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ZENTRUM FÜR INFEKTIONSFORSCHUNG – RESEARCH CENTRE FOR INFECTIOUS DISEASES 2014–2015

Wissenschaftlicher Bericht
Scientific Report 2014–2015

ZENTRUM FÜR INFEKTIONSFORSCHUNG
RESEARCH CENTRE FOR INFECTIOUS DISEASES

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SCIENTIFIC REPORT 2014-2015

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01

GENERAL REMARKS

SPEAKER'S REPORT 2014–2015

Infectious diseases have remained a global challenge to human health and thus a prominent topic of discussion at both the academic and political levels. Human history has been continuously impacted by infectious diseases, and despite major progress in understanding their causes and treatment, they remain a significant socio-economic burden to mankind. During the years 2014 and 2015, the Ebola virus outbreak in West Africa and the ongoing Zika virus epidemic in South America have reminded us of our vulnerability to emerging pathogens. The sweeping spread of antibiotic resistance throughout the world further highlights the risks posed by infections. Leading policy-makers placed the issue on the agenda for the G7 summit 2015 in Elmau and discussed the actions required to prevent us entering a post-antibiotic era.

The collaborative Research Centre for Infectious Diseases (ZINF) at the University of Würzburg has been addressing the molecular principles of host-pathogen interactions since 1993, by bringing together experts in microbiology, parasitology, virology and immunology as well as chemists and clinicians. Founded by Volker ter Meulen, Werner Goebel and colleagues with initial financial contributions from the Federal Ministry of Education and Research (BMBF), ZINF developed into a major scientific research programme at the University of Würzburg under the long-term leadership of Jörg Hacker. In recognition of its extraordinary success, the Bavarian Government and the University of Würzburg have continued to fund this programme. I have had the honour to serve as the Spokesperson of ZINF since 2011.

The present report covering the 2014–2015 period highlights the scientific projects and achievements of the Young Investigator groups that lie at the heart of ZINF, and aims to provide an overview of the research activities of ZINF members with relevance to infectious diseases. These were exceptionally busy and exciting years, with respect to changes in personnel, as well as networking and scientific achievements.

Since its beginning a core element of ZINF has been a Young Investigator programme whose four junior research groups have been considered as a paradigm for the promotion of early scientific independence within German universities. The success of the program has been further highlighted by ZINF Young Investigator Daniel Lopez who in 2015 accepted a professorship in Spain and has moved his lab to Centro Nacional de Biotecnologie - CISC, Madrid. During his time at the ZINF Daniel was awarded an ERC Starting Grant and published his research in leading journals. This includes his work revealing the selective pressures driving the co-evolution of bacterial strains that are genetically and phenotypically similar to the Vancomycin-intermediate *S. aureus* (VISA) found in clinics, which was published in Cell in 2014.

In May 2015, we organised a symposium to recruit a new ZINF young investigator. As a result, Sina Bartfeld joined us from Utrecht University and started her group in October the same year. Her work focuses on using gastric organoid models to study the interplay between infections, innate immunity and carcinogenesis. Organoids have increasingly been used as models for a variety of diseases and as alternative systems for drug testing. Their application to studying infectious diseases will ensure that the ZINF is involved in this cutting-edge research area. The success of the programme is also evident in our ability to continuously attract highly promising young investigators through other highly competitive funding programs, such as current group leaders Sebastian Geibel (Bayern Elite Network) and Ana Eulalio (BioSysNet).

As ever, our international Scientific Advisory Board (SAB) has been instrumental in selecting new group leaders and providing us with critical feedback on current and planned research activities. Their continued support is highly appreciated. 2015 saw the departure of Jean Langhorne (London), Richard Lucius (Berlin), and Mariagrazia Pizza (Siena) who completed their second term on the Board. We are indebted to their active participation in all ZINF matters and the enjoyable collaboration during the past years. Concomitantly, the SAB was expanded with Eric Pamer (Memorial Sloan Kettering Cancer Center New York City); Katja Becker (University of Giessen) and Kai Matuschewski (Humboldt University Berlin), all joining us in 2016. We are also grateful to Michael Gilmore (Boston), David Holden (London), Agneta Richter-Dahlfors (Stockholm), Gisela Storz (Bethesda) and Tone Tønjum (Oslo) for agreeing to continue to serve on this board until 2016. Finally, we are pleased that Christoph Dehio (Basel), Axel Brakhage (Jena) and Sebastian Suerbaum (Hannover) renewed their commitments. We look forward to working closely with the SAB in the coming years.

In terms of the ZINF members, on the 29th of July 2014 we lost a long-term member, esteemed colleague and friend Axel Rethwilm, Chairman of Virology at the Institute of Virology and Immunobiology. Axel will be missed both as a person and for his contribution to infectious diseases research in Würzburg (a retrospective of his career can be found in the report). In 2015, Lars Dölken replaced Axel as the Chair of Virology. Lars joined us from the University of Cambridge and will continue his systems biology studies of herpesvirus infections. Finally, Gabriela Krasteva-Christ, a new W2 professor at the Department of Anatomy and Cell Biology, also joins the ZINF working on the role specialised mucosal epithelial cells that use the canonical taste transduction cascade to detect bacterial pathogens.

From 2014 to 2015, several ZINF members were awarded prestigious prizes and appointments. Ute Hentschel-Humeida departs ZINF after accepting a Department Head position at the Helmholtz Centre for Ocean Research in Kiel. Cynthia Sharma received an offer for a Full Professorship (W3) and was awarded the 2015 DFG/BMBF Heinz Maier-Leibnitz-Preis. Vera Kozjak-Pavlovic received an offer for a W2 professorship at Goethe University, Frankfurt and was awarded the 2015 Marcella Boveri Research Prize from the University of Würzburg. Andreas Beilhack was awarded the 2015 m4 Award of the Bavarian Ministry of Economic Affairs and Media, Energy and Technology. Ana Eulalio was selected as a 2015 EMBO Young Investigator. Gerhard Bringmann received the 2014 Gusi Peace Prize and a doctorate *honoris causa* of the Université des Pays des Grands Lacs (ULPGL) in Goma (Democratic Republic of the Congo). Finally, Jörg Vogel was elected to the European Academy of Microbiology in 2015.

ZINF members serve the scientific community by holding important positions in several societies and corporations. Hartwig Klinker has been appointed a board member of Deutsche Gesellschaft für Infektiologie (2015-2017). Thomas Dandekar was nominated to the selection Committee of the Alexander von Humboldt Foundation. Jörg Vogel was nominated to the DFG Scientific Equipment Committee and the EMBO Long-term Fellowship Committee. Cynthia Sharma was elected as a Board member to the DGHM Study Group Board member for "Gastrointestinal Infections" and a GBM Study Group Board member for "RNA Biochemistry".

Infectious diseases research at the University of Würzburg is supported through both national and international funding initiatives. Milestones in 2014–2015 included the funding of a number of newly established Infect-ERA research networks. These networks are funded through the EU ERA-NET programme and involve groups from at least three different participating EU countries. Several ZINF members were successful in this funding scheme: coordinator Cynthia Sharma and Ana Eulalio with a network Junior consortium *Combining high-throughput and single-cell analyses to study RNA regulators important for the early steps of Campylobacter infection,* Lars Dölken as part of - *Early Determinants of DNA-Virus Lytic or Latent Infection,* Jörg Vogel as part of - *Commensalism versus disease? Asymptomatic carriage or urosepsis* as well as coordinator Daniel Lopez and Ana Eulalio with their network *Intracellular Staphlococcus aureus: deciphering bacterial and cellular factors involved in host cell invasion by clinically relevant strains to define new therapeutic approaches.*

Importantly, 2015 saw the successful application and evaluation of the DFG Research Training Group (GRK 2157 3D-Infect) to train doctoral students in the emerging area of *3-D Tissue Models for studying Microbial Infections by Human Pathogens*. I am grateful to its speaker Thomas Rudel for initiating this network. Starting in 2016, this training program brings together many senior and junior scientists of the ZINF and constitutes an important element in our quest to stay at the forefront of infection biology.

ZINF members continued to secure research grants in several established networks that aim to better understand infectious diseases, including the collaborative research centres DFG TransRegio 124 *Pathogenic fungi and their human host: Networks of interaction,* DFG TransRegio 34 *Pathophysiology of Staphylococci,* DFG Research Unit 2123 *Sphingolipid dynamics in infection control,* DFG Priority Program SPP1617 *Phenotypic heterogeneity and sociobiology of bacterial populations,* BMBF *MedVet-Staph - Interdisciplinary Research Network on the Zoonotic Impact of Staphylococcus aureus/MRSA* and the Bavarian Research Network for Molecular Biosystems (BioSysNet). Also, the University's Interdisciplinary Center for Clinical Research (IZKF) continues to promote infectious diseases research, with approximately one fifth of the IZKF funds going into projects related to infectious diseases.

The training of graduate students and postdoctoral researchers remains a key mission of ZINF. The Graduate School of Life Sciences at University of Würzburg, of which ZINF member Caroline Kisker serves as the dean, has been awarded further funding from 2012 to 2017 as part of the second phase of the German Excellence Initiative. The Infection & Immunity section of the GSLS is headed by ZINF members Thomas Hünig and Joachim Morschhäuser and contains three training programs (infection, immunomodulation, and anti-infectives). In 2014–2015, students benefitted from several high-profile courses, including the EMBO Practical Course *Non-*

coding RNA in infection, a Summer School teaching *Modern Methods in Infection Biology* and a workshop on *Current Practical Implementation of Genome Sequencing for Typing of Invasive Bacterial Pathogens,* which acquainted young scientists with cutting-edge technologies in infection biology.

ZINF members were involved in the co-organisation of numerous national and international meetings and conferences. To name a few, the 1st International Symposium of the Transregio 124 FungiNet took place in September 2015 in Jena. Würzburg hosted the International workshop *Sphingolipids in infection control and beyond* and the 4th International Conference *Strategies in Tissue Engineering.* Würzburg was also the location for the meeting of the DFG Africa Initiative on German-African cooperation *Projects in Infectology,* the 13th European Meningococcal Disease Society Meeting, the 8th Würzburger Infektiologisches Symposium, the 7th Würzburger Meningokokken-Workshop *Meningokokken und Haemophilus influenzae: Epidemiologie & Prävention* as well as the 7th Cooperation forum for *Drug Development*. Finally, ZINF members teamed up once again with the editors of the journal Molecular Microbiology to organise the third Molecular Microbiology Meeting held in Würzburg in 2014.

Students in Würzburg benefit from several high-quality seminar series that cover different aspects of infection biology. These include those hosted by the Institute for Virology and Immunobiology and the Tuesday night Microbiology Colloquium, which is jointly organised by the Institute for Hygiene and Microbiology, the Department of Microbiology and the Institute of Molecular Infection Biology. These seminars are extremely well attended, by students and faculty alike and have included a whole host of fantastic speakers including Luis Serrano (Spain), Feng Shao (China), Kim Orth (USA), Ralph Isberg (USA), Wolf-Dietrich Hardt (Switzerland), Peter Turnbaugh (USA), Matt Berriman (UK) and Judith Berman (Israel) to just name a few.

Future plans are being put into place to nurture interactions between groups in the ZINF including those with the clinics. A joint mini-symposium was held in early 2014 with the Helmholtz Institute for Infection Research in Braunschweig to stimulate interactions and collaborations focusing on the RNA-based regulation in infectious diseases, the outcome of which was a decision to strengthen ties between the two centres on the institutional level. Taken together, ZINF has been a vital instrument to bring together scientists with a keen interest in understanding the molecular cause of infectious diseases, and to encourage interdisciplinary research locally and internationally.

Let me finish by gratefully acknowledging the generous support given by the Bayerische Staatsministerium für Wissenschaft, Forschung und Kunst, and the presidium of the University of Würzburg for their continued support of the centre. ZINF is still going strong and new initiatives have been started to help us meet the challenges of infection disease research in the twenty-first century. We are looking forward to the next years of exciting research activities in ZINF.

Jörg Vogel
Spokesperson ZINF
Würzburg, April 2016

SPRECHERBERICHT FÜR DEN ZEITRAUM 2014–2015

Infektionskrankheiten waren auch in den vergangenen zwei Jahren sowohl in der Öffentlichkeit als auch in der Wissenschaft sehr präsent. Nach wie vor stellen sie eine enorme Herausforderung für die globale Gesundheitsfürsorge dar. Die Menschheitsgeschichte wurde schon immer von Infektionen und ihren Folgen tief beeinflußt. Trotz großer Fortschritte im Verständnis der Ursachen und Behandelbarkeit sind wir immer noch sehr für viele Infektionserreger anfällig. Der Ebola-Ausbruch in Westafrika 2014 und die gegenwärtig noch anhaltende Zika-Virus-Epidemie in Südamerika haben uns gerade in jüngster Zeit deutlich an diese Tatsache erinnert. Ebenso verdeutlicht die alarmierende Ausbreitung antibiotikaresistenter Bakterien das hohe Risiko, das von pathogenen Mikroorganismen ausgeht. Das Thema Antibiotikaresistenz stand daher 2015 auf der Agenda des G7-Gipfeltreffens in Elmau, wo Politiker notwendige Maßnahmen diskutierten, um eine drohende post-antibiotische Ära zu verhindern.

Das Zentrum für Infektionsforschung (ZINF) der Universität Würzburg widmet sich seit 1993 der Erforschung molekularer Prinzipien krankheitsverursachender Mikroorganismen. Dazu bringt es Experten aus Mikrobiologie, Parasitologie, Virologie und Immunologie sowie Chemiker und klinisch tätige Ärzte zusammen. Gegründet von Volker ter Meulen und Werner Goebel entwickelte sich das ZINF unter der langjährigen Leitung von Jörg Hacker zu einer herausragenden Forschungsinstitution an unserer Universität. In Anerkennung dieses Erfolgs wurde die anfängliche Finanzierung durch das Bundesministerium für Bildung und Forschung (BMBF) später durch die Bayerische Staatsregierung und die Universität Würzburg fortgeführt. Seit 2011 habe ich die Ehre, als Sprecher des Zentrums zu fungieren.

Der vorliegende Bericht umfaßt die Jahre 2014 und 2015. Er umreißt die Projekte und wissenschaftlichen Leistungen der Nachwuchsgruppen welche den Kern des ZINF bilden, und gibt einen Überblick über die Aktivitäten der ZINF-Mitglieder mit Bezug zur Infektionsforschung. Dies waren bewegte und spannende Jahre im Hinblick auf personelle Veränderungen, neue Zusammenarbeiten und wissenschaftliche Erfolge.

Seit seinen Anfängen bildet das Nachwuchsprogramm das Herzstück des ZINF. Es ist beispielgebend für die frühe Förderung von Unabhängigkeit talentierter junger Infektionsbiologen in Deutschland, aber auch insgesamt von Nachwuchswissenschaftlern an der Universität Würzburg. Der Erfolg des Programms wurde durch die Berufung von Daniel Lopez auf eine Professur am Centro Nacional de Biotecnologie - CISC- in Madrid im Jahr 2015 erneut unter Beweis gestellt. Während seiner Zeit am ZINF erhielt Daniel Lopez ein ERC Starting Grant und publizierte in führenden Fachzeitschriften. Zum Beispiel konnte seine Arbeitsgruppe einen alternativen Mechanismus der Resistenzentwicklung bei Staphylokokken aufdecken, der durch Kompetition der Bakterien in der ökologischen Nische entsteht. Die Ergebnisse wurden im Jahr 2014 in Cell veröffentlicht.

Im Mai 2015 fand ein Symposium statt, um die frei gewordene Nachwuchsgruppenleiterposition wieder zu besetzen. Dabei konnten wir Sina Bartfeld von der Universität Utrecht für das ZINF gewinnen. Ihre Forschung befaßt sich mit der Anwendung von Organoidmodellen, um das Zusammenspiel zwischen Infektionen, angeborenem Immunsystem und Krebsentstehung zu verstehen. Organoide werden zunehmend als Modelle zur Untersuchung von Krankheiten aber auch als Alternativen zu Tierversuchen bei der Prüfung von Medikamenten eingesetzt. Die Anwendung von Organoidmodellen in der Infektionsforschung sichert dem ZINF eine starke Position bei der Entwicklung dieses hochinteressanten Gebiets.

Wie immer war unser internationaler wissenschaftlicher Beirat eine unschätzbare Hilfe bei der Berufung neuer Arbeitsgruppenleiter und der Planung neuer Forschungsaktivitäten. Wir möchten uns an dieser Stelle noch einmal sehr für die konstruktive und kritische Begleitung bei allen Beiratsmitgliedern bedanken. 2015 schieden Jean Langhorne (London), Richard Lucius (Berlin) und Mariagrazia Pizza (Siena) nach zwei Amtsperioden aus dem Gremium aus. Wir sind ihnen für ihr großes Engagement und die erbauliche kollegiale Zusammenarbeit während der letzten Jahre zu großem Dank verpflichtet. Gleichzeitig haben Eric Pamer (Memorial Sloan Kettering Cancer Center New York City), Katja Becker (Universität Gießen) und Kai Matuschewski (Humboldt Universität Berlin) als neue Mitglieder für die Mitarbeit im SAB ab dem Jahr 2016 zugesagt. An dieser Stelle möchten wir uns bei Michael Gilmore (Boston), David Holden (London), Agneta Richter-Dahlfors (Stockholm), Gisela

Storz (Bethesda) und Tone Tønjum (Oslo) bedanken, die sich alle bereit erklärt haben, uns auch weiterhin in unserer Arbeit zu beraten. Wir freuen uns auf die enge Zusammenarbeit mit dem SAB in den kommenden Jahren.

Im Hinblick auf unsere ZINF-Mitglieder müssen wir leider auch eine traurige Mitteilung machen. Am 29. Juli 2014 verstarb nach langer Krankheit unser geschätzter Kollege und langjähriges ZINF-Mitglied Axel Rethwilm. Er hatte bis zu seinem Tod den Lehrstuhl für Virologie inne. Wir vermissen Axel sowohl als humorvollen Menschen und Freund als auch als begeisterten Wissenschaftler, der viel zum Erfolg der Infektionsforschung in Würzburg beigetragen hat. Ein ausführlicher Nachruf und eine Würdigung seiner wissenschaftlichen Leistungen findet sich auf Seite 24 in diesem Bericht. Im Jahr 2015 übernahm Lars Dölken von der Universität Cambridge den Lehrstuhl für Virologie. Er wird in Würzburg seine Arbeiten zur Systembiologie von Herpesvirusinfektionen fortsetzen. Schließlich können wir mit Gabriela Krasteva-Christ, W2-Professorin am Institut für Anatomie und Zellbiologie, ein neues ZINF-Mitglied begrüßen. Ihre Forschungsarbeit befaßt sich mit der Erkennung von bakteriellen Pathogenen durch Zellen des Geschmackssystems und die damit verbundenen Signalkaskaden.

In den Jahren 2014 und 2015 wurden Würzburger Infektionsforscher mit einer Reihe von renommierten Preisen und Auszeichnungen sowie Berufungen auf verantwortungsvolle Positionen geehrt. So wechselte Ute Hentschel auf eine W3-Professur für Marine Mikrobiologie am Helmholtz-Zentrum für Ozeanforschung in Kiel. Cynthia Sharma erhielt den Ruf auf eine W3-Professur und wurde 2015 mit dem Heinz-Maier-Leibnitz-Preis der DFG und des BMBF geehrt. Vera Kozjak-Pavlovic erhielt einen Ruf auf eine W2-Professur an der Goethe-Universität-Frankfurt und wurde im Jahr 2015 mit dem Marcella-Boveri-Forschungspreis der Universität Würzburg ausgezeichnet. Andreas Beilhack erhielt den m4-Award des Bayerischen Staatsministeriums für Wirtschaft, Medien, Energie und Technologie. Ana Eulaio wurde im Jahr 2015 als EMBO-Nachwuchswissenschaftlerin gewählt. Gerhard Bringmann erhielt den Gusi-Friedenspreis. Ebenso wurde ihm die Ehrendoktorwürde der Université des Pays des Grands Lacs (ULPGL) in Goma (Demokratische Republik Kongo) verliehen. Jörg Vogel wurde im Jahr 2015 in die Europäische Akademie für Mikrobiologie gewählt.

ZINF-Mitgleider sind in zahlreichen wissenschaftlichen Gremien und Gesellschaften aktiv. Hartwig Klinker wurde in den Vorstand der Deutschen Gesellschaft für Infektiologie (2015–2017) berufen. Thomas Dandekar wurde in das Auswahlkomitee der Alexander-von-Humboldt-Stiftung gewählt. Jörg Vogel ist Mitglied des Apparateausschusses der DFG und des EMBO Longterm Fellowship Komitees. Cynthia Sharma wurde in die jeweiligen Vorstände der Fachgruppen “Gastrointestinale Infektionen” der DGHM und “RNA-Biochemie” der GBM gewählt.

Die Infektionsforschung an der Universität Würzburg wird durch nationale und internationale Förderprogramme unterstützt. Ein Meilenstein der erfolgreichen Drittmitteleinwerbung war die Etablierung einiger neuer Infect-ERA-Forschungsverbünde. Diese Netzwerke werden durch das ERA-NET-Programm der EU gefördert und unterstützen die Zusammenarbeit von Wissenschaftlern aus mindesten drei europäischen Partnerländern. Eine Reihe von ZINF-Mitgliedern waren in diesem Programm erfolgreich: Koordinatorin Cynthia Sharma und Ana Eulalio mit einem Projekt zum Thema *Combining high-throughput and single-cell analyses to study RNA regulators important for the early steps of Campylobacter infection;* Lars Dölken als Partner im Netzwerk Early Determinants of DNA-Virus Lytic or Latent Infection; Jörg Vogel als Partner in einem Projekt mit dem Titel *Commensalism versus disease?* Asymptomatic carriage or urosepsis; sowie Koordinator Daniel Lopez und Ana Eulalio mit ihrem Netzwerk *Intracellular Staphylococcus aureus: deciphering bacterial and cellular factors involved in host cell invasion by clinically relevant strains to define new therapeutic approaches.*

Ein weiterer Erfolg war die positive Evaluierung und Gründung eines neuen Graduiertenkollegs (GRK 2157) durch die DFG zum Thema 3-D Tissue Models for studying Microbial Infections by Human Pathogens. Sprecher dieses neuen Graduiertenkollegs ist Thomas Rudel, dem wir sehr dankbar sind dass er diese Initiative auf den Weg gebracht hat. Das Kolleg bringt ab 2016 erneut etablierte Kollegen und Nachwuchswissenschaftler des ZINF zusammen, um ein spannendes und hochaktuelles Forschungsthema gemeinsam zu bearbeiten. Es bildet einen wichtigen Baustein in unseren Bemühungen um internationale Spitzenforschung in der Infektionsbiologie an unserer Universität.

Über die genannten Aktivitäten hinaus waren ZINF-Mitglieder bei der Einwerbung weitere Mittel in einer Reihe von Forschungsprogrammen aktiv und erfolgreich. Dies umfaßt den DFG Transregio-SFB 124 *Pathogenic fungi and their human host: Networks of interaction,* den DFG Transregio-SFB 34 *Pathophysiology of Staphylococci, die DFG-Forschergruppe 2123 Sphingolipid dynamics in infection control,* das DFG-Schwerpunktprogramm SPP1617 *Phenotypic heterogeneity and sociobiology of bacterial populations,* das BMBF-MedVetStaph-Netzwerk zum Thema *Zoonotic Impact of Staphylococcus aureus/MRSA* und das bayerische Forschungsnetzwerk für Molekulare Biosysteme (BioSysNet). Schließlich unterstützt das Interdisziplinäre Zentrum für Klinische Forschung (IZKF) weiterhin die Infektionsforschung an unserer Universität. Die enge Verbindung zwischen klinischer Medizin und Infektionsbiologie wird nicht zuletzt durch die Tatsache deutlich, dass ungefähr ein Fünftel der IZKF-Mittel derzeit in Projekte mit Bezug zu Infektionskrankheiten fließen.

Die Ausbildung von Doktoranden und Postdocs bleibt eine Schlüsselaufgabe des ZINF. Die Graduate School of Life Sciences (GSLS), mit ZINF-Mitglied Caroline Kisker als Dekanin, wird im Rahmen der zweiten Exzellenzinitiative weiter gefördert (2012–2017). Die GSLS-Klasse “Infektion und Immunität” wird von Thomas Hünig und Joachim Morschhäuser als Sprecher geleitet und bietet derzeit drei Programme zu den Themen Infektion, Immunmodulation und Antiinfektiva an. Im Berichtszeitraum 2014–2015 profitierten die Studenten von hochkarätigen Laborkursen und Workshops wie dem EMBO-Praxiskurs *Non-coding RNA in Infection,* einer Summer School zum Thema *Modern Methods in Infection Biology* und einem Workshop zu *Current Practical Implementation of Genome Sequencing for Typing of Invasive Bacterial Pathogens.* Diese Kurse boten den Studenten die Möglichkeit, sich mit aktuellen Methoden in der Infektionsforschung auch praktisch vertraut zu machen.

Das ZINF und seine Mitglieder waren auch in den vergangenen beiden Jahren bei der Organisation von Symposien und Tagungen aktiv. Alle Veranstaltungen an dieser Stelle aufzuzählen würde den Rahmen dieses Berichtes sprengen, deshalb seien stellvertretend hier nur einige genannt. So fand im September 2015 das erste Symposium des Transregio-SFB 124 FungiNet in Jena statt. Würzburg war Gastgeber des Internationalen Workshops *Sphingolipids in infection control and beyond* und der 4. Internationalen Konferenz *Strategies in Tissue Engineering.* Ebenso fand in Würzburg das Treffen der DFG-Afrika-Initiative zur Förderung Deutsch-Afrikanischer-Forschungskooperationen in der Infektiologie statt. Weitere Konferenzen waren das 8. Würzburger Infektiologische Symposium und der 7. Würzburger Workshop *Meningokokken und Haemophilus influenzae: Epidemiologie und Prävention* sowie das 7. Kooperationsforum *Drug Development.* Schließlich setzte das ZINF die bewährte Zusammenarbeit mit den Herausgebern der renommierten Fachzeitschrift Molecular Microbiology fort und organisierte 2014 das mittlerweile dritte *Molecular Microbiology Meeting* in Würzburg.

Neben diesen Konferenzen profitierten Studenten, Postdocs und Wissenschaftler in Würzburg von exzellenten Seminarreihen und Vorträgen. Dazu zählen die Seminare am Institut für Virologie und Immunbiologie und das Mikrobiologische Kolloquium, das gemeinsam vom Institut für Hygiene und Mikrobiologie, dem Lehrstuhl für Mikrobiologie und dem Institut für Molekulare Infektionsbiologie jeweils dienstagabends im Semester organisiert wird. Diese Seminare sind außerordentlich gut besucht und werden sowohl von Studenten als auch den ZINF-Mitgliedern wegen der ausgezeichneten internationalen Sprecher sehr geschätzt. So waren in den Jahren 2014 und 2015 Luis Serrano (Spanien), Feng Shao (China), Kim Orth (USA), Ralph Isberg (USA), Wolf-Dietrich Hardt (Schweiz), Peter Turnbaugh (USA), Matt Berriman (UK) und Judith Berman (Israel) zu Gast, um nur einige Namen zu nennen.

Zukünftige Entwicklungen betreffend fand Anfang 2014 ein Mini-Symposium mit Kollegen des Helmholtz-Zentrums für Infektionsforschung in Braunschweig statt, um Kooperationen auf dem Gebiet der RNA-basierten Regulation bei Infektionen zu initiieren. Ein Ergebnis des Treffens war die Vereinbarung einer künftigen engeren Zusammenarbeit beider Institutionen auf diesem Forschungsgebiet. Insgesamt hat sich das ZINF als äußerst lebendige Institution etabliert, um Wissenschaftler mit einem starken Interesse an molekularen Ursachen von Infektionskrankheiten miteinander zu vernetzen und interdisziplinäres Arbeiten auf lokaler und internationaler Ebene zu ermöglichen.

Lassen Sie mich am Ende noch einmal dem Bayerischen Staatsministerium für Wissenschaft, Forschung und Kunst für die großzügige Förderung, und dem Präsidium der Universität Würzburg für die kontinuierliche Unterstützung des Zentrums danken. Das ZINF ist weiterhin erfolgreich und neue Initiativen wurden bereits gestartet, um den Herausforderungen auf dem Gebiet der Infektionskrankheiten im 21. Jahrhundert zu begegnen. Wir freuen uns auf die nächsten Jahre mit spannender Wissenschaft und vielen neuen Forschungsaktivitäten.

Prof. Dr. Jörg Vogel
Sprecher des ZINF
Würzburg, April 2016

1.2. DIRECTORY OF PEOPLE ASSOCIATED WITH THE ZINF

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1. GENERAL REMARKS
1.3. STRUCTURE OF THE ZINF

The Research Centre for Infectious Diseases (ZINF) at the University of Würzburg was founded in 1993. It brings together bacteriologists, mycologists, parasitologists, virologists, immunologists, chemists, bioinformaticians, structural biologists and clinicians from the Medical, Biology and Chemistry Faculties.

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DFG German African Cooperation

Projects in Infectiology

Würzburg, 10-13 June 2015

International Symposium M3W3

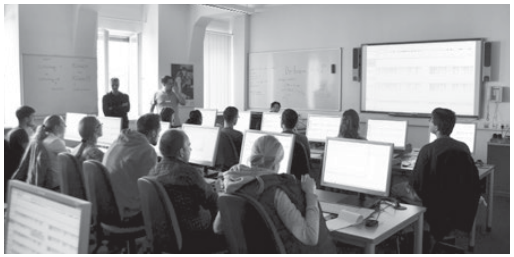
3rd Mol Micro Meeting

from 7-9 May 2014

EMBO Practical Course

Non-coding RNA in Infection

Würzburg, 12-18 October 2014



RETROSPECTIVE – AXEL RETHWILM

On the 29th of July 2014, the ZINF lost a long-term member, esteemed colleague and friend. Axel Rethwilm, Chair of Virology at the Institute of Virology and Immunobiology passed away prematurely at the age of 55. He joined the ZINF as an executive board member in 2003 and enthusiastically contributed to all ZINF activities even during the last years of his life when he fought increasing physical impairment by a progressive motor neuron disease.

Axel Rethwilm was internationally recognized for his seminal research on foamy viruses (FV) with which his name was almost synonymous. His enthusiasm for and knowledge of retroviruses in general, and FV in particular, resulted in numerous and valuable insights into FV molecular biology, life cycle, epidemiology, and the development of gene therapy vectors.

His work on FVs began when he was a doctoral student in Dieter Neumann-Haefelin's lab in Freiburg, and continued after joining the Institute for Virus Research at the German Cancer Research Center in Heidelberg. It was there that he molecularly cloned the first FV genome, originally referred to as human FV (HFV) although it was later renamed as prototypic FV (PFV), because it was revealed to be a human acquired chimpanzee FV. These experiments had a farreaching impact: Firstly, the availability of this infectious FV molecular clone enabled many laboratories, including his own, to reveal features that were so unique to the replication of FVs that they were termed "unconventional retroviruses". Secondly, through these and many subsequent experiments Axel revealed that FVs do not circulate in the human population and that the anecdotal, serologically confirmed PFV infections reflected zoonotically acquired apathogenic chimpanzee FVs. This finding laid the foundation for his later research interest in developing FVbased vector systems, which have shown promising results in preclinical testing for the treatment of inherited diseases.

Much of this work was performed during his years as a post doctoral researcher (1987–1989), then as a group leader (1989–1998) in Virology, which was at that time headed by Volker ter Meulen, an initiator and founding member of the ZINF. He moved with his group to Dresden, where he became Professor and Chair of Virology, only to return 5 years later to Würzburg to follow his former mentor in accepting to head Virology at the university. From 2003 until his premature death, he was a major figure in Würzburg´s research community and, particularly, in the infectious diseases research within the ZINF.

Axel´s dedication to nurturing enthusiasm for research within young scientists is reflected by the number of students that trained in his laboratory at early stages of their career, some of whom continued to focus on FV research. He also initiated the first DFG-funded German-African Graduate School (International Research Training Grant, IRTG) in which young scientists researched HIV, AIDS and associated infectious diseases. He generously supported the IRTG and associated PhD and MD students by providing stipends and travel grants from his personal funds.

As an executive board member of the German Society of Virology he actively contributed to many issues of general importance for virology in Germany and abroad, especially to the support of clinical virology, epidemiology and emerging infections.

As members of the ZINF, we miss Axel for his contributions to our research focus on infectious diseases, for his great sense of humour, and for his warm personality.

Sibylle Schneider-Schaulies and Thomas Hünig

02

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2. YOUNG INVESTIGATORS

2.1. DEEP SEQUENCING APPROACHES TO PATHOGENESIS

Our research focuses on the identification and characterization of small regulatory RNAs (sRNAs) and associated RNA-binding proteins in the pathogenic Epsilonproteobacteria, *Helicobacter pylori* and *Campylobacter jejuni*. We are especially interested in the functions and underlying molecular mechanisms of sRNAs during the stress response and virulence control in these widespread human pathogens.

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INTRODUCTION

Post-transcriptional regulation represents a central level of gene expression control in the cell in all kingdoms of life. Small regulatory RNAs (sRNAs) and RNA-binding proteins are key players in this regulatory process. In bacteria, the 50- to 200-nt-long sRNAs are a heterogeneous class of molecules that regulate gene expression in response to adverse growth and environmental stress conditions and have also been implicated in virulence control. Although genome-wide approaches have revealed hundreds of sRNAs in diverse bacteria, including many pathogens, most of the insight into their functions has come from work in enterobacteria. In contrast, little is known about sRNA-mediated regulation (riboregulation) in Epsilonproteobacteria. These include the gastric pathogen, *Helicobacter pylori*, the causative agent of gastric cancer, as well as the related food-borne pathogen, *Campylobacter jejuni*, the most common cause of bacterial food-borne disease to date. Epsilonproteobacteria, like 50% of all bacteria, lack a homolog of the RNA chaperone Hfq, a key player in sRNA-mediated regulation in enterobacteria. Thus, we are interested in whether they employ distinct auxiliary protein factors in post-transcriptional regulation or if their sRNAs function by other novel mechanisms independent of a protein cofactor.

RESEARCH HIGHLIGHTS

The development of next generation sequencing technology and its application to cDNA (RNA-sequencing) has enabled the analysis of most cellular RNA molecules in a single sequencing experiment at unprecedented resolution. This has greatly facilitated transcriptome annotation including the determination of transcript boundaries and identification of novel transcripts. For example, our differential RNA-sequencing approach (dRNA-seq) allowed us to define a genome-wide map of transcriptional start sites (TSS) in *H. pylori* and revealed an unexpected number of sRNAs in *H. pylori*. To understand how transcriptome differences contribute to phenotypic differences among closely related strains, we have applied a comparative dRNA-seq approach to multiple *Campylobacter* strains and developed a novel, generic method for the automated annotation of TSS to provide genome-wide promoter maps. While our comparative approach has revealed that the majority of TSS are conserved among strains, we also observed strain-specific promoter usage and sRNA repertoires, which likely contribute to strain-specific gene regulation.

Based on our global transcriptome datasets, we are now using *Helicobacter and Campylobacter* as new model organisms for riboregulation in bacterial pathogens and bacteria that lack Hfq. Using genomics, biochemical, molecular biology and genetics approaches we are elucidating the functions and physiological roles of sRNAs along with their underlying molecular mechanisms in stress responses and virulence. For example, the abundant RepG sRNA from *Helicobacter* directly targets a homopolymeric G-repeat in the 5'UTR of a chemotaxis receptor mRNA and thereby represses the expression of the pH-sensing chemotaxis receptor TlpB. While the sRNA sequence is conserved, the G-repeat varies in length in different *Helicobacter pylori* strains and leads to strain-specific regulation. Using a variety of in *vivo* and in *vitro* experiments we have shown that the length of the G-repeat determines the outcome of sRNA-mediated regulation (activation or repression) by affecting the translation of *tlpB* mRNA. This example represents an unexpected twist in sRNA-mediated regulation and a new connection between variable simple sequence repeats and fine-tuning of post-transcriptional regulation. Since Epsilonproteobacteria lack an apparent Hfq homolog, we are searching for alternate RNA-protein (RNP)-complexes and RNA binding proteins as well as RNases that are important for post-transcriptional regulation in these bacteria. Using co-immunoprecipitation combined with RNA-seq (RIP-seq) we have globally investigated direct RNA binding partners of the translational regulator CsrA in *Campylobacter*. This has revealed many flagellar mRNAs to be direct CsrA targets and identified the mRNA of the major flagellin as the main CsrA target while also functioning as an RNA antagonist of this protein.

Infection studies of human pathogens are often impeded by the use of artificial in vitro cell culture or animal models, which are limited in their ability to comprehensively mimic the infection situation and disease development. In a collaborative project with Prof. Heike Walles (Dept. of Tissue Engineering and Regenerative Medicine) we are developing new three-dimensional (3D) infection models using tissue engineering to mimic the microenvironment of human tissue. We have established infections with *Campylobacter* using a small-intestine model. To monitor the infection process we are, for example, investigating the ability of the bacteria to survive in the 3D model or to disrupt the epithelial barrier. Analysis of mutant strains has revealed different infection outcomes in 3D tissue models compared to standard 2D cell cultures, indicating that the 3D models can reveal infection phenotypes that are not evident in standard infection assays.

FUTURE DIRECTIONS

In addition to studying sRNA functions and mechanisms and identifying novel associated protein factors, we aim to further develop deep sequencing-based approaches and bioinformatics-based analyses to study bacterial infections. To identify RNA regulators of virulence genes we will employ RNA-seq to monitor the transcriptomes of host and pathogen in parallel using cell culture as well as 3D tissue models. In this direction we are developing a new 3D stomach tissue model to further investigate *Helicobacter* infections. These models and approaches will also be useful to study other pathogens and the development of new therapeutic and diagnostic tools.

Fig. 1: Transmission electron microscopy image of the food-borne pathogen *Campylobacter jejuni* at 3,000x magnification.

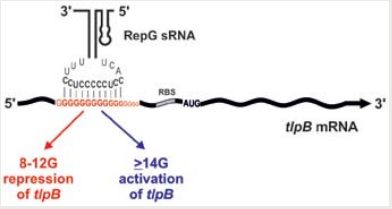

Fig. 2: RepG sRNA from *Helicobacter pylori* directly interacts with its C/U-rich loop with a length-variable homopolymeric G-repeat in the mRNA leader of the chemotaxis receptor TlpB. The length of the G-repeat determines the outcome of RepG-mediated regulation and leads to the repression of *tlpB* for 8-12Gs and to activation of *tlpB* for longer repeats of more than 13Gs.

SELECTED PUBLICATIONS

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

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Förstner KU, Vogel J, **Sharma CM** (2014) *READemption – A tool for the computational analysis of deep-sequencing based transcriptome data.* **Bioinformatics** 30:3421-3

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Pernitzsch SR, **Sharma CM** (2012) *Transcriptome Complexity and Riboregulation in the Human Pathogen Helicobacter pylori.* **Frontiers in Cellular and Infection Microbiology** 2:14

PRIZES AND AWARDS

2015 Heinz Maier-Leibnitz Preis (DFG), Young investigator award of the German Research Foundation

2014-16 ESCMID (European Society of Clinical Microbiology and Infectious Diseases) Research Fellowship

2014 ESCMID/FEMS Research Fellowship awarded for ESCMID research project

2. YOUNG INVESTIGATORS
2.2. CELL-CELL COMMUNICATION AND SIGNAL TRANSDUCTION

Bacteria often reside within complex communities called biofilms. My group investigates the signalling networks within biofilm dwelling bacteria that are involved in cell-cell communication and the molecular principles that bacteria use to translate these signals into the relevant physiological response.

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INTRODUCTION

The survival, proliferation, and differentiation of bacteria depend on their ability to interpret the signals they receive from the surrounding environment and to translate them into the correct physiological responses. If the signalling process does not function correctly then the organism is at risk. The organisation of signalling molecules into networks enables cells to robustly sense the presence of extracellular small-molecule signals that activate specific signalling transduction pathways, which in turn induce the expression of specific genes required to adapt the cell's physiology.

In multicellular organisms, cell-to-cell signalling occurs by diverse and sophisticated molecular mechanisms from direct contact to signalling over short or large distances. However, cell-cell signalling is also crucial for the survival of unicellular organisms such as bacteria. Although bacterial signal transduction has traditionally viewed as simpler than that of eukaryotes due to the reduced number of signalling components, they are able to respond to complex environmental changes and undergo extremely complex developmental processes. Therefore, it is possible that additional organisational principles relevant to these signalling networks remain to be discovered and provide an important level of regulation for the processing and integration signalling information in bacteria.

We recently discovered a new level of spatial organization of bacterial signalling networks. Bacteria organize their signal transduction components into functional membrane microdomains constituted by specific lipids that are structurally similar to lipid rafts described in eukaryotic cells. The assembly of bacterial lipid rafts involves the biosynthesis and aggregation of polyisoprenoid lipids in the membrane and their co-localization with flotillin proteins. Flotillin proteins are membrane-bound chaperones that localize exclusively to lipid rafts, where they potentially recruit the protein cargo to lipid rafts and facilitate their oligomerisation. The perturbation of bacterial lipid rafts inevitably leads to a potent and simultaneous impairment of all raft-harboured signal transduction pathways. Consequently, the disassembly of lipid rafts in pathogens such as *Staphylococcus* aureus simultaneously inhibit numerous infection-related processes. Therefore we are interested in understanding the molecular principles of the role of lipid rafts in controlling important signalling pathways in physiology and pathophysiology.

RESEARCH HIGHLIGHTS

The identification of membrane platforms in bacteria that are functionally and structurally equivalent to eukaryotic lipid rafts revealed an unexpected level of sophistication in signaling transduction and membrane organization in bacteria. We have been using *Bacillus subtilis* and the pathogen *S. aureus* as model organisms to perform a comprehensive molecular and functional characterization of bacterial lipid rafts. As an initial starting point we have developed a molecular toolbox for *S. aureus*, which enables us to efficiently genetically manipulate the pathogen and generate a number of transcriptional and translational reporter strains. We have successfully applied these tools to study the role of the cytoskeleton in defining cell shape in stapylococci.

We have also been studying the function of lipid rafts in *B. subtilis* and *S. aureus*. In *B. subtilis* we have begun to try to understand the principles involved in the organization and assembly of lipid rafts in bacteria. This has involved determining the composition of lipid rafts and their organization using a variety of methods including proteomics, transcriptomics and super-resolution microscopy. We have also investigated the role of a major protein component of lipid rafts, flotillin. The overproduction of flotillin alters specific signal transduction pathways that are associated with the membrane microdomains of bacteria. This resulted in significant physiological defects in cell division and cell differentiation caused by an unusual stabilization of the raft-associated protease FtsH.

In addition, we are interested in the role of co-evolution of different bacterial strains within a clonal community and how the emerging mutants spatially segregate specific traits within the community. We are focusing on identifying the selection pressures that drive the enormous genomic and phenotypic diversity of *S. aureus* clinical isolates. Using an *in vitro* biofilm assay to perform in time evolution experiments we have revealed that a single clone can evolve in a step-wise manner into phenotypically distinct clones with clinically relevant attributes. For example, an early arising strain produced toxins and antibiotics that led to the evolution of a subsequent strain that is resistant to the presence of these antibiotics. Importantly, interactions between these different evolving clones drove the evolution strains that were genetically and phenotypically similar to the Vancomycin-intermediate *S. aureus* (VISA) strains found in clinic.

FUTURE DIRECTIONS

We are expanding the studies of bacterial lipid rafts to other clinically-relevant species and gram-negative bacteria. Moreover, we will further characterize the architecture of bacterial lipid rafts and their protein and lipid composition, to understand their assembly and identify and characterize the signalling pathways that depend on the presence of microdomains. We are also using a collection of small molecules to alter the integrity of bacterial lipid rafts and inhibit several infection related physiological processes. We are interested in implementing these anti-raft compounds as antimicrobial agents to ultimately develop new antimicrobial strategies to fight infectious diseases.

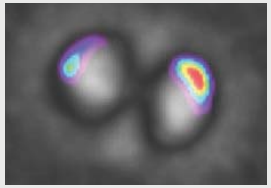

Fig. 1: S. aureus cells expressing a fluorescently labeled copy of the protein flotillin. Flotillin accumulates in bacterial lipid rafts and it localizes in discrete regions of the membrane.

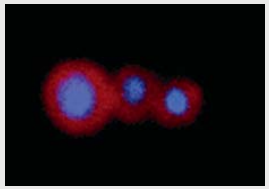

Fig. 2: Our molecular toolbox allows us a fine genetic manipulation of *S. aureus* cells to precisely modify the physiology of cells. Here we show a microscopy picture of *S. aureus* cells in which the activity of the cell wall biosynthesis machinery has been altered by genetic manipulation. As a consequence, cells exhibit different growth sizes. Nile Red dye has been used for membrane staining. DNA staining (blue).

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Mielich-Suss B, Schneider J, **Lopez D** (2013) *Overproduction of Flotillin Influences Cell Differentiation and Shape in Bacillus subtilis.* **mBio** 4:e00719-13

Yepes A, Schneider J, Mielich B, Koch G, Garcia-Betancur JC, Ramamurthi KS, Vlamakis H, **Lopez D** (2012) *The biofilm formation defect of a Bacillus subtilis flotillin-defective mutant involves the protease FtsH.* **Molecular Microbiology** 86:457-71

2. YOUNG INVESTIGATORS
2.3. TRYPANOSOMA GENE REGULATION

Using the protozoan parasite *Trypanosoma brucei*, the causative agent of African sleeping sickness, the group studies the epigenetic mechanisms leading to the formation of chromatin structures that promote and repress transcription. One key question is how changes in chromatin structure can help the parasite to evade the host immune response via antigenic variation.

