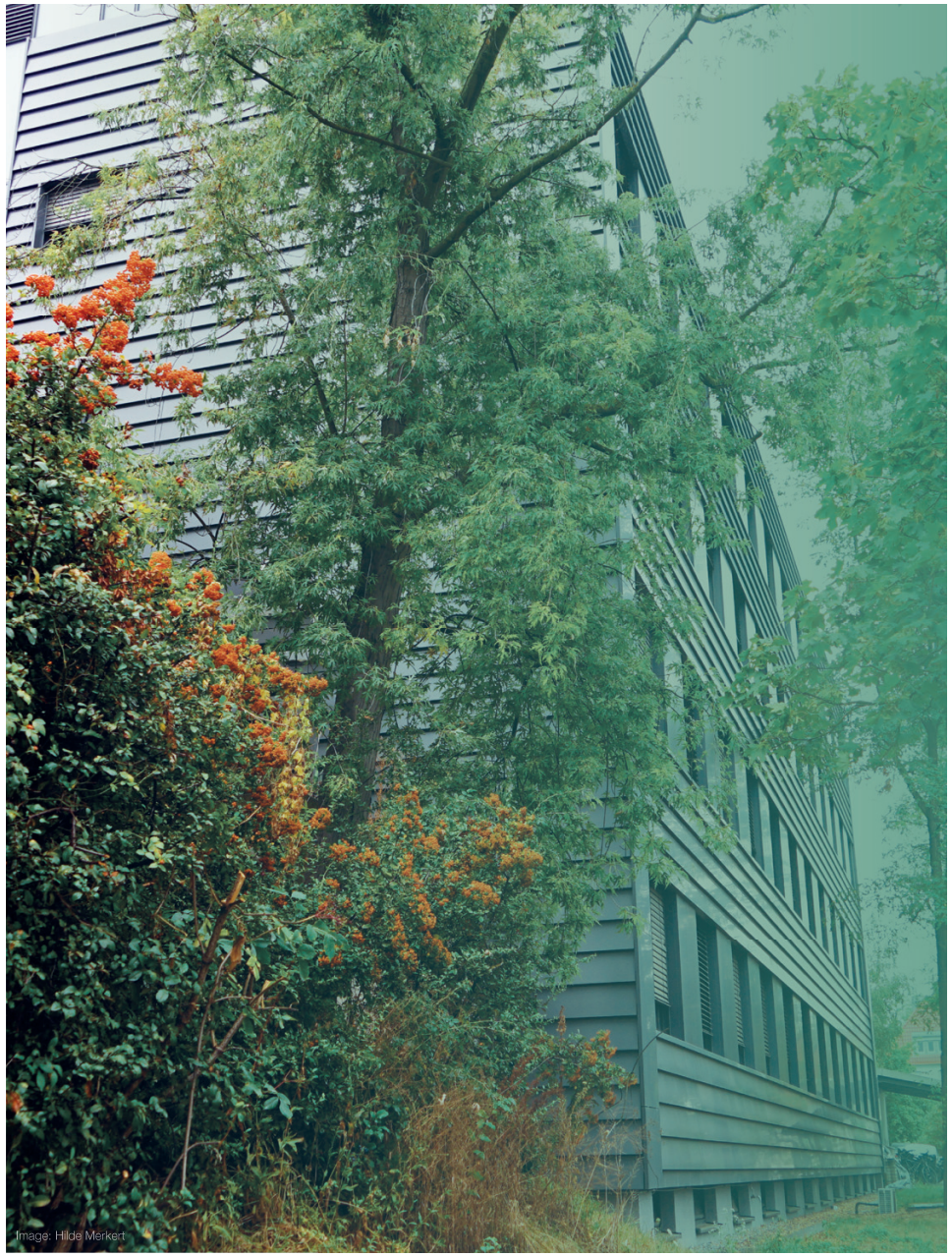


Image: Hilde Merkert

3.3
INSTITUTE FOR VIROLOGY AND IMMUNOBIOLOGY – DEPARTMENT OF VIROLOGY

LARS DÖLKEN

FLORIAN ERHARD

BHUPESH PRUSTY

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

Wang X, Hennig T, Whisnant AW, Erhard F, Prusty BK, Friedel CC, Forouzmand E, Hu W, Erber L, Chen Y, Sandri-Goldin RM, **Dölken L#**, Shi Y# (2020) *Herpes simplex virus blocks host transcription termination via the bimodal activities of ICP27.*
Nature Communications 11(1):293
#corresponding authors

Whisnant AW, Jürges CS, Hennig T, Wyler E, Prusty B, Rutkowski AJ, L'hernault A, *et al.*, 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
#corresponding authors

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

AWARDS

ERC Consolidator Grant 2022: *Deciphering cellular and viral determinants of lytic HSV-1 infection, latency and reactivation* (DecipherHSV)

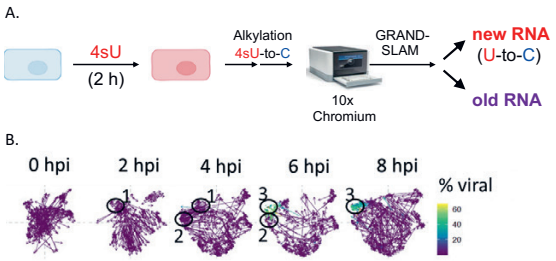
RESEARCH INTERESTS

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 (HIRI), we developed single cell SLAM-seq (scSLAM-seq) and pioneered this for 10x Chromium sequencing. 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 optimized for 10x Chromium sequencing. (B) Tracking SARS-CoV-2 infected human epithelial cells over time.

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
#corresponding authors

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

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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

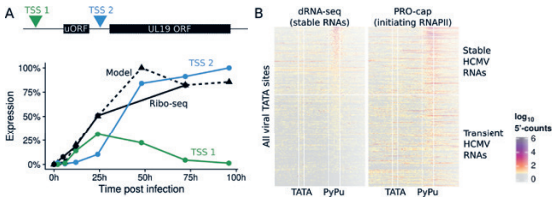
RESEARCH INTERESTS

Technologies such as next generation sequencing and mass spectrometry offer countless opportunities in systems biology research. We develop computational and statistical methods and tools for analyzing such "omics" data, with a special interest in single cell and temporal resolution as well as the estimation of statistical uncertainty in quantitative parameters. By leveraging these approaches and developing mathematical models for their integrative analyses in various herpesvirus models, we study the mechanisms by which viruses take over or modulate their host cells and evade immune responses. We believe that technological advances accompanied by new computational methods will pave the way towards understanding complex systems such as virus infection.

HIGHLIGHTS & OUTLOOK

Metabolic RNA labeling provides elegant means to analyze the temporal transcriptome dynamics in bulk or single cells but requires sophisticated computational methods. Our GRAND-SLAM approach accurately quantifies newly transcribed and pre-existing RNA. Based on GRAND-SLAM we developed tools to improve read mapping of metabolic labeling data, to model gene expression kinetics, to dissect transcriptional/post-transcriptional gene regulation and to infer temporal single cell trajectories. Employing these tools, we demonstrated that the antiviral protein ZAP slows down Human cytomegalovirus (CMV) infection by specifically binding to and destabilizing mRNAs from the UL4/5 gene locus early in infection (with the Brinkmann and Munschauer labs). Furthermore, these tools coupled to new integrative mathematical modeling approaches showed that acute SPT6 depletion results in global processivity, elongation and termination defects of RNA polymerase II (RNAPII; with the Wolf lab).

Several labs studied the complexity of human CMV gene expression and identified >700 gene products, >7,000 sites of initiating RNAPII and complex temporal patterns of protein expression. We combined metabolic RNA labeling with transcription start site profiling to dissect the transcriptomic landscape throughout infection. We integrated all available data to establish a unifying model of CMV gene expression. Most notably, we found pervasive expression of transient RNA as a common feature of the virus with its human host and that the temporal dynamics of protein expression is governed by multiple promoters with distinct activity patterns throughout infection, which is a conserved feature of human, rhesus and murine CMV.



A. CMV gene expression is governed by multiple promoters. B. Only ~42% of all transcription initiation events in the CMV genome generate stable RNAs.

MEDICAL MICROBIOLOGY AND MYCOLOGY

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SELECTED PUBLICATIONS

Hennig T, Prusty AB, Kaufer BB, Whisnant AW, Lodha M, Enders A, Thomas J, Kasimir F, Grothey A, Klein T, Herb S, Jürges C, Sauer M, Fischer U, Rudel T, Meister G, Erhard F, Dölken L[#], **Prusty BK[#]** (2022) *Selective inhibition of miRNA processing by a herpesvirus-encoded miRNA.*
Nature 605(7910):539-544
[#]corresponding authors

Whisnant AW, Jürges CS, Hennig T, Wyler E, **Prusty BK**, 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

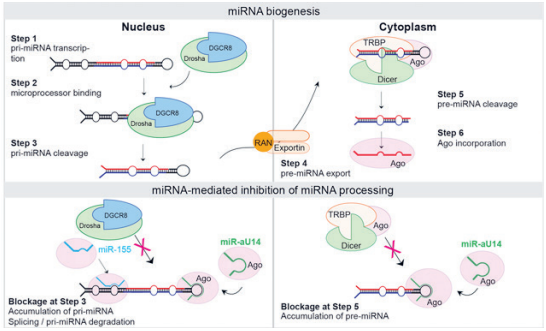
Rajeeve K, Das S, **Prusty BK**, Rudel T (2018) *Chlamydia trachomatis paralyses neutrophils to evade the host innate immune response.*
Nature Microbiology 3(7):824-835

RESEARCH INTERESTS

Human herpesviruses (HHVs) are large DNA viruses that often acquire lifelong latency. HHV-6 (both A and B) are prevalent betaherpesviruses. While primary infection is subclinical and self-limiting, virus reactivation is associated with several types of neuronal disorders, cardiac dysfunction, graft rejection. HHV-6 and HHV-7 are unique amongst the nine HHVs as they integrate into the telomeric region of chromosomes from where they can reactivate using the host cell telomeric loop machinery. Up to 1% of healthy individuals carry chromosomally integrated genetically inherited HHV-6 in all cells that is vertically transmitted in a Mendelian manner. A central focus of our research is how HHV-6 latency and reactivation are governed by intrinsic (e.g., viral miRNAs) and extrinsic (other pathogenic infections) factors or stimuli. Our research also focusses on understanding host-virus crosstalk during herpesvirus reactivation from single cell to organism level.

HIGHLIGHTS & OUTLOOK

HHV-6 reactivation is heterogenous in nature. We elucidated the unique characteristics of HHV-6 genome that was excised from the host DNA through the telomeric circle formation. To understand complexities of viral reactivation, we have developed a high-throughput cell-culture based model wherein viral reactivation results in the expression of GFP or RFP from the excised viral genome upon virus reactivation. This HHV-6 reactivation model has helped in the reliable screening of drugs and other triggers for viral reactivation, thereby serving as a key tool in several clinical research studies. We have shown that the key feature of viral reactivation was not the expression of bulk of the viral proteins, but rather the expression of viral small non-coding RNAs including miRNAs associated with enhanced mitochondrial fission. Recently we have shown that ectopic expression of HHV-6A miR-aU14 triggers extensive mitochondrial fission and interferes with the induction of type I interferons via both the RIG-I and cGAS pathway. Deletion of miR-aU14 from the HHV-6A genome abrogated the ability of the virus to reactivate from latency. Transfection of miR-aU14 into cells harboring latent HHV-6A genomes triggered mitochondrial fission and virus reactivation. These findings unravel the molecular mechanism of miR-aU14-induced HHV-6 re-activation from latency. Furthermore, we have identified miRNA-mediated inhibition of miRNA processing as a so far unknown cellular mechanism that HHV-6 learned to usurp to govern virus latency and reactivation.



Schematics showing mechanism of regulation of miRNA processing by other miRNAs through direct RNA:RNA interaction.

MORBILLIVIRUS PATHOGENESIS

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SELECTED PUBLICATIONS

Wiese T, Dennstädt F, Hollmann C, Stonawski S, Wurst C, Fink J, Gorte E, Mandasari P, Domschke K, Hommers L, Vanhove B, Seibel J, Rohr J, Buttmann M, Menke A, **Schneider-Schaulies J**, Beyersdorf N (2021) *Inhibition of acid sphingomyelinase increases regulatory T cells in humans.*
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Frontiers in Cell and Developmental biology 7:218

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Frontiers in Immunology 10:2363

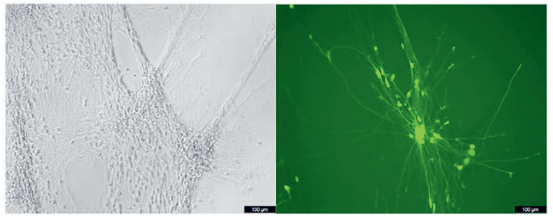
RESEARCH INTERESTS

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, and now also due to the SARS-CoV-2 pandemic, vaccination is not sufficiently applied in many countries and the numbers of measles cases is expected to increase. An antiviral therapy is urgently needed.

HIGHLIGHTS & OUTLOOK

We are using cultures of primary human peripheral blood mononuclear cells (PBMCs), human NTera-2 pluripotent stem cells differentiated to neurons (NT2-N cells), and post-mitotic neurons derived from Lund human mesencephalic (LUHMES) cell as model systems for MV infections of lymphocytes and neurons. Thereby, persistently infected postmitotic neurons 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. Combinations of inhibitors of host functions and the viral polymerase are being investigated to achieve virus elimination from persistently infected cells.



In vitro differentiated LUHMES neurons infected with recombinant wild-type measles virus expressing green fluorescent protein (strain MV-IC323-eGFP). (Foto by Julia Thoma, bachelor thesis, 2021).

VIRAL IMMUNOMODULATION

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SELECTED PUBLICATIONS

De Lira MN, Janaki Raman S, Schulze A, **Schneider-Schaulies S**, Avota E (2020) *Neutral sphingomyelinase-2 (NSM 2) controls T cell metabolic homeostasis and reprogramming during activation.* **Frontiers in Molecular Biosciences** 7:217

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Börtlein C, Draeger A, Schoenauer R, Kuhlemann A, Sauer M, **Schneider-Schaulies S**, Avota E (2018) *The Neutral Sphingomyelinase 2 Is Required to Polarize and Sustain T Cell Receptor Signaling.* **Frontiers in Immunology** 9:815

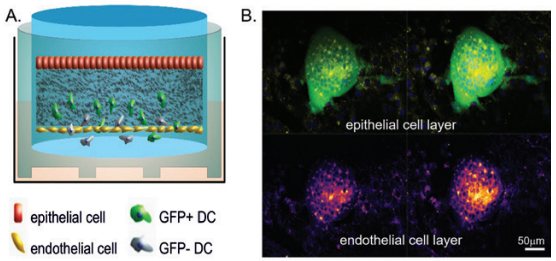
RESEARCH INTERESTS

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 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 and dendritic cells.

HIGHLIGHTS & OUTLOOK

MV interactions with the T cell surface efficiently induce T cell silencing. Dynamic changes of membrane lipid composition, specifically sphingolipid metabolites, were found to be crucial in this process. As a result of sphingomyelin breakdown catalyzed by sphingomyelinases, membrane microdomains are formed that act to segregate receptors and associated signalosomes and thereby regulate cellular signaling. MV interaction mediated activation of the neutral sphingomyelinase (NSM) was found to essentially account inhibition of actin cytoskeletal dynamics, an important parameter of T cell silencing. We also observed that NSM activity dampens overshooting T cell responses also under physiologic conditions, as revealed by elevated metabolic activity and an accelerated early response to co-stimulation in NSM2 ablated T cells. However, NSM2 deficient cells fails to support sustainment of T cell signaling and activation, as determined by inefficient polarization, dynamics, and stability of microtubules, metabolic reprogramming and directional motility. 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 analyses, and high resolution microscopy.



(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).

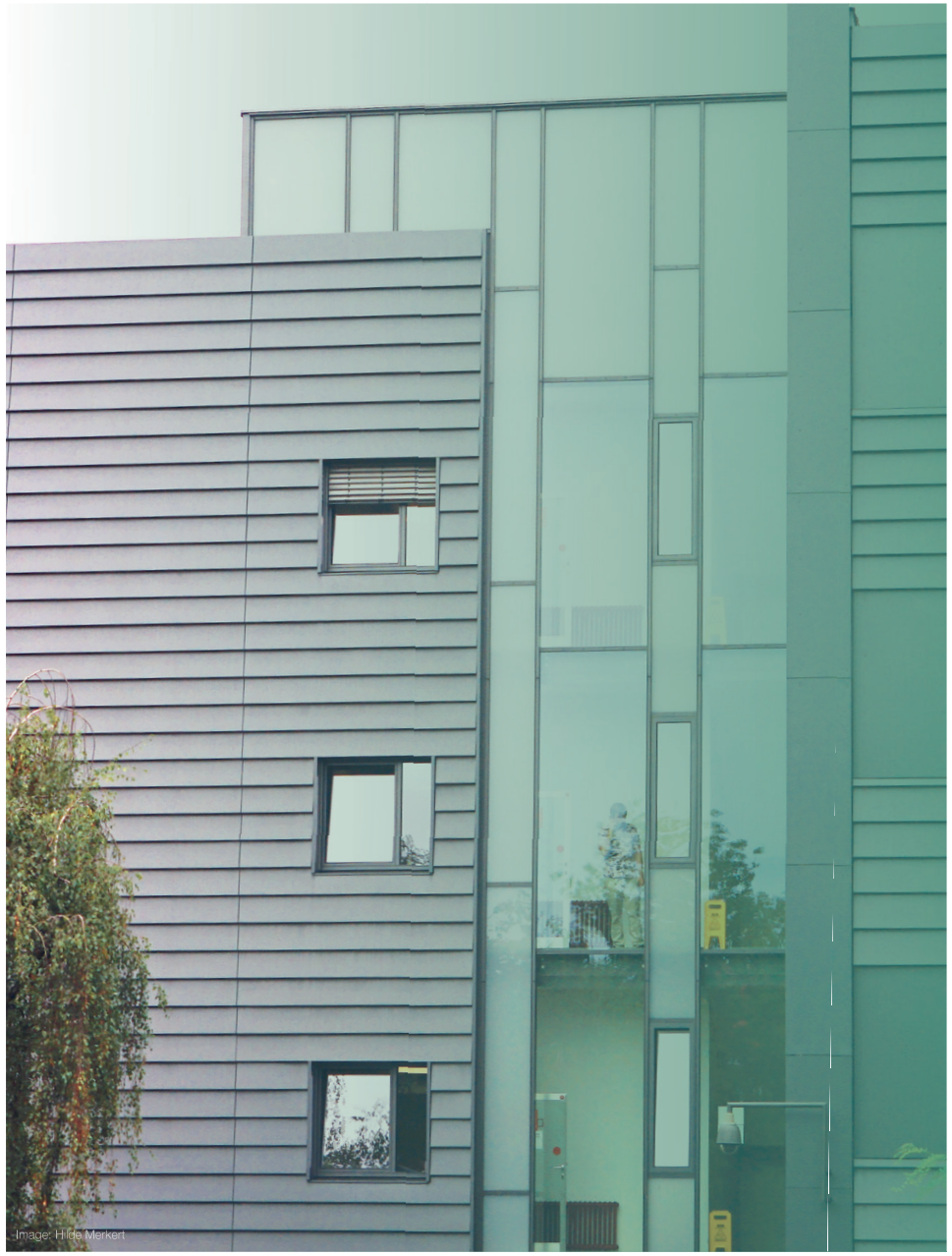


Image: Hilde Merkert

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, Knöpper K, Cruz de Casas P, Ugur M, Eickhoff S, Zou M, Shaikh H, Trivedi A, Grafen A, Yang T, Prinz I, Ohlsen K, Gomez de Agüero M, Beilhack A, Huehn J, Gaya M, Saliba AE, Gasteiger G, **Kastenmüller W** (2022) *Lymphatic migration of unconventional T cells promotes site-specific immunity in distinct lymph nodes.* **Immunity** 55(10):1813-1828.e9

Dähling S, Mansilla AM, Knöpper K, Grafen A, Utzschneider DT, Ugur M, Whitney PG, Bachem A, Arampatzi P, Imdahl F, Kaisho T, Zehn D, Klauschen F, Garbi N, Kallies A, Saliba AE, Gasteiger G, Bedoui S, **Kastenmüller W** (2022) *Type 1 conventional dendritic cells maintain and guide the differentiation of precursors of exhausted T cells in distinct cellular niches.* **Immunity** 55(4):656-670.e8

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** 21(11):1397-1407

RESEARCH INTERESTS

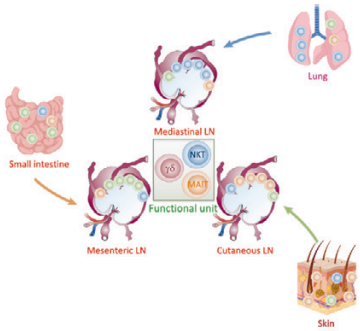
A central aspect of the cellular elements of the immune system is their capacity to rapidly migrate between and within organs. The group aims to understand the mechanistic basis of leukocyte migration and how the interaction between cells is orchestrated in order to mount an effective immune response. 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.

HIGHLIGHTS & OUTLOOK

Lymph nodes (LNs) function as immunological filters for lymph borne pathogens. Lymphatic transport of molecules and migration of myeloid cells to LNs are fundamental in this process as they continuously inform lymphocytes on changes in the drained tissues. In this project we asked whether other cell types besides dendritic cells (cDC) migrate via the lymph. We focused on unconventional T cells (UTC).

We recently showed that these tissue-derived UTC migrate via the lymphatic route to locally draining LNs similar to cDC. Because each tissue harbors a distinct spectrum of UTC with locally adapted differentiation states and distinct TCR repertoires, every draining LN is thus populated by a distinctive tissue-determined mix of these lymphocytes. On a functional level, we found that UTC cooperate in inter-connected units and generate and shape characteristic innate and adaptive immune responses that differ between LNs that drain distinct tissues. Lymphatic migration of UTC is therefore a key determinant of site-specific immunity initiated in distinct LNs with potential implications for vaccination strategies and immunotherapeutic approaches.

The figure schematically illustrates that different lymph nodes mount characteristic immune responses that are linked to the drained tissue. Unconventional T cells continuously colonize local draining lymph nodes due to their newly discovered lymphatic migration pattern. Since these T cells differ in their TCR repertoire and effector differentiation state between tissues, also the associated lymph nodes harbor a distinct set of these T cells that shape a characteristic immune response.



Different lymph nodes mount characteristic immune responses (LN = lymph nodes).

T CELL BIOLOGY

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SELECTED PUBLICATIONS

Haack S, Baiker S, Schlegel J, Sauer M, Sparwasser T, Langenhorst D, **Beyersdorf N** (2021) *Superagonistic CD28 stimulation induces IFN-γ release from mouse T helper 1 cells in vitro and in vivo.* **European Journal of Immunology** 51(3):738-741

Wiese T, Dennstädt F, Hollmann C, Stonawski S, Wurst C, Fink J, Gorte E, Mandasari P, Domschke K, Hommers L, Vanhove B, Schumacher F, Kleuser B, Seibel J, Rohr J, Buttmann M, Menke A, Schneider-Schaulies J*, **Beyersdorf N*** (2021) *Inhibition of acid sphingomyelinase increases regulatory T cells in humans.* **Brain Communications** 3(2):fcab020
*corresponding authors

Zenke S, Palm MM, Braun J, Gavrilov A, Meiser P, Böttcher JP, **Beyersdorf N**, Ehl S, Gerard A, Lämmermann T, Schumacher TN, Beltman JB, Rohr JC (2020) *Quorum Regulation via Nested Antagonistic Feedback Circuits Mediated by the Receptors CD28 and CTLA-4 Confers Robustness to T Cell Population Dynamics.* **Immunity** 52(2):313-327.e7

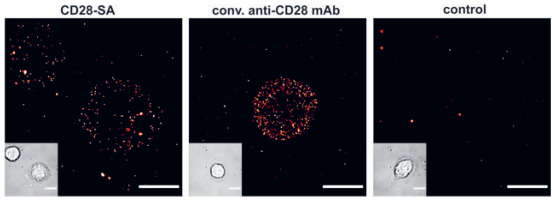
RESEARCH INTERESTS

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. The 'success' of measles virus is due to its high degree of infectivity and to its capacity to evade immunity by suppressing T cell responses. This means that the generation of key players of anti-viral immunity, i.e. $CD4^+$ T helper 1 cells (Th1), is hampered by measles virus. Here, our recent finding that fully differentiated Th1 cells rely on sensing 'danger' through the costimulatory receptor CD28 on the T cell surface offers novel opportunities to tackle viral immune escape. Using different formats of monoclonal antibodies (mAb) against CD28 we observed that CD28 is organized in microclusters on the surface of Th1 cells (Figure). The differential binding of superagonistic and conventional anti-CD28 mAb to these microclusters suggests that they are also functionally heterogeneous.

Apart from viruses, human pathogenic fungi like *Candida albicans* and *Aspergillus fumigatus* have also evolved strategies to evade the immune response. *C. albicans* and *A. fumigatus* secrete a number of immune evasion proteins which interfere with a crucial component of innate immunity, i.e. the complement system. In a long-standing collaboration with Prof. Peter Zipfel's group at the Hans Knöll Leibniz Institute in Jena we could not only describe novel modes of action of these fungal immune evasion proteins, but also develop mAb against the immune evasion proteins. These mAb ('FungiMAB') have shown beneficial effects in a mouse model of invasive *C. albicans* infection and will be further developed for therapeutic and diagnostic purposes in humans.



*d*STORM: Superagonistic (CD28-SA) and conventional anti-CD28 mAb binding to Th1 cells. Published in Haack *et al.*, 2020, European Journal of Immunology.

IMMUNOGENETICS

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SELECTED PUBLICATIONS

Herrmann T, Karunakaran MM (2022) *Butyrophilins: γδ T Cell Receptor Ligands, Immunomodulators and More.* **Frontiers in Immunology** 13:876493

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, *et al.*, 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

Herrmann T, Karunakaran MM, Fichtner AS (2020) *A glance over the fence: Using phylogeny and species comparison for a better understanding of antigen recognition by human γδ T-cells.* **Immunological Reviews** 298(1):218-236

RESEARCH INTERESTS

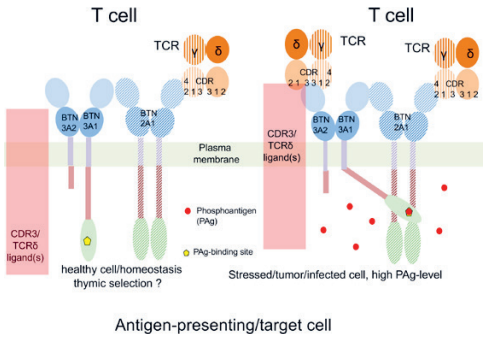
Vγ9Vδ2 T cells are effectors with anti-microbial and anti-tumor activity. Their eponymous Vγ9Vδ2 T-cell antigen-receptor recognizes phosphoantigens (PAg) accumulated in tumor or host cells. The PAg (E)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate (HMBPP) is found in many eubacteria and in apicomplexa 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 aminobisphosphophonates (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, PD-L1). 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. We identified the alpaca (*Vicugna pacos*) as the first non-primate species with functional Vγ9Vδ2 T cells, whose single BTN3A molecule merges functions of the three human BTN3s (Fichtner *et al.*, 2020). We are now analyzing how the protein domains of BTN3A molecules steer function and cooperation with other BTN3A molecules and with BTN2A1.

