Zentrum für Infektionsforschung
Research Center for Infectious Diseases

der Universität Würzburg
of the University of Wuerzburg

Julius-Maximilians-
UNIVERSITÄT
WÜRZBURG

Wissenschaftlicher Bericht
Scientific Report 2009-2011

Josef-Schneider-Str. 2/D15
97080 Würzburg
Germany

Phone: +49-931-3182575
Fax: +49-931-3182578
E-Mail: monika.meece@uni-wuerzburg.de
http://www.zinf.uni-wuerzburg.de/

Content

1 General remarks
1.1 Speaker‘s Report 2009-2011

Dear Colleagues,

Infectious diseases remain a global challenge to human health, both within and outside Germany. The severity of the problem in our own society was illustrated during the term of the present report (2009 - 2011) by last year’s outbreak of foodborne illness caused by a novel strain of *Escherichia coli* O104:H4 bacteria in northern Germany. Not only did this strain take the lives of 50 people, and caused disease in thousands more, it also impacted European economy and trade. Prior to that, the 2009 flu pandemic gave a dramatic example of how quickly infectious agents may develop through mutation and spread around the globe at a breathtaking pace. Originating in Mexico, the so-called “Swine Flu” took its toll in many countries, and led to public health crisis due to a shortage of vaccine world-wide. Other pathogens once thought to be under control are re-emerging to cause polio and tuberculosis.

The collaborative Research Center for Infectious Diseases (ZINF) at the University of Würzburg has been addressing the molecular principles of disease-causing organisms 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 programme is now funded entirely by the Bavarian Government and the University of Würzburg. Jörg Hacker departed in 2008 to head the Robert-Koch-Institute, Germany’s primary institution for health protection against infectious diseases, before attaining his current position as the President of German National Academy of Sciences Leopoldina. Following three important years with Matthias Frosch as the leader, I had the honour to be elected as the Spokesperson of ZINF in the spring of 2011.

The present annual report summarizes 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 that have contributed to a better understanding of infectious diseases from 2009 until 2011. These were three exceptionally busy and exciting years, with respect to changes in location and people, as well as networking and scientific achievements. One key change, which feels in the distant past, was the relocation of the Institute of Molecular Infection Biology (IMIB), which also hosts the Young Investigator groups, to a new research building in September 2009. We are now located on the clinical campus of the University, under the same roof with the Rudolf-Virchow-Centre, whose chair Martin Lohse together with Jörg Hacker had successfully lobbied for generous support from the Bavarian government to convert the former surgery department into a new home for interdisciplinary and synergistic biomedical research.

The 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. Its success is evidenced by the fact that two of our Young Investigators have recently accepted offers from other institutions, departing from ZINF in 2012; Gabriele Pradel, whose research focused on malaria transmission blocking strategies has left to head the Molecular Malaria group at RWTH Aachen, and more recently Sven Krappmann, a fungal biologist with a keen interest to understand the pathogenicity of *Aspergillus* species, who has accepted an offer for Associate Professorship (W2) of Clinical Microbiology and Immunology at the University of Erlangen-Nürnberg. To replace them, we organised two symposia (in March 2010 and April 2011) and succeeded in recruiting promising young scientists from high-profile institutions; in 2010, Daniel Lopez joined us from Harvard Medical School (Boston) to start a group on biofilm formation in Gram-positive pathogens such as staphylococci. The same year, Cynthia Sharma joined us from the Max Planck Institute for Infection Biology (Berlin) to establish a group whose aim is to use deep sequencing approaches to gain new insight into the biology of the important human pathogens in the *Helicobacter* and *Campylobacter* groups. The second symposium resulted in the recruitment of Nicolai Siegel from Institut Pasteur (Paris) who will investigate epigenetic gene regulation in parasites and complement the growing expertise in *Trypanosoma* research at the university. We were very pleased with both the number and quality of candidates who applied to these positions, demonstrating that Würzburg remains an attractive place for young researchers to look for research opportunities. Beyond the level of research, we are welcoming Stan Gorski, formerly a scientific editor in Heidelberg, who will play a major role in helping coordinate communication and the activities of ZINF members, and has already managed the preparation of the current report.

As ever, our international Scientific Advisory Board (SAB) was instrumental in selecting new group leaders and providing us with critical feedback on current and planned research activities. We are grateful for their service, including former SAB member Cesare Montecucco, who resigned from the board in 2009. Fortunately, Eliora Ron (Tel Aviv) has agreed to serve a second three-year term until 2012. Newly appointed members in 2009 were Axel Brakhage (Jena), Christoph Dehio (Basel), Jean Langhorne (London), Richard Lucius (Berlin), Mariagrazia Pizza (Siena), and Sebastian Suerbaum (Hannover). The SAB is currently undergoing another round of expansion (see chapter 1.3).

The success of the infectious disease researchers at the University of Würzburg is evidenced by a number of prestigious awards and appointments. Of the Young Investigators, Gabriele Pradel was awarded the Karl Asmus Rudolphi Medal 2010 of the German Society for Parasitology, while Cynthia Sharma received major awards from both the Robert Koch and the Ingrid zu Solms Foundations in 2011. At the senior researcher level, Heidrun Moll was elected as President of German Society for Parasitology in 2010, and Caroline Kisker was elected Member of the German National Academy of Sciences (Leopoldina) in 2011. Jörg Vogel received major Research Awards from the two major German societies for microbiology, VAAM (2010) and DGHM (2011). Moreover, he was one of the nine German scientists in 2011 to be awarded with the prestigious membership of EMBO, the European Molecular Biology Organisation.

We have continued our efforts to improve the scientific environment for infectious diseases research at the University of Würzburg through third-party funding. Milestones in 2009-2011 were the renewal of the collaborative research grant DFG SFB 630 (speaker Gerhard Bringmann) for the characterisation of novel antiinfective agents, and the successful start of a follow-up programme Medical Infection Initiative (speaker Matthias Frosch) which succeeds the previous BMBF center *PathoGenoMics*. ZINF members secured research grants in several national and European networks aimed at a better understanding of infectious disease, including ERA-NET, DFG TRR34 *Pathophysiology of Staphylococci*, DFG SPP1316 *Host-Adapted Metabolism of Bacterial Pathogens*, SPP 1580 *Intracellular compartments as places of pathogen-host-interactions* and the BMBF-funded network *RNomics of Infections*. The Interdisciplinary Center for Clinical Research (IZKF) recently elected ZINF board member Thomas Hünig as their spokesperson, reflecting the fact that IZKF also promotes infectious disease research with clinical relevance.

The training of graduate students and postdocs remains a key mission of ZINF. We actively supported the 2011 application for renewal of the university-wide Graduate School for Life Sciences (GSLS), of which ZINF member Caroline Kisker serves as the dean. Infection & Immunity is one of five sections of GSLS, and now contains three training programs (infection, immunomodulation, and antiinfectives). At the international level, the Research Training Group 1522, which is funded by DFG and its South African sister organisation NRF and involves Axel Rethwilm as the German speaker, held several joint symposia enabling doctoral researchers to present their work in Cape Town and Würzburg.

Our students and postdocs also benefitted from several high-profile meetings in Würzburg with relevance to infection disease research. Thomas Rudel was the lead-organizer of a FEMS-Leopoldina symposium *Emerging Topics in Microbial Pathogenesis*, and Jörg Vogel and Alex Böhm together with several of the ZINF Young Investigators partnered with the editors of the high-profile journal *Molecular Microbiology* to start a novel type of scientific meeting, which took place in 2011 and will continue in the following years.

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. The importance of ZINF for shaping the local research landscape was recently acknowledged by endowing it with the status of a Central Institution of the University in 2011. This would not have been possible without the unremitting efforts of Matthias Frosch, who secured this status during his several-year term as spokesperson of ZINF. We are indebted to him for safely steering the research centre during times of transition after both Jörg Hacker and Werner Goebel retired from an active role at ZINF.

Along the same line, we gratefully acknowledge 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. With its 20th anniversary lurking around the corner for 2013, we are looking forward to the next years of exciting research activities in ZINF.

Jörg Vogel
Würzburg, July 2012

1 General remarks
1.1 Sprecherbericht für den Zeitraum 2009-11

Liebe Kolleginnen und Kollegen,

Infektionskrankheiten stellen nach wie vor eine immense globale Herausforderung dar. Im aktuellen Berichtszeitraum (2009-2011) wurden wir an diesen Fakt auch hier in Deutschland auf besonders eindringliche Weise erinnert, als ein Ausbruch von Fällen blutiger Durchfälle und des hämolytisch-urämischen Syndroms (HUS) 50 Menschen das Leben kostete. Ursache war ein neuartiger Erreger, *Escherichia coli* O104:H4, der nicht nur zu tausenden von Erkrankungen führte, sondern auch das wirtschaftliche Leben in Europa empfindlich beeinträchtigte. Zuvor hatte bereits die Influenzapandemie von 2009 ein drastisches Beispiel dafür geliefert, in welch atemberaubender Geschwindigkeit sich Infektionserreger entwickeln und durch den internationalen Reiseverkehr verbreiten. Ursprünglich aus Mexiko stammend forderte die sogenannte "Schweinegrippe" ihren Tribut in zahlreichen Ländern und brachte Interventionsprogramme durch den Mangel an Impfstoff weltweit an ihr Limit. Andere Infektionskrankheiten wie Polio oder Tuberkulose, die wir längst unter Kontrolle glaubten, treten erneut auf und verursachen enorme Gesundheitsprobleme im globalen Maßstab.

Das Zentrum für Infektionsforschung (ZINF) der Universität Würzburg widmet sich seit 1993 der Erforschung molekularer Prinzipien krankheitserregender Mikroorganismen. Dazu bringt es Experten aus Mikrobiologie, Parasitologie, Virologie und Immunologie sowie Chemiker und klinisch tätige Ärzte zusammen. Gegründet von Volker ter Meulen, Werner Goebel und zahlreichen weiteren Kollegen 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) dauerhaft durch die Bayerische Staatsregierung und die Universität Würzburg gesichert. Jörg Hacker übernahm 2008 die Präsidentschaft des Robert-Koch-Institus, Deutschlands zentraler Einrichtung auf dem Gebiet der Krankheitsüberwachung und –prävention, bevor er seine jetzige Position als Präsident der Nationalen Akademie der Wissenschaften Leopoldina antrat. Nach drei wichtigen Jahren der Leitung des ZINF durch Matthias Frosch hatte ich im Frühjahr 2011 die Ehre, als Sprecher des Zentrums gewählt zu werden.

Der aktuelle Jahresbericht faßt die Projekte und wissenschaftlichen Leistungen der Nachwuchsgruppen zusammen, die den Kern des ZINF bilden. Darüber hinaus soll der Bericht einen Überblick über die Forschungsaktivitäten der ZINF-Mitglieder geben, die einen Beitrag zum besseren Verständnis von Infektionskrankheiten im Zeitraum 2009-2011 geleistet haben. Dies waren außerordentlich bewegte und spannende Jahre im Hinblick auf personelle und örtliche Veränderungen. Zuallererst ist hier der Umzug des Instituts für Molekulare Infektionsbiologie (IMIB), das auch die ZINF-Nachwuchsgruppen beherbergt, in ein neues Forschungsgebäude im September 2009 zu nennen. Wir befinden uns seither am Klinikcampus der Universität unter dem selben Dach mit dem Rudolf-Virchow-Zentrum. Dessen Leiter, Martin Lohse, hatte seinerzeit gemeinsam mit Jörg Hacker erfolgreich für die Umgestaltung der ehemaligen Chirurgischen Klinik in ein interdisziplinäres biomedizinisches Forschungszentrum geworben, und dieses Projekt durch die großzügige Unterstützung der Bayerischen Staatsregierung auf den Weg gebracht.

Herzstück des ZINF ist nach wie vor das Nachwuchsgruppenprogram m, das beispielgebend für die frühe Förderung unabhängiger junger Wissenschaftler in Deutschland ist. Der Erfolg der vier geförderten Gruppen zeigt sich nicht zuletzt darin, dass im Berichtszeitraum zwei Gruppenleiter Rufe an andere Universitäten erhielten. So wechselte Gabriele Pradel an die RWTH Aachen, wo sie ihre Arbeiten zur Blockierung der Malariaübertragung als Gruppenleiterin "Molekulare Parasitologie" fortsetzt. Kürzlich nahm Sven Krappmann, ein Mykologe mit dem Forschungsschwerpunkt *Aspergillus*, den Ruf auf eine W2-Professur für Klinische Mikrobiologie und Immunologie an die Universität Erlangen-Nürnberg an. Um die so freigewordenen Gruppenleiterstellen erneut zu besetzen, organisierten wir im März 2010 und April 2011 jeweils ein Symposium, in deren Ergebnis es uns gelang, vielversprechende junge Wissenschaftler von angesehenen internationalen Institutionen zu gewinnen. Im Jahr 2010 wechselte Daniel Lopez von der Harvard Medical School Boston an das ZINF, um eine eigene Arbeitsgruppe zum Forschungsthema Biofilme in Gram-positiven Bakterien (wie z.B. Staphylokokken) zu etablieren. Im selben Jahr begann Cynthia Sharma vom Max-Planck-Institut für Infektionsbiologie in Berlin ihre Arbeit mit dem Schwerpunkt auf Entwicklung und Anwendung von Hochdurchsatz-Sequenziermethoden zur Analyse bedeutender Humanpathogene wie etwa *Helicobacter* und *Campylobacter*.

Das zweite Symposium hatte die erfolgreiche Rekrutierung von Nicolai Siegel vom Pasteur-Institut in Paris zum Ergebnis. Er widmet sich epigenetischen Mechanismen der Genregulation in Parasiten und verstärkt damit die derzeit wachsende Expertise an der Universität auf dem Gebiet der Trypanosomen-Forschung. Bei der Auswahl waren wir hochzufrieden, sowohl was die Anzahl der Bewerber auf diese Positionen angeht als auch mit deren hohem wissenschaftlichen Niveau. Dies zeigt, dass der Standort Würzburg eine große Anziehungskraft für junge Wissenschaftler auf der Suche nach attraktiven Forschungsmöglichkeiten besitzt. Über die direkte Forschungsarbeit hinaus heißen wir Stan Gorski als neuen Wissenschaftskoordinator am ZINF willkommen. Er war früher Wissenschaftsredakteur in Heidelberg und wird künftig dabei helfen, die Aktivitäten des ZINF koordinieren. Er hat bereits die Erstellung des aktuellen Berichtes redaktionell betreut.

Wie immer war uns unser internationaler wissenschaftlicher Beirat eine unschätzbare Hilfe bei der Auswahl neuer Arbeitsgruppenleiter und der Planung neuer Forschungsaktivitäten. Wir möchten uns an dieser Stelle für die konstruktive und kritische Begleitung bei allen Beiratsmitgliedern herzlich bedanken. Dies gilt insbesondere dem ehemaligen Mitglied Cesare Montecucco, der 2009 aus dem Gremium ausschied. Wir freuen uns, dass Eliora Ron (Tel Aviv) sich bereit erklärt hat, für eine weitere Dreijahresperiode bis 2012 dem Beirat anzugehören. Neu berufene Mitglieder seit 2009 sind Axel Brakhage (Jena), Christoph Dehio (Basel), Jean Langhorne (London), Richard Lucius (Berlin), Mariagrazia Pizza (Siena), and Sebastian Suerbaum (Hannover). Derzeit wird der wissenschaftliche Beirat erweitert (siehe Kapitel 1.3).

Der Erfolg der Würzburger Infektionsforschung wird auch durch eine Reihe angesehener Forschungspreise und Ehrungen deutlich. Von den Nachwuchsgruppenleitern erhielt Gabriele Pradel 2010 die Karl-Asmus-Rudolphi-Medaille der Deutschen Gesellschaft für Parasitologie und Cynthia Sharma wurde mit den jeweiligen Hauptpreisen der Robert-Koch-Stiftung und der Ingrid-zu-Solms-Stiftung 2011 geehrt. Unter den ZINF-Mitgliedern wurde Heidrun Moll 2010 zur Präsidentin der Deutschen Gesellschaft für Parasitologie gewählt, und Caroline Kisker wurde 2011 als Mitglied in die Nationale Akademie der Wissenschaften Leopoldina aufgenommen.

Jörg Vogel erhielt die jeweiligen Forschungshauptpreise der beiden maßgeblichen deutschen mikrobiologischen Gesellschaften VAAM (2010) und DGHM (2011). Weiterhin wurde er als einer von insgesamt neun deutschen Wissenschaftlern 2011 mit der Mitgliedschaft in der *European Molecular Biology Organisation* (EMBO) ausgezeichnet.

Auch im vergangenen Berichtszeitraum haben wir unsere Bemühungen fortgesetzt, das Umfeld für die Infektionsforschung an der Universität Würzburg durch die Einwerbung von Drittmittel weiter zu verbessern. Meilensteine dabei waren die Verlängerung der Förderung des SFB 630 (Sprecher Gerhard Bringmann), der sich mit der Charakterisierung neuer antiinfektiver Substanzen befaßt, sowie der Start des Programmes Medizinische Infektionsgenomik (Sprecher Matthias Frosch), das dem BMBF-finanzierten Kompetenznetz *PathoGenoMics* folgt. Die ZINF-Mitglieder warben erfolgreich Drittmittel in zahlreichen nationalen und europäischen Programmen ein. Dazu gehören beispielsweise das ERA-NET, der DFG-finanzierte Transregio-SFB TRR34 *Pathophysiology of Staphylococci,* die DFG-Schwerpunktprogramme SPP1316 *Host-Adapted Metabolism of Bacterial Pathogens* und SPP1580 *Intracellular compartments as places of pathogen-host-interactions* sowie das BMBF-geförderte Netzwerk *RNomics of Infections*. Die kürzlich erfolgte Wahl des ZINF-Beiratsmitglied Thomas Hünig zum Sprecher des Interdisziplinären Zentrums für Klinische Forschung (IZKF) zeigt, wie sehr an der Universität Würzburg auf Infektionsforschung mit klinischer Relevanz Wert gelegt wird.

Die Ausbildung von Doktoranden und Postdoktoranden ist und bleibt eine Schlüsselaufgabe des ZINF. Folgerichtig haben wir 2011 aktiv die Bewerbung um Förderungsverlängerung der *Graduate School for Life Sciences* (GSLS), deren Dekanin das ZINF-Mitglied Caroline Kisker ist, im Rahmen der Exzellenzinitiative tatkräftig unterstützt. Infektion & Immunität ist eine von fünf Klassen der GSLS, und sie bietet derzeit drei Trainingsprogramme (Infektion, Imunmodulation und Antiinfektiva) an. Auf internationaler Ebene gab das Deutsch-Südafrikanische Graduiertenkolleg 1522 Doktoranden aus beiden Ländern die Gelegenheit, in den jeweiligen Partnerlaboratorien zu arbeiten und ihre Arbeit auf Symposien in Kapstadt und Würzburg vorzustellen. Das Kolleg, dessen Sprecher das ZINF-Mitglied Axel Rethwilm ist, wird durch die DFG und deren südafrikanische Schwesterorganisation NRF gefördert.

Unsere Studenten und Postdocs profitierten darüber hinaus von zahlreichen hochkarätigen Tagungen in Würzburg mit Bezug zur Infektionsforschung. So leitete Thomas Rudel die Organisation eines FEMS-Leopoldina-Symposiums zum Thema *Emerging Topics in Microbial Pathogenesis*. Jörg Vogel, Alex Böhm und die ZINF-Nachwuchsgruppenleiter schlossen sich mit den Redakteuren der angesehenen wissenschaftlichen Zeitschrift *Molecular Microbiology* zusammen, um eine neue Art von wissenschaftlicher Tagung ins Leben zu rufen, die dann auch erstmals 2011 in Würzburg stattfand und die aufgrund der positiven Resonanz in den kommenden Jahren fortgeführt werden wird.

Insgesamt hat sich das ZINF als äußerst lebendige Institution etabliert, um Wissenschaftler mit einem starken Interesse an molekularen Ursachen von Infektionskrankheiten zu vernetzen und interdisziplinäres Arbeiten auf lokaler und internationaler Ebene zu ermöglichen. Die Bedeutung, die das ZINF für die wissenschaftliche Profilschärfung unserer Universität hat, drückt sich auch im Status als Zentrale Einrichtung der Universität Würzburg aus, der dem ZINF kürzlich verliehen wurde. Dies wäre ohne die unermüdliche Arbeit von Matthias Frosch in seiner mehrjährigen Rolle als ZINF-Sprecher nicht möglich gewesen. Wir sind ihm dankbar dafür, dass er das Zentrum in den Zeiten des Übergangs, nachdem sowohl Jörg Hacker als auch Werner Goebel sich von ihrer aktiven Rolle im ZINF zurückgezogen hatten, sicher geführt hat.

Gleichfalls bedanken wir uns beim Bayerischen Staatsministerium für Wissenschaft, Forschung und Kunst für die großzügige Förderung, und beim Präsidium der Universität Würzburg für die kontinuierliche Unterstützung und Ermutigung. Ermutigt durch unseren früheren Erfolge haben wir neue Initiativen gestartet, um die Herausforderungen auf dem Gebiet der Infektionskrankheiten im 21. Jahrhundert zu meistern. Mit dem 20. Jahrestag seines Bestehens 2013 bereits fest im Blick, freuen wir uns auf die nächsten Jahre mit spannender Wissenschaft und vielen neuen Forschungsaktivitäten im ZINF.

Jörg Vogel
Würzburg, Juli 2012

1 General remarks
1.2 Members of the Research Center for Infectious Diseases (ZINF)

1.2.1 Speakers and Steering committee:

Prof. Dr. Jörg Vogel
Speaker (since 4/2011)
Institut für Molekulare Infektionsbiologie
Josef-Schneider-Str. 2/ D15
97080 Würzburg
Phone: +49-931-3182576
joerg.vogel@uni-wuerzburg.de

Prof. Dr. Hermann Einsele
Medizinische Klinik und Poliklinik II
Gebäude ZIM, Ebene: A3.-1
Oberdürrbacher Straße 6
97080 Würzburg
Phone: +49-931-201-40000
einsele_h@klinik.uni-wuerzburg.de

Prof. Dr. Axel Rethwilm
Institut für Virologie und Immunbiologie
Versbacher Str. 7
97078 Würzburg
Phone: +49-931-201-49554
axel.rethwilm@mail.uni-wuerzburg.de

Prof. Dr. Matthias Frosch
Speaker (3/2008-3/2011)
Institut für Hygiene und Mikrobiologie
Josef-Schneider-Str. 2/E 1
97080 Würzburg
Phone: +49-931-201-46160
mfrosch@hygiene.uni-wuerzburg.de

Prof. Dr. Thomas Hünig
Institut für Virologie und Immunbiologie
Versbacher Str. 7
97078 Würzburg
Phone: +49-931-201-49951
huenig@vim.uni-wuerzburg.de

Prof. Dr. Thomas Rudel
Lehrstuhl für Mikrobiologie
Theodor-Boveri-Institut für
Biowissenschaften, Biozentrum
Am Hubland
97074 Würzburg
Phone: +49-931-3184401
thomas.rudel@biozentrum.uni-wuerzburg.de

1.2.2 Young Investigator Group Leaders:

Dr. Daniel Lopéz
(since 2010)
Zentrum für Infektionsforschung
Josef-Schneider-Str. 2/ D15
97080 Würzburg
Phone: +49-931-3183831
daniel.lopez@uni-wuerzburg.de

Priv.-Doz. Dr. Gabriele Pradel
(2005-2011)
RWTH - Institut für Molekulare Biotechnologie
52074 Aachen
42B, Room 159
Worringerweg 1
Phone: +49-241-8028123
gabriele.pradel@molbiotech.rwth-aachen.de

Dr. T. Nicolai Siegel
(since 2012)
Zentrum für Infektionsforschung
Josef-Schneider-Str. 2/ D15
97080 Würzburg
Phone: +49-931-3188499
nicolai.siegel@uni-wuerzburg.de

Priv.-Doz. Dr. Sven Krappmann
(2007-5/2012)
Mikrobiologisches Institut
Universitätsklinikum Erlangen
Wasserturmstr. 3/5
D-91054 Erlangen, Germany
Phone: +49-9131-85-22580
Sven.Krappmann@uk-erlangen.de

Dr. Cynthia Sharma
(since 2010)
Zentrum für Infektionsforschung
Josef-Schneider-Str. 2/ D15
97080 Würzburg
Phone: +49-931-3182560
cynthia.sharma@uni-wuerzburg.de

1.2.3 Scientific Members of the Research Center for Infectious Diseases:

Dr. Alexander Böhm
Institut für Molekulare Infektionsbiologie
Josef-Schneider-Str. 2/D15
97080 Würzburg
Phone: +49-931-3183695
alexander.boehm@uni-wuerzburg.de

Prof. Dr. Ute Hentschel-Humeida
Julius-von-Sachs-Institut für Biowissen-
schaften
Julius-von-Sachs-Platz 3
97082 Würzburg
Phone: +49-931-3182581
ute.hentschel@uni-wuerzburg.de

Prof. Dr. Sibylle Schneider-Schaulies
Institut für Virologie und Immunbiologie
Versbacher Str. 7
97078 Würzburg
Phone: +49-931-201-49895
s-s-s@vim.uni-wuerzburg.de

Prof. Dr. Klaus Brehm
Institut für Hygiene und Mikrobiologie
Josef-Schneider-Str. 2/E1
97080 Würzburg
Phone: +49-931-3146168
kbrehm@)hygiene.uni-wuerzburg.de

Prof. Dr. Thomas Herrmann
Institut für Virologie und Immunbiologie
Versbacher Str. 7
97078 Würzburg
Phone: +49-931-201-49955
herrmann-t@vim.uni-wuerzburg.de

Prof. Dr. Alexandra Schubert-Unkmeir
Institut für Hygiene und Mikrobiologie
Josef-Schneider-Str. 2/E1
97080 Würzburg
Phone: +49-931-3146721
aunkmeir@hygiene.uni-wuerzburg.de

Prof. Dr. Dr. h.c. Gerhard Bringmann
Lehrstuhl für Organische Chemie I
Am Hubland
97074 Würzburg
Phone: +49-931-3185323
bringman@chemie.uni-wuerzburg.de

Prof. Dr. Caroline Kisker
Rudolf-Virchow-Zentrum/
Experimentelle Biomedizin
Josef-Schneider-Str. 2/D15
97080 Würzburg
Phone: +49-931-3180381
caroline.kisker@virchow.uni-wuerzburg.de

Priv.-Doz. Dr. August Stich
Missionsärztliche Klinik
Abt. Tropenmedizin
Salvatorstr. 7
97067 Würzburg
Phone: +49-931-791-2821
stich@missioklinik.de

Prof. Dr. Thomas Dandekar
Lehrstuhl für Bioinformatik
Biozentrum
Am Hubland
97074 Würzburg
Phone: +49-931-3184551
dandekar@biozentrum.uni-wuerzburg.de

Prof. Dr. Hartwig Klinker
Medizinische Klinik und Poliklinik II
Zertifiziertes Zentrum für Infektiologie (DGI)
Oberdürrbacher Straße 6
97080 Würzburg
Phone: +49-931-201-40043
Klinker_H@medizin.uni-wuerzburg.de

Prof. Dr. Max Topp
Med. Klinik und Poliklinik II
Immun- und Gentherapie
Versbacherstraße 5
Gebäude E4
97078 Würzburg
Phone: +49-931-201-40015
Topp_M@medizin.uni-wuerzburg.de

Prof. Dr. Markus Engstler
Lehrstuhl für Zell- und Entwicklungsbiologie
Biozentrum
Am Hubland
97074 Würzburg
Phone: +49-931-3180060
markus.engstler@biozentrum.uni-wuerzburg.de

Prof. Dr. Manfred Lutz
Institut für Virologie und Immunbiologie
Versbacher Str. 7
97078 Würzburg
Phone: +49-931-201-49957
m.lutz@vim.uni-wuerzburg.de

Prof. Dr. Ulrich Vogel
Institut für Hygiene und Mikrobiologie
Josef-Schneider-Str. 2/E1
97080 Würzburg
Phone: +49-931-3146802
uvogel@hygiene.uni-wuerzburg.de

Dr. Ana Eulálio
Institut für Molekulare Infektionsbiologie
Josef-Schneider-Str. 2/D15
97080 Würzburg
Phone: +49-931-3189078
ana.eulalio@uni-wuerzburg.de

Prof. Dr. Heidrun Moll
Institut für Molekulare Infektionsbiologie
Josef-Schneider-Str. 2/D15
97080 Würzburg
Phone: +49-931-3182627
heidrun.moll@uni-wuerzburg.de

Prof. Dr. Heike Walles
Lehrstuhl für Tissue Engineering und Re-
generative Medizin
Röntgenring 11
97070 Würzburg
Phone: +49-931-3188828
heike.walles@uni-wuerzburg.de

Prof. Dr. Roy Gross
Lehrstuhl für Mikrobiologie
Theodor-Boveri-Institut für
Biowissenschaften, Biozentrum
Am Hubland
97074 Würzburg
Phone: +49-931-3184403
roy@biozentrum.uni-wuerzburg.de

Prof. Dr. Joachim Morschhäuser
Institut für Molekulare Infektionsbiologie
Josef-Schneider-Str. 2/D15
97080 Würzburg
Phone: +49-931-3182152
joachim.morschhaeuser@uni-wuerzburg.de

Priv. Doz. Dr. Wilma Ziebuhr
Institut für Molekulare Infektionsbiologie
Josef-Schneider-Str. 2/D15
97080 Würzburg
Phone: +49-931-3182154
w.ziebuhr@mail.uni-wuerzburg.de

1 General remarks
1.3 Members of the Scientific Advisory Board (SAB)

Prof. Eliora Ron (2005-2012)
Department of Molecular Microbiology
& Biotechnology
University of Tel Aviv
Ramat Tel Aviv
69978 Tel Aviv / ISRAEL
Phone: +972-3-64-09379
Email: eliora@post.tau.ac.il

Prof. Cesare Montecucco (2006-2009)
Dipartimento di Scienze Biomediche
Sperimentali
Università degli Studi di Padova
Via G. Colombo 3
35121 Padova / ITALY
Phone: +39-049-827-6058
Email: cesare.montecucco@unipd.it

Prof. Axel Brakhage (2009-2012)
Leipnizinstitut für Naturstoff-Forschung
und Infektionsbiologie
Hans-Knöll-Institut
Beutenberg 11 a
07745 Jena
Phone: +49-3641-532-1001
Email: axel.brakhage@hki-jena.de

Prof. Christoph Dehio (2009-2012)
Biozentrum der Universität Basel
Abteilung Infektionsbiologie
Klingelbergstr. 50/70
4056 Basel / SCHWEIZ
Phone: +41-61-267-2140
Email: christoph.dehio@unibas.ch

Prof. Richard Lucius (2009-2012)
Lehrstuhl für Molekulare Parasitologie
der Humboldt-Universität zu Berlin
Institut für Biologie
Philippstr. 3
10115 Berlin
Phone: +49-30-209-36053
Email: richard.lucius@rz.hu-berlin.de

Prof. Jean Langhorne (2009-2012)
The National Institute for Medical
Research
Division of Parasitology
The Ridgeway, Mill Hill
London, NW7 1AA / UK
Phone: +44-208 / 816-2558
Email: jlangho@nimr.mrc.ac.uk

Prof. Sebastian Suerbaum (2009-2012)
Medizinische Hochschule Hannover
Institut für Medizinische Mikrobiologie
und Krankenhaushygiene
Carl-Neuberg-Str. 1
30625 Hannover
Phone: +49-511-532-6769
Email: suerbaum.sebastian@mh-hannover.de

Dr. Mariagrazia Pizza (2009-2012)
Novartis Vaccines and Diagnostics
Via Fiorentina 1
5300 Siena / ITALY
Phone: +39-577-24-3390
Email: mariagrazia.pizza@novartis.com

New members of the SAB from 2012:

Prof. Michael Gilmore
Department of Ophthalmology
(Microbiology and Immunobiology)
Harvard Medical School
Mass Eye and Ear Infirmary
243 Charles St.
Boston, MA 02114 -USA
Phone: +1-617-573-3845
Email: michael_gilmore@meei.harvard.edu

Prof. David Holden
Centre for Molecular Microbiology
and Infection
Imperial College London
2.21 Flowers Building
South Kensiington Campus
London. SW7 2AZ – UK
Phone: +44-20-7594-3073
Email: d.holden@imperial.ac.uk

Prof. Agneta Richter-Dahlfors
Department of Neuroscience
Karolinska Institutet
Retzius väg 8
S-17177 Stockholm – SWEDEN
Phone: +8-524 874 25
Email: Agneta.Richter.Dahlfors@ki.se

Dr. Gisela Storz
Cell Biology and Metabolism Program
NICHD, Building 18T, Room 101
18 Library Dr MSC 5430
National Institutes of Health
Bethesda, Maryland 20892-5430 – USA
Phone: +1-301-402-0968
Email: storz@helix.nih.gov

Prof. Tone Tønjum
CMBN and Institute of Microbiology
University of Oslo
Rikshospitalet
NO-0027 Oslo – NORWAY
Phone: +47-23074065
Email: tone.tonjum@medisin.uio.no

2 Young Investigator Groups of the ZINF
2.1 Malaria: Transmission Blocking Strategies

CONTACT DETAILS

PD Dr. phil. nat. Gabriele Pradel

Zentrum für Infektionsforschung
Josef-Schneider-Str. 2/D15
97080 Würzburg

since January 2012:
Institute for Molecular Biotechnology
RWTH Aachen University
Worringerweg 1
52074 Aachen

Phone: +49-241-8028123
E-Mail: gabriele.pradel@molbiotech.rwth-aachen.de
www.molbiotech.rwth-aachen.de/Groups/molmalaria

RESEARCH GOALS

- *Investigate the assembly of multimeric protein complexes in the malaria parasite sexual stages*
- *Evaluate the plasmodial proteasome as a transmission blocking drug target*
- *Unveil the mechanisms of host cell egress by activated malaria gametocytes*
- *Determine the impact of human complement on sexual reproduction of malaria parasites*
- *Evaluate sexual stage antigens as malaria transmission blocking targets*

Summary

The tropical disease malaria, which is caused by the protozoan parasite *Plasmodium*, is a major health threat as well as a great economic burden. Currently, there is no vaccine in circulation for the treatment of malaria, and pharmaceutical approaches are increasingly encountering parasite drug resistance. The intra-erythrocytic multiplication cycles of the parasite within the human host cause the typical symptoms of the disease, such as fever and anemia. Sexual reproduction, on the other hand, takes place in the midgut of the mosquito vector, once the parasites have been taken up with the blood meal, and the sexual stage parasites play a crucial role for the completion of the life cycle and transmission of the disease. The sexual stages represent a bottleneck in the spread of the parasite with an approximate 1000-fold loss in abundance occurring during transmission to the mosquito. They are therefore prime targets for transmission blocking strategies that are intended to eliminate all parasites that have entered the sexual pathway and which would thus inhibit it's further development ini the mosquito vector. Transmission-blocking strategies provide a stopgap measure against the transmission of drug-resistant genotypes from human to human by the mosquito. It is the aim of the group to characterize plasmodial proteins that are important for sexual stage differentiation and reproduction of *P. falciparum*, the causative agent of the deadly malaria tropica, and that thus may represent promising candidates for transmission blocking strategies.

Major Research

- *The assembly of multimeric protein complexes in the parasite sexual stages*

Parasite transmission is mediated by sexual precursor cells, the intraerythrocytic gametocytes that form in the human host. We have shown that during gametocyte differentiation, a high number of surface-associated adhesion proteins are expressed, which assemble into multimeric protein complexes (MPCs). Mass spectrometric analysis of precipitated MPCs identified an additional MPC component, a plasmodial protein with WD40 domains, suggesting a role of the protein in the assembly and stability of the MPCs. Indirect immunofluorescence assays revealed that the WD40 protein co-localizes with the MPCs. It is now our aim to investigate the molecular composition of the gametocyte MPCs in detail and to functionally characterize the WD40 protein.

- *The plasmodial proteasome as a novel transmission blocking drug target*

We have demonstrated that the antibiotic thiostrepton and its derivatives interfere with the plasmodial proteasome, a multimeric protease complex important for degradation of ubiquitinated proteins. Thiostrepton rapidly kills blood stage parasites and also exhibits gametocytocidal activity by eliminating gametocytes. Expression profiling has revealed that the plasmodial proteasome is present in the nucleus and cytoplasm of trophozoites, schizonts and gametocytes. Our data indicate that the proteasome of *Plasmodium* might represent a novel multi-stage drug target for chemotherapeutic intervention and transmission blocking purposes.

- *Mechanisms of host cell egress by activated gametocytes*

Gametocytes are transmitted from the human to the mosquito during a blood meal. In the midgut they become activated by external stimuli and subsequently egress from the enveloping erythrocyte, which is a crucial step for the parasite to prepare for fertilization. We have shown that *P. falciparum* gametocytes exit the erythrocyte by an inside-out type of egress. The parasitophorous vacuole membrane (PVM) ruptures at multiple perforation sites within less than a minute following activation, a process that is sensitive to the cysteine protease inhibitor E-64d. Following PVM rupture the inner membrane complex begins to disintegrate.

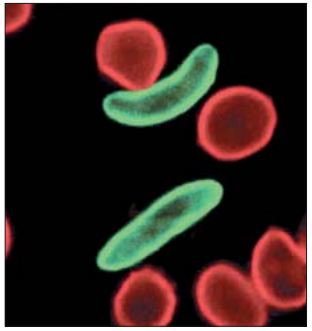


Fig. 1: Plasmodium falciparum gametocytes expressing Pfs230 (green). Erythrocytes counterstained with Evans Blue (red).

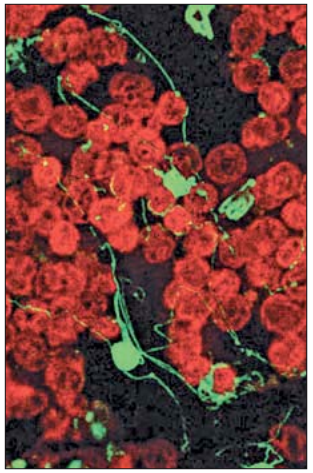


Fig. 2: Formation of nanotubes in activated Plasmodium falciparum gametocytes. Gametocytes labeled with anti-Pfs230 (green), erythrocytes counterstained with Evans Blue (red).

At 15 minutes post-activation, the erythrocyte membrane ruptures at a single breaking point, which can be inhibited by the cysteine/serine inhibitors TLCK and TPCK. In all cases inhibitor treatment resulted in interrupted gametogenesis.

- *The splicing-associated PfCLK kinases in the parasite blood stages*

We have investigated the roles of two cyclin-dependent kinase-like (CLK) kinases, PfCLK-1, and PfCLK-2. Both PfCLKs share homology with the yeast Serine/Arginine protein kinase Sky1p and are expressed throughout the asexual blood stages and in gametocytes. PfCLK-1 contains two nuclear localization sequences and PfCLK-2 possesses one of these sequences upstream of the C-terminal catalytic domains. Indirect immunofluorescence, western blot and electron microscopy data confirmed that the kinases are primarily localized in the parasite nucleus, with PfCLK-2 being also present in the cytoplasm. The two kinases are important for completion of the asexual replication cycle of *P. falciparum*, as demonstrated by reverse genetics approaches. In vitro kinase assays showed substrate phosphorylation by the PfCLKs, including the plasmodial alternative splicing factor PfASF-1. Our data indicate a crucial role of the PfCLKs for malaria blood stage parasites, presumably by participating in gene regulation through the post-transcriptional modification of mRNA.

- *The formation of filamentous cell-cell contacts between gametes during sexual reproduction*

Physical contact is important for the interaction between animal cells, but can represent a major challenge for protists like malaria parasites. We have identified small dynamic tubular structures in *P. falciparum*, which emerge from the surfaces of the forming gametes upon gametocyte activation in the mosquito midgut. These filaments can exhibit a length of more than 100 μm and contain the F-actin isoform actin-2. They actively form within a few minutes after gametocyte activation, originate from the parasite plasma membrane, and express adhesion proteins like Pfs230, Pfs48/45 or Pfs25 on their surface. The tubular structures represent long-distance cell-to-cell connections between sexual stage parasites. The malaria parasites may utilize these adhesive tubules in order to facilitate intercellular contact between gametes during sexual reproduction in the mosquito midgut.

- *Mechanisms of complement evasion by sexual stage parasites*

The human complement is a first line of defense against microbial infections. Numerous pathogens have evolved strategies to evade recognition and destruction by human complement by mimicking host cell surfaces. We have shown that the emerging gametes of *P. falciparum* bind the complement regulator factor H (FH) following transmission to the mosquito, which protects the cells from complement-mediated lysis by the blood meal. The human complement system is active in the mosquito midgut for approximately 1 h post-feeding. During this time period, macrogametes recruit FH and use surface bound FH to inactivate C3b. We identified the plasmodial transmembrane protein PfGAP50 on the macrogamete surface as the FH-binding protein. Loss of FH-mediated protection results in significantly impaired gametogenesis and inhibited parasite transmission to the mosquito. This is the first demonstration of a protozoan parasite co-opting human FH to evade complement-mediated lysis. FH-binding receptor proteins of the sexual stage parasites can in the future be exploited as novel transmission blocking vaccine targets.

SELECTED PUBLICATIONS

- *Sologub L, Kuehn A, Kern S, Przyborski J, Schillig R, Pradel G (2011) Malaria proteases mediate inside-out egress of gametocytes following parasite transmission to the mosquito.* ***Cell Microbiol*** *13:897-912*
- *Rupp I, Sologub L, Williamson KC, Scheuermayer M, Reininger L, Doerig C, Eksi S, Kombila DU, Frank M, Pradel G (2011) Malaria parasites form filamentous cell-to-cell connections during reproduction in the mosquito midgut.* ***Cell Res*** *21:683-696*
- *Aminake MN, Schoof S, Sologub L, Leubner M, Kirschner M, Arndt HD, Pradel G (2011) Thiostrepton and derivatives exhibit antimalarial and gametocytocidal activity by dually targeting parasite proteasome and apicoplast.* ***Antimicrobial Agents Chemother*** *55:1338-1348*
- *Simon N, Scholz SM, Moreira C, Templeton TJ, Kuehn A, Dude MA, Pradel G (2009) Sexual stage adhesion proteins form multi-protein complexes in the malaria parasite Plasmodium falciparum.* ***J Biol Chem*** *284:14537-14546*

EXTRAMURAL FUNDING

- *DFG SPP1580: Intracellular compartments as places of pathogen-host interactions. Project: the egress of malaria gametocytes form the red blood cell following parasite transmission to the mosquito*
- *Fraunhofer Future Foundation Malaria Project: Functional evaluation of vaccine candidates against the Plasmodium sexual stages*
- *EU 7th Framework Programme: Signalling in life cycle stages of malaria parasites*
- *DFG IRTG 1522: HIV/AIDS and associated Infectious Diseases in South Africa. Project: Generation and characterization of candidates for malaria/HIV combination therapy*
- *DFG SFB 479: Pathogen Variation and Host Response in Infectious Diseases. Project: Identification of molecular interactions during fertilization in the malaria pathogen Plasmodium falciparum*
- *DFG Emmy Noether programme: Characterization of a novel multi-adhesion protein family expressed in the sexual stages of the human malaria pathogen Plasmodium falciparum*

2 Young Investigator Groups of the ZINF
2.2 Aspergillus Pathogenicity

CONTACT DETAILS

PD Dr. rer. nat.
Sven Krappmann

Zentrum für Infektionsforschung
Josef-Schneider-Str. 2/D15
97080 Würzburg

since May 2012:
Institut für Klinische Mikrobiologie
Universitätsklinikum Erlangen
Friedrich-Alexander-Universität Erlangen-Nürnberg
Wasserturmstr. 3/5
D-91054 Erlangen, Germany
Phone: +49-9131-85-22580
E-Mail: Sven.Krappmann@uk-erlangen.de

RESEARCH GOALS

- *Analysis of fungal metabolism as a virulence determinant in invasive aspergillosis*
- *Gaining insights into the host-pathogen interplay during hematogenous dissemination*
- *Molecular characterisation of extant A. fumigatus sexuality*
- *New molecular tools for Aspergillus*

Summary

Filamentous fungi of the genus *Aspergillus* are omnipresent in the environment, residing in the soil or on decaying plant material. Besides their fundamental role in cycling macroelements such as nitrogen or carbon, these moulds have emerged as opportunistic pathogens in distinct clinical settings. The predominant species to cause aspergillosis is *A. fumigatus* (Fig. 1), which is widely distributed on a global scale. Its asexual spores usually enter a susceptible host by inhalation and result in invasive pulmonary aspergillosis that eventually may develop into a systemic form after dissemination via the blood stream. Given the fact that the virulence of *A. fumigatus* is a multi-factorial trait, its nutritional versatility has been coined as a determinant of pathogenesis, enabling the fungal pathogen to grow and thrive in the host. We have focused our work on nitrogen metabolism in *A. fumigatus*, its interplay with the host during hematogenous dissemination, and the extant sexuality of this ascomycete. By targeting the *A. fumigatus* oligopeptide transporter gene family, we have demonstrated redundancy in transport mechanisms for proteinaceous breakdown products. Profiling studies have illustrated the reprogramming of the fungal transcriptome in the presence of blood, and revealed an influence on thrombocyte aggregation. Furthermore, the molecular characterisation of *A. fumigatus* mating has established that the bipolar mating-type system is required for fruiting body formation.