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INTRODUCTION

To elucidate the fundamental mechanisms involved in the regulation of gene expression, we are using *Trypanosoma brucei*, an extracellular protozoan parasite that causes sleeping sickness in humans and nagana in cattle. Every year in Sub-Saharan Africa these diseases lead to the deaths of thousands of people and loss of livestock worth billions of dollars. To escape elimination by the host immune response, the parasite periodically switches its coat of variant surface glycoproteins (VSG), a process referred to as antigenic variation. The molecular mechanism of antigenic variation is not well understood, but several findings indicate that distinct chromatin structures ensure that only one of several hundred VSG genes is expressed at any given time.

For transcription of a specific gene to occur, RNA polymerase II (RNA Pol II) must locate the correct transcription start site (TSS) against a large background of genomic DNA sequences. In higher eukaryotes this involves the assembly of an elaborate complex of transcription factors to target the polymerase to the correct genomic locus. However, correct targeting also depends on the accessibility of these factors to the TSS since most DNA is packaged into chromatin, which is composed of DNA and proteins including arrays of nucleosomes. While the organization of DNA into dense chromatin structures presents an obstacle to the transcriptional machinery, it also provides an opportunity to regulate gene expression because chromatin structures can be locally and globally modified, making them highly dynamic. Structural changes in chromatin can be induced by the post-translational modification of histones or by the replacement of canonical histones with histone variants. While there is extensive knowledge of the enzymes that add or remove specific histone modifications or replace canonical histones with histone variants, it is not well understood in any organism how these enzymes are targeted to specific genomic loci. Furthermore, it is also not clear how transcriptionally active or repressed chromatin structures are established.

Thus, using trypanosomes to study the formation of chromatin structures, we hope to elucidate some of the very fundamental and evolutionarily conserved mechanisms of chromatin formation, while at the same time understanding the role of epigenetics in antigenic variation.

RESEARCH HIGHLIGHTS

Unusually for a eukaryote, *T. brucei* lacks RNA Pol II promoter motifs and its genes are arranged in long polycistronic transcription units, a feature that greatly reduces the number of TSSs. Previously, using ChIP-seq, we revealed that TSSs and transcription termination sites are marked by distinct chromatin domains that are strongly enriched in specific histone modifications and contain different histone variants. The small number of TSSs in combination with the distinct chromatin signature marking the boundaries of polycistronic transcription units makes this parasite an ideal organism to study the mechanism of targeted histone variant deposition. Therefore, we are currently investigating how, in the absence of DNA sequence motifs in *T. brucei*, the different histone modifications and histone variants are targeted to specific loci along the genome and what role they play in forming transcriptionally active or repressed chromatin regions across the nucleus.

Beyond chromatin dynamics, the group is also interested in post-transcriptional mechanisms of gene regulation in trypanosomes. The organization of genes in long polycistronic transcription units allows for very little regulation at the level of transcription initiation, suggesting an important role for post-transcriptional gene regulation, i.e. RNA maturation, stability and translation. However, the relative contribution of these processes to the final steady state levels of proteins is not well understood. To obtain genome-wide information on protein synthesis, we adapted a ribosome profiling approach to *T. brucei*. This technique is based on high-throughput sequencing of ribosome-protected RNA fragments and enabled us to perform the first genome-wide analysis of RNA translation and translational efficiency in a eukaryotic pathogen. We have found that translational efficiency varies greatly between life cycle stages of the parasite and ~100-fold between genes. Currently, we are searching for proteins and sequence motifs that promote or inhibit efficient translation. Importantly, the ability to map ribosome positions at sub-codon resolution has also allowed us to differentiate coding from noncoding RNA and enabled us to identify numerous long ncRNAs and hundreds of putative small peptides, many of which are regulated in a life-cycle specific manner.

FUTURE DIRECTIONS

We are aiming to combine system-wide approaches such as Hi-C, ChIP-seq, RNA-seq and ribosome-profiling with 'classical' biochemical and molecular techniques to obtain a comprehensive understanding of chromatin dynamics in trypanosomes, especially at regions involved in antigenic variation. A better knowledge of how gene expression is regulated and different chromatin structures are formed in *T. brucei* should help us understand how the parasite undergoes antigenic variation and may eventually facilitate medical intervention.

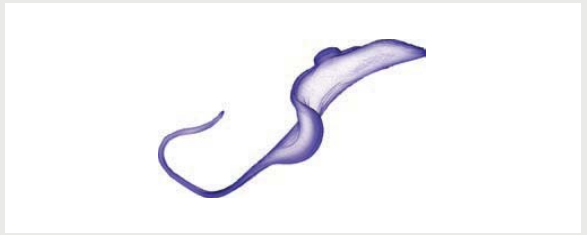

Fig. 1: Scanning electron micrograph of a long slender bloodstream form *T. brucei* parasite. (Courtesy of Thierry Blisnick, Philippe Bastin laboratory, Institut Pasteur, Paris.)

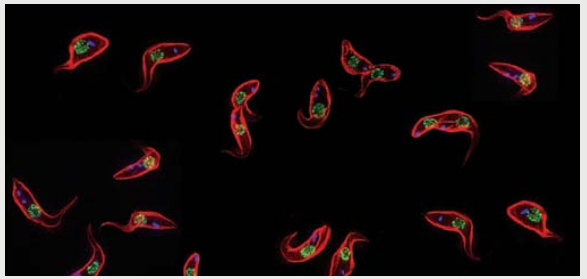

Fig. 2: Immunofluorescence analysis of *T. brucei*. Acetylated histone H4K10 (green), tubulin (red) and DNA (blue).

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Zhang Q, **Siegel TN**, Martins RM, Wang F, Cao J, Gao Q, Cheng X, Jiang L, Hon CC, Scheidig-Benatar C, Sakamoto H, Turner L, Jensen AT, Claes A, Guizetti J, Malmquist NA, Scherf A (2014) *Exonuclease-mediated degradation of nascent RNA silences genes linked to severe malaria.* **Nature** 513:431–435

Reynolds D, Cliffe L, Förstner KU, Hon CC, **Siegel TN**, Sabatini R (2014) *Regulation of transcription termination by glucosylated hydroxymethyluracil, base J, in Leishmania major and Trypanosoma brucei.* **Nucleic Acids Research** 42:9717–9729

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2. YOUNG INVESTIGATORS
2.4. HOST RNA METABOLISM

The main focus of the group is to understand the impact of bacterial infections on host cell RNA metabolism, with a special interest in the microRNA pathway, as well as the reciprocal role of host RNA metabolism on the life cycle of bacterial pathogens.

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INTRODUCTION

During the course of an infection, bacterial pathogens manipulate a vast range of host cellular functions to ensure their survival and replication. Among others, bacterial pathogens are known to induce the reorganization of the host cell cytoskeleton, modulate signal transduction pathways, membrane trafficking and pro-inflammatory responses. However, a largely unexplored question in host-pathogen interactions is the interplay between bacterial infection and RNA metabolism in the host cell. A properly functioning RNA metabolism is essential for a number of crucial host cell processes and therefore it is not surprising that pathogens have evolved sophisticated mechanisms to subvert these pathways for their own benefit.

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. In addition to their well-established functions in physiological and pathological host processes, it is becoming clear that miRNAs also play crucial roles during infections caused by different bacterial pathogens. While the expression of several host miRNAs is altered as part of the immune response to bacterial infections, considerably less is known regarding miRNAs that regulate bacterial infections and whether bacterial pathogens are also able to exploit host miRNAs to promote their own intracellular survival and proliferation.

The relationship between bacterial infections and RNA granules, in particular P-bodies (also known as mRNA processing bodies) and stress-granules, is another aspect of the bacterial-host interaction for which very little information is available. Considering that the formation and stability of RNA granules is strictly dependent on cellular RNA metabolism, any perturbation induced by bacterial pathogens in RNA granules is most likely a consequence of their effect on host RNA metabolism.

RESEARCH HIGHLIGHTS

We have been applying systems biology approaches, in particular high-throughput functional screening and RNA-sequencing, to identify and characterize miRNAs critical for infection with the model bacterial pathogens *Salmonella enterica* serovar Typhimurium and *Shigella flexneri*. *Salmonella* and *Shigella* are facultative intracellular bacteria and among the most common causes of lethality by food-borne diseases. To identify miRNAs regulating infection, we apply fluorescence microscopy-based high-throughput functional screening with genome-wide libraries of miRNA mimics and inhibitors. In parallel, by performing RNA-seq analysis of the small RNA population of *Salmonella* or *Shigella* infected cells, we identify miRNAs that are regulated upon infection. This is followed by a detailed investigation of miRNA targets and of the underlying mechanisms of action, using a combination of experimental and bioinformatic approaches.

Comparing the results obtained for these two closely related bacterial pathogens has shown that *Salmonella* and *Shigella* infections are regulated by a distinct subset of host miRNAs. We have identified miRNAs that affect *Salmonella* and/or *Shigella* at different stages of the infection cycle (e.g. invasion, maturation of the *Salmonella* containing vacuole, replication, intercellular spreading of Shigella).

Among the identified miRNAs, we have determined that the members of the miR-15 family inhibit *Salmonella* infection very efficiently, through repression of cyclin D1, a protein required for the G1/S transition. We have shown that the expression of miR-15 family members is decreased during infection by *Salmonella*, thus favoring host cell cycle progression and, ultimately, bacterial replication. We have also characterized the dual regulatory role of let-7i-3p in the context of *Salmonella* infection, revealing that let-7i-3p inhibits both adhesion of *Salmonella* to host cells and bacterial intracellular replication. Importantly, let-7i-3p expression is decreased upon *Salmonella* infection in both infected and bystander cells. This is the first description of a single host miRNA that is modulated by *Salmonella* to regulate two independent steps of infection, promoting both bacterial intracellular replication and dissemination.

Beyond the miRNA pathway, we are also interested in the interplay between bacterial pathogens and RNA granules (P-bodies and stress-granules). By comparing the impact of *Salmonella* and *Shigella* on the integrity of these RNA granules, we have discovered that *Shigella* inhibits the formation of stress-granules in host cells, while both bacteria are able to induce P-body disassembly. These findings reveal a clear interdependence between bacterial infection and host cell RNA metabolism.

FUTURE DIRECTIONS

In the next years we will characterize in detail the role played by selected miRNAs, identified by the combination of high-throughput screening and RNA-seq approaches, in the infection by *Salmonella* and *Shigella*. The identification of the targets of these miRNAs is expected to lead to the characterization of other previously unappreciated pathways relevant for bacterial infection. Furthermore, we plan to apply these approaches to other bacterial pathogens. Overall, we aim to obtain a better understanding of the interplay between bacterial infection and host cell RNA metabolism.

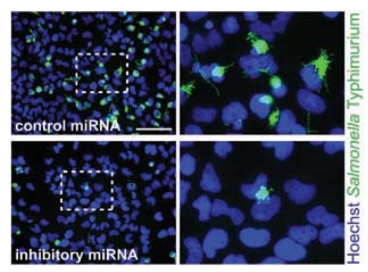

Fig. 1: Overexpression of selected microRNAs inhibits *Salmonella* infection. HeLa cells were transfected with selected microRNAs, followed by infection with *Salmonella* Typhimurium expressing GFP. The regions highlighted by the white squares are enlarged in the rightmost panels.

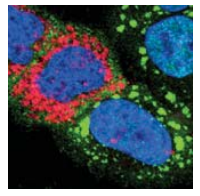

Fig. 2: Shigella infection inhibits stress-granule formation. HeLa cells were infected with *Shigella flexneri* expressing DsRed, and stress-granules were detected by staining the cells with anti-TIAR antibody.

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Eulalio A, Mano M, Dal Ferro M, Zentilin L, Sinagra G, Zacchigna S, Giacca M (2012) *Functional screening identifies miRNAs inducing cardiac regeneration.* **Nature** 492:376-81

Eulalio A, Schulte L, Vogel J (2012) *The mammalian microRNA response to bacterial infections.* **RNA Biology** 9:742-750

PRIZES AND AWARDS

2015 EMBO Young Investigator

2. YOUNG INVESTIGATORS
2.5. REGULATORY NETWORKS IN PATHOGENESIS

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.

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INTRODUCTION

An assembly of trillions of microorganisms comprising bacteria, archaea and eukaryotes inhabit the human body. While these microbes are, for the most part, harmless or beneficial to the host, occasionally some can cross the mucosal barriers and cause systemic, potentially fatal infections. In fact, many life-threatening infections in humans are caused by the very same bacterial or fungal species that comprise our microbiota. Despite their obvious medical importance, little is known about the mechanisms whereby commensal microbes turn into deadly pathogens and cause disease. A better understanding of the interactions between humans and members of their microbiota – opportunistic pathogens in particular – has the potential to open new avenues for intervention against infections caused by microbes that spread from our mucosal surfaces into the bloodstream.

Fungi remain particularly underrepresented in the studies of the microbiota. This is despite the fact that fungi have 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. In contrast to the vast resources dedicated to creating an inventory of the bacterial portion of the microbiome, only a few projects have attempted to identify the entire set of fungal species residing in and on mammals. Nevertheless, these studies are revealing that the taxonomical diversity of the fungal component of the microbiota is almost as rich as its bacterial counterpart. This underscores the need to investigate the fungi that inhabit the human body to understand how the mixed array of microbes that constitute our flora contribute to health and disease.

Candida 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 commonly habitates 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 healthy people, particularly females. 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.

RESEARCH HIGHLIGHTS

The microorganisms that share an ecosystem, *e.g.* the gut, typically not only compete with one another for nutrients but also establish mutually beneficial relationships with their neighbours. Accordingly, it would be expected that a significant proportion of the genetic circuitry that allows *C. albicans* to colonize the gut will be dedicated to cope with cohabiting microbes. To determine whether some of these genes control biological processes that are needed in the context of the gastrointestinal microbiota, we have analysed their requirement for gut colonisation in both conventional and germ-free mice. In the latter model, *C. albicans* is administered orally to animals that have been raised in a microbe-free environment, *i.e.* these rodents lack any indigenous flora. Our results indicate that a handful of gene circuits are dispensable for colonisation of the gut in germ-free mice despite the fact that they are absolutely required in conventionally raised rodents (and vice-versa). These findings hint, for the first time, that *C. albicans* harbours gene circuits that operate exclusively in the context of the surrounding microbiota to enable colonisation of the mammalian gut.

Virulence traits are often controlled by transcription regulators, *i.e.* sequence-specific DNA binding proteins. The regulators that sustain microbial proliferation in the host typically function by promoting the expression of the genes that mediate such traits. We have found a singular example in the human fungal pathogen *Candida albicans* in which a transcription regulator functions by repressing the expression of virulence genes, yet its overall role is to promote virulence. We have explained this apparent paradox by establishing that a major function of this protein, Zcf21p, is to set a default state of low expression of multiple cell wall components, which include virulence determinants. These components comprise GPI-anchored proteins, adhesins and enzymes that synthesize cell wall sugar decorations. Deletion or overexpression of *ZCF21* results in cell wall structure modifications that influence recognition and elimination of the fungus by macrophages. By controlling the expression of adhesins, *ZCF21* also prevents *C. albicans* self-aggregation. Balancing the expression of cell wall components—virulence determinants included—is therefore critical for *C. albicans* to assemble a cell surface configuration that is suitable to colonise mammalian tissues and evade immune surveillance.

FUTURE DIRECTIONS

We will continue and expand on our analysis of genetic determinants of *in vivo* fitness in *C. albicans*, particularly those modulated by the gut microbiota. Furthermore, we are incorporating mouse models of mucosal disease to study the contribution of several fungal genetic circuits to these infections. Overall we expect that these approaches will provide new insights into the role of the host microbiota in *C. albicans* gut colonisation and on the regulatory circuits underlying *C. albicans* proliferation in disparate host niches.

Fig. 1: Candida albicans cells expressing the yellow fluorescent protein and observed in a regular light microscope (left) or in a fluorescence microscope (right).

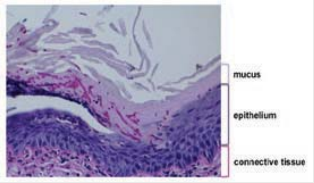

Fig. 2: Histopathology (magnification x40) of murine vaginal tissue after six days of infection with *C. albicans.* Round and filamentous forms of the fungus are stained in dark pink on top of the epithelium (in collaboration with Prof. Dr. Andreas Rosenwald, Pathology Institute, University Würzburg).

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Pérez JC, Kumamoto CA, Johnson AD (2013) *Candida albicans commensalism and pathogenicity are intertwined traits directed by a tightly knit transcriptional regulatory circuit.* **PLoS Biology** 11:e1001510

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2. YOUNG INVESTIGATORS
2.6. STRUCTURAL BIOLOGY OF MYCOBACTERIA

Pathogenic mycobacteria have evolved sophisticated ways to subvert the human immune defence. The group aims to understand one of their most important mechanisms – the secretion of proteins by the type VII secretion system.

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INTRODUCTION

Tuberculosis is a highly infectious respiratory disease caused by various strains of mycobacteria. According to recent figures from the World Health Organisation (WHO) accounts for 1.5 million deaths every year. The emergence of multi-drug resistant mycobacteria is particularly concerning with approximately half a million cases reported in 2014 alone.

Mycobacteria are commonly spread through aerosols such as those generated by coughing. Once inhaled, these pathogens are engulfed by alveolar macrophages in the lungs and targeted for destruction. However, mycobacteria have evolved sophisticated mechanisms to escape this fate. One of them is the secretion of specific proteins by a major protein secretion pathway, the ESX type VII secretion system, which comprises of five distinct secretion machines that are situated in the cell envelope. Each secretion machine has a different substrate specificity and is believed to be employed at different stages of the infection. For example, ESX-1 secreted proteins have been linked to the phagolysosomal escape of mycobacteria in macrophages, the compartment in which the bacteria are lysed, while ESX-5 secreted proteins play a role in granuloma formation. A granuloma is a cluster of immune cells, which mycobacteria exploit as replication niches, or for long-term persistence until reactivation causes the outbreak of tuberculosis. A molecular and functional understanding of the Type VII secretion machines is pivotal to the development of new anti-mycobacterial strategies, but this has been hampered by a lack of three-dimensional structure (see Figure).

A set of six conserved proteins EccA-E and MycP, are essential for secretion of the type VII substrate. Four of these core components, EccB, EccC, EccD and EccE assemble into a stable membrane embedded 1.5 MDa complex forming presumably a secretion pore. The protein transport across the type VII secretion system is powered by the substrate-specific ATPase EccC, which is an integral part of the secretion machine. The role of the cytosolic ATPase EccA in secretion is currently unknown. The protease MycP, is involved in substrate processing. Once in the periplasm, the protein substrate is possibly secreted by an independent outer membrane secretion system to the extracellular space.

RESEARCH HIGHLIGHTS

We have established strategies for the expression of the different Type VII secretion systems and are currently investigating ways to reconstitute these multi-component secretion machines. In parallel, we have established protocols for the extraction and purification of individual type VII components from the bacterial membrane. We are using thermal unfolding assays to screen conditions for the stabilization of these aggregation prone proteins. Important crystallization parameters such as detergent amount and monodispersity of the protein samples are determined by a combination of size-exclusion and multi-angle light scattering experiments. We have screened crystallization conditions for several Type VII components. Initial crystallization hits are being refined. Furthermore, we are establishing functional assays to investigate the secretion mechanism of the Type VII secretion system.

FUTURE DIRECTIONS

Due to their unambiguous role in virulence, our research focuses on the ESX-1 and ESX-5 secretion machines as models of type VII secretion systems in pathogenic mycobacteria. Our goal is to determine the first three-dimensional structures of these two type VII secretion machines by state-of-the-art structural methods such as cryo-electron tomography, cryo-electron microscopy (in collaboration with the Baumeister group at the Max Planck Institute for Biochemistry, Munich) and X-ray crystallography, permitting functional studies to generate a model of the type VII secretion mechanism. Overall, this project will improve our understanding of pathogen-host communication in tuberculosis and has the potential to provide the structural basis for the development of new therapeutics against tuberculosis.

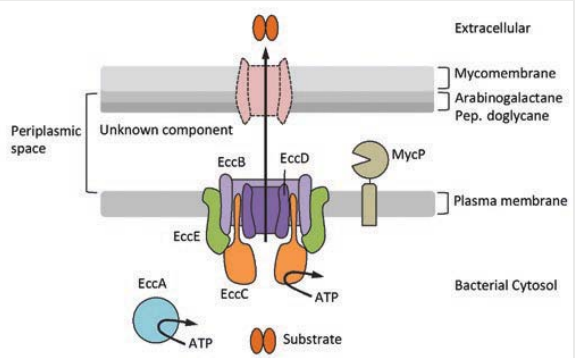

Fig. 1: Working model of the Type VII secretion system.
The components EccB (light purple), EccC (orange), EccD (purple) form the Esx secretion machine in *M. tuberculosis*, which is embedded in the cytoplasmic membrane. The ATPase EccC translocates the substrate (orange) from the cytoplasm into the periplasmic space, from where it is transported by an unknown component (pink) across the outer mycolate membrane into to the extracellular space. The cytosolic ATPase EccA (light blue) and protease MycP (beige) are essential for the substrate transport as well but not tightly associated with the Esx secretion machine.

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2. YOUNG INVESTIGATORS
2.7. ORGANOIDS AS HOST MODEL

The group, which was established in 2015, uses human stem cell-derived organoids as host models. We are particularly interested in gastric pathogens, such as *Helicobacter pylori* and Epstein Barr Virus, and their contribution to gastric carcinogenesis.

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INTRODUCTION

The gastrointestinal tract is lined by a single-layered epithelium that renews itself every 5 days and the stem cells that fuel this constant need for new cells 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 and the resulting inflammation are the lynchpin in cancer development. It is estimated, that approximately half of the 720,000 cases of gastric cancer deaths every year worldwide can be attributed to infection with one of two pathogens: The bacterium *Helicobacter pylori* and the virus Epstein Barr Virus (EBV). Both pathogens are very successful, as they infect about 50 and 95% of the world's population, respectively. In both infections, the carcinogenic process is not fully understood. This is in part due to a lack of suitable model systems.

Basic research for infection, biology, cancer research, as well as tests for drug discovery depends on the use of cell lines and animal models. While these models are extremely useful, they also have limitations. Animal models do not always fully represent the human disease and cancer cell lines allow only limited insights into pre-cancerous processes, because they represent the endpoint of the cancerous cascade. These limitations hamper the study of infections and especially ccarcinogenesis. New primary cell models are required that faithfully recapitulate epithelial organization, stem cell driven tissue regeneration and disease development.

Very recent 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 3-dimensional mini-versions of the organ from which they have been generated so called "organoids". Organoids have been grown from human small intestine, colon, stomach, liver, pancreas and prostate. Organoids are genetically stable and when transplanted back into mice, they integrate into the organ. Furthermore, paired organoids from healthy and tumor tissue from the same patient can be grown and the drug response of the organoids is associated with the mutational status. This leads to the conclusion that organoids not only faithfully represent the healthy epithelium, but also recapitulate the hallmarks of disease and are a useful model for drug development and testing. 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. Also, as organoids can be established from virtually every patient, the comparison of host reactions of a broader range of patient-derived organoids will enable the identification of patient-specific responses and possible risk factors for cancer development. Furthermore, it can be speculated, that the primary cells may enable the growth of pathogens, for which so far no model system exists.

RESEARCH AND FUTURE DIRECTIONS

We aim to further establish organoids as a standard *in vitro* model for infection research. Because of the importance of infections for gastric cancer, we will concentrate on the gastric system. Human gastric 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. Human gastric organoids harbor gastric stem cells next to the cells of the lineages of the human stomach, namely pit mucus cells, gland mucus cells, chief cells and endocrine cells. These cells all exist in parallel in a single organoid. Further, lineage differentiation can be directed using Wnt and Nicotinamide. This allows growing of specific cultures of different lineages of the stomach, such as lineages of the gastric pit or lineages of the gastric gland. For infection, we use microinjection of bacteria into the organoids. When organoids are infected with *H. pylori*, lineages of the glands mount a strong inflammatory response, while lineages of the pit react only marginally.

We are interested in the host's barrier function and the reaction of specific cell types to infection. We will combine organoid technology with system-wide approaches such as RNA-seq and targeted approaches such as CRISPR/Cas9 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. This will hopefully help to delineate the steps in infection-associated carcinogenesis and eventually provide new strategies for therapies.

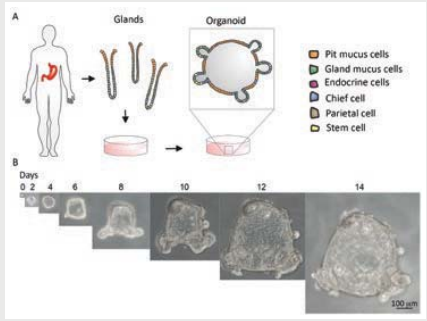

Fig. 1: 3D organoids from human gastric tissue. A) Starting from resection material from patients, we isolate the gastric glands, which contain the stem cells, as well as the differentiated cells of the stomach. Placed in culture, the stem cells proliferate and grow into 3D organoids that contain stem cells as well as differentiated cells of the stomach. B) Within 2 weeks, a single human gastric stem cell grows into an organoid. The organoid contains a single-layered polarized epithelium.

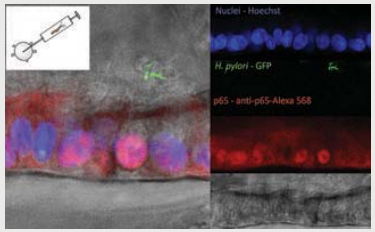

Fig. 1: Human gastric organoids activate NF-kappaB signalling after microinjection with *H. pylori*. 1 hour after microinjection of bacteria, organoids were fixed and NF-kappaB subunit p65 was stained using antibodies. Modified from Bartfeld et al. Gastroenterology 2015.

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03

INSTITUTIONS OF THE RESEARCH CENTRE FOR INFECTIOUS DISEASES

INSTITUTE OF MOLECULAR INFECTION BIOLOGY

INSTITUTE FOR HYGIENE AND MICROBIOLOGY

INSTITUTE FOR VIROLOGY AND IMMUNOBIOLOGY – CHAIR OF IMMUNOBIOLOGY

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DEPARTMENT OF MICROBIOLOGY, THEODOR BOVERI INSTITUTE, BIOCENTER

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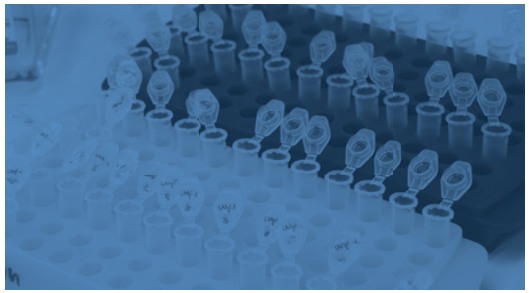

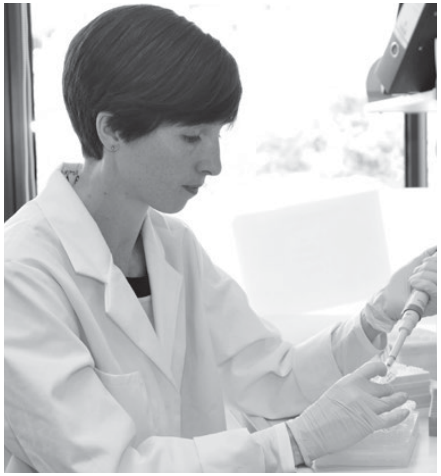

03.1

Institute of Molecular Infection Biology

JÖRG VOGEL

HEIDRUN MOLL

JOACHIM MORSCHHÄUSER

KNUT OHLSEN

TOBIAS ÖLSCHLÄGER

WILMA ZIEBUHR

The Institute of Molecular Infection Biology (IMIB) is an interdisciplinary research institution within the Medical Faculty of the University of Würzburg, with strong links to the Faculty of Biology. IMIB was founded in 1993 and has been chaired by Prof. Dr. Jörg Vogel since 2009.

Members of the institute investigate fundamental biological problems and molecular mechanisms, with a focus on pathogens and infectious disease processes. IMIB research involves the study of bacteria, parasites and fungi, as well as their eukaryotic host, and ranges from bacterial and eukaryotic cell biology and immunology to fundamental aspects of gene regulation and RNA biology. Furthermore, the institute is home to the groups of the prestigious ZINF Young Investigator program of the interfaculty Research Center for Infectious Disease Research (ZINF). IMIB researchers lecture university seminars and practical courses to biology, medical and dental students.

3.1. INSTITUTE OF MOLECULAR INFECTION BIOLOGY

3.1.1. RNA BIOLOGY

Non-coding RNAs play important regulatory roles in all domains of life. The group aims to understand the role of ncRNAs and RNA-binding proteins in the host and pathogen in the context of bacterial infections.

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INTRODUCTION

A combination of genetic, biochemical and genomic approaches has led to the discovery of a large number of non-coding RNAs with regulatory potential. These molecules include the small regulatory RNAs (sRNAs) of bacteria and numerous classes of small (microRNAs, siRNAs, piRNAs, snoRNAs) and long non-coding RNAs (lncRNAs) in eukaryotes many of whose functions are beginning to be understood. It is clear that non-coding RNAs regulate key cellular processes and have a major impact on the outcome of chronic and infectious diseases.

Interestingly, many of the pathogens responsible for important infectious diseases express regulatory RNAs that play an important role in virulence and stress responses. For example, bacterial pathogens are known to express a number of different subclasses of small RNAs including cis-antisense RNAs and the trans-encoded Hfq-dependent sRNAs. The latter sRNAs associate with the RNA chaperone Hfq, which facilitates their binding to target mRNAs by base-pairing. The outcome of these interactions impacts the translation or stability of a large proportion of mRNAs in a cell. Importantly, pathogens such as *Salmonella* Typhimurium encode hundreds of sRNAs, some of which regulate transcription factors or virulence genes required for pathogenesis.

Mammalian cells also utilise non-coding RNAs, such as microRNAs, as part of their anti-bacterial response. In addition, lncRNAs have recently been implicated in infections by regulating the ability of mice to clear persistent bacterial infection. RNA molecules do not exist alone in the cell; rapidly after synthesis they associate with a variety of RNA binding proteins (RBP), often to form more complex ribonucleoprotein particles (RNPs). The associated proteins regulate different aspects of RNA metabolism and influence the function and fate of the RNA molecules. Additionally, the RBPs themselves can be the regulated target of a noncoding RNA. In bacteria, the major RNA binding proteins Hfq and CsrA have been shown to be important for virulence, by facilitating the action of small RNAs or being regulated by noncoding RNA antagonists, respectively.

RESEARCH HIGHLIGHTS

During the last few years we have been using high-throughput sequencing technology to understand the full complement of coding and non-coding RNA transcripts in bacterial pathogens such as *Salmonella* Typhimurium. Following RNA-seq studies on pathogens alone, we have now reached the point where we can monitor RNA expression changes in the pathogen and the host simultaneously. This Dual RNA-seq approach has allowed us to reveal the functions of bacterial sRNAs by looking at the consequences of their activities on the host response. That is, in most cases, the deletion of a bacterial sRNA gene does not cause a macroscopic phenotype in standard cell culture-based virulence assays or an animal infection. However, by also analyzing transcript changes in the host, we have recently discovered novel molecular functions, for example, how the PinT sRNA times the transition between *Salmonella's* two major virulence programs during host cell infection.

Our functional characterization of *Salmonella* sRNAs, especially those that associate with the RNA chaperone Hfq, has recently focused on novel RNA species generated from the 3'UTRs of genes. This has revealed the functions of the 3'UTR-derived SroC and CpxQ sRNAs as the missing links in our understanding of the RNA-based regulation of amino acid pathways and the inner membrane stress response, respectively. In another study aimed at understanding the principles of gene regulation by small RNAs in bacterial pathogens, we identified a novel AND gate function whereby the Hfq-associated RprA sRNA acts together with a major transcription factor to regulate the conjugation of *Salmonella's* major virulence plasmid.

On the host side, our extensive Dual RNA-seq datasets have provided a wealth of opportunities to analyse the functions of host ncRNAs. A current primary interest is in infection-specific lncRNAs of mouse and human; how are these molecules employed to adjust the host response to infection by *Salmonella* and what are the underlying molecular mechanisms?

FUTURE DIRECTIONS

In the next few years we aim to use Dual RNA-seq to gain a new perspective on RNA expression patterns in infected tissues and exploit the sensitivity of this method to understand the hidden molecular functions of bacterial noncoding regulators of gene expression. To increase the resolution and be able to study RNA functions in *in vivo* settings of infection, a major goal is to establish generic single-cell RNA-seq approaches that can be applied to any bacterial pathogen of interest.

Almost all RNAs in cells are associated with RNA-binding proteins, which affect their stability and function. To understand their role, RNA-seq will be combined with *in vivo* cross-linking methods and proteomics for the *de novo* discovery of RNA interacting molecules and targets on a global level and with unprecedented resolution. Overall, we aim to obtain a comprehensive view of the role of ncRNAs and RNA binding proteins in bacterial infections.

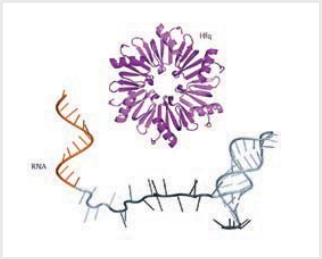

Fig. 1: Hfq and RybB sRNAs.

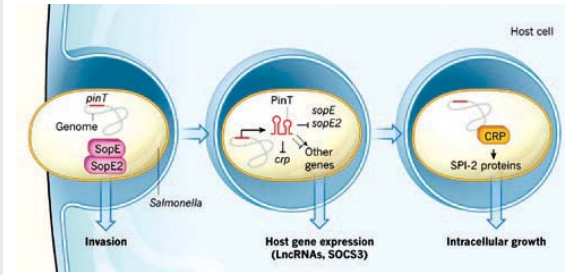

Fig. 2: PinT orchestrates gene expression in *Salmonella* and its host cells (figure source: Machner MP, Storz G (2016) Nature 529, 472-473).

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PRIZES AND AWARDS

2015 Elected to European Academy of Microbiology

3.1. INSTITUTE OF MOLECULAR INFECTION BIOLOGY
3.1.2. INFECTION IMMUNOLOGY

Infectious diseases caused by parasites represent a major worldwide disease burden. The group aims to analyze the interaction between parasites and the host's immune system, to develop novel vaccination strategies, identify new anti-parasitic compounds and to characterize their mode of action.

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INTRODUCTION

Leishmaniasis is considered a tropical affliction that is included in the WHO/Tropical Disease Research list of the six most important diseases, with a significant increase in the number of recorded cases in recent years. There is a growing interest in leishmaniasis in industrialized countries, due to the importance of travel medicine and the rising incidence of HIV and *Leishmania* co-infections. In addition to these clinical aspects, leishmaniasis represents one of the most important models to define the factors controlling the outcome of infectious diseases by cell-mediated immunity. This experimental system has provided a wealth of information on the immunological mechanisms leading to the restriction or facilitation of pathogen growth, with implications not only for infectious diseases but also for general aspects of immunoregulation.

In contrast to viral and bacterial infections, no vaccines are available to protect humans from parasite-induced diseases including leishmaniasis and, therefore, control measures rely exclusively on chemotherapy. The current treatments for leishmaniasis are unsatisfactory due to their toxic side effects, expense and the increasing problems with drug resistance. Thus, there is an urgent need to develop novel strategies for the prevention and the treatment of leishmaniasis and other parasite infections.

RESEARCH HIGHLIGHTS

Resistance and susceptibility to *Leishmania major* infection in the murine model is determined by the capacity of the host to mount either a protective Th1 response or a Th2 response associated with disease progression. Previous reports involving the use of cysteine cathepsin inhibitors indicated that cathepsins B (Ctsb) and L (Ctsl) play important roles in Th1/Th2 polarization during *L. major* infection in both susceptible and resistant mouse strains. Although it was hypothesized that these effects are a consequence of differential patterns of antigen processing, the mechanisms underlying these differences were not further investigated. Given the pivotal roles that dendritic cells and macrophages play during *Leishmania* infection, we generated bone-marrow derived dendritic cells (BMDC) and macrophages (BMM) from *Ctsb*$^{-/-}$ and *Ctsl*$^{-/-}$ mice, and studied the effects of Ctsb and Ctsl deficiency on the survival of *L. major* in infected cells. Furthermore, the signals used by dendritic cells to instruct Th cell polarization were addressed: the expression of MHC class II and costimulatory molecules, and cytokine production. We found that *Ctsb*$^{-/-}$ BMDC express higher levels of MHC class II molecules than wild-type (WT) and *Ctsl*$^{-/-}$ BMDC, while there were no significant differences in the expression of costimulatory molecules between cathepsin-deficient and WT cells. Moreover, both BMDC and BMM from *Ctsb*$^{-/-}$ mice significantly up-regulated the levels of interleukin 12 (IL-12) expression, a key Th1-inducing cytokine. These findings indicate that *Ctsb*$^{-/-}$ BMDC display more pro-Th1 properties than their WT and *Ctsl*$^{-/-}$ counterparts, and therefore suggest that Ctsb down-regulates the Th1 response to *L. major*. Moreover, they propose a novel role for Ctsb as a regulator of cytokine expression.

Nanoparticles (NP) may address the challenges caused by human diseases through improving diagnosis, vaccination and treatment. The uptake mechanism regulates the type of host response to the particle. Hence, understanding the import mechanisms as well as the cellular and subcellular interactions of NP is a prerequisite for their effective biomedical use. We have analyzed the uptake mechanisms of polystyrene NP and factors affecting their import in BMM. Labeling with the endocytic marker FM4-64 and transmission electron microscopy studies show that NP were internalized rapidly via endocytosis and accumulated in intracellular vesicles. Soon after their internalization, they trafficked to organelles with acidic pH. Analysis of the ultrastructural morphology of the plasma membrane invaginations or extravasations provides clear evidence for the involvement of several simultaneous uptake routes in the internalization of a given type of NP by mammalian cells, highlighting the complexity of the NP-cell interactions. Blocking distinct endocytic pathways by pharmacological inhibitors confirmed this finding. The potential to take up NP varies highly among different cell types in a time- and energy-dependent manner. Furthermore, infection and the activation status of bone marrow-derived macrophages significantly affect the uptake potential of the cells, indicating the need to understand the diseases' pathogenesis to establish effective and rational drug-delivery systems. The results enhance our understanding of the application of nanotechnology in biomedical sciences.

Intracellular pathogens are difficult to kill because their localization inside host cells provides protection against immunity and chemotherapies. Thus, successful treatment of diseases caused by intracellular pathogens may need combination therapies and effective delivery systems. Cutaneous leishmaniasis (CL) is caused by intracellular protozoan pathogens of the genus *Leishmania*. CL is a long established global problem, yet there are no suitable vaccine or chemotherapy options. In collaboration with Liam Good (University of London), and Lorenz Meinel (University of Würzburg), we have found that the well-tolerated cationic polymer polyhexamethylene biguanide (PHMB) is able to directly kill *L. major* and to enhance host-directed killing by improving the delivery of immunomodulatory nucleic acids. The study exemplifies parallel host- and pathogen-directed killing of an intracellular pathogen in the presence of effective drug delivery platforms. This general strategy holds great promise for therapy of a range of diseases caused by intracellular pathogens.

FUTURE DIRECTIONS

We will continue to test the newly identified immunoprophylactic and immunotherapeutic strategies for their potential to protect mammalian hosts from parasite infections, and to define the molecular mechanisms underlying their effects. Furthermore, we will explore chemotherapeutic agents with the capacity to boost the host immune system against *Leishmania* infection.

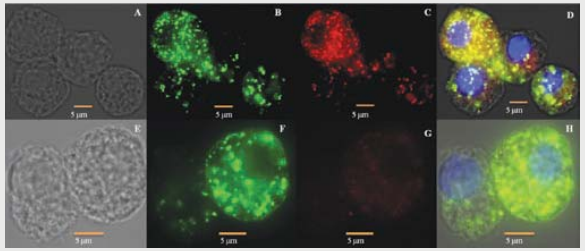

Fig. 1: Fluorescence microscopy images of macrophages after incubation with nanoparticles (A-D) showing co-localization with the endosomal marker FM4-64FX. Images (E-H) are negative control cells treated with only the nanoparticles. Bright field (A and E), nanoparticles (B and F), endosomal marker FM4-64FX (C and G), and merge of the channels (D and H) are depicted. Hoechst 33342 was used to stain the nucleus.

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3.1. INSTITUTE OF MOLECULAR INFECTION BIOLOGY
3.1.3. MYCOLOGY

The yeast *Candida albicans* is a member of the human microbiota, but also one of the most important fungal pathogens that can cause superficial as well as life-threatening disseminated infections. Our group studies the regulation of gene expression, switching between different cell morphologies, and genomic alterations to understand how *C. albicans* adapts to changes in its environment and evolves during its life-long association with the human host.

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INTRODUCTION

Infections by opportunistic pathogenic fungi have become a major medical problem in the past few decades, due to the increasing number of highly susceptible immunocompromised patients. 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. A variety of virulence-associated characteristics contribute to the ability of *C. albicans* to colonize and infect many different body locations, including the switching between different morphologies and metabolic adaptation to nutritional requirements in diverse host niches. In addition, *C. albicans* can generate genetic variants that are better adapted to permanent alterations in the host environment, as exemplified by the emergence of drug-resistant strains during antimycotic therapy. Our group studies the regulation of morphogenesis and other virulence traits, the role of nutrient sensing and acquisition systems 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 colonizaton and infection.

RESEARCH HIGHLIGHTS

C. albicans possesses a large gene family encoding zinc cluster transcription factors, which are unique to the fungal kingdom. Despite regulating important different aspects of *C. albicans* biology and pathogenicity, the functions of many of them have not been studied in detail. Gain-of-function mutations in several zinc cluster transcription factors, which result in the constitutive overexpression of their target genes, are responsible for resistance to the widely used ergosterol biosynthesis inhibiting antifungal drug fluconazole in many clinical *C. albicans* isolates. We have devised a method for the artificial activation of these transcription factors and generated a comprehensive library of *C. albicans* strains containing hyperactive forms of all zinc cluster proteins. Screening of this library identified previously unknown regulators of morphogenesis and drug resistance, for example the multidrug resistance regulator Mrr2. To elucidate how the activated transcription factors confer new phenotypes upon the cells, we determined the changes in gene expression by transcriptional profiling and found that Mrr2 regulates the expression of the major multidrug efflux pump *CDR1*. Subsequent analysis of *CDR1*-overexpressing, fluconazole-resistant clinical *C. albicans* isolates by other researchers demonstrated that several epidemiologically related isolates contained a mutated form of *MRR2* that was responsible for their drug resistance. Therefore, our collection of strains with artificially activated zinc cluster proteins has proven to be a highly useful tool to uncover the biological function of these transcriptional regulators and also to predict mechanisms that result in the generation of variants with clinically relevant phenotypes.

Transcription factors are activated in response to specific signals. For example, Upc2 upregulates the expression of ergosterol biosynthesis genes upon ergosterol depletion, which occurs in the presence of fluconazole. Two other zinc cluster transcription factors, Mrr1 and Tac1, upregulate the expression of the multidrug efflux pumps *MDR1* and *CDR1/CDR2*, respectively, in the presence of certain toxic compounds, but do not respond to fluconazole. To investigate whether the zinc cluster proteins themselves or coregulators are the targets of the inducers, we have generated hybrid transcription factors in which the DNA-binding domains were exchanged. When Upc2 was targeted to the Mrr1 or Tac1 target genes in this way, the hybrid transcription factors upregulated *MDR1* and *CDR1/CDR2*, respectively, upon stimulation with fluconazole, indicating that Upc2 itself was activated by fluconazole-mediated ergosterol depletion. Strikingly, these strains exhibited strongly increased fluconazole resistance, because they now induced the expression of multidrug efflux pumps in the presence of the drug. The acquisition of new target genes by transcription factors is an important mechanism in the rewiring of transcription networks and in the evolution of species. A systematic exchange of the DNA-binding domains of the zinc cluster proteins allows us to add a specific set of new target genes to a transcription factor and to assess which combinations produce variants with novel phenotypes that confer a selective advantage under certain adverse conditions.

Transcription factors often are the downstream targets of signal transduction pathways, many of which include protein kinases that activate or deactivate their target proteins by phosphorylation. To systematically study the role of all *C. albicans* protein kinases in the regulation of infection-related phenotypes, we are generating an isogenic set of deletion mutants of a *C. albicans* wild-type reference strain. The phenotypic analysis of a subset of mutants lacking so far uncharacterized protein kinases has uncovered novel regulators that control the transition from yeast to hyphal growth in response to specific environmental signals. The identification of their target proteins and their importance for colonization and infection will provide molecular insight into how *C. albicans* adapts to different environmental niches within its mammalian host.

FUTURE DIRECTIONS

We are currently investigating how regulatory proteins, especially protein kinases and transcription factors, promote morphological transitions and the interaction of *C. albicans* with the host and its immune system. By using comprehensive libraries of strains that contain artificially activated and hybrid transcription factors, we probe how gain-of-function mutations and the acquisition of new target genes enable *C. albicans* to evolve novel phenotypes. In addition, we investigate how highly drug-resistant *C. albicans* strains with multiple resistance mechanisms are generated and how they overcome the costs of resistance by further evolution.