BTN2A1 was identified 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 bind 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.

Another new task will be the analysis of the immunomodulatory function of BTN-molecules and BTN-specific antibodies with emphasis of reconstitution of T cell responses by BTN-specific monoclonal antibodies and commonly used drugs such as the aminobisphosphonate Zoledronate (Herrmann and Karunakaran, 2022).



Vγ9Vδ T cell activation: BTN2A1 binds CDR4 of Vγ9 of TCR (left). PAg binding to BTN3A1 exposes ligand(s) to other CDRs (right). (Herrmann & Karunakaran, 2022).

IMMUNE REGULATION

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SELECTED PUBLICATIONS

Eckert I, Ribechini E, **Lutz MB** (2021) *In Vitro Generation of Murine Myeloid-Derived Suppressor Cells, Analysis of Markers, Developmental Commitment, and Function.* **Methods in Molecular Biology** 2236:99-114

Eckert IN, Ribechini E, Jarick KJ, Strozniak S, Potter SJ, Beilhack A, **Lutz MB** (2021) *VLA-1 Binding to Collagen IV Controls Effector T Cell Suppression by Myeloid-Derived Suppressor Cells in the Splenic Red Pulp.* **Frontiers in Immunology** 11:616531

Nono JK, **Lutz MB**, Brehm K (2020) *Expansion of Host Regulatory T Cells by Secreted Products of the Tapeworm Echinococcus multilocularis.* **Frontiers in Immunology** 11:798

RESEARCH INTERESTS

Most of our typical pathogenic microbes have developed immune evasion strategies. We are investigating how different pathogens manipulate dendritic cells (DCs) and myeloid-derived suppressor cells (MDSCs) by activating their immune tolerance via regulatory T cells and suppressive mechanisms.

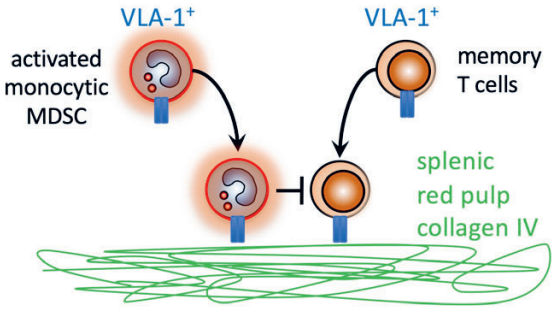
HIGHLIGHTS & OUTLOOK

While the detrimental role of MDSCs in mouse models and human patients with tumors or chronic infections has been widely demonstrated, it remains unclear how these cells are generated, which markers uniquely characterize them, and where and how immune suppression takes place *in vivo*.

We worked experimentally and by meta-analyzing on the identification of novel and characteristic surface structures of MDSCs. Our meta-analysis allowed the identification of most common transcriptional signatures of murine and human granulocytic and monocytic MDSC subsets. Experimental work on cell surface proteomic studies of the monocytic subset of murine MDSCs (M-MDSCs) revealed new markers that are currently investigated for their MDSC suppressor function.

In-vivo MDSCs have been identified mostly in the infected organs or the spleen where they are known to suppress T cell responses. It remains however, unknown how MDSCs are directed into these organs and which molecules mediate homing and adhesion and at which anatomical site. Previously, we found in mice that M-MDSCs migrate from the bridging channel areas into the white pulp to kill dendritic cells, thereby indirectly inhibiting naive T cell priming. Now we found that antigen-experienced T cells that migrate through the red pulp meet with M-MDSCs on collagen IV as a substrate through their expression of the VLA-1 integrin on both cell types. The common expression of this homing receptor is required to mediate T cell suppression.

In collaboration with Klaus Brehm's group, we identified a molecule within the group of excretory/secretory products of the fox tapeworm *Echinococcus multilocularis* that expanded and activated host Foxp3+ regulatory T cells after injection into mice. This novel molecule showed structural and functional similarities with the mammalian TGF-beta/activin family member activin A and was termed EmACT. Our data indicate that the tape worm secreted EmACT to generate a tolerogenic environment to undermine the host immune response.



Activated M-MDSCs and memory T cells upregulate the VLA-1 binding collagen IV in the murine splenic red pulp, allowing cell-cell contacts and resulting in T cell suppression.

3.5

DEPARTMENT OF MICROBIOLOGY, THEODOR BOVERI INSTITUTE, BIOCENTER

THOMAS RUDEL

CINDRILLA CHUMDURI

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

Stelzner K, Boyny A, Hertlein T, Sroka A, Moldovan A, Paprotka K, Kessie D, Mehling H, Potempa J, Ohlsen K, Fraunholz MJ, **Rudel T** (2021) *Intracellular Staphylococcus aureus employs the cysteine protease staphopain A to induce host cell death in epithelial cells.*
PLoS Pathogens 17(9):e1009874

Auer D, Hügelschäffer SD, Fischer AB, **Rudel T** (2020) *The chlamydial deubiquitinase Cdu1 supports recruitment of Golgi vesicles to the inclusion.*
Cell Microbiology 22(5):e13136

Rajeeve K, Vollmuth N, Janaki-Raman S, Wulff TF, Baluapuri A, Dejure FR, Huber C, Fink J, Schmalhofer M, Schmitz W, Sivadasan R, Eilers M, Wolf E, Eisenreich W, Schulze A, Seibel J, **Rudel T** (2020) *Reprogramming of host glutamine metabolism during Chlamydia trachomatis infection and its key role in peptidoglycan synthesis.*
Nature Microbiology 5(11):1390-1402

RESEARCH INTERESTS

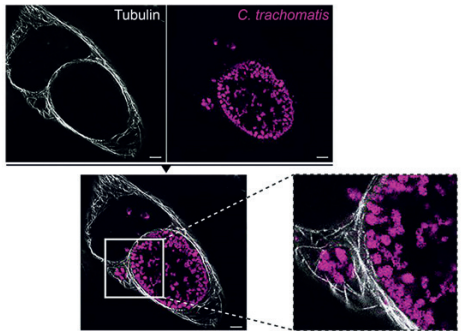
The group investigates pathogenicity mechanisms of the major human pathogens *Chlamydia*, *Neisseria gonorrhoeae*, and *Staphylococcus aureus*. Furthermore, there is a focus on the impact of bacterial infection on human diseases such as cancer.

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*), (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.



HeLa229 cells (labelled for tubulin) infected with *C. trachomatis* (anti-cHSP60, magenta) after 4× expansion microscopy, fixation, and permeabilization. Scale bar, 10 µm.

INFECTIONS AND CANCER BIOLOGY

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SELECTED PUBLICATIONS

Koster S, Gurumurthy RK, Kumar N, Prakash PG, Dhanraj J, Bayer S, Berger H, Kurian SM, Drabkina M, Mollenkopf H-J, Goosmann C, Brinkmann V, Nagel Z, Mangler M, Meyer TF, **Chumduri C** (2022) *Chlamydia coinfection inhibits HPV-induced safeguards of the cellular and genomic integrity in patient-derived ectocervical organoids.*
Nature Communications 13(1):1030

Chumduri C*, Gurumurthy RK*, Berger H, Dietrich O, Kumar N, *et al.*, Drabkina M, Arampatzi P, Son D, Klemm U, Mollenkopf HJ, Herbst H, Mangler M, Vogel J, Sallba AE, Meyer TF (2021) *Opposing Wnt signals regulate cervical squamocolumnar homeostasis and emergence of metaplasia.*
Nature Cell Biology 23(2):184-197
*equally contributing authors

Mi Y, Gurumurthy RK, Zadora PK, Meyer TF, **Chumduri C** (2018) *Chlamydia trachomatis promotes non-homologous end joining by modulating ATM signaling via protein phosphatase 2A.*
mBio 9(6):e01465-18

AWARDS

Start up Funding, University of Würzburg (2020)

RESEARCH INTERESTS

Metaplasia, prevalent in multiple organs, is an adaptive behavior of the tissue to withstand chronic stress such as deficient diet, acids, or smoking. Strikingly, metaplastic niches promote microbial evolution and increased pathogen colonization and cancer development; however, the underlying mechanisms remain enigmatic.

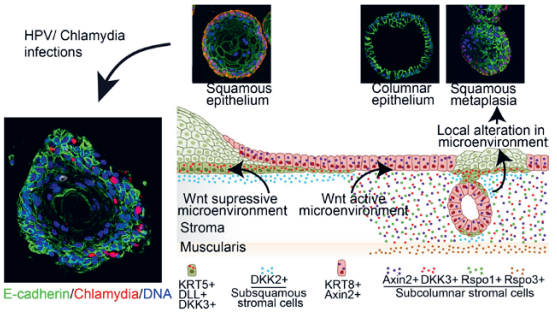
My group aims to understand the co-evolution of the host and pathogens and their interactions during metaplasia and cancer cascade. As a model system, we focus on squamocolumnar epithelial transition zones that are hot spots of metaplasia, infections, and cancers. My lab develops and applies patient- and mouse-derived 3D-organoid and *in-vivo* models to study host-pathogen cross-talks, tissue homeostasis, and model disease development. We adopt state-of-the-art technologies, including single-cell omics and spatial analysis of transcripts and proteins to decipher molecular cross-talks involved in pathogenesis.

HIGHLIGHTS & OUTLOOK

My recent seminal work provided comprehensive insights into uterine cervix homeostasis and mechanisms driving precancerous squamous metaplasia, a favorable niche for HPV and *Chlamydia* infections. We provided a complete single-cell atlas of healthy endo-ectocervix and squamous metaplastic tissues. We found that Wnt signaling from stroma is critical for maintaining the endo-ectocervical epithelial border homeostasis. Its perturbations induced by extrinsic factors like diet remodels the stromal cells promoting metaplasia development.

We pioneered long-term culture conditions for patient and mouse stem cell-derived 3D stratified ecto- and columnar endocervical organoids to study infections and carcinogenesis in authentic preclinical settings. Further, our established conditions to genetically manipulate the organoids opened avenues for addressing basic and translational research questions.

Utilizing this powerful development, we show the hazards of sequential infections with HPV and *Chlamydia* and the unique cellular microenvironment they create. Strikingly, *Chlamydia* impedes HPV-induced mechanisms that maintain cellular and genome integrity, including mismatch repair in the stem cells, thus potentially contributing to mutagenesis of the host genome. Our current and future research will focus on developing near-physiological complex 3D *in-vitro* models and investigate the host-pathogen interaction in driving pathogen colonization, persistence, and cancer development at metaplastic sites.



Model depicting squamocolumnar transition zone homeostasis and precancer metaplasia development driving pathogen colonization and carcinogenesis.

CELLULAR MICROBIOLOGY

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SELECTED PUBLICATIONS

Stelzner K, Boyny A, Hertlein T, Sroka A, Moldovan A, Paprotka K, Kessie D, Mehling H, Potempa J, Ohlsen K, **Fraunholz MJ**, Rudel T (2021) *Intracellular Staphylococcus aureus employs the cysteine protease staphopain A to induce host cell death in epithelial cells.* **PLoS Pathogens** 17(9):e1009874

Krones D, Rühling M, Becker KA, Kunz TC, Sehl C, Paprotka K, Gulbins E, **Fraunholz MJ** (2021) *Staphylococcus aureus α-Toxin Induces Acid Sphingomyelinase Release From a Human Endothelial Cell Line.* **Frontiers in Microbiology** 12:694489

Groma M, Horst SA, Das S, Huettel B, Klepsch M, Rudel T, Medina E, **Fraunholz MJ** (2020) *Identification of a Novel LysR-Type Transcriptional Regulator in Staphylococcus aureus That Is Crucial for Secondary Tissue Colonization during Metastatic Bloodstream Infection.* **mBio** 11(4):e01646-20

RESEARCH INTERESTS

During infections, *Staphylococcus aureus* is taken up by phagocytes, which remove a majority of the bacteria. However, some bacteria may persist in the host either by neutralizing host immune strategies or by hiding inside tissue cells. In the latter case, *S. aureus* often escapes from endocytic vesicles and replicates in the cytoplasm eventually killing host cells. Bacterial effectors and host factors as well as the underlying molecular mechanisms are still largely unknown. The research group aims to identify bacterial virulence factors as well as potential host pathways involved in *S. aureus* infections.

HIGHLIGHTS & OUTLOOK

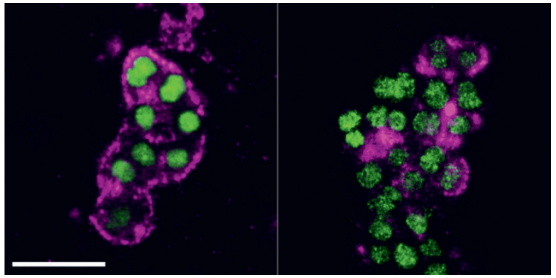
We identified a LysR-type transcriptional regulator in *S. aureus*, which is required to establish host infections specifically in kidneys or bones but is dispensable for liver infections. Since its regulon was unknown, we induced the production of the regulator and sequenced the transcriptome. We further demonstrated that transcription factor activity is repressed by glucose and requires copper. Our results thereby hint at metabolic adaptation of the pathogen in different host infection niches.

Once *S. aureus* is internalized by tissue cells, it can escape from its endocytic vesicles. Once in the host cytoplasm, *S. aureus* perturbs intracellular calcium levels, replicates and host cells die. We demonstrated that host cell death of cytoplasmic *S. aureus* requires the bacterial cysteine protease staphopain A, the targets of which are however unknown.

Extracellular *S. aureus* further uses one of its pore-forming toxins, α-toxin, to induce calcium influx into host cell membranes. Permeabilized membranes are repaired by a mechanism involving endocyctosis of damaged membranes, as well as recruitment of membrane repair enzymes such as lysosomal acid sphingomyelinase. Thus, the host cell uses a conserved repair mechanism already described for other toxins to reseal membranes damaged by staphylococcal α-toxin.

We further applied Expansion microscopy (ExM) to *S. aureus*-infected cells. ExM circumvents the diffraction limitation of classical microscopy techniques by swelling the sample. Therein, the rigidity of the staphylococcal cell wall was overcome by application of specific proteases and now enables us to image host-pathogen interactions with four-fold higher resolution.

We also investigate *S. aureus* virulence regulation by a long non-coding RNA, which we had previously identified to be an important factor in staphylococcal infections.



Expanded *S. aureus* (green). Left: in LAMP1-decorated vesicles (magenta). Right: associated with LC3-positive membranes (magenta). Scale bar: 10 µm.

PERTUSSIS

PROF. ROY GROSS

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SELECTED PUBLICATIONS

Kessie DK, Lodes N, Oberwinkler H, Goldman WE, Walles T, Steinke M, **Gross R** (2021) *Activity of Tracheal Cytotoxin of Bordetella pertussis in a Human Tracheobronchial 3D Tissue Model.* **Frontiers in Cellular and Infection Microbiology** 10:614994

Tragust S, Herrmann C, Häfner J, Braasch R, Tilgen C, Hoock M, Milidakis MA, **Gross R**, Feldhaar H (2020) *Formicine ants swallow their highly acidic poison for gut microbial selection and control.* **eLife** 9:e60287

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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

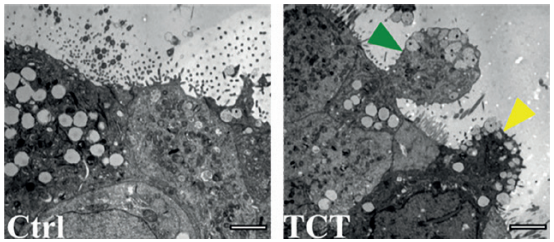
RESEARCH INTERESTS

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

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#corresponding authors

Koch RD, Hörner EM, Münch N, Maier E, **Kozjak-Pavlovic V** (2020) *Modulation of Host Cell Death and Lysis Are Required for the Release of Simkania negevensis.* **Frontiers in Cellular and Infection Microbiology** 10:594932

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

RESEARCH INTERESTS

We investigate 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, as well as ubiquitin-modifying enzymes in infection, focusing on the intracellular pathogen *Simkania negevensis*.

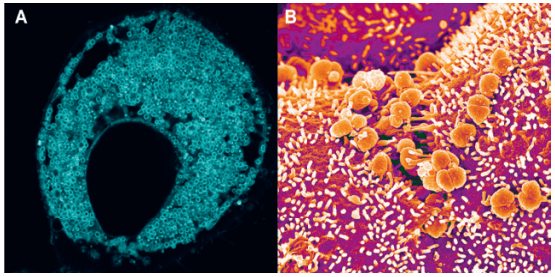
N. gonorrhoeae is an obligate human pathogen that causes gonorrhea. Neutrophils are the first responders during gonococcal infection. However, *N. gonorrhoeae* can survive the neutrophil attack, using them as a Trojan horse for spreading from the primary infection site.

S. negevensis is a *Chlamydia*-related obligate intracellular pathogen connected to pulmonary infections. The *S. negevensis* vacuole forms close contacts with the ER and mitochondria and depends on host cell lipids for development, which is why these bacteria are a good model for investigating 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. To study gonococcal infection in close-to-natural conditions, we have generated 3D tissue models using different epithelial cell lines and improved them by addition of endothelial cells and neutrophils. Newly, a collaboration with the University Hospital Würzburg and Fraunhofer ISC enabled us to develop a 3D model of peritoneum, as well as to test already established cornea models in infection research. We continued exploring *S. negevensis* infection by studying the sphingolipid involvement, as well as the role of ubiquitin-modifying enzymes these bacteria express. In addition, we adapted expansion microscopy and lipid staining using click chemistry for studying the structure of mitochondria and bacterial inclusion.

Our aims are to use advanced 3D tissue models to study interaction of bacteria with host cells, bacterial transmigration, and, after addition of neutrophils, the fate of gonococci upon contact with the cells of the immune system. The connection between mitochondria, sphingolipids, ubiquitylation, and *S. negevensis* remains in our focus. For this, we are currently working on procedures that will enable us to genetically modify *S. negevensis*, which will be the first time this has been accomplished so far.



(A) *S. negevensis* in HeLa cell – ceramide staining/4x expansion microscopy. (B) SEM of a *N. gonorrhoeae* infection of a 3D model of endometrium.

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

Seif M, Kakoschke TK, Ebel F, Bellet MM, Trinks N, Renga G, Pariano M, Romani L, Tappe B, Espie D, Donnadieu E, Hünniger K, Häder A, Sauer M, Damotte D, Alifano M, White PL, Backx M, Nerreter T, Machwirth M, Kurzai O, Prommersberger S, **Einsele H**, Hudecek M, Loeffler J (2022) *CAR T cells targeting Aspergillus fumigatus are effective at treating invasive pulmonary aspergillosis in preclinical models.* **Science Translational Medicine** 14(664):eabh1209

Einsele H, Kraus S (2021) *Genetic risk of CMV reactivation?* **Blood** 138(17):1516-1517

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

AWARDS

Bavarian Order of Merit (Bayerischer Verfassungsorden, 2022)

Erasmus Hematology Awards (2022)

RESEARCH INTERESTS

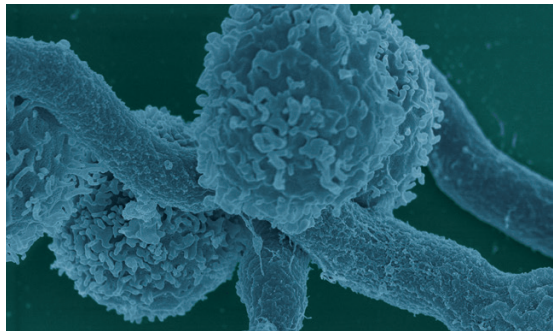
I) Invasive fungal infections (IFI) are a major threat worldwide. They are associated with unacceptably high mortality rates ranging from 30-90% and have been estimated to kill about one and a half million people every year globally. Despite this, their diagnosis is often delayed or even overlooked. IFI are no longer limited to well-defined high-risk patient cohorts but also include patients with chronic obstructive lung disease as well as patients suffering from severe influenza infections, cytomegalovirus, or COVID-19. Options for antifungal therapy are limited and mainly rely on only three classes of antifungals. In addition, we are faced with increasing antifungal drug resistance.

II) 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. CMVs are notorious for their ability to manipulate large parts the host immune system, in particular CD8 T cells as well as NK cells, by multiple hierarchically ordered mechanisms. The discovery of hundreds of new and nonconventional CMV gene products by novel high-throughput technologies indicates that viral immune modulation may be substantially more sophisticated than previously thought. At the same time, the respective viral proteins may also represent a large source of hitherto unappreciated peptide antigens for CD8+ T cells.

HIGHLIGHTS & OUTLOOK

I) We aim to obtain a comprehensive insight into interaction networks of fungal pathogens with their human host, and identify potential new targets and tools for improved diagnostics and treatment. We focus on the polymorphic yeast *Candida albicans* and the filamentous fungus *Aspergillus fumigatus* because they are by far the most important causes of life-threatening invasive mycoses in Europe.

II) An overarching objective is to close major gaps of knowledge about the immunological function of CMV gene products and their role in host immune system-pathogen interaction. In particular, we aim to understand the molecular interactions of CMV-infected cells (incl. antigen-presenting cells (APCs)) with T and NK cells at molecular, cellular, and organism level.



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

EXPERIMENTAL STEM CELL TRANSPLANTATION

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SELECTED PUBLICATIONS

Sueiro-Olivares M, Scott J, Gago S, Petrovic D, Kouroussis E, Zivanovic J, Yu Y, Strobel M, Cunha C, Thomson D, Fortune-Grant R, Thusek S, Bowyer P, Carvalho A, **Beilhack A**, Bignell E, Filipovic MR, Amich J (2021) *Fungal and host protein persulfidation are functionally correlated and govern fungal virulence and host antifungal potency.* **PLoS Biology** 19(6):e3001247

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Amich J, Mokhtari Z, Strobel M, Vialetto E, Sheta D, Yu Y, *et al.*, Krappmann S, Einsele H, Heinze KG, **Beilhack A** (2020) *3D light sheet fluorescence microscopy of lungs to dissect local host immune – Aspergillus fumigatus interactions.* **mBio** 11(1):e02752-19

AWARDS

EBMT Basic Science Award (2021)

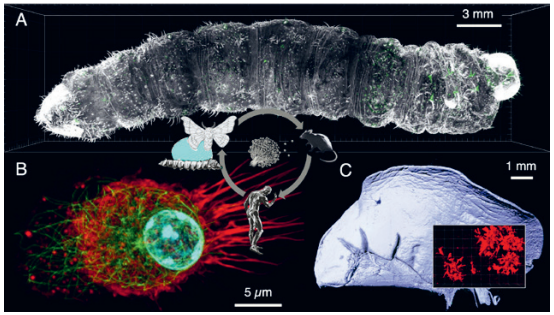
IMW Young Investigator Award (2021)

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 infections, cancer and inflammatory diseases. The fungus *Aspergillus fumigatus* can cause life-threatening fungal infections after allogeneic hematopoietic cell transplantation or in other situations of a perturbed immune system. Increasing fungal resistance mechanisms to antimycotics, 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 examine the interplay of host-pathogen interactions under *in vivo* conditions to develop novel therapies.

HIGHLIGHTS & OUTLOOK

To define host determinants of fungal infection and the pathogen-host interplay we employ *in vitro* and *in vivo* insect, mouse, and human models. 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 silkworms (*Bombyx mori*), mice, or human patient samples. 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 TRR124 FungiNet, we are investigating dynamic immune-pathogen interactions *in vivo*. As members of the DFG GRK 2157 3D Infect, we combine microscopy techniques as well as mouse and human 3D tissue 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. Recently we have expanded our endeavor to silkworms as an invertebrate model to investigate host-pathogen interactions and novel antifungal strategies. Combining basic research with our close ties to the clinics we aim to advance diagnostic and therapeutic strategies for patients suffering from acute and chronic opportunistic infections.



Silkworm-, mouse- and human models to examine (A) *A. fumigatus* (green) silkworm infection (B) alveolar macrophages (with U. Terpitz) and (C) mouse lung lobe after *A. fumigatus* infection (insert: red).

DIVISION OF INFECTIOUS DISEASES

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SELECTED PUBLICATIONS

Isberner N, Aghai F, Schirmer D, Kraus S, Grigoleit GU, **Klinker H** (2020) *Quantification of letermovir in human serum using high-performance liquid chromatography with diode array detection.* **Journal of Chromatography** 1159: 122399

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AWARDS

"Top Mediziner" in Germany for infectious diseases in the ranking of the "Focus" magazine (2020, 2021, 2022)

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).

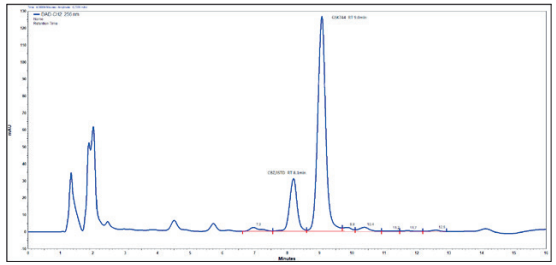
HIGHLIGHTS & OUTLOOK

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 different HIV-therapeutics during antiretroviral therapy in patients with HIV infection. A new method is currently being developed for the determination and quantification of cabotegravir, the first long-acting HIV integrase strand transfer inhibitor. 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 cabotegravir (GSK744, concentration 2.700 ng/ml). CBZ = carbamazepine = internal standard)

IMMUNITY AGAINST ASPERGILLUS SPP.