Major Research

- *Saprobic pathogen looking for food*

As an ubiquitously distributed environmental mould and opportunistic pathogen, *A. fumigatus* has evolved to feed on complex polymeric substrates and host tissue, respectively, by osmotrophy. This is characterised by extracellular degradation of the surrounding matrix by hydrolysis and uptake of breakdown products via specialised transporters. However, the role of these metabolic processes in pathogenesis is not well understood. To address this aspect of *Aspergillus* metabolism as a presumed virulence determinant, we have investigated the role of oligopeptide transport during invasive aspergillosis. The *A. fumigatus* genome encodes eight transporters that correspond to a single gene family, called opt. We have generated an *A. fumigatus* mutant strain devoid of oligopeptide transport activity by sequentially deleting all of the *opt* genes, this has also been combined with a deletion strain for the PrtT regulator of extracellular proteolytic activity. While the absence of oligopeptide transport alone did not influence the growth of *A. fumigatus* on proteinaceous substrates, a strong growth defect in the *optΔ; prtTΔ* mutant was evident on porcine lung agar (Fig. 2). This prominent phenotype, however, did not translate into a neutropenic murine model of invasive pulmonary aspergillosis, where the mutant strains remained as virulent as their wild-type progenitor isolates. In essence, these results demonstrate a high degree of redundancy in the mechanisms of degradation of proteinaceous substrates and uptake of primary breakdown products and highlight the nutritional versatility of *A. fumigatus* when exploiting complex growth substrates. In order to investigate a fungal-specific and less redundant pathway, we analysed the role of aromatic amino acid biosynthesis in pulmonary aspergillosis since this biosynthetic pathway is absent in mammalian hosts

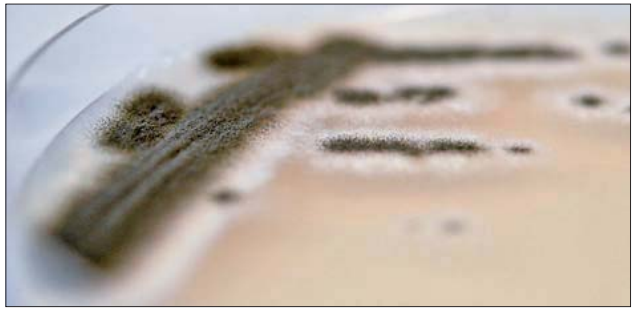


Fig. 1: The mould Aspergillus fumigatus. Close-up on a mycelium with conidiophores giving rise to the green-gray asexual spores that serve as infectious propagules.

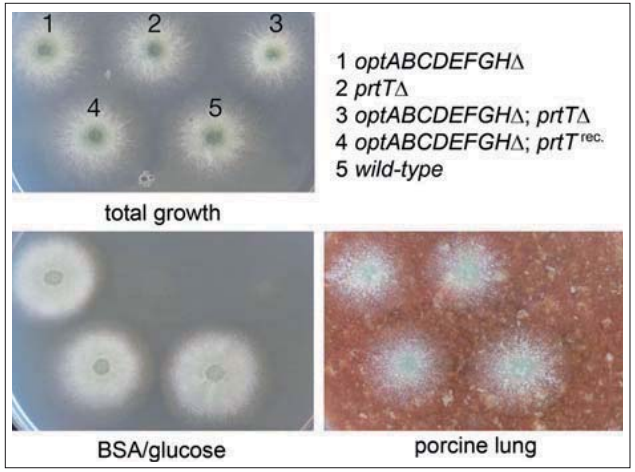


Fig. 2: Oligopeptide transport and regulation of extracellular proteolysis are required for growth of Aspergillus fumigatus on complex substrates. Deletion of the prtT gene in an octuple optΔ genetic background results in a synthetic growth defect on porcine lung tissue agar.

and therefore represents a potential target for antifungal substances. By generating a set of corresponding auxotroph *A. fumigatus* mutant strains, followed by *in vitro* phenotyping accompanied by *in vivo* gene silencing, we demonstrated the necessity of aromatic amino acid biosynthesis in pulmonary and systemic aspergillosis since the mutants were severely attenuated for virulence. This provides support for the targeting of this fungal-specific anabolic pathway as a promising candidate for antifungal therapy.

- *Characterising the fungus-host interplay on a bloody level*

Angioinvasion and dissemination via the bloodstream represent crucial events during the progression of aspergillosis in the susceptible host. This is likely to be reflected in changes in gene expression within the pathogen. In order to monitor the fungal transcriptome in human blood, a corresponding culture model was established and changes in transcript levels were assessed using microarrays. These profiling studies yielded insights into fungal adaptation processes during hematogenous dissemination, with remodelling of RNA-related processes, general metabolism, sterol synthesis and cell wall assembly, thus identifying potential novel virulence determinants for invasive aspergillosis. Moreover, we have investigated the interaction of *A. fumigatus* with components of host hemostasis. For this purpose, culture supernatants as well as morphotypes were assessed for their capacity to interfere with aggregation of human thrombocytes to find a pronounced effect: whereas addition of culture supernatants or hyphae results in a significant increase of aggregation, we have shown that secretion of proteases inhibits this cellular process. Most interestingly, a secondary metabolite produced by the fungus interferes with platelet aggregation in a dose dependent-manner, although the mechanistic details on this aspect of the intimate host-pathogen interplay remain to be discovered.

- *Components for fastidious sex*

The recently identified sexuality of *A. fumigatus* (teleomorph: *Neosartorya fumigata*), i.e., its ability to form fruiting bodies that contain recombinant ascospores, which takes place under highly specific environmental conditions, has recently been suggested to contribute to its virulence potential. By crossing compatible and unrelated clinical isolates of *A. fumigatus* we could demonstrate that sexual fruiting body formation is a general trait of this ascomycete. Moreover, by generating defined deletion mutants for the mating-type loci, the strict necessity of each *MAT1* idiomorph for successful cleistothecia formation was verified as well as their influence on expression of mating-related transcripts. More specifically, the cellular role of the NsdD transcriptional activator for sexual development was analysed to reveal its role in hyphal fusion, a prerequisite for heterokaryon formation and therefore sexual recombination.

SELECTED PUBLICATIONS

- *Hartmann T, Cairns TC, Olbermann P, Morschhäuser J, Bignell EM, Krappmann S (2011) Oligopeptide transport and regulation of extracellular proteolysis are required for growth of Aspergillus fumigatus on complex substrates but not for virulence.* ***Mol Microbiol*** *82:917-935*
- *Stuehler C, Khanna N, Bozza S, Zelante T, Moretti S, Kruhm M, Lurati S, Conrad B, Worschech E, Stefanovi S, Krappmann S, Einsele H, Latgé JP, Loeffler J, Romani L, Topp MS (2011) Cross-protective TH1 immunity against Aspergillus fumigatus and Candida albicans.* ***Blood*** *117:5881-5891*
- *Szewczyk E, Krappmann S (2010) Conserved regulators of mating are essential for Aspergillus fumigatus cleistothecia formation.* ***Eukaryot Cell*** *9:774-783*
- *Bergmann A, Hartmann T, Cairns T, Bignell EM, Krappmann S (2009) A regulator of Aspergillus fumigatus extracellular proteolytic activity is dispensable for virulence.* ***Infect Immun*** *77:4041-4050*

EXTRAMURAL FUNDING

- *DFG SPP1160: Colonisation and infection by human-pathogenic fungi*
- *DFG-KR2294/1-3: Cross-pathway control, nitrogen metabolism, and their role in pathogenicity of Aspergillus fumigates*
- *ERA-NET PathoGenoMics: TRANSPAT-Transcriptional networks controlling virulence in filamentous fungal pathogens*
- *ESF Research Networking Programme: FUMINOMICS - Functional genomics in Aspergillus fumigatus and new strategies to fight against the first fungal pathogen in Europe*
- *IZKF Würzburg: Analysis of host-pathogen interactions to investigate the influence of Aspergillus fumigatus on haemostasis (A-127)*
- *German Jose Carreras Leukaemia Foundation: In vivo imaging for molecular investigation of invasive aspergillosis after allogeneic stem cell transplantation*

2 Young Investigator Groups of the ZINF
2.3 Deep sequencing approaches to Pathogenesis

CONTACT DETAILS

Dr. rer. nat. Cynthia Sharma

Zentrum für Infektionsforschng
Josef-Schneider-Str. 2/D15
97080 Würzburg

Phone: +49-931-3182560
E-Mail: cynthia.sharma@uni-wuerzburg.de
www.imib-wuerzburg.de/research/sharma

RESEARCH GOALS

- *Establishing Helicobacter pylori and Campylobacter jejuni as new model organisms for riboregulation in pathogenic bacteria*
- *Determination of the regulation of sRNAs as well as their physiological roles and cellular targets*
- *Investigation of molecular mechanisms of sRNA-mediated regulation*
- *Characterization of the role of sRNAs during virulence and identification of marker genes of different clinical outcomes of infections*
- *Identification of protein factors involved in sRNA-mediated regulation*

Summary

Post-transcriptional regulation represents a central level of gene expression control in the cell. Non-coding RNAs and associated RNA-binding proteins have been described as key players in this process. The 50-200 nt long small RNAs (sRNAs) from bacteria are a heterogeneous class of molecules which regulate bacterial gene expression in response to adverse growth and environmental stress conditions. During the last decade, a large number of sRNAs have been identified in a wide range of bacteria. However, most studies on the functional characterization of these sRNAs have focused on enterobacteria, such as *Escherichia coli* and *Salmonella*. By contrast, almost nothing is known about riboregulation in Epsilonproteobacteria, including the major human pathogens such as *Helicobacter pylori*, the causative agent of gastric cancer, and *Campylobacter jejuni*, the most common cause of food-borne gastroenteritis. Our overall research goal is to establish *Helicobacter* and *Campylobacter* as new model organisms for riboregulation in pathogenic bacteria. Specifically, we focus on the identification of sRNAs and associated RNA-binding proteins as well as their functions and mechanisms in the stress response and virulence within these prevalent human pathogens. Furthermore, we apply and develop deep sequencing-based approaches (RNA-seq) for transcriptome analyses and identification of novel RNAs in both host and pathogen.

Major Research

- *Functional characterization of sRNA in H. pylori*

The Gram-negative Epsilonproteobacterium *Helicobacter pylori* colonizes the stomachs of about 50% of the world's population and leads to gastritis, ulcer, and even gastric cancer. While the genome sequences of several strains have revealed a high level of genetic diversity within putative protein coding genes, less is known about the extent of post-transcriptional regulation in this pathogen and it was even regarded as an organism that may lack riboregulation. However, we have recently developed a novel generic RNA-sequencing approach (dRNA-Seq) based on next-generation sequencing (NGS) technology which has revealed the high transcriptome complexity of the relatively small *H. pylori* genome, with extensive antisense transcription as well as an unexpected number of more than 60 sRNAs.

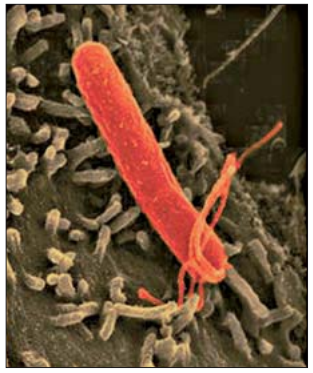


Fig. 1: Colorized scanning electron micrograph of H. pylori and human gastric epithelium cells.

We are currently functionally characterising these sRNAs in *H. pylori* to understand their potential roles during virulence. Besides the identification of factors and conditions that control sRNA expression and additional partners involved in riboregulation, we are especially interested in the molecular mechanisms of sRNAs. For example, we have shown that the very abundant sRNA, HPnc5490 represses the expression of the chemotaxis receptor TlpB, which represents the first example of a classical trans-encoded antisense-regulator in this bacterium. Using biocomputational predictions together with genetic and biochemical approaches we have shown that the HPnc5490 sRNA can bind to a G-repeat motif in the 5'UTR of *tlpB* mRNA (Fig. 2A) which leads to the decreased expression of *tlpB* (Fig. 2C). However, since the interaction site is distant to the tlpB-5'UTR, which mechanistically argues against the canonical sRNA regulatory mechanism of competition with ribosome binding, we are currently attempting to elucidate the mode of repression. The chemotaxis receptor TlpB has been suggested to sense low pH and to be required for host infection. Our prelimenary results indicate that HPnc5490 levels increase at low pH conditions, indicating a potential role of this sRNA in acid adaptation. In order to obtain further insight into the physiological role of HPnc5490, we are screening for regulators of HPnc5490 biogenesis by expression profiling under various stress and growth conditions. In addition, as described for HPnc5490, we have used similar approaches to identify target genes and functional roles of other abundant sRNAs in *H. pylori*.

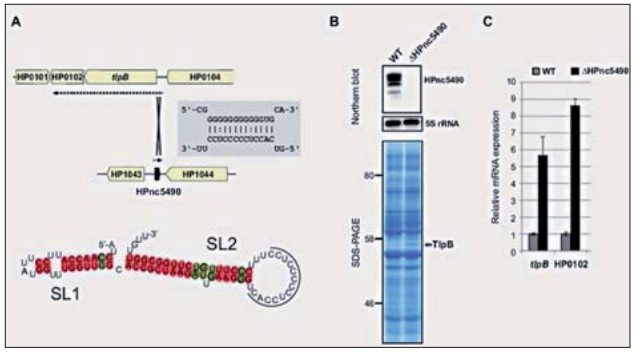


Fig. 2: A first example for a trans-acting antisense RNA in H. pylori. (A) Genomic context of the genes encoding the chemotaxis receptor TlpB and HPnc5490 sRNA. A consensus structure of HPnc5490 shown below together with the predicted 13 bp HPnc5490–tlpB RNA duplex reveals presentation of the predicted pairing residues by an accessible loop region. (B) Northern blot analysis confirms deletion of HPnc5490 RNA. SDS–PAGE showing accumulation of TlpB protein upon deletion of HPnc5490. Marker bands (kDa) are indicated to the left.

- *Comparative transcriptome analysis of Campylobacter strains and identification of sRNAs*

The dRNA-seq approach has enabled us to define a genome-wide map of transcriptional start sites (TSS) and operons in *H. pylori*. However, this study was limited to one bacterial strain. We have now performed a comparative dRNA-seq analysis of the primary transcriptomes of four isolates of the related pathogen, *Campylobacter jejuni*. *Campylobacter* is currently the most common cause of bacterial gastroenteritis in humans and has also been associated with several autoimmune disorders. Our comparative study reveals that the majority of TSS is conserved among strains but that there are also several strain-specific TSS, indicating divergence in transcriptional output. Moreover, Northern blot analysis confirmed the expression of several conserved and strain specific sRNA in *C. jejuni*. This represents the first comparative analysis of the primary transcriptomes and sRNA repertoire of multiple *C. jejuni* strains.

- *Identification of RNA binding proteins in H. pylori and C. jejuni*

Most of the functionally characterized sRNAs in enterobacteria require the RNA chaperone Hfq for their stability and function. Moreover, Hfq is required for virulence in many bacterial pathogens. However, 50% of all bacteria, including Epsilonproteobacteria, lack Hfq. Our goal is to identify and functionally characterize auxiliary protein factors involved in riboregulation in *Helicobacter* and *Campylobacter*. To this end, we have started to isolate ribonucleoprotein (RNP)-complexes, followed by proteomics and RNA-seq analyses of protein and RNA partners and subsequent biochemical analyses. This approach will begin to address the question if these bacteria use a different RNA-binding protein which replaces Hfq or whether their sRNAs act by novel mechanisms independent of a protein chaperone. Our overall research goal is to establish *Helicobacter* and *Campylobacter* as new model organisms for RNA research in virulent bacteria and bacteria that lack Hfq.

SELECTED PUBLICATIONS

- *Deltcheva E, Chylinski K*, Sharma CM*, Gonzales K, Chao Y, Pirzada ZA, Eckert MR, Vogel J, Charpentier E (2011) CRISPR RNA maturation by trans-encoded small RNA and host factor RNase III.* ***Nature*** *471(7340):602-7 *Equally contributing authors.*
- *Sharma CM, Papenfort K, Pernitzsch SR, Mollenkopf HJ, Hinton JC, Vogel J (2011) Pervasive post-transcriptional control of genes involved in amino acid metabolism by the Hfq-dependent GcvB small RNA.* ***Mol Microbiol*** *81(5):1144-1165*
- *Papenfort K, Bouvier M, Mika F, Sharma CM, Vogel J (2010) Evidence for an autonomous 5' target recognition domain in an Hfq-associated small RNA.* ***PNAS*** *107(47):20435-40*
- *Imov I, Sharma CM, Vogel J, Winkler W (2010) Identification of regulatory RNAs in Bacillus subtilis.* ***Nucleic Acids Research*** *38(19):6637-51*
- *Sharma CM, Hoffmann S, Darfeuille F, Reignier J, Findeiß S, Sittka A, Chabas S, Reiche K, Hackermüller J, Reinhardt R, Stadler PF, Vogel J (2010) The primary transcriptome of the major human pathogen Helicobacter pylori.* ***Nature*** *464(7286):250-5*

EXTRAMURAL FUNDING

- *Young Investigator fellowship of the Bavarian Academy of Sciences: Functional characterization of small regulatory RNAs in the human pathogen Helicobacter pylori*
- *Postdoc/Young Investigator grant of the Daimler-and-Benz-Foundation: Identification and functional characterization of RNA-binding proteins in Campylobacter jejuni*
- *BioSysNet, Associated Junior Group: Exploring RNA-binding proteins in Campylobacter jejuni*

AWARDS

- *2011 - Robert Koch Foundation, Post doctorate prize for young scientists*
- *2011 - Ingrid zu Solms Science Award*

2 Young Investigator Groups of the ZINF
2.4 Bacterial Cell Differentiation

CONTACT DETAILS

Dr. Daniel López

Zentrum für Infektionsforschung
Josef-Schneider-Str. 2/ D15
97080 Würzburg

Phone: +49-931-31-83831
E-Mail: daniel.lopez@uni-wuerzburg.de
www.imib-wuerzburg.de/research/lopez/

RESEARCH GOALS

- *Characterization of cell differentiation in staphylococcal communities*
- *Analysis of lipid rafts in bacteria*
- *Development of anti-raft small molecules to prevent infectious diseases*

Summary

A universal attribute of bacteria is their ability to grow associated with surfaces following a developmental process known as biofilm formation. The constituent cells of a biofilm are encased within an extracellular matrix that provides consistency and robustness to the microbial community. Biofilms have a profound impact in medicine, where they form on medical devices, catheters or contact lenses and serve as reservoir for bacteria that can be shed onto the body, leading to both acute and chronic infections. Previous work has revealed that cells within a biofilm are spatially constrained and these communities contain gradients of oxygen, nutrients and signalling molecules that generate different microenvironments. As a consequence, the bacteria differentiate into distinct subpopulations of cell types with distinct gene expression profiles, physiology and roles in biofilm formation. This heterogeneity contributes to the development of remarkably high levels of resistance to a wide variety of antimicrobial agents that is specifically observed biofilm-forming microbial communities compared to their planktonic counterparts. The pathogen *Staphylococcus aureus* forms biofilms (Figure 1) and is responsible for one of the most problematic biofilm-associated infections in clinical settings. Our research focuses on the identification of the distinct subpopulations of cell types generated during the process of biofilm formation, the signalling pathways involved in differentiation and the elucidation of the role of each one of these subpopulations. We are also exploring targeting the spatial organisation of the signalling pathways involved in biofilm formation as a novel therapeutic strategy.

Major Research

- *Differentiation of cellular subpopulations in Staphylococcal communities*

In *Bacillus subtilis* biofilms different subpopulations of cell types coexist with each having a specific role in the formation of the surface-associated multicellular communities. The coordination of and interplay between these constituent cell types requires a sophisticated cell-to-cell communication network based on self-produced signalling molecules. We have previously shown in *B. subtilis* that cell differentiation plays an important role in the formation of the communities. As part of the DFG priority programme SPP1617, we are extending these studies to understand the molecular mechanisms involved in the differentiation of cell types present in the biofilms of pathogenic bacteria such as *Staphylococcus aureus*. Our research currently focuses on the characterization of the distinct cell types that are fundamentally required to build *S. aureus* matrix-encased multicellular communities and the molecular mechanisms that drive their differentiation. One particular aspect we are interested in is the role of self-secreted small molecules and the generation of gradients within the biofilm, these gradients are likely to play important roles in the activation of the distinct gene expression programs involved in differentiation.

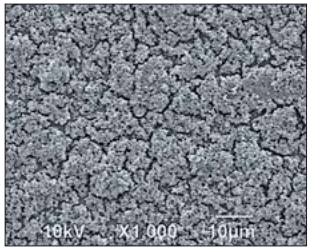


Fig. 1: Scanning electron micrograph of a microbial community of Staphylococcus aureus growing on a plastic surface for 24h. Cells of S. aureus attach to surfaces and generate coting pellicles.

- *Lipid microdomains in bacterial signal transduction and cell differentiation*

The occurrence and participation of the diverse cellular subpopulations in the process of biofilm development requires the coordination of their cellular physiology via cell-cell communication. One of our main priorities is elucidating the signalling transduction pathways and the secreted signalling molecules that are involved in the process of biofilm formation. In relation to bacterial communication mechanisms, we have previously found that a large collection of signalling proteins required for cell differentiation concentrate in membrane microdomains that differ in lipid composition to the bulk membrane. This suggests that bacteria have membrane platforms specialised in signal transduction that are functionally similar to lipid rafts in eukaryotic cells. The activity of the intrinsic signalling proteins is linked to the integrity of these microdomains since alteration of their architecture leads to a defect in the functionality of the associated proteins and the respective pathways. We are currently studying the broad collection of signalling pathways and physiological processes that are modulated by the proteins located in the functional membrane microdomains of the two closely-related organisms *Staphylococcus aureus* and *Bacillus subtilis*. Our interest in these two bacterial species resides in the conservation of a large number of signalling and gene regulatory pathways among them, yet they significantly differ in the architecture of the membrane microdomains. Our comparison studies aim to not only reveal the signalling transduction pathways that are generally associated with these membrane microdomains but also the proteins that have species specific roles in defining the architecture of the lipid rafts.

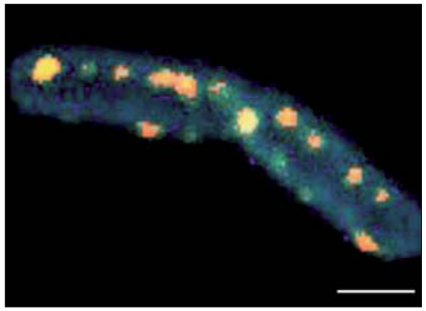


Fig. 2: Fluorescence micrograph of two B. subtilis cells labeled with the translational fusion FloT-YFP. FloT is a flotillin-like protein harbored in the functional membrane microdomain of B. subtilis. Fluorescence signal shows the typical distribution of FloT in puncta across the cytoplasmic membrane. Scale bar is 1 µM.

- *Development of anti-microdomain small molecules to prevent infectious diseases*

We also have focused our efforts to compose a collection of small molecules that are able to disrupt the membrane microdomains. The goal of the project is to open new avenues for the development of antimicrobials with additional activities against the signalling pathways required for cell differentiation and thus, biofilm formation. The innovative aspect of this project is to simultaneously inhibit the myriad of signalling transduction pathways that are dependent on the integrity of the lipid rafts by perturbing the architecture of these membrane platforms. We are using S. aureus as model organism to carry out clinical and molecular experiments of relevant to validate our portfolio of small molecules proven to have anti-lipd raft properties.

SELECTED PUBLICATIONS

- *Schneider J, Yepes A, Garcia-Betancur JC, Westedt I, Mielich B, López D (2012) Streptomycin-induced expression in Bacillus subtilis of YtnP, a lactonase-homologous protein that inhibits development and streptomycin production in Streptomyces griseus.* ***Appl Environ Microbiol*** *78(2):599-603*
- *López D, Kolter R (2010) Functional microdomains in bacterial membranes.* ***Genes Dev*** *24(17):1893-1902*
- *López D, Vlamakis H, Losick R, Kolter R (2009) Paracrine signaling in a bacterium.* ***Genes Dev*** *23(14):1631-1638*
- *López D, Fischbach MA, Chu F, Losick R, Kolter R (2009) Structurally diverse natural products that cause potassium leakage trigger multicellularity in Bacillus subtilis.* ***PNAS*** *106(1):280-285*

EXTRAMURAL FUNDING

- *DFG SPP1617: Molecular characterization of the distinct cell types required for the development of Staphylococcus aureus biofilms (LO-1804/2)*

2 Young Investigator Groups of the ZINF
2.5 Trypanosoma Gene Regulation

CONTACT DETAILS

Dr. T. Nicolai Siegel

Zentrum für Infektionsforschung
Josef-Schneider-Str. 2/D15
97080 Würzburg

Phone: +49-931-3188499
E-Mail: nicolai.siegel@uni-wuerzburg.de
www.imib-wuerzburg.de/research/siegel/

RESEARCH GOALS

- *Identification and molecular characterization of proteins and RNA molecules associated with transcription start and termination sites in T. brucei*
- *Identification of factors involved in the targeting of histone variants to specific sites in the genome*
- *Understanding the role of chromatin structure in antigenic variation*
- *Adaption of high-throughput sequencing-based techniques for use in T. brucei*

Summary

Trypanosoma brucei is 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 life stock 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 may ensure that only one of several hundred VSG genes is expressed at any given time. The mechanism of gene regulation in trypanosomes differs to most other eukaryotes, as most genes in *T. brucei* are arranged in polycistronic transcription units (PTUs) and the lack of canonical promoter motifs upstream of protein encoding genes means that the process of transcriptional initiation remains enigmatic. We are currently using a number of genome-wide and biochemical approaches to understand how chromatin defines RNA pol II transcription start sites (TSSs) and transcription termination sites (TTSs). We aim to elucidate how 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. A better knowledge of how different chromatin structures are formed in *T. brucei* should help us understand how the parasite undergoes antigenic variation and may eventually facilitate medical intervention.

Major Research

- *The role of chromatin in gene regulation*

The organisation and regulation of genes in trypanosomes fundamentally differs to most eukaryotes since most genes are organized in PTUs, are devoid of recognisable promoter motifs and the parasite appears to lack general transcription factors. It is therefore not clear how and to what extent transcription initiation is regulated in *T. brucei*, although there is increasing evidence that suggests that chromatin structure plays an important role in gene regulation. Just like in other eukaryotes, in trypanosomes DNA is packaged into chromatin, which is composed of a repeating structure of nucleosomes containing histone proteins. Although the primary sequences of trypanosome core histones diverge significantly relative to other eukaryotes, trypanosomes contain several histone modifications, including an extensively acetylated H4 tail. *T. brucei* also has one variant of each of the four core histones: H2AZ, H2BV, H3V and H4V. To understand the role of chromatin in regulating gene expression we previously performed genome-wide chromatin immunoprecipitation (ChIP) and sequencing (ChIP-seq) for *T. brucei*, which enabled us to examine the genome-wide distribution of different chromatin components. This approach revealed acetylated H4K10, two histone variants (H2AZ and H2BV) and the bromodomain-containing factor 3 to be strongly enriched at RNA pol II TSSs. Furthermore, we were able to use these marks to identify more than 60 previously unanticipated TSSs. To understand the function of the histone variants at RNA pol II TSSs, we performed co-IP experiments and observed that less H3 and H4 co-immunoprecipitated with variant histones compared to core histones, suggesting that nucleosomes containing H2AZ and H2BV are less stable than canonical nucleosomes. The analysis of TTSs, revealed a pattern apparently unique to trypanosomes, since they are enriched in the histone variants H3V and H4V.

Fig. 1: Scanning electron micrograph of a long slender bloodstream form T. brucei parasite.

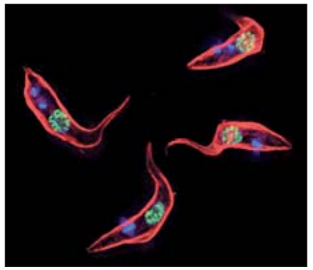


Fig. 2: Immunfluorescence analysis of T. brucei. Acetylated H4K1 (green), tubulin (red) and DNA (blue).

These findings suggest that histone variants and histone modifications play crucial roles in transcription initiation and termination in trypanosomes and that destabilization of nucleosomes by histone variants may be an evolutionarily ancient and general mechanism of transcription initiation, demonstrated in an organism in which general pol II transcription factors have been elusive. We are currently focusing our work on elucidating the molecular mechanisms involved in establishing these chromatin domains at TSSs and TTSs. To identify factors that associate with these chromatin domains we have epitope tagged histone variants and will perform pull down experiments in cell lysates and identify the associated factors using tandem mass spectrometry. Once these candidates have been validated *in vivo* we will aim to provide a deeper mechanistic understand of the assembly and establishment of these chromatin domains using *in vitro* chromatin reconstitution assays. We will use a depletion and adding back strategy to determine the molecular role of each identified component.

- *Identification of DNA sequence motifs involved in gene regulation*

Numerous studies have suggested that no specific DNA sequences are associated with transcription start and termination sites in trypanosomes. While the data from our recent genome-wide analyses confirmed the absence of a 'classic' promoter motif at RNA pol II TSSs, we were able to identify the presence of long guanine-runs and distinct AT-rich regions at TSSs. Currently, we are testing if sequences found at TSSs or TTSs can initiate or terminate transcription when inserted at ectopic loci and if insertion of these sequence elements at ectopic loci leads to establishment of distinct chromatin structures.

- *Spatial organisation of the Trypanosome genome*

Recent work in eukaryotes has demonstrated that the nucleus is highly compartmentalised and that spatial organisation plays an important role in regulating many nuclear processes. For example, in many eukaryotes condensed heterochromatic regions localise to the nuclear periphery to form silent domains of the genome, with current indications suggesting that the expression status of genes correlates with their positioning relevant to these domains. The development of chromatin conformation capture techniques has enabled the mapping of DNA sequences that associate with a gene in *trans* or in *cis* providing information on the contribution of genome topology to gene regulation. The contribution of genome organisation to antigenic variation in trypanosomes is not known, but may play a role in the selection and maintenance of expression of a single VSG gene as well as the switching between active genes. We aim to establish chromatin conformation capture techniques in *T. brucei* to study the influence of genome topology on antigenic variation and RNA pol II transcription.

SELECTED PUBLICATIONS

- *Siegel TN, Gunasekera K, Cross GA, Ochsenreiter T (2011) Gene expression in Trypanosoma brucei: lessons from high-throughput RNA sequencing.* ***Trends Parasitol*** *27:434-441*
- *Siegel TN, Hekstra DR, Wang X, Dewell S, Cross GA (2010) Genome-wide analysis of mRNA abundance in two life-cycle stages of Trypanosoma brucei and identification of splicing and polyadenylation sites.* ***Nucleic Acids Research*** *38:4946-4957*
- *Siegel TN, Hekstra DR, Kemp LE, Figueiredo LM, Lowell JE, Fenyo D, Wang X, Dewell S, Cross GA (2009) Four histone variants mark the boundaries of polycistronic transcription units in Trypanosoma brucei.* ***Genes & Dev*** *23:1063-1076*

3 Institutions of the Research Center for Infectious Diseases
3.1 Institute for Molecular Infection Biology

CONTACT DETAILS

Prof. Dr. Jörg Vogel

Institut für Molekulare Infektionsbiologie
Josef-Schneider-Str. 2/D15
97080 Würzburg

Phone: +49-931-3182576
E-Mail: joerg.vogel@uni-wuerzburg.de
www.imib-wuerzburg.de/research/vogel

RESEARCH GOALS

- *Understanding the regulation of virulence by bacterial small RNAs*
- *Harness deep sequencing for RNA discovery and transcriptomics*
- *Identify proteins involved in RNA-based regulation*
- *Understanding the roles of host microRNAs and long noncoding RNAs in bacterial infection*

3.1.1 RNA Biology

Summary

The RNA Biology group is interested in gene regulation by noncoding RNA molecules in bacterial pathogens and eukaryotic host cells. We use a wide range of biochemical, genetic, biocomputational and RNA deep sequencing approaches to discover new regulatory RNA molecules and their functions. Our work is aided by many fruitful collaborations with laboratories in Germany, Europe and overseas. Our primary goals are to understand how during bacterial infections, RNA molecules are used to regulate the expression of virulence genes in the pathogen, and of defense genes in the eukaryotic host, and thereby identify new routes and targets for the treatment of infectious diseases.

Major Research

- *Small regulatory RNAs in bacterial pathogens*

A major focus of our research is in small regulatory RNAs (sRNAs) that associate with the conserved RNA-binding protein Hfq in the model pathogen *Salmonella* Typhimurium. Hfq-dependent sRNAs constitute the largest post-transcriptional network presently known in bacteria, rivaling the regulating complexity of eukaryotic microRNAs. *Salmonella* expresses ~150 sRNAs from both core genomic regions that are conserved in the closely related *Escherichia coli* and from *Salmonella*-specific, pathogenicity islands. The Hfq-dependent sRNAs typically modulate protein synthesis by using short imperfect base-pairing with target mRNAs, thus altering translation and stability of the mRNA. We now understand that a single sRNA can regulate many target mRNAs using a highly-conserved short (≥7 nucleotide) seed sequence, yet how sRNAs act to select their target specificity in the background of thousands of other cellular transcripts is not understood. Equally, do proteins other than Hfq help mediate sRNA activity? Other fundamental questions which we are addressing are what are the benefits of using an RNA regulator versus a transcriptional factor in complex regulatory networks; how are the sRNAs themselves regulated; and how does this relate to virulence.
Our major recent findings in this area include the discover of non-canonical regulation in the coding sequence of target mRNAs and of well-defined seed sequences in several *Salmonella* sRNAs. New principles of gene regulation were also established; for example, we showed that small RNAs endow the bacterial envelope stress response, which is required for host survival by many pathogens, with an essential repressor function. Overall, our long-term endeavour to establish *Salmonella typhimurium* as a pathogenic model organism for RNA research came to fully bear fruit in the past three years. Our focus has now shifted to those sRNAs that regulate effector proteins of the *Salmonella* type-3 secretion systems which are required for cell invasion and intracellular survival.

- *RNA deep sequencing (RNA-seq)*

Massively parallel sequencing of cellular transcripts has been revolutionizing the discovery of coding and noncoding RNAs in virtually any organism. We were one of the first groups to use RNA deep sequencing in bacteria, and in the past three years we have developed generic methods such as differential RNA sequencing (dRNA-seq) to report the primary transcriptomes of the major human pathogen, *Helicobacter pylori* in 2010, and subsequently of many other species. This led to the discovery not only of many new small RNA molecules, but also of a new type of CRISPR/Cas defense system that seems to be particularly prominent in pathogenic bacteria that infect humans. We also pioneered the use of deep sequencing to identify the interaction partners of bacterial RNA binding proteins, for example, the small noncoding RNAs and mRNA targets of Hfq, for which we combined chromosomal epitope tagging of the protein with sequencing the co-immunoprecipitated RNA. Current projects use Illumina sequencing to discover new RNA-binding proteins and the

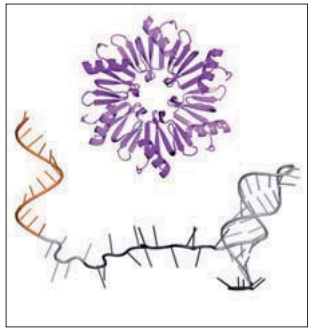


Fig. 1: Hfq and RybB sRNA

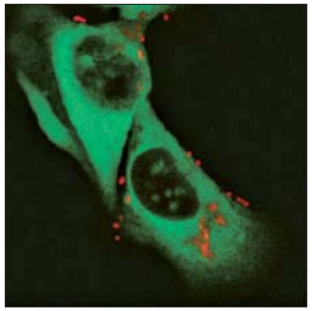


Fig. 2: Salmonella (red) invading epithelial cells (green).

landscape of post-transcriptional regulation in bacteria and host. Furthermore, we want to develop dual RNA deep sequencing as a robust tool to study—in parallel—the transcriptomes of bacterial pathogens and eukaryotic host over the course of infection, ideally at the single-cell level.

- *RNA-protein interactions*

Whereas there has been much progress on base pairing RNAs, the abundance and mechanisms of RNA molecules that target proteins to modulate their activity is little understood. For example, may RNA molecules serve to tether virulence proteins until they are needed, or how many enzymes are targeted by regulatory RNAs to fine-tune metabolism? We are using *in vivo* cross-linking and RNA deep sequencing (CLIP-seq) to discover new RNA-binding proteins and map RNA-protein contacts in pathogenic bacteria. The ultimate goal is to understand how many proteins a regulatory RNA or even mRNA "sees" from its birth to death, how many RNA-protein interactions there are in the cell, how many of these are productive versus non-productive, and what the productive ones look like at the molecular level.

- *MicroRNAs and Long Noncoding RNAs in infected eukaryotic hosts*

Research over the last decade has implicated microRNAs in a plethora of eukaryotic disease-related pathways, including the mammalian immune response, but surprisingly little remains known as to the microRNA response to bacterial infections. Likewise, it is estimated that the human and mouse genomes express several hundred long noncoding RNA (lncRNA) molecules, with transcript lengths in the range of less than 1 to more than 100 kilobases. These lncRNA seem to play important roles in the epigenetic control of gene expression and in organizing RNA-protein particles. We are investigating which microRNAs and lncRNAs play a role in the response to infections by *Salmonella* and other bacterial pathogens, again using systematic screening approaches followed by in-depth characterization of differentially expressed candidate molecule. One of our major achievements in this field was our 2011 discovery that the conserved Let-7 microRNA family is down-regulated by bacterial LPS in mouse and human cells, and that this removes a post-transcriptional break on the IL-6 and IL-10 cytokine mRNAs upon infection with *Salmonella*.

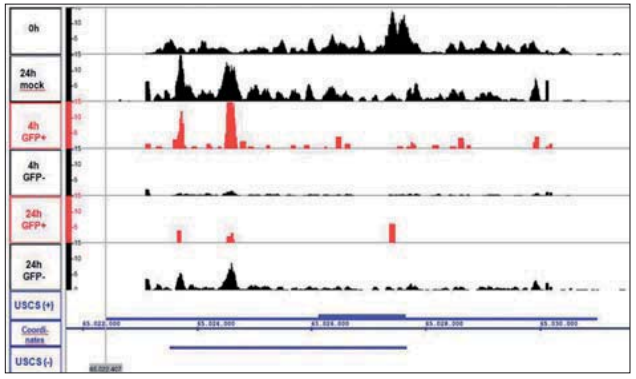


Fig. 3: Browser shot showing deep sequencing of MALAT lncRNA.

SELECTED PUBLICATIONS

- *Deltcheva E, Chylinski K, Sharma CM, Gonzales K, Chao Y, Pirzada ZA, Eckert MR, Vogel J, Charpentier E (2011) CRISPR RNA maturation by trans-encoded small RNA and host factor RNase III.* ***Nature*** *471:602-607*
- *Schulte LN, Eulalio A, Mollenkopf HJ, Reinhardt R, Vogel J (2011) Analysis of the host microRNA response to Salmonella uncovers the control of major cytokines by the let-7 family.* ***EMBO J*** *30:1977-1989*
- *Papenfort K, Bouvier M, Mika F, Sharma CM, Vogel J (2010) Evidence for an autonomous 5' target recognition domain in an Hfq-associated small RNA.* ***PNAS*** *107:20435-20440*
- *Sharma CM, Hoffmann S, Darfeuille F, Reignier J, Findeiss S, Sittka A, Chabas S, Reiche K, Hackermüller J, Reinhardt R, Stadler PF, Vogel J (2010) The primary transcriptome of the major human pathogen Helicobacter pylori.* ***Nature*** *464:250-5*
- *Pfeiffer V, Papenfort K, Lucchini S, Hinton JC, Vogel J (2009) Coding sequence targeting by MicC RNA reveals bacterial mRNA silencing downstream of translational initiation.* ***Nature Struct Mol Biol*** *16:840-846*

EXTRAMURAL FUNDING

- *BioSysNet, Associated Senior Group: Temporal control of gene expression by small RNAs*
- *DFG FOR1608: Unravelling the prokaryotic immune system. Project: CRISPR/Cas system in Neisseria meningitides*
- *DFG SPP1316: Host-Adapted Metabolism of Bacterial Pathogens. Project: a post-transcriptional link between Salmonella metabolism and virulence*
- *DFG grant: Cis/trans control of genes by a pH-responsive 5' UTR*
- *BMBF grant: Next-generation transcriptomics of bacterial infections*
- *DFG SFB/TRR34: Pathophysiology of Staphylococci in the Post-Genome-Era. Project: sRNA-mediated gene regulation in staphylococci: Impact on metabolism and biofilm expression*
- *DFG SPP1258: Sensory and regulatory RNA in prokaryotes. Projects: a) RNA deep sequencing & method development; b) Multiple target regulation by GcvB sRNA-Conserved sRNA in the RpoS regulon*
- *BMBF grant: RNomics in Infectious Diseases*

AWARDS AND PRIZES

- *2011 - Elected as an EMBO Member*
- *2011 - DGHM Senior Scientist Award*
- *2010 - VAAM Research Award*

3 Institutions of the Research Center for Infectious Diseases
3.1 Institute for Molecular Infection Biology

CONTACT DETAILS

Prof. Dr. rer. nat. Dr. med. habil. Heidrun Moll

Institut für Molekulare Infektionsbiologie
Josef-Schneider-Str. 2/D15
97080 Würzburg

Phone: +49-931-3182627
E-mail: heidrun.moll@uni-wuerzburg.de
www.imib-wuerzburg.de/research/moll/

RESEARCH GOALS

- *Analysis of the interaction between parasites and the host's immune system*
- *Development of dendritic cell-based vaccination strategies*
- *Characterization of the mode of action of new leishmanicidal compounds*

3.1.2 Infection Immunity

Summary

Leishmaniasis is considered a tropical affliction that is included in the World Health Organization/Tropical Disease Research list of the six most important diseases, with a sharp 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 development of a protective T cell response and, as a result, the outcome of the disease. 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 parasitic 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. The research activities of the Infection Immunology Unit deal with both aspects: the elaboration of new approaches to be used for vaccination and for immunotherapy.

Major Research

- *Dendritic cells as tools for novel vaccination strategies*

Dendritic cells (DC) have been recognized as critical determinants of the type of immune response against microbial pathogens. Thus, the rapidly expanding knowledge of DC immunobiology offers new perspectives for the development of vaccines against infectious diseases. Studies in our laboratory have provided the first proof of principle that several distinct DC populations, once properly conditioned *ex vivo*, indeed are able to induce complete protection against *Leishmania major* as a model microbial pathogen. Moreover, we showed that natural killer (NK) cells support the induction of protective immunity during DC-mediated vaccination. Recently, we investigated whether viable DC are required for inducing protection. We showed that *L. major* antigen-loaded DC that had been fixed with paraformaldehyde or exposed to UV irradiation, and even disrupted cells, are able to serve as an effective vaccine. Furthermore, we demonstrated the potential of DC-derived exosomes to mediate protective immunity against leishmaniasis. The route of antigen presentation to recipient T cells involves uptake of intravenously injected DC fragments into late endosomal compartments of splenic DC in the recipient. These findings suggest that the development of a cell-free vaccine for immunoprophylaxis against leishmaniasis and other infectious diseases is feasible.

- *Identification and characterization of leishmanicidal compounds*

At present, only few drugs are available for the treatment of human leishmaniasis. Antimonials, the main chemotherapeutic tool, cause serious side effects and promote chemoresistance. Thus, alternative drugs against leishmaniasis are desperately needed. To this end, our laboratory collaborates with different groups of the Faculty of Chemistry and Pharmacy of the University of Würzburg within the collaborative research center 630 (www.sfb630.uni-wuerzburg.de). Using a colorimetric assay, natural as well as chemically synthesized compounds are tested in a first screening step against *L. major* promastigotes. The most interesting compounds selected with this initial screening assay are further tested using a luciferase-transgenic *Leishmania* amastigote as-

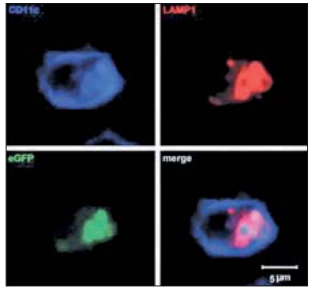


Fig. 1: Confocal micrograph of a CD11c-labeled dendritic cell (blue) containing phagocytosed eGFP-labeled particles (green) in the endosomal compartment (immunostained for LAMP-1, red).

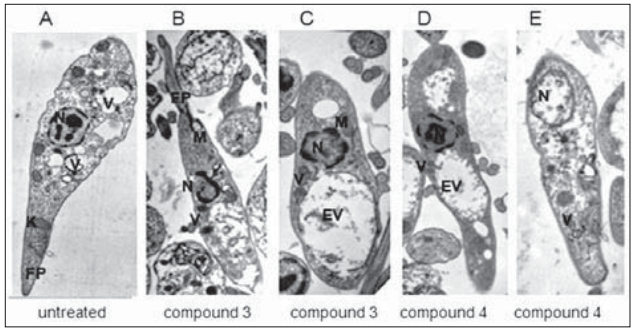


Fig. 2: Electron microscope images of Leishmania major parasites treated with arylisoquinolinium salts. (A) Non-treated parasites, (B, C) parasites treated with arylisoquinoline compound 3, (D, E) and parasites treated with arylisoquinoline compound 4 at 6 h of incubation. EV = empty vacuoles, FP = flagellar pocket, K = kinetoplast, M = mitochondria, N = nucleus, V = vacuoles.

say recently developed in our laboratory.
We previously demonstrated in cooperation with the laboratory of Prof. T. Schirmeister that two compounds of a series of peptidomimetic aziridine-2,3-dicarboxylates (compounds 13b and 13e) reduced the growth and viability of *L. major* and the infection rate of macrophages while not showing cytotoxicity against host cells. Both inhibitors targeted leishmanial cathepsin B-like cysteine cathepsin CPC, as shown by fluorescence proteinase activity assays and active-site labeling with biotin-tagged inhibitors. Furthermore, compounds 13b and 13e were potent inducers of cell death in promastigotes, characterized by cell shrinkage, reduction of mitochondrial transmembrane potential and increased DNA fragmentation. Transmission electron microscopic studies revealed the enrichment of undigested debris in lysosome-like organelles participating in micro- and macroautophagy-like processes. The release of digestive enzymes into the cytoplasm after rupture of membranes of lysosome-like vacuoles resulted in the significant digestion of intracellular compartments. However, the plasma membrane integrity of compound-treated promastigotes was maintained for several hours. Taken together, these results suggest that the induction of cell death in *L. major* by cysteine cathepsin inhibitors is different from mammalian apoptosis and is caused by incomplete digestion in autophagy-related lysosome-like vacuoles.
In collaboration with the laboratory of Prof. G. Bringmann, we demonstrated that representatives of *N,C*-coupled naphthylisoquinolines have excellent leishmanicidal activities. Structure-activity relationship studies showed that the cationic nitrogen and the lipophilicity are important for the antiparasitic function. In addition, we demonstrated that the compounds accumulated in acidic compartments and caused the formation of large cytoplasmatic vacuoles in promastigotes. The formation of large vacuoles followed by a total destruction of the cell strongly suggests an autophagic- or necrotic-like cell death. The results of our functional analyses with *N,C*-coupled naphthylisoquinolines and aziridine-2,3,-dicarboxylate-based inhibitors provide a basis for further improvement of the compound selectivity and for development of novel strategies for targeted delivery of drugs to parasitic organelles.