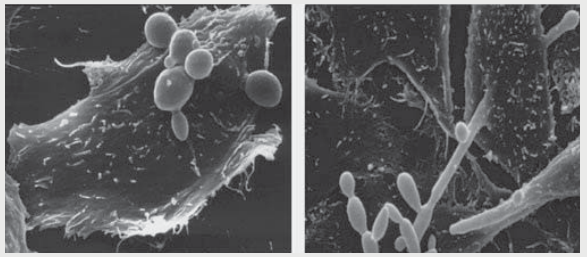

Fig. 1: Scanning electron micrographs of *C. albicans* yeast cells adhering to a human endothelial cell (left) and of *C. albicans* hyphae and pseudohyphae penetrating the host cells (right).

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3.1. INSTITUTE OF MOLECULAR INFECTION BIOLOGY
3.1.4. GRAM-POSITIVE COCCI

Gram-positive pathogens are the leading cause of hospital-acquired infections. The aim of our work is to unravel the regulatory processes that lead to pathogenicity, to visualize the dynamics of infections and to develop novel therapeutic strategies against *Staphylococcus aureus*.

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INTRODUCTION

Staphylococci are the most common causative agents of nosocomial infections. In particular, *Staphylococcus aureus* is able to cause a broad spectrum of diseases ranging from the formation of mild abscess to life threatening infections such as septicemia, endocarditis, pneumonia and osteomyelitis. This pathogen expresses an extraordinary number of virulence traits including leukotoxins, hemolysins, adhesins and degradation enzymes. Importantly, the difficulty in eradicating *S. aureus* infections is compounded by the bacterium's ability to acquire new antibiotic resistance determinants that favour its survival in the highly competitive hospital environment and the decline in therapeutic options due to the emergence of new types of multiple resistant strains. Methicillin- resistant *S. aureus* (MRSA) has emerged as serious threat during the past two decades in both health care facilities and the community at large. As a consequence it is likely that new strategies will be required to combat the pathogen. We have focused our research on the factors and processes that are associated with the pathogenesis of staphylococcal diseases and contribute to the establishment of these bacteria in the hospital environment. A major goal of our group is the development of immunotherapies and the identification of new potential antibiotics in order to combat staphylococcal infections, this also includes the identification of novel targets for antibiotic therapy. Moreover, we are developing *in vivo* imaging technologies to visualize the dynamics of staphylococcal infections and the efficacy of novel antistaphylococcal agents.

RESEARCH HIGHLIGHTS

Recently, we were able to generate a humanized antibody that recognizes multiple *S. aureus* isolates, including hospital-acquired and community-acquired methicillin-resistant strains (Fig. 1). The therapeutic efficacy of this antibody has been validated in experimental mouse infection models. Importantly, the monoclonal antibody activates professional phagocytes and induces highly microbicidal reactive oxygen metabolites in a dose-dependent manner. This results in the enhanced killing of bacteria by phagocytes derived from mice and patients who are prone to staphylococcal infections. Moreover, we have analysed the humoral immune response following vaccination of mice with live *S. aureus* by different routes to identify putative vaccine candidates. For this analysis we have used a recently developed protein array that detects anti-*S. aureus* antibodies. Interestingly, there was a significant difference in the antibody pattern depending on the route of vaccination. In general, intravenously vaccinated mice produced higher antibody titres and a broader spectrum of specificities compared to intramuscularly vaccinated animals. Importantly, a strong response to known virulence factors was induced in intravenously exposed animals suggesting that these antigens were produced during systemic exposure and were probably present to a lesser extent during muscle infection. The strength of the antibody response induced by vaccination with low doses of live *S. aureus* cells correlated with the level of protection in a challenge infection (Fig. 2).In addition, we are interested in the regulation of cellular functions by eukaryotic like Serine/Threonine kinases and phosphatases. A major focus of our work, as part of the transregional collobarative research center 34 (TR-SFB34), is to understand the cellular role of these enzymes. A major goal of our work was to elucidate the phosphorylation patterns in conserved intracellular metabolic pathways and specific functions that may be affected by post-translational modifications. The mapping of phosphorylated proteins revealed that in addition to proteins involved in metabolism, several factors associated with pathogenicity and virulence, such as the virulence regulator SarA, and the elastin-binding protein EbpS, were targeted by this family of kinases. This comprehensive phosphoproteome dataset provides an ideal basis for further investigation of the role of post-translational modifications in pathogenicity and virulence.

Furthermore, we are developing *in vivo* imaging technologies to visualize the dynamics of staphylococcal infections. In order to monitor the spread of phagocytic immune cells to the site of infection in a native context we are collaborating with the Physics department to establish novel *in vivo* imaging modalities based on nuclear magnetic resonance spectroscopy.

FUTURE DIRECTIONS

We are extending our research to understand the role of PknB-dependent phosphorylation during infection. Quantitative phosphoproteomics will be used to detect infection-related changes of the host phosphoprotein networks to learn more about manipulation of host signaling pathways by the pathogen. Furthermore, several *in vivo* imaging techniques will be applied to answer questions related to the spread of *S. aureus* in different disease models and the specific response of the host immune system by tracking the migration of immune cells. Finally, we aim to develop antibody-based immunotherapy for clinical application by combining several monoclonal antibodies with different modes of action.

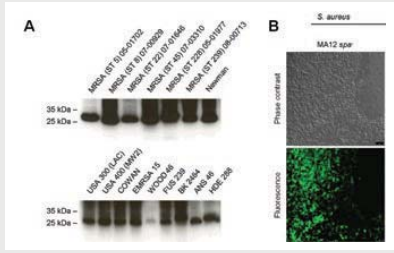

Fig. 1: IsaA conservation and expression by different clinically relevant *S. aureus* strains. Immunoblot analysis of IsaA in cell pellets of different clinically relevant strains (A). Specific binding of IsaA by hUK-66 IgG1by indirect immunofluorescence studies (B).

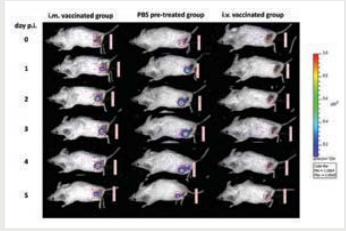

Fig. 2: Effect of live-cell *S. aureus* vaccination on infection in a thigh muscle abscess model. Bioluminescent *S. aureus* Newman lux (1 x 10^8 CFU) was administered into the left thigh muscle of mice, which were previously vaccinated with viable *S. aureus* Newman intravenously (i.v. vac.), intramuscularly (i.m. vac.) or treated with PBS (PBS). The expression of luciferase during infection resulted in photon emission. A bioluminescent signal was determined for each individual mouse in an oval region of interest at the site of infection by an *in vivo* imaging system.

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3.1. INSTITUTE OF MOLECULAR INFECTION BIOLOGY
3.1.5. ENTEROBACTERIA

The species *Escherichia coli* contains pathogenic, commensal as well as probiotic strains. The group aims to understand the molecular basis of the *E. coli* strain Nissle 1917's (EcN) anti-bacterial properties by studying the interaction between EcN and pathogenic bacteria such as enterohaemorrhagic *E. coli* (EHEC).

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INTRODUCTION

The species *Escherichia coli* contains not only commensal but also highly pathogenic and even probiotic strains. All *E. coli* share a common core genome, which facilitates the identification of genes that are specific to pathogenic or probiotic *E. coli* strains. The significance of *E. coli* as a pathogen was highlighted again in 2011 by the outbreak of an epidemic in Germany caused by shiga toxin (Stx) producing enteroaggregative *E. coli* (EHEC) of serotype O104:H4. This outbreak resulted in about 3,800 O104:H4 infected people and left more than 50 patients dead. Unfortunately, there is no specific therapy available to treat infections caused by EHEC. Antibiotic treatment is not recommended, because this has been shown to increase the production and release of Stx, which exacerbates the symptoms of the patient. An effective antibiotic-independent therapy is therefore urgently needed. One such therapy could be provided by the probiotic EcN, which is already licensed as a pharmaceutical under the trade-name Mutaflor and used for the treatment of ulcerative colitis and diarrhoea. Mutaflor has been in use for many decades and obtained GRAS (generally recognized as safe) status. However, its mode of action is still not well understood. Its effectiveness in keeping patients with ulcerative colitis in remission seems to be dependent on its ability to induce human alpha-defensin 2 production in human enterocytes via its flagellin FliC. By contrast, EcN is not effective in the treatment of Crohn's Disease patients. While initial reports of EnN's antagonistic effects against the classical EHEC serotype O157:H7 appeared in 2008, it remained unclear if EcN might also be able to interfere with growth and adhesion of and, most importantly, with Stx expression in the relatively newly evolved Stx-producing enteroaggregative *E. coli* (EHEC) of serotype O104:H4, also named EAHEC.

RESEARCH HIGHLIGHTS

Previously, in collaboration with the group of Klaus Fellermann (University Clinics Schleswig-Holstein), we have shown that EcN uses its flagellum not only for mobility but also to induce beta-defensin production in human enterocytes. Recently, we have described another role for the EcN's flagellum by revealing its function as an adhesin mediating binding to human gut biopsies, porcine mucin 2 and human, but not mouse, mucus. This adherence is independent of type 1, F1C and curli fimbriae but involves the EcN's flagellum, which recognises gluconate. Surprisingly, neither the surface exposed domain D3 of flagellin nor domain D2 mediates binding to mucin 2. Binding to mucin 2 turned out to be mediated by certain parts of domain D1 different from those interacting with TLR5.

We have also investigated certain safety aspects of EcN. EcN harbours a genomic island encoding genes for the synthesis of a yet to be identified polyketide. This polyketide induces DNA double strand breaks (DDSB) in host cells in a manner that is strictly dependent on direct contact between EcN and the eukaryotic cells. However, *in vivo* EcN is separated from the gut epithelial cells by a mucus layer, which led us to hypothesize that the mucus layer in the gut may prevent EcN induced genome damage. A protective role for the mucus layer was revealed by comparing the induction of DNA double strand breaks in non-mucus producing cells (HT29) interacting with EcN and those covered by a confluent mucus layer produced by HT29MTXE12 cells.

Recently, we have reported the *in vitro* inhibition of Stx production by EcN in the classical EHEC ("Big Five") as well as the O104:H4 outbreak strain from 2011. This finding supports the hypothesis of using EcN to treat patients suffering from EHEC infections. However, because Stx is encoded by a prophage in EHEC, we were concerned that EcN may becoming a Stx-producer due to a non-lytic stx-phage infection in people harbouring both EHEC and EcN. In fact, several *E. coli* K-12 strains tested became Stx producers after *in vitro* coincubation with certain EHEC strains. By contrast, we were unable to transform EcN into a Stx-producer by coincubation with any EHEC strain. Most likely, this is due to the different C-terminal loop of the outer membrane protein LamB in EcN and the K-12 strains. LamB functions as a receptor for lambda phages, and while the LamB sequence is identical in all tested K-12 strains, it differs in EcN. This property is another important safety aspect of EcN indicating that it could be used as a safe therapeutic option in the prevention and treatment of EHEC infections.

FUTURE DIRECTIONS

Work is in progress to exchange the different *lamB* genes between *E. coli* K-12 and EcN and test for stx-phage sensitivity/resistance. We are also aiming to identify the factors involved in the antagonistic activity of EcN against EHEC/EAHEC and elucidate their mechanism of action by analyzing the secretome and the transcriptome of EcN in single culture and co-culture with EHEC strains.

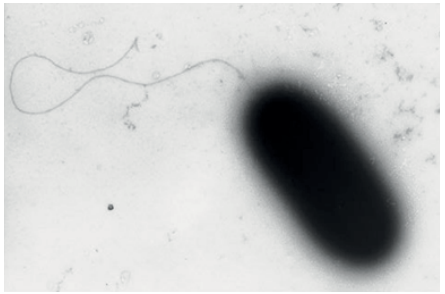

Fig. 1: Transmission electron micrograph of the monotrichously flagellated *E. coli* Nissle 1917.

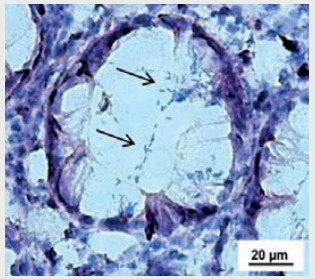

Fig. 2: Light microscopic image of a human gut biopsy cryosection with *E. coli* Nissle 1917 bacteria adhering to a cross-section of a crypt. Arrows point to adhering bacteria.

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3.1. INSTITUTE OF MOLECULAR INFECTION BIOLOGY
3.1.6. NOSOCOMIAL INFECTIONS BY STAPHYLOCOCCI

Staphylococci are common causes of hospital-acquired (nosocomial) infections. The research of the group focuses on the factors and processes that contribute to the establishment of these bacteria as pathogens in the hospital environment and beyond.

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INTRODUCTION

Staphylococci are primarily commensals residing on the skin and mucosa of humans and animals; but they also represent important pathogens causing a broad variety of diseases. The most prominent species in this respect is *S. aureus* which is armed with an array of highly potent virulence factors and which causes infections in both the hospital setting and in the community. By contrast, the large group of coagulase-negative staphylococci (CoNS) generally has a lower pathogenic potential and endangers mainly immunocompromised individuals in hospitals. CoNS are typical opportunistic pathogens associated with medical progress as the vast majority of infections are linked to the use of indwelling medical implants on which these bacteria form biofilms.

Antibiotic resistance is a common theme both in *S. aureus* and CoNS. Thus, methicillin-resistant *S. aureus* (MRSA) and methicillin-resistant CoNS (MR-CoNS) are widespread. As a matter of concern, methicillin-resistance is often accompanied by antibiotic resistance to other, unrelated antibiotic groups and classes, significantly limiting our opportunities to fight such infections. Health authorities have identified multi-resistant staphylococci as a serious threat to the public.

Recent progress in genome research has provided exciting novel insights into the biology of staphylococci, demonstrating that these versatile microorganisms can adapt very rapidly to changing environmental conditions. We have a strong interest in teaming basic research with public health issues aiming at an in-depth understanding of staphylococcal infections and laying the basis for future innovative prevention and treatment strategies. Currently, we focus on regulatory networks linking staphylococcal metabolism and virulence. Also, we investigate the mechanisms of biofilm formation on medical devices, which significantly contributes to therapy recalcitrance of CoNS infections; and finally, we study the role of CoNS as reservoirs for the evolution and spread of novel antibiotic resistance genes.

RESEARCH HIGHLIGHTS

While, until recently, MRSA occurrence was restricted to the health care setting, specific MRSA lineages are now also present in the community. Thus, during the last decade a novel MRSA clone emerged which is adapted to animals and spreads rapidly in livestock and pets. These livestock-associated MRSA (LA-MRSA) may carry, in addition to methicillin resistance, a variety of novel and uncommon antimicrobial resistance genes whose genetic origin is largely unknown. In a recent study, we identified CoNS as a putative reservoir of such genes in environmental samples from animal husbandries. Comprehensive resistance profiling of CoNS, obtained from pig farms, revealed alarmingly high resistance rates against a number of antibiotics commonly used in human and veterinary medicine. Many isolates carried rare (multi)resistance genes, and some isolates even displayed decreased susceptibilities towards last resort antibiotics such as linezolid and daptomycin, which have only recently been introduced into clinical practice. In particular, the species *Staphylococcus sciuri* seems to harbour a significant resistance gene pool that requires further attention. *S. sciuri* thrives both in soil and in warm-blooded hosts, and we hypothesise that members of the species might link host-colonising staphylococcal species with environmental bacteria, thereby contributing to the spread of resistance genes among staphylococci. In this respect, the high-level daptomycin resistance phenotype displayed by a number of *Staphylococcus sciuri* isolates is a worrisome finding. The molecular and genetic background of this insusceptibility is currently unknown and will be subject of further investigations.

Life in biofilms is another typical hallmark of staphylococci, notably of CoNS species such as *Staphylococcus epidermidis*. Biofilms have been proposed to functionally resemble a multicellular organism in terms of heterogeneous gene expression patterns. In a changing environment, this heterogeneity is likely to facilitate persistence and survival of the population as a whole, but may also support division of labour and maintenance of the biofilm structure. In various projects, we are studying the regulatory networks controlling biofilm formation as well as the factors that trigger metabolic heterogeneity and genetic adaptation, with a special emphasis on RNA-mediated regulatory mechanisms. Currently, we investigate T-box riboswitch-mediated control of methionine biosynthesis, which we found to be differentially expressed in staphylococcal biofilms. Also, we are analysing the role of non-coding RNAs in the regulation of metabolic pathways involved in biofilm matrix production and the influence of genetic stability of *S. epidermidis*.

FUTURE DIRECTIONS

In the near future we will continue to focus our research on the association between bacterial metabolism and virulence. By combining various 'omics' approaches with genetic and structural studies we will specifically address methionine biosynthesis control and the suitability of the pathway as a putative anti-infective target. In addition, we will analyze the biological significance of RNA-controlled metabolic heterogeneity on long-term survival and stress resistance in biofilms. Finally, we will investigate the molecular mechanism of the high-level daptomycin resistance in *S. sciuri* with the aim to prevent dissemination and transfer of this resistance phenotype at an early stage.

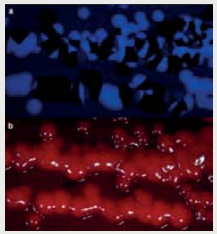

Fig. 1: Heterogeneous expression of a regulatory RNA in *S. epidermidis* colonies. (a) The effect is visualized by a promoter fusion of the regulator with the blue-fluorescent protein Cerulean. (b) Phenotype of the colonies on Congo red agar.

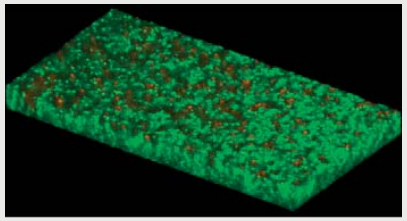

Fig. 2: Confocal laser microscopy and 3D-reconstruction of a *S. epidermidis* biofilm after live/dead staining. Live cells appear in green and dead bacteria in red.

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03.2 Institute for Hygiene and Microbiology

MATTHIAS FROSCH
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. The institute has been chaired by Prof. Dr. Matthias Frosch since 1996.

The IHM is responsible for the diagnosis of infectious diseases caused by bacteria, fungi and parasites, in addition to advising clinicians on the treatment and prevention of these diseases. Research activity within IHM focuses 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.

IHM also hosts the National Reference laboratories for meningococci and *Haemophilus influenzae* (NRZMHI) and the consiliary laboratory for echinococcosis. Teaching includes students of medicine, dentistry and related subjects.

3.2. INSTITUTE FOR HYGIENE AND MICROBIOLOGY

3.2.1. MOLECULAR SURVEILLANCE OF INVASIVE BACTERIAL INFECTIONS

Matthias Frosch is the chair of the Institute for Hygiene and Microbiology (IHM). The main tasks of the IHM are (i) research on infectious diseases and their causative agents, (ii) the laboratory diagnosis of infectious diseases caused by bacteria, fungi and parasites, (iii) the provision of advice to clinicians with respect to diagnosis, therapy and prevention of infectious diseases, (iv) hospital hygiene as well as (v) providing teaching and training for students of medicine, dentistry and related subjects.

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INTRODUCTION

The genomic and phenotypic diversity of bacterial isolates within a species is the focus of many research activities at the IHM. There is increasing evidence, that this diversity of pathogenic bacteria is key to understanding the complex interplay between pathogen and host and the correlations between certain bacterial finetypes and the clinical presentation, progression and outcome of infectious diseases.

Neisseria meningitidis, the meningococcus, is a paradigm of a commensal and pathogenic bacterium, many variants of which colonise the human nasopharynx. However, only a relatively small number of these variants, known as hypervirulent and hyperinvasive types, are associated with severe invasive and often lethal disease. Several groups at the IHM focus on deciphering the basis for virulence, analysing the complex interaction of commensal and virulent meningococci with the human host and developing tools for their identification and typing. The reports of the ZINF members Ulrich Vogel, Alexandra Schubert-Unkmeir and Christoph Schoen, working at the IHM, illustrate these research projects in more detail. Their research is stimulated by access to meningococcal strains collected and typed at the National Reference laboratory for Meningococci and *Haemophilus influenzae* (NRZMHi), which is hosted by the institute, and also access to clinical specimens from the IHM diagnostic laboratories that are involved in the diagnosis of infectious diseases in patients at the University Hospital and other local hospitals. Vice versa, these diagnostic laboratories also benefit from the research groups, such as the implementation of new methods for pathogen detection and typing. This is especially true for the hospital hygiene laboratory, where an increasing number of molecular and genome-based detection and typing methods have been introduced for nosocomial pathogens, for the analysis of transmission traits and in the surveillance of pathogens, providing early warning systems for the prevention of outbreaks.

RESEARCH HIGHLIGHTS

In addition to the work in the diagnostic laboratories and especially in the National Reference laboratory for meningococci and *Haemophilus influenzae*, which includes the identification and molecular typing of infectious agents as well as providing advice to public health institutions in case management, there is also a great interest in continuously improving laboratory surveillance of the diseases in collaboration with public health authorities at the European level. This has resulted in the development of new typing tools as well as in scientific studies on the population biology of the infectious agents.

Transnational collaborations between European Reference laboratories are being further promoted on behalf of the ECDC (European Centre for Disease Prevention and Control). Within this framework a laboratory network (IBD-labnet) comprising of all Reference laboratories on *Neisseria meningitidis, Haemophilus influenzae* and *Streptococcus pneumoniae* in the EU Member States is coordinated by the IHM and aims to harmonize laboratory surveillance of invasive bacterial diseases. The goal is to improve laboratory capacities to accurately characterize these invasive bacterial isolates. To fulfill this task, the IHM assists the participating National Reference laboratories to continuously improve laboratory performance with respect to the identification and characterization of *N. meningitidis, H. influenzae* and *S. pneumoniae* as well as the implementation of new techniques for routine diagnosis and typing. Moreover, and as a joint effort of all participating European National Reference laboratories for meningococci, the IHM together with the Norwegian Institute of Public Health, Oslo has contributed to the establishment of a centralised European Meningoccal Strain Collection (EMSC). The EMSC currently comprises of approximately 1200 meningococcal invasive isolates obtained from 17 European countries. The purpose of the EMSC is to provide a sustainable infrastructure for the comprehensive laboratory surveillance and control of invasive meningococcal disease in the EU and for the validation and implementation of new detection and typing tools. For example, the genomes of more than 800 meningococcal disease isolates have been sequenced using HiSeq2000 technology as part of a joint endeavour between IHM, the Norwegian Institute of Public Health, Oslo and the University of Oxford within the IBD-labnet. These genome sequences are currently being analysed to provide a baseline for interpreting the potential impact of novel MenB vaccines on circulating meningococci strains in Europe.

FUTURE DIRECTIONS

As part of its strong commitment to continuously optimise patient care, the IHM is engaged in improving and developing diagnostic test systems and typing tools. In this regard, the IHM will further promote the introduction of genome sequencing techniques in the routine clinical microbiology workflow to improve the diagnosis and control of infectious diseases.

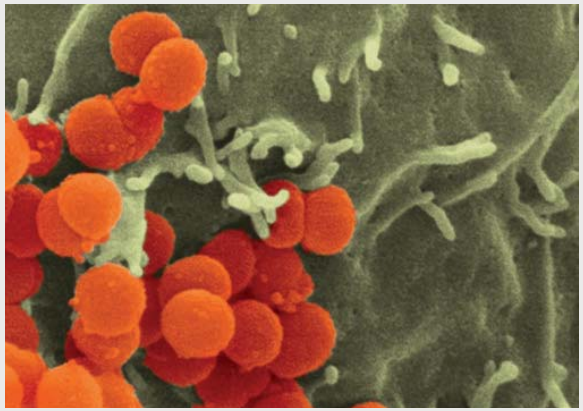

Fig. 1: Microvilli formation induced in human brain endothelial cells upon contact with *N.meningitidis.*

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3.2. INSTITUTE FOR HYGIENE AND MICROBIOLOGY
3.2.2. HELMINTH INFECTIONS

Parasitic flatworms are a major cause of human disease world-wide.
The group aims to understand host-parasite interaction mechanisms and parasite development using the tapeworm model system *Echinococcus multilocularis*.

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INTRODUCTION

Parasitic flatworms (e.g. trematodes and cestodes) are the causative agents of severe diseases and infect hundreds of millions of people, mostly in under-developed countries. A very important sub-group of these diseases are infections due to larval cestodes (tapeworms) such as alveolar (*E. multilocularis*; fox-tapeworm) and cystic (*E. granulosus*; dog-tapeworm) echinococcosis. These infections are characterized by growth and development of the parasite's metacestode larval stage in various host organs such as the liver, lung, and brain, eventually leading to vesicle obstruction, organ failure, and death.

Among larval cestode infections, alveolar echinococcosis (AE) is the most dangerous disease and involves an infiltrative, cancer-like growth of the metacestode within the host's liver, followed by the formation metastases in secondary organs (lung, brain). The infection is initiated by the oral uptake of infectious eggs that contain the first larval stage (oncosphere), which subsequently develop into the metacestode and protoscolex stages in a metamorphosis-like manner that is driven by totipotent parasite stem cells. These stem cells, called germinative cells, are the most important cell types of tapeworms and account for the enormous developmental plasticity of these organisms, for asexual proliferation of cestode larvae, and for the tremendous regeneration capacity (up to immortality) of adult and larval cestodes.

Current treatment options against larval cestode infections, particularly AE, are very limited. In a few cases, surgical removal of the parasite larvae can be achieved. In the remaining cases (>80%), benzimidazole-based chemotherapy, directed against parasite beta-tubulin, has to be used. However, beta-tubulin is highly conserved between parasite and host, resulting in significant adverse side effects. Furthermore, the drug's effects are parasitostatic (not parasitocidal) and have to be taken for very long periods of time (in some cases for the remainder of the patient's life).

RESEARCH HIGHLIGHTS

The group has developed important tools for studying molecular host-parasite interactions and parasite development, including *in vitro* cultivation systems for *Echinococcus* larvae and stem cells in which the infection of the intermediate host can be mimicked under laboratory conditions. Importantly, the group has, in collaboration with the Wellcome Trust Sanger Institute (Hinxton, UK), completed a whole genome sequencing project for *E. multilocularis*, accompanied by extensive next-generation transcriptome sequencing of the *E. multilocularis* life-cycle. These analyses have revealed extensive gene loss/gain in *Echinococcus* that is associated with the evolution of parasitism.

The project has revealed that cestode stem cells are unique among metazoans and lack several central components that usually regulate germline stem cell maintenance (e.g. PIWI, VASA), they also differ in gene expression profiles from stem cells of trematodes and free-living flatworms. The cestode stem cells have thus significantly modified the systems that control stem cell maintenance and differentiation and which could be involved in the tremendous regeneration capacity of these organisms.

Drug screening assays and transcriptomic analyses have indicated that the *Echinococcus* stem cells, which are the only proliferating cells in the parasite, are resistant to benzimidazoles, which could explain the high recurrence rates of parasite growth in AE patients after the discontinuation of chemotherapy. Future studies of new chemotherapeutic agents should thus focus on the parasite's stem cell system and, accordingly, genomic and transcriptomic analyses have revealed a plethora of potential drug targets, including a large number of druggable kinases, that are expressed in these cells. We have used the *in vitro* cultivation systems to demonstrate the anti-*Echinococcus* activities of several drugs that are currently in clinical use against cancer (e.g. Imatinib) and have shown that inhibitors of Polo-like kinases can specifically eliminate the stem cell population from metacestode vesicles.

Utilizing the *in vitro* cultivation systems for immunological studies, an immunomodulatory parasite protein, EmTIP, with significant homologies to the human T-cell immunomodulatory protein (TIP), has been characterized. EmTIP stimulated the production of IFN-gamma by mammalian T-cells, providing an explanation for the early induced Th1-dominated immune response in AE. EmTIP has also proven to be essential for the development of metacestode vesicles from parasite stem cells.

Finally, the group has also characterized a mobile genetic element of the TRIM (terminal retrotransposon in miniature) – family, which had undergone massive expansion in the genomes of taeniid cestodes (e.g. *Echinococcus* or *Taenia*) and which are massively expressed in the parasite's stem cells. Interestingly, TRIMs had differentially influenced the expression of nuclear genes in *E. multilocularis* and *E. granulosus*, which could account for the remarkable differences in metacestode morphology. More recently, the group has demonstrated that the *E. multilocularis* metacestode exclusively develops as posteriorized tissue where wingless-related (wnt) signaling is high and wnt-antagonists (which would define the anterior pole) are silenced. Interestingly, aberrant regulation of wnt signaling is also observed in many human cancers, pointing to similarities between malignant transformation in humans and *Echinococcus* metacestode formation.

FUTURE DIRECTIONS

Ongoing studies aim to elucidate the regulatory mechanisms that control stem cell dynamics in *E. multilocularis*, including the stem cell specific transcriptome, how cestodes maintain genome integrity and the molecular basis for the immortality of the cestode stem cell system. This will be accompanied by *in vitro* and *in vivo* studies to identify small molecule compounds that specifically target and eliminate parasite stem cells. Another focus will be the identification of specific excretory/secretory parasite factors that are involved in subverting the immune response of the host towards a tolerogenic environment.

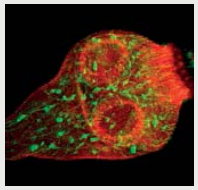

Fig. 1: E. multilocularis protoscolex after staining with phalloidin (muscles) and anti-acetylated tubulin (nervous system, flame cells).

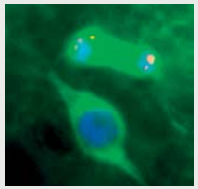

Fig. 2: E. multilocularis stem cells in interphase (below) and during mitosis (above) (staining: DAPI (blue), incorporated EdU (red), tubulin (green)).

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3.2. INSTITUTE FOR HYGIENE AND MICROBIOLOGY

3.2.3. EVOLUTIONARY AND FUNCTIONAL PATHOGENOMICS OF *neisseria meningitidis*

The human body is host to a large variety of different microorganisms collectively called the human microbiota, which contains both commensal and potentially pathogenic species. Using *Neisseria meningitidis* as a model the group aims to better understand the genetic and genomic basis for commensal and invasive behavior in human-adapted commensal pathogens.

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INTRODUCTION

The importance of the normal microbial populations within the human body in health and disease has received increasing attention in recent years. Although these populations are normally beneficial or neutral, some components such as commensal pathogens are responsible for more infections today than "classical" pathogens. The reality that commensal pathogens cause serious disease has raised questions about some of the original concepts of virulence factors. As a prime example, *Neisseria meningitidis* is a commensal bacterial species that colonizes the nasopharynx of up to 30% of the healthy human population. Whereas most isolates from healthy carriers are considered non-pathogenic, a small number of strains belonging to hyperinvasive lineages can cause invasive meningococcal disease (IMD) such as acute bacterial meningitis or sepsis (Figure 1). The work of our group focuses on a fundamental question regarding the genetic basis of meningococcal virulence. A basic assumption for pathogenic bacteria is that virulence is genetically determined by virulence factors encoded in the bacterial chromosome. However, the identity of these genetic factors and their evolution in meningococci remains poorly understood. In addition to differences in the gene complement between carriage and invasive strains, contrasting virulence properties could also result from altered regulation and expression of genes common to all meningococcal strains under infection-relevant conditions. However, currently little is also known about the potential differences in the transcriptomes of carriage and invasive meningococcal strains. Since classical candidate gene-based approaches have failed to identify a set of virulence genes in *N. meningitidis,* our group is employing a variety of molecular biological and genomic techniques, including comparative whole-genome sequencing, microarrays and RNA-sequencing to search for the elusive genetic virulence determinants.

RESEARCH HIGHLIGHTS

One research focus has been the contribution of metabolism to virulence in meningococci and whether differences in the allelic profile of metabolic genes, analyzed by multiple sequence typing, result in detectable phenotypic effects *in vitro*. By means of a computational meta-analysis of published genome-wide data (Figure 2) we have provided evidence that the metabolism of lactate, the oxidative stress response, and, in particular, glutathione metabolism as well as the denitrification pathway are intimately linked to meningococcal pathogenesis. We have also revealed metabolic differences between strains from hyperinvasive and carriage lineages, which have been experimentally confirmed by disparate *in vitro* growth of these two populations. These data indicate that strains from carriage and hyperinvasive lineages differ in the expression of regulatory genes involved particularly in stress responses and amino acid metabolism under infection relevant conditions.

As head of the laboratory for diagnostic microbiology at the IHM, the diagnosis and molecular epidemiology of human pathogens constitutes another increasingly important research focus. For example, as a partner in a collaborative project coordinated by Wilma Ziebuhr (IMIB) we have recently determined the antibiotic resistance profiles of 344 coagulase-negative staphylococci (CoNS) in livestock environments. This has enabled us to assess the potential of livestock-associated CoNS as putative reservoirs for the evolution and transfer of resistance genes. In addition, we are currently participating in a multi-center study addressing the epidemiology and prevention of parapneumonic pleural effusions and empyema thoracis in children in Germany coordinated by Johannes Liese (Children's Hospital of the University of Würzburg). This involves the molecular detection and identification of bacterial pathogens based on 16S rDNA sequencing.

FUTURE DIRECTIONS

Using human specimens such as venous blood and cerebrospinal fluid we will use comparative transcriptomics to analyze the differences in the expression and regulation of genes common to carriage and invasive meningococcal isolates under infection mimicking conditions. By using this approach we aim to embed our experimental results in a systems biological framework to achieve a comprehensive understanding of meningococcal pathogenicity. A future focus will also include the strengthening of existing and the establishment of new scientific collaborations with clinical partners both within the ZINF and beyond.

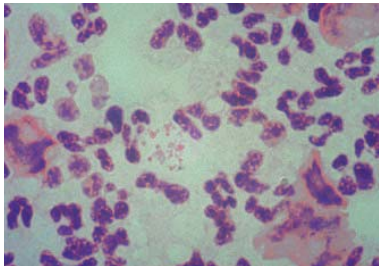

Fig. 1: Fig. 1: Gram staining of a cerebrospinal fluid sample from a patient suffering from acute meningococcal meningitis from the University Hospital Würzburg (1000 x).

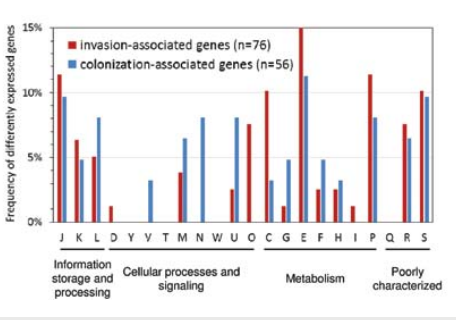

Fig. 2: Computational meta-analysis of transcriptomic data from several studies as given in Schoen et al. (2014) based on the COG classification scheme. Compared to the invasion-associated genes, the colonization-associated genes comprised in particular genes involved in cell motility and envelope biogenesis (COG functional categories N and V).
The invasion-associated genes in turn included genes for chaperon proteins and genes involved in protein synthesis and turnover (COG category O).

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3.2. INSTITUTE FOR HYGIENE AND MICROBIOLOGY
3.2.4. HOST-PATHOGEN INTERACTIONS

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

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INTRODUCTION

Neisseria meningitidis is an obligate commensal in humans, colonizing the nasopharyngeal mucosa usually without affecting the host, a phenomenon known as carriage. After the onset of colonization, *N. meningitidis* strains occasionally penetrate the mucosal membrane and enter the bloodstream to cause severe septicemia. Following bacteremia, *N. meningitidis* may bind and subsequently cross the blood-cerebrospinal fluid barrier to enter the subarachnoidal space, resulting in acute and purulent meningitis. The human blood-brain/blood-cerebrospinal fluid barrier (BBB/B-CSFB) is one of the tightest barriers in the human body. Among invasive pathogens, only a few are capable of invading the subarachnoideal space, thus suggesting that they have developed specific abilities to enable them to circumvent the BBB/B-CSFB.

As is the case for other bacterial pathogens, *N. meningitidis* can activate host cell signal transduction pathways to promote adhesion and uptake by the host cell. Preliminary data from our group have revealed that *N. meningitidis* is capable of activating the enzyme acid sphingomyelinase (ASM) to modulate ASM-generated ceramide levels in the membrane of brain endothelial cells. Ceramide has emerged as a biochemical mediator of diverse stimuli, including infection by some pathogenic bacteria and viruses. Ceramide molecules associate into large-membrane macrodomains, which serve as platforms for the concentration of signaling components, their assembly into higher-order complexes and the transmission of signals across the plasma membrane.

RESEARCH HIGHLIGHTS

Based on our initial observation that the activity of ASM is required for *N. meningitidis* uptake by infected human brain microvascular endothelial cells, we have begun an in depth analysis of the role of the ASM-ceramide system and involved signaling pathways. During the last two years we have shown that the interaction of *N. meningitidis* with brain endothelial cells causes the transient activation of ASM followed by ceramide release in brain endothelial cells. In response to *N. meningitidis* infection, ASM and ceramide are displayed in the outer leaflet of the cell membrane and condense into large ceramide-enriched membrane platforms that also accumulate ErbB2, an important receptor involved in meningococcal uptake. Both the pharmacological inhibition of ASM by amitryptyline as well as siRNA-mediated depletion of ASM abolished meningococcal uptake, whereas adhesion was not affected. The importance of ASM in *N. meningitidis* uptake was further supported by the natural ablation of the enzyme activity (NPDA fibroblasts). Mechanistically, we have observed that ASM activation is dependent on the binding of Opc-expressing meningococci to their attachment receptor, HSPG, followed by activation of phosphatidylcholine-specific phospholipase C. Interestingly, meningococcal isolates of the ST-8/ST-11 clonal complex, which lack the opc gene and are more likely to cause severe sepsis but rarely meningitis, barely invaded brain endothelial cells and were restricted in their ability to induce ASM and ceramide release.

We have also initiated a study to investigate the effect of *N. meningitidis* on the cell cycle in brain endothelial cells. In a similar way to viruses that perturb the cell cycle machinery to facilitate their own replication, bacteria can also manipulate checkpoints of the cell cycle to establish infection. Furthermore, a growing family of bacterial toxins and effectors has been described that interfere with the host cell cycle, named 'cyclomodulins'. Interestingly, we have found that *N. meningitidis* is also able to interfere with cell cycle progression and to differentially modulate cell cycle regulatory genes in brain endothelial cells, thereby arresting infected cells in S phase. Importantly, we have provided evidence that the outer membrane proteins of the colony opacity-associated (Opa) protein family as well as the Opc protein of *N. meningitidis* are sufficient to trigger the accumulation of cells in S phase. This indicates that these bacterial factors not only function as major adhesins and/or invasins, but that they can also act as 'cyclomodulins', and affect the cell cycle machinery. By using a focused cell cycle real-time PCR based array combined with integrated network analysis we have demonstrated the differential regulation of several cell cycle regulatory genes, including the cell cycle inhibitors $p21^{WAF1/CIP1}$ and cyclin G2. Their changes were observed on the protein level and/or re-localization in *N. meningitidis*-infected cells. Moreover, increased $p21^{WAF1/CIP1}$ expression was p53 independent and genetic ablation of $p21^{WAF1/CIP1}$ or cyclin G2 abrogated *N. meningitidis* induced S phase accumulation.

FUTURE DIRECTIONS

In the case of invasive meningococcal diseases (septicemia and /or meningitis) endothelial adhesion events must occur during circulation under conditions of physiological blood pressure. To investigate the bacterial and host factors, which contribute to this essential step of invasive meningococcal disease, we aim to develop an *in vitro* circulatory 2-D N. *meningitidis*-endothelium interaction model. We will implement laminar-flow chambers and video microscopy to study meningococcal infection in this environment. In addition, within the newly funded GRK 2157, we will seek to develop a human *in vitro* 3-D model of the BBB/BCSFB to study colonization and penetration of brain microvessels by *N. meningitidis*. Overall, we aim to obtain a more detailed understanding of the changes in host membrane structures during bacterial infection.

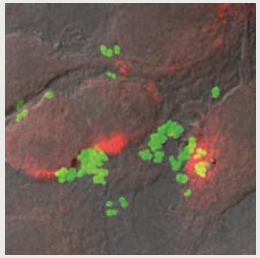

Fig. 1: N. meningitidis induces the formation of ceramide-enriched membrane platforms on brain endothelial cells (HBMEC).
HBMEC were infected with a GFP-expressing wildtype strain MC58 for 2 h, fixed, left intact, stained with anti-ceramide antibodies and secondary Cy3-conjugated anti-mouse-IgM antibodies and analyzed by confocal microscopy. Ceramides accumulate in close association with attached bacteria. (doi:10.1371/journal.ppat.1004160.g001)

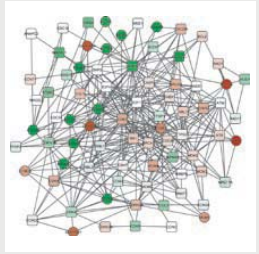

Fig. 2: N. meningitidis infection alters cell cycle gene expression in infected brain endothelial cells.
A transcriptome dataset was used to perform a network analysis. Network analysis revealed a cell cycle-specific module of 78 genes and 351 interactions. Colouring is according to the fold change where red denotes an overexpression in infected brain endothelial cells and green denotes a down-regulation, respectively. Circles represent significantly regulated genes, whereas squares represent associated genes below significance threshold. (Cell Microbiol Jul 7. doi: 10.1111/cmi.12482)

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3.2. INSTITUTE FOR HYGIENE AND MICROBIOLOGY
3.2.5. INFECTION EPIDEMIOLOGY AND PATHOGENESIS OF *neisseria meningitidis*

Neisseria meningitidis is a commensal pathogen of the human host. The group conducts infection epidemiology projects within the framework of the national reference laboratory for meningococci and *Haemophilus influenzae* (NRZMHi) and research on the meningococcal capsule.

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INTRODUCTION

Neisseria meningitidis colonizes the human host and is considered to be a commensal species that accidentally causes severe invasive disease in children and adolescents. The NRZMHi, a national reference laboratory funded by the Robert Koch-Institute and headed by Ulrich Vogel and Matthias Frosch for more than 10 years, provides the public health system with laboratory surveillance data of invasive meningococcal disease. Since 2008, the reference laboratory also conducts Germany-wide laboratory surveillance of invasive *Haemophilus influenza* infections. The data are continuously matched with statutory notification data to generate a robust and reliable dataset. This dataset is important for following national epidemiological trends and to address specific questions such the impact of vaccination recommendations. There is a vital collaboration with the Robert Koch-Institute. The reference laboratory is actively networking with other European reference laboratories. Ulrich Vogel is the president of the EMGM Society, an organization linking reference laboratories and epidemiologists. The capsule of meningococci is their major virulence factor. The group also conducts research to better understand capsule biosynthesis and its chemical modification with the ultimate goal to design improved capsule based vaccines.

RESEARCH HIGHLIGHTS

The reference laboratory identified the loss of the chromosomal capsule locus as the only mechanism that resultis in an unencapsulated phenotype in invasive H. influenzae isolates, the NTHi strains, which are increasingly recognized as a cause of bacteremia. This finding is important for laboratory diagnosis. Furthermore, the reference laboratory published the first representative dataset on ampicillin resistance in German invasive *H. influenzae* isolates and reported that genetic polymorphisms in the ftsI gene are of limited value for phenotype prediction. Penicillin resistance in meningococci was the topic of a further publication dissecting the mechanisms of penicillin resistance in meningococci and the closely related species *N. lactamica*, with whom genetic material is shared. In collaboration with partners from the Medical School Hannover, studies were published on the biochemistry of capsule synthesis in rare meningococcal serogroups. As the lead guest editor, Ulrich Vogel promoted the publication of a special issue entitled *"Twenty years of National Reference and Consultant Laboratories for Infectious Diseases in Germany"*. The special issue illustrates the capacity of the German network of reference laboratories and their impact on infection control.

FUTURE DIRECTIONS

We will pursue the introduction of next generation genome sequencing to generate DNA-sequence based typing data needed for the NRZMHi. Serological methods to measure vaccine response will be extended to serogroup B meningococci. Within the frame of a collaboration with the Medical School Hannover, capsule O-acetylation will be studied in *Neisseria meningitidis* and *Escherichia coli*.

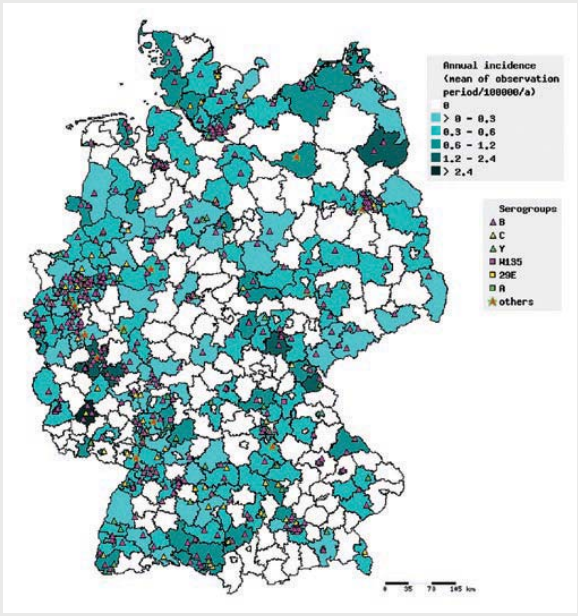

Fig. 1: Geographical distribution of cases of meningococcal disease in Germany 2014/2015. The graph shows the incidence rates in counties. It discriminates the meningococcal serogroups. The graph was generated using EpiScanGIS, the geographic information system now online for 10 years (www.episcangis.org).