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SELECTED PUBLICATIONS

Seif M, Kakoschke TK, Ebel F, Bellet MM, Trinks N, Renga G, Pariano M, Romani L, Tappe B, Espie D, Donnadieu E, Hünniger K, Häder A, Sauer M, Damotte D, Alifano M, White PL, Backx M, Nerreter T, Machwirth M, Kurzai O, Prommersberger S, Einsele H, Hudecek M, **Loeffler J** (2022) *CAR T cells targeting Aspergillus fumigatus are effective at treating invasive pulmonary aspergillosis in preclinical models.* **Science Translational Medicine** 14(664):eabh1209

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Seelbinder B, Wallstabe J, Marischen L, Weiss E, Wurster S, Page L, Löffler C, Bussemer L, Schmitt A, Wolf T, Becker J, Kalinke U, Vogel J, Panagiotou G, Einsele H, Westermann A, Schäuble S, **Loeffler J** (2020) *Triple RNA-Seq Reveals Synergy in a Human Virus-Fungus Co-infection Model.* **Cell Reports** 33:108389

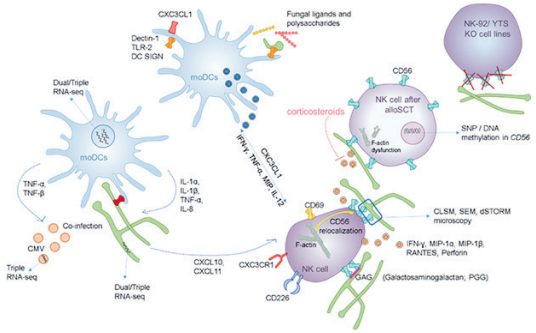
RESEARCH INTERESTS

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

We focus on immune recognition of AF, patients' genetic susceptibility to AF, and the molecular diagnosis of invasive fungal infections. We have shown TLR2-, TLR4-, and dectin-1-dependent activation of DCs by AF and that NK cells interact with and recognize AF via the NK cell receptor CD56 resulting in the release of Th1-like cytokines and fungal killing. We successfully identified the CD56 ligand on the fungal cell wall and could demonstrate effects of this polysaccharide to CD56 and its downstream pathway. Using live cell imaging and *d*STORM 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.

Our group extensively studies the role of chimeric antigen receptors (CAR) for antigens of AF on NK and T cells, and functionally characterizes PBMC and NK cells isolated from patients after allogeneic SCT during their *ex vivo* interaction with fungal pathogens. In parallel, we study the interaction of AF with other pathogens of the lung, focusing on CMV. Using dual and triple 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 CD226 as immune receptor on NK cells using CRISPR-Cas technology. We will also strive to better understand the pathophysiology of *Mucorales* infections. We have led several clinical studies on the diagnosis of fungal infections, and are actively contributing 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 I 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

Friedrich C, Taggenbrock RLRE, Doucet-Ladevèze R, Golda G, Moenius R, Arampatzi P, Kragten NAM, Kreymborg K, Gomez de Agüero M, Kastenmüller W, Saliba AE, Grün D, van Gisbergen KPJM, **Gasteiger G** (2021) *Effector differentiation downstream of lineage commitment in ILC1s is driven by Hobit across tissues.*
Nature Immunology 22(10):1256-1267

Bielecki P, Riesenfeld SJ, Hütter J-C, *et al.*, Tao L, Kedaigle AJ, Steach HR, York AG, Skadow MH, Yaghoubi P, Dionne D, Jarret A, McGee HM, Porter CBM, Licona-Limón P, Bailis W, Jackson RP, Gagliani N, **Gasteiger G**, Locksley RM, Regev A, Flavell RA (2021) *Skin-resident innate lymphoid cells converge on a pathogenic effector state.*
Nature 592(7852):128-132

Zeis P, Lian M, Fan X, Herman JS, Hernandez DC, Gentek R, Elias S, Symowski C, Knöpper K, Peltokangas N, Friedrich C, Doucet-Ladeveze R, Kabat AM, Locksley RM, Voehringer D, Bajenoff M, Rudensky AY, Romagnani C, Grün D[#], **Gasteiger G[#]** (2020) *In situ maturation and tissue adaptation of type 2 innate lymphoid cell progenitors.*
Immunity 53(4):775-792.e9
[#]corresponding authors

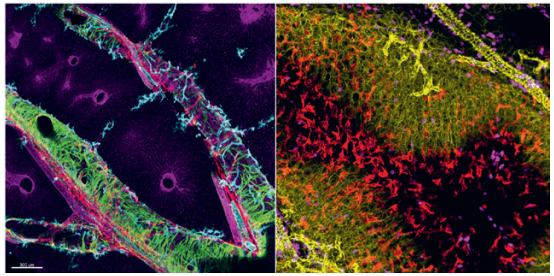
RESEARCH INTERESTS

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 frontline defense to infection, 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 further identified tissue-associated ILC progenitors that enable the local differentiation, tissue-specific imprinting, and specialization of ILCs. Studying how effector function is regulated in the tissue, we identified ILC1 subsets characterized by a “stem-like” expansion potential. The transcription factor Hobit is required for the differentiation of these cells into cytotoxic effectors. Our findings provide a novel conceptual framework that connects tissue-specific phenotypes of ILC1s along a uniform differentiation pathway. Currently, we are investigating how these mechanisms determine local host-pathogen interactions in tissue-specific microenvironments.

With support of the ERC, we are investigating differentiation of tissue-resident memory T cells in the context of a pathogen-experienced immune system, mimicking the “real-world” encounter of frequent human pathogens. In our quest to understand the local networks of tissue lymphocytes, we are employing genetic mouse models, experimental models of inflammatory diseases, tumors, and infection, and combine these with multiplexed microscopy, and single-cell and spatial sequencing to map the functional tissue architecture and cellular interactions that regulate tissue-immunity. In different projects we study the skin, lung, female reproductive tract, liver and salivary gland, which all represent clinically relevant infection niches. We further analyze human tissue samples to perform cross-species analyses and validations.



Tissue Niches of Immune Cells: Overview of liver lobuli and large vessels on the left, and, on the right side, a zoom-in highlighting tissue-resident macrophages (red) and T cells (violet).

HOST-MICROBIAL INTERACTIONS

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SELECTED PUBLICATIONS

Shmeleva EV, **Gomez de Agüero M**, Wagner J, Enright AJ, Macpherson AJ, Ferguson BJ, Smith GL (2022) *Smallpox vaccination induces a substantial increase in commensal skin bacteria that promote pathology and enhance immunity.*
PLoS Pathogens 18(4):e1009854

Feuerstein R, Forde AJ, Lohrmann F, Kolter J, Ramirez NJ, Zimmermann J, **Gomez de Agüero M**, Henneke P (2020) *Resident macrophages acquire innate immune memory in staphylococcal skin infection.*
eLife 9:e55602

Uchimura Y, Fuhrer T, Li H. Lawson M, Zimmermann M, Yilmaz B, Zindel J, Ronchi F, Sorribas M, Hapfelmeier S, Ganal-Vonarburg S, **Gomez de Agüero M**, McCoy KD, Sauer U, Macperson AJ (2018) *Antibodies set boundaries limiting microbial metabolite penetration and the resultant mamalian host reponse.*
Immunity 49(3):545-559

AWARDS

Best abstract presentation in *World of Microbiome Symposium: Pregnancy, birth and infancy* (2020)

RESEARCH INTERESTS

At birth, mammalian barrier tissues get colonized by trillions of microorganisms, which collectively form the commensal microbiota. This is the major supplier of metabolites involved in essential processes for the host, such as energy stockage and training of the mammalian immunity.

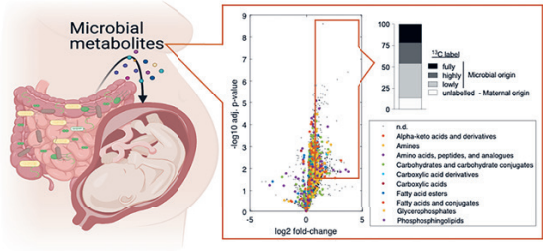
Recently, we and others have defined a critical window early in life for the microbiota to shape the immune system. Our previous work revealed the pivotal role of the microbiota during pregnancy and lactation for the development of the intestinal immune system. Indeed, maternal microbial-derived metabolites reach the offspring during the gestation and the lactation and shape the intestinal immunity to prepare the newborn for the challenges of birth.

The focus of our lab is to understand the crosstalk of the microbiota and its products with host cellular networks. Specifically, we try to elucidate which and how specific molecules mediate the effects of the microbiota on a mechanistic level. Functionally, we focus on the role of microbial derived metabolites on physiology and development.

HIGHLIGHTS & OUTLOOK

We use a sophisticated gnotobiotic research model based on an auxotrophic *E. coli* strain for exclusive gestational colonization with sterile offspring. Flow cytometry, histology, single cell RNA sequencing, and metabolic analysis of the perinatal skin allowed us to show that maternal microbiota shapes the development of the skin through the regulation of gene expression of epidermal stem cells. Thus, the differentiation of the keratinocytes to a more mature or specialized stage is impaired in the absence of maternal microbial signals. Unbiased metabolic analysis showed that circa 350 metabolites accumulate in the neonatal skin upon microbial exposure of the mothers. About 75% of them have a microbial origin, such as tryptophane, nicotinamide, essential amino acids, and vitamin B6 and derivates. Using our murine model and cyst-based organoid model, we have shown that carriers and receptors of these metabolites are enhanced in the epidermal stem cells. Consequently, neonatal permeability barrier and its regeneration is enhanced by gestational colonization.

Current projects investigate the impact of maternal microbiota and its metabolites on promoting the proper development of the skin barrier in newborns to prevent infections, autoimmune diseases, and allergy.



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

Hochrein SM, Wu H, Eckstein E, Arrigoni L, Herman JS, Schumacher F, Gerecke C, Rosenfeldt M, Grün D, Kleuser B, Gasteiger G, Kastenmüller W, Ghesquière B, Van den Bossche J, Abel DE, **Vaeth M** (2022) *The glucose transporter GLUT3 controls T helper 17 cell responses through glycolytic-epigenetic reprogramming.*
Cell Metabolism 34(4):516-532.e11

Wu H, Brand B, Eckstein M, Hochrein SM, Shumanska M, Dudek J, Nickel A, Maack C, Bogeski I, **Vaeth M** (2021) *Genetic ablation of the mitochondrial calcium uniporter (MCU) does not impair T cell-mediated immunity in vivo.*
Frontiers in Pharmacology 12:734078

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 21(11):1397-1407

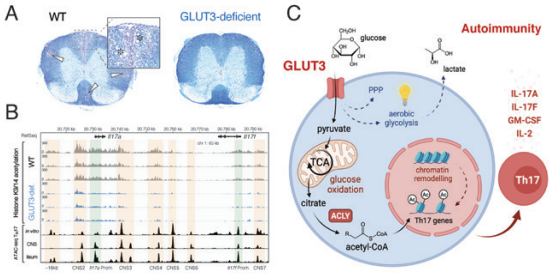
RESEARCH INTERESTS

Immunological tolerance is the 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 tolerance and immunity with a particular focus on the metabolic programming of lymphocytes. Over the last decades, it became clear that immunometabolism is not solely important to provide energy for the clonal expansion and effector function of lymphocytes, but also controls the epigenetic programming of immune cells. A deeper understanding of the metabolic-epigenetic regulatory circuits promises new therapeutic avenues to treat immune-related pathologies, such as infection, cancer, and autoimmunity.

HIGHLIGHTS & OUTLOOK

Immune responses to different types of pathogens are guided by specific T helper (Th) cells. Th17 cells are essential for the protection against extracellular bacteria and pathogenic fungi. Th17 cells not only produce their 'signature' cytokine IL-17 but also other inflammatory factors, which promote the influx of neutrophils and monocytes to the site of infection, thus orchestrating the clearance of the pathogens. However, sustained tissue inflammation can also initiate immunopathology, such as autoimmune diseases. One project in our laboratory investigates the metabolic control of Th17 differentiation, effector function, and memory formation in various tissue environments.

We showed that T cell activation increases the expression of SLC2A hexose transporters (GLUTs) to ensure sufficient glucose supply for the clonal expansion and effector differentiation of T cells. However, complete abrogation of glucose metabolism prevents the activation and effector function of T cells, thus bearing the risk of opportunistic infections. By contrast, ablation of GLUT3 does not interfere with Th17 cell activation and proliferation but affects selectively the expression of pro-inflammatory cytokines. Metabolomic and transcriptomic analyses linked GLUT3-dependent glucose metabolism to the generation of mitochondrial acetyl-CoA. The decrease in acetyl-CoA in GLUT3-deficient T cells causes an altered site-specific histone acetylation at the promoter regions of multiple effector cytokines. Based on the notion that glucose metabolism acts as a rheostat of T cell-mediated inflammation, we aim to dissect the transcriptional and epigenetic consequences and the specific glycolytic requirements of Th17 cells as a novel treatment strategy for inflammatory diseases.



GLUT3 controls autoimmune encephalomyelitis (A) through histone acetylation at the IL-17 gene locus (B) and glycolytic-epigenetic reprogramming of Th17 cells (C).

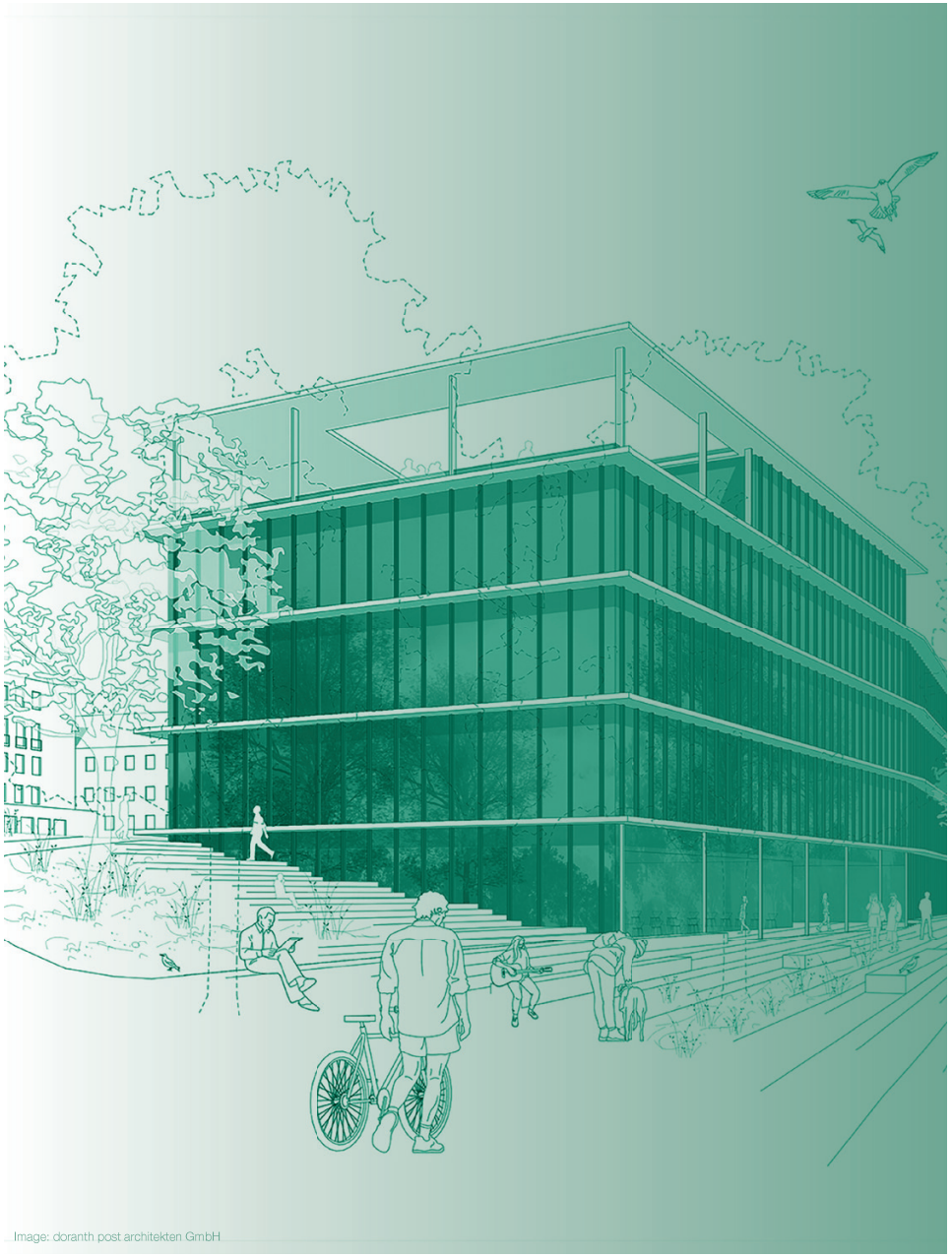


Image: doranth post architekten GmbH

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 Prof. Dr. 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

Popella L, Jung J, Popova K, Đurica-Mitić S, **Barquist L**[#], Vogel J[#] (2021) *Global RNA profiles show target selectivity and physiological effects of peptide-delivered antisense antibiotics.*
Nucleic Acids Research 49(8):4705-4724
[#]corresponding authors

Mika-Gospodorz B, Giengkam S, Westermann AJ, Wongsantichon J, Kion-Crosby W, Chuenklin S, Wang LC, Sunyakumthorn P, Sobota RM, Subbian S, 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 11(1):3363
[#]corresponding authors

Cain AK, **Barquist L**, Goodman AL, Paulsen IT, Parkhill J, van Opijnen T (2020) *A decade of advances in transposon-insertion sequencing.*
Nature Reviews Genetics 21(9):526-540

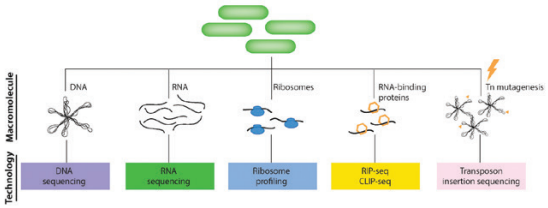
RESEARCH INTERESTS

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, Sharma S, Svensson SL, Kibe A, Weinberg Z, Alkhnbashi OS, Bischler T, Backofen R, Caliskan N, Sharma CM, **Beisel CL** (2022) *Spacer prioritization in CRISPR-Cas9 immunity is enabled by the leader RNA.*
Nature Microbiology 7(4):530-541

Wimmer F, Mougiakos I, Englert F, **Beisel CL** (2022) *Rapid cell-free characterization of multi-subunit CRISPR effectors and transposons.*
Molecular Cell 82(6):1210-1224.e6

Jiao C, Sharma S, Dugar G, Peeck NL, Bischler T, Wimmer F, Yu Y, Barquist L, Schoen C, Kurzai O, Sharma CM[#], **Beisel CL**[#] (2021) *Noncanonical crRNAs derived from host transcripts enable multiplexable RNA detection by Cas9.*
Science 372(6545):941-948
[#]corresponding authors

AWARDS

Pettenkofer Prize (2022)

Falling Walls Science Breakthroughs of the Year, Winner Life Sciences (2021)

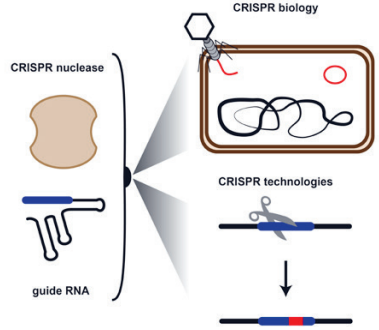
RESEARCH INTERESTS

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 and viral pathogens.

HIGHLIGHTS & OUTLOOK

The past two years brought important discoveries and advances for my research program. Through an ongoing collaboration with Cynthia Sharma's group, we showed that CRISPR RNAs could be derived from cellular transcripts unrelated to CRISPR-Cas systems and translated this discovery into a platform for multiplexed RNA detection. We are now working to commercialize this technology through the creation of a biotech start-up. Separately, through collaborations with multiple ZINF groups, we discovered that the leader region upstream of CRISPR arrays can promote the processing of the first CRISPR RNA, prioritizing defense against the most recently encountered invader.

Another important discovery came when assessing the impact of targeting endogenous transcripts with the RNA-targeting CRISPR nuclease Cas13a. There, we found that transcripts needed to be expressed above a certain threshold to drive an immune response, allowing the cells to ignore some self-targets as well as more benign invaders. Finally, we made numerous advances applying cell-free transcription-translation (TXTL) systems to characterize CRISPR-Cas systems. One important advance was applying TXTL to characterize multi-subunit CRISPR effectors, including those from Type I CRISPR-Cas systems, the most abundant and diverse type found in nature, as well as CRISPR transposons that have been co-opted for the DNA insertion. Going forward, we will continue exploring the diversity of CRISPR-Cas systems and looking to translate discoveries into new and improved technologies.



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

RECODING MECHANISMS IN INFECTIONS

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SELECTED PUBLICATIONS

Pekarek L, Zimmer MM, Gribling AS, Buck S, Smyth R#, **Caliskan N#** (2022) *Cis-mediated interactions of the SARS-CoV-2 frameshift RNA alter its conformations and affect the function.* **Nucleic Acid Research** 51(2):728-743
#corresponding authors

Zimmer MM, Kibe A, Rand U, Pekarek L, Ye L, Buck S, Smyth RP, Cicin-Sain L, **Caliskan N** (2021) *The short isoform of the host antiviral protein ZAP acts as an inhibitor of SARS-CoV-2 programmed ribosomal frameshifting.* **Nature Communications** 12(1):7193

Hill CH#, Pekarek L, Napthine S, *et al.*, Graham SC#, **Caliskan N#**, Brierley I# (2021) *Structural and molecular basis for Cardiovirus 2A protein as a viral gene expression switch.* **Nature Communications** 12(1):7166
#corresponding authors

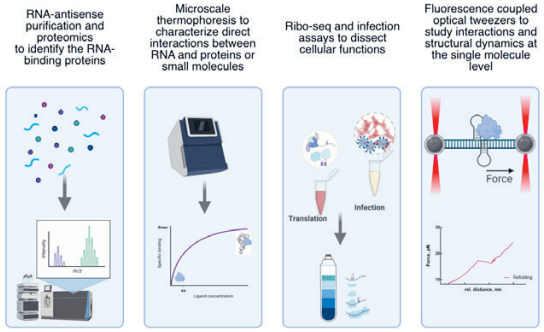
AWARDS

Zonta Wissenschaftspreis, International Zonta Club, Germany (2021)

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

RESEARCH INTERESTS

The coding regions of certain genes contain RNA signals that allow translation from alternative reading frames through recoding. One recoding strategy widely used by RNA viruses is programmed ribosome frameshifting. How recoding RNA elements are regulated during infections is still poorly understood. A detailed understanding of recoding events can aid the development of novel RNA-based therapeutic interventions. My research group investigates the functions and dynamics of RNA elements and regulators that drive these alternative translation events. We employ single-molecule techniques and complementary global cell-based analysis tools. We work with several single-stranded viruses including Corona and Retroviruses that are known to depend on recoding strategies for their replication. Our unparalleled approach recently allowed us to shed light onto viral frameshifting mechanisms, and identify novel regulatory interaction partners of the coronavirus frameshift element, which impact the way viral polyproteins are produced, and decrease SARS-CoV-2 propagation by more than 20-fold. We have recently leveraged this fundamental research to identify a novel natural compound that inhibits Coronavirus replication. We are now building on this molecular perspective to understand host-pathogen interactions by performing targeted CRISPR-Cas screens, ribosome profiling and RNA structural analysis on various models, including SARS-CoV-2, HIV-1 and HCV. We have great hope that we will be able to 'translate' the insights gained from these studies into novel antivirals.



Strategy to identify and explore the frameshift RNA interaction partners.

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.
- Using cutting-edge confocal assisted optical tweezers, we discovered that binding of the trans-acting protein ZAP-S to the frameshift stimulatory element of SARS-CoV leads to decrease in PRF & infectivity.
- 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 SARS-CoV-2 mRNA. This can be a promising therapeutic strategy to interfere with viral replication.

DECODING RNA-PROTEIN INTERACTOMES OF REGULATORY RNA IN INFECTION

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SELECTED PUBLICATIONS

Schmidt N, Lareau C, *et al.*, Dölken L, Lander ES, Caliskan N, Fischer U, Vogel J, Carr S, Bodem J#, **Munschauer M#** (2021) *The SARS-CoV-2 RNA-protein interactome in infected human cells.* **Nature Microbiology** 6(3):339-353
#corresponding authors

Basak A*, **Munschauer M***, Lareau CA, *et al.*, Mohandas N, Carr SA, Chen JJ, Orkin SH, Lander ES, Sankaran VG (2020) *Control of human hemoglobin switching by LIN28B-mediated regulation of BCL11A translation.* **Nature Genetics** 52:138–145
*equally contributing authors

Munschauer M#, Nguyen CT, Sirokman K, *et al.*, 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.
#corresponding authors

AWARDS

ERC Starting Grant on the topic: *Interrogating RNA-protein interactions underlying SARS-CoV-2 infection and antiviral defense* (2022)

RESEARCH INTERESTS

Many pathogenic human viruses utilize RNA both as their replicated genetic material and as their template for translating viral proteins. Ongoing research into RNA viruses has largely focused on understanding the functions and interactions of their encoded proteins.

However, little is known about viral RNAs and their regulation by host factors, impacting our ability to target viral RNA metabolism when developing the next generation of antivirals. To address this knowledge gap, the group is taking a powerful RNA-centric approach that for the first time enables the systematic characterization of the molecular interactions of viral RNA with the host cell proteome during viral infections. The group's overarching goal is to decode how RNA-protein interactions between virus and host shape the viral RNA life cycle and host defense mechanisms.

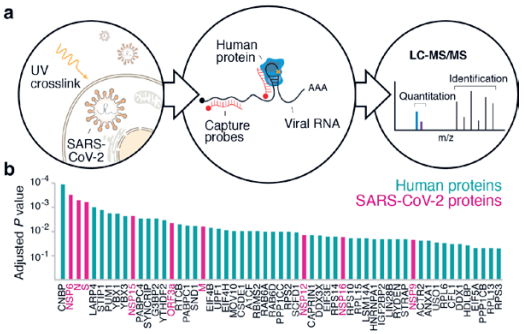

Illustration of the RNA antisense purification and mass spectrometry approach (a) to identify proteins in direct contact with SARS-CoV-2 RNA (b). Adapted from Schmidt *et al.* 2021.

HIGHLIGHTS & OUTLOOK

A highlight of the 2020-2022 period was the successful publication of the first global RNA-protein interaction atlas of SARS-CoV-2 in *Nature Microbiology*. In this work, we utilized an experimental technique known as RNA antisense purification, which was originally developed to study long non-coding RNAs, to identify proteins that directly bind SARS-CoV-2 RNA inside infected cells. In addition to RNA-binding proteins of the virus, we found more than 100 human proteins that directly interact with SARS-CoV-2 RNA. We demonstrated by genetic perturbation that CNBP and LARP1, two of the most strongly enriched viral RNA binders, restrict SARS-CoV-2 replication in infected cells. We then mapped the exact RNA binding sites of both of these newly identified antiviral proteins and noticed an intriguing binding pattern: LARP1 binds to the 5'-leader sequence that is present in all SARS-CoV-2 mRNAs. This mode of binding is similar to how LARP1 recognizes specific host mRNAs to regulate their translation.