SELECTED PUBLICATIONS

- *Bringmann G, Hertlein-Amslinger B, Kajahn I, Dreyer M, Brun R, Moll H, Stich A, Ioset KN, Schmitz W, Ngoc L H (2011) Phenolic analogs of the N,C-coupled naphthylisoquinoline alkaloid ancistrocladinium A, from Ancistrocladus cochinchinensis (Ancistrocladaceae), with improved antiprotozoal activities.* ***Phytochem*** *72:89-93*
- *Schurigt U, Schad C, Glowa C, Baum U, Thomale K, Schnitzer JK, Schultheis M, Schaschke N, Schirmeister T, Moll H (2010) Aziridine-2,3-dicarboxylate-based cysteine cathepsin inhibitors induce cell death in Leishmania major associated with accumulation of debris in autophagy-related lysosome-like vacuoles.* ***Antimicrob Agents Chemother*** *54:5028-5041*
- *Schnitze, JK, Berzel S, Fajardo-Moser M, Remer KA, Moll H (2010) Fragments of antigen-loaded dendritic cells (DC) and DC-derived exosomes induce protective immunity against Leishmania major.* ***Vaccine*** *28:5785-5793*
- *Remer KA, Roeger B, Hambrecht C, Moll H (2010) Natural killer cells support the induction of protective immunity during dendritic cell-mediated vaccination against Leishmania major.* ***Immunology*** *131:570-582*
- *Ponte-Sucre A, Gulder T, Gulder TAM, Vollmers G, Bringmann G, Moll H (2010) Alterations to the structure of Leishmania major induced by N arylisoquinolines correlate with compound accumulation and disposition.* ***J Med Microbiol*** *59:69-75*

EXTRAMURAL FUNDING

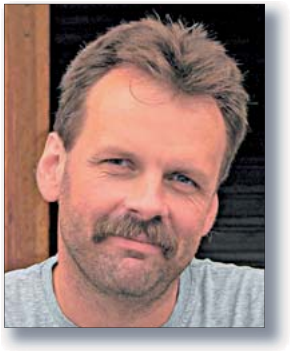
- *DFG SFB630: Identification, isolation and functional analysis of anti-infective compounds. Project: B3 (H. Moll and U. Schurigt)*
- *DFG IRTG1522: HIV/AIDS and associated infectious diseases in Southern Africa*

AWARDS AND PRIZES

- *2010 - Elected member of the Scientific Council of the Robert Koch Foundation*
- *2009 - Elected as President of the German Parasitology Society*
- *2009 - Re-elected as member of the Advisory Board of the German Society for Immunology*

3 Institutions of the Research Center for Infectious Diseases
3.1 Institute for Molecular Infection Biology

CONTACT DETAILS



Prof. Dr. rer. nat.
Joachim Morschhäuser

Institut für Molekulare Infektionsbiologie
Josef-Schneider-Str. 2/D15
97080 Würzburg

Phone: +49-931-3182152
E-mail: joachim.morschhaeuser@uni-wuerzburg.de
www.imib-wuerzburg.de/research/morschhaeuser

RESEARCH GOALS

- *Analysis of virulence -associated gene regulation in C. albicans*
- *Characterization of signaling pathways controlling morphogenesis*
- *Elucidation of the molecular basis of drug resistance*
- *Inhibition of virulence and resistance mechanisms*
- *Analysis of host adaptation mechanisms*

3.1.3 Mycology

Summary

Infections by opportunistic pathogenic fungi have become a major medical problem in the past decades, due to the increasing number of immunocompromised patients who are highly susceptible to such infections. 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 capacity of *C. albicans* to colonize and infect many different body locations. These include the switching between different morphologies and the metabolic adaptation to the 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. In our group we are studying the regulation of morphogenesis and other virulence traits, the role of nutrient sensing and acquisition systems in pathogenicity, and the molecular mechanisms of drug resistance in *C. albicans* to better understand how this important human fungal pathogen adapts to different niches and altered environmental conditions during colonizaton and infection.

Major Research

- *Control of filamentous growth of C. albicans*

In response to various environmental signals, *C. albicans* changes its morphology from the unicellular yeast form to multicellular filaments. This morphological transition, which facilitates tissue invasion, is also triggered by nitrogen limitation. The ammonium permease Mep2 mediates the uptake of the preferred nitrogen source ammonium into the cell and activates signal transduction pathways that induce filamentous growth when nitrogen sources become limiting. By creating mutated versions of Mep2 we could identify amino acid residues that are required for ammonium transport and/or signaling and thereby separate these two functions of the protein (Fig. 1). In addition, we could show that the protein kinase Npr1 is required for the transport function of Mep2, but Mep2 can stimulate morphogenesis independently of the kinase. We are currently trying to elucidate how Mep2 activates downstream signaling pathways to induce filamentation under appropriate conditions.

- *Regulation of white-opaque switching and its impact on host-pathogen interactions*

C. albicans strains that are homozygous at the mating-type locus can also switch from the normal yeast morphology (white) to an elongated cell type (opaque), which is the mating-competent form of this fungus. We have created derivatives of a switching-competent *C. albicans* strain which express *GFP* in the white phase and *RFP* in the opaque phase (and *vice versa*). These strains were used to study the interaction of white and opaque cells of *C. albicans* with human neutrophils, which play a central role in the host defense against this pathogen. Live cell imaging demonstrated that, when incubated with a mixture of the differentially labelled *C. albicans* cells, the neutrophils selectively attacked, phagocytosed, and destroyed cells in the white phase and ignored the opaque cells, despite frequent physical encounters (Fig. 2). These observations indicated that opaque

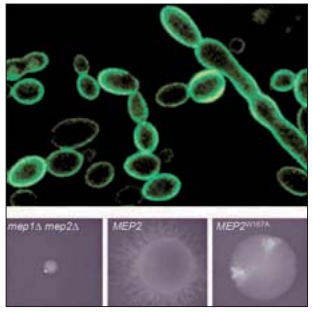


Fig. 1: Control of filamentous growth by the ammonium permease Mep2. The fluorescence micrograph (upper panel) shows the localization of GFP-tagged Mep2 in the cell membrane of C. albicans. The bottom panels show C. albicans colonies after several days of growth on agar plates containing limiting ammonium concentrations. A mutant lacking the ammmonium transporters Mep1 and Mep2 (mep1Δ mep2Δ) cannot grow under these conditions. Cells expressing wild-type MEP2 produce filamentous colonies, whereas a mutated Mep2 (MEP2^{W167A}) supports growth, but is unable to induce filamention.

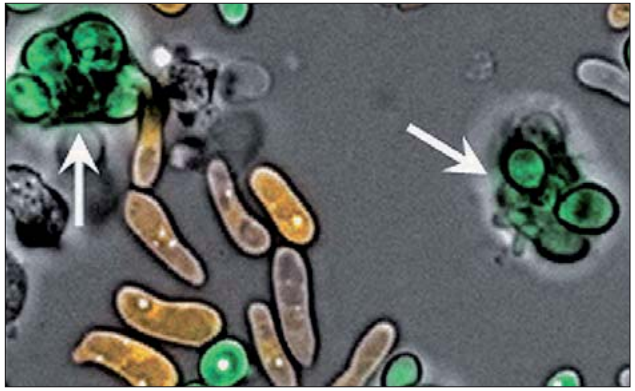


Fig. 2: Interaction of human neutrophils with white and opaque cells of a switching-competent C. albicans strain that expresses GFP from a white phase-specific promoter (white cells appear green) and RFP from an opaque phase-specific promoter (opaque cells appear orange). The neutrophils (arrows) attack and phagocytose only cells in the white phase.

cells, which are generally much less virulent than white cells, avoid recognition by certain immune cells, which may help them to remain undetected in some host niches.
Although white-opaque switching occurs spontaneously at a relatively low frequency, we found that it can also be induced by certain environmental signals in a strain-specific fashion. To identify signaling pathways that stimulate white-opaque switching, we have generated comprehensive tetracycline-inducible expression libraries encompassing all transcription factors, protein kinases and phosphatases encoded in the *C. albicans* genome. Screening of these libraries resulted in the identification of novel regulators of white-opaque switching, which provided important clues about the conditions that induce the transition to a mating-competent state in *C. albicans* to allow the exchange of genetic information.

- *Molecular mechanisms of drug resistance*

C. albicans can develop resistance to the widely used antifungal drug fluconazole, which inhibits ergosterol biosynthesis, by different mechanisms. These include the introduction of mutations in the *ERG11* gene encoding the drug target enzyme, the overexpression of *ERG11* and other ergosterol biosynthesis genes, and the upregulation of multidrug efflux pumps that transport fluconazole and other toxic compounds out of the cell. We have identified a transcription factor, the multidrug resistance regulator Mrr1, which controls the expression of the efflux pump *MDR1*, and found that gain-of-function mutations in Mrr1 are responsible for the constitutive *MDR1* overexpression in fluconazole-resistant clinical *C. albicans* isolates. In order to understand how Mrr1 mediates drug resistance, we have identified its target genes by transcriptional profiling, uncovered activation and regulatory domains of this transcription factor, and studied its interaction with additional proteins that are also involved in the regulation of efflux pumps and other drug resistance genes. We hope that a detailed understanding of the mechanisms of drug resistance will reveal strategies to overcome this significant clinical problem.

SELECTED PUBLICATIONS

- *Dunkel N, Morschhäuser J (2011) Loss of heterozygosity at an unlinked genomic locus is responsible for the phenotype of a Candida albicans sap4Δ sap5Δ sap6Δ mutant.* ***Eukaryotic Cell*** *10:54-62*
- *Neuhäuser B, Dunkel N, Satheesh SV, Morschhäuser J (2011) Role of the Npr1 kinase in ammonium transport and signaling by the ammonium permease Mep2 in Candida albicans.* ***Eukaryotic Cell*** *3:332-342*
- *Schubert S, Barker KS, Znaidi S, Schneider S, Dierolf F, Dunkel N, Aïd M, Boucher G, Rogers PD, Raymond M, Morschhäuser J (2011) Regulation of efflux pump expression and drug resistance by the transcription factors Mrr1, Upc2, and Cap1 in Candida albicans.* ***Antimicrob Agents Chemother*** *55:2212-2223*
- *Schubert S, Popp C, Rogers PD, Morschhäuser J (2011) Functional dissection of a Candida albicans zinc cluster transcription factor, the multidrug resistance regulator Mrr1.* ***Eukaryotic Cell*** *10:1110-1121*
- *Heilmann CJ, Schneider S, Barker KS, Rogers PD, Morschhäuser J (2010) An A643T mutation in the transcription factor Upc2p causes constitutive ERG11 upregulation and increased fluconazole resistance in Candida albicans.* ***Antimicrob Agents Chemother*** *54:353-359*
- *Dabas N, Schneider S, Morschhäuser J (2009) Mutational analysis of the Candida albicans ammonium permease Mep2p reveals residues required for ammonium transport and signaling.* ***Eukaryotic Cell*** *8:147-160*

EXTRAMURAL FUNDING

- *DFG IRTG1522: Epidemiology, diagnosis, and molecular mechanisms of multidrug resistance in Candida albicans and its impact on host-fungus interactions*
- *DFG-MO846/6: Phenotypic switching and genomic alterations as host adaptation mechanisms of the opportunistic fungal pathogen Candida albicans"*
- *DFG SFB630: Identification, isolation and functional analysis of anti-infective compounds. Project: Inhibition of virulence and resistance mechanisms of C. albicans Inhibition of virulence and resistance mechanisms of Candida albicans*
- *DFG-Mo846/7: Systematic functional analysis of the zinc cluster transcription factor family of the pathogenic yeast Candida albicans by artificial activation*

3 Institutions of the Research Center for Infectious Diseases
3.1 Institute for Molecular Infection Biology

CONTACT DETAILS

Dr. Alexander Böhm

Institut für Molekulare Infektionsbiologie
Josef-Schneider-Str. 2/D15
97080 Würzburg

Phone: +49-931-3183695
E-mail: alexander.boehm@uni-wuerzburg.de
www.imib-wuerzburg.de/research/boehm

since July 2012:
LOEWE-Zentrum für Synthetische Mikrobiologie
Microbial Signaling
Hans-Meerwein-Straße35043 Marburg
Phone: +49-6421-2822225
alexander.boehm@synmikro.uni-marburg.de

RESEARCH GOALS

- *Decipher the molecular biology of biofilms*
- *Unravel physiological stimuli governing biofilms*
- *Develop novel anti-biofilm strategies*

3.1.4 Microbial Signaling

Summary

Chronic and recurrent infections caused by biofilm-forming pathogens represent one of the biggest problems for the treatment of infectious diseases. Biofilms are densely packed aggregates of bacterial cells that are attached to a surface. In the context of an infection this can be an internal or external epithelium, or a foreign body device, such as a catheter or prosthetic implant. Bacteria in the biofilm communities are embedded in a self-produced slimy matrix consisting of polysaccharides and filamentous protein aggregates (pili or fimbriae). This matrix protects the cells within the biofilms from attacks by immune cells. In addition, biofilms harbor a subpopulation of bacterial cells that show little metabolic activity. Because most antibiotics are only effective against thriving bacteria, these so called persister cells are inert against the majority of clinically relevant anti-infectives. As a consequence, biofilm-related infections are very difficult to eradicate with conventional antibiotic therapy and patients suffering from such infections have to undergo repeated – sometimes endless – treatment cycles. Thus, novel strategies for the treatment of chronic infections are needed. To gain a better understanding of the basis of biofilm formation and to eventually aid the development of drugs that are effective against biofilms, we are studying the molecular biology of biofilm formation in *Escherichia coli*. Non-pathogenic, laboratory adapted *E. coli* serve as a model to address technically challenging molecular questions of a more general nature, while uropathogenic *E. coli* serve as study objects to study specific aspects of recurrent bladder infections (cystitis). A major focus of these studies is the molecular biology of the bacterial second messenger cyclic di-GMP (cdG). This signaling compound is a key factor for biofilm induction in the majority of bacterial species. Another focus is on the molecular biology and biochemistry of the exopolysaccharide poly-β-1,6-*D*-N-acetylglucosamine, an essential matrix component of the biofilms of several clinically relevant biofilm formers.

Major research

- *A molecular switch between chronic and acute infection*

When the intracellular concentration of the second messenger cyclic di-GMP is high, bacteria switch behavior to form sessile communities and generally curb the expression of virulence traits. In contrast, low concentrations of cdG favor the planktonic, motile life-style that is associated with acute virulence. The levels of cdG are adjusted by the antagonistic action of two families of signaling enzymes, diguanylate cyclases that harbor a characteristic "GGDEF" domain and synthesize cdG from two GTP molecules and cdG specific phosphodiesterases, which harbor a characteristic "EAL" domain and degrade cdG to linear dimeric GMP. Interestingly, *E. coli* encodes 29 GGDEF or EAL domain proteins and some bacterial pathogens can harbor more than 50 of these cdG-signaling proteins, but only a limited number of cdG-responsive output systems are known. The different enzymatically active GGDEF and EAL proteins carry a wide variety of N-terminal sensory domains, which upon perception of some, often unknown, stimulus control the activity of the output domains and as a consequence control the steady-state level of cdG. We are currently addressing; (i) how cdG elicits its downstream effects, (ii) why the bacterial cell needs so many cdG-signaling proteins, and (iii) what are the input signals that are sensed by the different cdG-signaling systems? For this we are using a combination of molecular and classical genetics, biochemistry, as well as imaging and systems biology approaches.

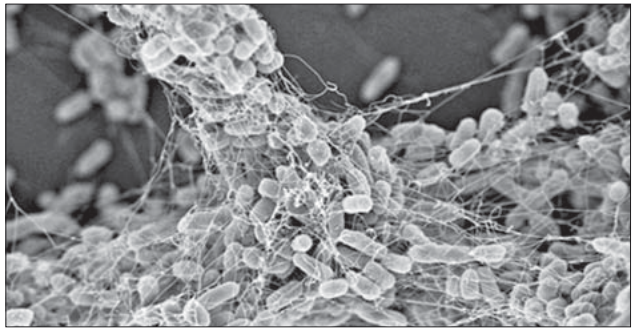


Fig. 1: Scanning electron micrograph of biofilm forming E. coli.

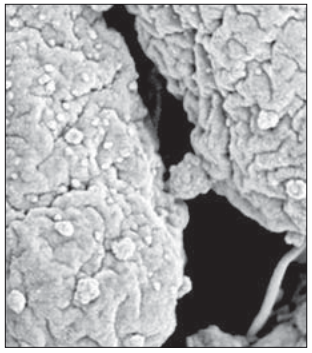


Fig. 2: High resolution scanning electron micrograph of two E. coli cells that are agglutinated via poly-GlcNAc.

- *Interference with a bacterial biofilm factor*

Despite being only distantly related, members of several clinically relevant genera (*Staphylococcus*, *Actinobacillus*, *Yersinia*, *Bordetella*, *Enterococcus*, *Acinetobacter* or *Klebsiella*) employ the polysaccharide adhesin poly-β-1,6-*D*-N-acetylglucosamine (poly-GlcNAc) as an essential biofilm matrix component. This aminosugar polymer is formed and exported across the cell envelope by a conserved group of proteins that have been shared between different bacterial species by horizontal gene transfer. Since poly-GlcNAc-mediated biofilm formation is an essential virulence property for several of the pathogens mentioned above, pharmacological interference with its synthesis is predicted to prevent biofilm formation. Towards the goal of identifying a pharmacological anti-biofilm compound we have developed a high-throughput screening system for inhibitors of poly-GlcNAc biosynthesis in *E. coli* and screened a library of ca. 30 000 compounds. Seven compounds have been identified that prevent poly-GlcNAc biosynthesis and biofilm formation in the low μM concentration range. At least two of these compounds exhibit broad range activity and are effective against *E. coli* and *Staphylococcus epidermidis* biofilms. We are collaborating with members of the SFB630 to further develop the efficacy and specificity of these anti-biofilm compounds. The ultimate goal of the project is to obtain a lead compound that is of interest to partners from the pharmaceutical industry.

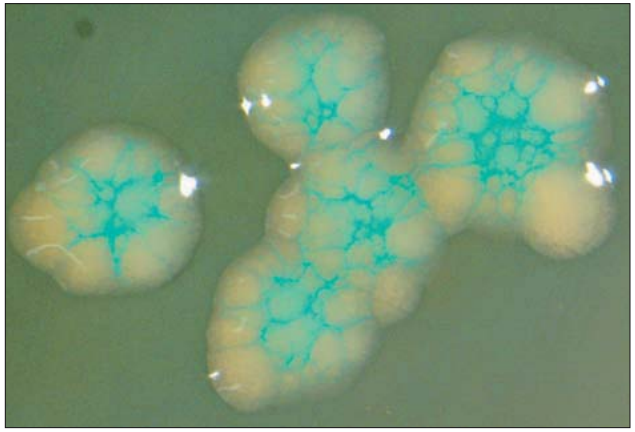


Fig. 3: Colonies of E. coli on an agar plate. The blue zones are areas where poly-GlcNAc is expressed.

SELECTED PUBLICATIONS

- *Boehm A, Kaiser M, Li H, Spangler C, Kasper CA, Ackermann M, Kaever V, Sourjik V, Roth V, Jenal U (2010) Second messenger-mediated adjustment of bacterial swimming velocity.* ***Cell*** *141:107-116*
- *Boehm A, Steiner S, Zaehringer F, Casanova A, Hamburger F, Ritz D, Keck W, Ackermann M, Schirmer T, Jenal U (2009) Second messenger signalling governs Escherichia coli biofilm induction upon ribosomal stress.* ***Mol Microbiol*** *72:1500-1516*

EXTRAMURAL FUNDING

- *DFG-Bo3733/1: Molecular principles of c-di-GMP dependent signaling cascades in Escherichia coli*
- *DFG-Bo3733/2: Molecular mechanism of swimming speed control in E. coli*

3 Institutions of the Research Center for Infectious Diseases
3.1 Institute for Molecular Infection Biology

CONTACT DETAILS

PD Dr. rer. nat. Ulrich Dobrindt

Institut für Molekulare Infektionsbiologie
Josef-Schneider-Str.2/D15
97080 Würzburg

since July 2010:
Institut für Hygiene
Bereich Mikrobielle Genomplastizität
Universität Münster
Mendelstraße 7
48149 Münster
Phone: +49-251-98002875
E-mail: dobrindt@uni-muenster.de

RESEARCH GOALS

- *Escherichia coli Patho-genomics*
- *Analysis of the regulation of virulence-associated genes in Escherichia coli*
- *Analysis of the impact of genome plasticity on microbial adaptation and evolution*
- *Characterization of virulence- or fitness-associated traits of extraintestinal pathogenic Escherichia coli*

3.1.5 Virulence Mechanisms of Pathogenic Enterobacteria

Summary

Pathogenic enterobacteria cause multiple diseases in humans and animals. For example, extraintestinal pathogenic *E. coli* (ExPEC) cause urinary tract infections, newborn meningitis and sepsis in man as well as severe systemic infections in poultry or acute bovine mastitis. In addition, ExPEC are the predominant causes of death from infectious diseases among the elderly as well as people with deficient immune response due to malignant diseases, chemotherapy, or immunosuppressive diseases. ExPEC strains associated with human and animal diseases are remarkably diverse and can cause acute symptomatic as well as chronic/subclinical infections. Interestingly, the ability of ExPEC to accumulate and express multiple virulence-associated determinants increases their fitness and adaptability and determines their potential to cause disease. These ExPEC virulence factors appear to enable the pathogens to exploit their hosts in ways unavailable to commensal strains in addition to their role in disease processes, and thus to spread and to persist in the bacterial community. In addition, the genome sizes between ExPEC vary significantly, with DNA acquisition by horizontal gene transfer as well as loss of genetic information and the occurrence of point mutations contributing to the genetic diversity among *Enterobacteriaceae* and the adaptation of these organisms to different growth conditions. Our research is focused on the identification and functional characterization of ExPEC virulence-associated traits using a functional genomics approach to understand the differences between commensals and ExPEC strains. The aim is to understand the molecular and epidemiological basis for pathogenicity and commensalism as well as for the establishment of acute symptomatic or chronic and asymptomatic infections.

Major Research

- *Identification of ExPEC virulence-associated traits*

We have chosen *E. coli* as a model organism since this species comprises non-pathogenic commensal as well as extraintestinal pathogenic variants that belong to the normal human intestinal flora. We have selected different clinical ExPEC isolates (uropathogenic *E. coli* strain 536, newborn meningitis-causing *E. coli* strain IHE3034, asymptomatic bacteriuria *E. coli* isolate 83972, bovine mastitis *E. coli* isolates EC1303 and 1470, avian pathogenic *E. coli* isolates as well as non-pathogenic *E. coli* strain Nissle 1917), sequenced their genomes and analysed their genome organisation, including the distribution of virulence-associated genes as well as the function and expression of important virulence- or fitness-associated factors.

Successful colonization of a niche requires

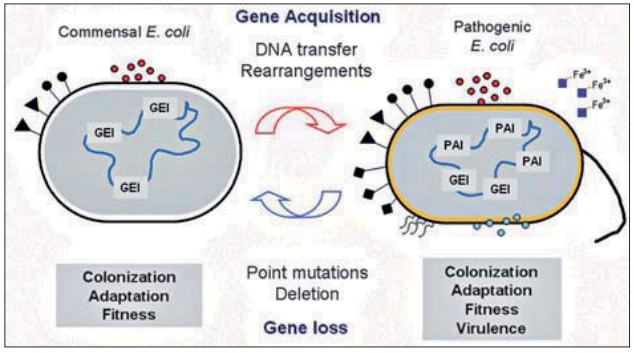


Fig. 1: Mechanisms involved in genome optimization of E. coli. Genome optimization involves DNA acquisition by horizontal gene transfer as well as DNA rearrangements. Furthermore, loss of genomic information due to point mutations or deletions affect the genome content. These mechanisms contribute to genetic variability and the generation of new phenotypes. GEI, genomic island; PAI, pathogenicity island.

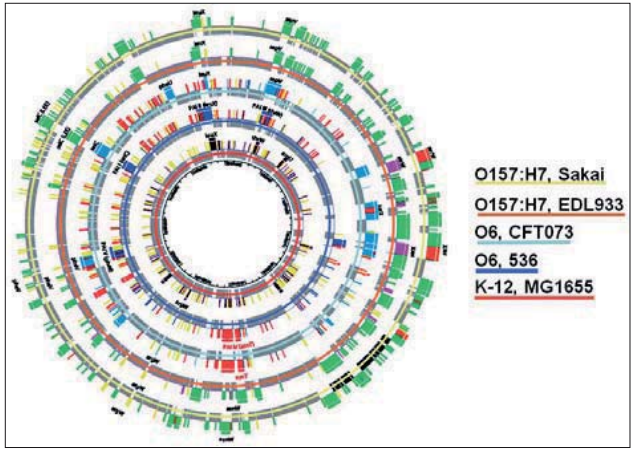


Fig. 2: Genome sequence comparison of five different pathogenic or non-pathogenic E. coli isolates. The conserved core genome is depicted as a grey line. Strain- or pathotype-specific genomic regions are indicated by boxes. Green: Pathotype-specific genomic regions of enterohemorrhagic E. coli; red and blue: pathotype-specific genomic regions of uropathogenic E. coli; pp, prophage. Foreign DNA regions are frequently associated with tRNA loci in the bacterial chromosome.

bacterial adaptation to the growth conditions encountered during infection, which necessitates a level of genome plasticity and positive selection. To correlate genetic flexibility and virulence potential of the bacteria with selective pressures imposed by the growth environment, we investigated (i) host-pathogen interactions, (ii) the mechanisms contributing to bacterial genome plasticity, and (iii) the driving forces behind bacterial adaptation. We have compared isolates from symptomatic or asymptomatic infections with commensals to promote the identification of bacterial properties and the molecular mechanisms involved in different forms of host-bacterium interaction, thus leading to different types of infection.
For example, we have studied the adaptation of asymptomatic bacteriuria *E. coli* strain 83972 to prolonged *in vivo* growth in the human urinary tract by comparative and functional genomics of ABU strain 83972 and different re-isolates obtained from deliberately colonized patients. This has revealed a smaller genome size and repotoire of functional virulence associated genes. The analysis of the underlying mechanisms will provide us with a better understanding of the processes involved in evolution of pathogenic bacteria and ExPEC pathogenesis. This approach will help us to identify bacterial traits required for symptomatic urinary tract infection or for persistent colonization and survival in the human urinary tract. The instability of pathogenicity islands (PAIs) and the role of PAI-encoded bacteriophage integrases for PAI deletion are being studied in detail as well as regulatory networks involved in virulence gene regulation. Furthermore, we aim at the functional characterization of novel virulence-associated genes in extraintestinal pathogenic *E. coli*.

SELECTED PUBLICATIONS

- *Zdziarski J, Brzuszkiewicz E, Wullt B, Liesegang H, Biran D, Voigt B, Grönberg-Hernandez J, Ragnarsdottir B, Hecker M, Ron E, Daniel R, Gottschalk G, Hacker J, Svanborg C and Dobrindt U (2010) Host imprints on bacterial genomes - rapid, divergent evolution in individual patients.* ***PLoS Pathogens*** *26;6(8):e1001078*
- *Moriel DG, Bertoldi I, Spagnuolo A, Marchi S, Rosini R, Nesta B, Pastorello I, Corea VA, Torricelli G, Cartocci E, Savino S, Scarselli M, Dobrindt U, Hacker J, Tettelin H, Tallon LJ, Sullivan S, Wieler LH, Ewers C, Pickard D, Dougan G, Fontana MR, Rappuoli R, Pizza M, Serino L (2010) Identification of protective and broadly conserved vaccine antigens from the genome of extraintestinal pathogenic Escherichia coli.* ***PNAS*** *107:9072-9077*
- *Fischer H, Lutay N, Ragnarsdóttir B, Yadav M, Jönsson K, Urbano A, Al Hadad A, Rämisch S, Storm P, Dobrindt U, Salvador E, Karpman D, Jodal U, Svanborg C (2010) Pathogen specific, IRF3-dependent signaling and innate resistance to human kidney infection.* ***PLoS Pathogens*** *23;6(9):e1001109*
- *Friedrich T, Rahmann S, Weigel W, Rabsch W, Fruth A, Ron E, Gunzer F, Dandekar T, Hacker J, Müller T, Dobrindt U (2010) High-throughput microarray technology in diagnostics of enterobacteria based on genome-wide probe selection and regression analysis.* ***BMC Genomics*** *11:591*

EXTRAMURAL FUNDING

- *DFG SFB479: Structure, function and distribution of pathogenicity islands in pathogenic enterobacteria*
- *ERA-NET PathoGenoMics: Deciphering the intersection of commensal and extraintestinal pathogenic Escherichia coli*
- *DFG-Do789/3-1: Characterization of Escherichia coli factors involved in the establishment of severe and chronic bovine mastitis*
- *BMBF FKZ 0315219B: Development of an automated software-assisted molecular-epidemiological typing of pathogenic bacteria using Escherichia coli as a model organism*
- *ERA-NET II PathoGenoMics: Pathogenomic approach to explore the use of bacterial interference as alternative treatment of recurrent urinary tract infections*
- *EMIDA ERA-NET PathoGenoMics: Combatting colibacillosis - a genomics based approach*

3 Institutions of the Research Center for Infectious Diseases
3.1 Institute for Molecular Infection Biology

CONTACT DETAILS

Dr. Ana Eulálio

Institut für Molekulare Infektionsbiologie
Josef-Schneider-Str. 2/D15
97080 Würzburg

Phone: +49-931-3189078
E-Mail: ana.eulalio@uni-wuerzburg.de
www.imib-wuerzburg.de/research/eulalio/

RESEARCH GOALS

- *Characterize the interplay between host cell microRNAs and bacterial infection*
- *Study the impact of bacterial infection on host cell RNA metabolism*
- *Role of bacterial non-coding RNAs in modulating key intracellular pathways in the host*

3.1.6 Host RNA Metabolism

Summary

During the course of 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 impact of bacterial infection on host cell RNA metabolism and its consequences on the bacterial life cycle. A proper RNA metabolism is essential to a number of crucial host cell functions and therefore it is not surprising that pathogens have evolved sophisticated mechanisms to subvert these pathways to their own benefit. To shed light on these processes, a systems biology approach will be taken to generate an atlas of host microRNAs regulated upon infection with representative bacterial pathogens in different eukaryotic cells. This will determine if a common microRNA signature exists for bacterial infection. Furthermore, we will investigate how bacterial pathogens impact other aspects of RNA metabolism in mammalian host cells, and whether this involves bacterial effector proteins. Finally, we will address the long-standing question of whether or not RNA serves as a communication molecule during bacterial infection, such that bacterial small non-coding RNAs are transferred into host mammalian cells to modulate their function.

Major Research

- *Interplay between host cell microRNAs and bacterial infection*

Bacterial pathogens (e.g. *Salmonella enterica*, *Helicobacter pylori*) induce significant changes in the mammalian host microRNA expression profile. While our previous work identified a small subset of miRNAs, including the let-7 family that controls cytokine expression, that are regulated in response to the presence of Salmonella, there is currently no comprehensive atlas of microRNAs that are regulated as a consequence of bacterial infection. Therefore, a major focus of our research is the identification of host microRNAs that are regulated upon infection with several representative bacterial pathogens, as well as the characterization of the mechanisms by which bacteria modulate host cell microRNA expression. Our ultimate goal is to determine whether different bacteria regulate a common set of host microRNAs or if a microRNA signature exists for infection by different bacteria, and to analyse the cell-type specificity of this response. We are also working on the identification of host cell microRNAs that regulate bacterial infection. The identification of these microRNAs will be instrumental to the development of novel therapeutic approaches against pathogenic bacteria, either through the modulation of selected microRNAs, or their targets.

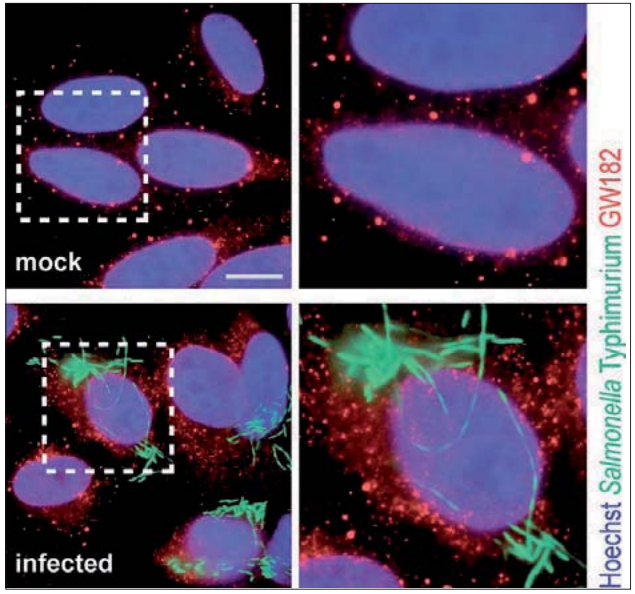


Fig. 1: Salmonella infection induces P-body disassembly. HeLa cells were mock-treated or infected with Salmonella Typhimurium expressing GFP. P-bodies were detected by staining the cells with anti-GW182 antibody. The regions highlighted by the white squares are enlarged on the rightmost panels. Scale bar, 10 µm.

- *Impact of bacterial pathogens on host cell RNA metabolism*

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 the cellular RNA metabolism, any perturbation of these structures induced by bacterial pathogens will likely have a consequence on host cell RNA metabolism. We aim to determine whether P-bodies, stress-granules, and/or their protein components are implicated in the regulation of RNA metabolism during bacterial infection, which will be important to determine whether and how bacteria interfere with RNA-related processes in their hosts. The reciprocal effect of RNA metabolism on bacterial infection will also be evaluated. Overall, with these studies we aim to characterize the impact of bacteria on cellular mRNA processing, stability and surveillance pathways.

- *Effect of bacterial non-coding RNAs on key host intracellular pathways*

One of the most intriguing questions that we aim to address is whether bacteria have developed a system to actively introduce RNAs inside host cells to modulate key cellular functions. This hypothesis is particularly pertinent taking into consideration that bacteria have evolved very efficient secretion systems for proteins and that a number of non-coding RNAs with, so far, unknown function have been identified in bacteria.

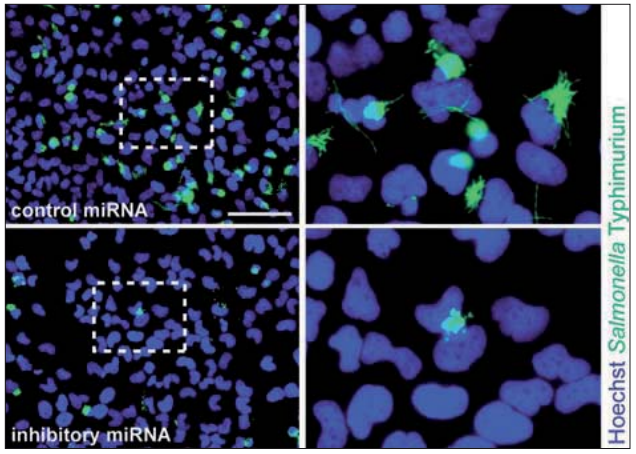


Fig. 2: Overexpression of selected microRNAs inhibits Salmonella infection. HeLa cells were transfected with selected microRNAs, followed by infection with Salmonella Typhimurium expressing GFP. The regions highlighted by the white squares are enlarged on the rightmost panels. Scale bar, 100 µm.

SELECTED PUBLICATIONS

- *Schulte L, Eulálio A, Mollenkopf H, Reinhardt R and Vogel J (2011) Analysis of the host microRNA response to Salmonella uncovers the control of major cytokines by the let-7 family.* ***EMBO J*** *30(10):1977-1989*
- *Eulálio A, Fröhlich K, Mano M, Giacca M and Vogel J (2011) A candidate approach implicates the secreted Salmonella effector protein SpvB in P-body disassembly.* ***PLoS One*** *6(3):e17296*
- *Heale BS, Eulálio A, Schulte L, Vogel J and O'Connell MA (2010) Analysis of A to I editing of miRNA in macrophages exposed to Salmonella.* ***RNA Biology*** *7:116-122*
- *Eulálio A, Helms S, Fritzsch C, Fauser M and Izaurralde E (2009) A C-terminal silencing domain in GW182 is essential for miRNA function.* ***RNA*** *15:1067-1077*

EXTRAMURAL FUNDING

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

3 Institutions of the Research Center for Infectious Diseases
3.1 Institute for Molecular Infection Biology

CONTACT DETAILS

PD Dr. Knut Ohlsen

Institut für Molekulare Infektionsbiologie
Josef-Schneider-Str. 2/D15
97080 Würzburg

Phone: +49-931-3182155
E-Mail: knut.ohlsen@uni-wuerzburg.de
www.imib-wuerzburg.de/research/ohlsen/

RESEARCH GOALS

- *Development of immune therapeutics against Staphylococcus aureus*
- *Regulation of cellular functions by eukaryotic-like serine/threonine kinases and phosphatases*
- *Establishment of in vivo imaging technology to study staphylococcal infections*
- *Identification and characterization of new targets for antimicrobial therapy*
- *Characterization of the adaptive immune response in systemic infections caused by S. aureus*

3.1.7 Gram-Positive Cocci

Summary

Staphylococcus aureus and *Staphylococcus epidermidis* are the most common causative agents of nosocomial infections. Due to the expression of an extraordinary number of virulence traits including leucotoxins, hemolysins, adhesins and degradation enzymes the pathogen is able to cause a broad spectrum of diseases ranging from the formation of mild abscess to life threatening infections like septicemia, endocarditis, pneumonia and osteomyelitis. 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 a decline in therapeutic options due to the emergence of new types of multiple resistant strains. In particular, methicillin-resistant *S. aureus* (MRSA) has emerged as major nosocomial pathogen 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.

Major Research

- *Development of antibody therapy against Staphylococcus aureus*

The emergence of multiple antibiotic resistant staphylococcal stains coupled with the severe associated clinical outcomes provide a strong rationale for the development of immunoglobulin-based therapeutic strategies. Traditionally, novel immunological approaches against bacterial pathogens require the generation of antibodies directed against cell surface exposed virulence-associated epitopes or toxins. However, while monoclonal antibodies targeting immunodominant antigens expressed in vivo during infection trigger the patient`s immune system to produce antibodies, the amount of these antibodies is often not sufficient to clear the infection. Therefore, we have developed a passive immunotherapy strategy based on immunodominant antigens, with one of the target antigens being a soluble lytic transglycosylase of *S. aureus*. The monoclonal antibody recognizes all *S. aureus* strains tested including hospital-acquired and community-acquired methicillin-resistant *S. aureus* strains and the therapeutic efficacy of this strategy has been validated in three experimental mouse infection models (Fig 1 and 2). The monoclonal antibody activates professional phagocytes and induces the production of highly microbicidal reactive oxygen metabolites in a dose-dependent manner, resulting in bacterial killing. Subsequently, the mouse monoclonal antibody has been humanized as prerequisite for therapeutical application in humans. These results provide strong indications that this novel antibody therapy approach against immunodominant antigens of *S. aureus* could be beneficial in the treatment of *S. aureus* invasive infections and potentially reduce the associated morbidity and mortality.

- *Cellular function by eukaryotic-like Serine/Threonine kinases and phosphatases*

While phosphotransfer based mechanisms of signal transduction play an important role in prokaryotes and eukaryotes, the existence of eukaryotic-like serine/threonine kinases (ESTKs) and phosphatases (ESTPs) have only recently been shown to be present in bacteria. This includes *Staphylococcus aureus* where functional ESTPK and corresponding ESTP have been identified and, based on homology to known ESTPKs/ESTPs, the kinase has been designated PknB or alternatively Stk/Stk1, and the phosphatase Stp. A major focus of our work, as part of the transregional collaborative research center 34 (TR-SFB34) is to understand the cellular role of these enzymes. The analysis of knockout mutants and kinase/phosphatase overexpressing strains has uncovered important functions of PknB/Stk and Stp as modulators of cell wall structure and susceptibility to cell wall-acting antibiotics such as certain β-lactams and tunicamycin. Furthermore, transcriptional profiling and phosphoproteome studies have revealed an important role of PknB/Stk in regulating the expression of genes associated with basic metabolic processes such as purine and pyrimidine biosynthesis, cell wall metabolism, autolysis, and glutamine synthesis as well as in virulence. Overall, we have revealed Ser/Thr phosphorylation/dephosphorylation as a common theme in the regulation of cellular functions such as determining metabolic activity and virulence in the major human pathogen *S. aureus*.

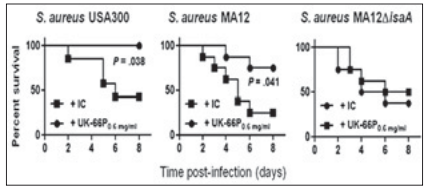


Fig. 1: Immunotherapy with monoclonal anti-IsaA antibodies (UK-66P) generates protection against lethal S. aureus challenge. Mice were challenged with the UK-66P antibody preparation or an isotype control antibody (IC).

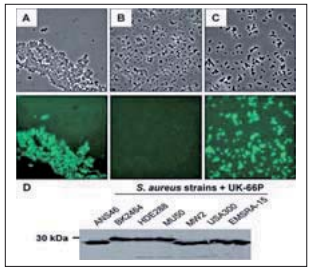


Fig. 2: Binding of the anti-IsaA monoclonal antibody UK-66P to the surface of staphylococci(A, C) including clinical S. aureus isolates. (A) UK-66P binds specifically wild-type S. aureus MA12. (B) Specificity can be demonstrated by a lack of UK-66P binding to the isogenic mutant strain MA12 ΔisaA (C) and binding of UK-66P to a S. aureus protein A knock out strain (Δspa) (x 100 magnification). (D) Reactivity of UK-66P to IsaA of representative clinical isolates.

- *In vivo imaging of staphylococcal infections*

Virulence of *S. aureus* is multifactorial process that is dependent on the expression of specific pathogenicity factors. To understand pathogenicity of *S. aureus* as complex process and to analyze particular virulence determinants it is essential to apply in vivo models that mimic the natural infection process. Although several animal models have been described it is still unknown which model is most relevant to evaluate a particular virulence determinant or the virulence potential of a laboratory or clinical strain. In order to monitor the infection process in a native context we are collaborating with the Physics department at the University of Würzburg to establish novel in vivo imaging techniques. These are based on a *S. aureus* strain (Xen29) expressing the *lux* operon (also part of TR-SFB 34), which can be visualised by bioluminescence imaging or in a separate approach using magnetic resonance imaging (MRI), which we have successfully applied to detect inflammatory lesions in soft tissue infection models (Fig. 3). We are subsequently using this method to monitor the mechanism and efficiency of antimicrobials in eradicating the infection.

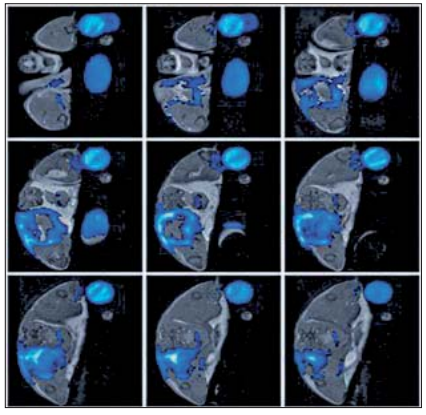


Fig. 3: Representative magnetic resonance (MR)-slice series of soft tissue infection by S. aureus. The hollow sphere formed by perfluorcarbon nanoparticles (PFC) during the acute phase of infection is indicated by blue colour. The depicted mouse received an injection of PFC at day 2 post-infection with the images being recorded 24hrs after administration.

SELECTED PUBLICATIONS

- Lorenz U, Lorenz B, Schmitter T, Streker K, Erck C, Wehland J, Nickel J, Zimmermann B, Ohlsen K (2011) Functional antibodies targeting IsaA of Staphylococcus aureus augment host immune response and open new perspectives for antibacterial therapy
  Antimicrob Agents Chemother *55:165-173*
- Menzel TM, Tischer M, François P, Nickel J, Schrenzel J, Bruhn H, Albrecht A, Lehmann L, Holzgrabe U, Ohlsen K (2011) Mode of action studies of the novel bisquaternary bisnaphthalimide MT02 against Staphylococcus aureus
  Antimicrob Agents Chemother *55:311-320*
- Cecil A, Rikanović C, Ohlsen K, Liang C, Bernhardt J, Oelschlaeger TA, Gulder T, Bringmann G, Holzgrabe U, Unger M, Dandekar T (2011) Modeling antibiotic and cytotoxic effects of the dimeric isoquinoline IQ-143 on metabolism and its regulation in Staphylococcus aureus, Staphylococcus epidermidis and human cells
  Genome Biology *12:R24*
- Donat S, Streker K, Schirmeister T, Rakette S, Stehle T, Liebeke M, Lalk M, Ohlsen K (2009) Transcriptome and functional analysis of the eukaryotic-type serine/threonine kinase PknB in Staphylococcus aureus
  J Bacteriology *191:4056-4069*

EXTRAMURAL FUNDING

- *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*
- *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-Bio3, FKZ 0315565: Immunotherapy against Staphylococcus aureus*
- *BMBF-Infection Genomics, FKZ 0315829E: Host-pathogen interaction: effects of secreted proteins of Staphylococcus aureus on cells and components of the immune system*
- *EU FP7 241796: Impact of specific antibiotic therapies on the prevalence of human host resistant bacteria (SATURN)*

3 Institutions of the Research Center for Infectious Diseases
3.1 Institute for Molecular Infection Biology

CONTACT DETAILS

Dr. rer. nat. Tobias Ölschläger

Institut für Molekulare Infektionsbiologie
Josef-Schneider-Str. 2/D15
97080 Würzburg

Phone: +49-931-3182150
E-Mail: t.oelschlaeger@uni-wuerzburg.de
www.imib-wuerzburg.de/research/oelschlaeger/

RESEARCH GOALS

- *Identification of substances that interfere with bacterial adhesion and invasion*
- *Characterising the mode of action of such inhibitory substances*
- *Elucidation of the molecular mechanisms involved in the probiotic functions of bacteria*
- *Optimising probiotic E. coli strain Nissle 1917*

3.1.8 Pathogenic Enterobacteria

Summary

The species *Escherichia coli* is an ideal model system for identifying the properties that distinguish pathogenic and even probiotic bacteria from commensal ones. The adhesion and invasion of host epithelial cells by pathogenic bacteria such as intestinal and extraintestinal *E. coli* represent the initial steps in the establishment of an infection. The adhesion of the bacteria to surfaces within the host provides an important counteraction against mechanical mechanisms (e.g. peristalsis, mucus secretion, flushing of the urinary tract) aimed at removing these microorganisms from the body. We are currently screening for compounds that are able to interfere with these two important steps in the infection process using in vitro assays. Probiotic bacteria, which are defined as live microorganisms mediating preventive or therapeutic effects on the host if administered in sufficient amounts, have attracted increasing attention in recent years as a potential alternative medication. This is, in part, due to increasing problems with antibiotic resistance in pathogenic bacteria and the expectation of fewer side effects caused by probiotic bacteria compared to other medications. However, the molecular basis for this probiotic activity is only poorly understood and we are currently identifying the genetic basis for these properties in the probiotic *E. coli* strain Nissle 1917 (EcN).