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03.3

Institute for Virology and Immunobiology – Chair of Immunobiology

ZINF MEMBERS:

THOMAS HÜNIG

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. Thomas Hünig has been the Chair of Immunology since 1990.

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. Members of the Institute provide immunology lectures for medical, biomedical, biochemistry and biology students.

3.3. INSTITUTE FOR FOR VIROLOGY AND IMMUNOBIOLOGY

3.3.1. IMMUNOLOGY

T-lymphocytes (T-cells) are central players of the immune system. As effectors, they destroy infected and tumor cells, and as coordinators of immune responses, they control their magnitude and quality. We are studying the rules governing the activation and the execution of effector functions of T-cells, with a focus on the key costimulatory receptor CD28.

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INTRODUCTION

Foreign and self antigens are initially presented to T-cells by dendritic cells (DC), which sense infectious agents with the help of pattern recognition receptors and instruct the T-cells if and what type of immune response they should mount. A key signal for the initiation of such responses is provided via the DC surface molecules CD80/86, which are engaged by the costimulatory receptor CD28 expressed by all resting T-cells. Antigen recognition (signal 1) and costimulation (signal 2) together induce full T-cell activation, i.e. proliferation and expression of effector functions.

Besides effector T-cells which exist as "killer" (CD8) or "helper" (CD4) cells, regulatory T-cells (Treg cells, CD4+Foxp3+) are of key importance in controlling the magnitude of immune responses and suppressing autoimmunity. Treg cells also require costimulation by CD28.

We have previously developed two important tools to study CD28 biology: a mouse strain in which CD28 can be inducibly deleted at any time point, and a set of monoclonal antibodies which either block or ligate CD28 in a very efficient way (CD28 superagonists; CD28SA).

In the past two years, we have extended our studies on the requirement of CD28 for effector and regulatory T-cell responses, and on therapeutic strategies aimed at activating regulatory T-cells through CD28SA.

With regard to the human immune system, this strategy suffered a major set back in 2006, when the fully humanized CD28SA TGN1412, intended for the treatment of autoimmune and inflammatory diseases, failed during a phase I trial. We now understand what led to the overdosing and the ensuing cytokine release syndrome during that study, and have resumed clinical development together with the company TheraMab.

RESEARCH HIGHLIGHTS

Using inducible CD28 deletion, we have found that costimulation by CD28 is of particular importance for regulatory T-cells, both in a cell intrinsic and in a cell extrinsic fashion (through the provision of the growth factor IL-2 by helper T-cells). Furthermore, our inducibly CD28 deleting mice have allowed us to study the controversial question whether this costimulator also contributes to secondary T-cell responses. We have indeed confirmed this point with regard to both CD4 and CD8 T-cells, using the allergic airway response for the former and the cytotoxic T-cell response to the intracellular bacterium *Listeria monocytogenes* for the latter.

With regard to the resumed development of TGN1412, now re-named TAB08 by its new owner, as an agent which activates and expands regulatory T-cells, we first developed a new *in vitro* system which resets the functionally disabled circulating T-cells (the only routinely available material for studies of the human immune system) back to their functionally active status in the tissues. This system has allowed us to identify conditions for the selective activation of Treg cells in humans. Indeed, based on the much smaller doses suggested by these *in vitro* studies, a new phase I trial has been successfully carried out by TheraMab, and an open-label study with 18 patients with rheumatoid arthritis has shown very promising results.

Beyond the resumption of human CD28SA development, we have applied our new "RESTORE" *in vitro* assay system to the study of virus- and tumor-specific immune responses. We have reported a dramatically increased sensitivity of these CD8 T-cell responses as compared to conventional assays with peripheral blood cells (see Fig. 1), which should improve the assessment of such responses in patient monitoring and vaccine development.

FUTURE DIRECTIONS

We are currently extending our attempts to make human peripheral blood mononuclear cells a more reliable diagnostic and research tool to regulatory T-cells, which are deprived of the cytokines during circulation that are responsible for maintaining their function and phenotype in the tissues. Furthermore, in collaboration with the group of Niklas Beyersdorf, we are studying the role of CD28-mediated costimulation to the functional programming and re-programming of CD4 T-cells in mice and humans. Understanding the underlying mechanisms of instructing CD4 T-cells to perform a certain set of functions will contribute to the development therapeutic strategies which promote wanted and avoid unwanted immune responses.

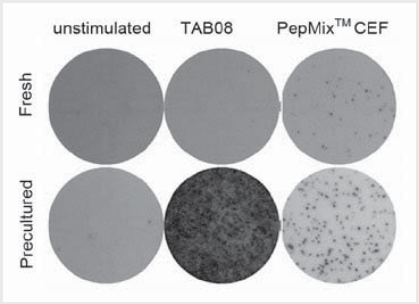

Fig. 1: RESTORE culture reveals cytokine response to the CD28 superagonist TAB08 (formerly TGN1412) and increases the sensitivity of CD8 T-cell responses to viral antigens. Human PBMC were stimulated over night in ELISPOT wells either immediately after isolation, or after first pre-culturing them at high density for 2 days. Each dot represents one IFNgamma-producing CD8 T-cells (From Wegner et al., BLOOD 2015).

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PRIZES AND AWARDS

2014 Main Research Award, Vogel Foundation

3.3. INSTITUTE FOR FOR VIROLOGY AND IMMUNOBIOLOGY
3.3.2. T CELL BIOLOGY

Innate and adaptive immunity interact to provide the host with a highly efficient defence 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.

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INTRODUCTION

To protect the host from diverse pathogens such as viruses, bacteria, parasites and pathogenic fungi, the immune system needs to be able to mount a variety of very different responses. Immune responses, thus, require orchestration in which CD4+ T helper cells play a central role. The diversity of the different immune responses is reflected by the plasticity of CD4+ T cells, which can differentiate into Th1, Th2 and Th17 cells. The negative aspect of this flexibility, however, is that an immune response, which is appropriate to kill, for example, a parasite (Th2) may fail to protect against a viral infection (Th1) and *vice versa*. Thus, in order to evade destruction by the immune system pathogens can either directly inhibit immune responses or divert them into an innocuous direction.

Apart from T helper cells the CD4+ T cell compartment also harbours Foxp3+ regulatory T cells (T_{reg} cells). This small subpopulation of CD4+ T cells is highly autoreactive, but instead of inducing immunopathology they are very potent inhibitors of autoimmunity and modulators of immune responses to microorganisms. Therefore, T_{reg} cells have received significant attention as potential targets of novel immunotherapies.

At the molecular level, T cells need to recognise a foreign antigen via their T cell receptor and they also need to receive a co-stimulatory signal resulting from ligation of the CD28 molecule expressed by the T cells. The requirement for co-stimulation helps to prevent inappropriate activation of T cells, which is potentially dangerous for the host as it may lead to immunopathology and autoimmune diseases. Moreover, Treg cells are more dependent on CD28-mediated co-stimulation than non-T_{reg} T cells. Therefore, CD28 co-stimulation provides a means to preferentially activate T_{reg} cells over non-T_{reg} T cells thus enabling the T_{reg} cells to suppress e.g. autoimmunity.

RESEARCH HIGHLIGHTS

During the first year of life infants are very susceptible towards so-called 'childhood diseases' such as measles. Unfortunately, in some children the measles virus persists in the brain after the acute infection, which may lead to a lethal form of encephalitis called Subacute Sclerosing Panencephalitis (SSPE) after a few years of latency. Together with Prof. Jürgen Schneider-Schaulies we have recently shown using a mouse model of measles virus infection of the brain that sphingolipid metabolism has a strong impact on viral replication. Upon CD28 stimulation, T_{reg} cells show a particularly high turnover of sphingolipids which appears to negatively affect their function. Therefore, genetically or pharmacologically reducing sphingolipid metabolism in mice increased T_{reg} cell activity and resulted in a poorer control of the measles virus infection. Our data are highly relevant for humans as the long-used anti-depressant Amitriptyline inhibits sphingolipid metabolism and also activates human T_{reg} cells *in vitro*.

Apart from the brain we are also investigating the consequences of viral infections of the heart, for example, by Coxsackie viruses, which are important triggers of acute myocarditis. As part of the 'Etiology, Titre-Course, and Survival' (ETiCS) study, led by Prof. Roland Jahns, we have been monitoring the immune phenotype of patients with myocarditis and first myocardial infarction to obtain insights into the generation of autoantibodies against the beta1-adrenergic receptor of the heart. The pathophysiological importance of these antibodies has been shown in rats and a novel immunotherapy to neutralize them is being developed.

Myocardial infarction (MI) has received much of our attention during recent years as CD4+ T cells play an important role in wound healing after MI. In collaboration with Prof. Stefan Frantz and PD Ulrich Hofmann we have shown that in particular T_{reg} cells positively influence this process. Moreover, therapeutic activation of T_{reg} cells with an anti-CD28 monoclonal antibody increased survival in an MI mouse model. Currently, we are preparing to test anti-CD28 monoclonal antibody treatment after MI in a large animal model as a prerequisite for the translation of this approach into humans.

Similar to the MI model, we have developed novel approaches in mice to prevent or treat acute Graft versus Host Disease (aGvHD), a potentially life-threatening complication of allogeneic bone marrow transplantations, using anti-CD28 monoclonal antibodies. As aGvHD patients are also susceptible to opportunistic fungal infections, for example by *Aspergillus* fumigatus or *Candida albicans*, we are currently studying the modulation of T cell immunity against *Candida albicans* by secreted fungal proteins. Together with Prof. Peter Zipfel we have shown that the pH-regulated protein 1 (Pra1) binds to mouse and human T cells inhibiting the function of Th1 cells. By generating monoclonal antibodies against these secreted proteins we are hoping to neutralize their function and provide a novel therapeutic strategy for treating these increasingly important infectious clinical complications.

FUTURE DIRECTIONS

Our future research will strongly focus on translational aspects of our various findings in pre-clinical animal models. This means that we will perform further *in vitro* testing using human T cells and, together with our clinical colleagues, we will work on strategies for proof-of-principle studies in humans.

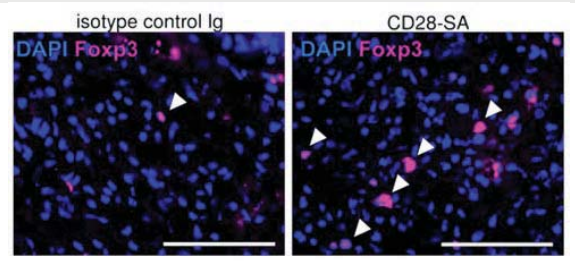

Fig. 1: Anti-CD28 antibody treatment of mice enhances wound healing after myocardial infarction. Application of a superagonistic anti-CD28 monoclonal antibody (CD28-SA, right) into mice two days after myocardial infarction increases the recruitment of $CD4^+$ $Foxp3^+$ regulatory T cells (T_{reg} cells, purple) into the infarct area compared to mice treated with an isotype control antibody (left). Cell nuclei are shown in blue. Scale bar; 100 µm. Published in: (Weirather J, et. al. (2014) Circulation Research 115: 55-67).

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3.3. INSTITUTE FOR VIROLOGY AND IMMUNOBIOLOGY
3.3.3. IMMUNOGENETICS

Non-conventional T cells recognize non-peptide antigens and act as bridge between the adaptive and innate immune systems. We aim to understand their antigen-recognition and co-evolution of antigen-receptors and antigen-presenting molecules.

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INTRODUCTION

Non-conventional T cells serve as bridge between adaptive and innate immunity. Their T cell antigen-receptors (TCR) do not recognize pathogen-specific antigens but classes of pathogen-derived and stress-induced molecules and thus act as pattern recognition receptors. These features and characteristic TCR rearrangements differ from MHC-restricted TCR. Functionally, our research focuses on two types of non-conventional or innate T cells. Both are defined by their eponymous TCR: The iNKT cells and the Vγ9Vδ2 T cells.

i(nvariant)NKT cells carry TCR with an invariant α chain defined by a Vα14Jα18 re-arrangement. They are effectors with anti-microbial, anti-tumor and immunomodulatory activity. Their major antigens are glycolipids that associate with non-polymorphic MHC I-like CD1d cell surface molecules. Their strongest antigens are bacterial sphingolipids with α-anomeric linked carbohydrates (e.g. α-Galactosyl ceramide: αGalCer). The binding of such ligands to CD1d oligomers are commonly used to directly identify iNKT.

Vδ2 T cells are expanded in many infectious diseases and possess anti-tumor activity. So far they have been found only in humans and higher primates. Their TCR contain characteristic rearrangements of the γ-chain (Vγ9JP), which is paired with Vδ2 containing δ-chains. They recognize pyrophosphorylated metabolites of isoprenoid synthesis, called phosphoantigens (PAg). The most potent PAg is (E)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate (HMBPP) which is the immediate precursor of isopentenyl pyrophosphate (IPP) in the non-mevalonate pathway found in many eubacteria and in apicomplexa such as *Plasmodium spp*. HMBPP is ten thousand times more potent than IPP, the central compound of either pathway of isoprenoid synthesis. Increased IPP levels in host cells also lead to Vγ9Vδ2 T cell-activation and are found in some tumours, after administration of aminobisphosphophonates (e.g. zoledronate), and also upon infection.

RESEARCH HIGHLIGHTS

Functional and phenotypic characterisation of rat iNKT cells has revealed remarkable similarities to human iNKT cells. We have recently focused on the molecular parameters that control antigen recognition by rat iNKT cells by comparing iNKT TCR of *in vitro* expanded iNKT cells and mutagenesis of rat, mouse and human iNKT cell receptors. This analysis has identified natural occurring variations at position 93, which flanks the CDR3 of the α-chain and at position 68 in the HV4α region as potent modulators of avidity for CD1d-αGalCer complexes. Both effects result from altering the orientation and rigidity of the CD1d-aGalCer-binding CDR1α and CDR3α (Fig. 1). Position 93 was also found to strongly affect cross-species reactivity of iNKT TCR. We have also performed the first systematic comparison of parameters controlling the *in vitro* loading of CD1d oligomers. Such oligomers are mandatory to directly identify the iNKT cells. Analysis of CD1d oligomers loaded with different antigens revealed unexpected species- and cell-specific effects of the CD1d-oligomers and the detergents used for their *in vitro* loading upon iNKT TCR binding. Finally, functional iNKT cells were identified in cotton rats and their TCR and CD1d characterized. Cotton rats are of especial interest since they serve as a model organism for human viral diseases such as measles and respiratory syncytial virus.

After identification of butyrophilin 3 A1 (BTN3A1) as a mandatory component for Vγ9Vδ2 TCR-mediated activation we have focused on defining the minimal molecular and genetic requirements for this type of activation. New reporter cells have enabled us to show that in addition to *BTN3A1* at least one other human chromosome 6 encoded gene is required for Vγ9Vδ2 T cell activation by PAg (Fig. 2), while activation using a BTN3-specific agonistic antibody displays no such requirement. In addition, we have found that in contrast to PAg-stimulation, activation by this antibody discriminates between TCR idiotypes and interferes with PAg mediated activation.

Finally, we have continued our analysis of the co-emergence of Vγ9, Vδ2 and BTN3 genes in placental mammals and their possible coevolution. Identification of typical Vγ9Vδ2 TCR rearrangements in alpaca (*Vicugna pacos*) identified this camelid as first candidate for a non-primate species to possess functional Vγ9Vδ2 T cells. We now aim to directly identify these cells in alpaca and have started an analysis of γδTCR and BTN3 genes of the nine-banded armadillo (*Dasypus novemcinctus*), a natural host and model of infection for *Mycobacterium leprae*.

FUTURE DIRECTIONS

We will further collaborate with Stefan Niewiesk, Ohio State University, Columbus on cotton rat iNKT cells and aim to test their role in virus infection and vaccination. We will also continue with our work on the non-conventional MHC class II molecules Eb2 (mouse) and Db2 (rat). A future focus will be on Vγ9Vδ2 T cells to finally harness these cells for tumor and infection control. This will also involve the search for Vγ9Vδ2 T cells in non-primate species as well as for chromosome 6 encoded gene(s) that are mandatory for PAg-mediated activation. Identification of such gene(s) will help to manipulate Vγ9Vδ2 T cells and is a prerequisite for generation of rodent animal models of functional Vγ9Vδ2 T cells.

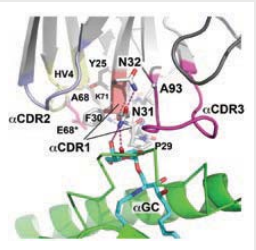

Fig. 1: HV4 modulates iNKT TCR binding to CD1d-antigen complexes. Homology model of the interface between the galactosylceramide-loaded rat CD1d and rat iNKT TCR highlighting the recognition and interaction of the TCR with the ceramide moiety (C-atoms colored in cyan). Alanine 68 in the HV4 element stabilizes CDR1 by hydrophobic interactions with Tyr25 and Phe30 located in CDR1α. Mutation of Ala68 to glutamate (indicated as transparent sticks with the C-atoms colored in magenta) leads to a steric clash of the introduced glutamate residue with Phe30 thereby altering the conformation of CDR1α. Modified from (Paletta et al 2015)

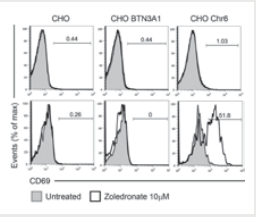

Fig. 2: Zoledronate pulsed CHO cell derivatives expressing BTN3A1 or bearing Chr6 differ in their capacity to activate primary human Vγ9Vδ2 T cells. FACS staining of Vδ2+ T cells after over-night co-culture of human PBMC with untreated or zoledronate-pulsed stimulator cells. Numbers indicate proportion Vγ9Vδ2 T cells positive for the activation marker CD69. Modified from (Riano et al 2014).

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3.3. INSTITUTE FOR FOR VIROLOGY AND IMMUNOBIOLOGY
3.3.4. IMMUNE REGULATION

Infective microbes have developed a number of strategies to avoid elimination by the host's immune system. We are investigating how different pathogens manipulate dendritic cells (DCs) and myeloid-derived suppressor cells (MDSCs) to induce immune tolerance by either stimulating regulatory T cells or suppressing effector T cell responses.

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INTRODUCTION

The generation of immune cells is driven by hematopoietic growth factors in the bone marrow. One of these factors, GM-CSF, induces the differentiation of immune effector cells such as neutrophils, macrophages, DCs as well as MDSCs.

DCs are well established as antigen presenting cells that can initiate $CD4^+$ and $CD8^+$ T cell immune responses against pathogens. This occurs when they are at a mature stage after activation. However, immature DCs are not only resting cells waiting to encounter a pathogen, in addition to their immunogenic functions, both the immature and semi-mature stages are involved in mediating immune tolerance to peripheral self-antigens. While this physiological process, which prevents autoimmunity, can be exploited therapeutically to treat autoimmunity, it is also widely exploited by pathogens. Major microbe immune evasion strategies, therefore, aim to prevent DC maturation or allow them to be only activated to a semi-mature stage. Induction of T cell anergy or regulatory T cells (Treg) are common tolerance mechanisms, but the DC subsets involved and the molecular details are not fully understood.

Pharmacological intervention strategies aiming to modulate immune responses include bacterial toxins conjugated to ligands that recognize cognate receptors on target cells. Ligand-receptor binding initiates internalization of the toxin-ligand-receptor complex, thereby inducing target cell killing. Such simplistic approaches, however, postulate rudimentary biological functions that may, in actuality, be far more complex processes *in vivo*.

RESEARCH HIGHLIGHTS

DCs respond to helminths by typically undergoing semi-maturation that allows the induction of a Th2 response. Together with the group of Kluas Brehm we have identified the EmTIP protein secreted by the tapeworm *Echinococcus multilocularis* as responsible for shifting the DC response towards the induction of a Th1 response, which is frequently observed during the early phases of helminth infections. By contrast, the tapeworm *Mesocestoides corti* showed that excretory/secretory products contain factors that specifically block a Th1-inducing DC phenotype by inhibiting their IL-12 production.

To investigate whether different DC subsets share the ability to induce T cell anergy or Treg, we generated monocyte-derived DCs from murine bone marrow using GM-CSF as well as conventional DCs (cDCs) and plasmacytoid DCs (pDCs) by adding the growth factor Flt3L. Surprisingly, cDCs and pDCs that were generated *in vitro* using Flt3L alone failed to exert tolerogenic functions on T cells, indicating that additional growth factors may be required.

The induction of T cell anergy as a T cell tolerance mechanisms by immature DCs is well established. However, the biological use of anergic T cells for immune tolerance has remained unclear. We have established an *in vitro* protocol to generate antigen-specific anergic T cells by stimulating them with immature DCs. Interestingly, we have found that a second stimulation of anergic T cells converts them into IL-10^+ Foxp3^- Treg of the Tr1 type. The conversion was dependent on simultaneous signals transmitted by the co-stimulatory CD28 molecule and the co-inhibitory CTLA-4 molecule.

FUTURE DIRECTIONS

We will further investigate the factors secreted by helminths, as part of this study we aim to identify additional individual molecules using proteomic approaches. Interesting candidates will be individually tested for interference with immune cells such as DCs and MDSCs. The failure to generate anergic or Treg upon treatment *in vitro* generated DCs with Flt3L has led us to search for cytokines that cooperate with Flt3L to generate specifically either subset of pDCs, $CD11b^+$ DCs or $CD103^+$ cDCs. Candidates are currently being tested. The observed *in vitro* conversion of anergic T cells into Tr1 cells will be subsequently tested in vivo.

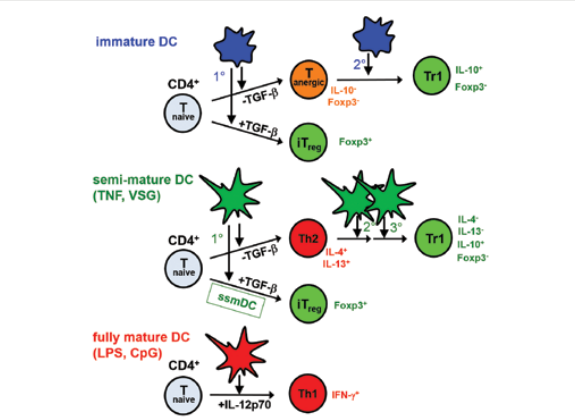

Fig. 1: Induction of $CD4^+$ T cell anergy, Treg subsets and polarized Th1/Th2 responses by DC can be directed by their maturation stages and cytokines.

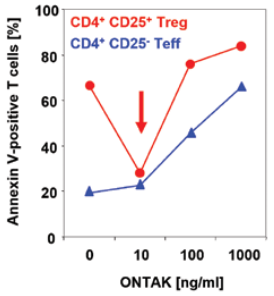

Fig. 2: Anti-apoptotic effects of the IL-2/diphteria toxin Ontak on human Treg and effector T cells.

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03.4

Institute for Virology and Immunobiology – Chair of Virology

LARS DÖLKEN

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 centres on analysing the regulatory principles involved in viral replication and gene expression. In addition, researchers are investigating the pathogenesis of several viruses and 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 is responsible for providing virus diagnostics to the University Clinics and members provide virology lectures for medical, biomedical, biochemistry and biology students.

3.4. INSTITUTE FOR VIROLOGY AND IMMUNOBIOLOGY
3.4.1. SYSTEMS BIOLOGY OF HERPESVIRUS INFECTIONS

Herpesviruses are large DNA viruses, which cause a broad spectrum of diseases ranging from common cold sores to cancer. Our group employs systems biology approaches combined with virus reverse genetics systems to study host cell modulation and immune evasion in various herpesvirus models.

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INTRODUCTION

Herpesviruses are not only important human pathogens, but they also represent interesting tools to study fundamental aspects of cell biology and immunology. They encode hundreds of viral gene products, which comprehensively modulate the host cell environment. Our group employs systems biology-based methodologies and cutting-edge sample pre-processing techniques to comprehensively study host cell modulation and immune evasion in various herpesvirus models. Herpes simplex virus 1 (HSV-1) is the causative agent of common cold sores as well as also being responsible for life-threatening encephalitis. During productive infection, the virus installs a profound shut-off of host gene expression. Our group studies the underlying molecular mechanisms and the involved cellular processes.

MicroRNAs regulate gene expression by sequencing-specific interactions with their target mRNAs. Herpesviruses express a number of virally encoded miRNAs at very high levels. These represent interesting targets for novel antiviral agents (so called 'AntagomiRs'). The human cytomegalovirus is an important pathogen in immunosuppressed patients and the causative agent of congenital infections affecting about 1:1000 new-borns. Employing the murine cytomegalovirus model (MCMV), we study the functional role and suitability of cytomegalovirus miRNAs as drug targets in productive and latent infection.

RESEARCH HIGHLIGHTS

To characterize the regulatory effects of both cellular and viral miRNAs expressed in human B-cells infected with Kaposi-sarcoma-associated herpesvirus (KSHV), we have employed a range of high-throughput technologies (4sU-tagging, RIP-ChiP, PAR-CLIP and quantitative proteomics). Integrative analysis revealed that approximately 50% of all miRNA-target interactions are context specific (Fig. 1). Our data provide a valuable resource for the design of studies targeting key KSHV and cellular miRNAs for novel therapeutic approaches.

Applying 4sU-tagging of newly transcribed RNA and ribosome profiling to lytic herpes simplex virus 1 (HSV-1) infection of primary human fibroblasts, we made the surprising observation that HSV-1 triggers widespread disruption of transcription termination of cellular but not viral genes. This results in extensive transcriptional activity for tens-of-thousands of nucleotides downstream of the normal transcript termination site (Fig. 2). Poly(A) read-through and transcription into downstream genes explained why hundreds of cellular genes that are seemingly induced by the virus are not translated into proteins.

FUTURE DIRECTIONS

We will identify the HSV-1 gene product(s) responsible for the disruption of transcription termination of cellular genes, detail the molecular mechanism and elucidate how termination of viral genes remains insensitive to this effect. We will employ a quantitative proteomics approach to identify and characterize novel viral factors acting at the plasma membrane to shield MCMV infected cells from recognition by natural killer cells and cytotoxic T cells. Upon virus entry into a cell, a decision is made whether the lytic or latent gene expression program is initiated. In the framework of the EU funded Infect-ERA consortium (eDEVILLI), we will identify and characterize novel determinants of this decision in various infection models. Finally, we will study the antibody response to all human herpesviruses and other pathogens in 10 000 individuals of a well-established cohort (EPIC Norfolk) and identify novel host factors important for the immunological control of infection.

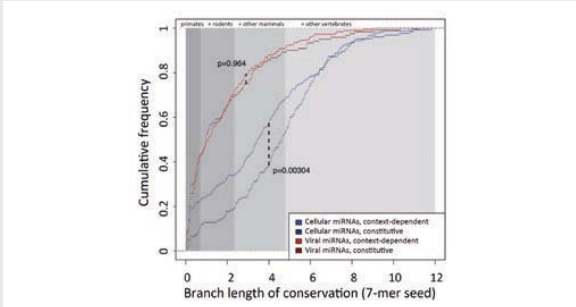

Fig. 1: Evolutionary conservation of seed sequences in target 3'-UTRs
Distributions of evolutionary conservation (branch lengths in 46 vertebrate species) of miRNA target sites. Shaded regions indicate the maximal branch lengths of target sites conserved in primates, in primates and rodents, in mammals, and in vertebrates. Constitutive target sites of these miRNAs are significantly more conserved than context-dependent target sites. In contrast, viral miRNAs show no evidence of evolutionary conservation.

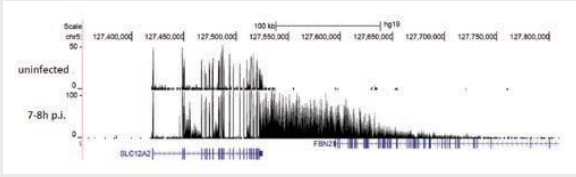

Fig. 2: Disruption of transcription termination in lytic HSV-1 infection
Newly transcribed RNA was labelled and purified from human fibroblasts prior to and 7-8h post HSV-1 infection. Sequencing reads mapping to a representative ≈400kb region of chromosome 19 are shown. During HSV-1 infection, the SLC12A2 poly(A) site is bypassed resulting in extensive transcriptional activity downstream of the gene's 3'-end extending for >100 000 nucleotides and antisense to FBN2.

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3.4. INSTITUTE FOR VIROLOGY AND IMMUNOBIOLOGY
3.4.2. MORBILLIVIRUS PATHOGENESIS

Morbilliviruses, which include the human pathogenic measles virus, cause devastating diseases in their specific hosts. The group is interested in the mechanisms of virus uptake, the function of host cell factors, the species specificity of infections, and the corresponding immune response.

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INTRODUCTION

Measles virus (MV) and canine distemper virus (CDV) belong to the genus Morbillivirus of the family Paramyxoviridae. Measles is not a "simple" children's disease, but can cause a number of complications such as diarrhoea, pneumonia, blindness, and various forms of encephalitis. Due to these complications and virally induced transient immunosuppression, 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, which occurs with a frequency of approximately 1:1000 – 10 000 cases. After an average 6 to 12 years of persistence 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. Since an effective vaccine is available, the World Health Organisation (WHO) has declared the aim of eradicating measles before 2020, however, due to socioeconomic problems this target will probably not be achieved.

We have established a mouse model of persistent measles virus infection of the CNS, which partially models the human disease SSPE, and has the potential to be used to analyse the antiviral immune response and also the effects of antiviral substances on acute and persistent brain infections. This approach promises to provide new insight into the mechanisms that influence the infection, such as alterations in the cell membrane, and intracellular host factors, as intrinsic factors or as part of the innate immune response.

RESEARCH HIGHLIGHTS

The group has been investigating the role of the adaptive immune response and regulatory T cells (Treg) in persistent brain infections. This has revealed that the expansion of Treg cells after the acute phase of the infection by superagonistic anti-CD28 antibodies leads to an enhancement of MV infection of the CNS. In agreement with this, the depletion of Treg cells by diphtheria toxin treatment (in DEREG-mice) reduced CNS infection. This clearly demonstrates that the persistent viral CNS infection is under sustained immunological control and that this mouse model can be used to investigate and characterize antiviral mechanisms and compounds.

CD28 has been previously shown to activate acid sphingomyelinase (Asm). We have found that in accordance with their CD28 dependency, Treg cells of wild-type (wt) mice displayed higher basal and CD28-induced Asm activity and contained more ceramide in their membranes compared to conventional $CD4^+$ T cells. Furthermore, the frequency of Treg cells among $CD4^+$ T cells, the turnover of the effector molecule CTLA-4, and their suppressive activity were increased in Treg cells from Asm-deficient mice. Moreover, we observed more infected neurons in the brains of Asm-deficient mice compared to wt in our Treg cell-sensitive MV infection model (Fig. 1). In agreement with genetic ablation, pharmacological inhibition of Asm *in vitro* in primary human peripheral blood mononuclear cells and *in vivo* in mice led to higher frequencies of Treg cells among $CD4^+$ T cells. Our data suggest that ASM-inhibiting drugs (as used during therapy of certain forms of depression) should be considered as potential immunomodulatory agents for the therapy of inflammatory and autoimmune disorders.

Another focus of the group is to investigate the role of the intrinsic antiviral factor APOBEC3G, which has previously been implicated in interfering with HIV infection. Interestingly, in the presence of APOBEC3G MV transcription and protein expression was reduced by 50-70%, and there was an increase in the mutation rate of the viral genome. However, in contrast to HIV infections, APOBEC3G-specific hypermutation was not observed. Our findings suggest that APOBEC3G not only impairs the activity and fidelity of the viral RNA polymerase, but also affects the expression of a number of host cell factors. These antiviral mechanisms are under investigation.

FUTURE DIRECTIONS

We will further investigate the role of host cell factors in morbillivirus infections to identify critical steps that can be targeted for therapeutic intervention. In addition, we will further investigate the role of specific membrane lipids, and the enzymes that process them such as sphingomyelinases, during viral infections and the immune response. This will be performed both in tissue culture and using the mouse model of persistent CNS infection within the framework of the DFG-supported research unit (Forschergruppe; FOR 2123) investigating "Sphingolipid dynamics in infection control".

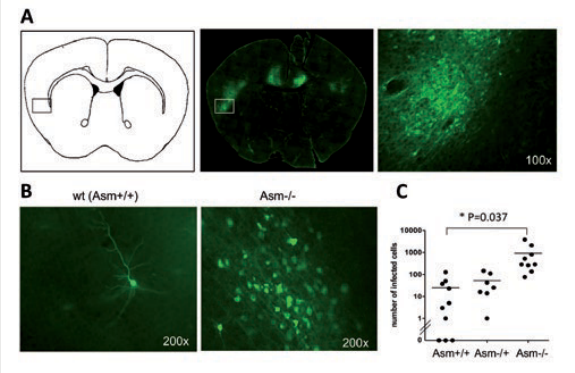

Fig. 1: Increased viral infection in brains of acid sphingomyelinase (Asm)-deficient mice. Coronal sections were prepared for histological analyses and the number of infected neurons was quantified. (A) Left and middle panels, schematic and microscopic general view (10x), and right panel enlargement (100x) of eGFP autofluorescence in a brain section from an $Asm^{-/-}$ mouse 7 days after infection. (B) Characteristic brain sections from wt control ($Asm^{+/+}$; left panel) and $Asm^{-/-}$ (right panel) mice (200x). (C) Quantification of the number of infected neurons (approx 50 sections per brain) from brains of mice 28 days after infection.

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3.4. INSTITUTE FOR VIROLOGY AND IMMUNOBIOLOGY
3.4.3. VIRAL IMMUNOMODULATION

Viruses can modulate the host immune response to facilitate their survival and replication. Using measles virus (MV) and endogenous retroviruses as model systems, the group aims to decipher how viruses take advantage of membrane receptors to interfere with the activation of antigen presenting and T cells.

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INTRODUCTION

Most viruses have evolved strategies to evade immune surveillance in order to survive and spread in their hosts. Many of them do so by encoding non-structural proteins that confer resistance to cell autonomous or innate immunity in their respective host cells. In addition to this strategy, a few human pathogenic viruses, including measles virus (MV), induce general immunosuppression, which in addition to dampening virus-specific immune responses, favors the establishment of secondary or chronic infections. Immunosuppression at an organ specific level can also be of vital importance to the host as revealed by the induction of tolerance against the semi-allogenic fetus in healthy pregnancy, and in these cases gene products of human endogenous retroviruses (HERV) are believed to be important. In both systems, viral envelope (env) proteins have been identified as the effectors required for the silencing of their target cells activity. In spite of directly targeting T cells, viruses often modulate the ability of antigen-presenting cells (APCs) involved in T cell silencing. This can be achieved by directly interfering with the ability of DCs to promote APC-mediated negative silencing of T cells, which may result in the formation of non-stimulatory APC/T cell conjugates. The group aims to both define viral interference with APC functions and the mechanisms involved in abrogating the relay of TCR signaling in these non-stimulatory conjugates. This is currently being investigated at the level of dynamic repatterning of membrane lipid and protein complexes.

RESEARCH HIGHLIGHTS

In line with the concept that viral envelope proteins effectively silence immune cell functions, the HERV env proteins abrogate the ability of DCs to recruit T cells into stimulatory conjugates. This was supported by reduced conjugation efficiencies, aberrant patterning of the immune synapse associated with loss of Ca2+ mobilisation and in the expansion of T cells.

To understand the mechanisms involved in virally induced T cell silencing at the membrane level, we have focused on the functional consequences of dynamic membrane changes induced by MV binding to its receptors on T cells. As major components of the cell membrane, sphingolipids, especially sphingomyelin and its metabolite ceramide, have been implicated in the differential segregation of receptors and their associated signalosomes into membrane microdomains, membrane curvature and the formation of protrusions. MV interaction with T cells induced the activation of neutral and acid sphingomyelinase (NSM and ASM), which almost entirely accounted for the observed inhibition of actin cytoskeletal dynamics in these cells. Genetic screening approaches have identified candidate genes potentially involved in MV-mediated T cell silencing which include both membrane receptors and proteins regulating cellular metabolic pathways. While addressing cytoskeletal and signaling alterations induced in response to MV-induced NSM activation, we observed that they were a result of deregulation of NSM activation, which normally occurs after TCR ligation in a strictly temporal and spatially confined manner. T cells that are genetically depleted of NSM or in which its enzymatic activity has been pharmacologically inhibited are hyper-responsive, suggesting that this enzyme physiologically dampens T cell activation. To follow sphingolipid compartmentalisation and trafficking in stimulated T cells directly, we have generated functional analogues suitable for click reactions.

FUTURE DIRECTIONS

During the next few years we will explore the hypothesis that efficiency and patterning of ceramide release acts to modulate immune synapse activity and identify the molecular targets involved. We will investigate the cross-regulation of sphingolipid-metabolising enzymes during T cell receptor co-stimulation and co-inhibition and the role of MV-induced changes in metabolic pathways especially with respect to T cell activation and sphingolipid breakdown. This will be done in close collaboration with groups within and associated with the Research Unit FOR2123 Sphingolipid dynamics in infection control.

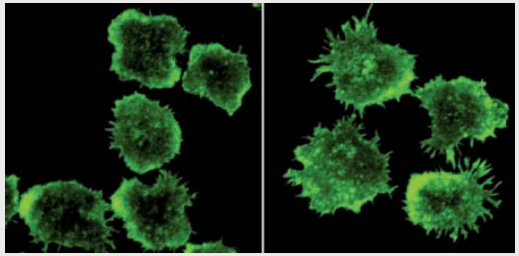

Fig. 1: Primary NSM-proficient (left) and –deficient (right) human T cells 60 mins following co-stimulation (stained with phalloidin after fixation).

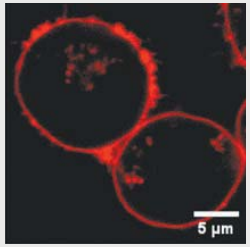

Fig. 2: Jurkat T cells fed with biofunctionalised C6-ceramide and subsequent detection by click reaction.

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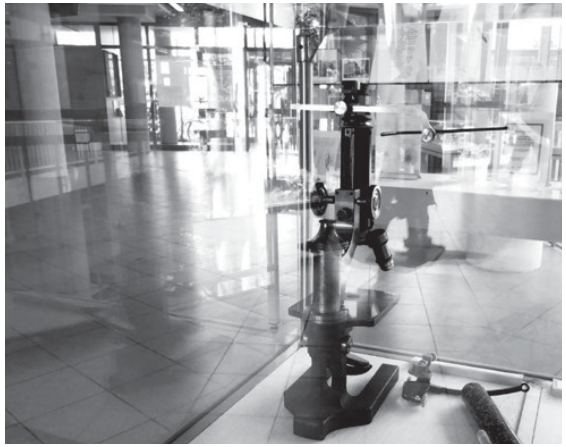

03.5

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THOMAS RUDEL

MARTIN FRAUNHOLZ

ROY GROSS

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

The research activities at the department centre on the pathogenicity mechanisms of different microorganisms, including the manipulation of various signalling cascades, non-coding RNAs and cellular processes such as the cell death pathways in the host. In this context the infection biology of obligate intracellular bacteria such as *Chlamydia* 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. Members of the department provide microbiology and infection biology lectures and practical courses for medical, biomedical, biochemistry and biology students.

3.5. DEPARTMENT OF MICROBIOLOGY
3.5.1. INFECTION BIOLOGY OF BACTERIA

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

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INTRODUCTION

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

Many bacterial pathogens have acquired the ability to manipulate key biological processes within the host to facilitate their replication and dissemination. Remarkably, infection-induced manipulation of host cells often subverts and overrides cellular fail-safe systems that normally protect them from chronic degenerative or proliferative diseases. We aim to understand how and why particular bacterial pathogens interfere with central protection pathways in the host cell such as apoptotic and non-apoptotic cell death and DNA damage repair. These cell protection pathways play a major role in preventing cancer development and their downregulation may thus facilitate or even cause cancer. We are particularly interested in *Chlamydia trachomatis*, an organism that has been associated with cervical and ovarian cancer. Infection by *Chlamydia* results in a similar deregulation of cellular protection pathways as in ovarian cancer cells and epithelial cells. Likewise, there is clinical evidence for antibodies against *Chlamydia* in a disproportionately large percentage of ovarian cancer patients. Beyond *Chlamydia* infections, epidemiological studies have suggested a co-occurrence of this pathogen with human herpes virus' (HHVs) in several human diseases. For instance, human herpes virus-6 (HHV-6) DNA is frequently detected in different grades of cervical lesions. Therefore, a main goal of our research is to understand chlamydial infections and co-infections and how they may contribute to cancer development.

RESEARCH HIGHLIGHTS

Many bacterial pathogens including *Chlamydia* induce severe DNA damage such as DNA double strand breaks (DSB) in their host cell during infection. We have investigated the role of the tumor suppressor p53 during *Chlamydia* infections and its impact on DNA damage response. DSB predominantly occur at chromosomal ends in *Chlamydia*-infected cells, causing telomere shortening. Consequently, host cells are subject to cell cycle arrest or senescence. Surprisingly, *Chlamydia* infection induces the degradation of p53 and repair of damaged DNA in primary human cells. Stabilization of p53 interferes with *Chlamydia* replication and development. Instead of inducing death of the infected cell, stabilization of p53 starves the bacteria of host nutrients required for chlamydial replication. Conversely, depletion of p53 in infected cells prevents p53-induced repression of the pentose phosphate pathway (PPP) responsible for DNA damage repair, allowing *Chlamydia* to obtain essential metabolites for growth. As such, our findings have established a p53-dependent antibacterial mechanism that limits metabolite resources required for survival of obligate intracellular bacteria.

A key signaling pathway in both cancer development and bacterial infection is the PI3 kinase (PI3K) signaling pathway. Intracellular, replicating *Chlamydia* induce a long-lasting activation of the PI3K pathway that is required for efficient replication but also for the downregulation and degradation of p53. By compiling data from proteomics and genome-wide RNA interference screens, we have identified the cell surface tyrosine kinase EphrinA2 receptor (EphA2) as a chlamydial adherence and invasion receptor that induces PI3 kinase (PI3K) activation, promoting chlamydial replication. We have shown that *C. trachomatis* interacts with and activates EphA2 on the cell surface resulting in bacterial and receptor internalization. During chlamydial replication, EphA2 remains active accumulating around the inclusion and interacts with the p85 regulatory subunit of PI3K to support the activation of the PI3K/Akt signaling pathway required for normal chlamydial development. Despite the depletion of EphA2 from the cell surface, *C. trachomatis* infection induces upregulation of EphA2 through the activation of the ERK pathway, which keeps the infected cell in an apoptosis-resistant state. Our findings provide the first evidence for a host cell surface receptor that is exploited for invasion as well as for receptor-mediated intracellular signaling to facilitate chlamydial replication. In addition, the engagement of a cell surface receptor at the inclusion membrane is a new mechanism by which *Chlamydia* subverts the host cell and induces apoptosis resistance.

FUTURE DIRECTIONS

We will continue to investigate pathogenicity mechanisms of different bacteria. With respect to obligate intracellular bacteria, metabolic adaptation to the host cell intracellular environment will be of special 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.

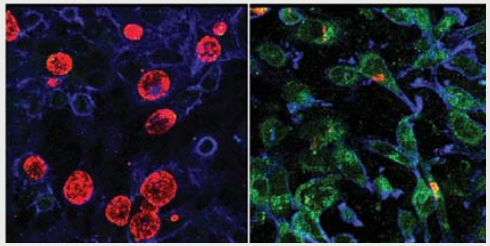

Fig. 1: Overexpression of wild-type p53 prevents formation of *Chlamydia* inclusion.

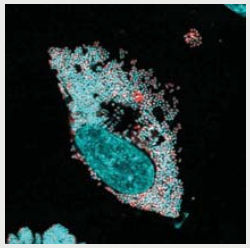

Fig. 2: Confocal microscopy image of a *Simkania negevensis*-infected A549 cell.

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3.5. DEPARTMENT OF MICROBIOLOGY
3.5.2. CELLULAR MICROBIOLOGY

Staphylococcus aureus is endocytosed by human cells, however, some strains such as certain methicillin-resistant *S. aureus* (MRSA) readily escape from the phagosome thereby avoiding eradication. The group focuses on the identification of bacterial virulence factors involved in phagosomal escape and cytotoxicity as well as host factors that support the intracellular survival of *S. aureus*. This alternative life style may prove crucial for dissemination and persistence of this important pathogen.

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INTRODUCTION

S. aureus causes a variety of diseases ranging from abscesses to endocarditis and sepsis. Treatment options are rapidly dwindling due to the emergence of methicillin-resistant *S. aureus* (MRSA), which are resistant to most beta-lactam antibiotics. The ability of the bacterium to withstand harsh environmental conditions combined with its resistance to a broad spectrum of antibiotics makes *S. aureus* an important healthcare-associated pathogen. Epidemic MRSA has recently increased in prevalence, and has begun to spread among and cause disease in previously healthy people that are not associated with predisposing risk factors.

Most of the clinical manifestations of *S. aureus* are due to extracellular bacteria; however, since *S. aureus* is able to survive within host cells, it constitutes a facultative intracellular pathogen. The bacteria are usually taken up by professional phagocytes such as neutrophils and macrophages but they are also able to enter epithelial or endothelial cells. *S. aureus* not only persists inside its host cell but it can also escape from the phagosome. We therefore sought to identify the factors facilitating intracellular virulence of *S. aureus*.