Beyond CNBP and LARP1, we found dozens of RNA-binding proteins that are known targets of pharmacological compounds. We tested four inhibitors and observed a clear reduction of viral replication for three compounds. Overall, our SARS-CoV-2 RNA-protein interactome provides valuable insights into the regulation of viral RNA in infected human cells. The group is now working on expanding these efforts towards different positive- and negative-sense RNA viruses and different RNA types generated during the various stages of the infection cycle.

SINGLE-CELL ANALYSIS

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SELECTED PUBLICATIONS

Wendisch D, Dietrich O, Mari T, von Stillfried S, Ibarra IL, Mittermaier M, *et al.*, Ochs M, Eils R, Müller-Redetzky H, Hauser AE, Luecken MD, Theis FJ, Conrad C, Wolff T, Boor P, Selbach M, **Saliba AE#**, Sander LE# (2021) *SARS-CoV-2 infection triggers profibrotic macrophage responses & lung fibrosis.* **Cell** 184(26):6243-6261.e27
#corresponding authors

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** 5(10):1202-1206
#corresponding authors

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** 182(6):1419-1440.e23
#corresponding authors

AWARDS

EMBO Young Investigator Award (2021)

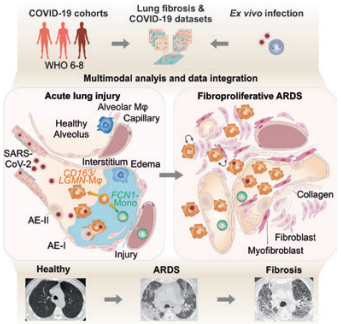
RESEARCH INTERESTS

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

Over the last years, the Single Cell Analysis lab has pioneered major technologies to study host-pathogen interaction at the single-cell level. In 2019, the lab has established RNA metabolic labeling at the single-cell level to study transcriptomic dynamics (scSLAM-seq). This method is revolutionizing our understanding of the earliest stage of host-pathogen interactions. In 2020, the Single-Cell Analysis lab developed one of the first protocols amenable to capture the transcriptome of a single bacteria. This technology is paving the way to understand the microbiome at the single cell level.

Also, the Single Cell Analysis group has been leading a major effort to decipher the pathomechanisms of severe COVID-19 in the blood and the lung. In the blood, they found that SARS-CoV-2 infection induces profound alterations of the myeloid compartment. Particularly, they uncovered the cellular basis of emergency myelopoiesis that is marked by immature and dysfunctional neutrophils in severe COVID-19. They discovered that monocyte-derived macrophages accumulate in the lung in COVID-19 ARDS ("acute respiratory distress syndrome") and these macrophages express genes associated with profibrotic functions. Finally, they uncovered that SARS-CoV-2 induces a profibrotic transcriptome and proteome profile in macrophages. Altogether, the Single Cell Analysis group made a leap forward by bringing the single-cell RNA-seq in the clinics.



Schematic illustration of lung remodeling after SARS-CoV-2 infection underlying severe COVID-19.

GENOME ARCHITECTURE AND EVOLUTION OF RNA VIRUSES

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SELECTED PUBLICATIONS

Pekarek L, Zimmer M. M, Gribling-Burrer AS, Buck S, **Smyth RP#**, Caliskan N# (2023) *Cis-mediated interactions of the SARS-CoV-2 frameshift RNA alter its conformation and affect the function.* **Nucleic Acids Research** 51(2):728-743
#corresponding authors

Ye L, Gribling-Burrer AS, Bohn P, *et al.*, Olguin-Nava M, Smith M, Caliskan N, von Kleist M, **Smyth RP** (2022) *Short- and long-range interactions in the HIV-1 5' UTR regulate genome dimerization and packaging.* **Nature Structural & Molecular Biology** 29(4):306-319

Zimmer MM, Kibe A, Rand U, Pekarek L, Ye L, Buck S, **Smyth RP**, Cicin-Sain L, Caliskan N (2021) *The short isoform of the host antiviral protein ZAP acts as an inhibitor of SARS-CoV-2 programmed ribosomal frameshifting.* **Nature Communications** 12(1):7193

Smyth RP, Smith MR, Jousset AC, *et al.*, Paillart JC, 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):e57

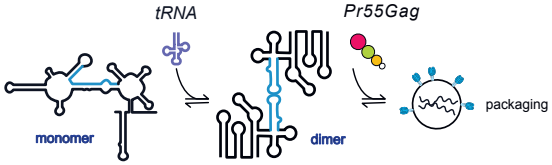
RESEARCH INTERESTS

Our group studies 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

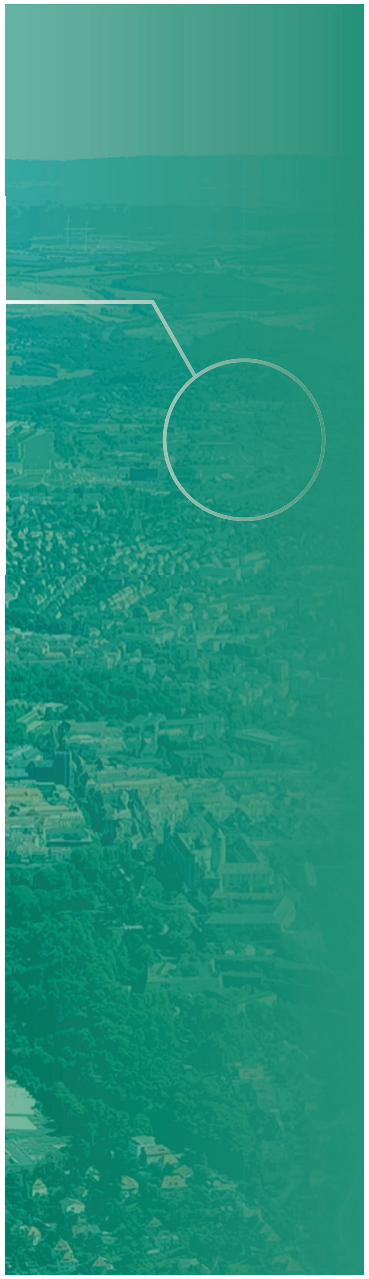
During infection, RNA viruses interact and modulate the host cell to further their replication. One important mechanism used by viruses to regulate their life cycle is the binding of host nucleic acids and/or protein factors to RNA structures in the genome. Using high-throughput RNA structure – function methodologies that we have developed (Smyth *et al.* 2015 Nat Meth; Ye *et. al.* 2022 Nat Struc Mol Biol) we have exhaustively profiled the HIV-1 5'UTR for novel functional elements. So far, we have identified several regions within the HIV-1 5'UTR that regulate translation, RNA dimerization and genome packaging. For instance, we were able to show that the genome of HIV-1 exists in two different RNA conformations. One of them is involved in genome packaging, the other remains in the host cell to be translated into new viral proteins. These two conformations therefore act like a molecular switch to direct the fate of the viral RNA, and thus viral replication. In another virus, SARS-CoV-2, we were able to use single molecule analysis to identify structural heterogeneity at the frameshifting site, which is an essential RNA structure used to finetune SARS-CoV-2 gene expression. We also mapped the binding site of a host antiviral factor to this structure, which was shown to inhibit SARS-CoV-2 frameshifting and replication.

Because the role of RNA structure dynamics in viral infection is poorly understood, we continue to invest energy into developing novel RNA structural probing technologies. We have recently established Nano-DMS-MaP-seq, which exploits the unique properties of nanopore sequencing to rapidly obtain structural information on long RNA molecules. Using Nano-DMS-MaP-seq we have resolved the structural landscape of HIV-1 transcripts in infected cells, showing that splicing introduces structural changes in the 5'UTR that prevent the non-productive packaging of spliced transcripts into viral particles. Ultimately, we will use single molecule RNA structural probing on nanopores to resolve the role of RNA structural ensembles in virally infected cells.



An RNA structural switch regulates the incorporation of the HIV-1 genome into viral particles.

Image: Nicolae Adrian



3.9
ZINF MEMBERS ASSOCIATED WITH OTHER INSTITUTES

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MARKUS ENGSTLER
Chair of Cell and Developmental Biology, Biocenter

ULRIKE HOLZGRABE
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SELECTED PUBLICATIONS

Liang C, Rios-Miguel AB, Jarick M, Neurgaonkar P, Girard M, François P, Schrenzel J, Ibrahim ES, Ohlsen K#, **Dandekar T#** (2021) *Staphylococcus aureus Transcriptome Data and Metabolic Modelling Investigate the Interplay of Ser/Thr Kinase PknB, Its Phosphatase Stp, the glmR/yvcK Regulon and the cdaA Operon for Metabolic Adaptation.*
Microorganisms 9(10):2148
#corresponding authors

Dunker C, Polke M, Schulze-Richter B, Schubert K, Rudolphi S, Gressler AE, Pawlik T, Prada Salcedo JP, Niemiec MJ, Slesiona-Künzel S, Swidergall M, Martin R, **Dandekar T**, Jacobsen ID (2021) *Rapid proliferation due to better metabolic adaptation results in full virulence of a filament-deficient Candida albicans strain.*
Nature Communications 12(1):3899

Gupta SK, Ponte-Sucre A, Bencurova E, **Dandekar T** (2021) *An Ebola, Neisseria and Trypanosoma human protein interaction census reveals a conserved human protein cluster targeted by various human pathogens.*
Computational and Structural Biotechnology Journal 19:5292-5308

RESEARCH INTERESTS

Our research group focusses on network biology: How do metabolic and signaling networks react to different environmental stimuli, how do they adapt and what does this tell us about the life-style of a cell, be it a microbial cell, a plant, a eukaryotic cell, or a cancer cell. We investigate and compare numerous biological networks and also medically relevant networks in health and diseased state. We have a strong interest in infection biology as we there can combine both aspects: the microbe (fungi, bacteria) and its life-style but also the diseased state of the host and how the different cellular networks respond in different cell types to the infection.

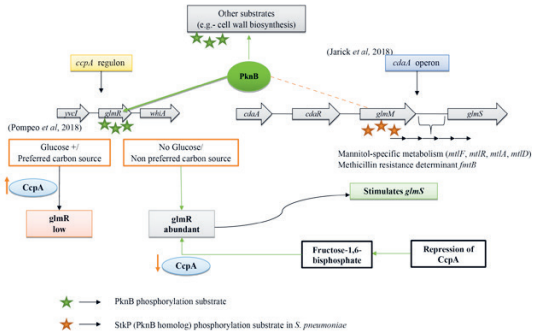
HIGHLIGHTS & OUTLOOK

We scrutinized bacterial and synthetic pathways (Eisenhaber *et al.*, 2022) and *Camponotus floridanus* protein interaction networks (Gupta *et al.*, 2020). We established CoxBase, an online platform to monitor *Coxiella burnetii* infections (Fasemore *et al.*, 2021), revealed a conserved human protein cluster targeted by various human pathogens (Gupta *et al.*, 2021c) and improved 3D tissue models for infection (Griffoni *et al.*, 2021). We introduced a high-specific real time PCR to identify *Trypanosoma cruzi* in Chagas disease (Kann *et al.*, 2020).

We studied stringent response in *Staphylococcus aureus* (Audretsch *et al.*, 2021), how intracellular *S. aureus* perturbs host cell Ca^{2+} homeostasis (Stelzner *et al.*, 2020) and investigated the interplay of Ser/Thr Kinase PknB, with *glmR/yvcK* regulon and *cdaA* operon (Liang *et al.*, 2021; Figure). Regarding plant bacterial infections, a meristem inoculation assay (Naseem *et al.*, 2020a), resulting immune-defense transcriptome (Naseem *et al.*, 2020b), and stem cell peptide and immune receptor interaction (Nassem *et al.*, 2020c) was described using the JIMENA software (Osmanoglu *et al.*, 2021).

Regarding *Candida albicans*, rapid proliferation and metabolic adaptation of a filament-deficient strain was described (Dunker *et al.*, 2021) and CEACAM1, 3, and 6 triggered cytokine release in human neutrophils (Klaile *et al.*, 2022). We compared *Aspergillus fumigatus* versus the genus *Aspergillus* (Gupta *et al.*, 2021). We analyzed herpes simplex virus genome (Whisnant *et al.*, 2020), reviewed alveolar regeneration in COVID-19 patients (Gupta *et al.*, 2021a) and showed that MHC Class II epitope presentation correlates with case fatality rates of COVID-19 (Liang *et al.*, 2021b).

New research will consider further protein interaction networks in infection biology.



S. aureus cell wall metabolism is regulated by the concerted action of *pknB*, *cdaA* operon, and *ccpA* regulon (see Liang *et al.*, 2021a).

MOLECULAR AND PHYSICAL PARASITOLOGY

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SELECTED PUBLICATIONS

Krüger T, Maus K, Kreß V, Meyer-Natus E, **Engstler M** (2021) *Single-cell motile behaviour of Trypanosoma brucei in thin-layered fluid collectives.*
The European Physical Journal E, Soft Matter 44(3):37

Schuster S, Lisack J, Subota I, Zimmermann H, Reuter C, Mueller T, Morriswood B, **Engstler M** (2021) *Unexpected plasticity in the life cycle of Trypanosoma brucei.*
eLife 10:e66028

Link F, Borges AR, Jones NG, **Engstler M** (2021) *To the Surface and Back: Exo- and Endocytic Pathways in Trypanosoma brucei.*
Frontiers in Cell and Developmental Biology 9:720521

AWARDS

Memento Research Award (2022)

RESEARCH INTERESTS

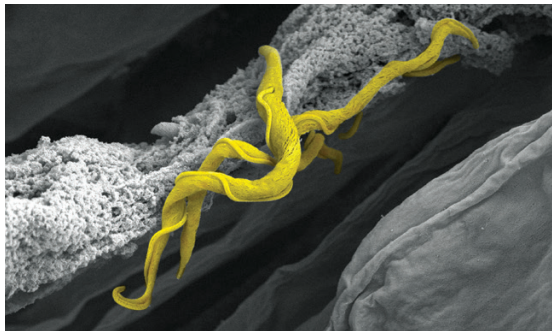
Motion is a hallmark of life. We study the physics of motion on very different scales, from molecules to organelles to cells and beyond. Our model system is the African trypanosome, a deadly blood parasite, which is perfect for the analysis of motion on different scales. Throughout their complex life 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

As part of the DFG SPP 2332 „Physics of Parasitism“, we are investigating the role of pure mechanics in the spread of parasites. Like all living beings, parasites must adapt optimally to an ecological niche. In the case of parasites, this niche is by definition hostile, as the host has developed defence strategies against the invader. Furthermore, the host is often infested by more than one parasite species, so that competition between parasites for the same infection niche can occur. Accordingly, avoiding interspecific competition is an important strategy for the evolutionary success of parasitism. We postulate that adaptations to the physics of the microenvironment play a crucial role in this process.

Furthermore, our work challenges the conservative view of the life cycle of parasites as a linear sequence of developmental stages. Using a series of high-end techniques, we have corrected the parasite life cycle and thus refuted two central dogmas of trypanosome biology.

We use the unusually defined cell surface coat of trypanosomes to address some fundamental questions in membrane biophysics. We will pursue our findings that protein crowding, by purely mechanical means, leads to the detachment of nanoparticles and nanotubes from the trypanosome plasma membrane. In addition, we are using 3D single-molecule tracking to unravel the molecular basis of the extremely fast membrane trafficking in trypanosomes. Finally, we are pioneering the field of single-cell mechanobiology by combining highly sensitive force measurements and single-cell transcriptomics.



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

Masota NE, Vogg G, Ohlsen K, **Holzgrabe U** (2021) *Reproducibility Challenges in the Search for Anti-bacterial Compounds from Nature.* **PLoS One** 16(7):e0255437

Saedtler M, Förtig N, Ohlsen K, Faber F, Masota N, **Holzgrabe U**, Meinel L (2020) *Anti-bacterial anacardic acid derivatives* **ACS Infectious Diseases** 6(7):1674-1685

Scheuplein N, Bzdyl N, Kibble E, Lohr T, **Holzgrabe U**#, Sarkar-Tyson M# (2020) *Targeting protein folding; a novel approach for the treatment of pathogenic bacteria.* **Journal of Medicinal Chemistry** 63(22): 13355-13388
#corresponding authors

AWARDS

Elsa Ullmann Medal awarded by the German Pharmaceutical Society (2021)

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.

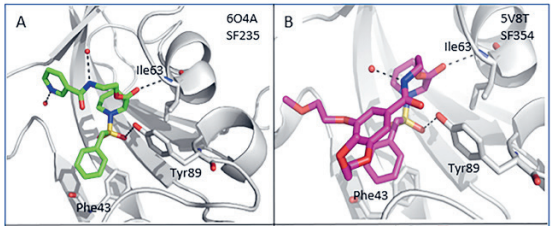
The latter is especially true for Gram-negative bacteria, such as *Pseudomonas*, *Klebsiella*, *Chlamydia*, and *Neisseria*. Blocking the entry of the bacteria, their invasion and their dissemination in the host by targeting virulence factors represent promising strategies to fight infections. Most Gram-negative 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 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 *K. pneumoniae*, as well as from *C. trachomatis*, *N. 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. For a new series of highly potent Mip inhibitors we have recently filed a patent.

Nature provides a large portion of antiinfectives in clinical use; they are often modified to improve the pharmacodynamics (PD) and pharmacokinetics (PK). For this reason, we are also looking into plants in order to find new lead structures, which we optimize with regard to PD and PK in addition to physicochemical properties, e.g., aqueous solubility. Furthermore, we broached the issue of the poor reproducibility of reported new antiinfective compounds from plant kingdom in literature.



Mip inhibitors for the treatment of infections by *Burkholderia pseudomallei* (Iwasaki J, Lorimer DD, *et al.*, 2022).

STRUCTURE-BASED DRUG DESIGN

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SELECTED PUBLICATIONS

Eltschkner S, Kehrein J, Le TA, Davoodi S, Merget B, Basak S, Weinrich JD, Schiebel J, Tonge PJ, Engels B, Sotriffer C#, **Kisker C#** (2021) *A Long Residence Time Enoyl-Reductase Inhibitor Explores an Extended Binding Region with Isoenzyme-Dependent Tautomer Adaptation and Differential Substrate-Binding Loop Closure.* **ACS Infectious Diseases** 7(4):746-758
#corresponding authors

Humphreys IR, Pei J, Baek M, Krishnakumar A, Anishchenko I, Ovchinnikov S, Zhang J, Ness TJ, Banjade S, Bagde SR, Stancheva VG, Li XH, Liu K, Zheng Z, Barrero DJ, Roy U, Kuper J, Fernández IS, Szakal B, Branzei D, Rizo J, **Kisker C**, Greene EC, Biggins S, Keeney S, Miller EA, Fromme JC, Hendrickson TL, Cong Q, Baker D (2021) *Computed structures of core eukaryotic protein complexes.* **Science** 374(6573):eabm4805

Peissert S, Schlosser A, Kendel R, Kuper J, **Kisker C** (2020) *Structural basis for CDK7 activation by MAT1 and Cyclin H.* **PNAS** 117(43):26739-26748

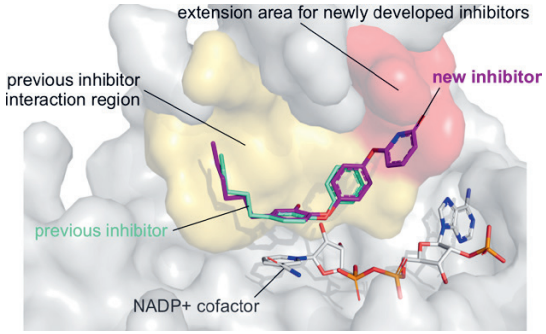
RESEARCH INTERESTS

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. *Staphylococcus aureus* and *Mycobacterium tuberculosis* are among these organisms for which multiple resistances are known. Methicillin resistant *S. aureus* strains are widespread in hospitals but also found in healthy individuals and cause a wide spectrum of diseases. For *M. tuberculosis*, multidrug- and extensively drug-resistant strains have been identified, leading to serious issues in the treatment of tuberculosis accompanied by high mortality rates.

HIGHLIGHTS & OUTLOOK

The essentiality of the bacterial fatty acid biosynthesis and its difference to the human synthesis pathway warrants the development of inhibitors targeting this system. The bacterial enoyl-acyl carrier protein reductase is a key enzyme in bacterial fatty acid synthesis, and in mycobacteria it is the main target of the front-line tuberculosis drug isoniazid. In *S. aureus* several inhibitors addressing the enoyl-acyl carrier protein reductase are currently in clinical trials. One goal towards the development of new antibacterial compounds is to obtain an improved drug-residence time (tR), which may raise the efficacy of a drug and importantly, extend its pharmacodynamic activity, and reduce off-target effects.

In a concerted effort, we designed the new bacterial enoyl-acyl carrier protein reductase inhibitor SKTS1 specifically against *S. aureus* based on the analysis of several *S. aureus* bound inhibitor structures in an attempt to increase its affinity and residence time. Our subsequent kinetic analysis showed that our newly developed inhibitor displays favorable binding properties and a long residence time of almost 6 h at 37 °C. To determine its exact binding mode, we solved the structure of the *S. aureus* bound complex, but also explored whether this newly developed inhibitor can target the mycobacterial enzyme. Interestingly, our combined structural and quantum mechanical calculations indicate that the inhibitor binds in two different tautomeric states to the two enzymes. Bound to the mycobacterial enzyme, it adopts the hydroxypyridine state, whereas the *S. aureus* enzyme accommodates the pyridone state. This unexpected result may pave the way for the development of inhibitors of isoenzymes that can adapt to differences in the targeted binding site and thereby ideally interact with the different isoenzymes.



Space filling model of the *S. aureus* enoyl-acyl carrier protein reductase substrate binding pocket.

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

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SELECTED PUBLICATIONS

Berger C, Bjørlykke Y, Hahn L, Mühlemann M, Kress S, Walles H, Luxenhofer R, Ræder H, **Metzger M**, Zdzieblo D (2020) *Matrix decoded - A pancreatic extracellular matrix with organ specific cues guiding human iPSC differentiation.* **Biomaterials** 244:119766

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

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

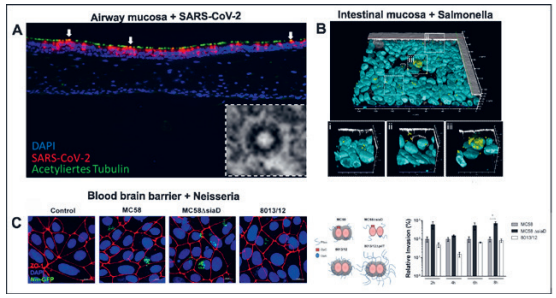
RESEARCH INTERESTS

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, to study the cellular and molecular mechanisms involved in 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 are the main contact surfaces for pathogenic microbes.

HIGHLIGHTS & OUTLOOK

Our 3D intestinal tissue model, comprised of epithelial & endothelial layers, a decellularized intestinal matrix scaffold, and immune cells, was used to study human enteric infections at a level of detail that is not achieved by conventional 2D monocultures. Upon *Salmonella* infection, the model mimics human gastroenteritis, in that it restricts the pathogen to the epithelial compartment, an advantage over existing mouse models. Within the epithelium there is a cell-specific response in terms of typical cytoskeletal re-arrangements and specific gene regulation also nicely reflecting the *in-vivo* phenotype. Dual RNA-seq of the *Salmonella*-infected model revealed crosstalk between epithelial, endothelial, monocytic, and natural killer cells as well as with the pathogen (with Prof. J. Vogel). 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* and other gastrointestinal pathogens such as *Helicobacter pylori* and *Campylobacter jejuni* (with Prof. C. Sharma).

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



Infected 3D *in-vitro* models of (A) the human airway, (B) the human gut, and (C) the blood-brain-barrier. Images by M. Steinke (A), T. Däullary (B), S. Gomes/A. Appelt-Menzel.

CHEMISTRY IN LIVING SYSTEMS

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SELECTED PUBLICATIONS

Fink J, Schumacher F, Schlegel J, Stenzel P, Wigger D, Sauer M, Kleuser B, **Seibel J** (2021) *Azidosphinganine enables metabolic labeling and detection of sphingolipid de novo synthesis.* **Organic and Biomolecular Chemistry** 19(10):2203-2212

Zimniak M, Kirschner L, Hilpert H, Geiger N, Danov O, Oberwinkler H, Steinke M, Sewald K, **Seibel J**, Bodem J (2021) *The serotonin reuptake inhibitor Fluoxetine inhibits SARS-CoV-2 in human lung tissue.* **Scientific Reports** 11(1):5890

Götz R, Kunz TC, Fink J, Solger F, Schlegel J, **Seibel J**, Kozjak-Pavlovic V, Rudel T, Sauer M (2020) *Nanoscale imaging of bacterial infections by sphingolipid expansion microscopy.* **Nature Communications** 11(1):6173

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

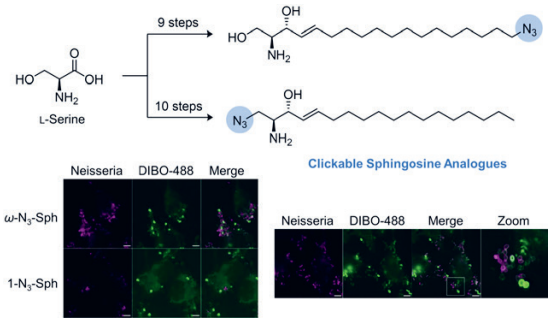
Sphingolipids in infectious diseases: Because sphingolipids are major components of membranes, their biosynthesis and metabolism and availability of their signaling inert or bioactive species substantially affect the biophysical properties of membranes and the subcellular redistribution of receptors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

Metabolic labeling of cell surfaces and in cells was established 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.

Identification and Validation of Drug-targets for SARS-CoV-2: Natural and natural like products have been screened as potential anti-infectives against SARS-CoV-2 infected cells. Also rational designed reporters were synthesized and used for studying of SARS-CoV-2 egress and the role of sphingolipid metabolism in SARS-CoV-2.

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, attractive strategy especially for tailoring the scaffold of enzymes while extending the canon of natural amino acids. We also follow ligand/inhibitor design of proteins, e.g., galectins, a recent promising source of cancer research. Galectin-1, which sits on the surface of all human cells, occurs in enormous quantities on tumor cells, making it an interesting target for diagnostics and therapy. Complex sugar molecules specifically binding to Galectin-1 are designed, which could help to recognize tumors at an early stage and to combat them in a targeted manner.



Sphingosine plays a crucial role in the intracellular survival of *Neisseria gonorrhoeae*.