Major Research

- *Early Steps during Establishment of an Infection*

The invasion of host epithelial cells by pathogenic bacteria renders them at least partially protected from the hosts immune system and the action of a multitude of antibiotics. Once intracellular these bacteria are able to establish a reservoir that can be the source of recurrent infections such as those in the urinary tract. In collaboration with several pharmaceutical companies, we have established *in vitro* host cell models using human urinary tract and gut epithelial cell lines as well as cryosections of human gut biopsies and urine samples from healthy volunteers to screen for compounds that interfere with the adhesion and invasion processes.These compounds have been screened against bacterial uropathogens such as *E. coli*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *Citrobacter freundii* as well as *Salmonella typhimurium* and several were shown to have anti-adhesive and anti-invasive effects in vitro. The substances identified are either part of drugs already in use *for treatment*/prevention of urinary tract infections or promising candidates for the development of new medication.

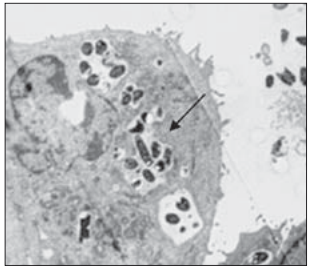


Fig. 1: Bacteria inside a host cell. Arrow points to bacteria inside a vacuole.

- *The Probiotic Escherichia coli Strain Nissle 1917*

We have selected the probiotic *E. coli* strain Nissle 1917 (EcN) as a model organism for probiotics since the safety and efficacy of this probiotic bacterium has been well documented. However, the molecular mechanisms responsible for its probiotic activity are rather limited. We have been able to identify genetic determinants and properties that are important for its probiotic nature. We have demonstrated *in vitro anti-invasive activity of EcN for Salmonella*, *Shigella*, *Yersinia* and *Listeria* and that this activity is mediated by a yet unknown secreted factor. We have shown that the flagella of EcN are a multi-purpose tool responsible for motility, induction of human λeta-defensin 2 and an adhesin for binding to human mucin 2, and this likely prevents the adhesion

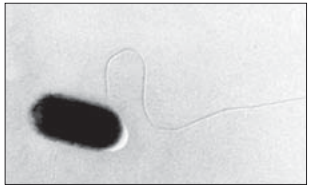


Fig. 2: Electronmicroscopical image of probiotic Escherichia coli strain Nissle 1917 which expresses only one flagella.

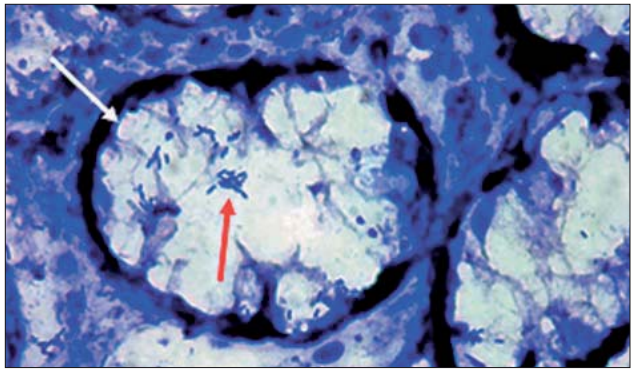


Fig. 3: Light microscopic picture of a cross-section through a crypt of a human gut biopsy with adherent EcN bacteria (red arrow). White arrow indicates the boundary of the crypt.

of the pathogenic bacteria. By contrast, the classical adhesins such as type 1 pili and F1C fimbriae are not able to mediate efficient adhesion to human mucin 2. Ongoing studies are examining additional molecular components of EcN that are important for its probiotic capabilities. One such project focuses on the ability of EcN to interfere with adhesion, growth and Shiga toxin activity of EHEC strains including the one responsible for the outbreak in 2011 in Germany. Finally, the potential basis for the treatment of Crown's disease patients with a recombinant EcN strain was approached by the construction of an EcN derivative able to synthesize and secrete human beta-defensin 2, because most patients suffering from this disease are unable to produce sufficient amounts of defensins in the gut.

SELECTED PUBLICATIONS

- *Schierack P, Kleta S, Tedin K, Babila JT, Oswald S, Oelschlaeger TA, Hiemann R, Paetzold S, Wieler LH (2011) E. coli Nissle 1917 affects Salmonella adhesion to porcine intestinal epithelial cells.* ***PLoS One*** *6(2):e14712*
- *Stritzker J, Weibel S, Seubert C, Götz A, Tresch A, van Rooijen N, Oelschlaeger TA, Hill PJ, Gentschev I, Szalay AA (2010) Enterobacterial tumor colonization in mice depends on bacterial metabolism and macrophages but is independent of chemotaxis and motility.* ***In J Med Microbiol*** *300:449-456*
- *Putze J, Hennequin C, Nougayrede JP, Zhang W, Homburg S, Karch H, Bringer MA, Fayolle C, Carniel E, Rabsch W, Oelschlaeger TA, Oswald E, Forestier C, Hacker J, Dobrindt U (2009) Genetic structure and distribution of the colibactin genomic island among members of the family Enterobacteriaceae.* ***Infect Immun*** *77:4696-4703*
- *Remer KA, Bartrow M, Roeger B, Moll H, Sonnenborn U, Oelschlaeger TA (2009) Split immune response after oral vaccination of mice with recombinant Escherichia coli Nissle 1917 expressing fimbrial adhesion K88.* ***Int J Med Microbiol*** *299:467-478*
- *Bickert T, Trujillo-Vargas CM, Duechs M, Wohlleben G, Polte T, Hansen G, Oelschlaeger TA, Erb KJ (2009) Probiotic Escherichia coli Nissle 1917 suppresses allergen-induced Th2 responses in the air ways.* ***Int. Arch Allergy Immunol*** *149:219-230*

EXTRAMURAL FUNDING

- *Pharmazentrale GmbH, Herdecke*
- *Rosenpharma GmbH, St. Ingbert*
- *Bionorica SE, Neumarkt*

3 Institutions of the Research Center for Infectious Diseases
3.1 Institute for Molecular Infection Biology

CONTACT DETAILS

PD Dr. med. Wilma Ziebuhr

Institut für Molekulare Infektionsbiologie
Josef-Schneider-Str. 2/D15
97080 Würzburg

Phone: +48-931-3182154
E-Mail: w.ziebuhr@mail.uni-wuerzburg.de
www.imib-wuerzburg.de/research/ziebuhr/

RESEARCH GOALS

- *sRNA regulation of metabolism and biofilm formation in Staphylococci*
- *Metabolic variability and bacterial cell differentiation in S. epidermidis biofilms*

3.1.9 Coagulase Negative Staphylococci

Summary

Coagulase-negative Staphylococci (CoNS) are notorious nosocomial pathogens which frequently cause biofilm associated infections that mainly affect immunocompromised patients carrying indwelling medical implants. Recent progress in genome research and molecular epidemiology have provided exciting novel insights into the biology of these bacteria, demonstrating that these versatile and flexible microorganisms can adapt very rapidly to changing environmental conditions both on the genetic and the regulatory level. We have a strong interest in teaming basic research with public health aiming at an in-depth understanding of CoNS infections and laying the basis for future innovative prevention and treatment strategies. Our research focuses on the factors and processes that contribute to the establishment of these bacteria as pathogens in the hospital environment. Specifically, this includes the mechanism of biofilm formation on medical devices, which significantly contributes to therapy recalcitrance of CoNS infections. We are in the process of determining the regulatory networks controlling biofilm formation, including the role of small regulatory RNAs (sRNAs), as well as factors that trigger metabolic heterogeneity and division of labour within staphylococcal biofilm communities. In addition, we also study the molecular function of mobile genetic elements and their impact on genome flexibility, adaptation and heterogeneous gene expression.

Major Research

- *sRNA-mediated regulation of metabolism and biofilm formation in Staphylococci*

Small non-coding RNA (sRNA) molecules have recently been identified as important players in gene regulation within many microorganisms. While previous research in Staphylococci has mainly focused on proteins as the major regulators of gene expression, we are exploring the contribution of sRNAs to the complex regulatory networks that govern staphylococcal physiology. Recent research has suggested a strong association between metabolism and virulence in Staphylococci. Notably, biofilm formation is a metabolically costly process that takes up a huge amount of carbon and energy resources for the production of the extracellular polymer substances (EPS) in which the bacteria become eventually embedded. As a consequence the expression of genes involved in biofilm formation are tightly regulated and controlled in response to many factors, including nutrient supply and external stress (e.g. antibiotics, temperature, osmolarity etc.). We have focused our research on the identification and functional characterisation of sRNAs that play a role in linking staphylococcal metabolism and virulence and utilized classical genetics, comprehensive transcriptome, proteome and metabolic profiling approaches to identify two sRNAs and their cognate mRNA targets. One of the sRNAs acts in *cis* and controls *de novo* amino acid biosynthesis, while the other exerts its effects in *trans* and is likely to influence biofilm formation and stress response in hospital-acquired *Staphylococcus epidermidis* isolates. We are currently aiming to evaluate these sRNAs as putative targets for antibiotics or modulatory substances to specifically influence biofilm formation and crucial metabolic pathways of Staphylococci.

- *Metabolic variability and differentiation in Staphylococcus epidermidis biofilms*

Bacterial biofilms represent highly organised structures that have been proposed to functionally resemble a multicelluar organism in terms of heterogenous gene expression patterns within the biofilm community. 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. *S. epidermidis* encounters very different environments when living on the skin, colonising an implant or being translocated into the bloodstream during a device-related infection, and the bacterium is therefore likely to respond via different gene expression patterns in response to these challenges. We found that the mobile genetic element IS*256* triggers diversity in *S. epidermidis* both by active transposition and by acting passively as cross-over points for homologous recombination events, eventually resulting in genome instability. This genome instability has also been detected during a clinical case of a persistent, generalised device-related *S. epidermidis* infection. The isolates recovered from this patient varied with respect to metabolic patterns and the nature of the extracellular polymer substances from which the biofilm was built (*i.e.* proteins vs. polysaccharides). Using this hypervariable *S. epidermidis* strain as a model organism, we have investigated the nature and impact of metabolic individuality on the structure and dynamics of *S. epidermidis* biofilm communities. Using transcriptome profiling methods we have determined the differentially expressed metabolic pathways in protein- and polysaccharide-mediated *S. epidermidis* biofilms; the co-existence of metabolic variants within biofilm-forming populations; as well as the quantitative proportion, spatial distribution and possible interactions of metabolic variants within the biofilm structure. Finally, we have further described the biological significance of phenotypic heterogeneity on long-term survival and stress resistance of biofilm-forming *S. epidermidis* communities.

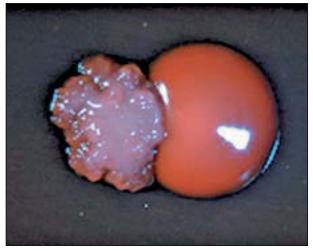


Fig. 1: Phenotypic variability of biofilm-forming Staphylococcus epidermidis grown on Congo red agar.

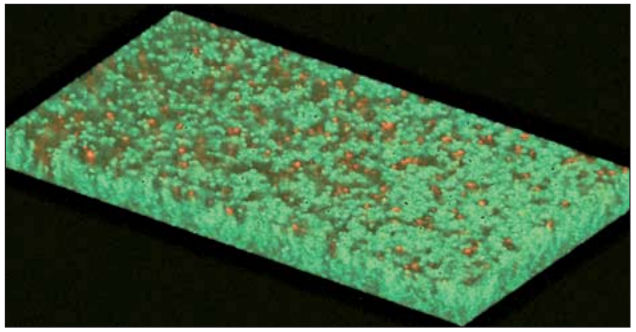


Fig. 2: Confocal laser microscopy and 3D-reconstruction of a Staphylococcus epidermidis biofilm after live/dead staining. Live cells appear in green and dead bacteria in red.

SELECTED PUBLICATIONS

- *Schoenfelder SM, Lange C, Eckart M, Hennig S, Kozytska S, Ziebuhr W (2010) Success through diversity - how Staphylococcus epidermidis establishes as a nosocomial pathogen.* ***Int J Med Microbiol*** *300:380-6*
- *Hennig S, Ziebuhr W (2010) Characterization of the Transposase Encoded by IS256, the Prototype of a Major Family of Bacterial Insertion Sequence Elements.* ***J Bacteriol*** *192:4153-63*
- *Weisser M, Schoenfelder SM, Orasch C, Arber C, Gratwohl A, Frei R, Eckart M, Flückiger U, Ziebuhr W (2010) Hypervariability of biofilm formation Cosevere infection in an immunocompromised patient.* ***J Clin Microbiol*** *48:2407-12*
- *Ziebandt AK, Kusch H, Degner M, Jaglitz S, Sibbald MJ, Arends JP, Chlebowicz MA, Albrecht D, Pantucek R, Doskar J, Ziebuhr W, Bröker BM, Hecker M, van Dijl JM Engelmann S (2010) Proteomics uncovers extreme heterogeneity in the Staphylococcus aureus exoproteome due to genomic plasticity and variant gene regulation.* ***Proteomics*** *10(8):1634-44*

EXTRAMURAL FUNDING

- *DFG SFB/TRR34: Pathophysiology of Staphylococci in the Post-Genomic Era*
- *DFG SPP1617: Phenotypic heterogeneity of bacterial populations*

3 Institutions of the Research Center for Infectious Diseases
3.2 Institute of Hygiene and Microbiology

CONTACT DETAILS

Prof. Dr. med. Matthias Frosch (Chair)

Institut für Hygiene und Mikrobiologie
Josef-Schneider-Str. 2/E1
97080 Würzburg

Phone: +49 931-201-46160
E-Mail: mfrosch@hygiene.uni-wuerzburg.de
www.hygiene.uni-wuerzburg.de/forschung/

RESEARCH GOALS

- *Evolutionary Pathogenomics of N. meningitidis*
- *Functional Genomics and Systems Microbiology of N. meningitidis*
- *Infection epidemiology of meningococci, Haemophilus influenzae and echinococcosis*

3.2.1 Hygiene and Medical Microbiology

Summary

The main tasks of the Institute for Hygiene and Microbiology (IHM) are (i) the 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) teaching and training for students of medicine, dentistry and related subjects.
The research activity of the IHM mainly focuses on the human pathogen *Neisseria meningitidis*. *N. meningitidis* usually lives as a commensal bacterium in the upper airways exclusively of humans but occasionally can also cause life threatening diseases such as acute bacterial meningitis or sepsis. Due to the lack of a suitable animal model the genetic basis of meningococcal virulence is currently poorly understood. By comparing the genomes and transcriptomes of invasive and carriage isolates we are experimentally investigating the genetic basis and the mechanisms of meningococcal pathogenicity as well as their evolution in ex vivo infection models.
The institute is also dedicated to the work of the reference laboratories for meningococci, *Haemophilus influenzae* and echinococcosis. As such, there is great interest in continuously improving laboratory surveillance of the diseases in collaboration with public health authorities at the European level. This results in the development of new typing tools as well as in scientific studies on the population biology of the infectious agents.

Major Research

A basic assumption for pathogenic bacteria is that virulence is genetically determined by virulence factors encoded in the bacterial genome. However, what these genetic factors are and how they might have evolved in meningococci is currently poorly understood and little is also known about potential differences in the transcriptomes of carriage and invasive meningococcal strains. Consequently, the work of our group focuses on the genetic basis of meningococcal virulence and why only certain meningococcal strains belong to the hyperinvasive lineages that cause the majority of invasive meningococcal disease.

- *Evolutionary Pathogenomics of N. meningitidis (C. Schoen, M. Frosch)*

By applying computational genome analyses together with comparative genome hybridization using microarrays (mCGH) of 29 meningococcal strains, we recently detected a novel association of meningococcal virulence with a recently described canonical genomic island termed IHT-E. This approach also revealed a differential distribution of genes encoding RTX toxin- and two-partner secretion systems among hyperinvasive and non-hyperinvasive lineages. Furthermore, we have demonstrated that recombination comprising lateral transfer of minimal mobile elements as well as prophages and homologous intragenic recombination in core genes has a profound impact on meningococcal population structure and genome composition.

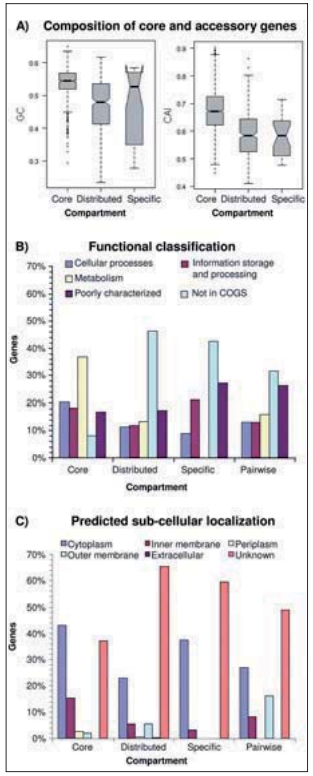


Fig. 1: Composition of the meningococcal pan-genome.

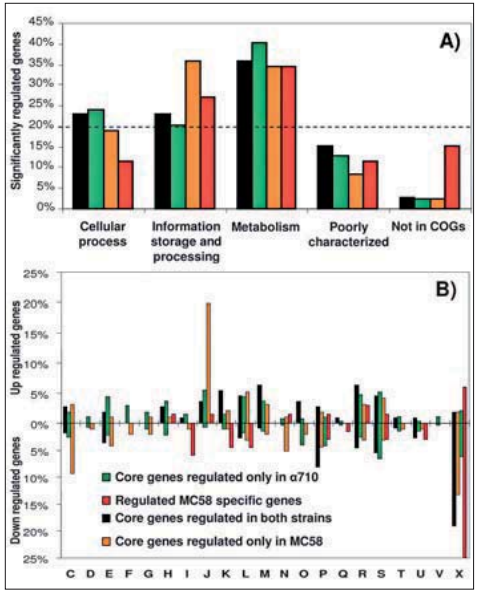


Fig. 2: Functional classification of genes differentially expressed upon adhesion to human FaDu nasopharyngeal cell lines in the two meningococcal serogroup B strains MC58 and α710.

- *Functional Genomics and Systems Microbiology of N. meningitidis (C. Schoen, M. Frosch)*

Our comparison of transcriptomes between a serogroup B strain from a hyperinvasive lineage and a related serogroup B carriage strain upon adhesion to human nasopharyngeal cells, revealed that almost 10% of the 1731 genes that both strains have in common were differently expressed. These include particular genes involved in inorganic ion as well as amino acid transport and metabolism, energy metabolism as well as stress response. In line with these transcriptomic differences, both strains also showed marked differences in their in vitro infectivity and in serum resistance. Our data thus support the concept of a polygenic nature of meningococcal virulence comprising differences in gene content as well as in the regulation of metabolic genes, and we suggest a prominent role for immune selection and genetic drift in shaping the meningococcal genome.

- *Infection epidemiology of meningococci, Haemophilus influenzae and echinococcosis (U. Vogel, K. Brehm, M. Frosch)*

At the Institute for Hygiene and Microbiology (IHM) the Federal Ministry of Health and the Robert Koch-Institute have established the National Reference Centre for Meningococci (NRZM, www.meningococcus.de). The activities of the NRZM include the identification as well as the serological and molecular typing of meningococci, an advisory service in case management and the counselling of public health departments in the epidemiological monitoring of putative outbreaks of meningococci diseases. The IHM is part of the pan-European network of reference centres, the "European Monitoring Group on Meningococci", and co-ordinates on behalf of the European Centre for Disease Prevention and Control (ECDC) the laboratory surveillance of invasive bacterial infection in all European Member States. Moreover, on behalf of the Robert Koch-Institute the institute also functions as consiliary laboratory for *Haemophilus influenzae* (www.haemophilus-online.de) and echinococcosis (www.echinococcus.de.), employing special state-of-the-art diagnostic tests and typing methods and providing advice on diagnosis, therapy, prevention and epidemiology.

SELECTED PUBLICATIONS

- *Joseph B, Schwarz RF, Linke B, Blom J, Becker A, Claus H, Goesmann A, Frosch M, Müller T, Vogel U, Schoen C (2011) Virulence evolution of the human pathogen Neisseria meningitidis by recombination in the core and accessory genome.* ***PloS One*** *6:e18441*
- *Joseph B, Schneiker-Bekel S, Schramm-Glück A, Blom J, Claus H, Linke B, Schwarz RF, Becker A, Goesmann A, Frosch M, Schoen C (2010) Comparative genome biology of a serogroup B carriage and disease strain supports a polygenic nature of meningococcal virulence.* ***J Bacteriol*** *192:5363-77*
- *Schubert-Unkmeir A, Konrad C, Slanina H, Czapek F, Hebling S, Frosch M (2010) Neisseria meningitidis induces endothelial cell detachment from the matrix and cleavage of occludin: a role for MMP-8 activity.* ***PLoS Pathogens*** *6:e1000874*

EXTRAMURAL FUNDING

- *DFG SPP 1316: Host-Adapted Metabolism of Bacterial Pathogens. Project: Gene regulatory mechanisms of metabolic adaptation in Neisseria meningitidis in ex vivo infection models*
- *BMBF grant: PathoGenoMik-Plus. Application of comparative genomics derived knowledge for surveillance and prevention of meningococcal disease*
- *BMBF grant: PathoGenoMik-Plus. Central Management*
- *BMBF grant: Medical Infection Genomics. Central Management*
- *BMG grant: National Reference Laboratory for Meningococci*
- *BMG grant: Consiliary Laboratory for Haemophilus influenzae*
- *BMG grant: Consiliary Laboratory for Echinococcosis*
- *NoE-EuroPathoGenomics: European Virtual Institute for Functional Genomics of Bacterial Pathogens*
- *EU/ECDC grant: EQA of invasive bacterial diseases in EU*
- *EU/ECDC grant: Laboratory surveillance of invasive pneumococcal disease in EU*
- *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*

CONTACT DETAILS

Prof. Dr. rer. nat. Klaus Brehm

Institut für Hygiene und Mikrobiologie
Josef-Schneider-Str. 2/E1
97080 Würzburg

Phone: +49-931-3146168
E-Mail: kbrehm@hygiene.uni-wuerzburg.de
www.hygiene.uni-wuerzburg.de/forschung/ag_brehm/

RESEARCH GOALS

- *Molecular characterization of host-parasite interaction in larval cestode infections*
- *Evolutionary adaptation of flatworm parasites to vertebrate and invertebrate hosts*
- *Development of novel chemotherapeutics against cestode and flatworm diseases*

3.2.2 Medical Parasitology

Summary

Infections due to larval cestodes (echinococcosis, cysticercosis) are devastating and of worldwide prevalence, yet largely understudied when compared to other infectious diseases. Using the fox-tapeworm *Echinococcus multilocularis* as a model system, we are studying aspects of molecular host-parasite interaction during an infection, including immunomodulation of the host immune response by parasite products as well as host-directed parasite development. Key tools for our investigations are several in vitro cultivation systems by which the entire life-cycle of *E. multilocularis* within the intermediate host can be mimicked under laboratory conditions. These include co-cultivation systems of parasite larval stages with host cells and a very sophisticated system for culturing totipotent parasite stem cells (neoblasts) that is highly suitable for carrying out invertebrate stem cell research. In collaboration with the Wellcome Trust Sanger Center we have also carried out a whole genome/transcriptome project for *E. multilocularis* which, together with other ongoing cestode sequencing projects, will facilitate investigations on parasite-host co-evolution and will provide a platform for target-based drug design and the identification of immunomodulatory molecules. As one focus, we are concentrating on evolutionarily conserved signalling systems which act at the host-parasite interface and fulfil key roles in molecular host-parasite communication and parasite development. The respective parasite molecules, which are mostly kinases against which a plethora of inhibitory compounds are available due to cancer research, are currently investigated aiming at promising drug targets for improved anti-cestode chemotherapy.

Major Research

- *In vitro cultivation and genetic manipulation of E. multilocularis larvae and stem cells*

The availability of suitable in vitro cultivation systems is vital for investigating molecular aspects of host-helminth interaction. We have developed several cultivation systems for *E. multilocularis* by which the entire infection cycle within the intermediate host liver can be re-constituted under laboratory conditions (Fig. 1). These systems are currently used to (1) investigate the influence of defined host hormones and cytokines on parasite development; (2) to provide parasite material for genomic, transcriptomic and proteomic approaches; (3) to study the secretome of larval cestodes and its influence on host cells; and (4) to screen small molecule compound libraries for drugs that exhibit anti-parasitic effects. We are currently also developing methods for targeted genetic manipulation of the parasite via RNA-interference and virus-based integration of foreign DNA into the parasite genome.

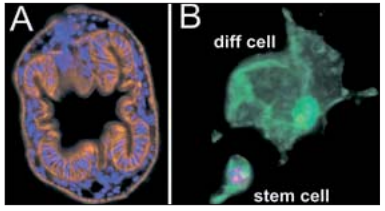


Fig. 1: E. multilocularis in vitro cultivation. A) Echinococcus protoscolex, phalloidin staining. Muscular system around suckers. B) Cultivated Echinococcus cells. Phalloidin staining (green) and BrdU-staining (pink) for DNA-synthesis. Note that only stem cells incorporate BrdU, indicating proliferation, but not differentiated cells (diff cell).

- *Host-parasite cross-communication involving evolutionarily conserved signalling systems*

Using several approaches we have identified parasite signalling systems that exhibit considerable homology to human cell-cell communication systems. These include RTKs of the insulin-, the EGF-, and the FGF receptor families including downstream signalling molecules of the MAPK cascade. We also identified conserved components of TGF-beta signalling such as type I/II receptor serine/threonine kinases, Smad transcription factors and cooperating members of the nuclear hormone receptor family. Based on data obtained through the *in vitro* cultivation systems which clearly indicate that host-derived hormones stimulate parasite proliferation and development, we are currently elucidating the molecular interactions between evolutionarily conserved parasite receptors and the corresponding host cytokines that are present in the parasite's primary target organ. Furthermore, we are analyzing the downstream events in the parasite such as the activation of the parasite's MAPK cascade, PI3 kinase signalling and Smad transcription factor activation. We thus aim to demonstrate that flatworm parasites utilize their close genetic relationship to mammals for successful establishment and maintenance within the host.

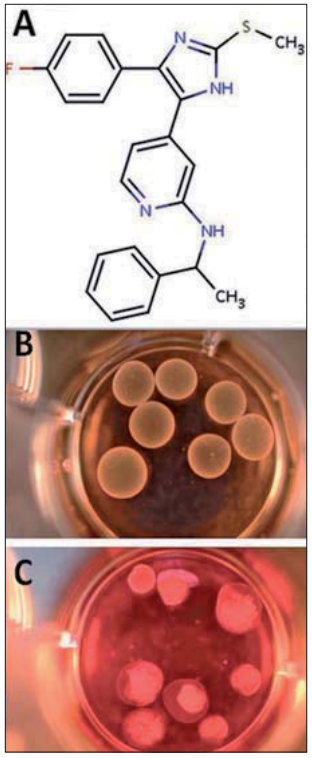


Fig.2: Effect of pyridinyl imidazoles on the E. multilocularis metacestode. Shown are the chemical structure of the pyridinyl imidazole compound ML3403 (A) as well as cultivated metacestode vesicles before (B) and after (C) treatment with 5 mM ML3403 for 4 days.

- *Targeting cestode signalling cascades to develop novel chemotherapeutics*

Current AE treatment options are very limited (surgery in 20% of cases, life-long chemotherapy). Due to their decisive role in parasite growth and development, we have suggested that the *E. multilocularis* receptor tyrosine kinases and the signalling factors of the MAPK cascade are promising targets for anti-parasitic chemotherapy. We are currently concentrating on EmMPK2, a p38 MAPK ortholog of *Echinococcus* with very interesting biochemical traits, several components of the Erk-like MAP kinase cascade (EmRaf, EmMKK2), parasite receptor tyrosine kinases (insulin- and FGF-receptor), and Abl-like kinases that are all expressed in parasite larval stages. These studies have led to the identification of pyridinyl imidazoles (p38 MAPK inhibitors) as novel anti-*Echinococcus* compounds (Fig. 2) and demonstrated that the anti-cancer-drug imatinib also exhibits profound anti-parasitic activities. Using in silico modelling and enzyme activity assays, compound libraries are currently being screened to identify small molecule inhibitors with high affinity for parasite kinases. Promising compounds will then be tested for anti-parasitic activity in the established in vitro and in vivo models.

- *Parasite genomics, transcriptomics and proteomics*

In cooperation with the the Wellcome Trust Sanger Institute we have performed a whole genome sequencing project for *E. multilocularis* which is currently in its final annotation phase. Using a combination of classical capillary sequencing and NGS, the parasite genome (113 Mb haploid) has been sequenced to ~150 fold coverage. In parallel, NGS transcriptome sequencing has been carried out for several larval stages and been used for in silico gene discovery, leading to the prediction of ~12.000 genes. Using material from the *E. multilocularis* cultivation systems, the entire parasite life cycle is currently being subjected to transcriptome deep sequencing. Furthermore, in cooperation with H. Ferreira (Porto Alegre) and use of gene prediction algorithms, the proteome of *E. multilocularis* (including the secretome) is currently being characterized.

- *The influence of Echinococcus excretory/secretory products on host immune cell function*

Studies on potentially immunomodulatory Echinococcus factors are particularly interesting since the parasite behaves like a 'perfectly transplanted organ', being able to persist for years and decades within the human host without being expelled by the immune system. Using the stem cell, metacestode and protoscolex cultivation systems, we recently engaged in investigations on the effects of 'early' and 'late' parasite E/S products on host immune cells (such as DC or T cells). These studies so far showed that E/S products of early infective stages are able to induce apoptosis and tolerogenic phenotypes in host DC. Furthermore, particularly E/S products of the metacestode were able to induce tolerogenic, regulatory T cells in vitro. Hence, the ability of *E. multilocularis* to establish an infection within the host liver, and to maintain asexual replication for years, might strongly depend on the ability of the parasite's early larval stages to induce tolerogenic properties in DC and T cells. Current efforts in this project aim at the molecular identification of specific E/S compounds with tolerogenic properties.

SELECTED PUBLICATIONS

- *Epping K, Brehm K (2011) Echinococcus multilocularis: molecular characterization of EmSmadE, a novel BR-Smad involved in TGF-β and BMP signalling.* ***Exp Parasitol*** *129:85-94*
- *Förster S, Günthel D, Kiss F, Brehm K (2011) Molecular characterisation of a serum-responsive, DAF-12-like nuclear hormone receptor of the fox-tapeworm Echinococcus multilocularis.* ***J Cell Biochem*** *112:1630-42*
- *Gelmedin V, Spiliotis M, Brehm K (2010) Molecular characterisation of MEK1/2- and MKK3/6-like mitogen-activated protein kinase kinases (MAPKK) from the fox tapeworm Echinococcus multilocularis.* ***Int J Parasitol*** *40:555-67*
- *Spiliotis M, Mizukami C, Oku Y, Kiss F, Brehm K, Gottstein B (2010) Echinococcus multilocularis primary cells: improved isolation, small-scale cultivation and RNA interference.* ***Mol Biochem Parasitol*** *174:83-7*
- *Bernthaler P, Epping K, Schmitz G, Deplazes P, Brehm K (2009) Molecular characterization of EmABP, an apolipoprotein A-I binding protein secreted by the Echinococcus multilocularis metacestode.* ***Infect Immun*** *77:5564-71*

EXTRAMURAL FUNDING

- *DFG grant: Evolutionary and functional relationships of cytokines expressed by the helminth E. multilocularis and its mammalian host*
- *DFG-GSLS: Molecular Characterization of Nuclear Hormone and Fibroblast Growth Factor Signalling in E. multilocularis*
- *DFG-GSLS: Characterization of totipotent stem cells and regeneration mechanisms in cestode parasites*
- *DFG RTG1141: Signal transduction: where cancer and infection converge. Project: Targeting flatworm signalling cascades for the development of novel anti-helminthic drugs*
- *DFG IRTG1522: HIV/AIDS and associated infectious diseases in Southern Africa. Project: Characterization of the influence of excretory/secretory products from E. multilocularis larvae on dendritic cell maturation and the interaction of Echinococcus E/S products with TLR and CTL surface receptors*

CONTACT DETAILS

Prof. Dr. med. Alexandra Schubert-Unkmeir

Institut für Hygiene und Mikrobiologie
Josef-Schneider-Str. 2/E1
97080 Würzburg

Phone: +49-931-3146721
E-Mail: aunkmeir@hygiene.uni-wuerzburg.de
www.hygiene.uni-wuerzburg.de/forschung/ag_schubert_unkmeir/

RESEARCH GOALS

- *Interaction of Neisseria meningitidis with cells of the human blood-brain/blood-cerebrospinal fluid (BB/B-CSF) barrier*
- *Modulation of tight junctions and signaling cascades during host-pathogen interactions*
- *Characterisation of transcriptional regulators*

3.2.3 Neisseria - host cell interactions

Summary

The group focuses on the molecular analysis of the interaction of *N. meningitidis* with human brain microvascular endothelial cells (HBMEC) in order to understand the processes involved in the crossing of the blood-cerebrospinal fluid (B-CSF) barrier. The B-CSF barrier is one of the tightest barriers in the human body. Among invasive pathogens, few are capable of invading the subarachnoideal space, thus suggesting that they have developed specific attributes to circumvent the B-CSF barrier. Using genetically defined *N. meningitidis* mutants, we have shown that *N. meningitidis* invasion of HBMEC depends on the expression of the Opc proteins and binding via human fibronectin to β1 integrins on the cell surface. When an integrin binds to extracellular ligands it clusters with other bound integrins, resulting in the formation of highly organized intracellular complexes known as focal adhesions. The focal adhesions incorporate a variety of molecules, including the cytoplasmic domains of the clustered integrins, cytoskeletal proteins, and an extensive array of signaling molecules. The high local concentrations of these molecules facilitate the activation of downstream intracellular responses via protein–protein interactions. We aim to use a combination of diverse approaches to attain a better molecular understanding of cellular signalling events occurring after the initial adhesion/invasion of *N. meningitidis* to brain endothelial cells.

Major Research

- *Modulation of tight junctions*

Neisseria meningitidis is a Gram-negative microorganism, colonizing the nasopharynx, from which it can seed the bloodstream before crossing the B-CSF barrier to cause meningitis. The exact mechanism by which *N. meningitidis* crosses this barrier is still poorly understood. Our initial work on the distribution of tight junctions of endothelial cells lining the B-CSF barrier established that matrix metalloproteinase (MMP)-8 plays a crucial role in the disassembly of the tight junction (TJ) component occludin and loss of cell adhesion, demonstrating that *N. meningitidis* affects the integrity of TJs of brain endothelial cells. We have demonstrated that the pathogen induces the release of active MMP-8, which in turn proteolytically degrades the TJ component occludin. Interestingly, at the same time Coureuil and colleagues showed that type IV pili of *N. meningitidis* induce the formation of ectopic early junction-like domains at the site of bacterial attachment causing the weakening of endothelial cell-cell TJs. The temporal sequence of events suggests that the weakening of cell-cell junctions by rerouting the intercellular junction molecules precedes MMP-8-mediated occludin disruption. This initial weakening of TJs may favour further protein degradation processes as described for occludin.

- *Cellular signalling cascades involved in bacterial uptake*

As a prerequisite of TJ disassembly, *N. meningitidis* must colonize and invade brain endothelial cells. The primary meningococcal invasins that facilitate bacterial uptake by endothelial cells are the Opa and Opc proteins. In particular the outer membrane protein Opc confers a tight association of the bacteria with the extracellular matrix (ECM) protein fibronectin and β1-integrins on the host cell surface of HBMEC. This interaction promotes the uptake of *N. meningitidis* by the endothelial cell and requires the active rearrangement of the actin cytoskeleton. However, at the beginning of the project the intracellular signals leading to β1 integrin-mediated uptake of *N. meningitidis* in brain endothelial cells were unclear.
A multiprotein complex is responsible for connecting integrins to the actin cytoskeleton and transferring signals into the cell. This multiprotein complex is enriched at integrin-rich focal contact sites and includes structural components as well as signalling enzymes such as the focal adhesion kinase (FAK), Src family kinases, phosphatidylinositol phosphate kinase type1γ and the integrin-linked kinase (ILK), which together orchestrate the dynamic linkage between the clustered integrins and the actin cytoskeleton. We were able to define Src family PTKs, in particular the c-Src, as an important signal protein in the invasion process. Moreover, we determined a role for the focal adhesion kinase (FAK), which functions in concert with Src in response to ligand-induced integrin clustering. Besides transferring integrin signals into the cell, c-Src also plays a significant role in signal transduction downstream of growth factor receptors and G protein-coupled receptors. The epidermal growth factor (EGF) and its receptor EGFR has also been well documented to couple with Src kinase for example to regulate cancer progression and are currently investigated.

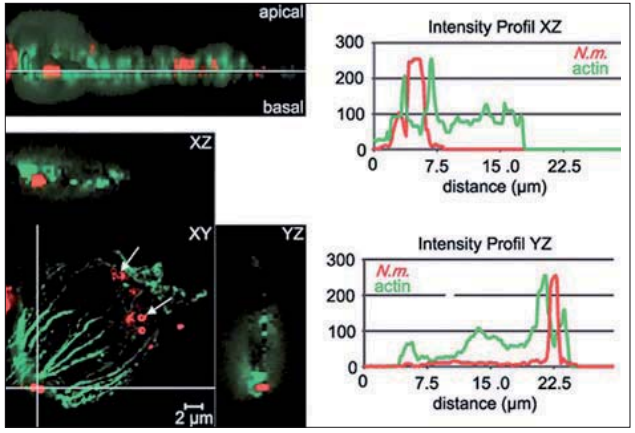


Fig. 1: Meningococci inducing the formation of actin stress fibers

- *Characterisation of transcriptional regulators*

N. meningitidis is a facultative pathogenic human commensal and strictly adapted to its niche within the human host, the nasopharynx. Little is known about the regulatory processes required for its adaptation to this environment. Therefore we started to analyse the role of the transcriptional regulator NMB1843, one of the two predicted regulators of the MarR family in the meningococcal genome. NMB1843 was designated FarR (NmFarR) due to its high sequence homology to FarR, the fatty acid resistance regulator in *N. gonorrhoeae*. Homology modeling of this protein revealed a dimeric structure with a characteristic winged helix-turn-helix DNA binding motif of the MarR family. NmFarR is highly conserved among meningococcal strains and its expression during exponential growth is controlled post-transcriptionally. We have used electrophoretic mobility shift assays (EMSAs) to show the direct and specific binding of FarR to the farAB promoter region. FarR was shown to directly and specifically repress expression of the Neisseria adhesin A (NadA), a promising vaccine candidate. The exact FarR binding site within the nadA promoter region was identified as a 16 bp palindromic repeat and we demonstrated its influence on nadA transcription. This was verified by microarray analyses, which also did not disclose further similarly regulated genes, rendering the FarR regulon currently the smallest reported regulon in meningococci.

SELECTED PUBLICATIONS

- *Kobsar A, Siauw C, Gambarayan S, Speer C, Schubert-Unkmeir A*, Eigenthaler M* (2011) Neisseria meningitidis induces platelet inhibition and increases vascular endothelial permeability via nitric oxide regulated pathways.* ***Thromb Haemost*** *106(6):1127-38*
- *Schubert-Unkmeir A, Konrad,C, Slanina H, Czapek F, Hebling S, Frosch M (2010) N. meningitidis induces endothelial cell detachment from the matrix and cleavage of occludin: a role for MMP-8 activity.* ***PLoS Pathogens*** *6(4):e1000874*
- *Slanina H, König A, Hebling S, Hauck CR, Frosch M, Schubert-Unkmeir A (2010) Entry of N. meningitidis into mammalian cells requires Src family Protein-tyrosine kinases.* ***Infect Immun*** *78(5):1905-14*
- *Schielke S, Huebner C, Spatz C, Nägele V, Ackermann N, Frosch M, Kurzai O, Schubert-Unkmeir A (2009) Expression of the meningococcal adhesion NadA is controlled by a transcriptional regulator of the MarR-familiy* ***Mol Microbiol*** *72:1054-1067*

EXTRAMURAL FUNDING

- *DFG- SCHU-2394/1-1 and DFG- SCHU-2394/1-2: Integrin-mediated signal transduction in endothelial cells during infection with N. meningitidis*

AWARDS AND PRIZES

- *2009 - Becton-Dickinson Scientific Award of the German Society for Hygiene and Microbiology*

3 Institutions of the Research Center for Infectious Diseases
3.2 Institute of Hygiene and Microbiology

CONTACT DETAILS

Prof. Dr. med. Ulrich Vogel

Institut für Hygiene und Mikrobiologie
Josef-Schneider-Str. 2/E1
97080 Würzburg

Phone: +49-931-3146802
E-Mail: uvogel@hygiene.uni-wuerzburg.de
www.hygiene.uni-wuerzburg.de/forschung/ag_vogel_claus/

RESEARCH GOALS

- *Mechanisms of meningococcal biofilm formation*
- *Interaction of meningococci with human neutrophils*
- *Mechanisms of serum resistance*
- *Population biology of meningococci*
- *Infection epidemiology of meningococci and Haemophilus influenzae*

AWARDS AND PRIZES

- *2010 - BioMerieux Diagnostic award of the German Society of Hygiene and Microbiology (Dr. Johannes Elias)*
- *2011 - Elected president of European Meningococcal Disease Society (EMGM)*

3.2.4 Hospital Hygiene and Medical Microbiology

Summary

Neisseria meningitidis colonizes the nasopharynx of the human host. The group explores the mechanisms of meningococcal biofilm development. The results of the studies not only enhance knowledge of the molecular mechanisms of biofilm formation, but also contribute to the understanding of differing epidemiological patterns of meningococcal lineages. This supports a model distinguishing spreaders and settlers. During meningococcal dissemination in the human host, neutrophils and serum complement provide a first line of defence. The group studies the interaction of meningococci with neutrophil extracellular traps and investigates the role of outer membrane vesicles. The modulation of outer surface antigens during interaction with serum is analysed. The group is dedicated to the work of the reference laboratories for meningococci and *Haemophilus influenzae*. As such, there is great interest to continuously improve laboratory surveillance of the diseases in collaboration with public health authorities. This results in the development of new typing tools as well as in scientific studies on the population biology of the two organisms.

Major Research

- *Meningococcal biofilms*

Biofilms are readily formed in vitro on glass or plastic surfaces by most clonal lineages of meningococci. They resemble micro-colonies described both in vivo and in cell culture models. We have characterized biofilm morphologies, antibiotic susceptibility, and mechanisms of biofilm formation by applying a flow system in collaboration with the group of Søren Molin at the DTU in Lyngby. Furthermore, we have demonstrated that extracellular DNA has a dual role in meningococcal biofilm formation and is used only by the lineages following the so-called "settler"-strategy, which is tightly associated with the host and presumably low transmission rates. Proteomic analysis of meningococcal biofilms revealed changes due to oxygen and nutrient limitation with proteins involved in ROS defense being up-regulated. Current analyses focus on differential modes of detachment of mature biofilms. In collaboration with the groups of Dörte Becher and Sven Hammerschmidt in Greifswald proteome analysis is extended to the comparison of outer membranes and outer membrane vesicles of meningococci of the "spreader" and "settler" types.

- *Interaction of meningococci with neutrophils and serum complement (M. Lappann, F. Günther, K. Hubert, U. Vogel)*

The interaction of meningococci with neutrophils is studied in the frame of a DFG funded project. Emphasis is laid on neutrophil extracellular traps (NETs), to which meningococci bind with high affinity, but against which the bacteria have developed a variety of escape strategies. Meningococci spontaneously release outer membrane vesicles, which might serve as vehicles for the transfer of effector molecules. The results obtained so far indicate effective silencing of neutrophil action by meningococcal blebs, a first candidate protein responsible for the effects has been identified and investigated.
A collaborative Eranet Pathogenomic project was dedicated to meningococcal serum resistance mechanisms beyond capsule and the factor H binding protein. A medium throughput screen highlighted the importance of phase variation of an adhesin, of LPS immunotypes, and of pilin. During the course of the project the transcriptome of a zinc uptake regulator zur was described and the zur box established.