RESEARCH HIGHLIGHTS

We have previously described that only a limited number of clinical strains are able to evade lysosomal killing, which would exclude a major role of phagosomal escape for intracellular virulence of *S. aureus*. We further demonstrated that rather than the pore-forming -hemolysin, it is the small membrane-active peptides, phenol-soluble modulins (PSM) that are involved in phagosomal escape. The expression of PSM are regulated by the quorum-sensing system and further boosted by the stringent response. PSM production is thus activated in spatially limited volumes such as in a phagosome. Due to their amphiphilic nature PSMs have detergent-like properties and thus are capable of interfering with the integrity of host cell membranes. *S. aureus* strains that produce high levels of PSMs, such as epidemic MRSA, efficiently translocate from the phagosome to the host cell cytoplasm. This process can be observed in a variety of cell types including those in the innate immune system. After phagosomal escape the bacteria change their transcriptional profile, replicate in the cytoplasm, and ultimately kill the host cell. We recently developed the necessary global techniques to monitor factors that i) lead to phagosomal escape, ii) are involved in intracellular cytotoxicity, and iii) are important virulence factors in infection models. Using genome-wide deep sequencing approaches we identified novel strategies of the pathogen which may serve as a basis for the development of new anti-infectives.

FUTURE DIRECTIONS

Our results indicate a fine-tuned host-pathogen interplay for intracellular *S. aureus*. It remains unclear, however, to which extent the observed phagosomal escape depends upon a specific host cell type or tissue and whether it is crucial for infections. The future challenge will be the development of suitable assays and techniques to investigate these phenomena in disease-related settings. Therefore, we currently develop techniques to detect phagosomal escape of *S. aureus* in vivo.

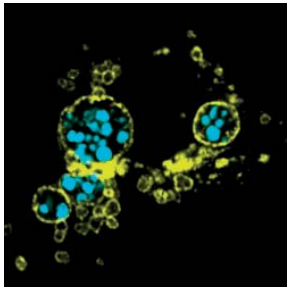

Fig. 1: S. aureus (cyan) is readily endocytosed by a lung epithelial cell and resides in late endosomes (yellow).

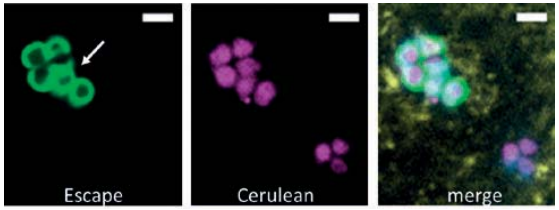

Fig. 2: S. aureus (magenta) escapes from phagosomes of a recombinant endothelial cell line. A reporter protein (green) is recruited to the bacterial cell wall only once *S. aureus* translocated to the cytoplasm of its host cell. The arrow indicates escaped *S. aureus*. Bar: 2 µm.

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3.5. DEPARTMENT OF MICROBIOLOGY
3.5.3. ENDOSYMBIONT BIOLOGY

Bacterial endosymbiosis is a major driving force in the evolution of life. Endosymbiotic bacteria are widespread in insects and have significantly contributed to the evolutionary success of this major group of animals. Thus, these animals must have evolved mechanisms to tolerate chronic infection by beneficial bacteria while discriminating and eradicating pathogenic bacteria.

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INTRODUCTION

More than 120 years ago Friedrich Blochmann described the presence of obligate mutualistic intracellular bacteria in an animal. These unculturable bacteria (*Candidatus* Blochmannia) are found in bacteriocytes in the midgut and ovaries of ants of the genus *Camponotus* and are transmitted vertically to the offspring. This bacteria-host association has existed for at least 50 Mio years. Previous work from our group has revealed a nutritional basis of the symbiosis: the bacteria produce essential amino acids for the host and are involved in nitrogen recycling, thereby enabling the animals to settle in nitrogen poor niches such as tropical rainforest canopies. Bacterial replication within the midgut is tightly coupled to the developmental cycle of the holometabolous host. The bacteria massively multiply only during pupation, while in adult animals the number of endosymbionts decreases rapidly. In the ovaries the bacteria constantly infiltrate newly developing oocytes. To address the question of how the bacteria are controlled in the midgut and the ovaries we characterized the ant`s immune transcriptome and began to investigate the distribution and transfer mechanism of these obligate intracellular bacteria in the ovaries.

RESEARCH HIGHLIGHTS

The genome sequence of *Camponotus floridanus* was recently established. Using our Illumina-based transcriptome analysis of immune challenged versus untreated animals, we started to re-annotate the genome sequence with a special emphasis on immune-regulated genes. This analysis revealed a complex innate immune system possessing many components known from *Drosophila melanogaster*, especially with regard to central signal transduction pathways (Toll-pathway, Imd-pathway, etc.). By contrast, a relatively small number of pattern recognition receptors (PRRs) recognizing microbe associated molecular patterns (MAMPs) and immune effectors were identified. However, correlating host gene expression with the massive endosymbiont multiplication in the midgut during pupation and in the ovaries led to identification of two pattern recognition receptors (PRRs) due to their expression profile. These PRRs are strongly and specifically up-regulated in the midgut during pupation and in the ovaries of egg-producing queen-less workers. These PRRs must be negative modulators of the immune response, since they are endowed with an amidase activity that cleaves peptidoglycan fragments to eliminate a major MAMP. Altogether, our data suggest a down-modulation of the immune response in the midgut during pupation and in the ovaries, thus allowing the expansion of the endosymbiont population. This assumption is strongly supported by experimental evidence for a dampening of the immune response in the midgut tissue but not in other body parts during pupation. Thus, these amidase PRRs appear to be key players in endosymbiont tolerance in *Camponotus floridanus*.

To investigate *Blochmannia* infiltration of the oocytes we have taken advantage of the fact that worker animals have strongly reduced ovaries which are quickly re-activated to produce haploid eggs when the animals are isolated from their queen. The germarium of the ovaries always remains free of bacteria, but they suddenly appear in cells of somatic origin after about four divisions of the stem cells which then differentiate in nurse cells and oocytes. Around the fifth division stage the bacteria are found free in the cytosol of the pro-oocytes and in virtually all cells of somatic origin including follicle cells, but they are never found in nurse cells. As egg chambers develop, the bacteria entirely disappear from somatic cells and are found exclusively and abundantly within the oocytes. As oocyte development progresses further the bacteria relocalize to the posterior pole of the eggs. During early stages of oogenesis when the bacteria start to appear in the cytoplasm of pro-oocytes many bacteria are found in host-derived vesicles indicating endocytotic processes to be involved in bacterial uptake.

FUTURE DIRECTIONS

The group aims to elucidate the molecular mechanisms involved in how insects tolerate chronic infections by mutualistic bacteria while at the same time they are able to eradicate pathogenic bacteria. To address this question the ant immune system will be further characterized with the aim to identify (immune) factors involved in the control of the endosymbionts present in the midgut and ovaries of the animals. In addition, the mechanism of bacterial entry into pro-oocytes and their cell tropism will be investigated further.

Fig. 1: A *Camponotus* species on a leaf (photograph by H. Feldhaar).

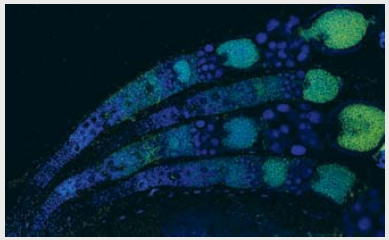

Fig. 2: Confocal image of two ovarioles of a queen-less *Camponotus floridanus* worker: DAPI-staining (blue), *Blochmannia* stained with Alexa488 (green) (photograph by Maria Kupper).

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3.5. DEPARTMENT OF MICROBIOLOGY
3.5.4. BACTERIAL INVASION AND INTRACELLULAR SURVIVAL

We investigate the factors involved in the low phosphate-dependent invasion and intracellular survival of *Neisseria gonorrhoeae*. Other parts of our research are dedicated to searching for novel substances that are active against chlamydial and neisserial infection and to exploring the role of mitochondria in infection processes.

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INTRODUCTION

Neiseria gonorrhoeae is a human pathogen that causes sexually transmitted disease gonorrhea, which includes complications such as pelvic inflammatory disease, sterility and in rare cases disseminated gonococcal infection. During infection, *N. gonorrhoeae* depends on pathogenicity factors, such as Pili for the initial adhesion, Opa proteins for invasion and PorB^{IA} porin, which seems to be of special importance in disseminated infections. PorB^{IA} porin interacts with the surface receptor SREC-I of epithelial cells and mediates bacterial invasion under low phosphate conditions. PorB^{IA} is also transported into mitochondria during infection, where it induces mitochondrial fragmentation and membrane potential loss, contributing to cell death.

Another important pathogenicity factor of *N. gonorrhoeae* is the macrophage infectivity potentiator (MIP) homolog, which is required for neisserial survival and proliferation within human macrophages. A similar protein is present in *Chlamydia trachomatis*, an obligate intracellular human-specific pathogen causing sexually transmitted diseases and trachoma. MIP protein represents an attractive target for novel antimicrobial substances.

RESEARCH HIGHLIGHTS

Part of our research has focused on PorB^{IA}, its structure and interaction with cell surface and mitochondria during infection. We have been particularly interested in low phosphate dependent invasion (LPDI) process that is mediated through the interaction of PorBIA with SREC-I receptor. We explored the underlying signaling pathways and role of neutral sphingomyelinase in LPDI.

We are also investigating novel substances against microbial infection. *C. trachomatis and N. gonorrhoeae* infection models have been used to test several classes of potential antibiotics, including substances isolated from the sponge marine-associated actinomycetes and MIP inhibitors. MIP inhibitors have a strong negative influence on survival of *N. gonorrhoeae* in neutrophils and infectivity and progeny generation in *C. trachomatis*, implying the importance of the MIP protein for the life cycle and pathogenicity of bacteria.

We are addressing the requirement of functional mitochondria during infection with intracellular pathogenic bacteria such as *C. trachomatis* and *Simkania negevensis*. We are also exploring mitochondrial biogenesis factors with a focus on novel proteins that are involved in the maintenance of cristae stability and respiratory chain assembly.

Finally, we were interested in the possible use of the optogenetic tools in infection biology. We have explored the mitochondria-targeted photoactivated adenylyl cyclase bPAC and endoplasmic reticulum-targeted cyclic nucleotide gated channels as tools for modulating cellular ATP levels and $Ca2^{+}$ signaling, both of which are important factors in infection processes.

FUTURE DIRECTIONS

Our future aim is to characterize pathogenicity factors that have been identified in transposon screens to be involved in the induction of cell death and invasion by *N. gonorrhoeae*. We are developing three-dimensional tissue models of cervical tissue to be able to study invasion, transcytosis and dissemination of *N. gonorrhoeae* in greater depth. Regarding antimicrobial substances, we will analyze in more detail how several candidate substances from sponge marine-associated actinomycetes impair the infectivity and growth of *C. trachomatis*. Finally, we will continue to explore photoactivatable proteins as research tools in infection biology.

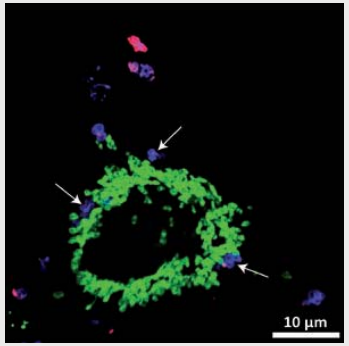

Fig. 1: Neisseria gonorrhoeae invading the cell under low phosphate conditions.

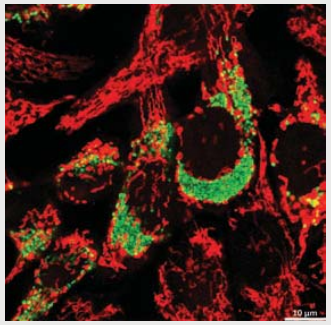

Fig. 2: Mitochondrial fragmentation in the course of infection with *Simkania negevensis*

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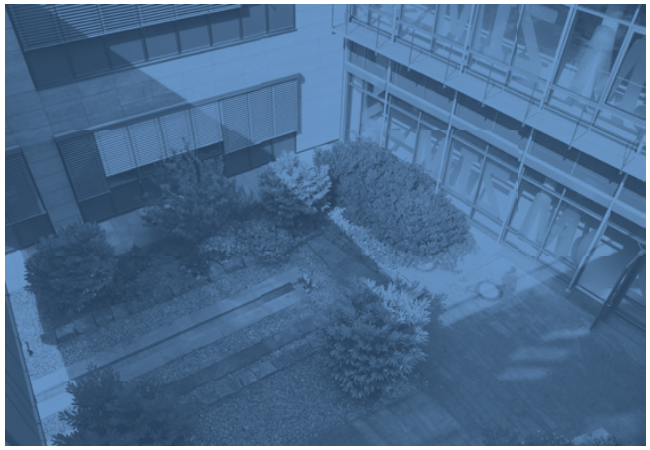

03.6

Department of Internal Medicine II

HERMANN EINSELE
ANDREAS BEILHACK
HARTWIG KLINKER
JÜRGEN LÖFFLER
ANDREW ULLMANN

The Department of Internal Medicine II at the University Hospital Clinics 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 Centre of Internal Medicine and Centre 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 implementing 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 virus hepatitis and opportunistic infections in immunocompromised patients.

3.6. DEPARTMENT OF INTERNAL MEDICINE II

3.6.1. INTERACTION OF IMMUNE EFFECTOR CELLS WITH *ASPERGILLUS FUMIGATUS*

Aspergillus fumigatus is a ubiquitious fungus that has the ability to initiate invasive infections in immunocompromised patients. The group aims to understand the pathophysiology of invasive aspergillosis and develop new strategies to improve diagnosis.

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INTRODUCTION

Aspergillus fumigatus is a saprophytic fungus that is found ubiquitously in the environment, where it plays an important role in the recycling of carbon and nitrogen. However, within the last two decades it has become one of the most important fungal pathogens. While inhaled conidia are efficiently cleared by the innate immune system of healthy humans, they can cause severe invasive disease in immunocompromised patients. In these immunocompromised hosts, the inhaled conidia are internalized by airway epithelial cells or pulmonary macrophages before undergoing germination and hyphal growth, leading to invasive aspergillosis (IA), with the primary site of infection being the lungs. Patients with neutropenia, T cell depletion, CD34-selected stem cell products, corticosteroid therapy, and cytomegalovirus infections are especially at risk of developing IA. Currently, there are a lack of reliable diagnostic tools and effective treatments, resulting in a high mortality rate of between 40 and 90 % in high-risk populations.

RESEARCH HIGHLIGHTS

Invasive aspergillosis (IA) is the most detrimental infection in patients with haematological malignancies. Although, IA may be perceived to be an uncommon disease with an incidence of 10,000 annual cases in Europe, there is increasing evidence that it is affecting a broader range of patients. In addition, IA is the most expensive opportunistic infection in immunosuppressed patients, with the annual cost in Europe being >100 million Euro. The major infectious diseases related interests of groups within the Dept. of Internal Medicine II are founded within the framework of two international and national research consortia.

A major problem in the management of IA is the poor diagnosis. Therefore, within the framework of the EU FP7 ERA-NET pathogenomics program (Invasive aspergillosis: Biomarkers for prevention, diagnosis and treatment response (aspBIOmics)), groups within the Dept. of Internal Medicine are developing and evaluating a battery of *in vitro* assays for a comprehensive multimodal analysis. This includes combining the detection of *Aspergillus fumigatus* elements (DNA, RNA, polysaccharides, proteins), host factors and the individual genetic susceptibility of the patients. The major benefit of this combined approach is the availability of a panel of biomarkers incorporated into rapid and sensitive *ex vivo* assays. This means that for the first time, a multi-parameter diagnostic strategy is being undertaken to target IA. This strategy has the potential to identify patients who are at highest risk of IA before the infection occurs. As a consequence, effective tailored prophylaxis can be provided and the success of antifungal therapy can be monitored.

The CRC/Transregio 124 (Pathogenic fungi and their human host: Networks of inter- action) aims to combine state-of-the-art research in mycology and immunology to gain novel insights into the pathophysiology of invasive mycoses. The explicit goal of this initiative is to use modern sophisticated high-throughput approaches in basic research to generate data that can be used to improve diagnosis and treatment of these infections. As part of this national consortium, which includes groups from the Friedrich Schiller University and Hans Knöll Institute, Jena and the Research Center for Infectious Diseases in Würzburg, research groups are characterising infection-relevant networks of *A. fumigatus* and host cells in response to the pathogen. To obtain a better understanding of IA, the groups are systematically investigating all levels of infection biology starting with the pathogen, via its interaction with single cell types (epithelial cells, DCs, alveolar macrophages, neutrophils, natural killer (NK) cells) and more complex infection models involving several cell types at the same time before moving to mouse models and clinical samples. These approaches will enable the elucidation of the regulatory circuits in both the pathogen and the host cells using functional genomics. The relevance of single genes/proteins in this process will be further studied by applying functional analyses (generation of knock-out mutants, biochemical analysis, cell culture and animal models, RNAi). Finally, based on these data, patient material will be analysed to provide the clinical relevance of experimental (primary cells, cell cultures, animal models) and computational models.

FUTURE DIRECTIONS

In the next few years we not only aim to provide new insight into the pathogenicity mechanisms of *Aspergillus fumigatus,* but also identify diagnostic biomarkers and potential targets for new antimycotic approaches, including the development of protocols for GMP- grade generation of DCs, NK and Treg cells suitable for clinical use.

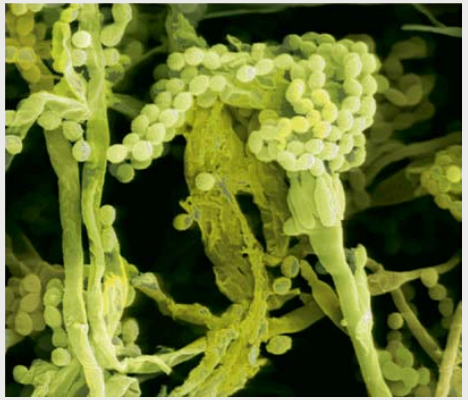

Fig. 1: Aspergillus fumigatus spores

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3.6. DEPARTMENT OF INTERNAL MEDICINE II
3.6.2. EXPERIMENTAL STEM CELL TRANSPLANTATION

Allogeneic hematopoietic cell transplantation can be a life-saving therapy for patients with high-risk malignant diseases. The group investigates beneficial and detrimental immune effector mechanisms – particularly anti-tumor effects, protection from graft-versus-host disease and opportunistic infections.

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INTRODUCTION

The fungus *Aspergillus fumigatus* can cause life-threatening fungal infections after allogeneic hematopoietic cell transplantation or in other situations when the immune system is perturbed. Imbalances in the immune system or disruption of cellular barriers can result in invasive pulmonary aspergillosis. Clearance of these infections is dependent on immune effector cells from the innate and adaptive immune system. Until now, only limited information has been available concerning the time-resolved progression and spatial distribution of *Aspergillus fumigatus* during infection and its dependence on the underlying predisposing condition. Furthermore, the dynamics of immune cell recruitment and the way in which they act in concert is not well understood. Our group employs various *in vivo* and *ex vivo* imaging techniques to visualize disease progression, immune cell recruitment and the physical interactions among immune cells and the pathogen under *in vivo* conditions. By modulating the immune system we are analyzing the changes in interaction patterns and its effect on the outcome of fungal infections. We aim to elucidate the interplay of host and pathogen under *in vivo* conditions to develop novel strategies to improve disease outcome.

RESEARCH HIGHLIGHTS

During the last few years we have been developing microscopy and imaging techniques to investigate complex immune processes *in vivo*. Together with Sven Krappmann (former ZINF Young Investigator, now at the University Hospital in Erlangen) we have developed systems to visualize luminescent *Aspergillus fumigatus* infection *in vivo* in a non-invasive manner. We have also developed a high-resolution multicolour light-sheet fluorescence microscopy (LSFM) technique to monitor dynamic immune responses in intact organs of mice or in biopsies from patients. This method has the advantage of being able to visualize and quantify single cell interactions within their three-dimensional tissue environment. We are continuing this endeavor together with Katrin Heinze (Rudolf Virchow Center, Würzburg) and have built a next-generation LSFM that enables the concomitant detection of four colour channels of mesocopic tissue specimens of up to 1cm in diameter. With Markus Sauer (Institute of Biotechnology & Biophysics, Würzburg) we are attempting to combine this method with super resolution microscopy. We have applied this approach to our *in vivo* animal models and elucidated the function of signalling pathways and essential transcription factors of defined T cell subsets after allogeneic hematopoietic cell transplantation. Non-invasive bioluminescence imaging in combination with multicolour fluorescence microscopy enabled us to pinpoint critical events after allogeneic transplantation. Using mouse models we have identified a time period of two weeks of massive alloreactive donor T cell migration in the blood after allogeneic hematopoietic cell transplantation before clinical aGVHD symptoms appeared. Based on these observations we have been able to define a collection of diagnostic markers to timely predict acute graft-versus-host disease. We have also identified potential therapeutic markers to foster transplantation tolerance without impairing desired effector functions such as the immune control of cancer cells as well as fungal and viral infections.

FUTURE DIRECTIONS

As members of the Collaborative Research Centre TRR124 *Pathogenic fungi and their human host: Networks of interaction* we will further develop and continue to employ our imaging and microscopy platform to investigate dynamic immune-pathogen interactions *in vivo*. Also we will take advantage of the strong bioinformatics core and our close ties with the clinics to elucidate critical host-pathogen interactions to improve diagnostics and therapeutic options for patients undergoing hematopoietic cell transplantation and/or suffering from chronic opportunistic infections.

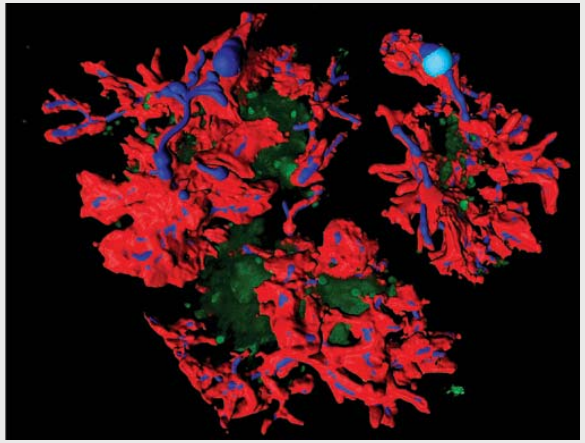

Fig. 1: Pulmonary Aspergillosis. Light sheet fluorescence microscopy of the intact lung allows visualizing *Aspergillus fumigatus* infection (red), quantifying fungal dissemination (computed hyphal filament length measurement in blue, autofluorescent lung tissue in green), and assessing immune cell interactions.

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PRIZES AND AWARDS

2015 m4 Award of the Bavarian Ministry of Economic Affairs and Media, Energy and Technology

3.6. DEPARTMENT OF INTERNAL MEDICINE II
3.6.3. DIVISION OF INFECTIOUS DISEASES

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

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INTRODUCTION

Worldwide, approximately 33 million people are living with HIV/AIDS. The availability of potent antiretroviral drugs to inhibit HIV replication has provided important clinical benefits for many patients. However, a lifelong treatment regime with complex medications places great demands on both patients and their physicians. Major problems associated with long-term antiretroviral therapy include adherence to antiretroviral treatments, drug resistance, toxicity, pharmacokinetics and pharmacological interactions. Chronic hepatitis C is also among the most frequent infections in the world (about 170 million cases) and is often complicated by liver cirrhosis and hepatocellular carcinoma. While antiviral treatments have recently dramatically improved, adequate drug exposure data are widely missing.

Invasive fungal infections are a life threatening complication in patients with haematological malignancies, especially those with acute myeloic leukemia or who are undergoing allogeneic stem cell transplantation. These patients often receive a number of different drugs for the underlying disease and for prophylaxis or treatment of complications. Therefore, drug interactions are a relevant problem in daily medical care.

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

RESEARCH HIGHLIGHTS

The laboratory specializes in developing and implementing methods for evaluating the pharmacokinetics and therapeutic drug monitoring of virostatic and antifungal agents.

One major focus is the pharmacokinetic evaluation of HIV protease inhibitors (PI) and non nucleoside reverse transcriptase inhibitors (NNRTI) during highly active antiretroviral therapy (HAART) in patients with HIV-infection. We have developed high-pressure liquid chromatographic (HPLC) methods for determining plasma levels of HIV-1 PI saquinavir, indinavir, ritonavir, nelfinavir, amprenavir, lopinavir, atazanavir, darunavir and tipranavir, the integrase inhibitor raltegravir, and for the NNRTI efavirenz, etravirine, and rilpivirine. Concentrations of nevirapine, another NNRTI, have been investigated using a gas chromatographic setup with nitrogen-phosphorous detection. In 2015, we established a new method to determine the levels of dolutegravir, a new HIV integrase inhibitor (see figure 1).

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.

For hepatitis C, antiviral treatment is dramatically changing. The division of infectious diseases is a study centre for many international phase II and III studies with investigational anti-HCV drugs (protease inhibitors, polymerase inhibitors, NS5A inhibitors) such as Paritaprevir, Ombitasvir, Dasabuvir, Grazoprevir, Elbasvir, , Daclatasvir, Simeprevir, Sofosbuvir, and Tegobuvir. A new HPLC-method for the simultaneous determination and quantification of Daclatasvir, Simeptrevir, and Ledipasvir has recently been established (see figure 2).

Clinical phase III studies in patients with haematological malignancies have mainly focused on fungal infections. In an investigator-initiated study (CASPHYLAX, initiated by Dr. Werner Heinz, Würzburg), we have been evaluating the pharmacokinetics and efficacy of caspofungin treatment for primary prophylaxis.

From 2011 to 2014, we have participated in a joint project with the Institute for Virology (Axel Rethwilm) to investigate the pharmacokinetics and drug monitoring of new direct-acting anti-HIV and anti-HCV antivirals. In addition, with respect to HIV we have participated in the NIH-and BMBF-sponsored worldwide START-study, one of the most important strategic HIV-studies, to evaluate the optimal timing for beginning antiretroviral therapy. The study is ongoing, the follow up of the patients is projected until 2021.

FUTURE DIRECTIONS

During the course of a previous International Research Training Group (IRTG1522), numerous clinical and pharmacokinetic data were collected from HIV-patients with different co-morbidities. We will perform a detailed analysis of these data, including a population study of the pharmacokinetics of antiretroviral drugs.

In the next few years, we will focus on the development of methods for the quantification of new anti-HIV- and HCV-agents. The determination of plasma concentrations of these drugs will provide insight into the individual pharmacokinetics of antiviral treatments in different patient groups and will contribute to improving the safety of long-term treatment.

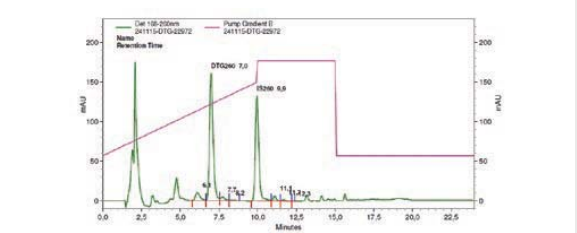

Fig. 1: HPLC illustration of Dolutegravir plasma concentration (DTG 2.793 ng/ml).

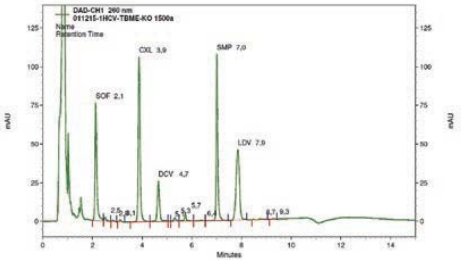

Fig. 1: HPLC run of simultaneous determination of Daclatasvir (DCV), Simeprevir (SMP), and Ledipasvir (LDV) (CXL = Chinoxalin = internal standard)

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3.6. DEPARTMENT OF INTERNAL MEDICINE II
3.6.4. IMMUNITY AGAINST *ASPERGILLUS* SPP.

Aspergillus fumigatus is a major cause of morbidity and mortality in different cohorts of immunocompromised patients. Our group aims to better understand the interaction of *A. fumigatus* with the innate and adaptive immune system and to characterize genetic susceptibility to the fungus.

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INTRODUCTION

Aspergillus spp. are ubiquitous moulds present as saprophytes in air, soil, and water. Therefore, humans are constantly exposed to their omnipresent spores. Spores are inhaled daily and exposure to the fungi can be considerable depending on the particular circumstances. In patients with a compromised immune system, deposition of the conidia on mucous membranes in the upper and lower respiratory tract enables their germination and the penetration of tissue barriers. Major groups of patients who are predisposed to invasive fungal infections are leukemia patients and patients after allogeneic stem cell and solid organ transplantation.

A. fumigatus is the predominant human pathogenic species that induces invasive aspergillosis (IA). The clinical features of IA are often non-specific with imaging and mycological analyses rarely confirming the diagnosis, making the discrimination between IA and other fungal infections particularly difficult. Medical progress and thus longer survival times have expanded the number of immunocompromised patients, and consequently the rate of IA has increased 14-fold in Europe in recent years, with an annual incidence of 10 000 cases in Europe. Lethality is around 85% and falls to 50% if patients are treated with antimycotic drugs. Furthermore, IA is the most expensive opportunistic infection in immunosuppressed patients with annual treatment costs in Europe of approximately €100 million. In-hospital stays due to complications arising from IA cause additional costs of € 75,000 per patient.

In contrast to most bacterial pathogens, *A. fumigatus* undergoes major morphological changes during the early phase of infection, resulting in different fungal surface structures. Spores are constantly inhaled and reach the lung alveoli. Cells of the innate immune system recognize the fungus and its different morphologies by distinct pattern recognition receptors (PRR), which induce cell specific as well as general defence mechanisms. The most important cells of the initial innate immune system are alveolar epithelia, alveolar macrophages, as well as dendritic cells (DC). To date, interactions between the fungus and cells of the innate immune system, such as natural killer cells (NK-cells) and granulocytes, during invasion into the blood vessels has not been well characterized.

RESEARCH HIGHLIGHTS

The research of my group is targeted towards immune recognition of *A. fumigatus,* patients' genetic susceptibility to this fungus, and the molecular diagnosis of invasive fungal infections. We have a long-term interest in extensively characterising the human and murine innate and adaptive immune responses to fungal pathogens. Immune cell populations studied in the laboratory include DCs, macrophages, monocytes, NK cells and PMN with a major focus on the relevance of innate immune receptors, anti-fungal effector mechanisms and the response of DCs to the fungus. By analysing the effect of recombinant antigens on the immune response to *A. fumigatus,* we have revealed TLR2-, TLR4-, and dectin-1 dependent activation of DCs by the fungus. Furthermore, we have shown that NK cells interact with and recognize *A. fumigatus,* which results in the release of Th1-like cytokines and fungal killing. In addition, we have revealed using a combination of live cell imaging and DStorm microscopy that DCs are key players in the activation of NK cells and that this activation is mediated by the C-type lectin Dectin-1. Recently, our group has also analysed the *in vitro* interaction of neutrophilic myeloid-derived suppressor cells and natural killer T cells with pathogenic fungi. Moreover, we have observed that microRNA levels are specifically induced in DC after contact with *A. fumigatus,* demonstrating a new regulation process in immune cells that encounter a fungal pathogen.

Another major research interest is the genetic susceptibility of patients to *A. fumigatus* infections. Genotyping of a large DNA bank identified single nucleotide polymorphisms that are potentially associated with the occurrence of *Aspergillus* infections. We have shown that defined point mutations in CXCL10, TLR5 and PTX3 are significantly associated with invasive aspergillosis.

We have also led many clinical studies investigating the diagnosis and treatment of fungal infections, including the emerging Mucorales infections and we are active leading contributors to the standardisation of Aspergillus diagnosis in Europe (through our activity in the European Aspergillus PCR Initiative Steering Committee [www.eapcri.eu]).

FUTURE DIRECTIONS

During the next few years we will focus our research on pathway analyses in different innate immune cells (macrophages, DC, NK cells) exposed to various *A. fumigatus* morphologies. Using a combined approach of parallel deep sequencing analyses of the fungus and the host, and siRNA knockdown of selected target genes, we aim to define specific immune-relevant pathways involved in aspergillosis. Our studies will also investigate the role of CD56 as adhesion and immune receptor on human NK cells, mRNA and miRNA profiles and the direct effects of rIFN on the fungus. Finally, we will focus on translational research, especially by functionally characterising PBMC and NK cells isolated from patients after allogeneic SCT during their *ex vivo* interaction with fungal pathogens. Another major focus will be the extension of our research focus to improve the molecular diagnosis of Mucorales infections and to better understand the pathophysiology of these emerging fungal infections.

Overall our aim is to develop patient-specific risk profiles and individual management strategies for patients suffering from IA.

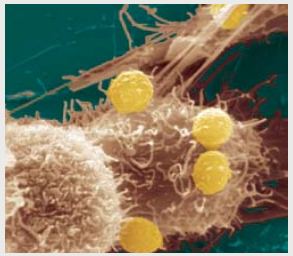

Fig. 1: Aspergillus fumigatus and monocyte-derived dendritic cells.

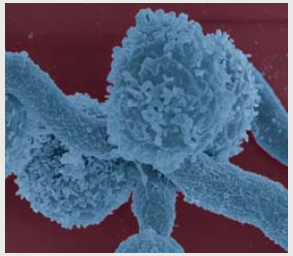

Fig. 2: Aspergillus fumigatus hyphae and activated human natural killer cells.

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3.6. DEPARTMENT OF INTERNAL MEDICINE II
3.6.5. CLINICAL INFECTIOUS DISEASES

Andrew Ullmann is the head of the Infectious Diseases division, whose main clinical focus is research various infections in the immunocompromised patient and resistance development in microbes. One of main focus of research is besides the treatment and diagnostics of filamentous fungal infections, the assessment of immune response to fungal diseases. Therefore, the group aims to develop new treatment options and diagnostic tools with new insight into the immune pathogenesis of filamentous fungi.

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INTRODUCTION

During the last decades invasive fungal infections have emerged as an important cause of life threatening infections. This not only occurs in the context of immunosuppression but is also frequently noted in non-neutropenic patients, especially in those requiring treatment in intensive care units (ICU). Despite the growing body of evidence and knowledge in this field the diagnosis and management of these complex infections remains challenging. In comparison to the incidence rate of other invasive fungal diseases, mucormycosis is rarely diagnosed. Although the treatment of aspergillosis has improved, only a few antifungal agents depict activity against mucormycosis species, which remains associated with a relatively high mortality rate. As for invasive aspergillosis, diagnostic procedures are challenging, however, in contrast to invasive aspergillosis, there is currently no recognized biomarkers available for the diagnosis of mucormycosis.

RESEARCH HIGHLIGHTS

The group has been recently established in the University Hospital Clinic. In addition, one of the major undertaken tasks has been the publication of new European guidelines for the diagnosis and management of fungal diseases. Invasive fungal infections (IFI) are life-threatening conditions that require rapid diagnostic and optimal management to mitigate their high morbidity and mortality rates.

Recent data compiled by the group underscores the importance of cellular immune response against filamentous fungi. Even in healthy volunteers T-cell response against fungi appears to be enhance compared to those not exposed (Figure 1). This first preliminary data could provide further diagnostic and therapeutic potential for patients with invasive fungal disease.

Another area of concern in the immunocompromised is CMV infections. Human cytomegalovirus (HCMV) infection is a leading viral cause of morbidity and mortality in allogeneic hematopoietic cell transplant (HCT) recipients. Available treatments are restricted by significant toxicities of and resistance to current medication. Besides Letermovir (previously known as AIC246) is a new highly potent anti-HCMV agent *in vitro*, with a novel mechanism of action targeting the viral terminase subunit pUL56, a component of the terminase complex involved in viral DNA cleavage and packaging other forms of preventions are thought. Momentary a new DNA vaccine against HCMV is in being evaluated in clinical trial.

FUTURE DIRECTIONS

This group focuses on translational research bringing results from bench science to the patients' bedside. Many projects are underway to standardize cellular and humoral immune responses against fungal infections. An animal infection model in the development to test for alternative treatment options besides antifungal agents.

Furthermore, novel antiviral agents and vaccines against herpes viridae will be another clinical research area of focus. Intensived clinical research is planned within the antimicrobial Stewardship Program of the University Clinic to improve patients' outcomes in various ITS areas.

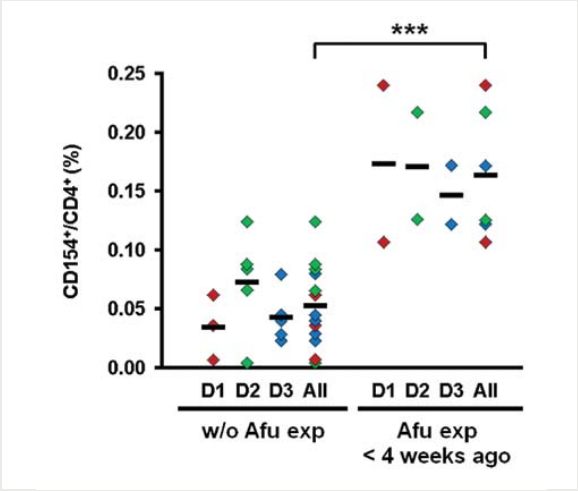

Fig. 1: Exposure to *Aspergillus* spores in a scientific laboratory is associated with elevated specific T-cell frequencies in laboratory personnel (Wurster S et al. at AAA Manchester 2016)

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04

ZINF MEMBERS ASSOCIATED WITH OTHER INSTITUTES

GERHARD BRINGMANN

THOMAS DANDEKAR

MARKUS ENGSTLER

UTE HENTSCHEL-HUMEIDA

ULRIKE HOLZGRABE

CAROLINE KISKER

GABRIELA KRASTEVA-CHRIST

AUGUST STICH

HEIKE WALLES

4. ZINF MEMBERS ASSOCIATED WITH OTHER INSTITUTES

4.1. NATURAL PRODUCTS CHEMISTRY

Natural products are a rich source of bioactive molecules. The aim of the group is the isolation, structural elucidation, total synthesis, biosynthesis, and pharmaceutical development of anti-infective and anti-tumoral agents from nature.

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INTRODUCTION

We consider natural products chemistry to be multidisciplinary *per se* and therefore try to approach this topic in a broad, highly interdisciplinary way, applying novel efficient methods of analytical, synthetic, computational, and medicinal chemistry. More specifically, we select sources for novel natural products – among them tropical plants (e.g. from promising families) and search for new compounds. This is not only done in a bioassay-guided way, but, even more efficiently, in a structure-oriented manner, by using our analytical triad HPLC-MS/MS-NMR-CD, assisted by quantum chemical circular dichroism (CD) calculations. This approach permits the 'early' recognition of novel-type molecules and the online elucidation of their full absolute stereostructures. The compounds are then isolated for structural confirmation and pharmacological investigation; these focus mainly on anti-infectious properties (antiplasmodial, antitrypanosomal, antileishmanial, anti-*Candida*, anti-biofilm, etc.), but also include anti-tumoral activities. We elaborate synthetic pathways for the most rewarding metabolites using biomimetic or merely synthetic strategies; for this purpose, we also develop novel synthetic methodology such as, e.g. the lactone method for the atroposelective construction of even highly hindered biaryl and hetero biaryl systems of any desired (and predictable) axial configuration.

RESEARCH HIGHLIGHTS

Naphthylisoquinoline alkaloids from tropical Ancistrocladaceae and Dioncophyllaceae plants are remarkable in many respects: biosynthetically because of their unprecedented origin of isoquinoline alkaloids from acetate units (and not from the usual amino acids), structurally because of the presence of stereogenic centers and rotationally hindered biaryl axes, and last, but not least, pharmacologically because of their promising anti-infective bioactivities.

We have been mainly focusing on the isolation, structural elucidation, and enantio- and atroposelective synthesis of structurally novel representatives of C,C- and N,C-coupled mono- and dimeric naphthylisoquinoline alkaloids, and on the detailed investigation of their bioactivity potential as active agents against the pathogens of infectious diseases. In this large project, which is part of our collaborative research centre "Recognition, Preparation, and Functional Analysis of Agents against Infectious Diseases" (SFB 630), we have, as an example, synthesized the new antimalarial agent dioncotetralone A from the natural product dioncophylline A under phenol-oxidative reaction conditions using lead(IV)acetate as the reagent. In contrast to dioncophylline A, dioncotetralone A bears two keto functions at C-8 and C-4', and it possesses an unprecedented Z-configured 7,1'-double bond with a helically distorted conformation, so that the two halves of the molecule are no longer orthogonal, but nearly co-planar to each other. Another remarkable new structural feature of dioncotetralone A is the additional stereogenic center at C-2', formed by the 'loss of aromaticity' in one half of the former naphthalene moiety. The full stereostructure of dioncotetralone A was successfully elucidated by the interplay of spectroscopic methods, in particular by 1D/2D NMR and electronic circular-dichroism (CD) spectroscopy, in combination with quantum-chemical CD calculations. Dioncotetralone A was found to display high activities against the chloroquine-resistant strain K1 of the malaria parasite *Plasmodium falciparum* with excellent half-maximal inhibitory concentration values.

Our key methodology for the spectroscopy-guided search for structurally rewarding naphthylisoquinoline alkaloids and related compounds from tropical plants is the analytical triad HPLC coupled to MS, NMR, and CD. This triad permits recognition and structural assignment of novel- type compounds from the peak in the chromatogram, including the full absolute stereostructure. The LC-CD option is even more valuable in combination with quantum-chemical CD calculations, which permits a secure interpretation of the spectra independent from any empirical rules. This combination of hyphenated analytical methods with computational investigations is unique in natural products chemistry. By using this concept, we have succeeded in establishing a large number of different stereostructures, with stereogenic centers or axes or with planar chirality, in many cases, our analytical method was the only possibility to assign the absolute configuration of complex chiral natural products. A convincing example is the discovery of the mbandakamines A and B, dimeric naphthylisoquinoline alkaloids with three consecutive chiral axes from a Congolese *Ancistrocladus* plant by this hyphenated analysis. These bioactive dimers possess the highest number of consecutive stereogenic biaryl axes ever found not only in naphthylisoquinolines, but also generally in natural products.

FUTURE DIRECTIONS

We are continuously aiming to improve the activities of the naphthylisoquinoline alkaloids and related compounds for further drug development. This requires the elucidation of the mode of action of the drugs and, in particular, the identification of the target protein, which we are pursuing by photo-affinity labelling studies, together with our cooperation partners from infection biology, pharmacy, and tropical medicine.

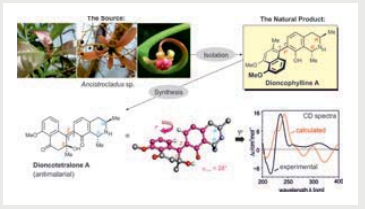

Fig. 1: Dioncotetralone A, a highly antiplasmodial non-natural oxidative product of dioncophylline A, a naphthylisoquinoline alkaloid isolated from tropical lianas belonging to two small plant families, the Ancistrocladaceae and Dioncophyllaceae, from West, Central and East Africa, and Southeast Asia.

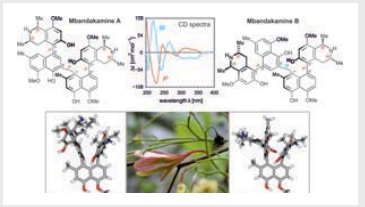

Fig. 2: Mbandakamines A and B, novel dimeric naphthylisoquinoline alkaloids from Congolese Ancistrocladus lianas, displaying an excellent and specific antimalarial activity against *Plasmodium falciparum:* the configuration at the central biaryl axis, which determines the orientation of the two strong naphthalene chromophores to each other, dominates the chiroptical properties of these two dimers, leading to nearly mirror-imaged CD spectra for mbandakamine A (P-configuration) and mbandakamine B (M-configuration), although all other stereogenic elements are identical.

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PRIZES AND AWARDS

2015 Honorary Doctorate, Université Libre des Pays des Grands Lacs, Democratic Republic of Congo

2014 Gusi Peace Prize for Humanitarianism & Scientific Research

4. ZINF MEMBERS ASSOCIATED WITH OTHER INSTITUTES
4.2. BIOINFORMATICS

Infections are complex multiparametric processes, involving many cell types, molecular networks and different environmental conditions. The group is interested in applying a variety of bioinformatic approaches to model host-pathogen interactions, from individual molecules to metabolic pathways as well as systems biology modeling approaches of regulatory networks and the dynamics of complex biological systems.

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INTRODUCTION

Bioinformatics traditionally follows the genetic flow of information from DNA to RNA to proteins. The assembled components have to be interpreted as a complete system with emergent properties, requiring cutting edge methods in systems biology and network modelling. The group's strong interest in infection biology results from the fact that all these aspects are combined in the interaction between host and pathogen during the infection process, two cellular systems in intimate contact involved in an intricate battle for survival. Starting from metabolic models, we also investigate system responses as well as regulatory components. Our approach is generic, we are interested in various infection models that include different hosts such as animals (e.g. mouse, man, Camponotus ants) and plants (e.g. Arabidopsis) and different infectious agents from fungi *(Candida albicans, Aspergillus fumigatus)*, bacteria *(Salmonella enterica, Staphylococcus aureus, Listeria)* to viridae (HIV, foamy virus; vaccinia virus). To fulfill our goals, we are developing new algorithms to model regulatory and metabolic networks as well as generating different and specific biological models of metabolism and regulation in different infection processes.