TROPICAL MEDICINE

PROF. AUGUST STICH

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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.* **Journal of Medicinal Chemistry** 61(8):3350-3369

Gertler M, Loik S, Kleine C, *et al.*, **Stich A**, Butenop J (2018) *West Africa Ebola outbreak - immediate and hands-on formation: the pre-deployment training program for frontline aid workers of the German Red Cross, other aid organizations, and the German Armed Forces, Wuerzburg, Germany 2014/15.* **Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz** 61(4):394-403

Lingscheid T, Kurth F, Clerinx J, Marocco S, Trevino B, *et al.*, **Stich A**, Pongratz P, Grobusch MP, Suttorp N, Witzenrath M, Hatz C, Zoller T, TropNet SchistosomiasisInvestigator Group (2017) *Schistosomiasis in European Travelers and Migrants: Analysis of 14 Years TropNet Surveillance Data.* **American Journal of Tropical Medicine and Hygiene** 97(2):567-574

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.

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.

Patient care during the 2019 Ebola outbreak in DRC.

TRANSLATIONAL PEDIATRICS

PROF. DOROTHEE VIEMANN

Chair of Translational Pediatrics, Department of Pediatrics

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www.ukw.de/kinderklinik/translationale-paediatrie

SELECTED PUBLICATIONS

Pirr S, Dauter L, Vogl T, Ulas T, Bohnhorst B, Roth J, **Viemann D** (2021) *S100A8/A9 is the first predictive marker for neonatal sepsis.* **Clinical and Translational Medicine** 11(4):e338

Willers M, Ulas T, Völlger L, Vogl T, Heinemann AS, Pirr S, Pagel J, Fehlhaber B, Halle O, Schöning J, Schreek S, Löber U, Essex M, Hombach P, Graspeuntner S, Basic M, Bleich A, Cloppenborg-Schmidt K, Künzel S, Jonigk D, Rupp J, Hansen G, Förster R, Baines JF, Härtel C, Schultze JL, Forslund SK, Roth J, **Viemann D** (2020) *S100A8 and S100A9 Are Important for Postnatal Development of Gut Microbiota and Immune System in Mice and Infants.* **Gastroenterology** 159(6):2130-2145

Ravens S, Fichtner AS, Willers M, Torkornoo D, Pirr S, Schöning J, Deseke M, Sandrock I, Bubke A, Wilharm A, Dodoo D, Egyir B, Flanagan KL, Steinbrück L, Dickinson P, Ghazal P, Adu B, **Viemann D**, Prinz I (2020) *Microbial exposure drives polyclonal expansion of innate γδ T cells immediately after birth.* **PNAS** 117(31):18649.-18660

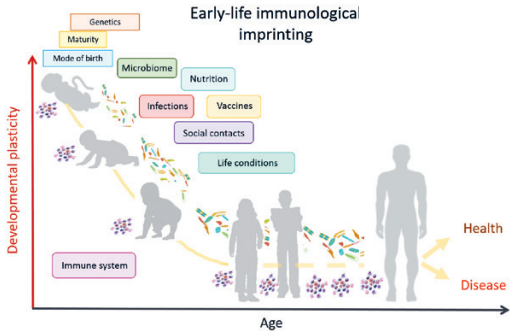
RESEARCH INTERESTS

Early childhood is a period of profound imprinting of biological systems. The reprogramming of the immune system after birth is a crucial step for the adaptation to the new extrauterine environment. We are interested in elucidating the factors, which train the immune system of children in a positive manner to prevent developing an increased risk for immune-mediated diseases such as susceptibilities to infections and chronic inflammatory diseases at the earliest possible time point in life. Our research focuses on the maturation of the innate immune system of children, mechanisms of inflammation, and host-pathogen interactions. To reach our goals, we involve experimental models and healthy study participants as well as patients including term and preterm babies followed longitudinally in birth cohorts.

HIGHLIGHTS & OUTLOOK

Whilst overall mortality from infectious diseases decreased significantly in the last decades, neonatal infections still remain one of the leading causes of death in children. We could show in experimental models and human birth cohorts of preterm infants that high amounts of the alarmins S100A8 and S100A9 protect neonates from hyperinflammatory immune responses and fatal courses of sepsis. Mechanistically, S100 alarmins regulate systemic as well as mucosal neonatal immunity, which in turn promotes the colonization with a health-promoting microbiome. Collectively, our findings culminated now in the set-up of a first preclinical study on the nutritional application of alarmins to vulnerable neonates to prevent sepsis and promote protective immune adaptation.

Multiple evidence suggests that postnatal immune maturation is primarily triggered by environmental influences. Particularly, mutual host-microbiota interactions seem to be crucial for life-long immune homeostasis, colonization resistance against pathogens, and overall health. We currently perform the MIAI study to monitor the development of the immune system in a birth cohort of term infants. Specifically, we are focusing on the maturation of innate immunity against the influenza A virus (IAV) in dependence of the developing microbiome. Superior goal of MIAI is to identify developmental check points that are both crucial for the postnatal tuning of anti-viral immunity and strongly affected by environmental imprinting. Such check points would be promising molecular targets accessible for early-life modification to prevent unfavorable development of anti-viral immunity.



The imprinting of the immune system during early childhood by endogenous and environmental factors is crucial for the establishment of life-long health.

4

RESEARCH PROGRAMS

4 RESEARCH PROGRAMS

CURRENT RESEARCH PROGRAMS OF ZINF MEMBERS

4.1

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

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

A08 HERMANN EINSELE
(Dept. of Internal Medicine II)
Gene-engineered CAR T-cells and macrophages to treat *Aspergillus fumigatus* infection

B01 THOMAS DANDEKAR
(Dept. of Bioinformatics)
Evolution of fungal virulence and host responses comparing *Candida*, *Lichtheimia* and *Aspergillus* spp

B02 Host-pathogen interactions triggering infection signal networks in *Aspergillus fumigatus*, *Candida albicans* and human immune cells

C01 CHRISTIAN PÉREZ
(ZINF and IZKF)
Molecular characterization of *Candida albicans* attributes during translocation and dissemination and the effects of immunotherapy

C02 JOACHIM MORSCHHÄUSER
(Institute of Molecular Infection Biology)
Regulation of *Candida albicans* virulence traits by protein kinase and transcription factor signaling pathways

C03 OLIVER KURZAI
(Institute for Hygiene and Microbiology)
Modulation of neutrophil antifungal activity by intrinsic and extrinsic stimuli

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

C07 MARTIN VAETH
(Institute of Systems Immunology)
Ionic regulation of Th17-mediated immune responses to *Candida* infection

4.2

DFG COLLABORATIVE RESEARCH CENTRE (CRC) SFB 1583

DECIDE - DECISIONS IN INFECTIOUS DISEASES

Infectious diseases are a major cause of suffering, morbidity, and mortality worldwide. In particular, the worldwide increase of multidrug-resistant pathogens and the constant emergence of new human pathogens pose immense challenges to modern medicine. Pathogen-directed therapies often lead to successful treatment of the patient. However, antibiotic, antifungal, or antiviral drugs cause the emergence of resistant germs. Moreover, current therapeutic approaches do not take the host immune response into account, which often contributes to the fatal outcome of many infectious diseases. Therefore, combating the pathogen alone is not always sufficient. Treatment strategies that focus on optimizing the host response rather than eradicating the pathogen itself are urgently needed. Therefore, it is necessary to identify and characterize decision points within the host that govern infectious disease processes. Once recognized, these can be harnessed for future therapeutic interventions.

Thus, the newly established Collaborative Research Centre DECIDE (DECisions in Infectious DisEases) aims to identify molecular mechanisms within the host that control the course of infectious diseases. In particular, three key decisions that determine the clinical outcome and severity of infections are being investigated: (1) containment versus active infection after initial contact; (2) active/acute versus persistent/chronic infection; (3) localized infection versus systemic spreading. In this CRC, the underlying mechanisms of host-pathogen interactions will be studied in unprecedented molecular detail, due to recent advances in cutting-edge technologies such as single-cell RNA-seq and complex human tissue and animal models. DECIDE researchers' extensive experience with a repertoire of pathogens allows them to study the interactions between microbes, host barrier tissues, and the immune system, as well as the microbiota in a unique multi-layered systems approach. In this way, the goal of this CRC is to identify overarching common and pathogen-specific molecular decision points in infectious processes that can serve as the basis for new prevention and treatment approaches for infectious diseases.

Projects involving ZINF members:

A01 DOROTHEE VIEMANN
(Dept. of Pediatrics)
Age-dependent airway epithelial determinants of severe human respiratory viral infections

A02 CYNTHIA SHARMA & SINA BARTFELD
(Institute of Molecular Infection Biology & ZINF/Institute of Biotechnology, TU Berlin)
Age-dependent intestinal epithelial determinants of infections with enteropathogenic *Escherichia coli* and *Campylobacter jejuni*

A03 MERCEDES GOMEZ DE AGÜERO
(Institute of Systems Immunology)
Molecular decision points that determine colonisation and infection risk in neonatal skin

A04 FRANZISKA FABER & ALEXANDER WESTERMANN
(Institute of Molecular Infection Biology)
Epithelial physiology and immune status as decision points in the initiation of toxin-induced *Clostridioides difficile* colitis

A05 GEORG GASTEIGER
(Institute of Systems Immunology)
Mechanisms of infection control by pathogen-educated epithelial-immune cell circuits

A06 ANDREAS BEILHACK & JÜRGEN LÖFFLER
(Dept. of Internal Medicine II)
Pulmonary *Aspergillus* infection progression determined by alveolar macrophages as initial responders

A07 LARS DÖLKEN
(Dept. of Virology)
Mechanisms facilitating local herpes simplex virus replication and control in the female reproductive tract

A08 CINDRILLA CHUMDURI
(Dept. of Microbiology)
Mechanisms of *Chlamydia* and human papillomavirus co-infection in metaplastic tissue of the uterine cervix

A09 JÖRG VOGEL
(Institute of Molecular Infection Biology)
Molecular decision points that determine colorectal cancer colonisation by *Fusobacterium nucleatum*

B01 THOMAS RUDEL
(Dept. of Microbiology)
Mechanisms driving chlamydial persistence and ascending infection in the female reproductive tract

Z01 Central tasks of the SFB 1583

B04 ANA RITA BROCHADO
(ZINF/Dept. of Microbiology)
Systems biology approach to identify key molecular decision points for intracellular persistence during infection

B05 ANTOINE-EMMANUEL SALIBA
(Helmholtz Institute for RNA-based Infection Research)
Uncovering host mechanisms underlying *Salmonella* persistent infection of intestinal epithelial cells

C01 **WOLFGANG KASTENMÜLLER**
(Institute of Systems Immunology)
Mechanisms underlying unconventional T cell function as decision points to prevent microbial spread via the lymph

C02 **MARTIN VAETH**
(Institute of Systems Immunology)
Metabolic control of innate and adaptive immune responses to cutaneous *Staphylococcus aureus* infection

C03 **OLIVER KURZAI & KNUT OHLSEN**
(Institute for Hygiene and Microbiology & Institute of Molecular Infection Biology)
The lung as a pathogen-specific entry site for systemic infection

C04 **MARTIN FRAUNHOLZ**
(Dept. of Microbiology)
Molecular decision points underlying the systemic spreading of *Staphylococcus aureus*

MGK **OLIVER KURZAI**
(Institute for Hygiene and Microbiology)
Integrated Research Training Group "DECIDE"

INF **THOMAS DANDEKAR**
(Dept. of Bioinformatics)
Data management platform to facilitate data integration and *in silico* identification of decision points in infection

Z02 **ANTOINE-EMMANUEL SALIBA & FLORIAN ERHARD**
(Helmholtz Institute for RNA-based Infection Research & Dept. of Virology)
Temporal and spatial single-cell genomics to map decision points in infection

4.3

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 findings into clinical applications.

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

4.4

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 commonly underappreciated. While HCMV infection of healthy individuals is usually subclinical, life-threatening HCMV disease is frequent among the immunocompromised. 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 knowledge gaps about immunological function of CMV gene products and their role in host immune system-pathogen interaction. The consortium aims to understand the molecular interactions of CMV-infected antigen-presenting cells with cytotoxic T cell 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. 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

4.5

DFG RESEARCH UNIT 5200

DISRUPT – EVADE – EXPLOIT: GENE EXPRESSION AND HOST RESPONSE PROGRAMMING IN DNA VIRUS INFECTION (DEEP-DV)

Nuclear replicating DNA viruses typically cause chronic infections and depend on complex host regulatory networks for their own gene expression. Failure or success at controlling gene expression networks ultimately determines whether the initial infection becomes abortive or proceeds to a productive or persistent phase. In this context, the central focus of the DEEP-DV consortium is to study the dedicated strategies employed by newly infecting DNA viruses to disrupt, evade, or exploit nuclear gene expression networks to achieve the desired infection outcome. The central hypothesis is that such viral strategies may vary depending on the specific nuclear environment and state of the host cell. However, there will be commonalities and as-of-yet undefined shared principles that are important across diverse nuclear DNA virus species and even across families. This is especially true for antiviral host responses and nuclear repressor complexes that have to be evaded or exploited by newly incoming viral genomes.

DEEP-DV will investigate the early events of nuclear DNA virus infection to define these principles. Importantly, while such mechanisms are usually interrogated in a single viral system, the projects in DEEP-DV investigate different DNA viruses of the herpes-, polyoma- and adenovirus families. This consortium brings together scientists with strong virological expertise, firm command of state of the art experimental methodologies (e.g., genome, transcriptome and epigenome analytics, RNP proteomics, single cell technologies and advanced imaging methods), and profound experience with bioinformatic data analysis. This endeavor seeks to open up new possibilities to understand and, ultimately, control acute and chronic DNA virus infections.

Projects involving ZINF members:

P02 **LARS DÖLKEN & FLORIAN ERHARD**
(Dept. of Virology)
Regulation and Herpes simplex virus 1 counter-regulation of transcriptional bursting kinetics in the early type I interferon response

4.6

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

4.7
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

4.8
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

4.9
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*
Central Project Z2: Ribosome Profiling & Bioinformatics

JÖRG VOGEL
(Institute of Molecular Infection Biology)
Characterizing the role of YjiS in *Salmonella* virulence

4.10
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 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 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)
Characterizing CRISPR-Cas systems with non-defensive functions
Prevalence, formation, and function of "extraneous" CRISPR RNAs derived from the extra repeat in CRISPR arrays

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*

4.11
DFG PRIORITY PROGRAM SPP 2330
NEW CONCEPTS IN PROKARYOTIC VIRUS-HOST INTERACTIONS – FROM SINGLE CELLS TO MICROBIAL COMMUNITIES

In recent years, revolutionary discoveries on the biology of prokaryotic viruses were made, including the finding that viruses can use small molecules to make group-level decisions, the discovery of intracellular molecular complexes made by viruses that blur the boundary between prokaryotic and eukaryotic life, and the multitude of novel anti-viral immune systems acting at the unicellular and multicellular level. The SPP 2330 brings together an interdisciplinary consortium on phage research, combining molecular microbiology, bioinformatics, mathematical

modelling, imaging techniques, structural biology, and biochemistry.

The SPP 2330 focuses on three scales of complexity of viral organization: viral cell biology, new unicellular and multicellular anti-viral defense strategies, and viral impact on multispecies microbial communities. The fundamental goals of this consortium are the understanding of new mechanisms in prokaryotic virus-host interactions at the molecular level as well as in the context of microbial communities. This will allow us to address the impact of different viral life styles on the evolution of anti-viral strategies and ultimately will shed light on the evolutionary arms race at the community level. Together, the concerted effort of this consortium will lead the field to uncover new concepts for these rapidly emerging topics and will open up new horizons in biology, with high potentials for applications in molecular biology, phage therapy, food processing, and agriculture.

Projects involving ZINF members:

CHASE BEISEL
(Helmholtz Institute for RNA-based Infection Research)
Interrogating the contributions of novel immune systems to anti-phage defense in their native bacterial hosts

MERCEDES GOMEZ DE AGÜERO
(Institute of Systems Immunology)
Dynamic and mechanisms of early life interactions between bacteriophage and its bacteria host in the skin

JÖRG VOGEL
(Institute of Molecular Infection Biology)
Molecular factors whereby giant phage ΦKZ modulates host protein synthesis

4.12

DFG PRIORITY PROGRAM SPP 2332

PHYSICS OF PARASITISM

Traditionally, parasitology was concerned mainly with organismic studies, while today's parasitology focuses on medically-relevant cellular and molecular mechanisms, at ever-increasing depth. "Physics of Parasitism" defines a new frontier in this field, namely the physics of parasites interacting with their hosts. This interaction is controlled by the anatomy of the parasites (Bauplan), the physics of their locomotion, and the mechanics of their attachment to host structures. Long periods of co-evolution have equipped parasites with high degrees of optimality such as, e.g., suckers and shields or refined locomotive devices that allow attachment and navigation in various body fluids, in crowded and confined spaces, and in highly viscous environments - often at surprisingly high speeds. Using a selection of complementary and tractable parasites that colonise representative host niches such as *Plasmodium*, *Toxoplasma*, and *Trypanosoma*, as well as metazoan parasites such as *Schistosoma*, *Fasciola*, and *Echinococcus*, the SPP 2332 aims to elaborate a comparative and quantitative framework of the physical constraints and mechanical forces acting at the dynamic parasite-host interfaces. We will measure the material properties and mechanics of parasites in their niches, uncover the physical basis of their locomotion, and determine the mechanical and physical basis for their attachment. The priority program uniquely combines expertise from parasitology, molecular cell biology, experimental and theoretical physics, mathematics and simulation science with the vision to expose novel ways of combating parasitic diseases based on mechanobiology, against which resistances are unlikely to evolve.

Projects involving ZINF members:

MARKUS ENGSTLER
(Dept. of Cell and Developmental Biology)
Mechanical strategies to avoid interspecies competition in trypanosomes and Central Coordination Project

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 coined to reflect this holistic approach. In this project, we will focus on ABR and its molecular mechanisms in staphylococci in three African regions 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

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 (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, 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 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.

4.15.3 MONITORING CONCEPTS FOR SARS-CoV-2 (COVMON)

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

The CoVMon consortium focused on the epidemiological characterisation of COVID-19 and efficient monitoring strategies of infection activity. Specifically, within the Wü-KiTa-CoV project, we evaluated the acceptance and practicability of different surveillance concepts for the early detection of SARS-CoV-2 infections in daycare children, daycare staff, and their household members. From October 2020 till March 2021, we offered different test methods in nine participating daycare centers in Würzburg. Test methods included symptom-based on-demand testing, continuous surveillance of asymptomatic children and childcare workers by midturbinate nasal swabs once or twice a week, and surveillance of asymptomatic study participants via self-sampled saliva samples twice weekly. Our aim was to provide a test strategy for daycare centers which is efficient, practical, and well accepted by parents, tutors and children in the long term.

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
BMBF CompLS

MACHINE LEARNING BASED MULTI-MODEL SIMULATOR FOR INFECTION RESEARCH (MUMOSIM)

Within the MuMoSim project we aim to take modelling in infection research to the next level. In collaboration with the working group of Prof. Figge at the Leibniz Institute for Natural Product Research and Infection Biology Hans-Knöll-Institute in Jena, we will implement a multi-model simulator for quantitative and predictive modelling in infection research supported by machine learning.

To model complex biomedical systems, we will use the „bottom-up" approach, in which most of the model parameters can be determined from original available data. The multi-model simulator will allow the quantitative description and stepwise integration of different types of experimental data. In successive rounds of experiments, higher level models can be implemented to produce quantitative predictions. The focus of this project is on quantitative and predictive modelling of bloodstream infections by microbial pathogens based on experimental data from whole blood infection assays in humans, with general applicability of the simulator to interacting cell and molecular systems in biomedicine.

Projects involving ZINF members:

OLIVER KURZAI
(Institute for Hygiene and Microbiology)

4.19
BMBF GO-BIO

EMPLOYING CRISPR-CAS12 FOR SENSITIVE AND MULTIPLEXED DIAGNOSTICS

This project supports the pre-commercial development of CRISPR-Cas12 nucleases as part of our diagnostic platform LEOPARD (Jiao *et al.*, 2021). As part of the project, we are evaluating the extent to which these nucleases can improve the sensitivity of LEOPARD. We are integrating more scalable readouts to detect a larger number of biomarkers in one test. The goal is to achieve key demonstrations of the technology to work toward a spin-off and development of real-world tests.

Projects involving ZINF members:

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

4.20
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.

4.20.1 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.

4.20.2 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.

4.21
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)

4.22
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*

4.23
ELSE KRÖNER CENTER FOR ADVANCED MEDICAL & MEDICAL HUMANITARIAN STUDIES WÜRZBURG – MWANZA/TANZANIA

To improve the medical care in the region around Mwanza, Würzburg's partner city in Tanzania, the "Else Kröner Center for Advanced Medical & Medical Humanitarian Studies Würzburg – Mwanza" was founded in summer 2020. The research and healthcare center can build on a longstanding interdisciplinary collaboration of all involved partners. The aim of the center is to strengthen and expand these medical and scientific cooperations in a coordinated and sustainable manner. The partners united under the roof of the EKC are the Julius-Maximilians-Universität (JMU), the University Hospital (UKW), the Medical Mission Institute (MI), and the German Leprosy and Tuberculosis Relief Association (DAHW),the Catholic University of Health and Allied Sciences (CUHAS), and the Bugando Medical Center (BMC).

Within the EKC, the education and vocational training of medical students is expanded within the scope of exchange programs and the development of joint study programs on Epidemiology & Biostatistics and Public Health. Promising researchers from CUHAS and BMC are supported as EKC PhD students within a bi-lateral PhD

program. Additionally, regular training visits of medical staff are organized between the partnering hospitals Importantly, the EKC also focuses on an improved community healthcare in the area around Lake Victoria. Emphasis is 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. The EKC is funded by the Else Kröner-Fresenius-Foundation for five years.

Projects involving ZINF members:

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

4.24

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.

4.25

FOR-COVID

BAVARIAN CONSORTIUM FOR RESEARCH ON THE PANDEMIC DISEASE COVID-19

Also in Germany and Bavaria society, politics, and science are facing new challenges in the SARS-CoV-2 pandemic. In an effort to face the pandemic and its major scientific questions, Bavarian universities and research institutes joined forces in the Bavarian research consortium FOR-COVID. The research partners in FOR-COVID are internationally renowned scientists with expertise in virological diagnostics, development of vaccines, evaluation of virus specific immunity, virus – cell interactions, as well as research in pathogenesis and therapy.

The mission of FOR-COVID is to contribute to the continuous international scientific efforts to combat COVID-19 and the pandemic. On the national level, FOR-COVID will closely interact and join forces with the project groups of a Saxonian research network.

Networks involving ZINF members:

Deciphering SARS-CoV-2 infection by scSLAM-seq and artificial intelligence approaches and machine learning

LARS DÖLKEN, FLORIAN ERHARD, &
ANTOINE-EMMANUEL SALIBA
(Dept. of Virology, Helmholtz Institute for RNA-based Infection Research)

The outcome of SARS-CoV-2 infection varies substantially at the single cell level: While in some cells, a vast amount of viral RNA is expressed within a few hours, other cells are able to control the infection. However, the underlying cause and mechanisms of this dichotomous infection progression are unknown. Using our newly developed technology for temporally resolved RNA sequencing in single cells, we aim to identify molecular factors that significantly influence the course of the infection. We will investigate several time points during infection of established cell lines as well as primary, *ex vivo* infected donor cells, and compare SARS-Cov-2 with two other important human pathogenic respiratory viruses (influenza A and RSV). Newly developed methods based on artificial intelligence will be used to analyse and integrate the obtained data. We will closely collaborate with other projects within FOR-COVID to investigate candidate proteins that interact with the viral genome as well as interferon-regulated genes. Our project will explore the underlying molecular principles of virus-host cell interactions and identify factors, which can prevent a productive infection.

Decoding the biology of SARS-CoV-2 infections from its direct *in vivo* RNA-protein interactome

JÖRG VOGEL & MATHIAS MUNSCHAUER
(Institute of Molecular Infection Biology, Helmholtz Institute for RNA-based Infection Research)

From the moment the novel coronavirus invades an organism, this organism serves as its host. Despite the urgent need for effective antiviral therapies, we still do not fully understand the molecular basis of SARS-CoV-2 infection and pathogenesis. This project aims to investigate how the novel coronavirus replicates within its host for which the viruses utilises host cell proteins. However, until now little is known about the part of the human proteome that directly interacts with viral RNA. Characterizing the interactions that SARS-CoV-2 viral RNAs make with host cell proteins during infection can improve our understanding of viral RNA functions and the host innate immune response. During the first funding

period, we published a pioneering study that resolved how SARS-CoV-2 RNAs interact with the host cell proteome. We identified more than 100 human proteins that specifically bind to SARS-CoV-2 RNA, mapped their direct RNA contact sites, and demonstrated the functional importance of several of these viral RNA binders for SARS-CoV-2 infections. In the next funding period, we aim to expand these foundational insights by mechanistically dissecting how the newly discovered antiviral RNA-binding protein CNBP functions, and elucidating whether CNBP can be harnessed as a therapeutic target. We will then focus on identifying molecular vulnerabilities of SARS-CoV-2 by resolving the interactions of double-stranded viral RNA, which will yield host proteins directly involved in viral RNA sensing and targeting. Connecting biochemical interactions to their potential roles in defining infection outcomes, we will elucidate the functional contribution of candidate RNA binders to cell-state transitions occurring at the single-cell level. This work will improve our understanding of viral infections at the molecular level and reveal novel antiviral mechanisms with potential for therapeutic exploration.

4.26

ORGANO-STRAT

ORGAN-SPECIFIC STRATIFICATION OF COVID-19

This network of university hospitals and high-security labs was formed to implement a standardized chain of procedure for organ models, directed infections, native tissue and autopsy samples, as well as analyses and data management in regards to research on COVID-19 and other diseases. A second goal was to create a larger number of organ-based models that will allow to perform studies from which meaningful conclusions can be drawn. Clarifying the direct or indirect involvement of central organ systems in COVID-19 is a particular challenge. „Organo-Strat" investigated this question using organoids and 3D cultures generated from human tissues or human adult stem cells. In the long term, the establishment of donor-specific native tissue- and organoid-banks will help to address strategies of personalized medicine.

Projects involving ZINF members:

P01 THOMAS RUDEL
(Dept. of Microbiology)

P02 MARKUS ENGSTLER
(Dept. of Cell and Developmental Biology)

P03 SINA BARTFELD
(ZINF)

4.27

INNO4VAC

INNOVATIONS TO ACCELERATE VACCINE DEVELOPMENT AND MANUFACTURE

Inno4Vac is a new interdisciplinary project funded by the Innovative Medicines Initiative 2 (IMI2) that aims to foster health innovation by incorporating scientific and technological breakthrough from the academic and biotech sectors into industry. It is coordinated by the European Vaccine Initiative (Germany), with the support from the Sclavo Vaccines Association (Italy), for the scientific coordination, and involves 41 partners from 11 different European countries, including 37 academic institutions and SMEs, as well as GSK, Sanofi Pasteur, CureVac and Takeda as industry partners.