- *Meningococcal molecular epidemiology and population biology*

The Institute for Hygiene and Microbiology hosts the National Reference Laboratory for meningococci (heads: M. Frosch, U. Vogel). The reference laboratory stimulates investigation into molecular epidemiology and typing strategies. The analysis of a community outbreak of meningococcal disease in North Rhine Westphalia dissected the causative clone by a combination of MLST, MLVA and antigen sequence typing in collaboration with A. van der Ende, Amsterdam. Using strains from this outbreak, the feasibility of next generation sequencing for meningococcal typing was tested in collaboration with D. Harmsen, Münster. Analysis of vaccine antigen sequences and antigen expression in meningococcal carriage isolates provided information about the possible effect on the commensal meningococcal population imposed by a new protein based meningococcus B vaccine. Using the large strain collection, the difference between meningococci expressing serogroups W135 and Y polysaccharide could be narrowed down to one amino acid in a glycosyltransferase and a diagnostic test was proposed. Furthermore, the reference laboratory played a key role in the systematic evaluation of vaccine antigen expression in European meningococcal disease isolates with regards to a novel investigational broad meningococcal vaccine, which is currently under regulatory review.

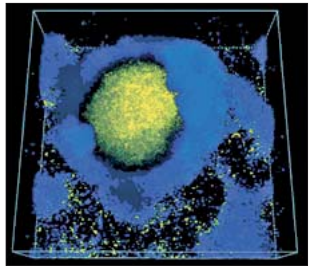


Fig. 1: Meningococcal mixed biofilm consisting of two different strains. The experiment resembles the interaction of genetically diverse meningococci in their sole niche, the nasopharynx. The interaction leads to genetic exchange supporting variation.

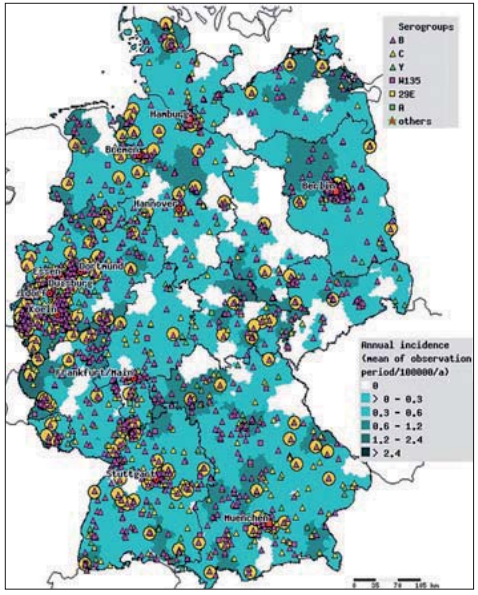


Fig. 2: Map from the geographic information system EpiScanGIS of the Reference Laboratory for Meningococci showing the distributions of cases of various meningococcal serogroups between 2007 and 2011. The most frequent subvariant B:P1.7-2,5:F1-5 of serogroup B meningococci is highlighted by yellow circles. (www.episcangis.org). The average annual disease incidence is provided according to the depicted colour code on the county level.

- *Infection epidemiology of Haemophilus influenzae*

The Institute for Hygiene and Microbiology hosts the Consulting Lab for *Haemophilus influenzae* since 2008 (heads: M. Frosch, U. Vogel). Enhanced surveillance has been established with the Federal State of Baden-Württemberg (collaboration with G. Pfaff) revealing a trend for increasing numbers of invasive disease with unencapsulated H. Influenzae in the elderly. The laboratory surveillance provided robust estimates of antimicrobial resistance of invasive isolates in Germany. To improve typing of H. Influenzae, capsule synthesis loci have been sequenced.

SELECTED PUBLICATIONS

- van Alen T, Claus H, Zahedi RP, Groh J, Blazyca H, Lappann M, Sickmann A, Vogel U (2010) Comparative proteomic analysis of biofilm and planktonic cells of Neisseria meningitidis. **Proteomics** 10:4512-21
- Elias J, Schouls LM, van de Pol I, Keijzers WC, Martin DR, Glennie A, Oster P, Frosch M, Vogel U, van der Ende A (2010) Vaccine preventability of meningococcal clone, Greater Aachen Region, Germany. **Emerg Infect Dis** 16:465-72
- Lappann M, Claus H, van Alen T, Harmsen M, Elias J, Molin S, Vogel U (2010) A dual role of extracellular DNA during biofilm formation of Neisseria meningitidis. **Mol Microbiol** 75:1355-71
- Claus H, Stummeyer K, Batzilla J, Mühlenhoff M, Vogel U (2009) Amino acid 310 determines the donor substrate specificity of serogroup W-135 and Y capsule polymerases of Neisseria meningitidis. **Mol Microbiol** 71:960-71
- Mordhorst IL, Claus H, Ewers C, Lappann M, Schoen C, Elias J, Batzilla J, Dobrindt U, Wieler LH, Bergfeld AK, Mühlenhoff M, Vogel U (2009) O-acetyltransferase gene neuO is segregated according to phylogenetic background and contributes to environmental desiccation resistance in Escherichia coli K1. **Environ Microbiol** 11:3154-65

EXTRAMURAL FUNDING

- *DFG grant: Mechanisms of host adaptation and immune evasion of Neisseria meningitidis: the role of biofilms and blebs*
- *DFG SFB 520: Immunomodulation. Project: Antigen expression in meningococcal biofilms*
- *ERA NET PathoGenoMics. Project: Genome wide screening of the human pathogen Neisseria meningitidis for proteins enhancing serum resistance and evaluation of their vaccine potential*
- *BMBF grant: Medical Infection Genomics, Cluster: Proteomics of meningococci and pneumococci. Project Würzburg*
- *BMG grant: National Reference Laboratory for Meningococci within the framework of the invasive bacterial infection network*
- *BMG grant: Consiliary Laboratory for Haemophilus influenzae within the framework of the invasive bacterial infection network*
- *Collaborative Research Agreements with GlaxoSmithKline and Novartis Vaccines*

3 Institutions of the Research Center for Infectious Diseases
3.3 Institute for Virology and Immunobiology – Chair of Immunobiology

CONTACT DETAILS

Prof. Dr. rer. nat. Thomas Hünig

Institut für Virologie und Immunbiologie
Versbacher Straße 7
97078 Würzburg

Phone: +49-931-201-49951
E-Mail: huenig@vim.uni-wuerzburg.de
www.virologie.uni-wuerzburg.de/en/lab_groups/research_group_prof_dr_rer_nat_thomas_huenig/

RESEARCH GOALS

- *Role of the costimulatory receptor CD28 in T-cell biology*
- *Manipulation of immune responses with CD28-specific monoclonal antibodies*
- *Understanding and manipulating the CD8 T-cell-mediated component of Multiple Sclerosis in a mouse model*

3.3.1 T-Cell Biology

Summary

The complete activation of T-lymphocytes upon interaction with professional antigen presenting cells requires the ligation of both the T-cell receptor and the costimulatory receptor CD28. To understand and to manipulate the role of CD28 in various aspects of immune regulation, we have generated different types of monoclonal antibodies (mAb) to rat, mouse and human CD28: "Conventional" CD28-specific mAb costimulate T-cell responses in vitro and block CD28/ligand interaction in vivo, while "Superagonistic" mAb are able to stimulate T-cell responses without apparent engagement of the TCR. These responses depend, however, on weak or "tonic" signals emanating from the T-cell antigen receptor (TCR). Whereas in rodent models, these mAb are potent inducers of regulatory T-cell responses, the application of a human CD28 "superagonist" TGN1412 caused a severe cytokine release syndrome during a first-in-human trial in 2006. Subsequently, we have developed a new assay for human T-cell responses based on peripheral blood mononuclear cells (PBMC), and have revealed that the dosing during this trial was at least 100-fold too high. We are also interested in the contribution of CD8 T-cells to the destruction of oligodendrocytes, which is a hallmark of the autoimmune disease Multiple Sclerosis (MS). To address this we generated a mouse that expresses ovalbumin (OVA) in the cytosol of oligodendrocytes. In this model, OVA-specific CD8, but not CD4 T-cells, detect the antigen if allowed access to the brain. We found, however, that even very high numbers of these activated, OVA-specific CD8 killer T-cells are perceived as autoimmune and are deleted thereby preventing damage. In contrast, if the brain is infected by a microbe that shares an antigen with the oligodendrocytes, these are recognised by the OVA-specific CD8 killer T-cells and destroyed leading to a similar demyelation phenotype to that observed in MS.

Major Research

- *Role of the costimulatory receptor CD28 in regulating immune responses*

CD28 is a cell surface receptor expressed on T-lymphocytes that is engaged by ligands expressed on professional antigen presenting cells during the initiation of immune responses. We have been interested in the function of CD28 for the past 15 years, and have developed a variety of tools for our studies: Blocking and stimulatory monoclonal antibodies, and a mouse strain in which CD28 can be deleted in an inducible and tissue-specific fashion.
Using this novel strain of inducibly CD28 gene deleting mice, which was developed by Dr. Fred Lühder (a former member of the group), we have now provided definitive evidence for the importance of CD28 in the maintenance of regulatory T-cell homeostasis and function. Furthermore, we could now address the controversial issue of whether secondary T-cell responses are dependant on CD28-mediated costimulation, and confirmed this in two different infection models.

- *Manipulation of immune responses with CD28-specific monoclonal antibodies*

Over the years, we have generated monoclonal antibodies (mAb) to rat, mouse and human CD28 and identified a conserved relationship between epitope binding and T-cell function. "Conventional" CD28-specific mAb costimulate T-cell responses in vitro and block the CD28/ligand interaction in vivo; they bind monvalently to the "top" of the homodimer near the natural ligand-binding site. "Superagonistic" mAb are able to stimulate T-cell responses without apparent engagement of the TCR, and bind laterally, allowing lattice formation. These responses depend, however, on weak or "tonic" signals emanating from the T-cell antigen receptor (TCR).
In the mouse system, we have confirmed earlier results obtained in rats showing that in vivo application of "superagonistic" CD28-specific mAb results in a disproportionate expansion and functional activation of regulatory T-cells, which in turn depends on the cytokine IL-2 produced by conventional T-cells. These findings in rodents are in contrast to the life-threatening cytokine release syndrome experienced by the healthy volunteers during a phase I clinical trial with the human CD28 superagonist TGN1412 in 2006. However, we have also found that removal of regulatory T-cells from the murine immune system before CD28SA treatment results in considerable systemic release of proinflammatory cytokines, indicating that it is the rapid activation of the regulatory T-cells which protects mice from cytokine release. We and others have further shown that in humans, toxic cytokine release is mediated by CD4 effector memory cells, a population which is frequent in adult humans but rare in clean laboratory rodents. Accordingly, regulatory T-cell activation was able to protect rats and mice, but not humans.

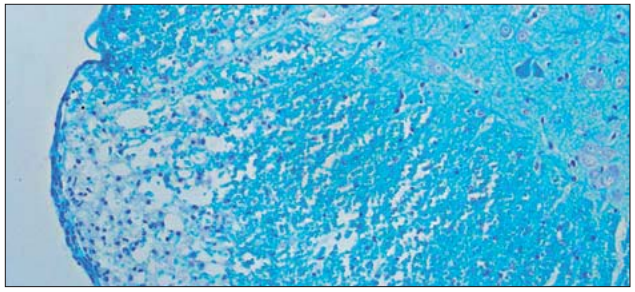


Fig. 1: Demyelination in spinal chord of mice expressing OVA in oligodendrocytes and challenged with OVA-specific CD8 T-cells plus OVA-Listeria i.c.

To further address the activity of the human CD28 superagonist TGN1412, we have developed a new in vitro system in which human peripheral blood-derived T-cells behave like those residing in tissues, allowing more sensitive read-outs of T-cell responses to activating agents. This system has enabled us for the first time to model the toxic potential of the CD28 superagonist TGN1412. Specifically, we have used the system to define a "minimum anticipated biological effect level" (MABEL) dose, at which initial functional T-cell responses are seen at less than 5% CD28 receptor occupancy.
In cooperation with the group of Niklas Beyersdorf and Thomas Kerkau, we have applied both blocking and activating CD28 mAb to study their potential to interfere with the development of graft-versus-host disease (GvHD), a complication of allogeneic bone marrow transplantation, and found therapeutic efficacy with both approaches, which was, however, mediated by distinct mechanisms.

- *CD8 T-cell-mediated autoimmunity in a new mouse model for Multiple Sclerosis*

We have generated transgenic mice expressing the model antigen Ovalbumin (OVA) as a sequestered cytosolic protein in oligodendrocytes. If a MHC class II restricted T-cell antigen receptor is crossed into this strain, the resulting CD4 T-cell population expressing this receptor remains ignorant of the sequestered antigen. However, introduction of an MHC class I restricted TCR results in lethal EAE at a young age, illustrating the capacity of CD8 T-cells to destroy oligodendrocytes and cause disease. To study this in a more physiological situation, single-transgenic ODC-OVA mice were infected with OVA-expressing listeria (Lm-OVA). This did not, however, result in disease, but rather in the deletion of the CD8 T-cells that recognize the oligodendrocytes. We found that even large numbers of such OVA-specific CD8 T-cells are deleted in the mice after recirculation through the brain, indicating that the brain somehow "realises" that these cells are autoimmune and initiates their destruction. However, if the infection is moved to the brain, the recirculating CD8 T-cells, which recognize the OVA-expressing oligodendrocytes, now are able to attack and destroy them. This indicates that if infected, the brain sacrifices oligodendrocytes in order to allow pathogen eradication. The lesions observed in the central nervous system of mice undergoing CD8 T-cell mediated demyelination in response to CNS infection and CD8 T-cell attack resemble those observed in human MS, and will provide a useful model for further mechanistic studies on the role of CD8 T-cells and infectious agents in the development of this disease.
The team of PD Dr. Thomas Kerkau and PD Dr. Niklas Beyersdorf is working on the significance and therapeutic manipulation of T cells in the context of pathological immune reactions. In addition to animal models of multiple sclerosis, we are particularly interested in the development of novel strategies for the treatment of Graft-versus-host-disease (GvHD), a major complication after allogeneic bone marrow transplantation. These strategies include both in vitro and in vivo manipulations of alloreactive conventional and regulatory T cells. Apart from GvHD, *Aspergillus fumigatus* infection is another major complication of bone marrow transplantation. Therefore, we are examining novel means to enhance *Aspergillus fumigatus*-specific T cells for future therapeutic applications in humans.

- *Mechanism of B-lymphocyte Differentiation*

The group of PD Ingolf Berberich focuses its research on the terminal differentiation of B cells to antibody-producing plasma cells (PC). After antigen-dependent activation B cells proliferate and finally differentiate to PC or memory cells. The regulatory circuits of transcription factors that control the identity of B cells and the PC differ dramatically. Currently, it is not well understood how the transition from B cells to PC is initiated at the molecular level. Using *in vitro* and *in vivo* experiments the lab evaluates if the transcription factor C/EBPß triggers this process. After terminal differentiation PC start to express the "T cell-specific" surface molecule CD28. In collaboration with Prof. Dr. Thomas Hünig the group asks how CD28 influences the physiology of PC and multiple myeloma cells.

SELECTED PUBLICATIONS

- *Romer PS, Berr S, Avota E, Na SY, Battaglia M, ten Berge I, Einsele H, Hunig T (2011) Preculture of PBMCs at high cell density increases sensitivity of T-cell responses, revealing cytokine release by CD28 superagonist TGN1412.* ***Blood*** *118:6772-6782*
- *Beyersdorf N, Ding X, Hunig T, Kerkau T (2009) Superagonistic CD28 stimulation of allogeneic T cells protects from acute graft-versus-host disease.* ***Blood*** *114:4575-4582*
- *Gogishvili T, Langenhorst D, Luhder F, Elias F, Elflein K, Dennehy KM, Gold R, Hunig T (2009) Rapid regulatory T-cell response prevents cytokine storm in CD28 superagonist treated mice.* ***PloS One*** *4(2):e4643*
- *Hunig T, Luhder F, Elflein K, Gogishvili T, Frohlich M, Guler R, Cutler A and Brombacher F (2010) CD28 and IL-4: two heavyweights controlling the balance between immunity and inflammation.* ***Medical Microbiology and Immunology*** *199:239-246*

EXTRAMURAL FUNDING

- *DFG SFB 581: Release and therapy of an ovalbumin-specific experimental autoimmune encephalomyelitis*
- *DFG IRTG 1522: The role of CD28 mediated co- stimulation in the control of secondary immune responses to infectious agents*
- *BayImmuNet: Development of an immunotherapy protocol for the prevention and treatment of Aspergillus fumigatus infection*

3 Institutions of the Research Center for Infectious Diseases
3.3 Institute for Virology and Immunobiology – Chair of Immunobiology

CONTACT DETAILS

Prof. Dr. rer. nat.
Thomas Herrmann

Institut für Virologie und Immunbiologie
Versbacher Straße 7
97078 Würzburg

Phone: +49-931-201-49955
E-Mail: herrmann-t@vim.uni-wuerzburg.de
www.virologie.uni-wuerzburg.de/en/lab_groups/research_group_prof_dr_thomas_herrmann/

RESEARCH GOALS

- *Analysis of the production and presentation of phosphoantigens and their recognition by Vγ9δ2 T cells*
- *Analysis of iNKT cell antigen-recognition and function in the rat*
- *Evaluation of the therapeutic potential of human Vγ9δ2 T cells*

3.3.2 Unconventional T-cells

Summary

Non-conventional or innate T cells differ from MHC restricted T cells in terms of antigen-recognition and function. Their T-cell antigen receptors (TCR) bind a wide range of often-unknown ligands and may also function as pattern recognition receptors. During infection they participate in the first line of defense and are also able to modulate the immune response. We have investigated the role of two types of innate T cells, human Vγ9δ2 T cells and iNKT cells. Human Vγ9δ2 T cells express the Vγ9δ2 T-cell antigen receptors (TCR), which recognizes pyrophosphate-containing isoprenoid-metabolites (phosphoantigens). The most potent phosphoantigen is E)-4-Hydroxy-3-methyl-but-2-enyl pyrophosphate (HMBPP), which massively activates Vγ9δ2 T cells in many bacterial infections as well as in parasitic infections with apicomplexa (Malaria, Toxoplasmosis). To better understand and manipulate their TCR-mediated activation, we are searching for a presumed phosphoantigen-presenting molecule and we are analyzing the production and presentation of microbial and host cell phosphoantigens. iNKT cells, which express a unique TCR that binds complexes of glycolipids and CD1d, respond most potently to bacterial sphongoglycolipids antigens. We are investigating iNKT cell physiology and the CD1d-ligand-iNKT TCR interaction in the rat, which serves as model for many human diseases. Furthermore, we have a long-standing interest in bacterial superantigens and work on the evolution of immuno-receptors.

Major Research

- *Vγ9δ2 T cells: Activation by phosphoantigens*

γδ T cells are the population of lymphocytes whose antigen-recognition and function is least understood. In comparison with MHC restricted αβ T cells, which in terms of antigen recognition and functional features are rather conserved between different vertebrate classes, γδ T cells are very divergent. A striking example is the Vγ9δ2 T cell population, which so far has been found only in higher primates. In healthy individuals about 1-5% of T cells express the eponymous Vγ9δ2 T cell antigen receptor (Vγ9δ2 TCR) but during a variety of bacterial infections or malaria and toxoplasmosis they can be expand to more than 50% of blood T cells. Their TCRs recognize phosphoantigens such as isopentenyl pyrophosphate (IPP) or HMBPP. The latter is the immediate precursor of IPP in the DOXP pathway of isoprenoid synthesis, which is used by most bacteria and by apicomplexan parasites. Its phosphoantigen-activity is more than 10000 fold higher than that of IPP and it is likely responsible for Vγ9δ2 T cell expansion in many infections. Our research aims for a better understanding of production, presentation and recognition of these metabolites. As part of our collaboration with Volker Kunzmann (Würzburg) on the therapeutic use of Vγ9δ2 T cells, we have shown that a variety of host and tumor cells can be rendered into Vγ9δ2 T cell activators by inhibiting the IPP consuming enzyme farnesyl pyrophosphate synthase (FPPS) either by aminobisphosphonates or by shRNA mediated knock down of FPPS expression.

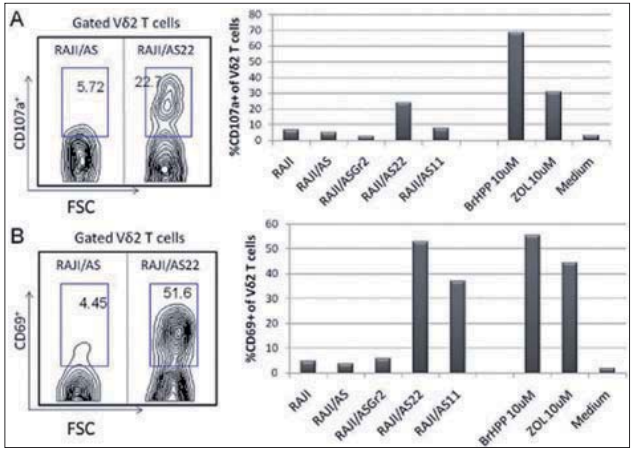


Fig. 1: FPPS knockdown in RAJI cells increases CD107a and CD69 expression and IFN-γ production by primary Vγ9Vδ2 T cells. A and B) The contour plots depict the gating strategy used to generate the data shown in the bar histograms. Representative FACS analysis of CD107 (A) or CD69 (B) induction after cocultures of PBL with RAJI cells alone, RAJI cells transduced with retroviral control vectors (AS or ASGr2) or RAJI cells retrovirally transduced with FPPS knockdown vectors (AS11 or AS22), RAJI cells and BrHPP (Phosphoantigen), RAJI cells and Zoledronate (FPPS inhibitor) or medium alone.

- *Vγ9δ2 T cells: Phenotype, function and analysis of T-cell antigen receptors.*

iNKT cells are immunomodulators and part of the first line of defense against infections where they exert multiple effector functions. Furthermore, there is increasing evidence that their crosstalk with the host microbiota affects host metabolism and inflammation. Their hallmark is the expression of a TCR comprising an invariant TCRα chain with a characteristic *AV14AJ18* rearrangement which recognizes self or microbial glycolipids (often sphingoglycolipids) presented by the non-polymorphic MHC class I like CD1d molecule. In order to characterize these cells in the important model organism rat, CD1d specific monoclonal antibodies with dual specificity for rat and mouse CD1d, TCR-transductants and rat-CD1d oligomers have been developed. A comparison of CD1d function and expression in rats and mice has revealed a nearly identical CD1d expression in hematopoietic tissues but striking differences in non-hematopoietic tissues. Most notable is the expression of CD1d in Paneth cells, which are known to play a pivotal role in the control of gut microbiota composition. Furthermore, high expression was detected in acinar cells of the rat pancreas, which suggests a function of CD1d beyond that of lipid presentation. The analysis of iNKT cells from F344 rats showed a high degree of similarity to human iNKT cells with respect to frequency, co-receptor expression, *ex vivo* expansion and cytokine production. LEW rats, which serve as model organism for autoimmune disease, were essentially iNKT cell deficient. Our current interest is the functional analysis of rat iNKT cells *in vitro* and *in vivo*, elucidation of the genetic basis of iNKT cell deficiency in the LEW rat and the analysis of the molecular basis of rat iNKT-TCR ligand interaction. In the case of the latter, we aim to investigate a possible link between *AV14* gene variation, ligand-binding of the TCR and development of iNKT cells.

- *Superantigens and MHC*

Superantigens are bacterial or viral products, which are presented by MHC class II molecules and activate a large proportion of T cells. An analysis of superantigen-presentation by the classical rat MHC class II molecules $RT1B^l$ and $RT1D^l$ was completed and identified functional splice variants of the presumed MHC class II pseudogenes *Db2* (rat) and *Eb2* (mouse). These were found to be extremely potent in the presentation of the superantigen of *Yersinia pseudotuberculosis* (YPM).

SELECTED PUBLICATIONS

- *Monzon-Casanova E, Steiniger B, Schweigle S, Clemen H, Zdzieblo D, Starick L, Müller I, Wang CR, Rhost S, Cardell S, Pyz E, Herrmann T (2010) CD1d expression in paneth cells and rat exocrine pancreas revealed by novel monoclonal antibodies which differentially affect NKT cell activation.* ***PLoS One*** *30;5(9):e13089*
- *Dlaske H, Karaüzüm H, Monzon-Casanova E, Rudolf R, Starick L, Müller I, Wildner G, Diedrichs-Möhring M, Koch N, Miyoshi-Akiyama T, Uchiyama T, Wonigeit K, Fleischer B, Overbeck S, Rink L, Herrmann T (2009) Superantigen-presentation by rat major histocompatibility complex class II molecules RT1.Bl and RT1.Dl.* ***Immunology*** *128:e572-81*
- *Li J, Herold MJ, Kimmel B, Müller I, Rincon-Orozco B, Kunzmann V, Herrmann T (2009) Reduced expression of the mevalonate pathway enzyme farnesyl pyrophosphate synthase unveils recognition of tumor cells by Vgamma9Vdelta2 T cells (2009)* ***J Immunology*** *182(12):8118-24*
- *Kunzmann V, Kimmel B, Herrmann T, Einsele H, Wilhelm M (2009) Inhibition of phosphoantigen-mediated gammadelta T-cell proliferation by CD4+ CD25+ FoxP3+ regulatory T cells.* ***Immunology*** *126(2):256-67*

EXTRAMURAL FUNDING

- *DFG grant: The rat as new model for the analysis of iNKT cell antigen-recognition and function*
- *IZKF Würzburg: The mevalonate pathway as therapeutic target in cancer*

3 Institutions of the Research Center for Infectious Diseases
3.3 Institute for Virology and Immunobiology – Chair of Immunobiology

CONTACT DETAILS

Prof. Dr. rer. nat. Manfred Lutz

Institut für Virologie und Immunbiologie
Versbacher Straße 7
97078 Würzburg

Phone: +49-931-201-49957
E-Mail: m.lutz@vim.uni-wuerzburg.de
www.virologie.uni-wuerzburg.de/en/lab_groups/research_group_prof_dr_manfred_lutz/

RESEARCH GOALS

- *To understand the mechanisms of T cell tolerance induction by dendritic cells against self-antigens*
- *The analysis of immune deviation by Trypanosoma brucei antigens via the semi-maturation of dendritic cells*
- *The effects of myeloid-derived suppressor cell activation on dendritic cell development*
- *Myeloid-derived suppressor cells as targets of immune escape of mycobacteria*

3.3.3 Immune Regulation

Summary

Induction of immune tolerance enables the immune system to recognise self-antigens, thereby preventing an autoimmune response. The mechanism of self-tolerance involves several different cell types including dendritic cells (DC), Myeloid-Derived Suppressor Cells (MDSC) and regulatory T-cells. DC are not only the key mediators of the immune response but they are also essential to maintain immunological tolerance. Their tolerogenic functions are mediated through „immature“ or „semi-mature“ activation stages while „mature“ or „licensed“ DC induce immunity. We are interested in the roles of these different cell types in the induction of tolerance, and microbial immune evasion strategies that target DC and lead to T-cell tolerance by mechanisms such as anergy, immune deviation and regulatory T-cells. For example, recent data indicate that certain *Trypanosoma brucei* antigens behave like endogenous inflammatory stimuli on DC maturation. Using a similar approach, we have also generated tolerogenic DC *in vitro* to modulate the immune response in mouse models of allergy and autoimmunity. MDSC play an important role in regulating the T-cell response, we have shown that their activation of suppressor function requires two combined signals, a bacterial pathogenic factor (LPS) together with interferon-γ. Other functional analyses following the MDSC marker Gr-1 suggest additional roles for these cells in apoptosis of neutrophils and myelopoiesis into macrophages via phosphorylation of STAT molecules. Our recent data indicate that *Mycobacterium tuberculosis* and BCG target MDSC by entering caveosomes to evade phagolysosomal degradation and activate their immunosuppressive activity.

Major Research

- *Immune deviation by Trypanosoma brucei antigens via the semi-maturation of dendritic cells*

The priming and polarisation of CD4+ T helper cells into type 2 cells (Th2) depends on the quality and quantity of antigen presentation, costimulation and cytokine production by dendritic cells (DC). This project aims to dissect the conditions leading to tolerogenic or immunogenic subtypes of Th2 responses. To achieve this, DC were exposed to the proinflammatory cytokine TNF or Th2-inducing variant surface glycoproteins (VSG) from Trypanosoma brucei and changes in transcription, protein expression and function were monitored in CD4+ T cells. The induction of Th2 polarisation is characterised by a cascade of specific molecular events including the activation of transcription factors STAT-6 and GATA-3, and the production of IL-4 and IL-13 cytokines. In addition, to GATA-3 activation, which is required for Th2 development, the process also involves other transcription factors such as c-Maf, C/EBPβ, JunB, IRF4, NF-κB1 p50, NIP45 and NFAT, with the latter being required for the IL-10 production by Th2 cells. However, IL-10 is also the major cytokine released by regulatory Tr1 cells, which can arise from Th2 responses after chronic antigen exposure. The investigation of such a Th2/Tr1 fine-tuning is important to understand the T cell responses against typical Th2-inducing microbes, which simultaneously raise an immune reaction by the host and also tolerogenic mechanisms that prevent microbial eradication. During the priming phase of naive CD4+ Th cells DC play a decisive role for their further differentiation. Different levels of DC maturation are directed by diverse pathogenic sources and have major impact on the subsequent Th cell polarisation. Our data reveal that DC matured by either TNF or VSG antigens reach only a semi-mature stage with 160-466 genes induced during a Th2 response, while full DC maturation results in changes in the expression of almost 5000 genes leading to Th1 immunity. This indicates that pathogens may evade immune surveillance by allowing inflammation but not strong gene induction at the level of DC.

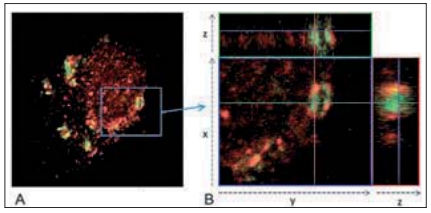


Fig. 1: Phagocytosis of mycobacteria by myeloid-derived suppressor cells (MDSC) into caveosomes. Heat-inactivated mycobacteria (BCG) were co-incubated with MDSC at 37°C, and then cytospin preparations stained for mycobacterial PPD (green) or caveolin-1 (red). The immunofluoresece image by confocal microscopy shows the presence of mycobacteria in caveolin-1+ compartments (A). Three-dimensional views further confirm this finding (B). Mycobacteria use target these cells and these specific compartments as mechanism of immune evasion. (Fotos: Dr. E. Ribechini, Marcel Münstermann, Nora Müller)

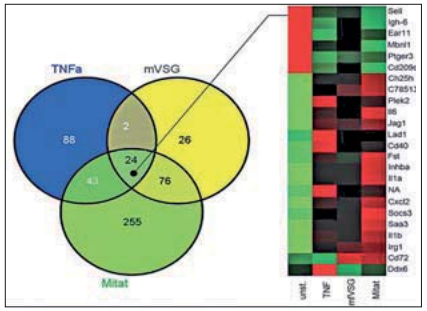


Fig. 2: An common inflammatory signature characterizes Th2-inducing dendritic cells. Dendritic cells were generated with GM-CSF from mouse bone marrow cells and treated with TNF or Trypanosoma brucei membrane VSG antigens (mVSG) or soluble MiTat antigens for 24h. Microarray analyses revealed a highly similar common DC gene regulation profile with only 24 overlapping genes characteristic for their Th2-inducing capacity.

- *Myeloid-derived suppressor cell activation by combined lipopolysaccharide plus interferon-γ treatment impairs dendritic cell development*

Myeloid-derived suppressor cells (MDSC) and dendritic cells (DC) are major controllers of immune responses. Previously, we have shown that bone marrow (BM) precursors cultured with GM-CSF develop into immature myeloid cells that can act as MDSC after 3-4 days, but lose this ability after 7-8 days when they further differentiate into DC. However, it remained unclear how T cell suppression by MDSC or T cell activation by DC are regulated. Subsequently, we have shown that in vitro treatment of BM-MDSC with combinations of LPS or inflammatory cytokines plus IFN-γ increases their NO release and activates the suppressor function of these BM-MDSC. At the same time the further development of these LPS/IFN-γ activated MDSC into DC was inhibited. In vivo, we identified two suppressive GR-1^{low} CD11b^{high} and GR-1^{high} CD11b^{low} MDSC populations within the steady state spleen, which could be expanded after LPS/IFN-γ injection and led to a reduced proliferation of CD8+ T cells primed by exogenous or endogenous DC. LPS/IFN-γ application also expanded the endogenous splenic CD4- CD8- DC subset, which however, remained inhibited in their MHC II and costimulatory molecule expression. Together our data indicate that combined pathogen/inflammatory and IFN-γ signals are required for MDSC activation *in vitro* and *in vivo* which control CD8+ T cell responses directly but also indirectly through interference with DC function.

- *Myeloid-derived suppressor cells as targets of immune escape of mycobacteria*

Myeloid-derived suppressor cells (MSDC) of the mouse are so far mostly cited as a heterogeneous population of Gr-1$^+$ CD11b$^+$ early myeloid cells induced by tumors. Only recently have two subsets of Ly-6C^{high} Ly-6G$^-$ and Ly-6C^{low} Ly-6G$^+$ MDSC been identified, however, these subsets are still heterogeneous and a clear dissection from non-suppressive cells has not been performed. The induction or functional roles of these MDSC subsets in infectious diseases have not been addressed. Our preliminary data indicate that *Mycobacterium tuberculosis* (Mtb) is not only a strong inducer of the two known subsets but also affects two new subsets. We are performing a detailed cellular, molecular and functional analysis of the four MDSC subsets and their role in vaccination by heat-killed Mtb and live infection. To achieve we are determing the kinetics of MDSC subset induction in different lymphatic organs after a subcutaneous sponge-based vaccination or lung infection and gene expression profiling via Ly-6C/G triggering and before and after Mtb activation to reveal the signalling pathways involved. Further functional assays on CD4$^+$ and CD8$^+$ T cell suppression and MDSC homing will define the *in vivo* functions of the MDSC subsets. Our intial work using confocal microscopy indicates that Mtb targets lipid raft structures in MDSC and enter caveolin-1$^+$ structures to prevent their degradation while maintaining MDSC supprerssive activity.

SELECTED PUBLICATIONS

- *Azukizawa H, Dohler A, Kanazawa N, Nayak A, Lipp M, Malissen B, Autenrieth I, Katayama I, Riemann M, Weih F, Berberich-Siebelt F, Lutz MB (2011) Steady state migratory RelB+ langerin+ dermal dendritic cells mediate peripheral induction of antigen-specific CD4+ CD25+ Foxp3+ regulatory T cells.* ***Eur J Immunol*** *41:1420-1434*
- *Pletinckx K, Stijlemans B, Pavlovic V, Laube R, Brandl C, Kneitz S, Beschin A, De Baetselier P, Lutz MB (2011) Similar inflammatory DC maturation signatures induced by TNF or Trypanosoma brucei antigens instruct default Th2-cell responses.* ***Eur J Immunol*** *41:3479-3494*
- *Ziegler-Heitbrock L, Ancuta P, Crowe S, Dalod M, Grau V, Hart DN, Leenen PJ, Liu YJ, MacPherson G, Randolph GJ, Scherberich J, Schmitz J, Shortman K, Sozzani S, Strobl H, Zembala M, Austyn JM, Lutz MB (2010) Nomenclature of monocytes and dendritic cells in blood.* ***Blood*** *116:e74-80*
- *Greifenberg V, Ribechini E, Rossner S, Lutz MB (2009) Myeloid-derived suppressor cell activation by combined LPS and IFN-gamma treatment impairs DC development.* ***Eur J Immunol*** *39:2865-2876*
- *Ribechini E, Leenen PJ, Lutz MB (2009) Gr-1 antibody induces STAT signaling, macrophage marker expression and abrogation of myeloid-derived suppressor cell activity in BM cells.* ***Eur J Immunol*** *39:3538-3551*

EXTRAMURAL FUNDING

- *DFG IRTG1522: Protective and productive inflammatory responses induced by microbial productsstudied at the level of dendritic cells*
- *DFG SFB581: Presentation of cerebral glycolipids by dendritic cells on CD1d and role of persistent CNS virus infections for the initiation of EAE*
- *DFG/TR52: Tolerogenic and Immunogenic T Helper 2 Programming by Differentially Matured Dendritic Cells*
- *DFG grant: Characterization of myeloid-derived suppressor cell subsets and their induction by Mycobacterium tuberculosis*
- *IZKF Würzburg with Prof. M. Eyrich: Immunogenicity of native versus in vitro generated dendritic cells from patients with glioblastoma - investigations on the identification and overcoming of tumor escape mechanisms*

3 Institutions of the Research Center for Infectious Diseases
3.4 Institute for Virology and Immunobiology – Chair of Virology

CONTACT DETAILS

Prof. Dr. med. Axel Rethwilm

Institut für Virologie und Immunbiologie
Versbacher Straße 7
97078 Würzburg

Phone: +49-931-201-49555
E-Mail: virologie@vim.uni-wuerzburg.de
www.virologie.uni-wuerzburg.de/en/lab_groups/research_group_prof_dr_med_axel_rethwilm/

RESEARCH GOALS

- *To understand the molecular biology of foamy viruses and other retroviruses*
- *Epidemiology of HIV/AIDS and development of drug Resistance in Africa*
- *Pathogenesis and epidemiology of respiratory viral infections*
- *Pathogenesis of neurodegenerative diseases*

3.4.1 Viral Infections

Summary

Foamy viruses (FV) are endemic in most non-human primates, cats, cattle and horses and undergo a replication pathway that distinguishes them from all other retroviruses. Thus, the family of retroviruses has been subdivided into the orthoretrovirus subfamily (harbouring all well known retroviruses from murine leukemia virus (MLV) to the lentivirus HIV) and the subfamily of spumaretrovirus (made up only of the genus foamy viruses). Following the molecular cloning of the first foamy virus genome, we have been interested in the molecular mechanism of replication and the development of resistance to antiviral compounds. We are also interested in the molecular basis of development of HIV-1 resistance to anti-retrovirals, including studies and clinical trials in Sub-Saharan Africa, as well as the identification of new antivirals and the response to the immune system to HIV-1 infection.

Major Research

- *Molecular Biology of Foamy Viruses (FV) (J. Bodem, C. Scheller, A. Rethwilm)*

Members of the subfamily of *Spumaretrovirinae* display significant differences in their mechanism of replication compared to other Retroviruses. We have a long-standing interest in the molecular basis of FV replication and in developing these benign viruses to be used as potential vectors for somatic gene therapy.

- *Epidemiology of HIV/AIDS and development of drug resistance (J. Bodem, B. Nowotny, C. Scheller, E. Koutsilieri, A. Rethwilm)*

While retroviruses such as HIV are popular targets for the development of antiviral compounds, they are known to quickly develop resistance against these substances. We are currently using both functional and structural approaches to elucidate the exact mechanisms involved in the development of resistance in HIV-1 and FV. We are also using other antiviral strategies to restrict HIV-1 replication, these involve identifying compounds that inhibit the interaction between the antiviral defence factor APOBEC3G and the viral infectivity factor Vif which is required for viral replication. To achieve this goal high-throughput systems are being developed to cost-effectively screen large compound libraries for antiviral activities

HIV infection is characterized by a general chronic immune activation that is believed to be the initial trigger for the virus-driven destruction of the immune system. In cooperation with Prof. Klinker (Department of infectious diseases) and Prof. Arendt (Neurology, Düsseldorf) we are investigating immune activation in different clinical phenotypes of HIV infection. We are also determining the effects of low-dose corticosteroids on HIV disease progression in a German HIV cohort (in cooperation with Dr. Ulmer, Stuttgart) and in HIV-patients in Tanzania.

In cooperation with Prof. Stich from the Medical Mission Hospital, Würzburg and Dr. Majinge and Dr. Kalluvya from Bugando Medical Center in Mwanza, Tanzania, we are undertaking large clinical trials targeting HIV infection in Sub-Saharan Africa. In a randomized interventional clinical study ("ProCort1") we are studying the effects of low-dose prednisolone treatment on the progression of HIV infection in antiretroviral therapy-naïve HIV patients. We are also investigating the spread of HIV drug-resistance into the therapy-naïve population and the prevalence of HIV-associated neurological disorders ("HAND1-study") in Tanzania and its association with different viral subtypes. These collaborations with East Africa benefit from the logistic and scientific background provided by the DFG-funded international research-training group (IRTG 1522) between the Universities of Stellenbosch and Capetown (South Africa) and the University of Würzburg.

- *Pathogenesis of Pneumoviruses (C. Krempl)*

Respiratory Syncytial virus (RSV) is major viral cause of serious lower respiratory tract disease in the pediatric world, in the elderly and in severely immunocompromized patients. However, an effective antiviral therapy or a licensed vaccine is still lacking due to a fragmentary understanding of pathogenicity mechanisms and lack of a permissive animal model. However, infection of mice with the closely related pneumonia virus of mice (PVM) causes symptoms that are similar to those induced by RSV-infection of humans. Thus, the group is using a reverse genetics approach to introduce defined mutations into the PVM genome to identify viral and host factors involved in RSV pathogenesis

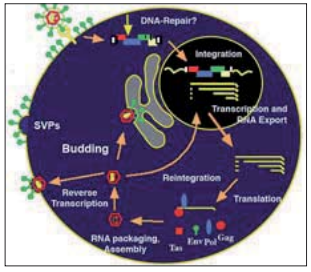


Fig. 1: The Foamy Virus Replication Cycle

- *Pathogenesis of measles and canine distemper virus (J. Schneider-Schaulies)*

Acute measles virus infection is associated with transient immunosuppression that may cause a variety of complications such as pneumonia. The virus may also persist in the host and cause the central nervous system (CNS) disease subacute sclerosing panencephalitis (SSPE), which leads to death. We have developed a model of a persistent viral CNS infection using immunologically normal mice and recombinant measles virus (MV). The manipulation of CD4+ CD25+ Foxp3+ regulatory T cells suggests that they can be utilized to regulate virus persistence in the CNS. We are also interested in the role and mechanism of deaminases in restricting negative-strand RNA viruses such as measles virus. In addition, the group is investigating the interaction of measles virus and Canine distemper virus (CDV) with host factors and characterising small molecule inhibitors of measles and CDV-induced cell fusion.

- *Neuroimmunology and Neurodegeneration of Prion Diseases (M. Klein)*

Prion diseases or transmissible spongiform encephalopathies (TSE) are infectious neurodegenerative diseases, in which PrPSc, an abnormal, detergent-insoluble, relatively protease-resistant isoform of the host prion protein (PrPC) accumulates within infected tissues. We are analysing the mechanisms involved in neuroinvasion after the PrPSc accumulates in the peripheral lymphoid tissue, the axonal transport of the infectious agent and the resulting prion-induced neurodegeneration.

- *Autoimmune etiopathogenesis of Parkinson´s disease (E. Koutsilieri, C. Scheller)*

Parkinson´s disease (PD) is characterized at the cellular level by the destruction of neuromelanin (NM)-containing dopaminergic cells and a profound reduction in striatal dopamine, which may be linked to autoimmunity. We have shown *in vitro* (in collaboration with Prof. Lutz) that human NM isolated from the substantia nigra of post-mortem brains could act as an immune stimulator for maturation and activation of dendritic cells, a prerequisite to initiate immune reactions against autoantigens. Studies in mice and patients with PD (in collaboration with Prof. Volkmann, Clinic and Policlinic of Neurology) aim to show whether NM may be a primary proinflammatory initiator in an autoimmune-based pathomechanism of PD.

- *Mutual interactions of HIV and dopamine - influence of HIV subtype diversity on HAND (E. Koutsilieri, C. Scheller)*

HIV infection causes neuropsychiatric complications manifesting in HIV-associated neurocognitive disorders (HAND). Our previous studies in the simian immunodeficiency virus (SIV)-infected rhesus monkey model have indicated a role of dopamine (DA) availability as a risk factor for developing brain pathology in immunodeficiency infection. We are studying the mutual interaction between HIV and dopamine in HIV-infected patients and its impact on the development and progression of HAND and the role the impairment of the dopamine transporter (DAT) and of different HIV subtypes play in this interaction (cooperation with Dr. du Plessis, Psychiatry, South Africa) in order to determine the influence of different HIV clades on HAND.

- *Clinical Virology (B. Weißbrich, J. Schubert)*

Our diagnostic department processes almost 40 thousand clinical samples each year. A variety of clinical virological questions are being addressed, such as the characterisation of a group of recently discovered respiratory viruses. To this end, molecular and serological diagnostic methods have been developed for the human bocavirus and the human polyomaviruses WU and KI in order to address the epidemiology and clinical relevance of these "new" viruses.