RESEARCH HIGHLIGHTS

Recently, we have developed Jimena, a Java-based genetic regulatory network simulation framework, to improve the efficiency of dynamic modelling of regulatory networks. The Jimena algorithm is able to enumerate *all* system states in networks, which is a major success compared to earlier efforts and demonstrated in different examples including plant-pathogen interactions. We have also generated a model of human T-cells during infection using convergence behaviour, which has enabled us to differentiate between direct, dynamic and total control of the involved biological networks.

Our modeling of plant pathogen interactions has focused on plant hormones and the role of cytokinins in the immune response. We have described the delicate balance between immunoprotective hormones in the plant host as well as immune compromising hormones, often triggered by a parasitic pathogen. Cytokinins modulate the immune dynamics in various plant species including *Arabidopsis*, tobacco and rice when challenged with different pathogens (types: biotrophic, necrotrophic and hemibiotrophic). By using dynamic modeling and system analysis, we revealed that they are able to influence the central immune pathways such as jasmonate and salicylate pathways of resistance. Since low and higher cytokinin levels change the immune response further, the result of an infection is also determined by the concentration changes in cytokinins. Recently, we have analysed the extent of transkingdom communication of cytokinins, for instance in the interaction of *M. tuberculosis* and the human host.

We are also studying Staphylococcal pathophysiology. Recent results have enabled us to elucidate the action and effect of naphthylisoquinolines as promising lead drug candidates against *S. aureus* infection. This analysis involved isotope labelling and the modelling of metabolism during infection. We are also interested in modeling animal-microbial interactions, for instance the Camponotus ant and its interaction with its endosymbiont Blochmannia, as well as Gram-negative pathogenic bacteria. Interactions between humans and pathogenic fungi are currently being studied within the *Collaborative Research Centre TRR124 Pathogenic fungi and their human host: Networks of interaction.* Furthermore, we are analysing host-pathogen interactions involving *A. fumigatus,* infection strategies in *Candida* and the targeting of fungal metabolism during infection using antibiotics, the latter being is part of the project ApsMetNet within the framework of the EU ERA-net program (Infect-ERA).

FUTURE DIRECTIONS

The infection biology knowledge gained from dynamic modelling of host-pathogen interactions will be instrumental for all future projects. Systems biology modelling, bioinformatics and omics analyses will also form the basis of new projects. For example, as part of the new DFG funded graduate students college GRK2157 "3D Tissue Models for Studying Microbial Infections by Human Pathogens" where we aim to elucidate new patho-mechanisms in human pathogens, focusing on Chlamydia.

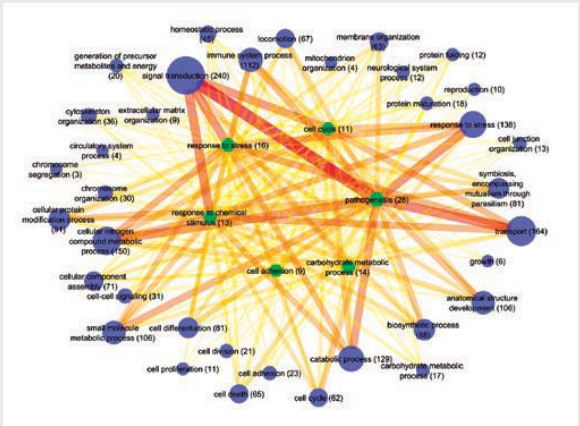

Fig. 1: Mus musculus–C.albicans network of functional gene ontology terms. Further interactions were analyzed including subnetworks in more detail. The analysis reveals a surprising variety of functional processes that are involved in mouse - *C. albicans* interactions (Remmele et al., 2015).

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4. ZINF MEMBERS ASSOCIATED WITH OTHER INSTITUTES
4.3. MOLECULAR AND PHYSICAL PARASITOLOGY

Motion is a hallmark of life. We study motion on very different scales, from molecules to organelles to cells and beyond. Our model system is the African trypanosome, a deadly blood parasite.

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INTRODUCTION

Trypanosomes have hundreds of VSG genes of which only one is expressed at any given time from one of 15 expression sites (ES). Stochastic switching to the expression of a new VSG forms the basis of antigenic variation, a process discovered in trypanosomes, but present in many pathogens. How antigenic variation works is only partly understood. Likewise, it is unclear how VSG coat density is maintained during the cell division cycle. This is of particular interest as all biosynthetic organelles in trypanosomes are present in single copies and have to be duplicated and positioned precisely to guarantee transport and recycling of new coat compounds – a process that requires finely-tuned control of molecular and vesicular motion.

The functioning of all biological processes relies on motion, at times directed and energy-dependent and at other times random and driven by thermodynamics. Signaling molecules must reach their destinations, as must vesicles and organelles. The environment obviously influences motion, a fact that is surprisingly neglected. Chemical and physical cues such as viscosity, pH, temperature, boundaries or obstacles must be taken into account for a proper understanding of the behavior of proteins in the cytoplasm or within biological membranes. Likewise, macromolecular and organelle trafficking is not only controlled by biological motors or the cytoskeleton but also by factors such as crowding and confinement.

African trypanosomes are perfect model organisms for the analysis of motion on different scales. The unicellular parasites are constantly motile throughout their complex life cycle. They prosper in the blood of their mammalian hosts, they penetrate into different tissues and they cross the blood-brain barrier. Once ingested with the bite of the transmitting tsetse fly, they must undergo dramatic cell biological changes in order to adapt to varying environments in the insect, a 30-day journey through mostly unknown 'terrain'. At all times, trypanosomes are covered with a dense coat of glycoproteins. Within the mammalian host the parasites are protected by variant surface glycoproteins (VSG), which completely cover the cell surface with some 10 million copies of the same protein. This VSG coat has to maintain its density and fluidity in order to function – a phenomenon that requires very accurate control of membrane and protein trafficking. This makes trypanosomes ideal models for studying the motion of vesicles and organelles.

RESEARCH HIGHLIGHTS

We have further developed our long-term interest in trypanosomes as prototypic microswimmers. Part of this endeavor is funded by the Physics DFG SPP 1726 "Microswimmers", as one of few biological projects. We are specifically looking at the amazing diversity of trypanosome morphotypes in the tsetse fly. The parasites populate the vector for several weeks before they become infectious towards mammals. We have detailed the cellular waveforms of the different types of trypanosomes and measured their location and density in subareas of the insect digestive system. This work was supported by advanced mathematical modelling, a nice demonstration of the recent advances in truly predictive simulation sciences. Using transgenic parasites and high-end imaging we have been able to track individual cells in very large swarms. We are now just beginning to understand the biological meaning behind the dramatic transitions between solitary and collective motion patterns; these principles can be translated to other systems, such as microbial biofilms. We have also exploited trypanosome motility for automated drug-screens in microfluidics systems – a more applied aspect of our research.

Another focus of our work is the development of trypanosomes. We have found a striking mechanistic connection between antigenic variation and gain of developmental competence. The enigmatic process of VSG surface coat switching is directly linked to the control of cell cycle progression and insect stage development. We have been able to identify molecular sensors in the trypanosomes expression site, a unique polymerase I-transcribed, polycistronic and telomeric transcription unit. Furthermore, we have shown that VSG and expression site control are not necessarily interdependent processes.

The VSG protein itself and the formation of the protective VSG coat has been a focus of our interests for a long time. But only recently, we have succeeded in establishing an *in vitro* system, which allows biophysical measurements of the VSG coat in artificial lipid bilayers. In parallel, we have developed techniques that allow direct comparison with the natural VSG coat on living trypanosomes. As a first and surprising result, we found that the molecular length of VSGs is optimized for diffusion-limited functions. This work is also the first example of a direct size-dependence of the diffusion of a GPI-anchored protein in biological membranes.

FUTURE DIRECTIONS

We have recently solved the complete protein structures of several VSGs. This – finally – allows a molecular examination of the trypanosome surface coat. The surprising features of the VSG structures will likely prompt us to fundamentally revise our current view. Our biophysical approach using single-molecule analyses of VSGs on living parasites and in defined systems should provide insight into the dynamics of the trypanosome surface coat. We will continue with our analysis of trypanosomes as versatile eukaryotic microswimmers. One focus will be on the tsetse fly parasites, the other on the dissemination and annidation of different trypanosome species in their vertebrate hosts. Lastly, we will intensify our studies on the molecular and genetic control of trypanosome development, with a special emphasis on the VSG expression site as a trypanosome master regulator.

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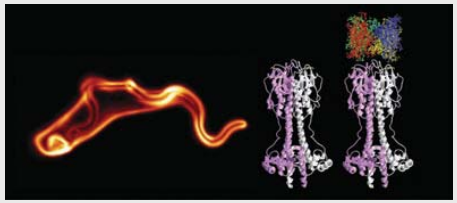

Fig. 1: Like many of the parasites that cause tropical diseases, *Trypanosoma brucei* employs genetic trickery to evade the immune systems of humans and other mammals. This involves changing the variant surface glycoprotein (VSG) coat that surrounds the parasite on a regular basis in order to remain one step ahead of the immune system of its host: while the immune system looks for invaders wearing a particular coat, the parasites are spreading through the host in a completely different coat. This image shows the VSG surface coat of a living trypanosome (left). The size of the VSG protein (middle) determines the diffusion properties. When the VSG is enlarged, for example by binding of streptavidin (right), the protein moves significantly slower, which has direct implications for parasite survival (see Hartel *et al.*, 2015).

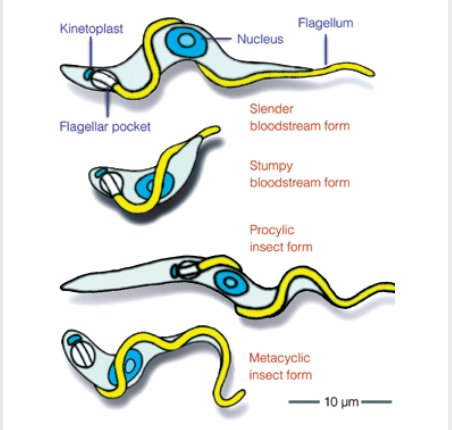

Fig. 2: Different life cycle stages of *Trypanosoma brucei* (see Krüger and Engstler, 2015).

4. ZINF MEMBERS ASSOCIATED WITH OTHER INSTITUTES
4.4. MARINE SPONGE-MICROBE INTERACTIONS

My group aims to provide an in-depth understanding of the physiology, metabolism and molecular mechanisms of interactions between marine sponges and their microbial symbiotic communities. Furthermore, we seek to isolate novel anti-infective secondary metabolites from marine sponge-associated actinomycetes.

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INTRODUCTION

Many species of sponges (phylum Porifera) harbour enormously dense and diverse communities of symbiotic microorganisms in their tissues, which can comprise up to 35% of the total sponge biomass. This remarkable microbial and chemical diversity, coupled with the ancient nature of the sponge-microorganism association, renders sponges important model systems to study metazoan host-microorganism evolution and interactions. Collectively, the animals and their microbial consortia boast an impressive metabolic and chemical repertoire that not only contributes to their nutritional ecology but has also fostered interest from the pharmaceutical industry due to their production of bioactive compounds.

In terms of microbial diversity, as many as 29 bacterial phyla, among them 12 candidate phyla and two archaeal lineages have thus far been identified in sponges. Recent amplicon sequencing studies have indicated the existence of as many as several thousand lineages of symbionts, making sponges one of the most diverse host-microbe associations in the marine environment. Sponges are now considered valuable systems for the study of high-diversity marine host-microorganism associations that resemble the human gut microbiome in several aspects. With the aid of next-generation sequencing technologies and the greater sequencing depth that they afford, a clearer picture of microbial diversity in these hosts is emerging and the factors that influence this diversity are being identified.

In terms of microbial function, we are now beginning to unravel the functions of sponge symbionts. In addition to a dedicated role in nitrogen metabolism where they recycle metabolic waste products of the sponge host such as ammonia, some lineages also seem to participate in carbon degradation. Moreover, the microbial symbionts may supplement the animal host with vitamins. However, much remains to be learnt about the various functions of microbial symbionts in the context of the sponge "holobiont".

Sponge-associated microorganisms are also of relevance from a bioprospecting perspective. These sessile animals are a particularly rich source of actinomycetes, which are prolific producers of secondary metabolites with various clinically relevant bioactivities. In this context, large strain collections have been established which are being screened for bioactivity. Bioactivity-guided fractionation in combination with metabolomics and genome sequencing is being used to isolate novel natural products with anti-infective properties. For example, we have reported the novel antioxidant and anti-protease activities of diazepinomicin, which has attracted considerable interest owing to its broad-spectrum anti-tumour activity.

RESEARCH HIGHLIGHTS

One research highlight pertains to the candidate phylum Poribacteria, members of which are nearly exclusively found in sponges. We have employed single-cell genomics to obtain comprehensive insights into the metabolic potential of individual poribacterial cells. Detailed analysis of carbohydrate metabolism has revealed their ability to degrade diverse carbon sources that likely originate from seawater and the host itself. Furthermore, the presence of specific glycoside hydrolases, uronic acid degradation pathways as well as several specific sulfatases provides strong support that Poribacteria also degrade glycosaminoglycan (GAG) chains of proteoglycans, which are key components of the sponge host matrix. Therefore, Poribacteria may be viewed as efficient scavengers and recyclers of a particular suite of carbon compounds that are unique to sponges as microbial ecosystems.

The group has also been involved in the discovery of another candidate phylum, Tectomicrobia in collaboration with J. Piel (ETH Zürich) and colleagues, members of which are highly enriched in the sponge *Theonella swinhoei.* The combination of metagenomics and single-cell genomics revealed that one phylotype, "Candidatus Entotheonella factor TSY1", produces almost all of the numerous natural products that were previously isolated from the sponge host. Overall, our efforts are directed at providing a deeper understanding of the high-complexity microbial ecosystems within sponges, and at providing research strategies to sustainably use this natural resource.

FUTURE DIRECTIONS

During the next few years, we will aim to combine in-situ work involving experimental manipulation and state-of-the-art physiological measurements with high-throughput -omics technologies to address basic questions in sponge microbiology and symbiosis research. In other words, we will place our omics-generated hypotheses into an ecological context. With regards to novel anti-infective discovery, we will sequence more actinomycete genomes from our collections with the aim of uncovering the hidden genomic potential for secondary metabolism. Genomics-data will be integrated with metabolomics-data to identify elusive metabolites that have been missed by current protocols. We will further explore the power of co-cultivation to elicit metabolites that are not produced in pure culture.

Fig. 1: The Mediterranean sponge *Aplysina aerophoba* as a model for sponge microbiology. Underwater photography: Janine Kamke, University of Würzburg.

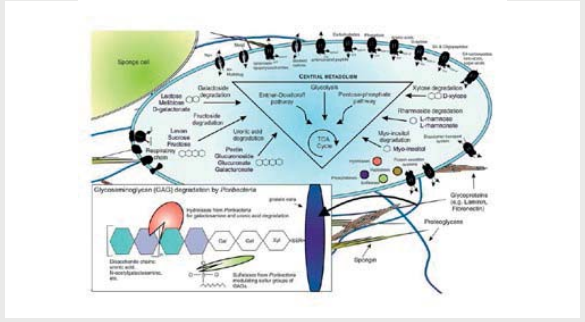

Fig. 2: Schematic overview of a poribacterial cell within the sponge extracellular matrix illustrating pathways of carbohydrate metabolism and glycosaminoglycan degradation by poribacterial enzymes. (Kamke et al. ISME J 2013)

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4. ZINF MEMBERS ASSOCIATED WITH OTHER INSTITUTES
4.5. MEDICINAL CHEMISTRY

New anti-infective drugs especially against Gram-negative bacteria and protozoa, such as trypanosoma and leishmania, are urgently needed due to the increasing levels of resistance to current antibiotics. We employ structure- and ligand-based drug design to develop and optimise optimise anti-trypanosomal and anti-leishmanial compounds and inhibitors of the virulence protein Mip (macrophage infectivity potentiator) present in Gram-negative pathogens.

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INTRODUCTION

The decline in the design and development of anti-infective drugs by the pharmaceutical industry has resulted in an almost empty drug pipeline. As many pathogens become more and more resistant to one or more antibiotics we are in danger of losing the arsenal of drugs against infections. This is especially true for Gram-negative bacteria. Recently, the WHO stated that infections by *Pseudomonas, Klebsiella, Chlamydia,* and *Neisseria* are becoming therapeutically problematic. However, for tropical diseases such as malaria, sleeping sickness and leishmanial infections the situation is even worse because of the lack of effective drugs without severe adverse effects in addition to resistance problems. Therefore, the Collaborative Research Center SFB630 at the University of Würzburg, has been focusing on the recognition, preparation and functional analysis of compounds against infectious diseases.

In order to overcome these problems it is necessary to find novel drugs against new targets, and new chemical structures. Until now most of the antibiotics in clinical use either interfere with the replication of bacteria and protozoa or with protein and cell wall biosynthesis, and thus, produce selection pressure which results in the development of resistance. However, blocking the entry of the bacteria and their dissemination in the host by targeting virulence factors, represent promising strategies to inhibit infections. Many of the Gram-negative bacteria express “macrophage infectivity potentiator” (Mip) proteins that are involved in these processes. Inhibition of Mip in *Legionella* and *Burkholderia* has been shown to attenuate infections.

RESEARCH HIGHLIGHTS

Within the framework of the Collaborative Research Center SFB630 and together with Banasri Hazra, Kolkata, India, we have searched for new sources of anti-leishmanial drugs in nature, i.e. the plant *Valeriana walichii,* which was previously known to have anti-infective activity. A first round of bioassay-guided fractionation provided highly active fractions whose activity was due to the presence of borneoyl caffeic carboxylates. Based on this finding we synthesised a smart library to derive structure-activity relationships. Subsequently, it became clear that the highly reactive moieties of the caffeic ester, i.e the Michael system and the catechol ring system (being called Pan-assay interference compounds = PAINS), are responsible for cytotoxicity and could be omitted without impacting the anti-leishmanial activity. In addition the ester, which is prone to hydrolysis *in vivo,* was replaced with an amide. These compounds were used to treat *L. major*- and *L. donovani*-infected BALB/c mice, respectively. In both models the cinnamonic and phenylpropionic acid derivatives substantially reduced the protozoa burden (in collaboration with U. Schurigt, Würzburg). Transmission light and electron microcopy together with flow cytometry revealed compound-induced mitochondrial swelling in *L. major* and *L. donovani* promastigotes and a loss of mitochondrial transmembrane potential. Thus, these compounds can be regarded as promising drug candidates against cutaneous and visceral leishmaniasis.

We have also been interested in the development of inhibitors of the Mip protein, which is responsible for invasion and dissemination of Gram-negative bacteria and has been proven to be a lethal target. Utilizing the crystal structure of the *Burkholderia pseudomallei* Mip (BpMip) and the *Legionella pneumophila* Mip (LgMip) complexed with the inhibitor we have designed highly active pipecolic ester-type inhibitors with low cytotoxicity. The most efficient inhibitors reduced cell death in Bp-infected macrophages. These compounds displayed sufficient solubility and lipophilicity in addition to appropriate pharmacokinetic properties. The in vivo activity of the best compounds are currently being evaluated in mice models. In addition, screenings using these compounds showed good inhibitory activity towards *Francisella tularensis* and *Yersinia pestis* Mip (in collaboration with D. Begley and P. Myler, Seattle, USA, I. Norville, Exeter, UK, and T. Inglis and M. Sarkar-Tyson, Perth, Australia) and *Neisseria meningitis,* and *Neisseria gonorrhoe* in addition to *Chlamydia trachomatis* (in collaboration with T. Rudel and V. Kozjak-Pavlovic, Würzburg). Taken together, we have preclinical candidates to be formulated for *in vivo* studies.

In a previous study bisquaternary bisnaphthalimide derivatives were found to be very active against trypanosoma and staphylococci, which may be due to distortion of the endoplasmic reticulum membrane. Interestingly, nitro-substituted compounds produced a red color in multi-resistant staphylococci. In collaboration with K. Ohlsen (ZINF), the color changes could be attributed to a stepwise reduction of the nitro group by a reductase that is overexpressed in resistant bacteria. The resulting bisamines are completely inactive.

FUTURE DIRECTIONS

Since Mip pipecolic acid-type inhibitors have proven to be active against a variety of Gram-negative bacteria, such as *Legionella, Burkholderia, Yersinia, Chlamydia* and *Neisseria,* they can function as virulence factor targeting drugs. We aim to identify better anti-infective compounds including those that covalently bind to the Mip to silence virulence more efficiently.

The observation that nitro-substituted bisnaphthalimides constitute a new mode of resistance. will be further investigated and we will determine if similar reactions occur for other nitro-substituted antibiotics in clinical use.

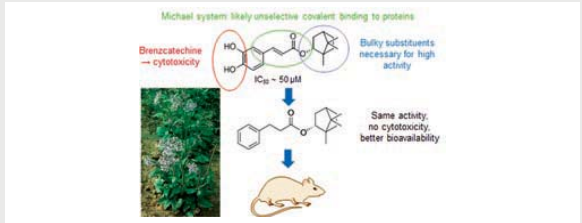

Fig. 1: Valeriana walichii and antileishmanial compounds

Fig. 2: Fractions isolated via semi-preparative HPLC. The colorless fraction/compound *1* and the red compound *2* were isolated from red bacterial cultures after 24 h incubation. The two yellow compounds *3* and *4* were isolated from bacterial cultures after 6 days incubation (after the disappearance of the red color).

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4. ZINF MEMBERS ASSOCIATED WITH OTHER INSTITUTES
4.6. STRUCTURE BASED DRUG DESIGN

The increasing emergence of pathogenic bacteria resistant to common antibiotics is a worldwide medical concern. My group aims to characterize new targets and to identify new lead compounds for the treatment of specific infectious diseases.

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INTRODUCTION

Based on estimates from the World Health Organization about one third of the world's population is infected with *Mycobacterium tuberculosis* and about 10% of these individuals will develop an active infection. Critical issues in the treatment and control of the disease include the emergence of multi-, and extensively-drug-resistant strains.

Staphylococcus aureus, which is carried intermittently or persistently by 30-50% of the adult population, has rapidly adapted to the presence of drugs used to treat staphylococcal infections. Hence, infectious diseases caused by resistant bacterial strains are becoming an urgent worldwide problem.

Bacterial fatty acid biosynthesis (FAS) fundamentally differs from its mammalian counterpart and may thus be selectively inhibited. We therefore focus our structure-based-drug design efforts on an essential protein in the bacterial FAS pathway, FabI (InhA in *M. tuberculosis*). An additional potential target for the treatment of a latent tuberculosis infection is the cholesterol metabolism pathway. Based on our structural and functional analyses, inhibitors targeting *these enzymes* may be developed or further improved raising the hope for novel antibiotics to treat resistant pathogens.

RESEARCH HIGHLIGHTS

The inability of mycobacteria to synthesize cholesterol and its utilisation during lipid-based metabolism in the host suggests that proteins involved in the transport of cholesterol into the bacteria and its subsequent metabolism may constitute promising new drug targets. It has been shown that cholesterol can be used as a sole carbon source but it has also been suggested that cholesterol metabolites are important for persistence. The *fadA5* gene is located in the Mtb cholesterol catabolism cluster and a bacterial strain lacking the *fadA5* gene displays an attenuated disease phenotype in comparison to the wild-type strain during the chronic phase of infection in a mouse model. In collaboration with Nicole Sampson's group (Stony Brook University, USA) we have analysed the FadA5 protein, which has revealed that FadA5 can utilize a steroid-CoA ketoester as a substrate and thus this protein can be classified as a degradative thiolase or a 3-ketoacyl-CoA thiolase. The structural characterization of the FadA5 protein has shown that the active form of the protein is a dimer with each monomer harbouring an active site composed of a catalytic triad with two cysteines and a histidine. To further decipher the role of FadA5 in cholesterol metabolism we aimed to capture snap-shots of the enzyme along its reaction pathway and determined the structures of this enzyme in complex with its CoA ligand and in the presence of a product steroid. Our structural characterization of a bound steroid and coenzyme A is a rare example of a thiolase ('like') enzyme in the presence of its product and reveals the first insights into steroid-enzyme-binding.

The high structural conservation of thiolases and the presence of six thiolases in humans raises the question if it is feasible to develop a FadA5 specific inhibitor. Three of the six human thiolases have already been structurally characterized and could therefore be readily compared to FadA5. For the three remaining thiolases we have generated models and subsequently compared them to the FadA5 structure. Interestingly, four of the thiolases most likely adopt a different fold around the steroid binding pocket whereas two human thiolases seem to be more closely related to FadA5 and we can not exclude the possibility of steroid binding. However, due to the presence of different amino acids in the binding pocket, it may be feasible to develop a specific FadA5 inhibitor.

Our previous work with the bacterial enoyl-acyl-carrier protein reductase (FabI) and its interactions with diphenylethers led us to analyse a related class of molecules, the pyridone inhibitors such as the compound CG400549, which has shown efficacy for the treatment of methicillin-resistant *Staphylococcus aureus* infections. Pyridone inhibitors are structurally very similar to diphenylethers but the phenol in the latter is replaced by a stable pyridone thus leading to improved pharmacokinetic properties. It has been assumed that the interaction with FabI is similar due to this minor exchange. However, we have shown that the two compound classes interact with the protein at different stages of the reaction cycle. Whereas the diphenylethers bind to the Enzyme-$NADP^+$ state, i.e. the enzyme-product complex, the 2-pyridones bind preferably to the Enzyme-NADPH state. The relevance of this preference is reflected by the fact that the affinity of the enzyme towards NADPH is much higher than for $NADP^+$. Importantly, our analysis regarding the interaction of *S. aureus* FabI with CG400549 has revealed the basis for this compound's very narrow spectrum activity and further design has resulted in an inhibitor with an extended antimicrobial activity.

FUTURE DIRECTIONS

Gaining insights into the role of proteins involved in cholesterol metabolism may lead the way towards the development of new inhibitors against the latent form of tuberculosis. We have analysed one of these enzymes, the FadA5 protein. The information obtained regarding the mechanism of the enzyme and the bound steroid should lead the way towards the development of a FadA5 specific inhibitor. Furthermore, we will continue to explore the possibility of targeting protein-protein interaction sites for drug development. In bacteria, the growing acyl chain has to be transported by the acyl-carrier protein sequentially from one enzyme to the next in the FAS cycle. The acyl carrier protein forms relatively short-lived complexes with its partners but these interactions are essential for catalysis. We will characterize complexes formed between the acyl-carrier protein and its binding partners in the FAS system and utilize this knowledge to develop new lead compounds that interfere with these interaction sites.

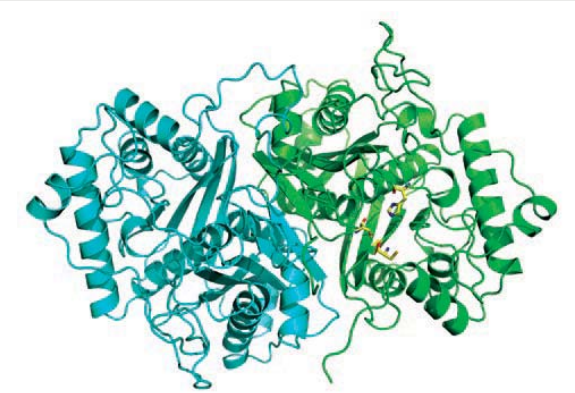

Fig. 1: The FadA5 dimer.

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4. ZINF MEMBERS ASSOCIATED WITH OTHER INSTITUTES

4.7. PULMONARY NEUROBIOLOGY

Specialized epithelial cells ("brush cells") located within various mucosal surfaces use the canonical taste transduction cascade to detect bacterial and potentially dangerous substances. The aim of our group is the characterization of this newly identified mechanism for pathogen recognition and elucidation of the consequences of its disturbance for the severity of infection.

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INTRODUCTION

Pneumonia represents an enormous burden worldwide due to dramatically increasing rates of drug-resistant bacteria. The absence of new efficient antibiotics strengthens the need for the development of novel antimicrobial strategies. Today, our knowledge of the interplay between the host and pathogens and the resulting infection and inflammation of the lung remains limited. Recognition of invading pathogens is a prerequisite for the initiation of immune responses and their subsequent elimination. The generally accepted view is that the host innate immune system recognizes invading pathogens using classical pattern recognition receptors (PRRs) (e.g. TLRs, NLRs). However, recent studies have shown that bacterial products such as quorum sensing molecules (QSM) act as agonists for non-immune receptors like canonical bitter taste receptors.

Taste receptors (TR) are present on the tongue and communicate information to the brain about the content of ingested foods to evoke the respective reflexes. There are two classes of receptors T1R (for sweet and umami sensation) and T2R (for bitter). There are at least 25 T2R human isoforms, which are tuned to a wide array of different bitter compounds. In the last few years, several groups including our own have identified T2Rs to be components of the canonical taste transduction cascade in a specialized epithelial cell type (termed solitary chemosensory cells or brush cells) in a variety of locations beyond the tongue, from the airway and gastrointestinal epithelia to the urethra. In the respiratory system, acyl-homoserine lactones (AHLs) secreted by *Pseudomonas aeruginosa* induce increased mucociliary clearance and protective respiratory reflexes. In addition, nose chemosensory cells are responsible for triggering local inflammation and initiating an immune response to the presence of bacterial metabolites.

An appealing concept has emerged that brush cells in the lower airways serve as sentinels to protect against the further ingression of potentially harmful bacterial substances into the lung. The role for bitter taste receptors (Tas2R) in innate immunity is particularly intriguing, as they have a various genetic variants. In line with this, genetic polymorphisms of T2R38 in humans result in altered receptor functionality, which correlates with susceptibility to chronic rhinosinusitis.

RESEARCH HIGHLIGHTS

During the last few years, we have invested our efforts into elucidating the function of airway brush cells. Although this epithelial cell type was discovered in the airways in the 1950's the function of the cells remained enigmatic. These cells have turned out to express the canonical taste transduction pathway (α-gustducin, phospholipase C β2 and the monovalent selective transient receptor potential cation channel member 5) for recognition of "bitter". We have developed animal models to study tracheal evoked reflexes *in vivo*. Application of bitter substances and bacterial products (among them QSM from *P. aeruginosa*), to the tracheal mucosa resulted in the release of acetylcholine (ACh) from brush cells followed by activation of sensory nerve fibers and depression of respiration. Recently, we have been exploring the hypothesis that ACh mediates a subsequent release of neuropeptides from nerve fibers innervating the trachea leading to neurogenic inflammation in the airways.

Based on our "sentinel" concept for the detection of pathogens present in the mucosal lining fluid and the initiation of averse reflexes such as defense mechanism, we hypothesised that these cells would also be present at other entry sites to the body. Indeed, we have identified them in the auditory tube, the conjunctiva and in the urethra. Moreover, the newly recognized urethral brush cells were activated by uropathogenic *E. coli* and have evoked an increase in micturition by cholinergic transmission.

To obtain a deeper understanding of the pathogen recognition spectrum of brush cells we have developed a protocol for the isolation of singe brush cells from the trachea and have performed the first next generation sequencing and bioinformatics analyses. We have been able to confirm the presence of known marker molecules, identify new markers and candidate genes that might play a role in the sensing of and protection against pathogens. We have also been working on establishing animal models of chronical *P. aeruginosa* and *Streptococcus pneumoniae* infections.

FUTURE DIRECTIONS

During the next few years, we will further characterize the airway brush cells. We plan to perform single-cell transcriptome analysis to identify different populations of brush cells in infected and non-infected airways. We aim to elucidate the consequence of disturbed mucosal taste transduction and the lack of this cell type (taste receptors and cholinergic signaling) for bacterial colonization and the severity of infection using different transgenic mouse strains. In addition, we are interested in elucidating paracrine-signaling pathways that couple the sensing of pathogens to innate immunity mechanisms such as mucociliary clearance.

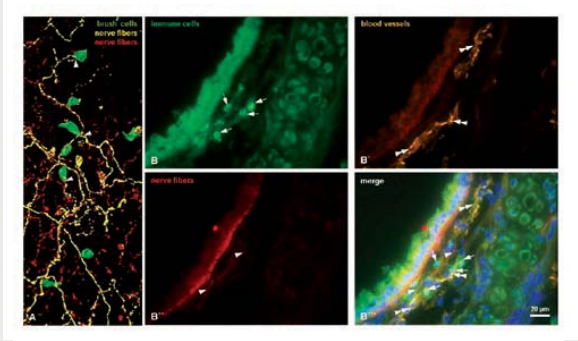

Fig. 1: Working hypothesis: Neurogenic inflammation in the airways, immunofluorescence. A) Epithelial brush cells (green) are contacted by nerve fibers (arrowheads). B) Activation of the cells stimulates subsequently nerve fibers (red, arrowheads, B´´) and leads to recruitment (vessels in yellow, B´) of immune cells (green, B).

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4. ZINF MEMBERS ASSOCIATED WITH OTHER INSTITUTES
4.8. TROPICAL MEDICINE

Tropical Medicine is a multisectorial field. It comprises travel medicine, which involves providing advice on vaccinations and how to avoid contracting infectious diseases. It also involves the diagnosis and treatment of tropical diseases and exotic infections. A side issue is migrant health, which focuses on improving the health of refugees and asylum seekers in this country. The most challenging aspect is medicine in the tropics, which frequently relates to medical care in resource-limited settings.

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INTRODUCTION

Usually the "Tropics" are geographically defined as an area of high temperature and humidity where the sun is directly overhead at least once a year. More than 8 million Germans annually travel to tropical and subtropical countries, thus exposing themselves to diseases that are unknown to many medical practitioners in this country. Pre-travel clinics help to reduce the risk by administration of necessary vaccinations and by advising travellers on the best methods of prophylaxis against malaria and other tropical diseases. Two percent of all returning travellers consult their doctor regarding symptoms connected with exposure to tropical diseases. Fever is the most alarming symptom and malaria must be ruled out in any person returning from endemic countries and with elevated temperature. In Germany, some 600 people are diagnosed with a plasmodial infection each year. Another important febrile disease, which is already more common than malaria, is dengue fever. This viral infection is transmitted by day active mosquitoes, which, due to global climate change, are already establishing stable colonies in southern Germany. Returning patients displaying symptoms such as diarrhoea are often infected by parasites, most commonly by the difficult-to-diagnose Giardia *intestinalis.* Skin conditions such as *Larva migrans cutanea,* staphylococcal pyodermia or erysipelas are also very common in returning travellers.

Another important aspect of tropical medicine is the area of migrant health. Eighteen percent of the population in Germany has a migrant background. Many suffer from diseases that are unknown to medical practitioners in this country, for example, sickle cell disease of familial Mediterranean fever. In some migrant communities, diseases such as chronic hepatitis C or HIV are more prevalent than in the German population. Others, such as extrapulmonary tuberculosis, are difficult to diagnose and require specialized knowledge for correct clinical management. Therefore medical care for migrants requires additional expertise. Würzburg is one of the leading centres in Germany with respect to this issue. A serious problem is the fact that refugees and asylum seekers in Germany have only limited access to our health care system, which places additional social responsibility from personnel involved in the medical care of this vulnerable and underprivileged group.

Tropical medicine also involves devising approaches to improve access to medical systems in many resource-limited settings. Social determinants such as a lack of education, gender inequity, conflicts and war, climatic changes leading to the loss of natural resources and poverty have direct and indirect influences on the health of millions of people. Thus tropical medicine is an access point into the new field of "Global Health".

RESEARCH HIGHLIGHTS

As part of the daily clinical routines, the department has been the first to detect a worldwide outbreak of sarcocystosis originating from Tioman Island in Malaysia, to report on the first European patient with Tana pox disease and to detect the first imported case of Japanese Encephalitis from Bali. There is also ongoing research on *Trypanosoma brucei,* the agent of African sleeping sickness, within the collaborative research centre "Recognition, Preparation, and Functional Analysis of Agents against Infectious Diseases" (SFB 630). This has led to the testing of synthetic molecules as possible drugs, and the successful identification of strong candidates with favourable therapeutic index.

The department has a strong research and training cooperation with the Catholic University of Health and Allied Sciences in Mwanza, Tanzania. The Bugando Medical Centre was the site of a double-blind randomised controlled clinical trial examining the effect of low dose steroids on the evolution of HIV infections. In cooperation with the Institute of Virology (Würzburg) and University of Stellenbosch, South Africa, we have revealed an alarming rate of primary drug resistance in patients with HIV infections. Both studies have been brought to the attention of WHO and have the potential to influence the treatment naive policy guidelines of HIV in Africa.

Parasitic infections are still highly prevalent in rural, semi-urban and even urban populations in Africa. We are involved in studies on novel approaches in the diagnosis of malaria, the prevalence of intestinal parasites such as *Strongyloides stercoralis* and *Giardia intestinalis* and on the co-morbidity of schistosomiasis and Hepatitis B.

FUTURE DIRECTIONS

During the next years we will intensify our cooperation with African universities in Tanzania, Ghana and South Africa, with HIV infection remaining a strong focus. HIV treatment programmes will be used to help to establish African health systems for the management of chronic non-communicable diseases such as hypertension and diabetes. Recently, the German Leprosy and Tuberculosis Relief Association, the world's largest leprosy relief organisation, which is based in Würzburg, has developed a new research agenda. In close cooperation with this non-governmental organisation, we will intensify our work on tuberculosis, leprosy and Buruli ulcer. In addition Würzburg is the study centre of a new nationwide project to detect and manage patients with Chagas disease in Germany. This work will be supported in collaboration with the *Universidad Católica de las Misiones* in Posadas, Argentina.

Fig. 1: Protective equipment in an Ebola treatment unit

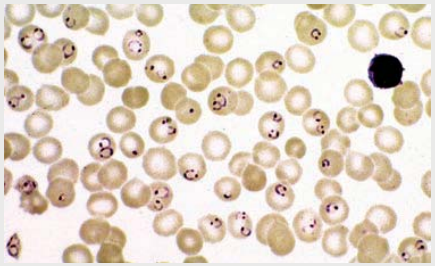

Fig. 2: Plasmodium falciparum in a patient with severe malaria

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PRIZES AND AWARDS

2015 Albert-Kölliker Teaching Prize

4. ZINF MEMBERS ASSOCIATED WITH OTHER INSTITUTES

4.9. TISSUE ENGINEERING

Tissue engineering has been successfully applied to create replacement structures for reconstructive surgery. The TERM team is interested in developing and applying complex multi-cellular three-dimensional (3D) tissue cultures that are able to mimic the microenvironment of human tissues to study important human bacterial or viral infections.

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INTRODUCTION

Tissue Engineering and Regenerative Medicine is an emerging multidisciplinary field involving biology, medicine and engineering. One of the aims of tissue engineering is to recapitulate and maintain the physiological function of cells or tissues *in vitro* for a longer period of time than is possible in simple two-dimensional cultures. This includes the development of novel biomaterials, bioreactors, and co-culture techniques. Thus, human tissue engineered models that reflect normal and pathological situations can be designed to investigate the underlying cellular and molecular mechanisms involved in specific infectious diseases. In this respect, models representing human barrier organs such as the gastrointestinal tract, the respiratory tract and the skin, which are the main contact sites for pathogenic microbes, are of particular interest.

RESEARCH HIGHLIGHTS

We have previously established a process for manufacturing a collagen matrix with a persisting blood circulation system (BioVaSc-TERM® technology). The matrix is based on a modified acellular porcine intestine with intact blood vessel structures and has been successfully used to generate *in vitro* gastrointestinal and respiratory tract models. The group uses primary (stem) cell protocols combined with synthetic or biological- based matrices that specifically mimic the *in vivo* microenvironment of selected tissues. These 3D tissue equivalents can be engineered to contain specific immune or vascular components and enable us to monitor different stages of infection without the need for testing in animals.

We have developed a 3D tissue-engineered human lower airway model (see Figure 1A) to study the interactions between the human specific pathogen *Bordetella pertussis,* which causes whooping cough, and its host (together with Roy Gross, Würzburg). It consists of a polarized respiratory epithelium that is anchored via a basement membrane to the underlying connective tissue, which includes fibroblasts. We have observed severe epithelial damage, such as cellular extrusions and impaired barrier integrity upon infection with *B. pertussis*.

The family of Enterobacteriaceae harbours many causative agents of severe microbial infections of the human host including *Salmonella enterica*. *Salmonella typhi* causes life-threatening typhoid fever in primates, based on its host restriction *in vivo* models are lacking. Studying the bacterial transmission across in the human intestinal epithelium required the generation of new human gastrointestinal barrier models (Figure 1B) that include a variety of differentiated cell types (together with Jörg Vogel, Würzburg). The same human gastrointestinal barrier models have been used to study *Helicobacter pylori* and *Campylobacter jejuni* infections. We have also been developing new human in vitro 3D intestine and stomach infection models to study pathogenesis of *Helicobacter* and *Campylobacter* (together with Cynthia Sharma, Würzburg).

Recently, we have developed a human blood-brain-barrier (BBB) *in vitro* model based on differentiated human induced pluripotent stem cells. The model consists of microvascular endothelial cells (ECs) as well as astrocytes, pericytes and neural stem cells, which interact with ECs and therefore influence BBB integrity (Figure 1C). Our BBB model will be used as preclinical research tool for drug transport or infection studies. It is also being used to study interactions and infections of strictly human specific pathogens, like *Neisseria meningitides* (together with Alexandra Schubert-Unkmeir, Würzburg), which causes diseases such as meningitis and sepsis.

FUTURE DIRECTIONS

We aim to further improve our models by using human iPS-derived cells and primary stem cells co-cultured with relevant *ex vivo* primary cells and apply a constant flow of medium using peristaltic pumps and bioreactor systems. These dynamic conditions produce cells with more *in vivo* like characteristics e.g. in morphology and protein expression levels. In addition, purified human peripheral blood leukocyte preparations containing specific cellular subsets (e.g., monocytes or neutrophils) will be added to study their contribution to the eradication of pathogens that have disseminated into the vascular compartment.

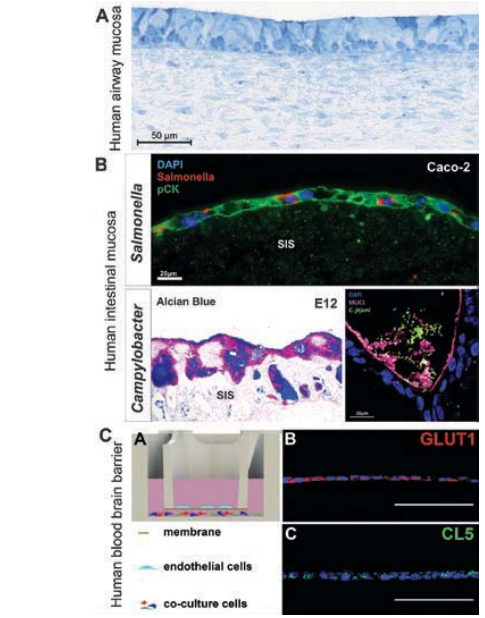

Fig. 1: (A)BioVaSc-TERM® (Biological Vascularized Scaffold), 3-D human airway mucosa model based on a biological collagen matrix produced by decellularization of jejunal gut segments of pigs (Methylene blue staining, provided by Maria Steinke, TERM). (B) Cross-sections of human gut models with a confluent polarized epithelial barrier. Immunohistochemistry of epithelial cells (upper image; cytokeratin: green; provided by Leon Schulte, AG Vogel) and mucus-producing cells (lower panel; Alcian Blue: purple; Mucin-2: red; provided by Mona Alzheimer, AG Sharma). infected with fluorochrome-coupled Salmonella (upper image: red) or Campylobacter strains (lower image: green). (C) Schematic overview of blood brain barrier (BBB) model in transwell system (CA). Immunofluorescence of BBB markers, glucose transporter 1, red (GLUT1; CB) and the tight junction protein claudin-5, green (CL5; CC). Cell nuclei stained with DAPI, blue (provided by Antje Appelt-Menzel, TERM). Scale bars indicate 100 µm.

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05

RESEARCH PROGRAMMES AND INFRASTRUCTURE

5. RESEARCH PROGRAMMES AND INFRASTRUCTURE

5.1
DFG Collaborative Research Centre SFB 630
Recognition, Preparation and Functional Analysis of Agents Against Infectious Diseases

The fight against infectious diseases is one of the biggest challenges in industrialized, emerging, and developing countries alike. Many less developed countries are severely affected by tropical diseases which are of low priority for drug development by the pharmaceutical industry. The industrialized countries face serious problems due to multi-drug resistant pathogens such as methicillin-resistant *Staphylococcus aureus* strains (MRSA). To meet these challenges, the CRC/SFB 630 has focused on the development of new drugs against infections caused by trypanosomes, *Leishmania,* plasmodia, staphylococci, especially MRSA, mycobacteria, *Candida, Neisseria* and *Chlamydia,* with a special emphasis on new lead compounds for targets in the pathogens that are not targeted by currently available antibiotics.

Research groups in project area A of the SFB design and synthesize novel compounds or isolate them from plants and sponges. These compounds are tested in the centralized project Z1 with respect to their anti-infectious properties and toxicity. The detailed mechanisms of action of the most effective compounds are characterized in project area B, using state-of-the-art technologies. Finally, project area C provides a detailed molecular understanding via computer-based approaches, in order to optimize promising lead compounds and their pharmacological properties.