Within this Inno4Vac initiative the Department of Microbiology aims at the development of complex infection models of the urovaginal mucosa with features close to the native human tissue regarding architecture and physiology as well as cell autonomous immune response. These models are used to explore the feasibility of exploiting immune cells of innate and adaptive immunity. Our focus is on *Neisseria gonorrhoeae* to establish infection models. These tissue models will be used for testing and validating vaccination strategies.

Projects involving ZINF members:

THOMAS RUDEL
(Dept. of Microbiology)

5

INFRASTRUCTURE

5 INFRASTRUCTURE

2020-2022

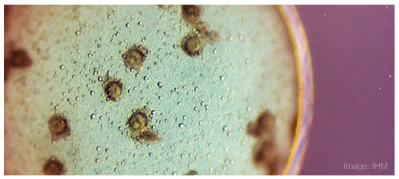
5.1
NRL FOR MENINGOCOCCI AND HAEMOPHILUS INFLUENZAE

The National Reference Laboratory (NRL) for meningococci and *Haemophilus influenzae* is hosted at the Institute for Hygiene and Microbiology at the University of Würzburg. 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



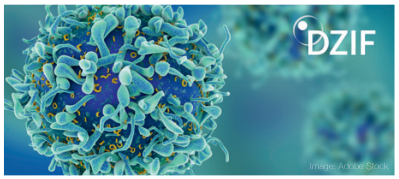
The Robert Koch Institute appoints the consulting laboratory for echinococcosis in Germany every second year for consultation, quality management, and development of diagnostic procedures. The Institute for Hygiene and Microbiology has been hosting the consulting laboratory for echinococcosis since 1997. 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 HEMATOPOIETIC 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 alloHPCT of an HLA-matched, *in vitro* T cell-depleted graft.

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

5.4
GERMAN CENTER FOR INTER-SECTORAL CONTROL OF NEGLECTED TROPICAL DISEASES (DZVT)

A particularly problematic area of global health is poverty-associated neglected tropical diseases (NTDs). NTDs cause devastating health, social, and economic ramifications. Since there are no good diagnostics or therapies available for many of the 20 NTDs listed by the WHO, over one billion people in 150 countries worldwide are suffering the devastating consequences caused by these diseases. To address these issues, seven institutions in Würzburg joined forces to found the "German Center for Intersectoral Control of Neglected Tropical Diseases" (DZVT) in 2019. Markus Engstler is initiator and founding member of the DZVT and brought together the University of Würzburg, the University Hospital Würzburg, the MedMissio Institute for Global Health, the University of Applied Sciences Würzburg-Schweinfurt, the DAHW German Leprosy and Tuberculosis Aid, the DGP German Society for Parasitology, and the Community Sant'Egidio Würzburg. In an internationally unique initiative, the goal of the DZVT is to enable a better collaboration between different disciplines in science and society. The Center will complement ongoing initiatives in the field of Global Health in Germany and exclusively offers the perspective for a sustainable, cross-sectoral, and successful fight against NTDs through collaboration. The DZVT brings together academic and practical knowledge in Germany and the affected countries. This way, it offers invaluable help and expertise for politics, the scientific community, those responsible in the affected countries, the implementing organizations, and ultimately the people suffering from NTDs.

For further information please visit **www.biozentrum.uni-wuerzburg.de/zeb/research/topics/dzvt/**.

5.5
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 comprised of the general assembly (meeting of all IZKF members), the executive board 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 enhance new topics. A close collaboration between clinical and basic research is required to receive funding by the IZKF. After up to three years, the projects should be transferred to external third-party funds. The IZKF invites proposals every 18 months and receives an average of 30-35 proposals with each call. Usually, 10-12 projects receive funding. With the latest call in 2021, the IZKF supported 31 projects in 6 project areas with the participation of 25 clinical departments and institutes.

Projects involving ZINF members:

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

AD427 SINA BARTFELD
(ZINF)
Characterization of the neonatal intestinal immune response and barrier function in human intestinal organoids

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

B458 CAROLINE KISKER
(Rudolf Virchow Center for Integrative and Translational Bioimaging)
Structural and functional characterisation of hemibodies and their target antigens

D420 OLIVER KURZAI
(Institute for Hygiene and Microbiology)
Simulation of fungal keratitis in a 3D cornea model

With the latest call in 2022 the IZKF is following the mission and the resulting strategic reorientation of the Faculty of Medicine: It replaces the classic subject- and disease-related project areas (inflammation, cancer, cardiovascular, neurology and education) with the new profile areas of the faculty:

- Cellular heterogeneity
- Complexity in tissue
- System/network diseases

The three new superordinate and interlocking profile areas set the framework for the various interdisciplinary research topics and cover the entire spectrum of translation.

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 took complementary as well as new paths in career support of young and advanced physicians by establishing a thematically open Clinician Scientists Program (CSP) in 2017 and an Advanced Clinician Scientist Program (ACSP) in 2019. In 2022 the Medical Faculty of Würzburg established a new program to promote academic independence through the acquisition of first own external third-party funding. The so called Bridging program, replaces the previous programs rotationPLUS, the First-Time-Applicant Program and the Returnee Program. For the first time, both Clinician Scientists and Medical Scientists can apply for funding.

All Clinician Scientist Programs are embedded in the Integrative Clinician Scientist College (ICSC), an umbrella structure established to provide uniform and coherent framework conditions for all Clinician Scientists and Advanced Clinician Scientists at the Medical Faculty of Würzburg. Joint symposia and joint coaching programs including peer group mentoring promote scientific exchange and team formation.

TWINSIGHT

One of the Clinician Scientists Program is the newly established Else Kröner-Fresenius Research College 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 (Department of Dermatology, Venerology, and Allergology) and Alma Zernecke-Madsen (Institute for Experimental Biomedicine). 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 patho-physiologically 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**.

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, est. 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**.

5.6
SINGLE-CELL CENTER WÜRZBURG

In 2021, the Helmholtz Institute for RNA-based Infection Research (HIRI) co-founded the Single-Cell Center Würzburg to further advance one of its core areas of discovery research and scientific expertise. The center is a joint venture with the JMU Faculty of Medicine, the University Hospital Würzburg (UKW), the Fraunhofer Translational Center for Regenerative Therapies (TLZ-RT), and the Max Planck Research Group at the Würzburg Institute of Systems Immunology (WüSI).

The center's objective is to investigate and elucidate infectious and other diseases at the level of individual cells. The data and knowledge generated from biological systems will eventually enable the earliest possible and most reliable prediction of disease progression and how it can be treated in the best possible way. The center combines local scientific, clinical and technical expertise relevant to innovative single-cell research leveraging the full range of scRNA-seq technologies for both eukaryotes and bacteria.

Starting from infection research, the Würzburg Single-Cell Center will also investigate cancer, neurodegenerative disorders or cardiovascular diseases at the single cell level. The broad spectrum of RNA sequencing technologies will be rapidly deployed and expanded in support of our research communities and priorities.

For further information please visit the website of the Single Cell Center Würzburg at **www.helmholtz-hiri.de/de/single-cell-center-1**.

5.7
CORE UNIT SYSTEMS MEDICINE

Genomics data are often the foundation of major discoveries in the field of biomedical and clinical research. Next-generation sequencing (NGS) and its various technologies provide powerful and essential tools allowing holistic insights into biological systems. The Core Unit Systems Medicine (CU SysMed), 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, provides expertise and technical resources to address the ever-growing demand for generation, analysis, and interpretation of genomics data.

The CU SysMed is a NGS core facility located at the Institute of Molecular Infection Biology that provides consultation on NGS and lab services to researchers at the University and the University Hospital in Würzburg as well as external research groups. Applications of high-throughput, deep sequencing technologies include, for example, mammalian exome sequencing, bacterial and viral genome sequencing, transcriptome sequencing (mRNA, ncRNA, total RNA, single cell RNA/ATAC). In addition, CU SysMed offers special sequencing protocols 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 is placed on the development and optimization of single-cell RNA sequencing (scRNA-seq) techniques for pathogenic prokaryotes.

The excellent reputation of our team has also been built on synergies between wet-lab scientists and bioinformaticians as well as on close collaborations with local researchers. The steering committee will continue to support the expansion of our service portfolio based on organizational priorities and requests from users of the local research community.

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

CENTRE FOR MICROBIAL SINGLE-CELL RNA-SEQ (MICROSEQ)

Building on the success of our NGS core facility and to leverage the full potential of single-cell transcriptomics for microbiology and infection research, we are establishing a Centre for Microbial Single-cell RNA-seq (MICROSEQ). The new centre will develop generic protocols for rapid, cost-effective and high-throughput bacterial scRNA-seq. It will provide state-of-the-art data analysis and visualisation tools, and offer training opportunities for young microbiologists from around the globe. In the international context, MICROSEQ is unique in its focus and collective expertise involving renown and local researchers and thereby complementing ongoing efforts by DFG to foster the application of NGS technology at German universities.

While single-cell RNA-seq (scRNA-seq) of eukaryotic cells has become routine using commercially available platforms, transcriptomics of individual microbes remains largely uncharted territory. Thanks to very recent breakthroughs in methodology including pioneering work from Würzburg scientists, however, bacterial scRNA-seq is now technically feasible. This state-of-the-art approach promises a new microbiology, for instance, by enabling high-resolution profiling of gene activity in complex microbial consortia such as the microbiome, or monitoring drug susceptibility of pathogens from clinical samples based on RNA signatures. Irrespective of the success of a few initial proof-of-concept studies, bacterial scRNA-seq is in its infancy stage.

Bacterial scRNA-seq is a promising and powerful tool not just in microbiology or infection biology. For example, persisters are a small subpopulation of bacteria that withstand antibiotic exposure potentially causing infection relapse. The underlying mechanisms remain unclear, however, persisters seem far from being transcriptionally inert within their host niche. Bacterial scRNA-seq of pathogenic persisters isolated from infected patients holds the potential to elucidate *in vivo* activities and reveal reasons for reactivation. We expect scRNA-seq to become an invaluable tool for the analysis of clinical samples.

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

The Graduate School of Life Sciences (GSLS) was awarded excellence status twice in the German Excellence Initiative and currently involves almost 800 doctoral researchers and >350 PIs from the faculties of Biology, Medicine, Chemistry and Pharmacy, Physics, and Human Sciences.

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. The GSLS offers structured training of doctoral researchers by a thesis committee, conference funding, training, lectures, mentoring and certification of activities. Furthermore, the GSLS supports postdoctoral researchers with fellowships aimed at the early and more advanced career stage. Importantly, the GSLS admits junior group leaders as full members who thereby are eligible to become primary supervisors in doctoral thesis committees.

PhD doctoral researchers: Through the GSLS, the doctoral researchers are offered supervision by a thesis committee comprising at least three PIs, training (scientific and transferable skill courses) and certification of activities (e.g., lectures, seminar series, and summer schools). The scientific and transferable skill courses are tailored to the need of the early (e.g., scientific writing/presentation and statistics), as well as advanced PhD stage (e.g., grant writing, job interview training and courses preparing for a career in industry). GSLS Travel Fellowships provide funding for doctoral researchers to attend national and international conferences. The GSLS furthermore runs a mentoring program for female PhD doctoral researchers entitled MENTORING Life Sciences to empower female researchers to face challenges they could come across during their scientific careers. The activities of this program include workshops, network meetings, career talks, meetings with guest speakers, peer groups, and mentor-mentee pairing.

Medical doctoral researchers: The Medical Faculty and the GSLS provide scholarships to medical students for pursuing a structured medical doctoral program within the GSLS. The curriculum is adapted to the one provided for PhD doctoral researchers and thus contains elements like travel fellowships and access to scientific and transferable skills courses offered by the GSLS.

Postdoctoral researchers: The GSLS offers a PostDoc Plus program (1 year duration) for selected postdoctoral researchers. The PostDoc Plus program supports the transition from a postdoctoral researcher to a scientifically independent junior group leader by providing funding to conduct initial experiments for external grant applications. Furthermore, postdoctoral researchers are eligible to participate in relevant transferable skills and scientific workshops conducted by the GSLS. The Career Development Fellowship of the GSLS aims at supporting recently graduated GSLS doctoral researchers for short periods (6 months) to finish their project and/or submit first grant applications.

SECTION INFECTION AND IMMUNITY

Section Speakers:

JUN. PROF. DR. FRANZISKA FABER
(Institute of Molecular Infection Biology/ZINF)

PROF. DR. GEORG GASTEIGER
(Institute of Systems Immunology)

PROF. DR. OLIVER KURZAI
(Institute for Hygiene and Microbiology)

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 2243) UBI

UNDERSTANDING UBIQUITYLATION: FROM MOLECULAR MECHANISMS TO DISEASE

UBI WÜRZBURG GRK2243

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:

A4 CAROLINE KISKER & THOMAS RUDEL
(Rudolf Virchow Center for Integrative and Translational Bioimaging (RVZ), Dept. of Microbiology)
Cross-regulation between eukaryotic E3 ligases and chlamydial infection

B1 CAROLINE KISKER
(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

B5 CAROLINE KISKER
(RVZ)
Structure-based design and synthesis of anti-microbial DUB inhibitors

B6 VERA KOZJAK-PAVLOVIC
(Dept. of Microbiology)
Ubiquitin-modifying enzymes of *Simkania negevensis* and their role in infection

6.3

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

3D TISSUE MODELS FOR STUDYING MICROBIAL INFECTIONS BY HUMAN PATHOGENS

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
(Dept. of Internal Medicine II)
Host-pathogen interactions revealed by 3D high-resolution microscopy

02 THOMAS RUDEL
(Dept. of Microbiology)
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
(ZINF)
Analysis of the innate immune response of gastrointestinal epithelium in 3D organoids

11 CINDRILLA CHUMDURI
(Dept. of Microbiology)
Investigating *Chlamydia*, HPV, and co-infection dynamics usind human primary 3D cervical epithelial models

12 THOMAS DANDEKAR & ANTOINE-EMMANUEL SALIBA
(Dept. of Bioinformatics, HIRI)
RNA-omics and Single Cell-omics of human pathogens in 3D tissue *ex-vivo* models

6.4

DFG RESEARCH TRAINING GROUP (GRADUIERTENKOLLEG GRK 2581) SPHINGOINF

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

SPHINGOINF
Sphingolipid 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 BEYERSDORF & SIBYLLE SCHNEIDER-SCHAULIES
(Institute for Virology and Immunobiology)
The NSM2 as virus effector: targets, topology and functional consequences in T cells

03 NIKLAS BEYERSDORF & 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

6.5

ELITE NETWORK BAVARIA (INTERNATIONAL DOCTORATE PROGRAM)

RNAMED: FUTURE LEADERS IN RNA-BASED MEDICINE

"RNAmed – Future Leaders in RNA-based Medicine" is a whole new graduate program, which started in late 2022. It is funded through the Elite Network Bavaria and offers up to 20 fully-funded PhD positions (4 years) in Würzburg, Munich or Regensburg.

RNA-based therapeutics have emerged in recent years for several diseases. With the exceptionally rapid development of RNA vaccines to counteract the SARS-CoV-2 pandemic it has become increasingly clear that RNA is on the verge of becoming another major molecule class for the fields of diagnostics, prevention and treatment of diseases.

RNAmed represents a diverse consortium of 11 world-leading scientists in the fields of RNA modification and delivery, CRISPR-Cas, microRNAs, noncoding RNA, RNA biology of infections, and RNA chemistry. Importantly, the program takes a highly interdisciplinary and holistic approach to endow doctoral students with the necessary knowledge and skills in the fast-growing area of RNA-based medicine. RNAmed students have the unique opportunity to undertake cutting-edge research combining the aforementioned expertise. An interdisciplinary committee of international scientists will guide and support PhD candidates throughout their PhD. Structured mentoring and training including summer schools, industry internships, hard and soft skill workshops and opportunities to present their work at international conferences will prepare students for careers as scientists in academia or industry, as entrepreneurs or as policy makers in the broader area of RNA-based medicine.

The program has put academic excellence and an open mind at its base. An international spirit, active networking, extracurricular activities and pharmaceutical translation are main features of RNAmed. The group consists of international PhD students, who are outstanding communicators and who leverage teamwork while embracing leadership. They are taught to think critically, to provide lasting value for society and to be enthusiastic about all things RNA. We expect them to drive precision medicine and targeted molecular therapies forward.

Spokesperson of RNAmed:

PROF. DR. JÖRG VOGEL
(Institute of Molecular Infection Biology, HIRI)

Participating ZINF members:

CYNTHIA SHARMA
(Institute of Molecular Infection Biology)

7
APPENDIX

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

Former position (retired):
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:
Vice-Rector for Research, 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:
Sen. Project Manager, Boehringer Ingelheim Pharma, Dept. of Cancer Immunology & Immunemodulation, 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:
Lab Operations Manager at BioLabs Heidelberg

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

2020-2022

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

Joint Symposium of the SFB/TRR 225 and GRK 2157 "Biofabrication meets Infection"
Sina Bartfeld, Vera Kozjak-Pavlovic, Marco Metzger, Thomas Rudel
Würzburg, 24 – 25 November 2022

6. Digitales Myelom-Forum 2022
Herrmann Einsele
Virtual Meeting, 19 November 2022

RNA Biology Course – Fall 2022
Redmond Smyth, Neva Caliskan
Würzburg, 24 – 28 October 2022

6th GRK 2157 Retreat, 3D Infect
Thomas Rudel
Würzburg, 19 – 21 October 2022

2022 International IBS Conference for Genomic Integrity
Caroline Kisker
Busan (South Korea), 18 – 20 October 2022

PhD Retreat of the IMIB, ZINF and HIRI
Bayreuth, 13 – 14 October 2022

Annual Meeting of the German Association for Synthetic Biology (GASB6)
Chase Beisel
Würzburg, 21 – 22 September 2022

International Symposium "Sphingolipids in Infection 2022"
J. Seibel
Würzburg, 20 – 22 September 2022

11th BMBF-funded Short Course on "Modern Methods in Infection Biology"
Thomas Dandekar
Würzburg, 19 – 23 September 2022

5. Digitales Myelom-Forum 2022
Herrmann Einsele
Virtual Meeting, 9 July 2022

1st Summer Symposium "Systems Immunology – Networks Across Scales"
Georg Gasteiger, Wolfgang Kastenmüller
Würzburg, 6 – 8 July 2022

Infection & Immunity Short Course – Spring 2022
Franziska Faber, Alexander Westermann
Würzburg, 16 – 20 May 2022

GRK2243 Symposium
Caroline Kisker
Würzburg, 9 – 11 May 2022

Keystone Symposium on Molecular & Cellular Biology "Small Regulatory RNAs: From Bench to Bedside"
Jörg Vogel
Santa Fe (United States), 1 – 4 May 2022

Science Communication Workshop
Neva Caliskan
Würzburg, 25 – 26 November 2021

4. Digitales Myelom-Forum 2021
Herrmann Einsele
Virtual Meeting, 20 November 2021

Fraunhofer Academy Workshop "Essentials of 3D Tissue Engineering"
Marco Metzger
Virtual Meeting, 10 – 11 November 2021

Bayresq.net Meeting
Lars Barquist, Ana Rita Brochado, Franziska Faber, Cynthia Sharma, Jörg Vogel
Würzburg, 25 October 2021

FOR 2799 Meeting – Receiving and Translating Signals via the γδ T Cell Receptor
Thomas Herrmann
Würzburg, 13 – 14 October 2021

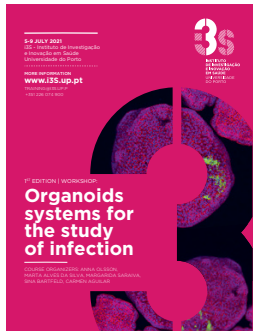
RNA Biology Course - Winter 2021
Chase Beisel, Neva Caliskan, Redmond Smyth
Würzburg, 6 – 12 October 2021

5th GRK 2157 Retreat, 3D Infect
Thomas Rudel
Würzburg, 4 – 5 October 2021

10th BMBF-funded Short Course on "Modern Methods in Infection Biology"
Thomas Dandekar
Virtual Meeting, 20 – 24 September 2021

1st Edition of the Organoids Systems for the Study of Infection
Carmen Aguilar, Sina Bartfeld
Porto (Portugal), 5 – 9 July 2021

3. Digitales Myelom-Forum
Herrmann Einsele
Virtual Meeting, 3 July 2021



14th Berlin Summer Meeting, MDC Berlin
Jörg Vogel
Virtual Meeting, 18 June 2021

26th Annual Meeting of the RNA Society
Jörg Vogel
Virtual Meeting, 25 May – 5 June 2021

Lecture course "Infection Biology"
HIRI Graduate Program "RNA & Infection"
Alexander Westermann
Virtual Meeting, 10 – 14 May 2021

1st International Symposium of Fusobacteria
Jörg Vogel
Virtual Meeting, 15 April 2021

3rd European CAR T-cell Meeting (EHA-EBMT)
Herrmann Einsele
Virtual Meeting, 4 – 6 February 2021

2. Digitales Myelom-Forum 2020
Herrmann Einsele
Virtual Meeting, 20 November 2020

9th BMBF-funded Short Course on "Modern Methods in Infection Biology"
Thomas Dandekar
Virtual Meeting, 21 – 25 September 2020

DMykG Annual Conference (Deutschsprachige Mykologische Gesellschaft)
Oliver Kurzai
Virtual Meeting, 16 – 18 September 2020

Temporal Single Cell Analysis Workshop (Single Cell Omics Germany)
Emmanuel Saliba
Virtual Meeting, 15 September 2020

1. Digitales Myelom-Forum 2020
Herrmann Einsele
Virtual Meeting, 4 July 2020

2nd European CAR T Cell Meeting (EHA-EBMT)
Herrmann Einsele
Barcelona (Spain), 30 January – 1 February 2020

7.3 SEMINARS AND COLLOQUIA

2020-2022

MICROBIOLOGY COLLOQUIUM

5 April 2022
Philip Adams, NIH, Bethesda, US
Transcriptome mapping of the Lyme disease pathogen reveals RNA regulators

11 February 2020
Herbert Schiller, Helmholtz Zentrum München
Longitudinal single cell transcriptomics of lung regeneration and fibrogenesis

28 January 2020
Ilan Rosenshine, Hebrew University of Jerusalem, IL
Molecular trade between bacteria and eukaryotic host mediated by membranous nanotubes

14 January 2020
Owen Fenton, University of North Carolina, US
Synthetic chemistry approaches towards non-viral *in vivo* mRNA delivery

14 January 2020
Brice Felden, Université de Rennes 1, FR
sRNA-encoded peptides in bacterial pathogens: Inspiration for novel antibiotics effective against MDR bacteria with limited resistance

RNA SEMINAR

8 November 2022
Benjamin Nilsson-Payant, Twincore Hannover
Defective viral genomes of segmented (-)RNA viruses – friend or foe?

25 October 2022
Maria Sokolova, Max Planck Institute for Multidisciplinary Sciences, Göttingen
Structure and function of unique virion RNA polymerases from crAss-like phage phi14:2 and thermophilic phage P23-45

18 October 2022
Peter Fineran, University of Otago, NZ
The recurring theme of RNA in phage defence and counter-defence

4 October 2022
Ben tenOever, NYU Langone, US
The pros and cons of splicing as an RNA virus

5 July 2022
Daniel Depledge, Hannover Medical School
Deciphering epitranscriptomes through nanopore sequencing – a virological perspective

21 June 2022
Torben Heick Jensen, University of Aarhus, DK
Nuclear sorting of RNA

11 May 2022
Katja Petzold, Karolinska Institute, Stockholm, SE
RNA Tango: How structural changes define RNA function

4 February 2020
David Corey, UT Southwestern, Dallas, US
Mechanisms and Applications of RNA interference

7 January 2020
Gunter Meister, University of Regensburg
Non-coding RNAs and RNA modifications as me mediators of post-transcriptional gene regulation

ORGANOID CLUB

3 November 2022
Michael Sigal, Max Delbrück Center, Berlin
Gastric epithelial stem cells in health and disease

Kim Bak Jensen, University of Copenhagen, DK
Intestinal epithelial stem cells in health and disease

6 October 2022
Ludovic Vallier, Berlin Institute of Health at Charité Berlin
Stem cells and organoids to study liver biology and diseases

1 September 2022
Christian Conrad, Berlin Institute of Health at Charité Berlin
Translational organoid screening and sequencing

Anne Grapin-Botton, Max Planck Institute of Molecular Cell Biology and Genetics, Dresden
Modeling mammalian pancreas development with organoids

7 July 2022
Sina Bartfeld, ZINF, Würzburg
Infection, innate immune signalling and cancer in the gut - organoids as disease model

Nicolas Rivron, Institute of Molecular Biotechnology, of the Austrian Academy of Sciences, AT
Blastoids: shaping the mammalian embryo for implantation

2 June 2022
Agnieszka Rybak-Wolf, Max Delbrück Center, Berlin
Therapeutic strategies for Herpes simplex virus driven encephalitis

5 May 2022
Leif S. Ludwig, Max Delbrück Center, Berlin
Lineage tracing in human hematopoiesis using single cell genomics

Alejo E. Rodriguez-Fraticelli, IRB Barcelona, ES
Clonal drivers of stem cell variation

7 April 2022
Aydan Bulut-Karslioglu, Max Planck Institute, Berlin
Modulating developmental timing by putting embryos to sleep

Vincent Pasque, KU Leuven, BE
Single-cell and integrated multi-omics of human development and stem cells

16 June 2021
Ole Pless, Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Hamburg
hiPSC-derived models for early stage drug discovery targeting infectious disease

9 June 2021
Theresia Stradal, Helmholtz Centre for Infection Research, Braunschweig
Studying host-pathogen interaction on cellular and molecular level

12 May 2021
Kadi Löhmussaar, University of Copenhagen, DK
Patient-derived organoids as a great tool to study cervical tissue dynamics in health and disease

5 May 2021
Hillary Kenny, University of Chigaco, US
Design and Implementation of a 3D organotypic model of the human mesothelium

SYSTEMS IMMUNOLOGY SEMINAR

28 November 2022
Verena Ruprecht, Center of Genomic Regulation, Barcelona, ES
Cell and tissue mechano-plasticity in the early embryo

27 October 2022
Maike Hofmann, University of Freiburg
CD8+ T cell responses in COVID-19 and chronic viral hepatitis

18 October 2022
Anna Lippert, Cambridge Institute for Medical Research, UK
How do T cell experience their environment? Studying molecular mechanisms of T cell sensing

13 October 2022
Bahtiyar Yilmaz, University of Bern, CH
Plasticity of the adult intestinal microbiota

10 October 2022
Tal Arnon, University of Oxford, UK
Spatiotemporal regulation of adaptive immune responses

24 June 2022
Jakob Zimmermann, University of Bern, CH
Noninvasive assessment of gut function using transcriptional recording sentinel cells

11 May 2022
Nina Cabezas-Wallscheid, Max Planck Institute of Immunobiology and Epigenetics, Freiburg
Regulation of dormant hematopoietic stem cells

7 April 2022
Dietmar Zehn, Technical University of Munich
Mechanisms that adjust and control the effector capacity of T cells

24 March 2022
Tobias Bald, University Hospital Bonn
Targeting immune checkpoints in cancer - are we barking at the wrong tree?