SELECTED PUBLICATIONS

- *Bodem J, Schied T, Gabriel R, Rammling M, Rethwilm A (2011) Foamy virus nuclear RNA export is distinct from that of other retroviruses.* ***J Virol*** *85:2333-234*
- *Hartl MJ, Bodem J, Jochheim F, Rethwilm A, Rösch P, Wöhrl BM (2011) Regulation of foamy virus protease activity by viral RNA - a novel and unique mechanism among retroviruses.* ***J Virol*** *85:4462-4469*
- *Kasang C, Kalluvya S, Majinge C, Stich A, Bodem J, Kongola G, Jacobs GB, Mlewa M, Mildner M, Hensel I, Horn A, Preiser W, van Zyl G, Klinker H, Koutsilieri E, Rethwilm A, Scheller C, Weissbrich B (2011) HIV drug resistance (HIVDR) in antiretroviral therapy-naive patients in Tanzania not eligible for WHO threshold HIVDR survey is dramatically high.* ***PLoS One*** *6:e23091*
- *Matthes D, Wiktorowicz T, Zahn J, Bodem J, Stanke N, Lindemann D, Rethwilm A (2011) Basic residues in the foamy virus Gag protein.* ***J Virol*** *85:3986-3995*

EXTRAMURAL FUNDING

- *DFG IRTG1522: AIDS and associated infectious diseases in Southern Africa 2008-2013 (Speaker A. Rethwilm)*
- *DFG-Bo 3006/1-2: Foamyvirus replication: Structure-function analysis of viral enzymes involved in generating genetic diversity or in conserving the viral genome*
- *DFG Kr 296, grant1-2: Pulmonary innate and adaptive immunity in a natural infection model for pneumoviruses; grant 2-1: Pathogenesis of pneumoviral infections in a natural infection model*
- *DFG-Schn320/17-1 and 18-1: Identification of host cell factors for negative-stranded RNA viruses and Adaptation of canine distemper virus to human host cells*
- *BMBF-01GU0821 (Rethwilm): Network foamy virus for gene therapy of Fanconi anemia (FoneFA), analysis of viral integration*
- *German Cancer Tumor Stem Cell Network (Nowotny/Rethwilm): Lentiviral Reporter gene vectors for preparation and isolation of tumor stem cells and characterization of stem cell-specific signaling pathways*

3 Institutions of the Research Center for Infectious Diseases
3.4 Institute for Virology and Immunobiology – Chair of Virology

CONTACT DETAILS

Prof. Dr.
Sibylle Schneider-Schaulies

Institut für Virologie und Immunbiologie
Versbacher Straße 7
97078 Würzburg

Phone: +49-931-201-49895
E-Mail: s-s-s@vim.uni-wuerzburg.de
www.virologie.uni-wuerzburg.de/en/lab_groups/research_group_prof_dr_sibylle_schneider_schaulies/

RESEARCH GOALS

- *Mechanisms of measles virus induced T cell paralysis*
- *MV entry into dendritic cells and consequences for sorting and transmission*
- *Viral immunomodulation at the level of dendritic cell (DC) interference*

3.4.2 Measles Viruses and Immunomodulation

Summary

The study of the effectors and targets involved in the escape of viruses from surveillance by innate and adaptive immune responses have greatly contributed both to the understanding of viral pathogenesis and general regulatory mechanisms in immunity. Suppression of T cell activation is a highly efficient means of immune evasion. In humans, this is successfully exploited by the measles virus (MV) where massive lymphopenia, an early switch to a Th2 dominated cellular immunity and the inability of peripheral blood T cells to expand in response to polyclonal activation, is typically observed. The strict dependence of MV entry and spread on a receptor confined to the hematopoietic system (CD150) largely explains the major aspects of MV pathogenesis. However, several important questions remain poorly resolved, such as how virus-specific immune responses are initiated and shaped, or how and which effectors promote generalized T cell suppression. Our research focus thus addresses key aspects of T cell interactions with professional antigen presenting cells, which are regulated by MV to promote T cell paralysis at the molecular level. This will not only be instrumental for MV pathogenesis, but also provide insight into general T cell control targets and effectors, which may apply to other immunosuppressive or malignant conditions.

Major Research

- *MV interaction with CD34+ hematopoietic stem and progenitor cells (HSPGs)*

In a collaborative study with the laboratories of Albrecht Müller and Thorsten Stühmer we have established that MV interaction with human CD34+ HSPGs or stroma cells *in vitro* does not detectably impair viability and differentiation. However, upon transfer into NOD/SCID mice, MV exposed HSPGs are substantially compromised in their ability to support short-term repopulation. Since MV-infected lymphocytes are known to home to the bone marrow (BM) in vivo and can efficiently transfer a virus to CD34+ HSPGs and stroma cells *in vitro*, this particular interaction is likely to contribute to generalised lymphopenia *in vivo*. We are currently interested in determining the signals that act within the BM environment to dampen the repopulation response.

- *Measles virus induced T cell paralysis: effectors, targets and immune synapse stability*

The MV glycoprotein complex expressed on virions and infected cells (including DCs) acts as effector structure promoting membrane signals that interfere with T cell receptor driven activation of the PI3/Akt kinase and downstream effectors including those regulating the reorganisation of the actin cytoskeleton. To this end the MV-promoted breakdown of membrane sphingomyelin and the formation of ceramide platforms in the outer membrane layer plays a role in morphological and functional T-cell paralysis. The respective receptor on T cells and its relevance in regulating thresholds of T cell activation are currently being analyzed along with the contribution of sphingomyelinase activation at the level of the immune synapse (IS) which proved to be highly unstable in conjugates formed between MV-infected DCs and T cells. We have established that, in addition to the MV gps, the upregulation and accumulation of repulsion

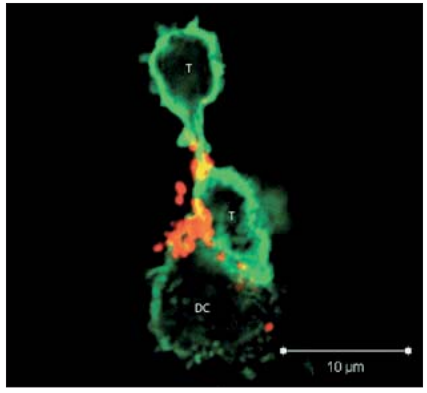


Fig. 1: Measles virus (detected by a surface glycoprotein specific antibody in red) can be transferred between dendritic (DC) and T cells (all labeled in green by Alexa-conjugated phalloidin) in synapse like or extended actin based protrusions.

receptors of the plexin/semaphorin family at the IS may contribute to its destabilization. As a second line, we are following the observation that MV-induced disruption of PI3K signaling affects the activity of splice accessory factors and thereby, accumulation of alternative splice variants in T cells. Based on the idea that these may act as T cell silencers, we have performed a whole genome wide Exon Array analysis to identify alternatively spliced gene products accumulating in response to PI3K abrogation.

- *MV interaction with DCs: from entry to transmission*

In line with MV mainly acting at the level of DCs to induce T cell paralysis, we have established that MV-induced maturation of these cells does not efficiently promote CCR5/CCR7 switching which would expectedly cause delayed homing to secondary lymphatics. We have also established that MV interacts with pattern recognition receptors, which promote antigen-presenting cell maturation, and, in common to many other ligands, capture MV (DC-SIGN), yet do not promote its uptake. In these studies, DC-SIGN signalling activates sphingomyelinases and this is prerequisite for plasma membrane recruitment of the MV entry receptor CD150 from an intracellular storage compartment. DC-SIGN mediated sphingolipid pathway activation and our work suggests that this may play an important role in regulating the trapping of its respective ligands and not entry. DCs loaded with MV are regarded as key for viral transport to the lymph nodes and subsequent transmission to scanning T cells. It is thus another focus of our work to analyse viral replication, trafficking of viral proteins and particle assembly in these cells. We have first approached these questions in standard cell lines by characterizing MV and cellular proteins that are able to promote formation of virus-like particles and budding sites. These observations are currently being transferred to and comparatively analysed in infected DCs. Moreover, the accumulation of viral and cellular proteins in organized structures that are consistent with the formation of virological synapses as sites of viral transmission from DCs to T cells is currently being investigated at the quantitative level.

SELECTED PUBLICATIONS

- *Avota E, Gulbins E, Schneider-Schaulies S (2011) DC-SIGN mediated sphingomyelinase-activation and ceramide generation is essential for enhancement of viral uptake in dendritic cells.* ***PLoS Pathog*** *Feb;7(2)*
- *Tran-Van H, Avota E, Boertlein C, Müller N, Schneider-Schaulies S (2011) Measles virus modulates dendritic cell/T cell communication at the level of plexinA1/neuropilin-1 recruitment and activity.* ***Eur J Immunol*** *41:151-163*
- *Boussaad I, Varangolo L, Hornich V, Rieger L, Krockenberger M, Stühmer T, Kranzfelder D, Müller MA, Schneider-Schaulies S (2011) Wild-type Measles Virus (MV) interferes with short term engraftment of human CD34+ hematopoietic progenitor cells.* ***J Virol*** *85:7710-7718*
- *Salditt A, Koethe S, Pohl C, Harms H, Becker S, Kolesnikova L, Schneider-Schaulies J, Schneider-Schaulies S (2010) Measles virus M protein driven particle production does not involve the ESCRT system.* ***J Gen Virol*** *91(6):1464–1472*
- *Gassert E, Avota E, Harms H, Krohne G, Gulbins E, Schneider-Schaulies S (2009) Induction of Membrane Ceramides: A Novel Strategy to Interfere with T Lymphocyte Cytoskeletal Reorganisation in Viral Immunosuppression.* ***PLoS Pathogens*** *5(10):e1000623*

EXTRAMURAL FUNDING

- *SFB479: Pathogen Variability and Host Reactions in Infectious Diseases. Project: Molecular mechanisms of measles virus induced immunosuppression*
- *DFG SCHN405/5-1: Induction of plasma membrane ceramides in T cells and their role in functional paralysis*
- *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 cross-talk and immune activation*
- *DFG IRTG1522 TP7: Targets, mechanisms and consequences of regulated T cell pre-mRNA splicing and their relevance as genetic markers of virally induced or general T cell suppression*
- *Deutsche Krebshilfe: Identification of molecular signatures downstream of PI3-kinase interference and their potential to act as suppressors of stimulated or malignant T cell activation and expansion*

3 Institutions of the Research Center for Infectious Diseases
3.5 Department of Microbiology, Theodor Boveri Institute, Biocenter

CONTACT DETAILS

Prof. Dr. Thomas Rudel (Chair)

Lehrstuhl für Mikrobiologie
Biozentrum der
Universität Würzburg
Am Hubland
97074 Würzburg

Phone: +49-931-3184401
E-Mail: thomas.rudel@biozentrum.uni-wuerzburg.de
www.mikrobio.biozentrum.uni-wuerzburg.de

RESEARCH GOALS

- *Molecular mechanisms underlying the interaction of pathogenic Neisseria and Chlamydia with their host cells*
- *Study the mitochondrial import route of bacterial pathogenicity factors*
- *Mechanisms of bacteria-organelle interactions*
- *Understanding the facultative intracellular lifestyle of S. aureus*
- *Unraveling pathogen-induced signaling cascades regulating to apoptosis inhibition or induction*

Summary

Microorganisms have evolved a wide variety of pathogenicity mechanisms, including the manipulation of various signalling cascades, non-coding RNAs and cellular processes such as the cell death pathways in the host. We are interested in the infection biology of obligate intracellular bacteria such as *Chlamydia and Simkania*, our aim is to understand the mechanisms by which they interfere with the apoptosis pathway to prevent their eradication. Analogously, one of the hallmarks of cancer cells is their insensitivity to a variety of apoptosis inducers. In this respect they are similar to the host cell persistently infected with *Chlamydia* in that they are resistant apoptosis. We are therefore attempting to decipher the underlying mechanisms, which may help to develop therapeutic strategies to treat both infection and cancer. Another focus is the molecular basis of disseminating gonococcal infections and identifying the factors required for dissemination and adaptation as well as the response of the host cell to the obligate human specific *Neisseria gonorrhoeae*. Moreover, we are currently analyzing the host cell death induced by *Staphylococcus aureus* as well as phagosomal escape mechanisms of these bacteria.

Major Research

- *Neisseria gonorrhoeae infection: Bacterial pathogenicity factors and host response (Thomas Rudel)*

N. gonorrhoeae is an obligate human specific pathogenic bacterium that causes the sexually transmitted disease, gonorrhea. This diplococcus preferentially colonizes the mucosal surface of the male urethra and the female cervix. In most cases, gonococci cause local infection but may also spread within the host to cause systemic infections leading to serious conditions such as arthritis, endocarditis, meningitis, and pneumonia. To cause systemic infection, bacteria have to cross the epithelial barrier by transmigration or by destroying the epithelial cells. A major focus of our research is the identification of the bacterial factors required for dissemination and adaptation as well as the response of the host cell to these hypervariable bacteria. We could show that the major outer membrane porin of serotype A ($PorB_{iA}$) triggers invasion into various host cells by engagement of the class F scavenger receptor, SREC. During local infection, the pore forming outer membrane protein PorB is translocated to the cytoplasmic membrane of host cells where it forms a nucleotide-regulated pore. PorB is also efficiently targeted to and integrated into the mitochondrial membranes causing mitochondrial damage, caspase activation and apoptosis. We could recently demonstrate that nucleotide binding is a prerequisite for PorB to damage mitochondria and sensitize host cells to apoptosis induction.

- *Infection with obligate intracellular bacteria (Thomas Rudel)*

C. trachomatis and *C. pneumoniae* are gram-negative, obligate intracellular bacteria. *C. trachomatis* causes blindness (affecting nearly 400 million people) and is among top three most common sexually transmitted diseases (90 million per year). *C. pneumoniae* is responsible for ~5-7 % of community acquired pneumonia cases. In addition, persistent chlamydial infection has been connected to highly prevalent diseases including arteriosclerosis and Alzheimer's disease. Obligate intracellular pathogens like *Chlamydia* reside in their host cells and have developed mechanisms to effectively prevent their eradication by actively interfering with host cell apoptosis. To delineate the host signaling pathways engaged by the pathogen we employ RNA interference-mediated loss of function approaches to identify host factors, whose ablation could sensitize infected host cells for apoptosis. Our results reveal that anti-apoptosis in *Chlamydia* infected cells involves multiple signaling pathways including Hif-1α regulated genes as well as the NF-kappa B, Raf-MAPK and the PI3K/AKT pathway known to be involved in cell growth and malignant transformation.

- *Import of proteins into mammalian mitochondria (Vera Kozjak-Pavlovic)*

Mitochondria are organelles of endosymbiotic origin that play a role in energy production, cell signaling, metabolism and

Fig. 1: Interaction of Neisseria gonorrhoeae with epithelial cells.

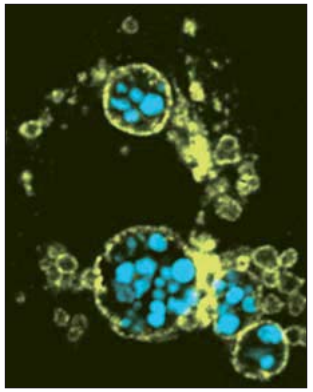


Fig. 2: Phagosomes of airway epithelial cells (yellow) harboring Staphylococcus aureus expressing a fluorescent protein. The workgroup of Dr. Fraunholz investigates escape of S. aureus from such host cell phagosomes to avoid lysosomal killing.

apoptosis. The vast majority of mitochondrial proteins are transcribed from nuclear DNA and imported from the cytosol. Intricate machineries for protein import in the outer (OMM) and inner mitochondrial membrane (IMM) serve this purpose. These machineries are sometimes used by bacterial and viral pathogens as a delivery route for proteins that modulate mitochondrial function. Our research focus is the study of the transport route of such proteins, as well as exploring their submitochondrial localization and interaction partners. We have been able to show that PorB from *N. gonorrhoeae* bypasses the classical sorting pathway for β-barrel proteins, which relies on the sorting and assembly machinery (SAM) in the OMM. Instead, PorB mislocalizes to the intermembrane space/IMM compartment, leading to the dissipation of membrane potential, an important prerequisite for the apoptosis induction during infection with *N. gonorrhoeae*. We also demonstrated that human mitochondria readily import neisserial, but not enterobacterial β-barrel proteins, in spite of their overall similarity. The reason for this selectivity is the ongoing research interest of the group.

- *Cellular microbiology of the intracellular chlamydia-like organism Simkania negevensis (Adrian Mehlitz)*

The interaction between intracellular bacteria, their vacuole and host organelles are not well defined. We are using *S. negevensis* - a recently discovered organism from the order of *Chlamydiales* - to investigate the mechanisms of bacteria-organelle interaction. *Simkania* is growing obligate intracellularly in amoeba and mammalian cells, showing a strong interaction with host organelles like mitochondria and the endoplasmic reticulum. We are interested in both similarities and differences between *Chlamydia* and *Simkania*, which might explain differences in vacuole biology and modulation of the host cell. Of special interest are secreted effector proteins and interactions with host organelles.

- *Phagosomal escape of Staphylococcus aureus (Martin Fraunholz)*

We aim at understanding the facultative intracellular lifestyle of *S. aureus*, a pathogen that has gained attention for its resistance to multiple common antibiotics (known as methicillin-resistant *S. aureus* or MRSA). We believe that the intracellular localization of the pathogen contributes to its virulence. Internalized bacteria have to evade disinfection by host cell phagolysosomes. For that purpose, *S. aureus* employs strategies to escape from these antibacterial compartments. Whereas this escape previously had been linked to a pore-forming toxin, we demonstrated that a small amphiphilic peptide is able to act during phagosomal escape in concert with a sphingomyelinase. However, not all strains of *S. aureus* seem to follow this strategy. Hence, we investigate alternative virulence factors involved in *S. aureus* phagosomal escape.

SELECTED PUBLICATIONS

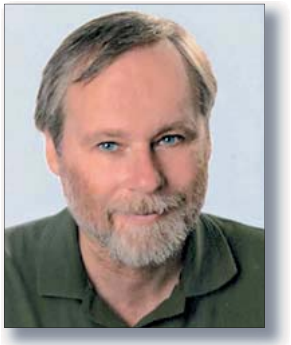
- *Kozjak-Pavlovic V, Ott C, Götz M, Rudel T (2011) Neisserial Omp85 protein is selectively recognized and assembled into functional complexes in the outer membrane of human mitochondria.* ***J Biol Chem*** *286:27019-26*
- *Albrecht M, Sharma CM, Reinhardt R, Vogel J, Rudel T (2010) Deep sequencing-based discovery of the Chlamydia trachomatis transcriptome.* ***Nucleic Acids Res*** *38(3):868-877*
- *Gurumurthy RK, Mäurer AP, Machuy N, Hess S, Pleissner KP, Schuchhardt J, Rudel T, Meyer TF (2010) A loss-of-function screen reveals Ras- and Raf-independent MEK-ERK signaling during Chlamydia trachomatis infection.* ***Sci Signal*** *3(113):ra21*
- *Karlas A, Machuy N, Shin Y, Pleissner KP, Artarini A, Heuer D, Becker D, Khalil H, Ogilvie LA, Hess S, Mäurer AP, Müller E, Wolff T, Rudel T, Meyer TF (2010) Genome-wide RNAi screen identifies human host factors crucial for influenza virus replication.* ***Nature*** *463(7828):818-822*
- *Kepp O, Gottschalk K, Churin Y, Rajalingam K, Brinkmann V, Machuy N, Kroemer G, Rudel, T (2009) Bim and Bmf synergize to induce apoptosis in Neisseria gonorrhoeae infection.* ***PLoS Pathog*** *5:e1000348*

EXTRAMURAL FUNDING

- *EU FP6: Regulation of small RNAs by infection*
- *ERA Net PathoGenoMics: Functional genomics of host-pathogen interactions using high-throughput screenings: a novel approach towards identifying therapeutic/prophylactic targets. Project: Bacterial factors required for disseminating gonococcal infections*
- *BMBF NGFNplus: RNomics of Infectious Diseases. Project: RNomics of Bacterial Infections*
- *DFG Deutsch-Israelische Projektförderung (DIP): A search for new cancer drug targets: the E4ORF4 network of cancer cell-specific apoptosis*
- *DFG grant: Import and assembly of mitochondrial outer membrane proteins – identification of new factors and import signals*
- *DFG SFB/TRR34: Pathophysiology of Staphylococci in the Post-Genomic Era (C11)*
- *DFG SFB 630: Active Agents against Acute and Disseminating Infections by Neisseria (B9)*
- *BMBF grant: Pathogen-Host Interactomes and Signaling Complexes in Bacterial Infections*
- *DFG SPP1580: Simkania negevensis containing vacuoles: formation, trafficking and subversion of host signaling*

3 Institutions of the Research Center for Infectious Diseases
3.5 Department of Microbiology, Theodor Boveri Institute, Biocenter

CONTACT DETAILS



Prof. Dr. Roy Gross

Lehrstuhl für Mikrobiologie
Biozentrum der
Universität Würzburg
Am Hubland
97074 Würzburg

Phone: +49-931-3184403
E-Mail: roy@biozentrum.uni-wuerzburg.de
www.mikrobio.biozentrum.uni-wuerzburg.de/research/prof_dr_roy_gross/

RESEARCH GOALS

- *Evolution of host-pathogen interactions*
- *Tolerance versus control of obligate bacterial endosymbionts by the innate immune system of insects*
- *Characterization of antimicrobial strategies of social insects*
- *Elucidation of TCS-based signal transduction networks in Helicobacter species and L. monocytogenes*

3.5.2 Bacteria-Host Interactions

Summary

The interaction of bacteria with eukaryotic hosts has a long history dating back to the first appearance of a eukaryotic cell. Accordingly, many mechanisms that bacteria use to interact with their eukaryotic hosts were acquired early during evolution, e.g. during their interaction with protists or invertebrates. Bacteria - host interactions can be beneficial for both partners (mutualistic interactions), or they can be detrimental to the host (pathogenic interactions), with all facets in between these relationships being possible. Our major research interest regards basic questions about bacteria - host interactions, their evolution, and adaptation mechanisms of the interacting organisms. To unravel differences and/or similarities between molecular mechanisms utilised in beneficial or pathogenic interactions, we have extended our previous research focus on pathogenic bacteria (*Helicobacter* and *Listeria*) to a mutualistic bacteria-host interaction (*Blochmannia* in carpenter ants).

Major Research

- *Intracellular bacterial endosymbionts of insects (Roy Gross)*

More than 100 years ago Friedrich Blochmann described the presence of intracellular bacteria in an animal for the first time. These bacteria reside in the midgut and ovarial cells of ants of the genus *Camponotus* (carpenter ants). They are classified within the γ-subclass of the *Proteobacteria* in the novel genus *Candidatus* Blochmannia (gen. nov.). The genome sequence of *Blochmannia floridanus* revealed a strongly reduced genome size of only about 705 kb with a strong AT bias (75% AT). Transcriptional profiling of the endosymbiont during developmental stages of the holometabolous ant host revealed only mild transcriptional responses. In fact, most transcriptional regulators known from free-living *Enterobacteriaceae* have been lost during the long-lasting relationship between the two partners (estimated about 50 Million years ago). Despite the unusual AT-content, the basic transcriptional machinery still resembles that of *E. coli* and typical σ^{70} and σ^{32} dependent promoters were identified and shown to be functional. We were able to uncover the biological function of the endosymbionts, since we could show that the bacteria enrich the diet of the animals with essential amino acids. This explains at least in part the vast radiation of members of the genus *Camponotus*, which can be found in virtually all terrestrial habitats on Earth, but in particular, these animals are massively present in nitrogen poor environments such as tropical rainforest canopies. We could show that the number of endosymbionts increases dramatically during pupation of an individual, when Blochmannia infects virtually all midgut cells. Thus, in this stage the midgut itself is transformed into a huge symbiotic organ. With increasing age of the adult animals, the endosymbiosis deteriorates leading to a strong reduction in bacterial numbers. This shows a strong correlation of the developmental cycle of the animals with replication of the endosymbionts suggesting the existence of sophisticated control mechanisms of the host over the bacterial partner.

This finding has led us to the current focus of our research: We are attempting to understand how, on the one hand, a chronic (and essential) infection with *Blochmannia* is maintained and controlled by the animals, while, on the other hand, pathogenic microorganisms are successfully defeated. Interestingly, the endosymbiont *Blochmannia* still provokes an immune response comparable to that mounted against potentially harmful bacteria. Thus, despite millions of years of co-habitation, the endosymbiont is still recognized as non-self, indicating that the immune system may be directly involved in the control of the endosymbionts. By a genome-wide transcriptome analysis we have identified about 500 genes differentially regulated upon septic injury of the animals. Among these genes, two encode host immune factors that are highly upregulated during pupation of the animals and only in their midgut, but not in other body parts. This regulation pattern therefore perfectly matches the time point and location of endosymbiont replication. Both proteins are known to be negative regulators of the immune response in *Drosphila melanogaster* and it is likely that they also down modulate the immune response of the ant. This down modulation of the immune response is probably a key event allowing efficient replication of the bacteria in the midgut during pupation.

In parallel, we started to characterize the antimicrobial weapons of the ant host. Overall, the antimicrobial repertoire of these social insects appears to be quite limited, since we found only three genes encoding antimicrobial peptides. This is a very low number as compared to other non-social insects such as *Drosophila melanogaster,* which

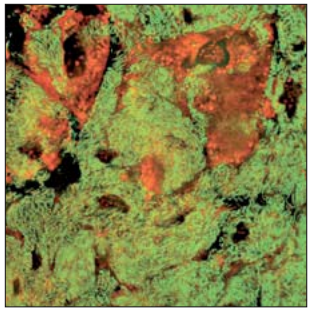


Fig. 1: Intracellular localization of the endosymbiont Blochmannia floridanus (stained in green) inside bacteriocytes within the midgut of the host animal, the ant Camponotus floridanus.

encodes about 20 antimicrobial peptides. However, one of the antimicrobial peptide genes of *Camponotus floridanus* encodes hymenoptaecin, a peptide known from other *Hymenoptera*. This gene is massively upregulated after pathogen infestation and, most interestingly, it has a very particular structure. It codes for a large precursor protein containing seven repeated hymenoptaecin domains. Thus, proteolytic cleavage of the precursor protein gives rise to seven antimicrobial peptides indicating a massive amplification of the immune response. Since there is significant sequence variability in the mature hymenoptaecin peptides, the antimicrobial repertoire of the animals might be much more complex than previously thought. In the future, we will further characterize host factors involved in the control of the endosymbiont population and pathogen infestation thus guaranteeing protection of the host against pathogens and undesired replication of the endosymbionts, but also ensuring appropriate endosymbiont numbers required in different developmental stages.

- *Two-component signal transduction in Helicobacter species and Listeria monocytogenes (Dagmar Beier)*

Two-component systems (TCS) enable bacteria to perceive environmental stimuli and to adapt to changes in their environment. Commonly adaptation is brought about by a change in the gene expression profile mediated by a response regulator (RR) protein that is activated via phosphoryl group transfer from a cognate histidine kinase (HK) in the presence of an appropriate stimulus. In this project the human and avian *Helicobacter* species *H. pylori* and *H. pullorum* and the human pathogen *Listeria monocytogenes* are used as model organisms for the analysis of transcriptional networks that are governed by TCS. Recently, we could show that histidine residue H94 in the periplasmic input domain of the sensor kinase of the TCS ArsRS, which is the master regulator of the acid response of *H. pylori*, is crucial for pH sensing. Currently we are focusing on the comparative characterization of the essential *Helicobacter* RR orthologs HP1043 (*H. pylori*) and HPMG439 (*H. pullorum*), which represent a degenerate orphan RR and an orthodox TCS protein, respectively. Lately, work on *L. monocytogenes* TCS focused on their role in the cell envelope stress response of this Gram-positive bacterium. We could demonstrate that the $LiaSR_{Lm}$ TCS is activated by cell-active antibiotics and governs the remodeling of the cell envelope via the massive upregulation of membrane associated and extracytoplasmic proteins. Interestingly, $LiaS_{Lm}$ is a bifunctional sensor protein whose phosphatase activity towards $LiaR_{Lm}$~P is stimulated by the interaction with the membrane protein $LiaF_{Lm}$ in the absence of inducing stimuli.

SELECTED PUBLICATIONS

- *Ratzka C, Liang C, Dandekar T, Gross R, Feldhaar H (2011) Immune response of the ant Camponotus floridanus against pathogens and its obligate mutualistic endosymbiont.* ***Insect Biochemistry & Molecular Biology*** *41:529-536*
- *Stoll S, Feldhaar H, Fraunholz MJ, Gross R (2010) Bacteriocyte dynamics during development of a holometabolous insect, the carpenter ant Camponotus floridanus.* ***BMC Microbiology*** *20:308*
- *Stoll S, Feldhaar H, Gross R (2009) Transcriptional profiling of the endosymbiont Blochmannia floridanus during different dievelopmental stages of its holometabolous ant host.* ***Environ Microbiol*** *11:877-888*
- *Fritsch F, Mauder N, Williams T, Weiser J, Oberle M, Beier D (2011) The cell envelope stress response mediated by the LiaFSRLm three-component system of Listeria monocytogenes is controlled via the phosphatase activity of the bifunctional histidine kinase LiaSLm.* ***Microbiology*** *157:373-386*
- *Müller S, Götz M, Beier D (2009) Histidine residue 94 is involved in pH-sensing by histidine kinase ArsS of Helicobacter pylori.* ***PLoS ONE*** *7;4(9):e6930*

EXTRAMURAL FUNDING

- *ERA Net PathoGenoMics: SPATELIS – spatio temporal analysis of Listeria-host protein interactions. Project: Characterization of regulatory networks of L. monocytogenes controlled by two-component systems*
- *COST Action FA0701: From fundamental studies to pest and disease management. Subproject in Work package 3: Molecular basis of the interaction of ants with obligate intracellular endosymbionts and pathogens*
- *DFG SFB567: Mechanisms of interspecific interaction of organisms. Project C2: Biology of Endosymbiosis of Bacteria and Ants*
- *DFG-Gr1243/8-1: Genetic and immunological interactions between pathogenic and mutualistic bacteria and the ant host*

3 Institutions of the Research Center for Infectious Diseases
3.6 Department of Internal Medicine II

CONTACT DETAILS

Prof. Dr. Hermann Einsele
(Chair)

Medizinische Klinik und Poliklinik II
ZIM - Zentrum Innere Medizin
Zimmer-Nr.: A3.-1.918
Oberdürrbacher Straße 6
97080 Würzburg

Phone: +49-931-201-40001
E-Mail: Einsele_h@klinik.uni-wuerzburg.de
www.medizin2.uk-wuerzburg.de/startseite.html

RESEARCH GOALS

- *Adoptive immunotherapy of infections in the immune compromised host involving cells of the innate/adoptive immune system*
- *Role of the innate immune system controlling fungal infections*
- *Infections in the immunocompromised host (esp. Herpes virus/fungal infection)*

3.6.1 Clinical Immunology

Summary

The section of hematology/oncology and the newly created centre of stem cell transplantation have recently initiated a stem cell transplantation programme that has rapidly become one of the largest in Germany. The centre uses a number of innovative techniques in stem cell transplantation such as cord blood and haploidentical stem cell transplantation. The procedures used in the programme involve severe forms of immunosuppression and thus are potentially subject to a wide range of infectious complications. Therefore, together with the section of infectious diseases (Head: Prof. Klinker), which concentrates on HIV infection and opportunistic infections in HIV-infected patients, we are treating a large patient population suffering from various forms of infectious diseases. Thus, several research projects have been initiated to investigate different forms of opportunistic infections including, fungal infections, CMV infections, EBV and respiratory virus infections, toxoplasmosis. The clinical studies investigate the role of adoptive T cell therapy and DC vaccination for CMV, EBV, adenovirus infections and invasive fungal infections in addition to a new immunotherapeutic approach to Aspergillus infection using T cell therapy and antibodies to gliotoxin.

Major Research

- *Characterization of Pathogen-specific CTL/Th1 and adoptive regulatory T cells and cell therapy post transplant*

Reconstitution of pathogen-specific T cells following allogeneic stem cell transplantation is essential to prevent and/or control various infection complications post-transplant. We are monitoring pathogen-specific T cell responses in patients undergoing allogeneic stem cell transplantation. We have developed tetramer-staining and intracellular cytokine staining (including Elispot) assays and clinically applied these novel tools of immunomonitoring to these heavily immunocompromised patients to define patients at high risk of infectious complications. Based on these findings we have been the first group in Europe to select and transfer pathogen-specific T cells. Using novel selection devices (MHC multimers, CCs) we have been able to generate pathogen-specific T cell lines directed at CMV/ADV/fungal pathogens at high purity and a low risk of including alloreactivity. To address the clinical situation of multiple infectious complications in these severely immunocompromised patients we have developed strategies to select multi-pathogen specific T cells. In order to control the inflammatory response associated with the activation/reactivation of these pathogen-specific T cells, different subsets of regulatory T cells are reconstituted, expanded and activated during the course of infections. The group has started to define and functionally characterize the different subsets of regulatory T cells in herpes virus and fungal infection. One translational aspect especially in fungal infection is the cotransfer of effector and regulatory T cells to mediate infection control but also to prevent immunopathogenesis by damping the inflammatory response following activation and expansion of pathogen-reactive T cells.

- *Role of innate/adoptive immune responses in fungal infection and fungus-cell interaction*

The group has been exploring *Aspergillus fumigatus* cell interactions with DCs, neutrophils, NK and γδ- T cells. The group was the first to describe Dectin-1 as an important PRR on DCs during the fungal-pathogen interaction. We have also described additional PRRs and their role in activating various signaling pathways in different cell populations of the innate immune response. Our recent work is addressing the role of NK cells as a first line immune response to *Aspergillus fumigatus* infection.

SELECTED PUBLICATIONS

- *Khanna N, Stuehler C, Conrad B, Lurati S, Krappmann S, Einsele H, Berges C, Topp MS (2011) Generation of a multiple pathogen-specific T-cell product for adoptive immunotherapy based on activation-dependent expression of CD154.* ***Blood*** *118:1121-31*
- *Stuehler C, Khanna N, Bozza S, Zelante T, Moretti S, Kruhm M, Lurati S, Conrad B, Worschech E, Stevanović S, Krappmann S, Einsele H, Latgé JP, Loeffler J, Romani L, Topp MS (2011) Cross-protective TH1 immunity against Aspergillus fumigatus and Candida albicans.* ***Blood*** *117:5881-91*
- *Bouzani M, Ok M, McCormick A, Ebel F, Kurzai O, Morton CO, Einsele H, Loeffler J (2011) Human NK cells display important antifungal activity against Aspergillus fumigatus, which is directly mediated by IFN-γ release.* ***J Immunol*** *187:1369-76*
- *Feuchtinger T et al. (2010) Adoptive transfer of pp-65 specific T-cells for the treatment of chemorefractory cytomegalovirus disease or reactivation after haploidentical and matched unrelated stem cell transplantation.* ***Blood*** *116:4360-7*
- *Seggewiss R, Einsele H (2010) Immune reconstitution post allogeneic transplantation and expanding options for immunomodulation: an update.* ***Blood*** *115:3861-8*

EXTRAMURAL FUNDING

- *EU FP 6 Strep MANASP: Development of novel management strategies for invasive aspergillosis*
- *EU FP 7 NanoII: Nanoscopically-guided induction and expansion of regulatory hematopoietic cells to treat autoimmune and inflammatory processes*
- *ERA Net PathoGenoMics: AspBIOmics - Invasive aspergillosis: Biomarkers for prevention, diagnosis and treatment response*
- *BayImmuNet: Development of an immunotherapy protocol for the prevention and treatment of A. fumigatus infection*
- *BMBF: Development, laboratory and clinical evaluation of an innovative diagnostic system for pathogenic fungi*
- *Wilhelm Sander Foundation: Analysis of the innate immunity response against aspergillosis*

AWARDS AND PRIZES

- *2011 - Honorary Fellow of the Royal College of Pathology (London)*

3 Institutions of the Research Center for Infectious Diseases
3.6 Clinic for Internal Medicine II

CONTACT DETAILS

Prof. Dr. med. Dr. med. habil. Hartwig Klinker

Universitätsklinikum Würzburg
Medizinische Klinik und Poliklinik II
ZIM - Zentrum Innere Medizin
Zimmer-Nr.: A4.+3.448
Oberdürrbacher Straße 6
97080 Würzburg

Phone: +49-931-201-40043
E-Mail: Klinker_h@klinik.uni-wuerzburg.de
www.medpoli.uni-wuerzburg.de/hepinf

RESEARCH GOALS

- *Pharmacokinetics of antiretroviral treatments in patients with HIV-infection*
- *Detection of direct anti HCV acting agents in human serum*
- *Drug-drug interactions and pharmacokinetics in antifugal prophylaxis and treatment with azole antifungal agents in patients after stem cell transplantation*

3.6.2 Division of Infectious Diseases

Summary

Globally, there are in the order of 33 million people are living with HIV/AIDS. While the availability of potent antiretroviral drugs to inhibit HIV replication has led to important clinical benefits for many patients, the lifelong treatment with a complex medication makes great demands on both patient and physician. The major problems associated with long-term antiretroviral therapy are the adherence to antiretroviral drugs, drug resistance, toxicity, pharmacokinetics and pharmacological interactions. Chronic hepatitis B and C are among the most frequent infections in the world (together accounting for around 500 million cases) and are often complicated by the development of liver cirrhosis and hepatocellular carcinoma. Although antiviral treatment has dramatically improved during the last years, it remains difficult to perform, it is complicated by a lack of data on adequate drug exposure and associated with many side effects. In addition to these viral infections, invasive fungal infections are also a life threatening complication in patients with haematological malignancies, especially in 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 diseases and for prophylaxis or treatment of complications, this makes drug-drug interactions an important consideration during their daily medical care. The laboratory and clinical research of the Division of Infectious Diseases is focused on innovative antiinfective strategies in the field of HIV-infection, chronic hepatitis B/C, and opportunistic infections in immunocompromised hosts. A major part of our research concerns pharmacokinetic analysis for the detection and quantification of different antiviral and antifungal agents.

Major Research

- *Pharmacokinetics of virostatic and antifungal agents*

The division of Infectious Diseases treats a broad range of infections. Our main focus is in the diagnosis and therapy of opportunistic infections in immuncompromised hosts, for example, after chemotherapy or organ trans-plantation, HIV and AIDS, acute as well as chronic viral hepatitis, tuberculosis and infections with multiresistant pathogens. The laboratory specialises in the development and implementation of methods for the evaluation of pharmacokinetics and therapeutic drug monitoring of virostatic and antifungal agents. One major focus is the pharmacokinetic evaluation of HIV protease inhibitors (PI) and nonnucleoside 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 determination of plasma levels of HIV-1 protease-inhibitors saquinavir, indinavir, ritonavir, nelfinavir, amprenavir, lopinavir, atazanavir, darunavir and tipranavir, as well as the nonnucleoside reverse transcriptase inhibitors efavirenz and etravirine. The concentrations of nevirapine, another NNRTI, have been investigated by a gas chromatographic setup with NP-detection. During 2010 we developed a new chromatographic method for the determination of raltegravir levels, the first HIV-integrase inhibitor (Figure 1).

Invasive fungal infections (IFI) are a life threatening complication in patients with haematological malignancies. The antifungal triazoles voriconazole and posaconazole are broadly used either for treatment or prophylaxis of IFI. Voriconazole is metabolized by the CYP P450-system and shows inhibitory activity for several isoenzymes of CYP (2C9, 2C19 and 3A4) and posaconazole inhibits cytochrome P450 enzymes. To perform pharmacokinetic studies we have established a combined assay for the determination of serum concentrations of both triazoles.

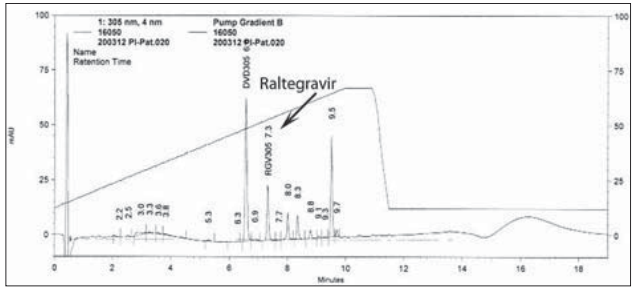


Fig. 1: HPLC illustration of raltegravir plasma oncentration (690 ng/ml)

- *HIV-infection and chronic viral hepatitis B and C clinical studies*

The center is nationally and internationally well known for its clinical trial activities, especially concerning infections with HIV and chronic hepatitis B or C. This includes a leading role in a large study to investigate the long-term safety of entecavir, a nucleoside analogue for the treatment of chronic hepatitis B (lead investigator for Germany: Prof. H. Klinker), and a separate focus on the regression of liver fibrosis during antiviral therapy. The antiviral treatment of hepatitis C has dramatically changed during the last few years. The division of infectious diseases is a study center for many international phase II and II studies with investigational anti-HCV drugs (protease inhibitors, polymerase inhibitors) like TMC435, GS-5885, GS-9451, Tegobuvir, BMS-650032, ABT-267, ABT-333, ABT-450, Danoprevir, and BI 201335.

Since 2011, we have initiated a joint project with the Institute for Virology and Immunobiology (a collaboration with Prof. A. Rethwilm) on the molecular investigation of the pharmacokinetics and drug monitoring of new direct-acting anti-HIV and anti-HCV antivirals. This is supported by the interdisciplinary center for clinical research (IZKF) at the University of Würzburg.

With respect to HIV, we have participated in the NIH (National Institute of Health, Bethesda) sponsored, worldwide START-study which is evaluating the optimal timing for the beginning of antiretroviral therapy. In addition, we are associated with the International Research Training Group IRTG 1522, and performing, and performing pharmacokinetic investigations together with the Universities of Cape Town and Stellenbosch (South Africa) in HIV-infected patients undergoing high active antiretroviral therapy in South Africa.

Clinical studies in patients with haematological malignancies mainly focus on fungal infections. Due to the different indications, the underlying risk profiles and timing of treatment, different compounds, therapies and strategies are under investigation in phase II and II trials. In an investigator initiated study (CASPHYLAX) pharmacokinetic, and efficacy for primary prophylaxis of caspofungin are being investigated (ClinicalTrials.gov Identifier: NCT01318148). Another study investigates the safety, tolerability and pharmacokinetic of an echinocandin, a liposomal polyene or the combination of both in stem cell transplant patients. These clinical therapeutic trials are accompanied and assisted by diagnostic research and surveys to the incidence of fungal disease.

SELECTED PUBLICATIONS

- *Pretorius E, Klinker H, Rosenkranz B (2011) Therapeutic Drug Monitoring during antiretroviral therapy.* ***Ther Drug Monit*** *33:265-274*
- *Heinz WJ, Zirkel J, Kuhn A, Schirmer D, Lenker U, Keller D, Klinker H (2011) Relevance of timing for determination of posaconazole plasma concentrations.* ***Antimicrob Agents Chemother*** *55:3621-3623*
- *Mocroft A, Wyatt C, Szczech L, Neuhaus J, El-Sadr W, Tracy R, Kuller I, Shlipak M, Angus B, Klinker H, Ross M (2009) INSIGHT SMART Study Group. Interruption of antiretroviral therapy is associated with increased plasma cystatin C.* ***AIDS*** *23:71-82*
- *Kahle K, Langmann P, Schirmer D, Lenker U, Keller D, Helle A, Klinker H, Heinz WJ (2009) Simultaneous determination of voriconazole and posaconazole concentrations in human plasma by high-performance liquid chromatography.* ***Antimicrob Agents Chemother*** *53:3140-3142*

EXTRAMURAL FUNDING

- *DFG IRTG 1522: HIV associated infectious diseases in South Africa*
- *BMWi EXIST grant: Outsourcing of a diagnositc laboratory for therapeutic drug monitoring (03EGSBY044)*
- *NIH and BMBF: START - Strategic Timing of Antiretroviral Treatment*
- *IZKF Würzburg: Molecular investigations into the pharmacokinetics and drug monitoring of new direct-acting anti-HIV and anti-HCV antivirals (Z-4/106)*

AWARDS AND PRIZES

- *2009 - Albert Kölliker Prize, Medical Faculty, University of Würzburg*

4 ZINF members associated with other institutes
4.1 Institute of Organic Chemistry

CONTACT DETAILS

Prof. Dr. Dr. h.c.
Gerhard Bringmann

Lehrstuhl für Organische Chemie I
Am Hubland
97074 Würzburg

Phone: +49-931-31-85323
E-Mail: bringman@chemie.uni-wuerzburg.de
Website: http://www-organik.chemie.uni-wuerzburg.de/lehrstuehlearbeitskreise/bringmann

RESEARCH GOALS

- *Isolation, structural elucidation, total synthesis, biosynthesis, and pharmaceutical development of anti-infective and anti-tumoral agents from nature*
- *Spectroscopically-guided search and online identification of novel compounds by hyphenated techniques like HPLC-MS/MS-NMR-CD in combination with quantum chemical CD calculations*
- *Chiral porphyrins; materials inspired from nature*

Summary

Our group pursues natural products chemistry with structural, biosynthetic, and pharmacological facets. We consider natural products chemistry as 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 rewarding sources for novel natural products – among them, *i.a.*, tropical plants 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 CD (circular dichroism) calculations. This approach permits the 'early' recognition of novel 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 antitumoral activities. We elaborate synthetic pathways to the most rewarding metabolites using biomimetic or merely synthetic strategies; for this purpose, we also develop novel synthetic methodology, for example the lactone method for the atropo-selective construction of even highly hindered biaryl and hetero biaryl systems of any desired (and predictable) axial configuration.

Major Research

- *Naphthylisoquinoline alkaloids: 'new' plants, unique structures, an unprecedented type of chiral axis, a novel pathway to isoquinoline alkaloids, and high anti-infectious activities*

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 mainly focus 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, elaborated a highly convergent and stereoselective first access to the alkaloids ancistrocladinium A and B, which possess an unprecedented iminium-aryl axis, via a short sequence of eight linear steps. Since ancistrocladinium A and related compounds were found to exhibit very good anti-infective activities (in particular against *Leishmania major*) with a comparably low cytotoxicity against mammalian cells, we have developed a concept for the identification of the pharmacophore of such *N,C*-coupled arylisoquinolines using structure-activity relationship (SAR) studies. We managed to successfully elaborate a most efficient synthetic strategy giving rise to the generation of more than 250 structurally simplified derivatives showing the broad substrate variability of the pathway. By changing particular structural parameters we could specifically improve the selectivity of the activity against a given parasite (*e.g.*, *Plasmodium falciparum*, *Trypanosoma* spp., or *Leishmania* spp.). These SAR studies finally paved the way for a systematic optimization of the activity-cytotoxicity ratio, e.g. by QSAR calculations, resulting in the preparation of highly active and biocompatible anti-infective agents. This synthetic work furthermore helped provide sufficient quantities of the most active compounds for further biotesting *in vitro* and *in vivo*, and preparing synthetic analogs with simplified structures and improved activities and ADMET parameters. The main emphasis in efficiently improving the activities for further drug development is the search for the mode of action and, in particular, the establishment of the target protein, which we pursue, by photo-affinity labelling studies, together with our cooperation partners within the SFB 630 network.