Candidate compounds will undergo further pharmaceutical improvements and will be analyzed in animals following a corresponding "galenical formulation". This represents a prerequisite for pre-clinical studies, which will be pursued with the help of non-profit organizations such as the 'Drugs for Neglected Diseases Initiative' or the 'Medicine for Malaria Venture'.

Projects involving ZINF members

Project Area A: Preparation, characterization and optimization of agents

A1 Ulrike Holzgrabe
(Institute for Pharmacy and Food Chemistry)
Small molecules for the treatment of infectious diseases

A2 Gerhard Bringmann
(Dept. of Organic Chemistry)
A new class of active agents against infectious diseases

A5 Ute Hentschel-Humeida
(Dept. of Botany II)
Sponge-associated actinomycetes as sources for novel anti-infectives

Project Area B: Interaction with cellular and molecular systems

B2 Joachim Morschhäuser
(Institute for Molecular Infection Biology)
Inhibition of virulence and resistance mechanisms of *Candida albicans*

B3 Heidrun Moll
(Institute for Molecular Infection Biology)
Mitochondria, endosomes and autophagolysosomes as targets of leishmanicidal agents

B5 Knut Ohlsen
(Institute for Molecular Infection)
Drug-induced gene expression in staphylococci and magnetic resonance-based imaging of infections

B7 Caroline Kisker
(Rudolf-Virchow Center)
Structure-based drug design on essential enzymes from pathogens

B8 Markus Engstler
(Dept. of Cell and Developmental Biology)
VSG as an unexpected drug target for sleeping sickness

B9 Thomas Rudel and Vera Kozjak-Pavlovic
(Dept. of Microbiology)
Active agents against acute and disseminating *Neisseria* infections

Central Project

Z1 Tobias Ölschläger
(Institute for Molecular Infection Biology)
August Stich
(Medical Mission Clinic)
Laboratory for the central evaluation of potential anti-infective agents

5.2.
DFG Collaborative Research Centre/ SFB Transregio 34
Pathophysiology of Staphylococci in the Post-Genome Era

Staphylococcus aureus is a dangerous pathogen and a leading cause of bacterial infection in hospitals and in the community throughout the world. This microbe is a prominent example of the current antibiotic resistance crisis, one of the major threats to health in the 21st century. However, *S. aureus* is also a fascinating model organism to study host-pathogen interactions. Humans are exposed to these bacteria often within the first hours of life. These encounters have a multi-facetted outcome, ranging from symptomless colonisation and mild skin infections to life threatening disease. Despite extensive efforts in the field, we still lack an effective vaccine to protect from *S. aureus.* The bacterium is equipped with an impressive assortment of fitness and virulence factors, including a wide variety of immune evasive compounds. Intricate regulation networks enable it to withstand hostile environmental conditions, such as nutrient limitation, oxidative stress or anaerobic conditions. In recent years, *S. aureus* has also been recognised as a facultative intracellular pathogen that can persist inside endothelial and epithelial cells and establish a chronic infection. Transregio 34 addresses multiple dimensions and complexity of this topic by an inter-disciplinary approach and new methodology. It aims to partner bacteriologic and immunologic expertise with quantitative biomolecular analytics, structural biology, genomics, bioinformatics, haematology, and imaging. In the postgenomic era, the availability of whole-genome sequences of *S. aureus* and its human host has paved the way for comprehensive analysis of transcription profiles, proteins and metabolites. It is now possible to obtain biological fingerprints of bacteria and host at unprecedented detail. This opens avenues for a new quality in the understanding of cell physiology, pathophysiology and infection biology. The CRC/TRR34 will focus on host-pathogen interaction during *S. aureus* colonisation and infection, progressing from cell culture systems of increasing complexity to animal models of infection and studies with human subjects.

Projects involving ZINF members

A2 Knut Ohlsen
(Institute for Molecular Infection Biology)
Phosphoproteomic analysis of *Staphylococcus aureus:* Functional characterization of kinases and identification of their substrates

A8 Thomas Dandekar
(Dept. of Bioinformatics)
A systems biology perspective of metabolic and regulatory adaptation of *Staphylococcus aureus* to infection-related conditions

B4 Wilma Ziebuhr
(Institute for Molecular Infection Biology)
Regulation of methionine metabolism in staphylococci: Impact on fitness and virulence

C6 Jörg Vogel
(Institute for Molecular Infection Biology)
Post-invasion events in *Staphylococcus aureus* infected host cells – A combined transcriptomics/ proteomics *in vivo* approach

C11 Thomas Rudel and Martin Fraunholz
(Dept. of Microbiology)
Host cell death induced by *Staphylococcus aureus* and its linkage to phagosomal escape

Z1 Thomas Dandekar
(Dept. of Bioinformatics)
An integrated view of adaptation of *Staphylococcus aureus*

Z3 Knut Ohlsen
(Institute for Molecular Infection Biology)
In vivo imaging of *Staphylococcus aureus* infections

5.3.
DFG Collaborative Research Centre/ SFB Transregio 124
Pathogenic Fungi and their Human Host: Networks of Interaction

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/Transregio brings together researchers from the Friedrich Schiller University and Hans Knöll Institute in Jena and the Research Center for Infectious Diseases in Würzburg to obtain comprehensive insight into the medically important fungi *C. albicans* and *A. fumigatus* and their interactions with the human host. The aims of the CRC/Transregio are to identify pathogenic determinants specific for each fungus and investigate the specific roles of epithelial barriers, the mechanisms of the innate immunity and potential contributions of the adaptive immune system to the pathogenesis of fungal infections. These will form the basis for elucidating the complex mechanisms of fungal infections and identify common principles of fungal pathogenesis. Finally, the insight 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 clinical samples will be available for the analyses and greatly contribute to fulfilling the potential of developing the basic science (bench) to the patient (bedside).

Projects involving ZINF members

A2 Hermann Einsele and Jürgen Löffler
(Dept. of Internal Medicine II)
Interaction of *Aspergillus fumigatus* with human natural killer cells, dendritic cells and human alveolar epithelia

A3 Andreas Beilhack
(Dept. of Internal Medicine II)
In vivo analysis of temporal and spatial disease progres-

sion and immune cell recruitment during invasive *Aspergillus fumigatus* and *Candida albicans* infections

B1 Thomas Dandekar
(Dept. of Bioinformatics)
Modelling interactions between the host and fungal pathogens by combining metabolic pathway analysis and evolutionary game theory

B2 Thomas Dandekar
(Dept. of Bioinformatics)
Interaction networks of signalling molecules and pathways between the pathogenic fungi *Aspergillus fumigatus* and Candida albicans and their human host

C2 Joachim Morschhäuser
(Institute for Molecular Infection Biology)
Regulation of *Candida albicans* virulence traits by protein kinases

C6 Thomas Hünig amd Niklas Beyersdorf
(Institute for Virology and Immunobiology)
Role of secreted *Candida albicans* proteins in immune evasion and pathogenicity

5.4. DFG Research Unit 1680 Unravelling the Prokaryotic Immune System

The CRISPR-Cas system (CRISPR: clustered regularly interspaced short palindromic repeats, Cas: CRISPR-associated) is an adaptive and heritable resistance mechanism against foreign genetic elements. The CRISPR-Cas system consists of clusters of repetitive chromosomal DNA in which short palindromic DNA repeats are separated by short spacers, the latter being sequences derived from the invader. In addition, a set of proteins, the Cas proteins, is involved. The system is somewhat functionally analogous to RNA interference in eukaryotes and it is of great interest to compare the prokaryotic and eukaryotic mechanisms.

CRISPR-Cas ribonucleoprotein complexes target homologous nucleic acids: DNA in case of the bacterial CRISPR interference system and RNA in case of the archaeal CRISPR-RAMP subtype. However, this major difference is only based on observations in a single archaeal species *(Pyrococcus furiosus)* and a few selected bacteria, and a clear link to the respective relevant protein components is so far missing. Furthermore, the identity of the target, and how targeted invading elements are inactivated or even destroyed, remains unknown. Similarly, it is not known how the spacer sequences are acquired and incorporated into the bacterial genome. The CRISPR-Cas system in prokaryotes has some conserved features but seems to be also highly variable. The CRISPR spacer and repeat sequences have different sequences and lengths. The Cas proteins belong to approximately 45 different protein families. For most of these proteins their functional roles are unclear. Moreover, bioinformatic analyses suggest the presence of certain protein components in cyanobacteria and some chloroflexi, which otherwise occur exclusively in archaea. Despite the progress made in understanding CRISPR function, many questions regarding the structure and function of its key components remain to be answered.

The novel approach of this Research Unit is to take seven different bacterial and archaeal organisms to define the common main features of the CRISPR system and to unravel the species-specific unique subsystems using a comparative approach with the help of mass spectrometry, crystallography and bioinformatics.

Projects involving ZINF members

B2 Jörg Vogel
(Institute for Molecular Infection Biology)
A CRISPR/Cas subtype Nmeni/CASS4 system in the human pathogen *Neisseria meningitidis*

5.5. 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 or invasion, intracellular trafficking, compartmentalization and regulation of cell autonomous defense responses. Because immune responses can also be regulated at the level of sphingolipid dynamics, this pathway most likely controls decisive elements in the pathogenesis of infectious diseases where pathogen uptake, spread and dissemination are counteracted by host cell autonomous, innate and adaptive immune responses.
To address the role of sphingolipid dynamics in infection control, the research unit brings together relevant groups from the University of Würzburg and the University of Duisburg-Essen. The unit contains expertise in the infection biology of medically important pathogens such as measles virus (MV), *Neisseria meningitidis, Neisseria gonorrhoeae* and *Mycobacterium tuberculosis,* sphingolipid biology in infectious viral and bacterial disease pathogenesis, T cell biology and immunotherapy as well as macrophage biology.

The unit will focus on the regulatory role of sphingolipid dynamics in both the host and pathogen. This includes regulating the adhesion, activation, and differentiation and effector functions of T cells at a molecular and cellular level as well as in experimental infection models. In addition to the effect of sphingolipid dynamics on pathogen adhesion and invasion, trafficking and modulation of host cell functions essential in the control of bacterial pathogens will be analysed.

Projects involving ZINF members

TP1: Sibylle Schneider-Schaulies
(Institute for Virology and Immunobiology)
Sphingomyelinase activation in T cells: Implications for T cell activation and paralysis

TP2: Niklas Beyersdorf and Jürgen Schneider-Schaulies
(Institute for Virology and Immunobiology)
Role of sphingolipids in the regulation of anti-viral T cell responses

TP3: Alexandra Schubert-Unkmeir
(Institute for Hygiene and Microbiology)
Analysis of the functional relevance of sphingomyelinases and ceramide in meningococcal pathogenesis

TP4: T. Rudel *(Dept. of Microbiology)*
Sphingolipids in gonococcal infection

5.6. DFG Priority Program SPP 1316 Host-adapted Metabolism of Bacterial Pathogens

Pathogens encounter many different environments during the infection process. To survive and replicate within a host cell, pathogens must adapt their metabolism to the available nutrients and physical conditions. During this time they must also coordinate their metabolism with their life-cycle. Therefore, to understand how bacteria adapt to the host environment and cause disease, it is not sufficient to understand the function of specific virulence determinants such as toxins or invasins. It is clear that the co-evolution of host and pathogen has also resulted in an adaptation of the metabolism of the pathogen. Researchers within SPP1316 will investigate how bacterial pathogens adapt their metabolism during colonization of host organisms, how the metabolism of pathogenic bacteria and the host organism is interconnected and which mechanisms of control are active. Projects in this SPP thus aim to identify metabolic pathways that are important for the bacteria during infection and to determine the metabolic fluxes. This will reveal the metabolic reactions of the host organisms and the genetic mechanisms of metabolic adaptation.

Projects involving ZINF members

Thomas Dandekar *(Dept. of Bioinformatics)*
Modeling metabolism in bacterial infections

Thomas Dandekar *(Dept. of Bioinformatics)*
Modeling metabolism in intracellular infections comparing *Salmonella* and *Listeria*

Thomas Dandekar *(Dept. of Bioinformatics)*
Metabolism of intracellular *Salmonella enterica:* One lifestyle in intra-cellular infections

Christoph Schoen *(Institute for Hygiene and Microbiology)*
Gene regulatory mechanisms of metabolic adaptation in *Neisseria meningitidis* in *ex vivo* infection models

Jörg Vogel *(Institute for Molecular Infection Biology)*
A post-transcriptional link between *Salmonella* metabolism and virulence

5.7. DFG Priority Program SPP 1617 Phenotypic Heterogeneity and Sociobiology of Bacterial Populations

The DFG-funded Priority Program SPP1617 brings together microbiologists from all fields of bacteriology (e.g., infection biology, terrestrial microbiology, biotechnology etc.) with theoreticians from the mathematical and physical sciences. In a combined interdisciplinary effort, SPP1617 aims at a deeper understanding of the complexity of bacterial populations and the theoretical modelling and prediction of their diversity. Focal point of the research is the generation of phenotypic variation in bacterial communities, the evolutionary mechanisms that gave rise to genotypes expressing diverse phenotypes as well as the biological significance of the process. Individual projects cover cell-cell communications and the production of common goods, the division of labour as well as bet-hedging strategies in bacteria of medical, biotechnological and ecological interest.

Projects involving ZINF members

Daniel Lopez *(Research Centre for Infectious Diseases)*
Molecular characterization of the cell types required for the development of *Staphylococcus aureus* biofilms

Wilma Ziebuhr *(Institute for Molecular Infection Biology)*
Heterogeneous gene expression, metabolic variability and differentiation in *Staphylococcus epidermidis* biofilms

5.8. DFG Priority Program SPP 1784 Chemical Biology of Native Nucleic Acid Modifications

Natural covalent nucleic acid modifications form a new hidden layer of information in the genetic code beyond the classical four letter alphabet. The Priority Program was established to unravel this code. A network of researchers with backgrounds in chemical biology, structural biology, enzymology and bioinformatics will gain deeper insight into where, how and why native nucleic acid modifications occur and how they influence cellular processes. Prospective participants will address current challenges in detection, localization, recognition, and function of naturally occurring modifications in RNA and DNA. Modifications as defined in the program, are specifically introduced to the nucleic acid by cognate enzymes, and do not include chemical lesions, DNA or RNA damages inflicted by light, reactive oxygen species, chemicals, and the like.

Projects involving ZINF members

Cynthia Sharma *(Research Centre for Infectious Diseases)*
Identification and functional characterization of pseudouridine in mRNAs and non-coding RNAs of the bacterial human pathogen *Campylobacter jejuni*

Jörg Vogel *(Institute for Molecular Infection Biology)*
Discovery & characterization of RNA modifications in a bacterial pathogen

5.9. DFG German-African Cooperation Projects in Infectiology

The DFG funds joint research projects between scientists in Germany and Africa investigating infectious diseases and their social implications. The program focuses on the investigation of neglected infectious diseases in humans and animals but also research on topics of their social and economical impact.

African Sleeping Sickness is a deadly neglected disease. Transmitted by the infamous tsetse fly, the unicellular trypanosomes not only infect humans, but also sheep, goat and cattle. The socio-economic burden in sub-Saharan Africa is enormous. The few drugs available are ancient and highly toxic. Furthermore, diagnosis is very difficult. Although trypanosomes are widely ignored as infectious agents, the parasites have become a model system for molecular cell biologists. The main reason for the attention trypanosomes have received in the past decades is their ability to adapt to very diverse environments, such as the mammalian circulation or the fly midgut. In host blood, trypanosomes evade the immune response through antigenic variation of their cell surface, which consists of a dense layer of variant surface glycoproteins (VSG). A second mechanism that allows trypanosomes to prosper in blood was discovered in the course of the current project: the parasites remove antibodies from the cell surface by exploiting hydrodynamic flow, which acts on the cell surface as the result of incessant, directional motility. In this way, antibody-bound VSGs are dragged against the swimming direction towards the posterior end of the cell, where the flagellar pocket, which harbours the unusually processive endocytosis machinery, is located. The antibodies are internalized and transported to the lysosome for destruction. The aim of our cooperative research project is to unravel the role of antibody removal as a trypanosome virulence factor. The first funding period had a strong capacity building aspect. We equipped our partner laboratory at ICIPE in Nairobi and established reliable and solid logistics. Since experimental animal infections are crucial for the success of our endeavour, we teamed up with KARI-TRC at Muguga, Kenya. During the next funding period we will focus on the role of various trypanosome morphotypes and cell cycle stages found in the course of natural infections. For this, we will not only apply modern techniques such as RNA-seq, electron tomography and dSTORM, but also conduct fieldwork in remote endemic regions in Kenya, Uganda and the Congo.

Projects involving ZINF members

Markus Engstler *(Dept. of Cell and Developmental Biology)*
Antibody clearance as a virulence factor in African sleeping sickness

5.10. BMBF Medical Infection Genomics

The funding initiative "Medizinische Infektionsgenomik" (Medical Infection Genomics) is a research program financially supported by the Federal Ministry of Education and Research (BMBF). It consists of eleven research clusters that focus on genome research of pathogenic microorganisms. During the funding period from 2011 to 2013 the participating groups of the Medical Infection Genomics network have focused on human pathogenic bacteria that are of high socioeconomic relevance for the public health system in Germany. This is especially the case for those that are widely disseminated in hospitals or that pose a particular threat for the public health system due to their high rate of antibiotic resistance or their high virulence potential. Examples of the pathogens studied in the network include, *Escherichia coli, Pseudomonas aeruginosa, Enterococcus faecali, Salmonella typhimurium, Chlamydia trachomatis Mycobacterium tuberculosis, Legionella pneumophila Helicobacter pylori, Streptococcus pneumonia* and *Neisseria meningitidis.*

The eleven research clusters aim for a comprehensive understanding of the infectious agents and their adaptation to the human host during the infection process. By unravelling the complex interactions between the pathogen and the human host the ultimate goal of the funding initiative is to provide the basis for further improving the prevention, diagnosis and therapy of infectious diseases. The Medical Infection Genomics network is coordinated by Prof. Matthias Frosch, head of the Institute for Hygiene and Microbiology at the University of Würzburg.

Projects involving ZINF members

Matthias Frosch *(Institute for Hygiene and Microbiology)*
Central management of the Medical Infection Genomics consortium

Thomas Rudel *(Dept. of Microbiology)*
Pathogen host interactomes and signaling complexes in bacterial infections

Ulrich Vogel *(Institute for Hygiene and Microbiology)*
Proteomics of meningococci and pneumococci – from *in vitro* biofilms to *in vivo* infection

Jörg Vogel (Institute for Molecular Infection Biology)
Next generation transcriptomics for bacterial infections

5.11. BMBF MedVet-Staph
Interdisciplinary Research Network on the Zoonotic Impact of Staphylococcus aureus/MRSA

Staphylococcus aureus, including methicillin-resistant *S. aureus* (MRSA) are major human and zoonotic pathogens. Recently, certain defined MRSA clonal lineages were found to spread in industrialized animal husbandry. These livestock-associated (LA)-MRSA were detected in food-producing animals and food samples, but they also occur as colonizers in companion animals and humans. LA-MRSAs have a significant potential to cause disease and they add to the increasing burden of healthcare associated infections in Germany. The MedVetStaph consortium brings together the expertise of microbiologists, infectiologists, epidemiologists and veterinarians to study the epidemiology, molecular biology and ecology of LA-MRSA. The goal of the programme is to provide policy makers and public health authorities with solid scientific data to implement efficient intervention and control measures to contain the further spread of these bacteria.

Projects involving ZINF members

Wilma Ziebuhr *(Institute for Molecular Infection Biology)*
Influence of antibiotic resistant staphylococcal species on persistence and dissemination of LA-MRSA

5.12. The Bavarian Research Network for Molecular Biosystems (BioSysNet)

In the past, scientists have studied individual genes and gene products, leading to a detailed mechanistic understanding of the functions within living cells in health and disease. Recently, new systemic methods have become available that significantly extend these classical approaches. They have made it possible to sequence entire genomes, to identify most gene products in living cells, and to map interaction networks between components of living systems. This has led to the founding of a new research field called molecular systems biology or molecular systems research. This new research field requires a high level of interdisciplinarity, involving geneticists, molecular biologists, structural biologists, mathematicians and bioinformaticians. It provides a means to answer fundamental and complex biological questions and provides insight into the inner workings of cells and revealing the molecular mechanisms that generate and maintain living systems.

The Bavarian State Ministry of Sciences, Research and the Arts established the Bavarian Research Network for Molecular Biosystems at the end of 2011, as part of its effort to strengthen research, innovation and technology in Bavaria. The objective for the network is to bring together local expertise in systems biology within Bavaria to obtain a holistic view of living cells. The network comprises of 24 groups and supports five new, independent junior researchers in developing their own independent research programs as well as established junior and senior groups with interests in molecular biosystems.

Projects involving ZINF members

Ana Eulalio *(Institute for Molecular Infection Biology)*
RNA: the missing link in bacterial pathogen-host interactions

Cynthia Sharma *(Research Centre for Infectious Diseases)*
Exploring RNA-binding proteins in *Campylobacter jejuni*

Jörg Vogel *(Institute for Molecular Infection Biology)*
Temporal control of gene expression by small RNAs

5.13. ERA-NET

Infectious diseases (ID) cause tens of thousands of deaths each year in Europe. Despite all the measures taken to address ID, different factors have contributed to recent challenges: (i) the threat of emerging ID (16 new and 5 re-emerging infectious diseases were identified in the last 2 decades - NIH), (ii) mass migration, global travellers and growth of congested urban slums, (iii) misuse and overuse of antibiotics, (iv) co-infection with at least two pathogens. Hence, continuous global effort and novel avenues of research are required to decipher the role of the new factors in the development of ID.

Through this initiative, ERA-NET partners aim to understand all basic aspects of complex human infection biology questions such as co-infection that are not limited to specific pathogens, the cross-talk between host and pathogens, as well as the relationship between microbial environment and infection. The ERA-NET consortium funds high quality and cutting edge transnational and translational research bringing together basic, applied, technology-driven and clinical research approaches to a broad variety of topics regarding human infectious diseases.

Networks involving ZINF members

PathoGenoMics

Herman Einsele *(Dept. Internal Medicine II)*
Invasive aspergillosis: Biomarkers for prevention, diagnosis and treatment Response (aspBIOmics)

Invasive aspergillosis (IA) is the most detrimental infection in patients with haematological malignancies. Although IA may be perceived to be an uncommon disease with an incidence of 10,000 patients annually in Europe, there is increasing evidence that IA is affecting a broader range of patients. In addition, IA is the most expensive opportunistic infection in immunosuppressed patients; the annual cost in Europe is >100 million Euro. A major problem in the management of IA is the poor diagnosis. Therefore, the network aspBIOmics aims to evaluate a battery of *in vitro* assays for a comprehensive multimodality analysis, combining the detection of *Aspergillus fumigatus* elements (DNA, RNA, polysaccharides, proteins), host factors and the individual genetic susceptibility of the patients. The advance of this combined approach will be the availability of a panel of biomarkers incorporated into rapid and sensitive *ex vivo* assays. For the first time, a multi-parameter diagnostic strategy is undertaken to target IA. This strategy has the potential to identify patients who are at highest risk of IA before the infection occurs. Consequently, effective tailored prophylaxis can be administered and the success of antifungal therapy can be monitored.

ERA-NET

Thomas Dandekar *(Dept. of Bioinformatics)*
Systematic identification of antifungal drug targets by a metabolic network approach (AspMetNet)

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

Thomas Rudel *(Dept. of Microbiology)*
Co-infection as a cause of ovarian cancer (CINOCA)

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

Cynthia Sharma *(Research Center for Infectious Diseases)*
Ana Eulalio *(Institute for Molecular Infection Biology)*
Combining high-throughput and single-cell analyses to study RNA regulators important in the early steps of *Campylobacter* infection (CampyRNA)

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

Lars Dölken *(Dept. of Virology)*
Early Determinants of DNA-Virus Lytic or Latent Infection (eDEVILLI)

Severe disease caused by herpes viruses typically does not surface during the initial infection of the otherwise healthy host, but rather when the virus reactivates from latency in immunocompromised individuals, such as organ transplant recipients and AIDS patients. Understanding the mechanisms that contain viral infection and push the virus into latency immediately upon infection may enable their use for life-saving preventive and therapeutic measures. The eDEVILLI consortium focuses on the characterization of the molecular mechanisms, which define whether a DNA virus infection will result in latency or in lytic infection. By combining a systems biology approach with cutting edge genetic manipulation of both the host cell and the virus we will define the host and the viral factors that bind to viral genomes immediately upon infection and shape the decision whether an incoming virus will trigger the lytic cycle, or if it will remain latent.

Jörg Vogel *(Institute for Molecular Infection Biology)*
The nice bug: Commensalism versus disease - Asymptomatic carriage or urosepsis

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

Daniel Lopez *(Research Centre for Infectious Diseases)*
Ana Eulalio *(Institute for Molecular Infection Biology)*
Intracellular *Staphylococcus aureus:* deciphering bacterial and cellular factors involved in host cell invasion by clinically relevant strains to define new therapeutic approaches (StaphIN)

Staphylococcus aureus (S. aureus) infections represent a major health problem in both hospital and community settings. *S. aureus* ability to fight antimicrobial therapies is associated with its capacity to form biofilms and to acquire resistance to conventional antibiotics. This consortium will perform a systematic analysis of a large collection of *S. aureus* clinical isolates to assess the ability of the different strains to invade, replicate and persist within host cells. In addition, bacterial and host factors relevant for *S. aureus* intracellular lifestyle will be characterized. The ultimate goal is to exploit the acquired knowledge to develop therapeutic strategies, with impact on the prevention and/or treatment of persistent nosocomial infections.

5.14. 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 7 major clinical trials, three of which are already underway, and 3 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)

5.15. National Reference Laboratory for Meningococci and *Haemophilus influenzae*

The National Reference Laboratory (NRL) for meningococci and *Haemophilus influenza* is hosted at the Institute for Hygiene and Microbiology at the University of Würzburg and is headed by Matthias Frosch and Ulrich Vogel. The NRL has been commissioned by the Robert Koch Institute to conduct representative laboratory surveillance of invasive meningococcal disease and invasive infections caused by *Haemophilus influenzae* in Germany. Laboratory surveillance of both infectious agents is performed in close collaboration with the Robert Koch Institute. 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 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. 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. It analyzes the strain coverage of meningococcus B vaccines. Annual reports for both infectious agents are available at http://www.nrzmhi.de/. A geographic information system can be accessed at www.episcangis.org.

5.16.
The Consulting Laboratory for Echinococcosis

The Robert Koch Institute appoints the consulting laboratory for echinococcosis every second year for consultation, quality management and development of diagnostic procedures. The Institute for Hygiene and Microbiology has hosted 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 the following services:

1. Information regarding the prevention and epidemiology of different types of echinococcosis.
2. Information on the diagnosis, differential diagnosis, and therapy.
3. Detection of antibodies against *Echinococcus multilocularis* and *E. granulosus* in human sera.
4. Microscopy of cyst aspirates, sputa and other liquid samples as well as solid tissue obtained at surgery for echinococcal structures.
5. Parasitological analysis of stained and covered microscopic slides for echinococcal structures and differentiation of the parasite.
6. Detection of echinococcal DNA by PCR (after consultation with the treating physician).

There is a close connection of the consulting laboratory and the research group of Klaus Brehm of the Institute for Hygiene and Microbiology, who investigates the host parasite relationship of alveolar echinococcosis. The consulting laboratory is available online at http://www.echinococcus.de.

5.17.
IBD-labnet
Coordination of Activities for Laboratory Surveillance of Invasive Bacteria Diseases

The European Centre for Disease Prevention and Control (ECDC) has funded the IBD-labnet since September 2008 within the framework of the program "Laboratory surveillance and external quality assurance of invasive bacterial diseases in EU" and since October 2011 the follow-up program "Coordination of Activities for Laboratory Surveillance of Invasive Bacteria Diseases."

The IBD-labnet is coordinated by Matthias Frosch from the Institute for Hygiene and Microbiology and aims to harmonize the laboratory surveillance of invasive bacterial diseases caused by *Neisseria meningitidis, Haemophilus influenza* and *Streptococcus pneumoniae* in Europe and EEA/EFTA countries.

The critical importance of valid and accurate typing data for comparability of surveillance data means that a key objective of the laboratory network is the standardization and harmonization of typing methods. The members of this consortium, the National Reference Laboratories for *N. meningitidis, H. influenzae* and *S. pneumonia,* are also supported in the strengthening of their laboratory capacity to accurately characterize the invasive isolates. Therefore, the IBD-labnet assists the participating National Reference Laboratories to continuously improve their laboratory performance in the identification and characterization of *N. meningitidis, H. influenzae* and *S. pneumonia* as well as the implementation of new techniques for routine work.

The major activities of the IBD-labnet include:
1. The assessment of the laboratory performances by the distribution of external quality assurance exercises.
2. The improvement of the laboratory performances by the organisation of training workshops or exchange programs.
3. The harmonization of methods for antimicrobial susceptibility testing, interpretation and reporting for *N. meningitidis, H. influenzae* and *S. pneumoniae.*
4. The standardization and harmonization of methods for DNA-based serotyping and molecular typing of *S. pneumoniae.*
5. The establishment of a European meningococcal strain collection.

5.18.
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.

Projects involving ZINF members

Klaus Brehm *(Institute for Hygiene and Microbiology)*
Functional genomics in *Echinococcus multilocularis*

5.19.
Deutsches Zentrum für Infektionsforschung (DZIF):
Prophylactic Application of Escalating Doses of Donor-derived Central Memory T-Lymphocytes (Tcm) after Allogeneic Hematopoetic Progenitor Cell Transplantation (HPCT) to Prevent Infectious Complications (PACT): A Prospective, First in Man, Open Phase I/IIa Clinical Trial

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

5.20.
Interdisciplinary Centre for Clinical Research (IZKF)

The IZKF Würzburg organizes the Medical Faculty's internal funding for research. It was founded in 1996 within the federal advancement program 'Health Research 2000" of the Federal Ministry of Education and Research. Since 2004, it has been entirely funded by the Free State of Bavaria. Its major goal is the strengthening of clinical research through interdisciplinary cooperation between clinical research and basic research in the biomedical sciences. In 2013, its funding volume was approx. 5 Mio. Euro.

The IZKF supports interdisciplinary clinically relevant research at the university through three main programs:

- Research project grants within defined scientific areas.
- The promotion of young researchers in medicine through the establishment of IZKF Junior Research Groups.
- Infrastructure development through the establishment of core facilities and instrumentation.

The funding decisions are based on peer review methods and transparent fund management on three different levels:
- The general assembly („Zentrumskonferenz").
- The executive board, which is responsible for decisions on funding requests.
- The External Scientific Advisory Board, which plays an active role in the center's activities and participates in the assessment of each project proposal.

The aim of IZKF-project grants is to facilitate interdisciplinary research between groups at the university and to enable the funding of research into new topics within the focus of the medical faculty. Cooperation between clinical researchers and basic researchers in biomedicine is a precondition for a successful grant application. After up to three years of an IZKF-promotion it is expected to transfer the projects into external third-party funding.

The IZKF-Junior Career Program aims to support young independent researchers in merging clinical and biomedical research at the earliest possible stage of their medical career. Together with the direct Junior Career Programs, the IZKF also supports young and motivated scientists of the Medical Faculty with IZKF-research grants.

In order to enhance the local infrastructure, the IZKF has established several Core Facilities. Those with specific relevance to infectious disease research include:
- The core facility 'Microarray-Unit' was established in 2001 and broadened the spectrum of services as the "IZKF-Service Unit for Microarray applications and bioinformatic analysis of high throughput methods". In 2013, it was incorporated into the Core Unit 'Systems Medicine' which is co-financed by the Medical Faculty. It is a service partner for high throughput techniques for researchers at the University and the University Clinics.
- The IZKF extended support for the "Centre for Experimental Molecular Medicine (ZEMM)" which allows IZKF members access to the ZEMM's central animal management.
- The IZKF has also recently established the "Service Unit for confocal microscopy and flow cytometry-based cell sorting".

Projects Involving ZINF members

Andreas Beilhack *(IZKF, Dept. of Internal Medicine II)*
Targeting essential transcriptional pathways to disrupt fungal infection.

Hartwig Klinker (*Dept. of Internal Medicine II*) and
Axel Rethwilm *(Institute for Virology and Immunobiology)*
Therapeutic drug monitoring in the therapy of HIV and HCV infections

Christian Perez *(IZKF)*
Candida-host interactions

Sibylle Schneider-Schaulies
(Institute for Virology and Immunobiology)
HERV and immune reactions during pregnancy

Cynthia Sharma *(ZINF)*, Heike Walles (*Dept. Tissue Engineering and Regenerative Medicine)*, Jürgen Löffler (*Dept. of Internal Medicine II)*
New infection models based on tissue engineering for the human pathogens *Helicobacter pylori* and *Campylobacter jejuni*

5.21. Graduate School of Life Sciences (GSLS)

For many years the Faculties of Medicine and Biology at the University of Würzburg have offered high-level structured graduate training. This culminated in the foundation of the International Graduate School (IGS) by the University Senate in 2003 and the University of Würzburg Graduate Schools (UWGS) in 2006, which ensured common graduation standards and rules for all graduate schools. The Graduate School of Life Sciences (GSLS) was successful in its application to the "Excellence Initiative of the Federal and State Governments" and obtained funds to support fellowships and other activities within the GSLS. In addition to the section Biomedicine and the MD/PhD program three further sections, i.e. Infection and Immunity, Neuroscience and Integrative Biology, were founded.

The Graduate School of Life Sciences (GSLS) is the largest and most strongly integrated graduate school at the University of Würzburg after the successful implementation of programs from the Excellence Initiative application.

The GSLS now houses doctoral researchers of all collaborative research programs – such as the DFG-funded collaborative research centers ("Sonderforschungsbereiche"), research training groups ("Graduierten-kollegs") and clinical research groups ("Klinische Forschergruppen"), as well as other collaborative pro¬grams funded by the Federal Ministry of Education and Research (BMBF), the European Union and other sources. The school is currently divided into five separate sections, Biomedicine, Infection and Im-munity, Neuroscience, Integrative Biology and Clinical Sciences. Each section usually comprises different programs of about 15 to 25 doctoral researchers. These programs are the scientific as well as social "home" of the doctoral researchers.

A special fellowship program of the GSLS is the core element of funding by the Excellence Initiative. So far 111 fellows from 25 different countries have been supported by the GSLS. The number of GSLS members has risen to more than 220 principal investigators from all participating faculties. In 2015 the number of doctoral researchers registered in the doctoral study program "Life Sciences" rose to more than 360. Since the MSc program FOKUS Master Life Sciences has been introduced in the winter term 2012/13 31 students have been admitted. In the meantime, 12 students have finished. In the Postdoc Plus program, 15 postdoctoral researchers have successfully applied for the GSLS research grants. Five manuscripts have been accepted for publication and four grant applications have been prepared. Since 2013, 86 MD students have registered in the GSLS; in 2016 the first students are expected to graduate.

Key elements of training in the Graduate Schools

- The traditional single supervisor ("Doktorvater") is replaced by a thesis committee of three principal investigators (PIs).
- A panel of training activities is offered, from which an individual program is tailored to each doctoral researcher.
- Doctoral researchers actively participate in the program by offering and organizing courses and symposia.
- A set of requirements has to be met to warrant a common quality standard.

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

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

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

Section Infection and Immunity
Section Speakers:
Thomas Hünig *(Chair of Immunology)*
Joachim Morschhäuser *(Institute for Molecular Infection Biology)*

The topic "Infection and Immunity" represents an internationally recognized major research focus of the University of Würzburg.

Strong interdisciplinary bonds between the Faculties of Medicine, Biology, and Chemistry & Pharmacy are hallmarks of this research field in Würzburg. Scientists from the participating faculties cover all the relevant disciplines and methodological approaches in infectious disease research. The network of researchers in the section "Infection and Immunity" however also explores such -seemingly- quite different phenomena as the genesis and control of cancer or aspects of symbiosis in plant biology. The scientific program spans research on host-pathogen interactions, genome research in pathogenic microbes, identification and characterization of novel anti-infectives, molecular processes of immune response in various host organisms including humans, mechanisms of tumorigenic processes induced by microbes, and new concepts in immune therapy. This comprehensive coverage of topics will guarantee the broadest possible training for doctoral researchers, yet provide a focus on common and converging mechanisms.

5.22. Graduate School (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 we aim to develop and apply novel human 3D infection models based on engineered human tissues.

Within this project, scientists from different disciplines take a novel route to investigate microbial infections under close-to-natural conditions. Host-microbe interactions are investigated in engineered three-dimensional (3D) human tissues. The planned application of next generation analysis technology (e.g. single cell and dual RNA-Seq; super-resolution imaging; gene silencing in primary cells) will enable us to gain unprecedented insights into the molecular mechanisms underlying human infections.

Such advanced research combining complex primary infection models and next-generation technologies at the highest level requires the education of a new generation of scientists familiar with the underlying principles and applications of these techniques. Therefore, the interdisciplinary training of the PhD students in state-of-the-art and emerging technologies together with continuous scientific exchange are the key elements of this Research Training Group.

The GRK 2157 integrates the long-standing expertise in infectious diseases at the University of Würzburg and new technologies into an exciting new focus on 3D human tissue models. We expect to develop integrated concepts relating to the mechanisms by which microbes overcome different infection barriers in humans. The repertoire of pathogens includes measles virus, different bacterial pathogens and trypanosomes. Understanding the key events of natural infections will form a basis to design new preventive and therapeutic strategies to combat infectious diseases.

Focus of research
We aim 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. Our approach fosters the study of infections in 3D human tissue models reflecting the natural infection site in humans. 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 will be utilized for infection experiments with selected human-specific microbes (*Chlamydia, Neisseria, Campylobacter, Bordetella, Salmonella, Trypanosoma* and *measles virus)*.

We plan to 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 consists of more than one cell type, and certain cell types may be selectively engaged during traversal of microbes through infection barriers such as the epithelial layer. Moreover, individual cells within natural tissues 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 for two general read-outs: 1) bioimaging (super-resolution fluorescence imaging, dSTORM, PALM, in vivo fluorescence imaging, BLI etc.), and Raman Spectroscopy will be used to obtain overall optical and physical information of cell behaviour; 2) single- and multi-cell next-generation RNA- and DNA-sequencing combined with bioinformatics analysis will provide information on gene expression changes during the course of infection.

Besides the discovery of the basic principles of infections and validation or disproval of data generated with "classical" model systems, the identification of infection-induced signalling pathways, changes in cellular trafficking, cell-cell transmission or other infection related phenotypes will likely yield new targets for the development of therapeutic strategies to protect from or combat bacterial, parasite and viral infections.

All students will work on interdisciplinary scientific projects. To provide them with a sound intellectual foundation the thesis committee will develop an individual education program for students during their graduate training. This will result in a tailored, broad and comprehensive education of each student.

Projects involving ZINF members

Project 1:
Andreas Beilhack *(IZKF, Dept. of Internal Medicine II)* and Markus Sauer *(Dept. of Biotechnology & Biophysics)*
Host-pathogen interactions revealed by 3D high-resolution microscopy

Project 2:
Thomas Rudel *(Chair of Microbiology)* and Thomas Dandekar *(Dept. of Bioinformatics)*
Host factors required for the initiation and propagation of *Chlamydia trachomatis* infections

Project 3:
Vera Kozjak-Pavlovic and Thomas Rudel *(Dept. of Microbiology)*
Bacterial and host cell factors important for the invasion and dissemination of *Neisseria gonorrhoeae*

Project 4:
Alexandra Schubert-Unkmeir *(Institute of Hygiene and Microbiology)*
Meningococcal ligands and molecular targets required for adhesion and penetration of the blood-cerebrospinal fluid barrier under shear stress

Project 5:
Cynthia Sharma *(Institute for Molecular Infection Biology)*
Virulence factors and regulators required during *Campylobacter jejuni* infections

Project 7:
Sibylle Schneider Schaulies *(Institute for Virology and Immunobiology)*
Membrane and protein microdomains governing measles virus transmission at entry and exit interface

Project 8:
Jörg Vogel *(Institute for Molecular Infection Biology)* and Heike Walles *(Dept. of Tissue Engineering and Regenerative Medicine)*
Establishing a human intestinal tissue model to study host and pathogen determinants that restrict *Salmonella enterica* infection

Project 9:
Markus Engstler *(Dept. of Cell and Developmental Biology)*
Development of tsetse fly-transmitted African trypanosomes in human skin tissue models

5.23. Core Unit for Systems Medicine

To obtain a holistic view of a biological system requires high-throughput technologies such as mass-spectrometry for proteomics and metabolomics, next-generation RNA and DNA sequencing and high-content screening platforms. The large quantities of data generated by these methods can be integrated and used to model biological entities in a global fashion. While such approaches open doors to new insights they require additional expertise to handle devices and to establish necessary protocols as well as to computationally evaluate the data. Due to these requirements the hurdle to establish one or more high-throughput methods is rather high for a single research group. To lower this barrier the Medical Faculty at the University of Würzburg has decided to create a central institution that can assist such groups by providing access to the necessary instruments and expertise. For this purpose the Core Unit Systems Medicine was founded in 2013 and is located at the Institute of Molecular Infection Biology.

As a joint institution the Core Unit Systems Medicine provides its services to research groups of the University and the University Hospital. Consulted by a steering committee, it will continue to expand its portfolio of high-throughput methods based on requests of the local research community.

06

APPENDIX

6. APPENDIX
6.1. ALUMNI YOUNG INVESTIGATOR GROUP LEADERS

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.