5 October 2020
Florian Wimmers, Stanford University, US
Systems immunological assessment of the immune response to infections and vaccines at the single-cell level

23 July 2020
Dominic Grün, University of Würzburg
Deciphering cell fate decisions at single-cell resolution

VIROLOGY AND IMMUNOBIOLOGY SEMINAR

5 December 2022
Thomas Schulz, Hannover Medical School
Exploring key steps in the life cycle of Kaposi Sarcoma-associated Herpesvirus as possible new antiviral targets

28 November 2022
Sarina Ravens, Hannover Medical School
Deciphering underlying mechanisms of postnatal gamma delta T cell adaptation

14 November 2022
David Vöhringer, University Hospital Erlangen
Regulation of innate and adaptive Type 2 immunity

6 October 2022
Andrew Kueh, The Walter and Eliza Hall Institute of Medical Research, Melbourne, AU
The use of CRISPR/Cas systems as diagnostic tools

11 July 2022
Sebastian Kobold, Hospital of the Ludwig-Maximilians-University Munich
Migratory engineering of T cells for cancer therapy

4 July 2022
Melanie Brinkmann, Helmholtz Centre for Infection Research, Braunschweig
License to stay: how human cytomegalovirus disrupts, evades and exploits the host

13 June 2022
Wolfgang Preiser, University of Stellenbosch, ZA
The South African Covid experience

7 June 2022
Mathias Munschauer, HIRI, Würzburg
The SARS-CoV-2 RNA-protein interactome at subgenome resolution

30 May 2022
David Vermijlen, Université libre de Bruxelles, BE
The development and function of human innate γδ T cells

23 May 2022
Ulrich Schaible, Research Center Borstel
Towards novel treatment concepts in tuberculosis

16 May 2022
Bart Haagmans, Erasmus Medical University Center, Rotterdam, NL
Organoids to study the pathogenesis of emerging coronaviruses

7 February 2022
Philippe Bousso, Institut Pasteur, Paris, FR
Quorum sensing mechanisms in the immune system

31 January 2022
Dominic Grün, University of Würzburg
Immune cell differentiation through the lens of single-cell genomics

17 January 2022
Volker Thiel, University of Bern, CH
It's been a long way - 20 years of coronavirus reverse genetics

10 January 2022
Julie Déchanet-Merville, University of Bordeaux, FR
Understanding gamma-delta T cell recognition of tumors toward their use in immunotherapy

13 December 2021
Thomas Winkler, University of Erlangen-Nürnberg
CMV infection in Graft-versus-Host Disease: B and T cell immunity

15 November 2021
Brian Evavold, University of Utah, US
Mechanobiology of T cells: To Catch a Bond

8 November 2021
Chris Benedict, La Jolla Institute for Immunology, US
Defining the cytomegalovirus CD4T cell landscape

5 July 2021
Ben Willcox, University of Birmingham, UK
Unique innate-like and adaptive paradigms in the human gd T cell compartment: room for everything

28 June 2021
Thomas Mettenleiter, Friedrich-Löffler-Institute, Federal Research Institute for Animal Health, Greifswald
The Ebola of pigs – African Swine Fever

14 June 2021
Michael Weekes, University of Cambridge, UK
New insights into viral immune evasion from quantitative multiplexed proteomics

7 June 2021
Gordon Brown, University of Exeter, UK
C-type lectins: Key regulators of immunity

31 May 2021
Peter Zipfel, Leibniz Institute for Natural Product Research and Infection Biology, Jena
Complement and Innate Immunity: The Role in Infections and Autoimmune Diseases

10 May 2021
Branka Horvat, Institut National de la Santé et de la Recherche Médicale (INSERM), Lyon, FR
SARS-CoV-2-induced activation of human endogenous retrovirus W envelope expression

3 May 2021
Claudia Kemper, National Heart, Lung, and Blood Institute, Bethesda, US
Unexpected role for complement in normal cell physiology

26 April 2021
Dmitry Gabrilovich, AstraZeneca, Gaithersburg, US
Myeloid-derived suppressor cells in regulation of tumor progression

12 April 2021
David Bloom, University of Florida, US
An *in vitro* human neuronal model of Herpes Simplex Virus latency: Insights into the dynamic processes of latency and reactivation

18 January 2021
John Ziebuhr, University of Gießen
The complex and unique enzymology of corona virus RNA synthesis – an update

7 December 2020
Marco Colonna, Washington University, St. Louis, US
Harnessing innate immunity in the therapy of neuro-degeneration and cancer

30 November 2020
Burkhard Becher, University of Zürich, CH
The T cell phagocyte interface in inflammation

23 November 2020
Noam Stern-Ginossar, Weizmann Institute of Science, Rehovot, IL
The translation landscape in SARS-CoV-2 infected cells

9 November 2020
Burkhard Ludewig, Kantonsspital St. Gallen, CH
Immunostimulatory fibroblasts in tumors and inflamed tissues

2 November 2020
Paul Bieniasz, The Rockefeller University, New York, US
The neutralizing antibody response to SARS-CoV-2

26 October 2020
Michael Mühlebach, Paul-Ehrlich-Institute, Langen
Measles virus and the immune system – risks and chance of close combat

19 February 2020
Jürgen Groll, University of Würzburg
Biofabrication: Status of the Field and Activities at FMZ

29 January 2020
Frank Horling, BioAgilytix, Hamburg
Development strategies for therapeutic proteins: from early research to market authorization

13 January 2020
Tobias Lenz, University of Hamburg
Trade-offs between pathogen resistance and autoimmunity shape genomic variability of MHC immune genes

OTHER SEMINARS

Only selected seminars of ZINF members or related to infectious diseases are listed.

27 October 2022
Peter Fineran, University of Otago, NZ
Not all viruses are bad: are viruses of bacteria our friends?

19 October 2022
Redmond Smyth, HIRI, Würzburg
Probing the structure and function of viral RNAs

Bhupesh Prusty, University of Würzburg
Regulation of miRNA processing by other miRNAs through sequence specific RNA:RNA interactions

27 September 2022
Caleb Lareau, Stanford University, US
Selection dynamics and latent viral reactivation in human T cells

29 July 2022
David Mayo Muñoz, University of Otago, NZ
Hfq and small RNA regulation of multiple CRISPR-Cas systems in *Serratia*

11 July 2022
Nils Birkholz, University of Otago, NZ
Unexpected layers of regulation in phage anti-CRISPR deployment

20 October 2021
Chase Beisel, HIRI, Würzburg
CRISPR-Cas systems and the dilemma(s) of adaptive immunity

Antoine-Emmanuel Saliba, HIRI, Würzburg
Uncovering host-pathogen interaction modalities using single-cell RNA-seq and RNA metabolic labeling

24 February 2021
Neva Caliskan, HIRI, Würzburg
Structural and molecular basis for Cardiovirus 2A protein as a viral gene expression switch

Mathias Munschauer, HIRI, Würzburg
The SARS-CoV-2 RNA–protein interactome in infected human cells

BIOZENTRUMS-KOLLOQUIUM

15 January 2020
Yannick Schwab, EMBL, Heidelberg
Exploring cell types at sub-cellular resolution with multimodal correlative imaging: combination of gene expression atlases, X-ray imaging and volume electron microscopy

7.4 FUNDING

2020-2022

AGUILAR, CARMEN

BMBF (01KI2107): FiRe-Upec – Exploiting host pathways to treat antibiotic resistant uropathogenic Escherichia coli infections

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

BMBF Organo-Strat: Organ-specific Stratification in Covid-19

IZKF (A-D-427): Characterization of the neonatal intestinal immune response and barrier function in human intestinal organoids

BARQUIST, LARS

StMWK Bayresq.net: New Strategies against Multi-Resistant Pathogens by Means of Digital Networking Rbiotics: RNA antibiotics

BEILHACK, ANDREAS

DFG SFB/TRR 124: FungiNet – Pathogenic fungi and their human host: Networks of interaction (Project A03): I*n vivo* analysis of temporal and spatial disease progression and immune cell interaction during invasive *Aspergillus fumigatus* infection

DFG SFB/TRR 221: Modulation of graft-versus-host and graft-versus-leukemia immune responses after allogeneic stem cell transplantation (Projects B09): Regulation of tissue-resident myeloid cells controling acute and chronic GvHD; (Projects B11): Targeting the reciprocal interaction of GvHD and atherosclerosis after allogeneic HSCT; (Project Z02): Animal engineering and complex transplantation models

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

Else-Kröner-Forschungskolleg for Interdisciplinary Translational Immunology (Coordinator), Else-Kröner-Fresenius-Stiftung (second funding period)

Bayerische Forschungsstiftung (WP2TP3): FortiTher – Tumor diagnostics for individualized therapy

BEISEL, CHASE

ERC Consolidator Grant: CRISPR Combo

DFG SPP 2141: Much more than defence – the multiple functions and facets of CRISPR-Cas (BE 6703/1-1 and BE 6703/1-2): Characterizing CRISPR-Cas systems with non-defensive functions (BE 6703/3-1): Prevalence, formation, and function of "extraneous" CRISPR RNAs derived from the extra repeat in CRISPR arrays

DFG SPP 2330: New concepts in prokaryotic virus-host interactions - from single cells to microbial communities (BE 6703/2-1): Interrogating the contributions of novel immune systems to anti-phage defense in their native bacterial hosts

BMBF GO-Bio (16LW0132): Employing CRIPSR-Cas12 for sensitive and multiplexed diagnostics

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

SPRIND: BacDefense - Harnessing bacterial defense systems as novel human antiviral agents

StMWi Medical Valley Award: CRISPR-Dx - An innovative CRISPR technology for the detection of multiple biomarkers

BEYERSDORF, NIKLAS

DFG SFB 1525: Cardio-Immune Interfaces (Project A02): T cells as a therapeutic target in an acute myocardial infarction pig model; (Project C05): Role of anti-heart autoimmunity for disease progression in patients with acute decompensation of heart failure

DFG SFB/TRR 124: FungiNet – Pathogenic fungi and their human host: Networks of interaction (Project C06): Secreted fungal proteins in immune evasion and pathogenicity

DFG GRK 2581: SPHINGOINF - Metabolism, topology and compartmentalization of membrane proximal lipid and signaling components in infection (Project 01): The NSM2 as virus effector: targets, topology and functional consequences in T cells; (Project 03): Sphingolipids balancing CD4+ Foxp3+ regulatory and effector T cell responses in chronic viral infections

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

BMBF (031L0156C): *In-vitro* test methods to evaluate the efficacy of immunological therapies for malignant melanoma

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

StMWK Bayresq.net: New Strategies against Multi-Resistant Pathogens by Means of Digital Networking (StressRegNet): Identifying stressor-regulator pairs involved in bacterial stress response, virulence, and antibiotic sensitivity using high-throughput approaches and machine learning

CALISKAN, NEVA

ERC Starting Grant: T-FRAME - Real-time analysis of ribosomal frameshifting and its impact on immunity and disease

RNA Society: RNA Salon-Würzburg

CHUMDURI, CINDRILLA

DFG GRK 2157: 3D Infect – 3D Tissue Models for Studying Microbial Infections by Human Pathogens (Project 11): Investigating *Chlamydia*, HPV and co-infection dynamics using human primary 3D cervical epithelial models

DFG (CH 2527/2-1): The impact of HPV and *Chlamydia* (co-)infections on the cellular crosstalk and squamous metaplasia development in the Cervical Transition Zone

DANDEKAR, THOMAS

DFG SFB/TRR 124: FungiNet – Pathogenic fungi and their human host: Networks of interaction (Project B01): Evolution of fungal virulence and host responses comparing *Candida*, *Lichtheimia* and *Aspergillus* spp; (Project B02): Host-pathogen interactions triggering infection signal networks in *Aspergillus fumigatus*, *Candida albicans* and human immune cells

DFG SFB/TRR 221: Modulation of graft-versus-host and graft-versus-leukemia immune responses after allogeneic stem cell transplantation (Projects INF): Data integration platform and systems medicine efforts to foster GvL and GvHD research

DFG GRK 2157: 3D Infect – 3D Tissue Models for Studying Microbial Infections by Human Pathogens (Project 12): RNA-Omics and Single Cell-omics of human pathogens in 3D tissue *ex vivo* models

IZKF (A-401): NAFLD – The role of the intestinal myco-biome in the pathogenesis of the non-alcoholic fatty liver disease

DÖLKEN, LARS

ERC Consolidator Grant: Herpesvirus Effectors of RNA Synthesis, Processing Export and Stability

ERC Consolidator Grant: Deciphering cellular and viral determinants of lytic HSV-1 infection, latency and reactivation (DecipherHSV)

DFG SFB 1525: Cardio-Immune Interfaces (Project A04): Role of inflammation, autoimmunity and common viral infection in arrhythmogenic cardiomyopathy

DFG GRK 2581: SPHINGOINF - Metabolism, topology and compartmentalization of membrane proximal lipid and signaling components in infection (Project 01): The NSM2 as virus effector: targets, topology and functional consequences in T cells

DFG FOR 2830: Advanced Concepts in Cellular Immune Control of Cytomegalovirus (Project 01): Integrative analyses of CMV translatomes and MHC-I ligandomes

DFG FOR 5200: Disrupt - Evade - Exploit: Gene expression and host response programming in DNA virus infection (DEEP-DV) (Project 02): Regulation and Herpes simplex virus 1 counter-regulation of transcriptional bursting kinetics in the early type I interferon response

DFG (DO 1275/6-1): Functional analysis of downstream open chromatin induced in HSV-1 infection

DFG (DO 1275/10-1): Deciphering pro- and antiviral factors for CMV infection by heterogeneity sequencing

DFG (DO 1275/14-1): Functional single-cell genomics of human cytomegalovirus infection

StMWK (FOR-COVID): Deciphering SARS-CoV-2 infection by scSLAM-seq and artificial intelligence

EINSELE, HERMANN

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; (Project A08): Gene-engineered CAR T-cells and macrophages to treat Aspergillus fumigatus infection

DFG SFB/TRR 221: Modulation of graft-versus-host and graft-versus-leukemia immune responses after allogeneic stem cell transplantation (Project A03): Advanced CAR T cell engineering to augment the graft-versus-leukemia effect of allogeneic HSCT

DFG SFB/TRR 338: LETSIMMUN – Lymphocyte Engineering for Therapeutic Synthetic Immunity (Project Z02): Bench-to-Bedside Advanced Therapy Medicinal Product (ATMP) Development Platform

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

DFG KFO 5001: ResolvePain – Peripheral mechanisms of pain and their resolution (Project P1): Bortezomib-induced painful neuropathy: risk factors, resilience and resolution

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

BMBF Nationales Centrum für Tumorerkrankungen (NCT) WERA

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

ENGSTLER, MARKUS

EU Horizon 2020- MSCA-ITN PHYMOT - Physics of Microbial Motility – ESR9: Evolution of microswimmer designs in distinct micro-environments

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 SPP 2332: Physics of Parasitism (EN 305/13-1): Mechanical strategies to avoid interspecies competition in trypanosomes; (EN 305/12-1): Coordination

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

DFG (FE 1432/3-1): Membrane Biophysics of African Trypanosomes

BMBF Organo-Strat: Organ-specific Stratification in Covid-19

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 SFB 1525: Cardio-Immune Interfaces (Project PS2): Single-cell assays to investigate inflammatory dynamics in cardiovascular diseases

DFG FOR 2830: Advanced Concepts in Cellular Immune Control of Cytomegalovirus (Project 01): Integrative analyses of CMV translatomes and MHC-I ligandomes

DFG FOR 5200: Disrupt - Evade - Exploit: Gene expression and host response programming in DNA virus infection (DEEP-DV) (Project 02): Regulation and Herpes simplex virus 1 counter-regulation of transcriptional bursting kinetics in the early type I interferon response

DFG (ER 927/2-1): Deciphering pro- and antiviral factors for CMV infection by heterogeneity sequencing

DFG (ER 927/6-1): Characterization of cryptic peptides presented by MHC-I

DFG (ER 927/7-1): Time-resolved single cell genomics of human cytomegalovirus (hCMV) infection in myeloid cells

Marie Skłodowska-Curie Action (MSCA) Innovative Training Network VIROINF (ESR 6): Conservation of regulatory elements and effector mechanisms in lytic and latent cytomegalovirus infection

StMWK (FOR-COVID): Deciphering SARS-CoV-2 infection by scSLAM-seq and artificial intelligence

FABER, FRANZISKA

DFG (FA 1113/2-1): Mechanisms of Hfq-mediated gene regulation by small regulatory RNAs in *Clostridium difficile*

DFG (FA 1113/4-1): Characterization of the RNA-binding protein KhpB - mechanisms of RNA binding and the regulation of metabolism & virulence in *C. difficile*

DZIF: The sporulation pathway as a pathoblocker target in *Clostridioides difficile*

StMWK Bayresq.net: New Strategies against Multi-Resistant Pathogens by Means of Digital Networking Rbiotics: RNA antibiotics

FRAUNHOLZ, MARTIN

DFG GRK 2581: SPHINGOINF - Metabolism, topology and compartmentalization of membrane proximal lipid and signaling components in infection (Project 06): Determining the role of sphingomyelinases in *S. aureus* phagocytosis

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

GASTEIGER, GEORG

ERC Starting Grant: Tissue-resident Lymphocytes – Development and Function in “real life” Contexts

DFG SFB 1525: Cardio-Immune Interfaces (Project A03): Pathomechanisms of Immunosenescence in the post-myocardial infarction healing response

DFG Emmy Noether Grant: Adaptive-innate lymphocyte crosstalk – mechanisms, functions, and consequences

DFG SFB/TRR 338: LETSIMMUN – Lymphocyte Engineering for Therapeutic Synthetic Immunity (Project B03): Engineering tissue-resident lymphocytes for the modulation of tissue-microenvironments

DFG SPP 1937: Innate lymphoid cells (GA 2129/2-1): Tissue-niches and cellular interactions of mouse and human ILCs at single-cell resolution

GOMEZ DE AGÜERO, MERCEDES

DFG SFB/TRR 221: Modulation of graft-versus-host and graft-versus-leukemia immune responses after allogeneic stem cell transplantation (Projects B09): Regulation of tissue-resident myeloid cells controlling acute and chronic graft versus host disease

DFG SPP 2330: New concepts in prokaryotic virus-host interactions - from single cells to microbial communities (GO 3241/1-1): Dynamic and mechanisms of early life interactions between bacteriophage and its bacteria host in the skin

QIAGEN NGS Research Grant

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, (HE 2346/8-2): Phylogeny and species comparison as tools for understanding antigen recognition by human γδ 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

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

DFG SFB 1525: Cardio-Immune Interfaces (Project A01): Elucidating the role of monocyte – Treg interactions as key drivers of cardiovascular remodelling after myocardial infarction

DFG GRK 2581: SPHINGOINF - Metabolism, topology and compartmentalization of membrane proximal lipid and signaling components in infection (Project 03): Sphingolipids balancing CD4+ Foxp3+ regulatory and effector T cell responses in chronic viral infections

DFG SFB/TRR 338: LETSIMMUN – Lymphocyte Engineering for Therapeutic Synthetic Immunity (Project B06): Engineering a sustainable and non-exhausting CD8+ T cell response

KISKER, CAROLINE

DFG GRK 2243: UBI – Understanding Ubiquitylation: From Molecular Mechanisms to Disease (Project A06): Cross-regulation between eukaryotic E3 ligases and chlamydial infection; (Project B01): Structural and functional analysis of the Fbw7-Usp28 complex; (Project B03): Mechanism of substrate recognition by chlamydial DUBs; (Project B04): Function of chlamydial DUBs during infection; (Project B05): Structure-based design and synthesis of antimicrobial DUB inhibitors

DFG (KI 562/13-1): The functional and molecular architecture of the CAK complex

IZKF (B-458): Structural and functional characterisation of hemibodies and their target antigens

Deutsche Krebshilfe: Using nucleotide excision repair as a therapeutic aim in cancer therapy

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*

DFG GRK 2243: UBI – Understanding Ubiquitylation: From Molecular Mechanisms to Disease (Project B6): Ubiquitin-modifying enzymes of *Simkania negevensis* and their role in infection

DFG GRK 2581: SPHINGOINF - Metabolism, topology and compartmentalization of membrane proximal lipid and signaling components in infection (Project 08): Mitochondrial sphingolipids and their role in infection

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): Modulation of neutrophil antifungal activity by intrinsic and extrinsic stimuli

DFG GRK 2581: SPHINGOINF - Metabolism, topology and compartmentalization of membrane proximal lipid and signaling components5 in infection (Project 05): The role of Sphingolipids in Innate Immune Recognition of *Candida albicans*

BMBF InfectControl: FINAR & FINAR 2.0 – Fungal Infections and Azole Resistance

BMBF InfectControl: RAI students – Rational use of antibiotics through information and communication: New target group - students of human medicine and pharmacy

BMBF InfectControl: Monitoring Concepts for SARS-CoV-2 – Epidemiology and Co-Infections (CoVMon)

BMBF Center for Sepsis Control and Care CSCC: QUANTIM – Quantification of Innate Immune Function in Whole Blood Infection Assays

BMBF CompLS (TP B): MuMoSim – Machine learning based multi-model simulator in infection research

IZKF (A-401): NAFLD – The role of the intestinal mycobiome in the pathogenesis of the non-alcoholic fatty liver disease

IZKF (D-420): Simulation of Fungal Keratitis in a 3D Cornea Model

BMG/RKI grant (1369-240): NRZMyk – Nationales Referenzzentrum für Invasive Pilzinfektionen

Else-Kröner-Fresenius-Stiftung: Else Kröner Center for Advanced Medical & Humanitarian Studies Würzburg - Mwanza

Bavarian State Ministry for Health and Care (StMG) via the Bavarian State Office for Health and Food Safety (LGL): Surveillance of SRAS-CoV-2 Infections in Day Care Centers via homebased bi-weekly Saliva Sampling and/or Rapid Antigen Tests

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

Wilhelm Sander-Stiftung (2020.017.1): Functional evaluation of human natural killer cells with synthetic antigen-specific receptors (CAR NK) for the add-on treatment of infections with *Aspergillus fumigatus*

Bavarian State Ministry for Health and Care (StMG) via the Bavarian State Office for Health and Food Safety (LGL): Surveillance of SRAS-CoV-2 Infections in Day Care Centers via homebased bi-weekly Saliva Sampling and/or Rapid Antigen Tests

LUTZ, MANFRED

DFG (LU 851/14-1): Conversion of anergic non-regulatory into Foxp3-IL-10+ regulatory T cells by dendritic cells *in vivo*

DFG (LU 851/18-1): Induction of myeloid-derived suppressor cells (MDSCs) by mycobacteria vaccines

IZKF (A-408): Induction of memory regulatory T cells during allergy immunotherapy

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 colon model to study host-commensal-pathogen interactions under hypoxic conditions

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

Bayerische Forschungsstiftung: FORTiTher – Research association for tumor diagnostics for individualized therapy

Else-Kröner-Foundation: UroVasC - Reconstruction of the lower urinary tract with vascularized SIS (BioVaSc-TERM®)

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 kinase and transcription factor signaling pathways

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

ERC Starting Grant: Interrogating RNA-protein interactions underlying SARS-CoV-2 infection and antiviral defense (COVIDecode)

SPRIND: BacDefense - Harnessing bacterial defense systems as novel human antiviral agents

StMWK FOR-COVID: Decoding the biology of SARS-CoV-2 infections from its direct *in vivo* RNA-protein interactome

OHLSEN, KNUT

DFG (OH 97/8-1): Modification of vancomycin to overcome bacterial resistance

BMBF Health Research (GFTARV62): PyrBac – Target validation for pharmaceutical drug development: Validation of pyruvate kinase as novel metabolic target to combat antibiotic resistant bacteria

BMBF Health Research (16GW0297): TRANsACT - T-box riboswitches as novel antibacterial targets: Validation of RNA-mediated methionine biosynthesis control in staphylococci as tool and proof of principle

PÉREZ, CHRISTIAN

DFG SFB/TRR 124: FungiNet – Pathogenic fungi and their human host: Networks of interaction (Project C01): Molecular characterization of *Candida albicans* attributes during translocation and dissemination and the effects of immunotherapy

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

PRUSTY, BHUPESH

BMBF (01EJ2204E): Mitochondrial dysfunction and metabolic alterations in ME/CFS

Amar Foundation: SARS-CoV-2 and Infectious origin of Chronic Fatigue Syndrome

ME Research UK: Role of HHV-6-induced mitochondrial dysfunction in myalgic encephalomyelitis (ME) and chronic fatigue syndrome (CFS)

Gemeinnützige Stiftung zur Unterstützung Der Betroffen und zur Erforschung von undiagnostizierten Krankenheiten: Understanding potential infectious triggers and mitochondrial dysfunction in ME/CFS

HHV-6 Foundation and GoFundMECFS: HHV-6 infection and development of ME/CFS

RUDEL, THOMAS

ERC Advanced Grant: Neutrophil – *Chlamydia* Interactions at the Crossroad of Adaptation and Defence

Innovative Medicines Initiative 2 (IMI2) EU Horizon 2020 and The European Federation of Pharmaceutical Industries and Associations (efpia): Inno4Vac - innovations to accelerate vaccine development and manufacture (WP15): Development of model and assay prototypes – Urovaginal

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 A6): Cross-regulation between eukaryotic E3 ligases and chlamydial infection; (Project B03): Mechanism of substrate recognition by chlamydial DUBs; (Project B04): Function of chlamydial DUBs during infection

DFG GRK 2581: SPHINGOINF - Metabolism, topology and compartmentalization of membrane proximal lipid and signaling components in infection (Project 07): Sphingolipid trafficking and function in Chlamydiales infection

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

DFG (RU 631/17-1): An integrated approach using dual 13C-profiling and RNA-sequencing for unravelling the metabolic programs of the intracellular forms of *Chlamydia trachomatis* and their host cells