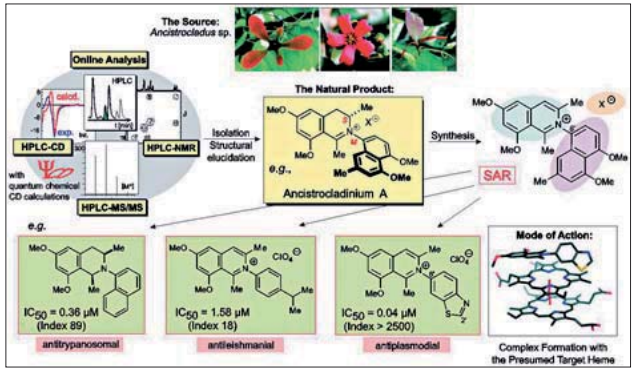


Fig. 1: Identification of ancistrocladinium A, a representative of a new subclass of N,C-coupled naphthylisoquinoline alkaloids, i.e., linked via an unprecedented $N_{iminium}$-C_{aryl} axis: structural elucidation online, by HPLC-MS/MS-NMR-CD assisted by quantum chemical CD calculations, atroposelective total synthesis; synthesis of simplified structural analogs with high and specific antitrypanosomal, antileishmanial, or antiplasmodial activities – depending on the individual structure, and with reduced toxicities; further improvement by identifying the mode of action and the target molecules, together with our cooperation partners within the SFB 630 network.

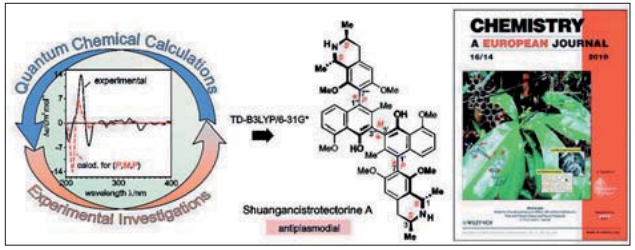


Fig. 2: Assignment of the absolute axial configurations of shuangancistroctectorine A from the Chinese plant Ancistrocladus tectorius by comparison of the experimental LC-CD spectrum with the spectrum calculated for the P,M,P isomer.

- *Hyphenated analytical methods: online recognition and full structural elucidation right from the peak in the chromatogram*

Our key methodology for the spectroscopy-guided search for structurally rewarding secondary metabolites like 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 shuangancistrotectorines, dimeric naphthylisoquinoline alkaloids with three consecutive chiral axes from a Chinese *Ancistrocladus* plant by this hyphenated analysis. These bioactive dimers possess is the highest number of consecutive stereogenic biaryl axes ever found not only in naphthylisoquinolines, but also in natural products in general.

SELECTED PUBLICATIONS

- *Bringmann G, Hertlein-Amslinger B, Kajahn I, Dreyer M, Brun R, Moll H, Stich A, Ioset KN, Schmitz W, Ngoc LH (2011) Phenolic analogs of the N,C-coupled naphthylisoquinoline alkaloid ancistrocladinium A, from Ancistrocladus cochinchinensis (Ancistrocladaceae), with improved antiprotozoal activities.* ***Phytochemistry*** *72:89-93*
- *Ponte-Sucre A, Gulder T, Gulder TAM, Vollmers G, Bringmann G, Moll H (2010) Alterations to the structure of Leishmania major induced by N arylisoquinolines correlate with compound accumulation and disposition.* ***J Med Microbiol*** *59:69-75*
- *Bringmann G, Gulder T, Hertlein B, Hemberger Y, Meyer F (2010) Total synthesis of the N,C-coupled naphthylisoquinoline alkaloids ancistrocladinium A and B and related analogues.* ***J Am Chem Soc*** *132:1151-1158*
- *Xu M, Bruhn T, Hertlein B, Brun R, Stich A, Wu J, Bringmann G (2010) Shuangancistrotectorines A-E, dimeric naphthylisoquinoline alkaloids with three chiral biaryl axes, from the Chinese plant Ancistrocladus tectorius.* ***Chem Eur J*** *16:4208-4216*
- *Ponte-Sucre A, Gulder T, Wegehaupt A, Albert C, Rikanovic C, Schäflein L, Frank A, Schultheis M, Unger M, Holzgrabe U, Bringmann G, Moll H (2009) Structure-activity relationship and studies on the molecular mechanism of leishmanicidal N,C-Coupled arylisoquinolinium salts.* ***J Med Chem*** *52:626-636*

EXTRAMURAL FUNDING

- *Speaker/Coordinator DFG SFB630: Recognition, Preparation, and Functional Analysis of Agents against Infectious Diseases*
- *DFG-KFO 216: Characterization of the Oncogenic Signaling Network in Multiple Myeloma: Development of Targeted Therapies*
- *DFG-Br 699/14-2: Molecular phylogeny and chemotaxonomy of the Ancistrocladaceae plant family*
- *DFG-Br 699/12-2: Enantioselective synthesis of bisbibenzyl natural products of the isoplagiochin type with combined axial and helical chirality*
- *Else-Kröner-Fresenius-Foundation: Coordinator of the project: Re-installment of Excellence at the University of Kinshasa*
- *DFG SFB567: Mechanisms of Interspecific Interactions of Organisms (Project B-8)*
- *DFG SPP1152: Evolution of Metabolic Diversity*
- *Deutsche Josè Carreras Leukämie-Stiftung e.V.: Development and Precilinical Evaluation of a Novel-Type Pro-Pro-Drug*

4 ZINF members associated with other institutes
4.2 Department of Bioinformatics

CONTACT DETAILS

Prof. Dr. Thomas Dandekar

Lehrstuhl für Bioinformatik
Biozentrum, Am Hubland
Universität Würzburg
97074 Würzburg

Phone: +49-931-3184551
E-Mail: dandekar@biozentrum.uni-wuerzburg.de
biozentrum.uni-wuerzburg.de/thomas_dandekar.html

RESEARCH GOALS

- *Systems biology of cellular networks including infection*
- *Metabolic modelling in pathogens*
- *Modelling host-pathogen interactions*
- *Bioinformatical analysis of individual protein and RNAs*

Summary

The increased volume and complexity of data currently being generated in infection biology research requires sophisticated bioinformatics tools in order obtain a global overview of the infection process. Our research focuses on the modelling molecular interactions and the interaction between host and pathogen during infection. We perform detailed modelling of metabolism of different prokaryotes, with a focus on pathogenic bacteria such as *Staphylococcus aureus*, *Salmonella* and *Listeria*. We are also interested in elucidating the cellular signalling networks involved in host-pathogen interactions, for example, in Arabidopsis plants challenged with *Pseudomonas syringae*. Besides infection biology, other areas of interest are systems biology of organismic interactions and metabolism in cellular networks. As part of this work we also develop new algorithms such as JANE for transcriptomics, (e.g. of endosymbionts such as blatta bacteria) single cell sequencing (e.g. of pori bacteria and reconstruction of their metabolism) and new databases such as repositories describing protein-protein interactions in human cells.

Major Research

- *Pathophysiology and treatment of Staphylococci infections*

We are investigating the adaptation of metabolism, protein-protein interactions and protein complexes to different physiological conditions such as glucose limitation, aerobic or anaerobic growth. Furthermore, we are developing new algorithms during the course of the project for genome annotation and genome comparisons. A current focus is the annotation of pathogenic Staphylococcal genomes with interesting properties regarding their cell wall structure. Our goal is to gain a better understanding of the different levels of regulation and adaptation in metabolism, both in terms of the dynamics of protein complexes as well as the factors affecting their expression, for example, small regulatory RNAs.
A separate project, addresses the effects of antibiotics on pathogens, for instance regarding the effect of different isochinolines on different Staphylococcal strains compared to their effects on human cells. In collaboration with the faculty of chemistry, metabolic modelling and analytical chemistry approaches have identified GBAP143 as a promising first lead compound for a new antibiotic. However, since system effects such as neurotoxicity must also to be taken into account, we are currently investigating the properties and modelling further isochinolines.

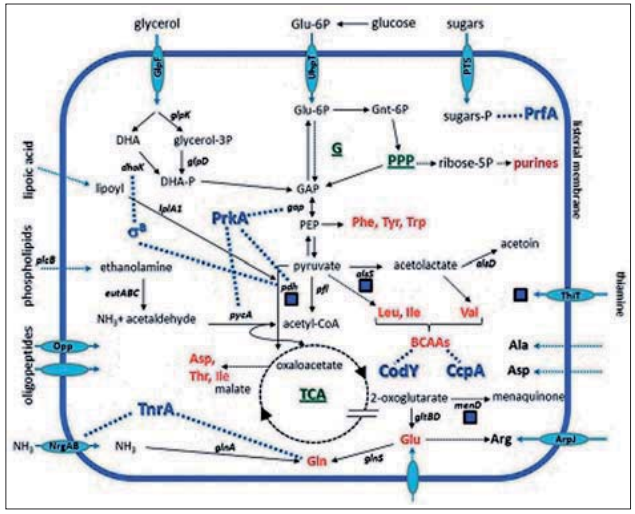


Fig. 1: Simplified view of listerial metabolic enzymes, transporters and pathways relevant during infection. Pathways modelled (arrows) and key regulatory interactions (dashed lines). Blue square: thiamine; red: synthesized amino acids, complex pathways in green. G, glycolysis; PEP, phosphoenolpyruvate; P, phosphate. Similar studies are done on metabolic complexes in Staphylococci.

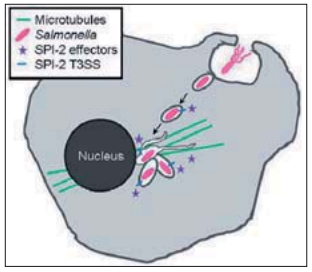


Fig. 2: Salmonella and host cell.We investigate the metabolic flow, involved pathways and enzymes while Salmonella is taken up by host cells either by Salmonella-induced invasion (T3SS-1 triggered) or phagocytosis. Effector proteins via the T3SS-2 induce maturation and endosomal markers. Salmonella-induced filaments (SIFs) formation coincides with Salmonella replication between 4 and 6h after infection.

- *Pathogen metabolism during infection*

We also study the metabolism of pathogens such as *Salmonella* and *Listeria* during infection. We use isotopologue data analysis (in collaboration with PD Eisenreich, TU Munich) to identify metabolic pathways or verify predicted fluxes important for intracellular survival in these pathogens. Furthermore, we have identified, using a combination of genetic techniques (in collaboration with PD Fuchs, Weihenstephan) and metabolic modelling, key enzymes involved in secondary metabolism and amino acid metabolism, which are important for Listeria survival in macrophages. Similar studies are being conducted with Salmonella and their life style in the Salmonella containing vacuole (collaboration partner: Prof. Hensel, Osnabrück).

We participate in several other collaborations and projects with groups in infection biology on different parasites and pathogens, for instance with Prof. Brehm, Prof. Engstler, Prof. Rudel, Dr. Sharma and Dr. Ziehbuhr.

- *Other host-bacterial interactions*

Apart from pathogenesis we are also interested in understanding other host-bacterial interactions, in particular, symbiosis and comparing this to more aggressive lifestyles such as predatory lifestyles in sponges feeding on bacteria and pathogenic bacteria in ants being attacked by proteobacteria (the latter in collaboration with Prof. Roy Gross, Dept. of Microbiology). This integrated view has provided new insights in symbiosis and interesting new species-specific metabolic pathways in poribacteria (in collaboration with Prof. Hentschel, Dept. of Botany II).

Furthermore, there are five other groups in the bioinformatics department (chair: T. Dandekar). These include statistical modelling (AG Müller) and interactomics (AG Dittrich) with many links to the infection biology as well as phylogenetics (AG Wolf), evolutionary computation (AG Schultz) and genomics (AG Förster). Important methodological approaches that are applied to infection biology include the analysis of gene expression data during infection, the analysis of human host interactions, phylogenetic trees of prokaryotic proteins, evolutionary analysis of immune peptides and transcriptomics of immune responses.

SELECTED PUBLICATIONS

- *Liang C, Liebeke M, Schwarz R, Zühlke D, Fuchs S, Menschner L, Engelmann S, Wolz C, Jaglitz S, Bernhardt J, Hecker M, Lalk M, Dandekar T (2011) Staphylococcus aureus physiological growth limitations: Insights from flux calculations built on proteomics and external metabolite data.* ***Proteomics*** *11:1915-35*

- *Cecil A, Rikanovic C, Ohlsen K, Liang C, Bernhardt J, Oelschlaeger TA, Gulder T, Bringmann G, Holzgrabe U, Unger M, Dandekar T (2011) Modeling antibiotic and cytotoxic effects of the dimeric isoquinoline IQ-143 on metabolism and its regulation in Staphylococcus aureus, Staphylococcus epidermidis and human cells.* ***Genome Biol*** *12:R24*

- *Siegl A, Kamke J, Hochmuth T, Piel J, Richter M, Liang C, Dandekar T, Hentschel U (2011) Single-cell genomics reveals the lifestyle of Poribacteria, a candidate phylum symbiotically associated with marine sponges.* ***ISME J*** *5:61-70*

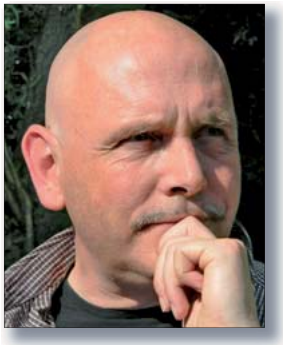
- *Schauer K, Geginat G, Liang C, Goebel W, Dandekar T, Fuchs TM (2010) Deciphering the intracellular metabolism of Listeria monocytogenes by mutant screening and modelling.* ***BMC Genomics*** *11:573*

EXTRAMURAL FUNDING

- *BMBF grant: Analysis of PGI and P2Y12 Signalling in human platelets*
- *DFG SFB688/TPA2: Molecular mechanisms of the interactions of cAMP-/cGMP-dependent protein kinases and vWF/GPIb-regulated signaling cascades in human thrombozytes*
- *DFG TR34/TPA8: Systems biological analysis of the central carbohydrate metabolism and involved protein complexes in Staphylococcus aureus*
- *DFG TR34/TPZ1: Integration of bioinformatical tools for an omics databank in a Staphylococcus aureus Wiki environment*
- *DFG Da 208/12-1: Modelling the crosstalk between TNFR1 and TNFR2 receptor in human cells*
- *DFG Da 208/13-1: Metabolism of intracellular Salmonella enterica: One lifestyle in intra-cellular infections*
- *DFG Da 208/10-2: Host adapted metabolism of bacterial infections: Data integration and refined metabolic modelling*
- *DFG GR1243/7-2: Genetic and immunologic basis of pathogenic and mutualistic interactions between bacteria and their ant hosts*

4 ZINF members associated with other institutes
4.3 Department of Cell and Developmental Biology (Zoology I)

CONTACT DETAILS



Prof. Dr. Markus Engstler

Lehrstuhl für Zell- und
Entwicklungsbiologie
Biozentrum, Am Hubland
University of Würzburg
97074 Würzburg

Phone: +49-931-3180060
E-Mail: markus.engstler@biozentrum.uni-wuerzburg.de
www.zeb.biozentrum.uni-wuerzburg.de/research/cellular_dynamics_engstler/

RESEARCH GOALS

- *The role of trypanosome motility in host and vector infection*
- *Structure and function of the prototypic GPI-anchored protein VSG*
- *Control of organelle segregation and formation in the cell cycle*
- *Comparative evolutionary analysis of vertebrate trypanosomes*

Summary

African trypanosomes are extracellular parasites that cause human sleeping sickness. Key to their success has been the ability to endocytose essential macromolecules from the mammalian host without exposing the machinery involved to the attention of the immune system, which has led to the evolution of an extraordinary system for membrane traffic. The parasite utilises the extensive traffic to allow the differential sorting, internalization and recycling of abundant glycosylphosphoinositol anchored proteins (VSGs). We have found that trypanosome motility is critical for the infection of host and vector and, thus, represents a virulence factor that we aim to exploit for the systematic discovery of new drug targets against one of the most neglected diseases.

Major Research

- *The role of trypanosome motility in the infection of host and vector.*

The life cycle of trypanosomes alternates between proliferating and cell cycle arrested stages. When an infected tsetse fly feeds on a mammalian host, metacyclic trypanosomes enter the dermal connective tissue through the saliva of the fly, resulting in a local skin infection. After two to 4 weeks the parasite actively migrates via the lymphatic system into the bloodstream. We have found that in the bloodstream African trypanosomes continuously swim and thereby generate directional flow fields on their cell surface. These flow forces become functional when the surface coat, which is dominated by variant surface glycoproteins (VSG), is attacked by host immunoglobulins. Antibody-VSG complexes are caught by hydrodynamic forces and dragged towards the rear of the cell, where they are endocytosed. This means that pure physical forces can sort proteins in the plane of the plasma membrane. One major goal our recent work is to experimentally verify that bloodstream form trypanosomes swim at velocities that are required and sufficient for hydrodynamic removal of host effector molecules bound to the parasite's cell surface. In the first step we have detailed the pure physical impact of the crowded environment in the vertebrate bloodstream on trypanosome motility. In addition to bloodstream forms we have started analyzing how trypanosomes also move in the tsetse fly. Therefore, we have initiated a collaborative research project with the aim of detailing the motion pattern of various tsetse stages in the insect. Likewise, in collaboration with partners in Kenya, we are studying the behavior of trypanosomes in their natural host.

- *Structure and function of the prototypic GPI-anchored protein VSG*

As extracellular parasites, trypanosomes are continuously exposed to the host's immune system. By exchanging the dominant cell surface protein, the variant surface glycoprotein (VSG), long slender forms are able to escape the immune response. This process is called antigenic variation. The trypanosome genome includes several hundred different VSG genes. However, only one VSG is expressed and located at the cell surface at any given time. During an increase in parasitaemia, the host produces antibodies against this specific glycoprotein. By chance, a few cells switch their expression to another, immunologically distinct VSG. From these newly switched cells another population of trypanosomes is able to grow until the antibody attack directed

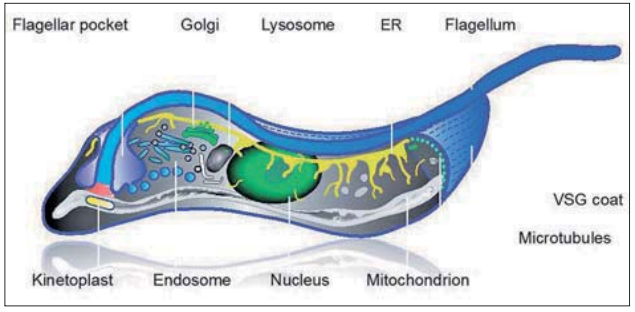


Fig. 1: Schematic drawing of the trypanosome cell.

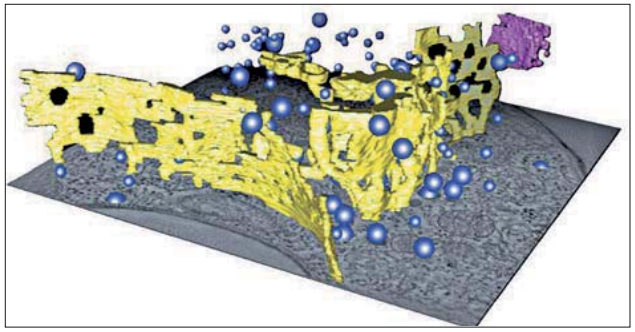


Fig. 2: 3D-reconstruction of the trypanosome endosome apparatus based on serial electron tomography.

against their surface protein also eliminates these cells before a switch to yet another VSG occurs. The regulatory mechanisms involved in determining the activity of expression sites are not fully understood, but our studies and the work of others suggest that epigenetic processes are involved. Both, antigenic variation and antibody clearance can protect the parasite from immune attack only if the surface coat maintains both, its extremely high density and mobility of the VSG protein. If protein mobility would be reduced, the mechanism of antibody clearance would fail and even a minute decrease in coat density would allow host immunoglobulins to recognize invariant surface proteins hidden beneath the VSG. In both cases, the host would rapidly clear the parasite from its circulation. Our preliminary reverse genetic experiments suggest that any increase in VSG surface concentration causes the immediate and dramatic reduction of VSG mobility, followed by rapid cell death. Likewise, any genetic interference with VSG expression results in cell cycle arrest and death. Thus, understanding how trypanosomes make and maintain their surface could unravel the Achilles' heel of this elusive parasite and pave the way for new and urgently needed therapeutics.

- *Control of organelle segregation and formation in the cell cycle*

We have mapped the cell cycle of bloodstream stage trypanosomes with respect to organelle segregation/formation. The aim was to temporally monitor the formation of a new endosome. Surprisingly, endosome formation starts relatively early during the cell cycle, however, the 'new' endosome is not yet functional. The gain of endosomal function is directly connected to the maturation of the new flagellar pocket that occurs rather late in the cell cycle. Thus, we face the interesting phenomenon of having two endocytosis machineries, only one of which is active.

- *Comparative evolutionary analysis of vertebrate trypanosomes*

Trypanosomes infect an extraordinarily wide range of vertebrates. We have postulated that a long period of coevolution with highly diverse hosts has shaped the trypanosome cell surface. We are exploring the evolution of cell surface processes in unicellular eukaryotic parasites and are detailing the cell surface architecture of a representative set of species, quantifying membrane dynamics, endocytic recycling and cell motility. These approaches are being combined with genome sequencing, transcriptome analyses and glycoproteomics in order to correlate this information with trypanosome virulence, phylogenetic position and host range.

SELECTED PUBLICATIONS

- *Zaburdaev V, Uppaluri S, Pfohl T, Engstler M, Friedrich R, Stark H (2011) Langevin dynamics deciphers the motility pattern of swimming parasites.* ***Physical Review Letters*** *106:208103*
- *Uppaluri S, Nagler J, Stellamanns E, Heddergott N, Herminghaus S, Engstler M, Pfohl T (2011) Impact of microscopic motility on the swimming behavior of parasites: straighter trypanosomes are more directional.* ***PLoS Computational Biology*** *7:e1002058*
- *Subota I, Rotureau B, Blisnick T, Ngwabyt S, Durand-Dubief M, Engstler M, Bastin P (2011) ALBA proteins are stage regulated during trypanosome development in the tsetse fly and participate in differentiation.* ***Mol Biol Cell*** *22:4205-4219*

EXTRAMURAL FUNDING

- *DFG grant: Molecular analysis of fast endocytosis and membrane recycling in Trypanosomes*
- *DFG SPP1207: Nature inspired fluid mechanics*
- *DFG GRK1114: Lateral diffusion and correlation of membrane anchored proteins in various length scales*
- *DFG GRK1114: 4D-tracking pathogener Mikroorganismen mittels digitaler In-line Holographie*
- *DFG PAK296: Antibody clearance as virulence factor in African sleeping sickness*
- *DFG SFB630: Recognition, Preparation, and Functional Analysis of Agents against Infectious Diseases. Project: VSG as unexpected drug target for sleeping sickness*

4 ZINF members associated with other institutes
4.4 Department of Botany II

CONTACT DETAILS

Prof. Dr. Ute
Hentschel Humeida

Lehrstuhl für Botanik II
Julius-von-Sachs-Institut für Biowissenschaften
Julius-von-Sachs-Platz 3
97082 Würzburg

Phone: +49-931-3182581
E-Mail: ute.hentschel@uni-wuerzburg.de
www.bot2.biozentrum.uni-wuerzburg.de/wissenschaftforschung/hentschel/

RESEARCH GOALS

- *Microbe-host interactions*
- *Genomic analysis of the marine sponge microbiome*
- *Discovery of novel anti-infectives from marine actinomycetes*

Summary

Marine sponges (phylum Porifera) often contain dense and diverse microbial communities, which can comprise up to 35% of the animal's biomass. The remarkable microbial and chemical diversity, coupled with the postulated ancient nature of the sponge-microorganism association, make sponges important model systems for the study of metazoan host-microorganism evolution. In addition, the exploration of this relationship provides access to biotechnologically important symbiont-derived natural products. Sponges are considered valuable systems for the study of high-diversity marine host- microorganism associations, much like the human gut for terrestrial systems. With the aid of next-generation sequencing technologies, a clearer picture of the microbial diversity in these hosts is being obtained and the factors that influence this diversity are being identified. We are currently using metagenomic and single-cell genomic methods to investigate the metabolic capabilities of sponge-associated microorganisms. A second major focus of the lab is the discovery of novel, anti-infective drugs from the marine sponge associated microbiota.

Major Research

- *Diversity and function of the marine sponge microbiome*

Many marine sponges (Porifera) are associated with large amounts of microorganisms that can contribute up to 35% of the animal's biomass (Fig. 1). We aim to characterize the microbial community within sponges and to investigate the factors that are responsible for its formation. Cultivation-independent, 16S rRNA gene based studies as well as amplicon sequencing have revealed a phylogenetically complex, yet strikingly uniform microbial signature in sponges from the different oceans. Members of the sponge-specific microbiota are metabolically active and permanently associated with their sponge host. This approach has identified a novel candidatus phylum 'Poribacteria' and single cell genomic analysis has provided the first functional insights into the genomic repertoire of this elusive candidate phylum. Metagenomic libraries constructed from sponge-associated microbial consortia serve as 'genomic store-houses' that are probed for metabolic and/ or other functional genes of interest. These efforts have revealed microbial nitrification as a major pathway in sponges as well as eukaryote-domain containing proteins as putative players in mediating host-microbe interactions.

In order to investigate the vertical symbiont transmission via the sponge reproductive stages, underwater settlement experiments using Scuba diving were performed in the Florida Keys. Molecular and microscopical analysis of different reproductive stages has shown that the entire microbiota is vertically transmitted. This improved our understanding of the mechanistic aspects of vertical transmission, particularly during the early phases shortly after fertilisation and the later stages after larvae morphogenesis. Clearly, the transmission of symbionts through the larvae is an important, wide-spread and possibly evolutionarily ancient mechanism for the establishment of the sponge-microbe association.

In addition to harbouring beneficial symbionts, sponges can succumb to disease, which has been speculated to be caused by marine pathogenic bacteria. We have thus turned our attention to two sponge diseases using the Caribbean sponges *Xestospongia muta* and *Amphimedon compressa* as experimental models. We have shown that severe degradation in the outer tissue layers and loss of cyanobacterial symbionts occurs in *X. muta*. Reinfection experiments were performed for both sponge species to test Koch's postulates in the sponge model, but failed to demonstrate infectivity. In fact, to this date, we have not observed a correlation between sponge disease and an infectious agent. We therefore postulate that sponge bleaching is most likely linked to stress afflicted by globally increasing ocean temperatures.

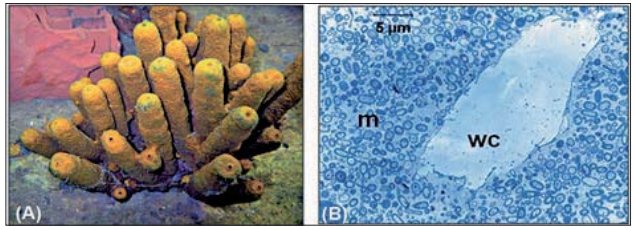


Fig. 1: The Mediterranean sponge Aplysina aerophoba. Underwater photograph (A), transmission electron micrograph (B) and phylogenetic tree (C) showing the diversity of sponge-specific symbionts. m = microorganisms, wc = water canal.

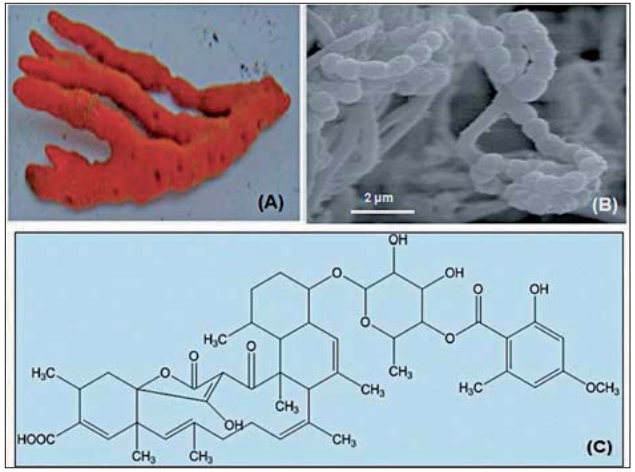


Fig. 2: The mediterranean sponge Axinella polyploides (A), source of the novel bacterial species, Streptomyces axinellae, (B) from which four new tetromycin derivatives with pronounced anti-trypanosomal and protease inhibitory activities were isolated (C).

- *Plant-microbe interactions*

Surprisingly little is known about the microbial ecology of the plant phyllosphere, which is defined as the cumulative habitat of plant leaf surfaces. Considering the sheer size of the phyllosphere (globally estimated at 6.4 x 10^8 km^2) and its importance for the function of the world's ecosystem, the characterisation of its microbiology is a worthwhile endeavour. We have compared the microbial populations of native plants with experimentally or genetically altered lines, such as, those with altered cuticular wax compositions (in collaboration with M. Riederer, U. Hildebrandt, University of Würzburg). This comparative approach has revealed how specific plant leaf properties help shape the composition of their microbial associates. In addition we are focusing on identifying specific interactions between microbes and plants.

- *Novel Anti-infectives*

Sponges and plants, particularly tropical ones, are known as rich sources of secondary metabolites with bioactive activities, however, in this regard the associated microorganisms are far less studied. We have established an extensive strain collection of sponge-associated actinomycetes, which were subsequently screened against clinically relevant microbial pathogens and parasites. This required the use of novel screening assays, such as anti-protease (T. Schirmeister, University of Mainz) and immunomodulatory activities (T. Hünig, University of Würzburg). The elucidation of the selected compounds structures was performed in close collaboration with an organic chemistry group (G. Bringmann, University of Würzburg). So far, several bioactive compounds, such as four new tetromycin derivatives from a novel bacterial species, *Streptomyces axinellae*, were discovered with this interdisciplinary approach (Fig. 2). In order to render the large fraction of uncultivated sponge-associated microbiota accessible for small molecule discovery, metagenomic strategies were employed, which identified gene clusters encoding for type I polyketide synthases (PKS-I), non-ribosomal peptide synthases (NRPS) as well as halogenase genes.

SELECTED PUBLICATIONS

- *Angermeier H, Kamke J, Abdelmohsen UR, Krohne G, Pawlik JR, Lindquist NL, Hentschel U (2011) The pathology of sponge orange band disease affecting the Caribbean barrel sponge Xestospongia muta.* ***FEMS Microb Ecol*** *75(2):218-230*
- *Pimentel-Elardo SM, Buback V, Gulder TA, Bugni TS, Reppart J, Bringmann G, Ireland CM, Schirmeister T, Hentschel U (2011) New tetromycin derivatives with anti-trypanosomal and protease inhibitory activities.* ***Mar Drugs*** *9(10):1682-97*
- *Schmitt S, Hentschel U, Taylor MW (2011) Deep sequencing reveals diversity and community structure of complex microbiota in five Mediterranean sponges.* ***Hydrobiologia*** *doi:10.1007/s10750-011-0799-9*
- *Siegl A, Kamke J, Hochmuth T, Piel J, Richter M, Liang C, Dandekar T, Hentschel U (2010) Single cell genomics reveals the lifestyle of Poribacteria, a candidate phylum symbiotically associated with marine sponges.* ***ISME J*** *5(1):61-70*
- *Siegl A, Hentschel U (2010) PKS and NRPS gene clusters from microbial symbiont cells of marine sponges by whole genome amplification.* ***Environ Microbiol Rep*** *2:507-513*

EXTRAMURAL FUNDING

- *DFG SFB630: Recognition, preparation and functional analysis of agents against infectious diseases. Project: Novel anti-infective substances from marine sponge-associated microbiota*
- *DFG GRK1342: Molecular and functional analysis of lipid-based signal transduction systems. Project: The role of cuticular lipids in plant surface/microbe interactions*
- *DFG SFB567: Mechanisms of specific interactions between organisms. Project: Investigations on the symbiosis of the sponge Aplysina aerophoba with associated microorganisms*
- *DFG HE 3299/1-3: Investigations on co-evolution between marine sponges (Porifera) and associated microorganisms*

4 ZINF members associated with other institutes
4.5 Rudolf Virchow Center

CONTACT DETAILS

Prof. Dr. Caroline Kisker

Head of Structural Biology Division
Rudolf-Virchow-Zentrum
Universität Würzburg
Josef-Schneider-Str. 2 / Building D15
97080 Würzburg

Phone: +49-931-3180380
E-Mail: Caroline.Kisker@virchow.uni-wuerzburg.de
virchow.uni-wuerzburg.de/kiskerlab/

RESEARCH GOALS

- *Identification and improvement of novel inhibitors against human pathogens*
- *Structural and functional characterization of essential components of human pathogens*
- *Characterization of protein - ligand interactions*

Summary

Tuberculosis, an infectious disease caused by *Mycobacterium tuberculosis*, remains one of the leading causes of death in the world. In 2008 there were approximately 10 million new infections and 1.3 million people died from this disease. According to the World Health Organization roughly one third of the world's population is infected. The rapid emergence of dangerous multi-, extensively- and lately also totally drug resistant *M. tuberculosis* strains (MDR-TB, XDR-TB and TDR-TB, respectively) prohibit the effective cure of the disease and renders it a global health threat. Consequently, the identification of new drug targets and the development of novel TB chemotherapeutics that circumvent existing drug resistance mechanisms are urgently needed. Mycobacteria contain a unique cell wall which consists, among other molecules, of mycolic acids, very long chain fatty acids that provide protection and allow the bacteria to persist in the human macrophage. Inhibition of mycolic acid biosynthesis impairs the integrity of the cell wall which is essential for the viability of the bacteria. KasA and InhA are key enzymes involved in the biosynthesis of long-chain fatty acids within the bacterial type II fatty acid biosynthesis (FAS-II) pathway. This pathway shares only low homology with the mammalian FAS-I system, and is a validated target for the development of new drugs. Isoniazid, a front-line prodrug for the treatment of tuberculosis, and the antimicrobial agent triclosan demonstrate the clinical applicability of FAS-II inhibitors. These compounds were shown to inhibit the trans-2-enoyl ACP reductase InhA, which catalyzes the last and rate-limiting step of each fatty acid elongation cycle. Our work has focused on understanding the inhibition mechanism of InhA and KasA by small molecules using both kinetic and structural studies. These have been used as a basis for structure based drug design approaches to optimise the chemical properties of the compounds required for in vivo drug activity. We are using a similar approach to develop new inhibitors against these enzymes in collaboration with the group of Peter Tonge, (Stony Brook University, NY), and within the Collaborative Research Center 630.

Major Research

- *Structure based drug design of novel InhA inhibitors*

We initially characterized the FASII enoyl-ACP reductase, InhA and the corresponding enzyme, FabI, from *Escherichia coli* in the presence of the antimicrobial agent triclosan to decipher why this molecule is a slow tight binding inhibitor of the *E. coli* enzyme with a Ki of 7 pM, whereas it is an uncompetitive inhibitor of InhA associating with a Ki of 0.2 µM. Structural analysis of the complexes revealed that a substrate-binding loop becomes ordered in the *E. coli* enzyme when the inhibitor was bound whereas it remained disordered in the InhA triclosan bound structure. Our ongoing structure based drug design efforts have resulted in a series of triclosan analogs - alkyl-diphenyl ethers that are nanomolar inhibitors of InhA, with activity against drug resistant strains of *M. tuberculosis*. However, they remained rapid reversible inhibitors with a short residence time and our structures revealed that the substrate-binding loop remained disordered. We have therefore further modified the alkyl-diphenyl ethers in a rational manner to promote interactions between the inhibitor and the substrate-binding loop. The resulting inhibitor, PT70, showed an improved affinity in the picomolar range for InhA compared to the first generation compounds. In addition, PT70 is a slow onset inhibitor of InhA with a significantly improved residence time of 24 min, which is 14,000 times longer than the parent compound. This increased drug-target residence time is an important parameter in determining potential *in vivo* drug activity. The 1.8 Å crystal structure of the ternary InhA-NAD+-PT70 complex revealed the molecular details of enzyme-inhibitor recognition. It also supported our hypothesis that slow onset inhibition is coupled to ordering of the substrate binding loop, which leads to closure of the substrate binding pocket. Slow binding and improved residence time are expected to result in significant improvements towards *in vivo* antibacterial activity.

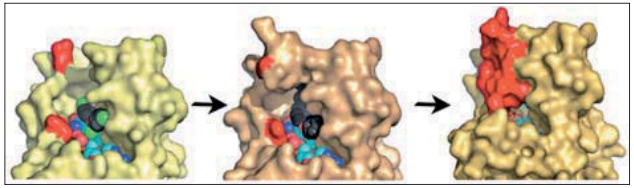


Fig. 1: View into the active site of InhA in the presence of the inhibitors triclosan (left), the alkyl diphenylether 8PP (middle) and PT70 (right). Only in the presence of PT70 the substrate binding loop becomes ordered.

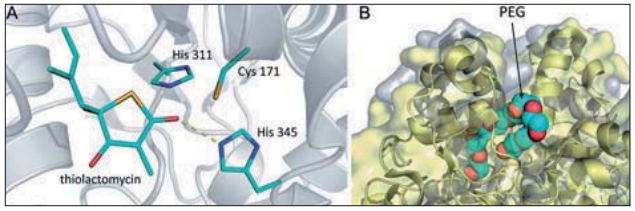


Fig. 2: (A) The active site of KasA in the presence of the inhibitor thiolactomycin. The active site residues His 311, Cys 171 and His 345 as well as the inhibitor are highlighted. (B) Ribbon presentation of KasA. The bound PEG molecule which provides a view into the hydrophobic acyl binding cavity is shown in all bonds presentation.

- *Characterization of the β-ketoacyl ACP synthase I KasA*

We determined the first structure of the beta-ketoacyl-acyl carrier protein synthase, KasA, in its apo-form and bound to thiolactomycin (TLM), a natural product thiolactone isolated from *Nocardia sp*. This inhibitor is a promising lead compound since it displays favourable physicochemical properties, has shown to be effective in mouse infection models, is a reversible KasA inhibitor and inhibits Gram-positive and Gram-negative bacteria. Furthermore it has been shown that TLM displays only low affinity for the FAS-I system. KasA catalyzes the condensation between malonyl-AcpM and the growing acyl chain via a ping-pong mechanism. In the first step an acylated KasA intermediate is generated through a transfer of the acyl chain to the active site cysteine. In the second step the acyl chain is elongated by two carbons through the second substrate malonyl AcpM in a condensation reaction with the intermediate. Previous work has shown that the inhibitor can bind to the apo and the acylated form of the enzyme. We therefore solved the structures of KasA with TLM utilizing an acyl-enzyme mimic represented by a Cys171Gln variant and the wild-type enzyme. Our structures provide the first clues for the preferential binding of TLM to the acylated form of the enzyme. Furthermore, detailed insights have been obtained into the interaction of the inhibitor with KasA and reveal the importance of the TLM isoprene moiety for KasA inhibition.

Two of our structures revealed an additional unexpected feature and clearly defined the acyl-binding channel in KasA due to the presence of bound polyethylene glycol molecules, mimicking an acyl chain of about 40 carbons in length. Our structures provide a view into the hydrophobic acyl binding cavity, which contains numerous hydrophobic amino acids and thereby ideally accommodates the growing fatty acid chain. A comparison with the homologous enzyme from *E. coli*, which synthesizes only short chain fatty acids, revealed that the acyl-binding pocket is significantly truncated in the *E. coli* enzyme. In KasA, side-chain and backbone atoms from an α-helix are reoriented and thereby permit binding of longer acyl chain substrates. Additionally, long polar side chains point into the channel in the *E. coli* structure, thereby blocking further access while in KasA short hydrophobic side chains facilitate fatty acid binding. Importantly, the polyethylene glycol molecule is in close proximity to the bound TLM molecule. Based on these results one possibility for the development of improved lead compounds is a combination of a polyethylene glycol moiety with a TLM derivative to increase its specificity.

SELECTED PUBLICATIONS

- *Schaefer B, Kisker C, Sotriffer CA (2011) Molecular dynamics of Mycobacterium tuberculosis KasA: implications for inhibitor and substrate binding and consequences for drug design.* ***J Comput Aided Mol Des*** *25:1053-69*
- *Lee W, Luckner SR, Kisker C, Tonge PJ, Engels B (2011) Elucidation of the Protonation States of the Catalytic Residues in mtKasA: Implications for Inhibitor Design.* ***Biochemistry*** *50:5743-5756*
- *Luckner SR, Liu N, Am Ende CW, Tonge PJ, Kisker C (2010) A slow, tight-binding inhibitor of InhA, the enoyl-ACP reductase from Mycobacterium tuberculosis.* ***J Biol Chem*** *285:14330-14337*
- *Machutta CA, Reddy BG, Luckner SR, Kapilashrami K, Ruzsicska B, Simmerling C, Kisker C, Tonge PJ (2010) Slow onset inhibition of bacterial {beta}-keto-acyl-ACP synthases by thiolactomycin.* ***J Biol Chem*** *285:6161-9*
- *Luckner SR, Machutta CA, Tonge PJ, Kisker C (2009) Crystal structures of Mycobacterium tuberculosis KasA show mode of action within cell wall biosynthesis and its inhibition by thiolactomycin.* ***Structure*** *17:1004-1013*

EXTRAMURAL FUNDING

- *DFG SFB630: Identification, isolation and functional analysis of anti-infective compounds. Project: 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*
- *Rudolf Virchow Center for Experimental Biomedicine – DFG Research Center, FZ82*
- *DFG-Ki562: The structural and functional characterization of the XPD and UvrA-UvrB proteins involved in Nucleotide Excision Repair*

AWARDS AND PRIZES

- *2011 - Elected member of the German National Academy of Sciences Leopoldina*

4 ZINF members associated with other institutes
4.6 Department of Tissue Engineering and Regenerative Medicine

CONTACT DETAILS

Prof. Dr. Heike Walles

Lehrstuhl Tissue Engineering und
Regenerative Medizin
Röntgenring 11
97070 Würzburg

Phone: +49-931-3188828
E-Mail: heike.walles@uni-wuerzburg.de
www.term.uk-wuerzburg.de/

RESEARCH GOALS

- *Tissue Engineering of skin, liver, intestine, trachea, heart valves and blood vessels*
- *Development of biological scaffolds*
- *Establishment of 3D organoid test and disease models for preclinical studies*
- *Regenerative Medicine: GMP-conformed development of transplants and cell therapeutics (ATMPs), planning and organization of preclinical and clinical studies phase I/II*

Summary

Tissue engineering and regenerative medicine is an emerging multidisciplinary field involving biology, medicine, and engineering, it has therapeutic applications, where tissue is grown either in a patient or outside the patient before being transplanted. In addition, diagnostic applications have been developed where the tissue is generated in vitro and used for testing drug uptake and metabolism, toxicity, and pathogenicity as an alternative system to animal experiments. The tissue engineering and regenerative medicine group focuses mainly on the development of human *in vitro* test systems that reflect important properties of the human body that enable investigations according to the ADMET-criteria (Absorption, Distribution, Metabolism, Excretion, Toxicity). This involves the development of novel biomaterials, bioreactors, and co-cultivation of different primary and stem cells. By combining these technologies human tissue models reflecting normal and pathological situations can be designed in order to investigate the underlying molecular mechanisms that cause distinct infectious diseases. In addition, the Fraunhofer Project Group "Regenerative Technologies for Oncology" is also integrated within the department. This group uses a natural scaffold (BioVaSc®) for the generation of vascularized tissue models *in vitro*. These models provide the methodological basis for numerous collaborations within the medical faculty as well as the ZINF and will be used for the development of new diagnostic methods in as well as individual treatments of inflammatory, tumorigenic or infectious diseases.

Major Research

- *Bioreactor technology*
  (J. Reboredo, T. Schwarz)

One of the aims of tissue engineering is to maintain the physiological function of the cells or tissues *in vitro* for a longer period of time than is possible in simple 2-D cultures. To achieve this, the cell's microenvironment *in vivo* must be closely mimicked *in vitro*. This includes a sufficient nutrient supply, the stimulation of cells with specific growth factors and cytokines, the provision of a carrier/extracellular matrix structures as well as mechanical signals, which vary from tissue to tissue in type and intensity. Studies have shown that mechanical parameters such as media flow, rotation, tension, extension or pulsation stress are critical for the development of bioartificial tissues. Our group has longstanding experience and expertise in the development and design of both bioreactors and computer-controlled incubator systems for tissue engineering and regenerative medicine (Fig. 1). In the last two years the complete bioreactor layout was also established in collaborating laboratories such as the Technical University Berlin, the University of Natural Resources and Applied Life Sciences (BoKu) in Vienna, Austria and University of Bergen, Norway.

- *Development of biomaterials and vascularized human tissue models*
  (A. Appelt, G. Dandekar, M. Haddad-Weber, H. Kirch, M. Metzger, C. Moll, S. Nietzer, J. Reboredo, M. Schweinlin)

In vivo cells and tissues of multi-cellular organisms are embedded within a natural extracellular matrix (ECM) consisting of many different proteins such as collagen and fibronectin. Thus, while the ECM acts primarily as a support structure for the cells it is also involved in additional functional tasks such as the control of proliferation, differentiation or apoptosis. Our group develops both synthetic and biological-based matrices that are specifically adapted to mimic the *in vivo* microenvironment of selected tissues (Fig. 2). We have previously established a process for manufacturing a collagen matrix with a persisting blood circulation system (BioVaSc® technology). The matrix is based on a modified acellular porcine intestine, with intact blood vessel structures. To establish 3D test systems the BioVaSc® matrix was seeded not only with tissue specific cells but also tumor cells. Therefore, for the first time it is possible to investigate *ex vivo* the role of the blood vessel system during the development of cancer, inflammatory or infectious diseases. Based on the BioVaSc® technology, intestinal, lung, trachea and blood-brain-barrier models have also been established and functionally tested. In projects funded by the BMBF (PeTrA and LipoTrans) these human intestinal tissue models have been used to evaluate the ability of different nanomaterial- or polymer-based formulations to transport low bioavailable drugs such as lipophilic substances across the gut or blood-brain barrier.

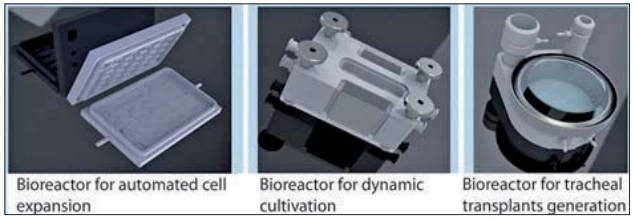


Fig. 1: Examples of various bioreactor prototypes used in the tissue engineering department.