FORMER YOUNG INVESTIGATOR GROUP LEADERS

HEIDRUN MOLL
CURRENT POSITION
C3-Professorship at the University of Würzburg
Institut für Molekulare Infektionsbiologie

RESEARCH AT THE ZINF
1993 – 1999
Pathogenicity of *Leishmania*

MICHAEL LANZER
CURRENT POSITION
C4-Professorship at the University of Heidelberg
Universitätsklinikum Heidelberg
Hygiene-Institut/Abt. Parasitologie

RESEARCH AT THE ZINF
1994 – 1999
Pathogenicity of human malaria parasites

JOACHIM MORSCHHÄUSER
CURRENT POSITION
C3-Professorship at the University of Würzburg
Institut für Molekulare Infektionsbiologie

RESEARCH AT THE ZINF
1997 – 2000
Pathogenicity of *Candida*

JOACHIM REIDL
CURRENT POSITION
Professorship at the University of Graz
Karl Franzens Universität Graz

RESEARCH AT THE ZINF
1996 – 2003
Virulence of Gram-negative bacteria

KATJA BECKER
CURRENT POSITION
C4-Professorship at the University of Gießen
IFZ-Biochemie der Ernährung des Menschen

RESEARCH AT THE ZINF
1999 – 2000
Malarial parasites as targets for the development of antiparasitic drugs

KLAUS ERB
CURRENT POSITION
Head of Dept. Allergologie und Immunologie
Department of Pulmonary Research, Boehringer Ingelheim Pharma GmbH & Co. KG

RESEARCH AT THE ZINF
1999 – 2004
Immunology of intracellular pathogens and allergic disorders

MATTHIAS LEIPPE
CURRENT POSITION
C4-Professorship at the University of Kiel
Zoologisches Institut, Abteilung Zoophysiologie
Christian-Albrechts-Universität

RESEARCH AT THE ZINF
2001 – 2003
Molecular Parasitology

CHRISTOF HAUCK
CURRENT POSITION
W3-Professorship at the University of Konstanz
Lehrstuhl für Zellbiologie

RESEARCH AT THE ZINF
2001 – 2006
Pathogen-host communication

SVEN HAMMERSCHMIDT
CURRENT POSITION
W3-Professorship at the University of Greifswald
Interfakultäres Institut für Genetik
und Funktionelle Genomforschung

RESEARCH AT THE ZINF
2003 – 2007
Pathogenicity of *Streptococcus pneumoniae*

UTE HENTSCHEL
CURRENT POSITION
W3-Professorship at the Helmholtz Center
for Ocean Research Kiel
Marine Microbiology, GEOMAR

RESEARCH AT THE ZINF
2004 – 2008
Novel Antiinfectives

ANN-KRISTIN MÜLLER
CURRENT POSITION
Group Leader at the Department of Parasitology
Universitätsklinikum Heidelberg
Hygiene-Institut Abt. Parasitologie

RESEARCH AT THE ZINF
2007 – 2008
Biology of rodent malaria parasites

GABRIELE PRADEL
CURRENT POSITION
W2-Professorship at the RWTH Aachen
Institut/Abt RWTH-InstitutInstitut für Molekulare Biotechnologie

RESEARCH AT THE ZINF
2005 – 2011
Malaria: Transmission blocking strategies

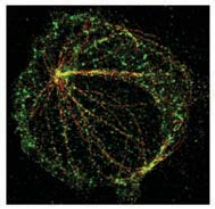
SVEN KRAPPMANN
CURRENT POSITION
W2-Professorship at the University of Erlangen
Klinische Mikrobiologie und Immunologie

RESEARCH AT THE ZINF
2005 – 2012
Aspects of *Aspergillus fumigatus* pathogenicity

DANIEL LÓPEZ
CURRENT POSITION
Tenured Scientist Group Leader at the Dept. of Microbial Biotechnology, Spanish National Centre for Biotechnology (CNB), Madrid

RESEARCH AT THE ZINF
2010 – 2015
Bacterial cell differentiation

6. APPENDIX
6.2. MEETING WORKSHOPS ORGANIZED BY ZINF MEMBERS 2014-15

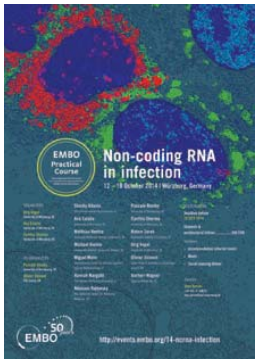


8th Joint Ph. D. Students Meeting of SFB630, SFB 766 and FOR854 "New Trends in Infectious Disease Research"
Retzbach, 15–17 December 2015

CSHL Asia "Bacterial Infection and Host Defense"
Jörg Vogel (Institute of Molecular Infection Biology)
Suzhou, China, 2–6 November 2015

Bavarian Academy of Sciences and Humanities Workshop "High-Throughput and Single Cell Approaches in Infection Biology"
Cynthia Sharma (Research Centre for Infectious Diseases)
Munich, 22–23 October 2015

EMBO Symposium "The Non-Coding Genome"
Jörg Vogel (Institute of Molecular Infection Biology)
EMBL Heidelberg, 18–21 October 2015

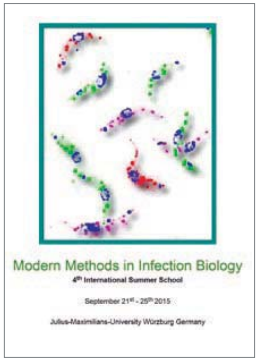


4th International Summer School "Modern Methods in Infection Biology"
Thomas Dandekar (Chair of Bioinformatics)
Würzburg, 21–25 September 2015

ICAAC Symposium "RNA in infection pathogenesis"
Jörg Vogel (Institute of Molecular Infection Biology)
San Diego, 17–21 September 2015

13th European Meningococcal Disease Society Meeting
Ulrich Vogel (Institute for Hygiene and Microbiology)
Amsterdam, 15–17 September 2015

Gordon Research Conference "Microbial Adhesion & Signal Transduction"
Jörg Vogel (Institute of Molecular Infection Biology)
Newport, 26–31 July 2015

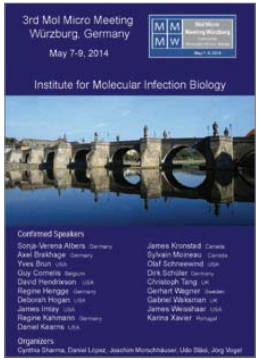


Final Symposium "Best of SFB 630 - and Future Perspectives"
Gerhard Bringmann, Ulrike Holzgrabe (Collaborative Research Centre 630)
Würzburg, 22 July 2015

SphingoFOR 2123 "Workshop Sphingolipids in infection control and beyond"
Sibylle Schneider-Schaulies (Institute for Virology and Immunobiology)
Würzburg, 25–26 June 2015

DFG German African Cooperation "Projects in Infectiology"
Markus Engstler (Chair of Cell and Developmental Biology)
Würzburg, 10–13 June 2015

7th Würzburger Meningokokken-Workshop "Meningokokken und *Haemophilus influenzae:* Epidemiologie & Prävention"
Ulrich Vogel (Institute for Hygiene and Microbiology)
Würzburg, 12 June 2015



4th International Conference "Strategies in Tissue Engineering"
Heike Walles (Chair of Tissue Engineering & Regenerative Medicine)
Würzburg, 10–12 June 2015

Chronische Virushepatitis "Update 2015"
Hartwig Klinker (Clinical Internal Medicine II, Center for Infectiology DGI)
Würzburg, 28 January 2015

EMGM Workshop "Current Practical Implementation of Genome Sequencing for Typing of Invasive Bacterial Pathogens"
Ulrich Vogel (Institute for Hygiene and Microbiology)
Frankfurt, 2 December 2014

EMBO Practical Course "Non-coding RNA in Infection"
Ana Eulalio, Stan Gorski, Cynthia Sharma, Jörg Vogel
(Institute of Molecular Infection Biology)
Würzburg, 12–18 October 2014

8. Würzburger Infektiologisches Symposium
Hartwig Klinker, Andrew Ulllmann (Clinical Internal Medicine II)
Würzburg, 19 July 2014

International Symposium M3W3 "3rd Mol Micro Meeting"
Cynthia Sharma, Daniel Lopez, Joachim Morschhäuser, Jörg Vogel
(Institute of Molecular Infection Biology)
Würzburg, 7–9 May 2014

Chronische Virushepatitis "Update 2014"
Hartwig Klinker (Clinical Internal Medicine II, Center for Infectiology DGI)
Würzburg, 22 January 2014

6. APPENDIX
6.3. SEMINARS AND COLLOQUIA

MICROBIOLOGY COLLOQUIUM

15 Dec 2015
Jeanne Salje | Oxford Tropical Medicine Research Unit, Bangkok, Thailand
Orientia tsutsugamushi: a major human pathogen in tropical South East Asia and an intriguing model organism for studying host-pathogen cell biology

01 Dec 2015
Per Ljungdahl | Stockholm University, Sweden
The cell biology of extracellular amino acid sensing in yeast

24 Nov 2015
Jacques Neefjes | Netherlands Cancer Institute, Amsterdam, NL
How Salmonella causes gallbladder carcinoma in India: an example of cancer initiation by pathogens

17 Nov 2015
Sigal Ben-Yehuda | Hebrew University Jerusalem, Israel
New concepts in bacterial intercellular interactions

10 Nov 2015
Melanie Blokesch | EPFL, Lausanne, CH
Killing for DNA – the type VI secretion system of *Vibrio cholerae* fosters horizontal gene transfer

03 Nov 2015
Kai Thormann | University of Giessen
Bacterial cells getting organized – how to place flagella

27 Oct 2015
Julia Frick | University of Tübingen
Host microbe interaction in chronic inflammatory diseases

14 July 2015
Gabriela Krasteva-Christ | University of Würzburg
The bitter and sweet taste of infection

07 July 2015
Till Voss | Swiss Tropical & Public Health Institute, Basel, CH
Epigenetic gene regulation facilitates immune evasion and transmission of malaria parasites

30 June 2015
Susanne Hartmann | Free University of Berlin
Immunoregulation: Lessons from parasitic nematodes

23 June 2015
Denise Monack | Stanford School of Medicine, USA
The yin and yang of chronic Salmonella infections

09 June 2015
Peter Turnbaugh | UCSF, San Francisco, USA
Predicting and preventing the metabolism of drugs by the human gut microbiome

02 June 2015
Lars Dölken | University of Würzburg
High resolution gene expression profiling – New insights into herpesvirus host cell modulation

26 May 2015
Katharina Gaus | University of New South Wales, Australia
Molecular insights into the regulation of T cell signaling

19 May 2015
Han Remaut | VIB / Vrije Universiteit Brussel, Belgium
Forming amyloid fibrils: the bacterial way

05 May 2015
Petr Broz | Technical University Munich
Sensing the enemy within: Innate immune detection of intracellular bacteria

28 April 2015
Andreas Peschel | University of Tübingen
Staphylococcus aureus – from commensal to killer bug

21 April 2015
Percy Knolle | Technical University Munich
The liver in T cell immunity against viral infection

14 April 2015
Carol Kumamoto | Tufts University, Boston, USA
Candida albicans: Sensing the host environment?

27 Jan 2015
Johannes Hegemann | Heinrich-Heine University, Düsseldorf
Host cell entry by Chlamydia

20 Jan 2015
Tim Gilberger | Bernhard-Nocht-Institute for Tropical Medicine, Hamburg
Red blood cell invasion by the malaria parasite

08 Dec 2015
Salomé Leibundgut-Landmann | University of Zürich, CH
Antifungal defense at mucosal barriers

13 Jan 2015
Thomas Meyer | Max Planck Institute for Infection Biology, Berlin
Towards an understanding of bacterial carcinogenesis!

16 Dec 2014
Ralph Isberg | Tufts University School of Medicine, Boston, USA
Microbial community behavior during growth in deep tissue sites

09 Dec 2014
Mathias Herrmann | Saarland University Hospital, Homburg
Disease mechanisms in *Staphylococcus aureus* endovascular infection

25 Nov 2014
Wolf-Dietrich Hardt | ETH Zürich, CH
Salmonella diarrhea: how the pathogen invades the gut ecosystem

18 Nov 2014
Constance Ciaudo | ETH Zürich, CH
Multiple functions of the RNAi pathway in mouse embryonic stem cells

11 Nov 2014
August Stich | Medical Mission Hospital, Würzburg
Do microbes have the last word? The example of Ebola

04 Nov 2014
Lucas Jae | The Netherlands Cancer Institute, Amsterdam, NL
Hemorrhagic Fever Virus entry deciphered by haploid genetics

28 Oct 2014
Jeroen Raes | KU Leuven, NL
Studying the human microbiome using metagenomics

21 Oct 2014
Richard Bennett | Brown University, Providence, USA
Mechanisms of Genetic and Epigenetic Variation in *Candida albicans*

08 July 2014
Judith Berman | Tel Aviv University, Israel
Dynamic ploidy change and the rapid appearance of drug resistance

01 July 2014
Rainer Haas | Max von Pettenkofer Institute, LMU Munich
Helicobacter pylori-host interactions: role of the vacuolating cytotoxin and the cag-Type IV secretion system

24 June 2014
Urs Greber | University of Zürich, CH
Decoding the Cell – insights from virus-host interactions

17 June 2014
Christine Clayton | Heidelberg University
Networks of gene expression regulation in trypanosomes

10 June 2014
Constantin Urban | Umea University, Sweden
Mass matters: Interaction studies of fungal pathogens with host cells

03 June 2014
Till Strowig | Helmholz Centre for Infection Research, Braunschweig
Intestinal microbiota and local inflammatory responses

27 May 2014
Sara Lustigman | The Lindsley F. Kimball Research Center, The New York Blood Center, USA
Development of a novel parasite-derived protein adjuvant for vaccine sparing

20 May 2014
Jean-Pierre Gorvel | Centre d'Immunologie de Marseille-Luminy, France
Brucella infection, from bench to bed side

13 May 2014
Feng Shao | National Institute of Biological Sciences, Beijing, China
Biochemical dissection of bacterial virulence and macrophage innate immunity

06 May 2014
Kristine Arnvig | MRC National Institute for Medical Research, Mill Hill, USA
Regulatory RNA in *Mycobacterium tuberculosis* – still in the dark ages?

29 April 2014
Sam Alsford | London School of Hygiene & Tropical Medicine, UK
High-throughput phenotyping in *Trypanosoma brucei* – or how the parasite contributes to its own demise

15 April 2014
Paul Fey | University of Nebraska Medical Center, USA
Amino acid metabolism in *Staphylococcus aureus* and its relevance in infection

08 April 2014
Matthew Berriman | Welcome Trust Sanger Institute, Cambridge, UK
Comparative and functional genomics of parasitic helminths

04 Feb 2014
Luis Serrano | Centre for Genomic Regulation, Barcelona, Spain
Quantitative systems understanding of a model bacterium: *Mycoplasma pneumoniae*

28 Jan 2014
Jacques Schrenzel | University Geneva, CH
S. aureus, a sticky bug?

21 Jan 2014
Kim Kline | Nanyang Technological University, Singapore
Stealth strategies of *Enterococcus faecalis*

14 Jan 2014
Kim Orth | UT Southwestern, Dallas, USA
Black Spot, Black Death, Black Pearl: The Tales of Bacterial Effectors

07 Jan 2014
Boris Turk | J. Stefan Institute, Ljubljana, Slovenia
Protease signaling: cysteine cathepsins and their regulation

VIROLOGY AND IMMUNOBIOLOGY SEMINARS

07 Dec 2015
Martin Ludlow | Hannover
Viral determinants of morbillivirus cross-species infections

23 Nov 2015
Elga de Vries | Amsterdam, NL
The neurovascular unit in health and disease: the role of sphingolipids

16 Nov 2015
Stephan Ehl | Freiburg
Immunopathology as a consequence of immunodeficiency: a paradox?

12 Nov 2015
Peter Friedl | Nijmegen, NL
Serial killing of cancer cells by cytotoxic T cells

02 Nov 2015
Beate Sodeik | Hannover
Herpes Simplex Virus – A hitch hiker's guide through the cell

26 Oct 2015
Andrew MacDonald | Manchester, UK
Dendritic cells: central players in coordination of Type 2 inflammation

17 July 2015
Peter O' Hare | London, UK
New insight into host responses to virus infection: Revising the single step growth cycle

06 July 2015
Karl-Sebastian Lang | Essen
Enforced viral replication in antiviral immune response

29 June 2015
Bernard Vanhove | Nantes, France
Immunomodulation with CD28 antagonists

24 June 2015
Nicholas Proudfoot | Oxford, UK
Coupling transcription to RNA processing in mammals: making mechanistic sense of genomic analysis

22 June 2015
Klaus Überla | Erlangen
Overcoming a bias in the quality of the HIV Env antibody response by intrastructural help

08 June 2015
Ulrich Kalinke | Hannover
Anti-viral interferon responses in periphery and brain

11 May 2015
Andreas Villunger | Innsbruck, Austria
Bcl2 family proteins in lymphocyte development

04 May 2015
Klaus Dornmair | Munich
Disease-related B- and T-cells and their targets in multiple sclerosis

27 April 2015
Luis Graca | Lissabon, Portugal
Multiple regulatory pathways leading to immune tolerance

20 April 2015
Erika Pearce | Saint Louis, USA
Metabolic regulation of T-cell function and fate

09 March 2015
Brigitta Stockinger | London, UK
Fate decisions of IL-17 and IL-22 producing T cells

12 Jan 2015
Marcus Altfeld | Hannover
Antiviral NK cell function in HIV infection

08 Dec 2014
Oliver Fackler | Heidelberg
Host-Cell Interactions of HIV-1

01 Dec 2014
Georg Schett | Erlangen
Why does inflammation stop in gout? – A new mechanism for resolution of inflammation

03 Nov 2014
Andrea Ablasser | Lausanne, CH
The role of intracellular DNA sensing mechanisms in pathogen-triggered innate immunity

06 Oct 2014
Tim Hughes | Cardiff, UK
Complement and Atherosclerosis

24 Sept 2014
Michaela Gack | Boston, USA
Mechanisms of RIG-I-like receptor activation and manipulation by Paramyxoviruses

08 July 2014
Alexander Steinkasserer | Erlangen
The CD83 molecule: A viral target for immune escape – its soluble form induces regulatory T cells

30 June 2014
Christian Münz | Zürich, CH
Human tumorvirus infection and immune control *in vivo*

16 June 2014
Alex Scheffold | Berlin
Human T cells sensing environmental antigens

03 June 2014
Christopher S. Sullivan | Austin, USA
RNAi: a tool for the enemy during viral infection of mammalian cells

02 June 2014
Nathaniel R. Landau | New York, USA
SAMHD1 restriction of HIV-1: Starving the Virus

26 May 2014
Stéphane Emiliani | Paris, France
A novel LEDGF/p75-associated complex regulates HIV latency

12 May 2014
Friederike Berberich-Siebelt | Würzburg
The importance – and unimportance – of NFAT for CD4+ Treg cells

28 April 2014
Veronika von Messling | Langen
Morbillivirus-host interactions: Getting in, around, and out

14 April 2014
Dietmar Zehn | Lausanne, CH
T cell differentiation in chronic infection and autoimmunity

24 Feb 2014
Ben Berkhout | Amsterdam, NL
HIV-1 studies: from the nucleotide composition of its RNA genome to establishment of the viral reservoir.

17 Feb 2014
Ulf Dittmer | Essen
The role of Tregs in chronic viral infections

17 Feb 2014
Leo James | Cambridge, UK
Intracellular antibodies – in the wrong place, at the right time

27 Jan 2014
Kevin Maloy | Oxford, UK
Innate immune receptor circuits in intestinal homeostasis

20 Jan 2014
Thomas Dobner | Hamburg
Adenoviruses: dual model in virus-host interactions

6. APPENDIX
6.4. FUNDING

2.1 CYNTHIA SHARMA

DFG (Sh580/1-1): Functional characterization of two acid-regulated small RNAs in *Helicobacter pylori*

IZKF (Interdisciplinary Center for Clinical Research, Würzburg): New 3D-infection models based on tissue-engineering to study pathogenesis of *Helicobacter pylori and Campylobacter jejuni* (Co-applicants: Sharma, Walles, Löffler, Melcher)

BioSysNet, Associated Junior Group: Exploring RNA-binding proteins in *Campylobacter jejuni*

Young Academy fellowship of the Bavarian Academy of Sciences: Functional characterization of small regulatory RNAs in the human pathogen *Helicobacter pylori*

Young Investigator grant of the Daimler-and-Benz-Foundation: Identification and functional characterization of RNA-binding proteins in *Campylobacter jejuni*

ESCMID Research Grant 2014 and ESCMID/FEMS Research Fellowship 2014: New 3D-infection models based on tissue-engineering to study pathogenicity of *Helicobacter pylori* and *Campylobacter jejuni*

DFG (Sh580/2-1): International conference grant "M3W3: 3rd Mol Microl Meeting Würzburg"

Infect-ERA (ERA-NET), 2nd call, Junior Consortium: CampyRNA; Combining high-throughput and single-cell analyses to study RNA regulators important for the early steps of *Campylobacter* infection (Coordinator: C. Sharma; Co-applicants: A. Eulalio, Germany; M. Mano, Portugal; K. Schauer, France)

DFG SPP 1784 Chemical Biology of native Nucleic Acid Modifications (Sh580/4-1): Identification and characterization of pseudouridine in mRNAs and non-coding RNAs of the bacterial human pathogen *Campylobacter jejuni*

EMBO Practical Course Grant: "Non-coding RNAs in infection" (Applicants: J. Vogel, A. Eulalio, C. Sharma, O. Voinnet, P. Romby, S. Gorski)

Project within Research Training Group (GRK 2157) 3D-Infect: 3-D Tissue Models for studying Microbial Infections by Human Pathogens (Coordinators: Thomas Rudel, Heike Walles; will start in April 2016)

2.2 DANIEL LOPEZ

DFG SPP1617 Phenotypic Heterogeneity and Sociobiology of Bacterial Population (LO1804-2/1): Cell Differentiation in multicellular Communities of *Staphylococcus aureus*

DFG SPP1617 Phenotypic Heterogeneity and Sociobiology of Bacterial Population (LO1804-2/2): Molecular characterization of the distinct cell types required for the development of *Staphylococcus aureus* biofilms

ERC Starting Grant 2013: BacRafts

2.3 NICOLAI SIEGEL

DFG (SI 1610/2-1): Unraveling the mechanism of targeted histone variant deposition in *Trypanosoma brucei*

DFG (SI 1610/3-1): Unraveling the role of trypanosomal ncRNA in the regulation of antigenic variation

2.4 ANA EULALIO

BioSysNet, Junior Group: RNA: the missing link in bacterial pathogen-host interactions

Infect-ERA (ERA-NET), 2nd call, Junior Consortium: CampyRNA – Combining high-throughput and single-cell analyses to study RNA regulators important for the early steps of *Campylobacter infection* (Principal Investigator: Ana Eulalio; other consortium members: Cynthia Sharma (coordinator), Germany; Miguel Mano, Portugal; Kristine Schauer, France)

DFG (BR 4837/1-1): Functional and molecular characterization of host cell microRNAs controlling *Salmonella infection*

EMBO Practical Course Grant: "Non-coding RNAs in infection" (Applicants: J. Vogel, A. Eulalio, C. Sharma, O. Voinnet, P. Romby, S. Gorski)

EMBO Young Investigator Programme: MicroRNAs in host-bacterial pathogen interactions

Infect-ERA(ERA-NET), 3rd call, Consortium: StaphIN – Intracellular *Staphylococcus aureus:* deciphering bacterial and cellular factors involved in host cell invasion by clinically relevant strains to define new therapeutic approaches (Principal Investigator: Ana Eulalio; other consortium members: Daniel Lopez (coordinator), Spain; Miguel Mano, Portugal; Francois Vandenesch, France; Tristan Ferry, France)

2.4 CHRISTIAN PEREZ

Bavaria California Technology Center (BaCaTeC) (Förderprojekt Nr. 11): Molecular mechanisms of evolution of gene regulatory circuits

Knauf Private Donation: Identification of *Candida albicans* traits modulated by the mammalian gut microbiota

Volkswagen Stiftung: A feast within us: Targeting microbial interactions inside us to discover smarter therapeutic strategies

2.6 SEBASTIAN GEIBEL

Elitenetzwerk Bayern (Project N-BM-2013-246): Structural biology of mycobacterial secretion machines

3.1.1 JÖRG VOGEL

BioSysNet, Associated Senior Group: Temporal control of gene expression by small RNAs

DFG FOR1680 Unravelling the prokaryotic immune system (Vo875/7-1): CRISPR/Cas system in *Neisseria meningitides*

DFG FOR 1680 (Vo875/7-2): Investigation of the prokaryotic immune systems I-B and I-D in archaea

DFG SPP1316 Host-Adapted Metabolism of Bacterial Pathogens (Vo875/6-1): A post-transcriptional link between *Salmonella* metabolism and virulence

DFG (Vo 875/5-1): Cis/trans control of genes by a pH-responsive 5' UTR

BMBF Medical Infection Genomics: Next generation transcriptomics in bacterial infections

DFG SFB/TRR34 Pathophysiology of Staphylococci in the Post-Genome-Era (Project B04): sRNA-mediated gene regulation in staphylococci: Impact on metabolism and biofilm expression

DFG SFB/TRR34 Pathophysiology of Staphylococci in the Post-Genome-Era (Project C06): Post-invasion events in *Staphylococcus aureus*-infected host cells – A combined transcriptomics/proteomics in vivo approach

BMBF grant (e:Bio): RNAsys – System Biology of RNA

SPP1784 Chemical Biology of native Nucleic Acid Modifications (Vo875/13-1): Identification and Characterization of RNA modifications in the model organism Salmonella

Infect-ERA (ERA-NET), 2nd Call, Consortium: The Nice Bug – Commensalism versus disease? Asymptomatic carriage or urosepsis (Principal Investigator: Jörg Vogel; other consortium members: Catharina Svanborg (coordinator), Sweden; Eliora Ron, Israel; Ulrich Dobrindt, Germany; Alberto Mantovani, Italy)

DFG (Vo875/14-1): Small regulatory RNAs from 3' regions of mRNAs

EMBO Practical Course Grant: "Non-coding RNAs in infection" (Applicants: J. Vogel, A. Eulalio, C. Sharma, O. Voinnet, P. Romby, S. Gorski)

Project within Research Training Group (GRK 2157) 3D-Infect: 3-D Tissue Models for studying Microbial Infections by Human Pathogens (Coordinators: Thomas Rudel, Heike Walles; will start in April 2016)

3.1.2 HEIDRUN MOLL

DFG SFB630 Identification, Preparation and Functional Analysis of Agents against Infectious Diseases. (Project B3): Identification and characterization of leishmanicidal compounds

Graduate School of Life Sciences, Excellence Initiative by the German federal and state governments

3.1.3 JOACHIM MORSCHHÄUSER

DFG (MO 846/6-2): Phenotypic switching and genomic alterations as host adaptation mechanisms of the opportunistic fungal pathogen *Candida albicans*

DFG SFB/TR 124 Pathogenic fungi and their human host: Networks of interaction: Regulation of *Candida albicans* virulence traits by protein kinases

DFG (MO846/7-1): Systematic functional analysis of the zinc cluster transcription factor family of the pathogenic yeast *Candida albicans* by artificial activation

DFG SFB 630 Identification, isolation and functional analysis of anti-infective compounds (Project B2): Inhibition of virulence and resistance mechanisms of *Candida albicans* by artifical activation

3.1.4 TOBIAS ÖLSCHLÄGER

DFG SFB630 Identification, isolation and functional analysis of anti-infective compounds (Project Z1): Central Laboratory

3.1.5 KNUT OHLSEN

DFG SFB/TRR34 Pathophysiology of Staphylococci in the Post-Genome-Era (Project A2): Phosphoproteome studies to characterize serine/threonine protein kinases and phosphatases in *Staphylococcus aureus* and (Project Z3): In vivo imaging of staphylococcal infections

DFG SFB630 Determination of mode of action of novel anti-staphylococcal compounds using DNA-microarray technology (Project B5): Drug-induced gene expression in staphylococci

BMBF Go-Bio (FKZ 0315565): Immunotherapy against *Staphylococcus aureus*

EU FP7 241796: Impact of specific antibiotic therapies on the prevalence of human host resistant bacteria (SAT URN)

3.1.6 WILMA ZIEBUHR

DFG SFB/TRR34 Pathophysiology of Staphylococci in the Post-Genome Era (Project B4): Regulation of methionine metabolism in staphylococci: Impact on fitness and virulence

BMBF MedVet-Staph: Interdisciplinary Research Network on the Zoonotic Impact of *Staphylococcus aures*/MRSA (Project 01KI1014E): Influence of antibiotic resistant staphylococcal species on persistence and dissemination of LA-MRSA

DFG SPP1617 Phenotypic Heterogeneity and Sociobiology of Bacterial Population (Zi-665-2): Heterogeneous gene expression, metabolic variability and differentiation in *Staphylococcus epidermidis* biofilms

3.2.1 MATTHIAS FROSCH

BMBF Medical Infection Genomics. Central Management

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

RKI grant (1369-378): Consiliary Laboratory for Echinococcosis

EU/ECDC grant: Coordination of activities for laboratory surveillance of invasive bacterial diseases (*N. meningitidis, H. influenzae* and *S. pneumoniae*) in Member States and EEA/EFTA countries

3.2.2 KLAUS BREHM

DFG-GSLS: Characterization of totipotent stem cells and regeneration mechanisms in cestode parasites

DFG-GSLS: Utilization of the *Echinococcus* kinome for the development of novel drugs against echinococcosis

Wellcome Trust Strategic Award – Flatworm Functional Genomics Initiative (FUGI): Development of cestode functional genomics tools (107475/Z/15/Z)

3.2.3 CHRISTOPH SCHOEN

DFG SPP1316 Host-Adapted Metabolism of Bacterial Pathogens

(SCHO 1322/1-1): Gene regulatory mechanisms of metabolic adaptation in *Neisseria meningitidis* in ex vivo infection models

3.2.4 ANDREA SCHUBERT-UNKMEIR

DFG FOR 2394/1-2 Sphingolipids dynamics in infection control (P03: SCHU 2394/2-1): Analysis of the functional relevance of SMases and ceramide in meningococcal pathogenesis

DFG (SCHU 2394/3-1): Untersuchungen zum Einfluß der Meningokokken-Infektion auf die Aktivierung von Rezeptor-Tyrosin-kinasen sowie auf den Zellzyklus

BaCaTec (Bavaria California Technology Center) (Förderprojekt Nr. 12): Role of non-receptor tyrosine kinases and activated signaling pathways in bacterial adherence and invasion of host cells

Project within Research Training Group (GRK 2157) 3D-Infect: 3-D Tissue Models for studying Microbial Infections by Human Pathogens (Coordinators: Thomas Rudel, Heike Walles; will start in April 2016)

3.2.5 ULRICH VOGEL

DFG (VO718/6-1): Mechanisms of host adaptation and immune evasion of *Neisseria meningitidis:* the role of biofilms and blebs

DFG (VO718/7-1): Characterization of sialic acid specific O-acetyl-transferases: from neuroinvasive bacteria to human hosts

BMBF Medical Infection Genomics: Proteomics of meningococci and pneumococci. Project Würzburg

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

Collaborative Research Agreements with Novartis Vaccines

Novartis (Amendment No. 4 of the research agreement): Development of a validated method to detect functional antibodies induced by *Neisseria meningitidis* serogroup B vaccine

Schülke & Mayr GmbH (OMLO113): Phase II study to assess bacterial count reduction of the OML concentrations in comparison to a placebo in patients with mild gingivitis

3.3.1 THOMAS HÜNIG

DFG SFB/TR 124 Pathogenic fungi and their human host (Project C6): Role of secreted *Candida albicans* proteins in immune evasion and pathogenicity

DFG (HU 295/12-1): Einfluss des CD28-Signals auf die funktionelle Programmierung und Re-Programmierung von Maus- und humanen Gedächtnis- sowie induzierten regulatorischen T-Zellen

3.3.2 NIKLAS BEYERSDORF

AiCuris GmbH & Co. KG, Wuppertal: Comparative study of the effects of ILM and 2010 Proleukin on mouse and rat lymphocytes *in vitro* and *in vivo* and therapeutic impact on experimental autoimmune encephalomyelitis of the Lewis rat (2008-2010: Thomas Hünig, Würzburg)

DFG SFB/TR 124 Pathogenic fungi and their human host (Project C6): Role of secreted *Candida albicans* proteins in immune evasion and pathogenicity

DFG Research Unit 2123 Sphingolipid dynamics in infection control: Role of sphingolipids in the regulation of anti-viral T cell responses (P02; with Jürgen Schneider-Schaulies, Würzburg)

DFG (BE4080/2-1): The role of CD28-mediated signals in programming and reprogramming of mouse and human memory and induced regulatory T cells (with Thomas Hünig, Würzburg)

Deutsche José Carreras-Leukämie-Stiftung (DJCLS R 13/25): The influence of CD28 expression by allogeneic T cells on acute Graft versus Host Disease (aGvHD) and Graft versus Tumor (GvT) effect in an inducible knock-out model (Co-applicant Thomas Kerkau, Würzburg)

Interdisziplinäres Zentrum für Klinische Forschung (IZKF) Würzburg (E-298): Therapeutic modulation of regulatory T cells in minipigs to improve wound healing and survival after myocardial infarction (Co-applicants: Anna Frey and Thomas Kerkau)

3.3.3 THOMAS HERRMANN

DFG (2346/6-1): The rat as new model for the analysis of iNKT cell recognition and function

Wilhelm-Sander-Stiftung (907.1): γδ T Zell- und Antikörper-vermittelte Immuntherapien gegen das Multiple Myelom: Mechanistische Grundlagen für neue Strategien

DFG (HE 2346/7-1) Vγ9Vδ2 T Zellen: Identifizierung in nicht-Primatenspezies und Analyse der molekularen Determinanten der Antigenerkennung

Universitätsbund Würzburg: Genomische Kartierung der Phosphoantigen-vermittelten Aktivierung humaner γδ T Zellen

3.3.4 MANFRED LUTZ

DFG IRTG1522 HIV/AIDS and associated Infectious Diseases in Southern Africa (TP11): Protective and productive inflammatory responses induced by microbial products studied at the level of dendritic cells

DFG (LU851/6-1): Characterization of myeloid-derived suppressor cell sub-sets and their induction by *Mycobacterium tuberculosis*

DFG (LU851/8-1): Control of the homeostatic regulatory T cell pool by RelB expression in steady state migratory dendritic cells

Wilhelm Sander Foundation (Nr. 2013.60.1): Functional roles of direct and bystander release of IL-12 by dendritic cells for T cell activation and anti-tumor immunity

3.4.1 LARS DÖLKEN

British Medical Research Council (MRC) (G1002523): Regulatory role of non-coding RNAs in herpesvirus infections

NHS Blood & Transplant (WP11-05): Non-coding RNAs in herpesvirus infections

NHSBT Trust Fund (TF044): Defining the genetic basis of herpesvirus suppression and reactivation using GWAS in INTERVAL blood donors

DFG (Do1275/2-1): Systems biology analysis of HSV-1 host shut-off

Infect-ERA (ERA-NET), 2nd Call Consortium: Early Determinants of DNA-Virus Lytic or Latent Infection (eDEVILLI) (Principal Investigator: Lars Dölken; other consortium members: Luka Cicin-Sain (coordinator), Germany; Maria Masucci, Sweden; Harald Wodrich, France; Mathias Müller, Austria)

3.4.2 JÜRGEN SCHNEIDER-SCHAULIES

DFG FOR 2123 Sphingolipid dynamics in infection control (SCHN 320/24-1): Role of sphingolipids in the regulation of anti-viral T cell responses

3.4.3 SYBILLE SCHNEIDER-SCHAULIES

DFG (SCHN405/6-1): Effectors, mechanisms and consequences of sphingomyelinase-dependent regulation of actin dynamics in measles virus induced T cell paralysis

DFG (SCHN405/7-1): Regulation of plasma membrane ceramide generation in dendritic cells (DCs): impact on pathogen uptake and sorting, receptor crosstalk and immune activation

DFG FOR2123 Sphingolipid dynamics in infection control (SCHN405/10-1): Sphingomyelinase activation in T cells: Implications for T cell activation and paralysis

DFG FOR 2123 (SCHN 405/11-1): Central project

Interdisziplinäres Zentrum für Klinische Forschung der Universität Würzburg (A-169): Endogenous Retroviruses as immune modulators in healthy and impaired human pregnancies (with Ulrike Kemmerer)

Project within Research Training Group (GRK 2157) 3D-Infect: 3-D Tissue Models for studying Microbial Infections by Human Pathogens (Coordinators: Thomas Rudel, Heike Walles; will start in April 2016)

3.5.1 THOMAS RUDEL

DFG SFB/TRR34 Pathophysiology of Staphylococci in the Post-Genomic Era (Project C11): *Staphylococcus aureus* induced host cell death mechanisms

DFG SFB 630 Recognition, Preparation and Functional Analysis of Agents against Infectious Diseases (Project B9): Active Agents against Acute and Disseminating Infections by *Neisseria*

BMBF Medical Infection Genomics: Pathogen-Host Interactomes and Signaling Complexes in Bacterial Infections

DFG SPP1580 Intracellular Compartments as Places of Pathogen-Host-Interaction: *Simkania negevensis* containing vacuoles: formation, trafficking and subversion of host signaling

IZKF (B-192): Chlamydia and ovarian cancer (Project partner: Jörg Wischhusen)

DFG FOR2123 Sphingolipid dynamics in infection control (Project P04): Sphingolipids in gonococcal infection

Infect-ERA (ERA-NET), 1st Call Consortium: Co-infection as a cause of ovarian cancer (CINOCA) (Principal Investigator: Thomas Rudel; other consortium members: Thomas Meyer (coordinator), Germany; Maria Masucci, Sweden; Christoph Bock, Austria; Fernando Garcia-Alcalde, Germany; Christina Fotopoulou, UK)

Research Training Group (GRK 2157) 3D-Infect: 3D-Tissue Models for studying Microbial Infections by Human Pathogens (Coordinators: Thomas Rudel, Heike Walles; will start in April 2016)

3.5.2 MARTIN FRAUNHOLZ

DFG (FR1504/2-1): Identification of virulence factors mediating phagosomal escape of *Staphylococcus aureus* by transposon insertion site deep sequencing

DFG SFB/TRR34 Pathophysiology of Staphylococci in the Post-Genomic Era (Project C11): *Staphylococcus aureus* induced host cell death mechanisms

3.5.3 ROY GROSS

DFG (GR1243-8/1): Genetic and immunologic basis of pathogenic and mutualistic interactions between bacteria and their ant hosts

Project within Research Training Group (GRK 2157) 3D-Infect: 3D-Tissue Models for studying Microbial Infections by Human Pathogens (Coordinators: Thomas Rudel, Heike Walles; will start in April 2016)

3.5.4 VERY KOZJAK-PAVLOVIC

DFG SFB630 Recognition, Preparation and Functional Analysis of Agents against Infectious Diseases (Project B9): Compounds against acute and disseminating *Neisseria* infection

Project within Research Training Group (GRK 2157) 3D-Infect: 3D-Tissue Models for studying Microbial Infections by Human Pathogens (Coordinators: Thomas Rudel, Heike Walles; will start in April 2016)

3.6.1 HERMAN EINSELE

European Commission, FP7 Health-F2 – collaborative project OPTATIO" Optimizing Targets amd Therapeutics In higH risk and refractOry Multiple Myeloma (HEALTH-F2-2012-278570): Drug testing in vivo: Development and use of MM in vivo models (Consortium partners: W. Willenbacher (Coordinator), Austria; H. Einsele, Germany; R. Hajek, Czech Republic; D. Ribatti, Italy; T. Masszi, Hungary; R. Greil, Austria; M. Kubbutat, Germany; G. Keri, Hungary; B. Hofer, Austria; M. Aracil, Spain; S. Kirchner, Germany; B. Frick, Austria)

DFG SFB-TR 124 Pathogenic fungi and their human host: Networks of interaction (Project A02 Löffler/Einsele): Interaction of *Aspergillus fumigatus* with human natural killer cells, dendritic cells and human alveolar epithelia

DFG KFO-CRU 216 (KFO 216/2): Characterization of the Oncogenic Signaling Network in Multiple Myelom: Development of Targeted Therapies: (Project 6 Chatterjee/Einsele): The heat shock protein/signaling interface as a therapeutic target in mutliple myeloma and in Graft-versus-Host-Disease; (Project Z1 Rosenwald/Einsele/Beilhack): Centralized sample preparation, pathology and preclinical in vivo models

Wilhelm-Sander-Stiftung, Wilhelm-Sander-Therapieeinheit Multiples Myelom (2013.900.1): Risikoadaptierte Stratifizierung und interdisziplinäre Behandlung des Multiplen Myeloms

European Commission, FP7 Health-2013 – Innovation 2, collaborative project, Eu-FP7: Donor T Cells for Immune Control (T-Control) (Health-F4-2013-601722): Clinical trial for the treatment of infections and tumor relapse after allogeneic HSCT; Clinical trial for the treatment of acute steroid refractory GVHD after allogeneic HSCT (Consortium partners: H. Einsele (coordinator); L. Germeroth, Germany; A. Madrigal, UK; F. Falkenburg, Netherlands; B. Fuchs, Germany)

3.6.2 ANDREAS BEILHACK

Subsets EU-FP7 program – NanoII (229289): WP2, WP10 Joint projects with Hermann Einsele)

Else-Kröner-Forschungskolleg (Physician-Scientist program) for Interdisciplinary Translational Immunology (Coordinator), Else-Kröner-Fresenius-Stiftung, (first funding period 2010_Kolleg.52, second funding period 2014_Kolleg.52)

IZKF Research Group for Experimental Stem Cell Transplantation (B233)

EU-FP7 OPTATIO (278570-2): WP4 Joint project with Hermann Einsele

DFG SFB/TR 124 Pathogenic fungi and their human host: Networks of interaction: (Project A3): In vivo analysis of temporal and spatial disease progression and immune cell recruitment during invasive *Aspergillus fumigatus* and *Candida albicans* infection

DFG Clinical Research Unit 216-2: Molecular Networks in Multiple Myeloma

Deutsche José Carreras Leukämie-Stiftung (DJCLS R 10/15): Exploring invasive aspergillosis after allogeneic hematpoietic cell transplantation with in vivo imaging

DFG FOR 1586 Skelmet - Mesenchymale und osteogene Signalwege in der Knochenmetastasierung (P9): T Zell-Interaktionen mit der Multiplen Myelom-Nische

m4 Award of the Bavarian Ministry of Economic Affairs and Media, Energy and Technology

Project within Research Training Group (GRK 2157) 3D-Infect: 3D-Tissue Models for studying Microbial Infections by Human Pathogens (Coordinators: Thomas Rudel, Heike Walles; will start in April 2016)

3.6.3 HARTWIG KLINKER

NIH and BMBF (01 KG 0915): START - Strategic Timing of Antiretro- viral Treatment

IZKF Würzburg: Molecular investigations into the pharmacokinetics and drug monitoring of new direct-acting anti-HIV and anti-HCV antivirals (Z-4/106)

3.6.4 JÜRGEN LÖFFLER

DFG SFB/TR124 Pathogenic fungi and their human host: Networks of interaction (Project A2 Löffler/Einsele): Intercation of *Aspergillus fumigatus* with human natural killer cells, dendritic cells and human alveolar epithelia

IZKF (Interdisciplinary Center for Clinical Research, Würzburg): New 3D-infection models based on tissue-engineering to study pathogenesis of *Helicobacter pylori* and *Campylobacter jejuni* (Co-applicants: Sharma, Walles, Löffler, Melcher)

Sanderstiftung (Projekt 2015.083.1): Diagnostische Strategien bei Krebspatienten mit respiratorischen Schimmelpilzinfektionen

4.1 GERHARD BRINGMANN

Speaker and coordinator of the DFG Collaborative Research Centre SFB 630 Recognition, Preparation, and Functional Analysis of Agents against Infectious Diseases (Project A2): A New Class of Agents against Pathogens of Tropical Diseases

DFG Clinical Research Unit (Klinische Forschergruppe) KFO 216: Characterization of the Oncogenic Signaling Network in Multiple Myeloma: Development of Targeted Therapies

Deutsche Josè Carreras Leukämie-Stiftung e.V. „Development and Precilinical Evaluation of a Novel-Type Pro-Pro-Drug"

Group leader and coordinator "The Scholarship System BEBUC, a unique concept for the sustainable re-instalment of excellence at Congolese Universities" (Foundation Else-Kröner-Fresenius-Stiftung)

4.2 THOMAS DANDEKAR

DFG SFB/TRR34 Pathophysiology of Staphylococci in the Post-Genome-Era (Project A8): Systems biological analysis of the central carbohydrate metabolism and involved protein complexes in *Staphylococcus aureus*

DFG SFB/TRR34 Pathophysiology of Staphylococci in the Post-Genome-Era (Project Z1): Integration of bioinformatical tools for an omics databank in a *Staphylococcus aureus* Wiki environment

DFG (Da 208/13-1): Metabolism of intracellular *Salmonella enterica:* One life-style in intracellular infections

DFG (Da 208/10-2): Host adapted metabolism of bacterial infections: Data integration and refined metabolic modelling

Infect-ERA (ERA-NET), 1st Call, Consortium: Systematic identification of antifungal drug targets by a metabolic network approach (AspMetNet) (Principal Investigator: Thomas Dandekar; other consortium members: Sven Krappmann (coordinator), Germany; Hubertus Haas, Austria; Nir Osherov, Israel)

Project within Research Training Group (GRK 2157) 3D-Infect: 3D-Tissue Models for studying Microbial Infections by Human Pathogens (Coordinators: Thomas Rudel, Heike Walles; will start in April 2016)

4.3 MARKUS ENGSTLER

DFG SFB630 Recognition, Preparation, and Functional Analysis of Agents against Infectious Diseases (Project B08): VSG as unexpected drug target for sleeping sickness

DFG German-African Cooperation Projects in Infectology: (EN 305/5-1 and EN 305/7-1) Antibody clearance as virulance factor in African sleeping sickness

DFG SPP1726: 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

Project within Research Training Group (GRK 2157) 3D-Infect: 3D-Tissue Models for studying Microbial Infections by Human Pathogens (Coordinators: Thomas Rudel, Heike Walles; will start in April 2016)

4.4 UTE HENTSCHEL-HUMEIDA

DFG SFB630 Recognition, preparation and functional analysis of agents against infectious diseases (Project A5): Novel anti-infective substances from marine sponge-associated microbiota

DFG GRK1342 Molecular and functional analysis of lipid-based signal transduction systems (Project A8): Phyllosphere Mircobiology: The role of cuticular lipids in plant surface/microbe interactions

EU-FP7 SeaBiotech: From sea-bed to test-bed: harvesting the potential of marine biodiversity for industrial biotechnology: Genomic and metagenomic bioprospecting

4.5 ULRIKE HOLZGRABE

DFG SFB630 Recognition, Preparation and Functional Analysis of Agents against Infectious Diseases (Project A1): Small Molecules against Infectious Diseases

NATO SfP-984835: Mip as a Therapeutic Target to treat Bio-Welfare Threat Agents

Bayerische Forschungsstiftung, Spring and Parachute, AZ 1037-12

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

4.6 CAROLINE KISKER

DFG SFB630 Identification, isolation and functional analysis of anti-infective compounds (Project B7): Structure based Drug Design of essentiell enzymes of *M. tuberculosis* and other pathogens

Graduate School of Life Sciences, Excellence Initiative by the German federal and state governments, GSC 106

DFG (Ki562/7-1): Molecular Interplay in eukaryotic nucleotide excision repair

DFG FOR 2314/1 Targeting therapeutic windows in essential cellular processes for tumor therapy (Project 06): Targeting oncoprotein stability for cancer therapy

DFG (Ki562/2-2): The structural and functional characterization of the XPD and UvrA-UvrB proteins involved in Nucleotide Excision Repair

4.7 GABRIELA KRASTEVA-CHRIST

DFG (KR 4338/1-1): Untersuchung zur Sensor- und Transmitterfunktion der Atemwegsbürstenzellen

DFG SFB TR 84 Innate Immunity of the Lung: Mechanisms of Pathogen Attack and Host Defence in Pneumonia (Project A06): Pathogen recognition by taste receptors and coupling to mucociliary clearance

4.8 AUGUST STICH

DFG SFB630 Identification, isolation and functional analysis of anti-infective compounds (Project Z1): Central Laboratory

4.9 HEIKE WALLES

Bavarian Research Foundation: ForMosA

IDEAS-European Research Council

EU-FP7: VascuBone

Bayern Fit Programme: Regenerative Technologies in Oncology (Bayern FIT VI/3-6622/453/12): Basalmembran und Neurofibromatose

IZKF (Interdisciplinary Center for Clinical Research, Würzburg): New 3D-infection models based on tissue-engineering to study pathogenesis of *Helicobacter pylori* and *Campylobacter jejuni* (Co-applicants: Sharma, Walles, Löffler, Melcher)

Research Training Group (GRK 2157) 3D-Infect: 3D-Tissue Models for studying Microbial Infections by Human Pathogens (Coordinators: Thomas Rudel, Heike Walles; will start in April 2016)

6. APPENDIX
6.5. PUBLICATIONS

2.1 CYNTHIA SHARMA

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