BMBF Organo-Strat: Organ-specific Stratification in Covid-19

SALIBA, ANTOINE-EMMANUEL

DFG SFB 1525: Cardio-Immune Interfaces (Project PS2): Single-cell assays to investigate inflammatory dynamics in cardiovascular diseases

DFG GRK 2157: 3D Infect – 3D Tissue Models for Studying Microbial Infections by Human Pathogens (Project 12): RNA-Omics and Single Cell-omics of human pathogens in 3D tissue *ex vivo* models

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

NIH: High-throughput detection of transcriptomic and epitranscriptomic variation and kinetics using MarathonRT

BMMV: ImmuBat - Immune responses of potential reservoir bat species: viral detection and temperature-dependent immune cell plasticity at single cell resolution

StMWK (FOR-COVID): Deciphering SARS-CoV-2 infection by scSLAM-seq and artificial intelligence

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 GRK 2581: SPHINGOINF - Metabolism, topology and compartmentalization of membrane proximal lipid and signaling components in infection (Project 01): The NSM2 as virus effector: targets, topology and functional consequences in T cells

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

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 GRK 2581: SPHINGOINF - Metabolism, topology and compartmentalization of membrane proximal lipid and signaling components in infection (Project 04): Role of Sphingosine-1 phosphate and S1P1-3 receptors in the pathophysiology of meningococcal meningitis

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 GRK 2581: SPHINGOINF - Metabolism, topology and compartmentalization of membrane proximal lipid and signaling components in infection (Project 09): Sphingolipid metabolic pathways in infection control by the use of chemically synthesized modified sphingolipids and in the era of sphingolipidomics

DFG FOR 2123: SphingoFOR – Sphingolipid dynamics in infection control (SE 1410/7-1): Coating of endotracheal tubes with sphingosine to prevent bacterial growth and ventilator-associated pneumonia

SHARMA, CYNTHIA

ERC Consolidator Grant: Exploring the expanding universe of RNA-binding proteins in bacteria (bacRBP)

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 2002: Small Proteins in Prokaryotes, an Unexplored World (SH 580/7-1 and SH 580/7-2): Central Project Z02, Ribosome Profiling and Bioinformatics; (SH 580/8-1 and SH 580/8-2): 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 and SH 580/9-2): Mechanisms and functions of endogenous RNA-targeting by CRISPR-Cas9 in *Campylobacter jejuni*

StMWK Bayresq.net: New Strategies against Multi-Resistant Pathogens by Means of Digital Networking (StressRegNet): Identifying stressor-regulator pairs involved in bacterial stress response, virulence, and antibiotic sensitivity using high-throughput approaches and machine learning

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

VAETH, MARTIN

DFG SFB 1525: Cardio-Immune Interfaces (Project B05): Mitochondrial membrane remodelling regulates metabolism and controls innate and adaptive immune responses to myocardial infarction

DFG SFB 1526: Pathomechanisms of Antibody-mediated Autoimmunity (PANTAU): Insights from Pemphigoid Diseases (Project B06): Targeting mitochondrial metabolism in pemphigoid diseases

DFG SFB/TRR 124: FungiNet – Pathogenic fungi and their human host: Networks of interaction (Project C07): Ionic regulation of Th17-mediated immune responses to *Candida* infection

DFG SFB/TRR 338: LETSIMMUN – Lymphocyte Engineering for Therapeutic Synthetic Immunity (Project C05): Metabolic reprogramming to optimize the cellular fitness and function of engineered T cells

DFG (VA 882/2-1): Induction of NFATc1 Controls the Fate of Activated T Cells

DFG (VA 882/3-2): The brain-type glucose transporter GLUT3 controls the function of regulatory T cells

VIEMANN, DOROTHEE

DFG EXC 2155: RESIST - Resolving Infection Susceptibility (Project B01): Impact of microbiota on the development of the immune system in preterm neonates and their susceptibility towards respiratory and septic diseases

DFG (VI 538/9-1): The postnatal maturation of human innate immunity against influenza infections and the associated risk for severe influenza diseases in dependence on the developing gut microbiome

DFG (VI 538/6-3): Perinatal programming and postnatal reprogramming of innate immunity in preterm infants and its implications for diseases complicating the outcome after preterm birth

BMBF (01EK2103B): PROSPER -PRevention Of Sepsis by PERsonalized nutritional S100A8/A9 supplementation to vulnerable neonates

Bill & Melinda Gates Foundation: S100 alarmins in protecting infants against enteric infections

VOGEL, JÖRG

DFG GRK 2157: 3D Infect – 3D Tissue Models for Studying Microbial Infections by Human Pathogens (Project 08): Establishing a human colon model to study host-commensal-pathogen interactions under hypoxic conditions

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; (VO 875/20-2): Characterizing the role of YjiS in *Salmonella* virulence

DFG SPP 2330: New concepts in prokaryotic virus-host interactions - from single cells to microbial communities (VO 875/23-1): Molecular factors whereby giant phage ΦKZ modulates host protein synthesis

DFG (VO 875/18-1): Gottfried Wilhelm Leibniz Preis

DFG (VO 875/19-1): Understanding PinT, a noncoding RNA timer of virulence gene expression

FWO EOS (40007496): deCiphering bacterial peRsIsTence of Individual Cells down to Atomic Level

StMWK Bayresq.net: New Strategies against Multi-Resistant Pathogens by Means of Digital Networking (Rbiotics): RNA antibiotics

StMWK FOR-COVID: Decoding the biology of SARS-CoV-2 infections from its direct *in vivo* RNA-protein interactome

StMWK Programm zur Förderung von Corona-Forschungsprojekten: Entschlüsselung der molekularen Vorgänge einer SARS-CoV-2 infizierten Zelle

VOGEL, ULRICH

BMBF (01KX2021): Nationales Forschungsnetzwerk der Universitätsmedizin (NUM)

RKI grant (1369-237): National Reference Laboratory for Meningococci and *Haemophilus influenzae*

WESTERMANN, ALEXANDER

ERC Starting Grant: Deciphering commensal-host-pathogen metabolic interactions to combat intestinal infections (GUT-CHECK)

DFG (WE 6689/1-1): Regulatory RNAs and RNA-binding proteins in Bacteroides thetaiotaomicron

ZIEBUHR, WILMA

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/01KI2009E): Reducing the AMR burden in farm environments: Impact on human commensals and zoonotic pathogens

BMBF Health Research (16GW0297): TRANsACT - T-box riboswitches as novel antibacterial targets: Validation of RNA-mediated methionine biosynthesis control in staphylococci as tool and proof of principle

7.5 PUBLICATIONS

2020-2022

Please note that only publications of ZINF members that are relevant for infectious disease research are listed below.
ZINF members are listed in alphabetical order.

AGUILAR, CARMEN

Aguilar C*, Cruz AR*, Rodrigues Lopes I, Maudet C, Sunkavalli U, Silva RJ, Sharan M, Lisowski C, Zaldívar-López S, Garrido JJ, Giacca M, Mano M, Eulalio A (2020) *Functional screenings reveal different requirements for host microRNAs in Salmonella and Shigella infection.* **Nature Microbiology** 5(1):192-205
*equally contributing authors

Aguilar C, Alves da Silva M, Saraiva M, Neyazi M, Olsson IAS, Bartfeld S (2021) *Organoids as host models for infection biology - a review of methods.* **Experimental & Molecular Medicine** 53(10):1471-1482

Aguilar C, Costa S, Maudet C, Vivek-Ananth RP, Zaldívar-López S, Garrido JJ, Samal A, Mano M, Eulalio A (2021) *Reprogramming of microRNA expression via E2F1 downregulation promotes Salmonella infection both in infected and bystander cells.* **Nature Communications** 12(1):3392

Wallaschek N, Reuter S, Silkenat S, Wolf K, Niklas C, Kayisoglu Ö, **Aguilar C**, Wiegering A, Germer CT, Kircher S, Rosenwald A, Shannon-Lowe C, Bartfeld S (2021) *Ephrin receptor A2, the epithelial receptor for Epstein-Barr virus entry, is not available for efficient infection in human gastric organoids.* **PLoS Pathogens** 17(2):e1009210

Aguilar C*, Pauzuolis M*, Pompaiah M, Vafadarnejad E, Arampatzi P, Fischer M, Narres D, Neyazi M, Kayisoglu Ö, Sell T, Blüthgen N, Morkel M, Wiegering A, Germer CT, Kircher S, Rosenwald A, Saliba AE, Bartfeld S (2022) *Helicobacter pylori shows tropism to gastric differentiated pit cells dependent on urea chemotaxis.* **Nature Communications** 13(1):5878
*equally contributing authors

Herrera-Uribe J, Zaldívar-López S, **Aguilar C**, Entrenas-García C, Bautista R, Claros MG, Garrido JJ (2022) *Study of microRNA expression in Salmonella Typhimurium-infected porcine ileum reveals miR-194a-5p as an important regulator of the TLR4-mediated inflammatory response.* **Veterinary Research** 53(1):35

BARQUIST, LARS

Bauriedl S, Gerovac M, Heidrich N, Bischler T, **Barquist L**, Vogel J, Schoen C (2020) *The minimal meningococcal ProQ protein has an intrinsic capacity for structure-based global RNA recognition.* **Nature Communications** 11(1):2823

Barquist L (2020) *Plugging Small RNAs into the Network.* **mSystems** 5(3):e00422-20

Cain AK, **Barquist L**, Goodman AL, Paulsen IT, Parkhill J, van Opijnen T (2020) *A decade of advances in transposon-insertion sequencing.* **Nature Reviews Genetics** 21(9):526-540

Elliott AG, Huang JX, Neve S, Zuegg J, Edwards IA, Cain AK, Boinett CJ, **Barquist L**, Lundberg CV, Steen J, Butler MS, Mobli M, Porter KM, Blaskovich MAT, Lociuro S, Strandh M, Cooper MA (2020) *An amphipathic peptide with antibiotic activity against multidrug-resistant Gram-negative bacteria.* **Nature Communications** 11(1):3184

Gerovac M, El Mouali Y, Kuper J, Kisker C, **Barquist L**, Vogel J (2020) *Global discovery of bacterial RNA-binding proteins by RNase-sensitive gradient profiles reports a new FinO domain protein.* **RNA** 26(10):1448-1463

Michaux C, Hansen EE, Jenniches L, Gerovac M, **Barquist L**, Vogel J (2020) *Single- Nucleotide RNA Maps for the Two Major Nosocomial Pathogens Enterococcus faecalis and Enterococcus faecium.* **Frontiers in Cellular and Infection Microbiology** 10:600325

Mika-Gospodorz B, Giengkam S, Westermann AJ, Wongsantichon J, Kion-Crosby W, Chuenklin S, Wang LC, Sunyakumthorn P, Sobota RM, Subbian S, 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** 11(1):3363
#corresponding authors

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

Venturini E, Svensson SL, Maaß S, Gelhausen R, Eggenhofer F, Li L, Cain AK, Parkhill J, Becher D, Backofen R, **Barquist L**, Sharma CM, Westermann AJ, Vogel J (2020) *A global data-driven census of Salmonella small proteins and their potential functions in bacterial virulence.* **microLife** 1(1):597

Abd El Ghany M, **Barquist L**, Clare S, Brandt C, Mayho M, Joffre E, Sjöling Å, Turner AK, Klena JD, Kingsley RA, Hill-Cawthorne GA, Dougan G, Pickard D (2021) *Functional analysis of colonization factor antigen I positive enterotoxigenic Escherichia coli identifies genes implicated in survival in water and host colonization.* **Microbial Genomics** 7(6):000554

Chihara K, **Barquist L**, Takasugi K, Noda N, Tsuneda S (2021) *Global identification of RsmA/N binding sites in Pseudomonas aeruginosa by in vivo UV CLIP-seq.* **RNA Biology** 18(12):2401-2416

Fuchs M, Lamm-Schmidt V, Sulzer J, Ponath F, Jenniches L, Kirk JA, Fagan RP, **Barquist L**, Vogel J, Faber F (2021) *An RNA-centric global view of Clostridioides difficile reveals broad activity of Hfq in a clinically important gram-positive bacterium.* **PNAS** 118(25):e2103579118

Jiao C, Sharma S, Dugar G, Peeck NL, Bischler T, Wimmer F, Yu Y, **Barquist L**, Schoen C, Kurzai O, Sharma CM, Beisel CL (2021) *Noncanonical crRNAs derived from host transcripts enable multiplexable RNA detection by Cas9.* **Science** 372(6545):941-948

Ponath F, Tawk C, Zhu Y, **Barquist L**, Faber F, Vogel J (2021) *RNA landscape of the emerging cancer-associated microbe Fusobacterium nucleatum.* **Nature Microbiology** 6(8):1007-1020

Popella L, Jung J, Popova K, Đurica-Mitić S, **Barquist L#**, Vogel J# (2021) *Global RNA profiles show target selectivity and physiological effects of peptide-delivered antisense antibiotics.* **Nucleic Acids Research** 49(8):4705-4724
#corresponding authors

Hör J, Jung J, Đurica-Mitić S, **Barquist L**, Vogel J (2022) *INRI-seq enables global cell-free analysis of translation initiation and off-target effects of antisense inhibitors.* **Nucleic Acids Research** gkac838

Prezza G, Ryan D, Mädler G, Reichardt S, **Barquist L**, Westermann AJ (2022) *Comparative genomics provides structural and functional insights into Bacteroides RNA biology.* **Molecular Microbiology** 117(1):67-85

Popella L, Jung J, Do PT, Hayward RJ, **Barquist L#**, Vogel J# (2022) *Comprehensive analysis of PNA-based antisense antibiotics targeting various essential genes in uropathogenic Escherichia coli.* **Nucleic Acids Research** 50(11):6435-6452
#corresponding authors

Vialetto E, Yu Y, Collins SP, Wandera KG, **Barquist L**, Beisel CL (2022) *A target expression threshold dictates invader defense and prevents autoimmunity by CRISPR-Cas13.* **Cell Host & Microbe** 30(8):1151-1162.e6

Yair Y, Michaux C, Biran D, Bernhard J, Vogel J, **Barquist L**, Ron EZ (2022) *Cellular RNA Targets of Cold Shock Proteins CspC and CspE and Their Importance for Serum Resistance in Septicemic Escherichia coli.* **mSystems** 7(4):e0008622

BARTFELD, SINA

Bauer M, Nascakova Z, Mihai AI, Cheng PF, Levesque MP, Lampart S, Hurwitz R, Pfannkuch L, Dobrovolna J, Jacobs M, **Bartfeld S**, *et al.*, Meyer TF, Janscak P, Müller A (2020) *The ALPK1/TIFA/NF-κB axis links a bacterial carcinogen to R-loop-induced replication stress.* **Nature Communicatons** 11(1):5117

Josenhans C, Müthing J, Elling L, **Bartfeld S**, Schmidt H (2020) *How bacterial pathogens of the gastrointestinal tract use the mucosal glyco-code to harness mucus and microbiota: New ways to study an ancient bag of tricks.* **International Journal of Medical Microbiology** 310(2):151392

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

Aguilar C, Alves da Silva M, Saraiva M, Neyazi M, Olsson IAS, **Bartfeld S** (2021) *Organoids as host models for infection biology - a review of methods.* **Experimental & Molecular Medicine** 53(10):1471-1482

Bartfeld S (2021) *Realizing the potential of organoids- an interview with Hans Clevers.* **Journal of Molecular Medicine (Berlin)** 99(4):443-447

Kayisoglu Ö, Schlegel N, **Bartfeld S** (2021) *Gastrointestinal epithelial innate immunity-regionalization and organoids as new model.* **Journal of Molecular Medicine (Berlin)** 99(4):517-530

Kayisoglu O, Weiss F, Niklas C, Pierotti I, Pompaiah M, Wallaschek N, Germer CT, Wiegering A, **Bartfeld S** (2021) *Location-specific cell identity rather than exposure to GI microbiota defines many innate immune signalling cascades in the gut epithelium.* **Gut** 70(4):687-697

Koo BK, **Bartfeld S**, Alev C (2021) *Organoids: ready for the revolution?* **Journal of Molecular Medicine (Berlin)** 99(4):441-442

Wallaschek N, Reuter S, Silkenat S, Wolf K, Niklas C, Kayisoglu Ö, Aguilar C, Wiegering A, Germer CT, Kircher S, Rosenwald A, Shannon-Lowe C, **Bartfeld S** (2021) *Ephrin receptor A2, the epithelial receptor for Epstein-Barr virus entry, is not available for efficient infection in human gastric organoids.* **PLoS Pathogens** 17(2):e1009210

Aguilar C, Pauzuolis M, Pompaiah M, Vafadarnejad E, Arampatzi P, Fischer M, Narres D, Neyazi M, Kayisoglu Ö, Sell T, Blüthgen N, Morkel M, Wiegering A, Germer CT, Kircher S, Rosenwald A, Saliba AE#, **Bartfeld S#** (2022) *Helicobacter pylori shows tropism to gastric differentiated pit cells dependent on urea chemotaxis.* **Nature Communications** 13(1):5878
#corresponding authors

Kozjak-Pavlovic V, Song W, **Bartfeld S**, Metzger M (2022) *Editorial: 3D tissue models in infection research.* **Frontiers in Cellular and Infection Microbiology** 12:969132

Samperio Ventayol P, **Bartfeld S** (2022) *Immune cell-stem cell interactions in regeneration and repair: who's calling the shots?* **Development** 149(8):dev200228

BEILHACK, ANDREAS

Amich J, Mokhtari Z, Strobel M, Vialetto E, Sheta D, Yu Y, Hartweg J, *et al.*, Thusek S, Schmiedgen K, Arslan B, Pinnecker J, Thornton CR, Gunzer M, Krappmann S, Einsele H, Heinze KG, **Beilhack A** (2020) *Three-Dimensional Light Sheet Fluorescence Microscopy of Lungs To Dissect Local Host Immune-Aspergillus fumigatus Interactions.* **mBio** 11(1):e02752-19

Ashour D, Arampatzi P, Pavlovic V, Förstner KU, Kaisho T, **Beilhack A**, Erhard F, Lutz MB (2020) *IL-12 from endogenous cDC1, and not vaccine DC, is required for Th1 induction.* **JCI Insight** 5(10):e135143

Horvat S, Yu Y, Böjte S, Teßmer I, Lowman DW, Ma Z, Williams DL, **Beilhack A**, Albrecht K, Groll J (2020) *Engineering Nanogels for Drug Delivery to Pathogenic Fungi Aspergillus fumigatus by Tuning Polymer Amphiphilicity.* **Biomacromolecules** 21(8):3112-3121

Yu Y, Albrecht K, Groll J, **Beilhack A** (2020) *Innovative therapies for invasive fungal infections in preclinical and clinical development.* **Expert Opinion on Investigational Drugs** 29(9):961-971

Bäuerlein CA, Qureischi M, Mokhtari Z, Tabares P, Brede C, Jordán Garrote AL, Riedel SS, Chopra M, Reu S, Mottok A, Arellano-Viera E, Graf C, Kurzwart M, Schmiedgen K, Einsele H, Wölfl M, Schlegel PG, **Beilhack A** (2021) *A T-Cell Surface Marker Panel Predicts Murine Acute Graft-Versus-Host Disease.* **Frontiers in Immunology** 11:593321

Eckert IN, Ribechini E, Jarick KJ, Strozniak S, Potter SJ, **Beilhack A**, Lutz MB (2021) *VLA-1 Binding to Collagen IV Controls Effector T Cell Suppression by Myeloid-Derived Suppressor Cells in the Splenic Red Pulp.* **Frontiers in Immunology** 11:616531

Majumder S, Jugovic I, Saul D, Bell L, Hundhausen N, Seal R, **Beilhack A**, Rosenwald A, Mougiakakos D, Berberich-Siebelt F (2021) *Rapid and Efficient Gene Editing for Direct Transplantation of Naive Murine Cas9+ T Cells.* **Frontiers in Immunology** 12:683631

Shaikh H, Vargas JG, Mokhtari Z, Jarick KJ, Ulbrich M, Mosca JP, Viera EA, Graf C, Le DD, Heinze KG, Büttner-Herold M, Rosenwald A, Pezoldt J, Huehn J, **Beilhack A** (2021) *Mesenteric Lymph Node Transplantation in Mice to Study Immune Responses of the Gastrointestinal Tract.* **Frontiers in Immunology** 12:689896

Sueiro-Olivares M, Scott J, Gago S, Petrovic D, Kouroussis E, Zivanovic J, Yu Y, Strobel M, Cunha C, Thomson D, Fortune-Grant R, Thusek S, Bowyer P, **Beilhack A**, Carvalho A, Bignell E, Filipovic MR, Amich J (2021) *Fungal and host protein persulfidation are functionally correlated and modulate both virulence and antifungal response.* **PLoS Biology** 19(6):e3001247

Yu Y, Wolf AK, Thusek S, Heinekamp T, Bromley M, Krappmann S, Terpitz U, Voigt K, Brakhage AA, **Beilhack A** (2021) *Direct Visualization of Fungal Burden in Filamentous Fungus-Infected Silkworms.* **Journal of Fungi** 7(2):136

Ataide MA, Knöpper K, Cruz de Casas P, Ugur M, *et al.*, Trivedi A, Grafen A, Yang T, Prinz I, Ohlsen K, Gomez de Agüero M, **Beilhack A**, Huehn J, Gaya M, Saliba AE, Gasteiger G, Kastenmüller W (2022) *Lymphatic migration of unconventional T cells promotes site-specific immunity in distinct lymph nodes.* **Immunity** 55(10):1813-1828.e9

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Ullrich E, **Beilhack A**, Wolf D (2022) *Editorial: Novel and Improved Methods for the Prevention and Treatment of Graft-Versus-Host Disease (GVHD).* **Frontiers in Immunology** 13:966389

Vargas JG, Wagner J, Shaikh H, Lang I, Medler J, Anany M, Steinfatt T, Mosca JP, Haack S, Dahlhoff J, Büttner-Herold M, Graf C, Viera EA, Einsele H, Wajant H#, **Beilhack A#** (2022) *A TNFR2-Specific TNF Fusion Protein With Improved In Vivo Activity.* **Frontiers in Immunology** 13:888274
#corresponding authors

BEISEL, CHASE

Beisel CL (2020) *Methods for characterizing, applying, and teaching CRISPR-Cas systems.* **Methods** 172:1-2

Collias D, Leenay RT, Slotkowski RA, Zuo Z, Collins SP, McGirr BA, Liu J, **Beisel CL** (2020) *A positive, growth-based PAM screen identifies noncanonical motifs recognized by the S. pyogenes Cas9.* **Science Advances** 6(29):eabb4054

Collins SP, **Beisel CL** (2020) *Your Base Editor Might Be Flirting with Single (Stranded) DNA: Faithful On-Target CRISPR Base Editing without Promiscuous Deamination.* **Molecular Cell** 79(5):703-704

Jacobsen T, Ttofali F, Liao C, Manchalu S, Gray BN, **Beisel CL** (2020) *Characterization of Cas12a nucleases reveals diverse PAM profiles between closely-related orthologs.* **Nucleic Acids Research** 48(10):5624-5638

Marshall R, **Beisel CL**, Noireaux V (2020) *Rapid Testing of CRISPR Nucleases and Guide RNAs in an E. coli Cell-Free Transcription-Translation System.* **STAR Protocols** 1(1):100003

Siedler S, Rau MH, Bidstrup S, Vento JM, Aunsbjerg SD, Bosma EF, McNair LM, **Beisel CL**, Neves AR (2020) *Competitive Exclusion Is a Major Bioprotective Mechanism of Lactobacilli against Fungal Spoilage in Fermented Milk Products.* **Applied and Environmental Microbiology** 86(7):e02312-19

Wandera KG, Collins SP, Wimmer F, Marshall R, Noireaux V, **Beisel CL** (2020) *An enhanced assay to characterize anti-CRISPR proteins using a cell-free transcription-translation system.* **Methods** 172:42-50

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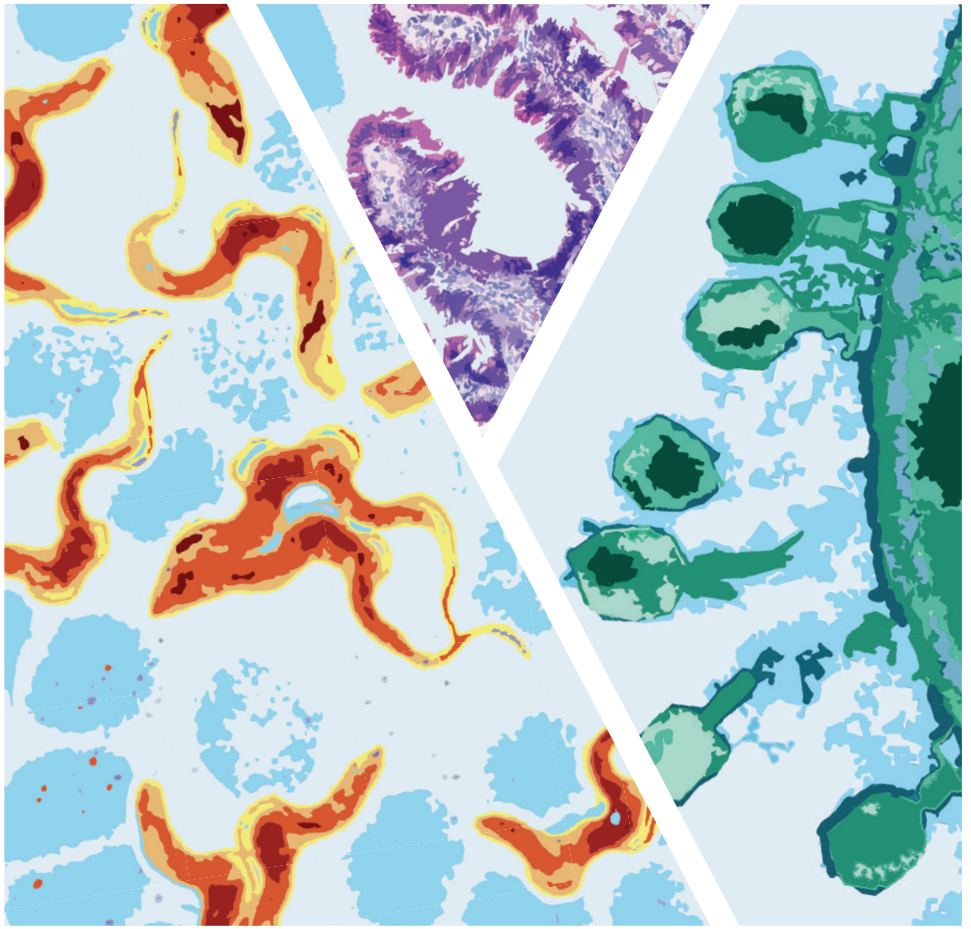

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