- *Use of tissue engineered human 3D cultures in infectious research*
  (A. Appelt, M. Bonn, S. Kurdyn, M. Metzger, C. Moll, J. Nickel, M. Schweinlin)

There are many potential applications of the human 3D culture models to infectious disease research in order to analyze the interaction of bacteria, viruses or yeast with eukaryotic host cells. The 3D tissue equivalents offer a simple but efficient model to monitor the different steps of an infection without the need for testing in animals, they also facilitate drug-screening procedures. In addition, the study of pathogen effectors and host targets involved in infections can be studied by the inclusion of specific immune components. The group currently has several local collaborative projects that include: (i) Human blood-liquor model to analyze infection with *N. meningitidis 2390* (Dr. Schubert-Unkmeir), (ii) Human intestinal barrier model to analyze probiotic enterobacteria interactions (Dr. Ölschläger) and salmonella infection (Prof. Vogel), (iii) Human lower airway tissue models to study interrelations with respiratory syncytial viruses and bacteria (Prof. Gross, Dr. Krempl), (iv) Human skin models to analyze Graft versus Host Diseases (GvHD) (PD Dr. Mielke) and sleeping sickness by *Trypanosoma brucei* (Prof. Dr. Engstler)

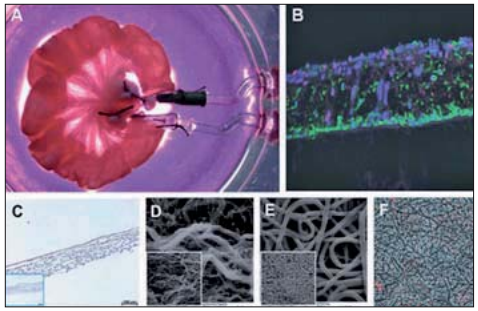


Fig. 2: (A) The biological vascularized scaffold (BioVaSc®) used as basis for the generation of autologuous transplants as well as human tissue and disease models. (B) Example: Immunohistological characterisation of a BioVaSc® human neurofibromatosis (NF-1) model (red: anti-p53, green: anti-CD44, blue: DAPI). (C) Section through an acellularized BioVaSc segment (small intestinal submucosa = SIS). (D) Electron microscopy of BioVasc/SIS. (D) Biodegradable, electrospinned PLGA scaffold coated with basal lamina components (fibronectin, collagen IV, laminin) mimicking the natural SIS matrix (in cooperation with Prof. J. Groll, Department for functional materials in medicine and dentistry). (F) N. meningitidis 2390 pathogen (red dots) can bind on laminin and fibronectin of spinning matrix (in cooperation with Dr. Schubert-Unkmeyer, Institute for Hygiene and Microbiology)

- *Fraunhofer Project group "Regenerative technologies for oncology"*
  (G. Dandekar, S. Kurdyn, M. Metzger, S. Nietzer, J. Nickel)

The experimental research and development focuses on the isolation and characterization of human (tumor-) stem cells isolated from intestinal mucosa as well as the enteric nervous system. These cells are being used to construct complex human vascularized tumor tissues. In the EU-funded project "Skinheal", methods will be used to characterize a vascularized human skin melanoma model in terms of metastatic processes.

SELECTED PUBLICATIONS

- *Pusch J, Votteler M, Göhler S, Engl J, Hampel M, Walles H, Schenke-Layland K (2011) The physiological performance of a three-dimensional model that mimics the microenvironment of the small intestine.*
  ***Biomaterials** 32(30):7469-78*
- *Schanz J, Pusch J, Hansmann J, Walles H (2010) Vascularised human tissue models: A new approach for the refinement of biomedical research.*
  ***J Biotechnol** 1;148(1):56-63*
- *Mertsching H, Schanz J, Steger V, Schandar M, Schenk M, Hansmann J, Dally I, Friedel G, Walles T (2009) Generation and transplantation of an autologous vascularized bioartificial human tissue.*
  ***Transplantation** 27;88(2):203-10*
- *Schanz J, Hampel M, Mertsching H, Walles T (2009) Experimental tracheal patching using extracellular matrix scaffolds.*
  ***Ann Thorac Surg** 87(4):1321-2*
- *Mertsching H, Hansmann J (2009) Bioreactor technology in cardiovascular tissue engineering.*
  ***Adv Biochem Eng Biotechnol** 112:29-37*

EXTRAMURAL FUNDING

- *Frauenhofer Future Foundation: Tissue Engineering on Demand*
- *State Bavaria Program 'BayernFit': Regenerative Technologies in Oncology*
- *EU large scale project: VascuBone*
- *BMBF grant: Bioartificial Trachea*
- *Mildred Scheel Foundation: 3-D Tumor progression of malign melanomas*
- *BMBF grant: PeTrA*

AWARDS AND PRIZES

- *2009 - Fraunhofer award: Technics for human beings*

5 Research Programmes and Teaching
5.1 SFB 630: Identification, Preparation and Functional Analysis of Agents against Infectious Diseases

CONTACT DETAILS

Coordinating Speaker:
Prof. Dr. rer. nat. Dr. h.c.
Gerhard Bringmann
Institut für Organische Chemie
Am Hubland
97074 Würzburg
Phone: +49-931-3185323
bringman@chemie.uni-wuerzburg.de

Vice Speaker:
Prof. Dr. rer. nat. Ulrike Holzgrabe
Lehrstuhl für pharmazeutische Chemie
Am Hubland
97074 Würzburg
Phone: +49-931-3185460
u.holzgrabe@pharmazie.uni-wuerzburg.de

Vice Speaker:
Prof. Dr. rer. nat. Dr. med. habil.
Heidrun Moll
Institut für Molekulare Infektionsbiologie
Josef-Schneider-Str. 2 / D15
97080 Würzburg
Phone: +49-931-3182627
heidrun.moll@uni-wuerzburg.de

General Information

The fight against infectious diseases is of even increasing importance these days, in developing countries as well as in industrial settings due to the massive occurrence of resistances. The goal of the SFB 630 is to contribute to the development of urgently needed novel anti-infective drugs.
Three distinct project areas cover the different aspects of the agent-based anti-infectives research. In project area A, novel compounds are prepared and characterized regarding their physico-chemical properties. The evaluation of the anti-infective potential of all compounds against a variety of clinically relevant pathogens is one task of the Central Laboratory that is performed under the regiment of a profound quality management system. The detailed interaction of active agents with cellular compartments and biological molecules of the pathogens are analyzed in project area B. Virtual screening, theoretical calculations and modellings of their mode of action based on the three dimensional structure of the target in project area C allow the rapid optimization of the anti-infective activities.

Project Area A
Prof. U. Holzgrabe (A1)
Prof. Dr. h.c. G. Bringmann (A2)
Prof. T. Schirmeister (A4)
Prof. U. Hentschel Humeida (A5)

Project Area B
Prof. J. Morschhäuser (B2)
Prof. H. Moll, Dr. U. Schurigt (B3)
PD K. Ohlsen, Prof. P. Jakob (B5)
Prof. C. Kisker (B7)
Prof. M. Engstler (B8)
Prof. T. Rudel, Dr. V. Kozjak-Pavlovic (B9)

Project Area C
Prof. B. Engels (C3)
Prof. C. Sotriffer (C7)

Central Laboratory
Dr. T. Ölschläger, Prof. A. Stich, Prof. Dr. L. Meinel (Z1)

Major Research Interests

The research in the SFB focuses on the development of new drugs against infections caused by trypanosomes, *Leishmania*, plasmodia, Staphylococci, especially MRSA, mycobacteria, *Candida*, *Neisseria*, and *Chlamydia*. In target-based approaches, the agents are designed to inhibit a cellular process or even a specific enzyme essential for the pathogen. Knowledge of the three dimensional structure of the target allows modeling, docking and quantum mechanical calculations to propose a tailored inhibitor molecule for the chemical synthesis. Validated target structures comprise proteinases of trypanosomes, *Leishmania* and plasmodia (A4, B3, B7, C3, C7), the causative agents of sleeping sickness, leishmaniasis and malaria, respectively. Furthermore, surface molecules responsible for adhesion, invasion or the evasion of the human immune system (in *Neisseria*, B9 and trypanosomes, B8), the fatty acid synthesis pathway that is essential for cell wall building in mycobacteria (B7, A1, C7) and efflux pumps that mediate drug resistance in the opportunistic human pathogen *Candida albicans* (A1, B2) are targeted.
Additionally, ligand-based approaches in which the molecular target is unknown lead to highly active and selective anti-infectives. Not only synthetic and recombinatoric chemistry, but also plant extracts and sponge-associated actinomycetes are used as rich sources for novel agents. Naphthylisoquinolines for example, which originally were derived from tropical lianas, are active against and selective for various parasites and bacteria species (A1, B3, B5, B8) depending on the individual structure of the molecule. In *Leishmania*, naphthylisoquinolines are shown to accumulate in acidic vesicles and provoke autophagocytosis (A2, B3). Fluoroquinoline amides and bisnaphthalimides display prominent trypanosomicidal properties (A1, B9), The anti-trypanosomal activity of bisnaphthalimides corresponds to their DNA-binding capability, whereas that of the fluoroquinolines is – rather unexpectedly – independent of the process of DNA replication (A1, B5, B9). Their detailed mode of action is under particular investigation.
So far, several compounds of different structural classes were shown to exhibit excellent activities and low cytotoxic effects. These lead structures are further analyzed regarding their pharmacokinetic properties (Z1) and their efficiency in animal models (B3, B5, B9) - also with sophisticated *in vivo* imaging techniques (B5) - in order to develop them towards true candidates for clinical trials.

5 Research Programmes and Teaching
5.2 SFB 567 Mechanisms of Interspecific Interactions of Organisms

CONTACT DETAILS

Professor Dr. rer. nat. Markus Riederer
(Speaker)
Julius-von-Sachs-Institut for Biosciences
Julius-von-Sachs-Platz 3
97082 Würzburg
Phone: +49-931-3186200
E-Mail: sfb-567@botanik.uni-wuerzburg.de
www.sfb567.uni-wuerzburg.de

General Information

The Coordinated Research Centre (Sonderforschungsbereich, SFB) 567 "Mechanisms of Interspecific Interactions of Organisms" at the Julius-Maximilians-Universität Würzburg was established to provide a substantial multidisciplinary contribution to the investigation of interactions between organisms belonging to different species – symbioses in a broader sense. This will be achieved by investigating interacting systems from a wide spectrum of species and over several levels of organization. The integrative approach will combine molecular and organismic biology with an aim to strengthen and intensify the technical and conceptual exchange between these two mainstream fields of modern biology represented by various disciplines within three faculties (biology, medicine, chemistry and pharmacy).

Major Research Interests

The 13 projects are utlilising approaches based on physiology, molecular biology, ecology, evolutionary biology and biophysics. A broad systematic spectrum of interaction systems are being analyzed by applying techniques from infectious biology, phytopathology and analytical chemistry in order to address the following central questions:

- What are the mechanisms underlying interspecies recognition in different interaction systems?
- What kind of information flow is required for the establishment and maintenance of interactions?
- How is the flow of information and resources generated within the interaction partners and how is it finally transmitted?
- What is the role of the phenotypic plasticity of the partners with respect to establishment and maintenance of interaction?
- What are the molecular, morphological and behavioural adaptations that can be explained as an evolutionary consequence of interaction?

Only the comparative assessment and integration of results based on a wide range of levels of complexity can elucidate common principles, characteristics and benefits of symbioses.

The SFB 567 is subdivided into three project areas: "Recognition and Reaction", "Signals in the Interaction Partners" and "Continuity and Evolution". It includes projects involving the ZINF members Prof. Dr. Roy Gross (Department of Microbiology) and Prof. Dr. Ute Hentschel Humeida (Department of Botany II).

- *Recognition and Reaction*

This project area focuses on signals that lead to the unilateral or mutual recognition of interaction partners and investigates mechanisms involved in the development of compatibility or incompatibility between organisms of different species. This includes the analysis of characteristics affecting the recognition of hosts and non-hosts and pathogen defense reactions in plant and animal systems on the molecular and cellular scales.

- *Signals in the Interaction Partners*

The central objects of investigation in this project area are the signals and resulting adaptations that are formed within organisms as a response to biotic interaction.

- *Continuity and Evolution*

This project area is concerned with the regulation and maintenance of interspecific interactions, investigating a broad spectrum of tight and obligate symbiotic systems. Regulatory aspects of even intracellular symbioses (bacteria/ants, microbes/sponges) and mutual interactions of more than two partners (plant/bee/herbivore) are analyzed.

5 Research Programmes and Teaching
5.3 SFB 581: Molecular models for diseases of the nervous system

CONTACT DETAILS

Project Area A5:
Prof. Dr. rer. nat. Thomas Hünig
Institut für Virologie und Immunbiologie
Versbacher Straße 7
97078 Würzburg
Phone: +49-931-201-49951
E-Mail: huenig@vim.uni-wuerzburg.de

Project Area A9:
Prof. Dr. rer. nat. Manfred Lutz
Institut für Virologie und Immunbiologie
Versbacher Straße 7
97078 Würzburg
Phone: +49-931-201-49957
E-Mail: m.lutz@vim.uni-wuerzburg.de

Project Area A5 (Thomas Hünig)

- *Release and therapy of ovalbumin-specific experimental autoimmune encephalomyelitis*

It is becoming increasingly clear that besides the well studied subsets of proinflammatory CD4 T-cells, CD8 T-cells also contribute to the pathogenesis of multiple sclerosis (MS).

Within the past funding periods of this SFB project, a transgenic mouse line was generated which expresses the model antigen ovalbumin (OVA) selectively as a cytoplasmic protein in oligodendrocytes. Apparently, the antigen is well sequestered, because introduction of a transgenic, MHC II-restricted Ova-specific TCR (OT-II) does not result in negative selection or peripheral activation of CD4 T-cells.

In contrast, double transgenic mice expressing the ODC-OVA transgene together with an MHC I-restricted TCR (OT-I) undergo fulminant experimental autoimmune encephalomyelitis (EAE) with a penetrance of about 90%. Additional inactivation of the RAG-1 gene, which blocks the development of additional lymphocytes besides those expressing OT-I, increases the penetrance of disease to 100%. The reason why CD8 (but not CD4) T-cells are pathogenic in this system is their capacity to recognize peptide fragments derived from the cytosolic antigen (OVA) presented by MHC class I, and thus to attack the oligodendrocytes.

In this model system for the role of CD8 cells in MS, we have recently shown that it is, in principle, possible to block activation and cytotoxic effector function of this cell type with monoclonal antibodies directed specifically at the autoantigen (here: OVA) – derived peptide presented by an MHC I molecule. Such a blockade leaves other, non-autoimmune CD8 T-cells undisturbed in performing their important functions such as the destruction of virus infected cells.

While ODC-OVA/OT-I double transgenic mice develop motoric defects already two weeks after birth, we have not succeeded in inducing EAE in adult ODC-OVA mice by active immunization with OVA. Rather, OVA-specific CD8 T-cells are being eliminated in these mice after their activation in the periphery.

During the last funding period of the SFB, we want to elucidate the mechanism of this form of adult tolerance induction. We suspect that the central nervous system is uniquely equipped to destroy autoreactive CD8 T-cells in situ.

Project Area A9 (Manfred Lutz)

- *Presentation of cerebral glycolipids by dendritic cells on CD1d*

The activation of myelin peptide-specific CD4+ and CD8+ T cells leads after their invasion into the CNS of mice to the initiation of experimental autoimmune-encephalomyelitis (EAE). For this T cell activation mature dendritic cells (DC) as a major prerequisite as presenters of autoantigenic peptides. Recent evidence suggest that also glycolipids (GL) may serve as CD1-restricted antigens in autoimmune diseases such as multiple sclerosis (MS) and EAE. In addition oxidative stress and cerebral infections may induce oxidized GL that could serve as altered-self-ligands for pathogen receptors. By this DC can on one hand recognize these ligands through pathogen receptors and get activated but also present cerebral GL on CD1d molecules to NKT cells in an immunogenic fashion and thereby substantially contribute to EAE development. This would certainly be further enhanced in mice with cerebral virus infections. On the other hand tolerogenic DC and NKT cells could prevent EAE in a GL-specific manner.

The precise mechanisms of DC activations by oxidized glycolipids, the responsibe receptors involved in this, the role of a cerebral CNS infection as well as the DC mediated presentation of GL and the resulting auto-agressive or auto-protective GL-specific NKT cell responses are not fully understood.

By the use of CD1d-/- mice the effects of such activated DC can be studied in the context of EAE induction and in a murine model of cerebral measles infection. In an established model of EAE protection by tolerogenic DC we will then test GL antigens for their use in tolerance therapy. Aim of these studies is to get a deeper insight in the cooperation of oxidative autoimmune-mediated and infectious influences for the EAE induction as a model fpr neuro.inflammatory disorders such as MS.

5 Research Programmes and Teaching
5.4 Transregio-Collaborative Research Center 34, Pathophysiology of Staphylococci in the Post-genomic Era

CONTACT DETAILS

Deputy Coordinator site Würzburg:
PD Dr. rer. nat. Knut Ohlsen
Institut für Molekulare Infektionsbiologie
Josef-Schneider-Str. 2/D15
97080 Würzburg

Deputy Coordinator site Würzburg:
Prof. Dr. rer. nat. Thomas Rudel
Lehrstuhl für Mikrobiologie, Biozentrum
Am Hubland
97074 Würzburg

Coordinating Speaker:
Professor Dr. rer. nat. Michael Hecker
Institute für Mikrobiologie und Molekuarbiologie
Friedrich-Ludwig-Jahn-Straße 15
17487 Greifswald

www.uni-greifswald.de/forschen/sonderforschungsbereiche/staphylokokken.html

General Information

The aim of this SFB/Transregional collaborative research center (TR34) is to take advantage of the great opportunities offered by the post-genome era to achieve a new quality of understanding of the life processes of the important human pathogen Staphylococcus aureus. The research projects are grouped in four parts: in part A (5 projects), the general physiology of S. aureus is considered.
The regulation of cell-surface-bound and extracellular virulence factors is the focus of part B (3 projects). Project area C (7 projects) deals with the behaviour of the pathogen in the host. Part Z (4 projects) offer state of the art technologies to all projects to discover and analyze S. aureus metabolism and pathogenicity.

Projects involving members of the ZINF
PD Dr. K. Ohlsen (A2, Z3)
Prof. T. Dandekar (A8, Z1)
PD Dr. W. Ziebuhr (B4)
Prof. J. Vogel (B4)
Prof. T. Rudel (C11)

The projects of the groups in Würzburg deal especially with different aspects of host-pathogen interactions. Project part A2 studies eukaryotic-type serine/threonine protein kinases (ESTPKs) and protein phosphatases that are probably involved in the regulation of several physiological pathways.
In the A8 project, functional genomics technologies are used to identify concentrations and complex formation of proteins involved in central carbon metabolism. Furthermore, systems biology approaches will be applied to construct models which will allow prediction of key complexes and their roles in adaptation scenarios that are also of importance in infection settings.
A new and emerging field that is becoming the increasing focus in model bacteria such as E. coli and B. subtilis is the role of small regulatory RNAs in cell physiology. It can be expected that these crucial molecules also play a role in the control of virulence. This novel issue is being addressed in project part B4. Specifically, a sRNA was found that is encoded upstream of the ica-operon in S. epidermidis which is probably involved in the regulation of the ica-expression. This small RNA could thus influence pathogenicity via production of PIA (polysaccharide intercellular adhesin), synthesized by enzymes encoded by the ica-operon. Also, the search for novel sRNAs will be continued by applying state-of-the-art high-throughput sequencing to Staphylococcus strains and mutants currently under investigation within the collaborative research network. Subsequently, such new small regulatory RNAs can be analyzed for their role in cell physiology, stress adaptation, and virulence. The aim of project C11 is the molecular definition of host cytotoxicity induced during S. aureus infection. The signaling pathways responsible for cytotoxic effects of different S. aureus strains will de delineated and the role of bacterial effectors involved in these pathways will be defined. In particular, the role and mechanism of mitochondrial association of alpha-toxin and PVL will be analyzed. Finally, the in vivo relevance of cell death signaling induced by S. aureus infection will be verified in animal models using the imaging platform of the SFB in project part Z3.
In project part Z1 a S. aureus database will be established processing large-scale datasets. This database will create new insights into physiology and pathophysiology of S. aureus by integration of metabolite data, enzyme data including kinetics, protein data including protein interactions, and offers analysis of genomes, regulatory motifs, gene expression and cellular networks in S. aureus.
The aim of the project Z3 is the implementation of in vivo imaging platform techniques (bioluminescence, fluorescence, MRI, and PET) to visualize the dynamics of S. aureus infections and corresponding morphological and physiological changes in host tissues (Fig. 1). Overall, these data will provide an overview on the dynamics of bacterial spread in the host and its 3D distribution.

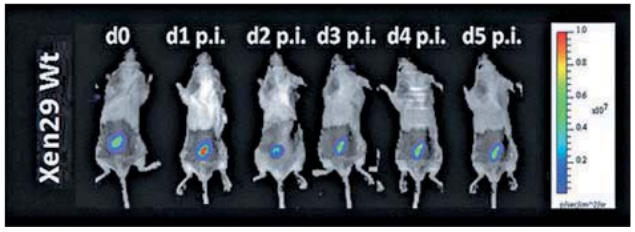


Fig. 1: Bioluminescent S. aureus strain Xen29 in an abscess infection model.

5 Research Programmes and Teaching
5.5 IRTG 1522: HIV/AIDS and associated infectious diseases in Southern Africa

CONTACT DETAILS

Speaker:
Prof. Dr. med. Axel Rethwilm

Institut für Virologie und Immunbiologie
Versbacher Str. 7
97078 Würzburg
Phone: +49-931-201-49554
Email: irtg1522@uni-wuerzburg.de
www.gk-1522.uni-wuerzburg.de

General

The International Research Training Group 1522 (IRTG1522) on HIV/AIDS and associated Infectious Diseases in Southern Africa involves universities in Würzburg and Cape Town. Its aim is to intensify scientific relations between Germany and South Africa. At the University of Würzburg 11 PhD student plus 2 MD student stipends financed by the DFG together with 12 PhD student stipends financed by the NRF at the Universities of Stellenbosch and Cape Town were created as part of the IRTG. Thematically divided in three areas, there are 12 research projects on infectious diseases. The partners in South Africa provide patient samples that cannot be obtained in Germany. These can be investigated by methods available in Würzburg but rarely in South Africa. South Africa is scientifically the most developed country in Africa and has a infrastructure that allows biomedical research to be conducted on the same level with Germany, enabling synergistic effects on research. The main corner stone of this IRTG is a student exchange programme between the participating universities that permits students from Würzburg to spend research time in Cape Town and vice versa.
Questions on clinical virology and basic questions on HIV and virus-induced immunosuppression are investigated in area one. In area two some HIV-associated infectious agents (bacteria, worms, and other eukaryotic parasites) are investigated. In area three questions on the immunology of infectious agents are followed. Numerous connecting aspects bridge the research fields of different areas. The speaker on the South African side of this IRTG is Prof. Wolfgang Preiser from the „Medical Virology„ of Stellenbosch University.

Research Projects:

Area I	*Area II*	*Area III*
The impact of therapeutic drug monitoring on antiretroviral therapy *Prof. Dr. Hartwig Klinker and Prof. Dr. August Stich*	***Epidemiology, diagnosis, and molecular mechanisms of multidrug resistance in Candida albicans and its impact on host-fungus interactions*** *Prof. Dr. Joachim Morschhäuser*	***Characterization of the role of C-type lectins in dendritic cell interactions with Leishmania parasites*** *Supervisor: Prof. Dr. Heidrun Moll*
Study of drug-resistant HIV *Dr. Jochen Bodem*	***Characterization of the influence of excretory/secretory products from Echinococcus multilocularis larvae on dendritic cell maturation and the interaction of Echinococcus E/S products with TLR and CTL surface receptors*** *Supervisor: Prof. Dr. Klaus Brehm*	***Protective and productive inflammatory responses induced by microbial products studied at the level of dendritic cells*** *Supervisor: Prof. Dr. Manfred Lutz*
Molecular Epidemiology of HIV *Prof. Dr. Axel Rethwilm*	***Staphylococcus aureus population structure and host cell interaction in chronic infection*** *Supervisor: Prof. Dr. Dr. Bhanu Sinha*	***The role of CD28 mediated co-stimulation in the control of secondary immune responses to infectious agents*** *Supervisor: Prof. Dr. Thomas Hünig*
Influence of different HIV subtypes on HIV dementia *Prof. Dr. Eleni Koutsilieri und PD Dr. Carsten Scheller*	***Generation and characterization of candidates for malaria/HIV combination therapy*** *Supervisor: Dr. Gabriele Pradel*	
Targets, mechanisms and consequences of regulated T cell pre-mRNA splicing and their relevance as genetic markers of virally induced or general T cell suppression *Prof. Dr. Sibylle Schneider-Schaulies und Dr. Susanne Kneitz*		

5 Research Programmes and Teaching
5.6 BayImmuNet: Project team at the Würzburg University Hospital

CONTACT DETAILS

Project management:
Professor Dr. med. Max Topp
Würzburg Universtiätsklinikum
Medizinische Klinik II
Oberdürrbacher Str. 6
97080 Würzburg
Phone: +49-931-201-40013
E-Mail: topp_m@klinik.uni-wuerzburg.de

Member of the Coordinating Committee:
Prof. Dr. rer. nat. Thomas Hünig
Institut für Virologie und Immunbiologie
Versbacher Straße 7
97078 Würzburg
Phone: +49-931-201-49951
E-Mail: huenig@vim.uni-wuerzburg.de

General Information

BayImmuNet is a unique network established in Germany in 2008, and has set itself the goal of achieving faster translation of new approaches in immunotherapy into clinical application.
The projects are subdivided in two general lines of funding. The first line of funding involving five “translational immunotherapy” project teams started in September 2008 work studying immunotherapy approaches in the fight against tumour diseases and infections. In the second line of funding the projects are focused on clinical phase I / II studies and preclinical technology development. These project teams started their work on September 1, 2009.

Research Project

Development of an immunotherapy protocol for the prevention and treatment of Aspergillus fumigatus infection

Invasive aspergillosis (IA) caused by the opportunistic pathogenic fungus Aspergillus fumigatus (A.fumigatus) constitutes a serious complication in patients suffering from acute leukaemia and in patients undergoing allogeneic stem cell transplantation (SCT) and is associated with exceedingly high infection-related morbidity and mortality.
Healthy individuals are protected from A. fumigatus by innate and adaptive immunity. In contrast, A. fumigatus can become pathogenic in the immunocompromised host by either a lack or a dysfunction of monocytes/granulocytes/dendritic cells (DC) and antigen-specific Th1 cells resulting in IA or by an imbalance of the adaptive immunity causing immune pathology through excessive tissue damage. In addition, A. fumigatus itself secretes immunosuppressive mycotoxins which either inhibit APC function or induce monocyte death. Recent data by Luigina Romani showed that mice can be protected from a lethal A. fumigatus challenge by transfer of Th1 T-cells, by DC vaccination as well as by induction of Treg T cells. Our group has identified in human subjects immunodominant A. fumigatus derived T-cell epitopes as well as an A.fumigatus derived protein, which can condition DCs for better inflammatory response. We are, therefore, proposing to extend our previous work to 1) determine aspergillus derived proteins, which have a proinflammatory action on dendritic cells and, therefore, potentially contribute to efficient recruitment of innate and adaptive immunity 2) identify more immunodominant proteins inducing a Th1 T-cell response for adoptive immunotherapy 3) reprogram aspergillus-specific Th1 T-cells to Treg's for control of immunopathology of the infection 4) generate an anti-gliotoxin neutralizing antibody 5) translate the results into GMP products as bases for immunotherapy of A. fumigatus infection. 6) conduct a phase I/II trial in patients with probable and proven invasive aspergillosis.

5 Research Programmes and Teaching
5.7 BMBF: National Genome Research Network (NGFN) in the Program of Medical Genome Research

CONTACT DETAILS

Coordinator:
Prof. Dr. Jürgen Brosius
Westfälische Wilhelms-Universität
Münster

Project coordination in Würzburg:

Prof. Dr. rer. nat. Jörg Vogel (TP2)
Institut für Molekulare Infektionsbiologie
Josef-Schneider-Str. 2/D15
97080 Würzburg
Phone: +49-931-3182576
E-Mail: joerg.vogel@uni-wuerzburg.de

Prof. Dr. rer. nat. Thomas Rudel (TP5)
Lehrstuhl für Mikrobiologie
Biozentrum der
Universität Würzburg
Am Hubland
97074 Würzburg
Phone: +49-931-3184401
E-Mail: thomas.rudel@biozentrum.uni-wuerzburg.de

General Information

The National Genome Research Network (Nationales Genomforschungsnetzwerk, NGFN) is funded by the Federal Ministry of Education and Research (BMBF). The network contains 26 genome research programmes, which aim to identify genes involved in the development of cardiovascular and metabolic diseases, cancer, neurological disorders, infections and inflammation.

Based on recent whole genome sequences in various model organisms and computational and experimental mining of non-protein coding RNA molecules (ncRNAs) it is clear that not only proteins but also RNAs are important entities of the cell, functioning both as housekeeping or regulatory RNAs. An important class of regulatory ncRNA genes encodes small RNA molecules, so called microRNAs (miRNAs), which play important roles in various biological processes, such as development, differentiation, apoptosis or proliferation. Related small RNAs that are double-stranded, termed short interfering RNAs (siRNAs), are involved in natural RNA interference (RNAi) in natural processes of the cell including host defense. There is a growing body of evidence that ncRNA molecules also play important roles during infection. The RNomics project focuses on the role of ncRNAs during life threatening infections such as AIDS, malaria, typhus or bacterial meningitis. However, they also play important roles during frequent but less threatening infections such as chlamydiosis, infectious gastritis or toxoplasmosis. The goal is to identify ncRNAs that are encoded by the pathogen itself and also ncRNA genes encoded by the host that are activated during infection. The analysis of the *in vitro* and *in vivo* functional roles of the identified ncRNAs during pathogenicity or host defense may reveal novel and efficient strategies of prevention and therapy of the corresponding infections. This is of upmost importance in light of increasing resistance of pathogens against known drugs. The research performed the RNomics programme aims to provide novel and efficient strategies in the fight against infections, which, worldwide is a major threat to human health.

The RNomics in Infections programmmes is coordinated by Prof. Jürgen Brosius (University of Münster) and contains two projects from research groups at the University of Würzburg, Prof. Jörg Vogel and Prof. Thomas Rudel.

Major Research Projects

Coordinator Prof. Dr. Jürgen Brosius (Westfälische Wilhelms-Universität Münster)

TP1 Richard Reinhardt (MPI für Molekulare Genetik) - Ultra-High-Parallel Sequencing and Biocomputational Analysis of ncRNA

TP2 Prof. Jörg Vogel (Universität Würzburg) - RNomics of bacterial infections

TP3 Prof. Lutz Walter (Deutsches Primatenzentrum Göttingen) - RNomics of viral infections

TP6 Prof. Jürgen Brosius (Universität Münster) - RNomics of eukaryotic parasites

TP5 Prof. Thomas Rudel (Universität Würzburg) - RNomics of bacterial infections

5 Research Programmes and Teaching
5.8 BMBF Joint Project: Medical Infection Genomics – Genome research on pathogenic bacteria

CONTACT DETAILS

Speaker:
Prof. Dr. med. Matthias Frosch

Institute for Hygiene and Microbiology
Josef-Schneider-Str. 2/E1
97080 Würzburg
Phone: +49-931-3146160
E-Mail: mfrosch@hygiene.uni-wuerzburg.de
www.medizinische-infektionsgenomik.de/en/

Dr. rer. nat. Gabriele Gerlach
(Office)
+49-931-3146901

General Information

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 focused on the genome research on pathogenic microorganisms.

During the funding period from 2010 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 thahat are widley 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.

The eleven research clusters aim for a comprehensive understanding of the infectious agents and their adaptation to the human host during the infectious 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 the further improvement of 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. Besides scientists of the University of Würzburg further research groups from different German universities and non-university research institutions, hospitals and industry are members of the network.

Major Research Interests

Four research groups of the University of Würzburg are involved in the funding initiative:

The research cluster "Next generation transcriptomics for bacterial infections" is coordinated by Prof. Jörg Vogel (head of the Institute for Molecular Infection Biology) and aims to establish next-generation sequencing as a novel tool to study the gene expression profiles of the bacterial pathogen and the eukaryotic host in parallel over the course of infection.

Prof. Ulrich Vogel (Institute for Hygiene and Microbiology) is a member of the research cluster "Proteomics of meningococci and pneumococci - from *in vitro* biofilms to *in vivo* infection" coordinated by Prof. Sven Hammerschmidt from the University of Greifswald. The aim of this project is to employ a time resolved protein profiling of meningococci and pneumococci to gain new information on the cellular physiology and virulence of these human pathogens.

Dr. Knut Ohlsen (Institute for Molecular Infection Biology) is part of the research cluster "Host-pathogen interactions: effects of secreted proteins of *Staphylococcus aureus* on cells and components of the immune system " coordinated by Dr. Susanne Engelmann from the University of Greifswald. The research groups aim to gain new insights into immune evasion mechanisms.

The research cluster "Pathogen-host interactomes and signalling complexes in bacterial infections" is coordinated by Prof. Thomas Rudel (head of the Department of Microbiology) and focuses on the investigation of the pathogen-host interactome of the etiological agents for a range of important human infections such as typhoid fever, tuberculosis, trachoma, Legionnaires disease, gastritis and peptic ulcer diseases.

5 Research Programmes and Teaching
5.9 The National Reference Centre for Meningococci (NRZM)

CONTACT DETAILS

Prof. Dr. med. Matthias Frosch
Prof. Dr. med. Ulrich Vogel
Institute for Hygiene and Microbiology
Josef-Schneider Str. 2, Bau E1
97080 Würzburg
Phone: +49-931- 3146006
E-Mail: nrzm@hygiene.uni-wuerzburg.de
www.meningococcus.de

General information

The NRZM has been commissioned by the Robert Koch Institute to establish new methods and perform fine typing of meningococcal strains, advise laboratories and public health authorities with respect to diagnosis, epidemiology and prevention of meningococcal disease, to establish quality assurance systems, and to collaborate with international networks and institutions. Annually, 400-600 samples from patients with invasive meningococcal disease are processed. Key activities of high priority include serogroup determination, fine typing, and antibiotic resistance testing. Culture-independent analysis by sensitive PCR assays and DNA sequencing is performed on 100-150 samples per annum. Detailed information for laboratories, public health services, and patients are available at the homepage of the NRZM (www.meningococcus.de). The NRZM issues annual reports to the Robert Koch Institute, the results are made publicly available on the website, the NRZM furthermore is dedicated to publish its results in peer-reviewed journals.

Focus of the NRZM (2009-2011):

1. Finetyping: MLVA typing has been further developed to supplement MLST and antigen finetyping for community outbreaks caused by the ST-41/44 complex of meningococci. The association of the variation of MLVA loci with the number of transmission events is currently investigated in collaboration with Paula Kriz, Prague.
2. Genome sequence typing: in collaboration with Dag Harmsen, Münster, the NRZM performed a feasibility study regarding the use of personal genome sequencing machines for typing of meningococci.
3. Infection epidemiology: The NRZM is collaborating with the Robert Koch Institute to match data from the statutory notification system with the laboratory surveillance data. This effort resulted in a robust dataset, which will allow the investigation of virulence differences between fine types. Data from 2002 to 2010 have been matched to analyze the impact of the German serogroup C vaccine recommendation.
4. Antimicrobial resistance: The NRZM has participated in European projects on molecular mechanisms of rifamipicin resistance in meningococci. Furthermore, the NRZM contributed to the GERMAP 2 project of the Paul Ehrlich Society and the Federal Office for Health Related Consumer Protection.
5. Serology: the NRZM has implemented serum bactericidal assay into its diagnostic program. The assays are available to test the vaccine response in patients with increased risk of meningococcal infection. A research collaboration has been established with the vaccination office in Dresden to investigate the immune response to polysaccharide conjugate vaccines by splenectomised patients (Jörg Wendisch, Dresden). A study has been conducted to assess the duration of antibody persistence in laboratory workers. Studies on pediatric risk patients have been published under the lead of the Department of Pediatrics, Innsbruck.
6. Vaccine evaluation: The NRZM has been part of the EU-5 consortium, which investigates the strain coverage in Europe of a novel MenB vaccine developed by Novartis. The NRZM also investigated the strain coverage in the Czech Republic in collaboration with the Czech National Institute of Public Health.

The NRZM is an active partner of the European Monitoring Group on Meningococci. Ulrich Vogel is the current president of the EMGM Society (http://emgm.eu/).

Matthias Frosch is coordinator of the ECDC-funded project "*Coordination of Activities for Laboratory Surveillance of Invasive Bacteria Diseases*", which commenced in September 2008 and aims at the harmonization of the laboratory surveillance of invasive bacterial diseases caused by *N. meningitidis*, *H. influenza* and *S. pneumoniae*. The network supports the standardization of typing methods and assists the participating national reference laboratories to continuously improve their laboratory performance on the identification and characterization of *N. meningitidis*, *H. influenzae* and *S. pneumonia* as well as to implement new techniques in routine work. External quality assurance (EQA) schemes are provided regularly by the network to assess the individual laboratory performances.

The NRZM leads the Network for Invasive Bacterial Infections of the Robert Koch Institute. In 2011 a joint project with the reference laboratory for pneumococci and the consulting laboratory for diphtheria commenced which aims at the investigation of the prevalence of *H. influenzae*, *S. pneumoniae*, *N. meningitidis*, *S. aureus*, and Corynebacteria in the elderly.

5 Research Programmes and Teaching
5.10 The Consulting Laboratory for *Haemophilus influenzae*

CONTACT DETAILS

Prof. Dr. med. Matthias Frosch
Prof. Dr. med. Ulrich Vogel
Institute for Hygiene and Microbiology
Josef-Schneider-Str. 2/E1
97080 Würzburg
Phone: +49-931-3146006
E-Mail: nrzm@hygiene.uni-wuerzburg.de
www.haemophilus-online.de/

General information

The consulting laboratory for *Haemophilus influenzae* has been transferred from the University of Mainz to the Institute for Hygiene and Microbiology in Würzburg in December 2007. Its new home also harbours the Reference Centre for Meningococci, which has a proven expertise in molecular epidemiology of invasive bacterial pathogens. Both laboratories are part of the quality management system at the Institute for Hygiene and Microbiology.

The consulting laboratory offers the following services:

1. Identification of strains belonging to the genus *Haemophilus*.
2. Capsular serotyping and genotyping and MLST of *H. influenzae*.
3. Advice to primary laboratories and clinicians regarding diagnosis and management of diseases caused by *H. influenzae*.
4. Antimicrobial resistance testing.
5. Serological analysis of vaccine response.

Projects between 2009 and 2011:

- Molecular biology of capsule expression: A new diagnostic PCR for serotype e has been developed on the basis of sequencing the capsule synthesis locus. The evolution of the capsule locus has been addressed by deciphering the sequences of serotype c and d.
- Serology: Antibodies elicited by Hib vaccination are measured using commercial ELISA assays. A research collaboration has been established with the vaccination office in Dresden to investigate the immune response to Hib vaccination in splenectomised patients (Jörg Wendisch, Dresden).
- Infection epidemiology: Enhanced surveillance has been established with the Public Health Authorities in Baden-Württemberg revealing increasing incidence rates in the elderly patient caused mostly by non-typeable Hi. The successful project has been continued in 2012 and will be extended to other federal states. In collaboration with the RKI and the Federal State Offices the under-reporting of capsule typing data in Germany has been successfully addressed.
- Antimicrobial resistance: A systematic analysis of the proportion of ampicillin resistance in invasive *H. influenza* has revealed the numbers of β-lactamase producing strains and β-lactamase negative strains. This study included a comprehensive analysis of *fts*I genotypes.

The consulting laboratory and its annual reports are available at http://www.haemophilus-online.de/.

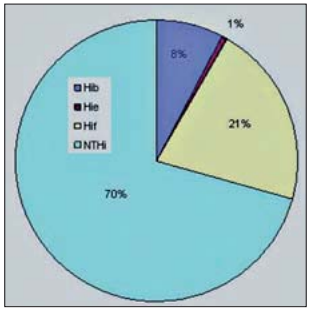


Fig. 1: Serotype distribution of invasive H. influenzae isolates in 2010.

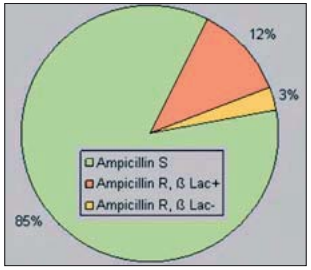


Fig. 2: Ampicillin resistance in invasive H. influenzae isolates.

5 Research Programmes and Teaching
5.11 The Consulting Laboratory for Echinococcosis

CONTACT DETAILS

Prof. Dr. med. Matthias Frosch
Prof. Dr. rer. nat. Klaus Brehm
PD Dr. Dennis Tappe
Institute for Hygiene and Microbiology
Josef-Schneider-Str. 2/ E1
97080 Würzburg
Phone: +49-931-3146168
E-Mail: kbrehm@hygiene.uni-wuerzburg.de
dtappe@hygiene.uni-wuerzburg.de
www.echinococcus.de

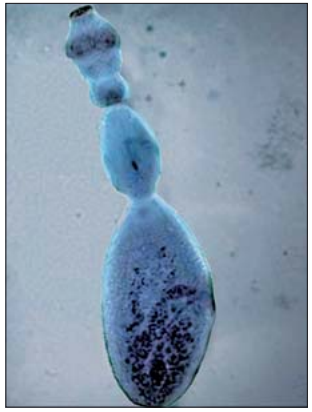
General information

The consulting laboratory for echinococcosis is appointed by the Robert Koch Institute every second year for consultation, quality management and development of diagnostic procedures.
The Institute for Hygiene and Microbiology has been hosting the consulting laboratory for echinococcosis since 1997. The consulting laboratory is an assigned set point laboratory for interlaboratory comparison tests. It is also involved in the preparation and updating of quality standards for microbiological diagnostic procedures (MIQ).

The consulting laboratory offers the following services:

1. Information about prevention and epidemiology of different types of echinococcosis.
2. Information about diagnosis, differential diagnosis, and therapy.
3. Detection of antibodies against *Echinococcus multilocularis* and *E. granulosus* in human sera. Several screening tests and confirmatory assays are available for the primary diagnosis of alveolar and cystic echinococcosis (ELISA, HAT, Western Blot). Both crude and recombinant antigen preparations are employed for serodiagnosis. Serological follow-up investigations of patients after surgery and under antiparasitic chemotherapy are also provided.
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).

The consulting laboratory for echinococcosis has participated in several seroepidemiological studies in northern and southern Germany. The diagnostic performances of different serological tests have been systematically analyzed for the primary diagnosis of echinococcosis. Moreover, multiple follow-up surveys of patients after surgery have been conducted. The consulting laboratory is involved in the diagnosis and follow-up investigation of complicated clinical cases on a regular basis. 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 Research Programmes and Teaching
5.12 Graduate School of Life Sciences

CONTACT DETAILS

Dean:
Prof. Dr. rer. nat. Caroline Kisker
Rudolf-Virchow-Zentrum
der Universität Würzburg
Josef-Schneider-Str. 2/D15
97080 Würzburg
Phone: +49-931-3180381
E-Mail: caroline.kisker@virchow.uni-wuerzburg.de
www.graduateschools.uni-wuerzburg.de/life_sciences

Vice Deans:
Prof. Dr. rer. nat. Dr. med. habil.
Heidrun Moll
Institut für Molekulare Infektionsbiologie
Josef-Schneider-Str. 2/D15
97080 Würzburg
Phone: +49-931-3182627
E-Mail: heidrun.moll@uni-wuerzburg.de

Prof. Dr. med. Martin Lohse
Rudolf-Virchow-Zentrum
der Universität Würzburg
Versbacher Str. 9
D - 97078 Würzburg
Phone: +49-931-201-48401
E-Mail: lohse@toxi.uni-wuerzburg.de

GSLS office:
Dr. rer. nat. Gabriele Blum-Oehler
Phone: +49-931-3181474
E-Mail: gabriele.blum@uni-wuerzburg.de

General Information

For many years the Faculties of Medicine and Biology have offered high-level structured graduate training at the University of Würzburg. Several DFG-funded graduate programs (Graduiertenkollegs) provided early experience with structured graduate training at the University of Würzburg. For example the MD/PhD-program initiated by the Faculties of Biology and Medicine in 1996/7 which was the first such program in Germany. Following discussions within the university on modern forms of graduate training the "International Graduate School" (IGS) was founded by the University Senate in December 2003. This "International Graduate School" was initiated to cover the academic spectrum of the entire university, with separate graduate schools catering for the specific scientific and training needs of its diverse disciplines.
The Section of Biomedicine was initiated in the IGS in 2003 by unifying several programs and their doctoral researchers. The GSLS was successful in the "Excellence Initiative of the Federal and State Governments" and obtained funds to support fellowships and other activities. At this time further sections, i.e. Infection and Immunity,Neuroscience and In tegrative Biology, were added to the GSLS.

Recent developments in the Graduate School of Life Sciences

The Graduate School of Life Sciences (GSLS) is the largest and most integrated graduate school at the University of Würzburg. The plans were set forth in the successful application within the DFG Excellence Initiative and have been sucessfully put into practice.
The GSLS now houses doctoral researchers of all collaborative research programs – such as the DFG-funded collaborative research centers ("Sonderforschungsbereiche"), research training groups ("Graduiertenkollegs") and clinical research groups ("Klinische Forschergruppen"), as well as other collaborative programs 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 Immunity", "Neuroscience" and "Integrative Biology" and "Clinical Sciences". Doctoral researchers of the MD/PhD program are integrated into the respective sections according to their research interests. 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. To date more than 1500 standardized written applications have been evaluated in the recruitment rounds, and interviews with more than 250 candidates have been performed by the admission board in Würzburg. The fellows, currently 67, come from 19 different countries, underscoring the international character of the GSLS.
The number of formal members of the GSLS has risen to more than 180 principal in-

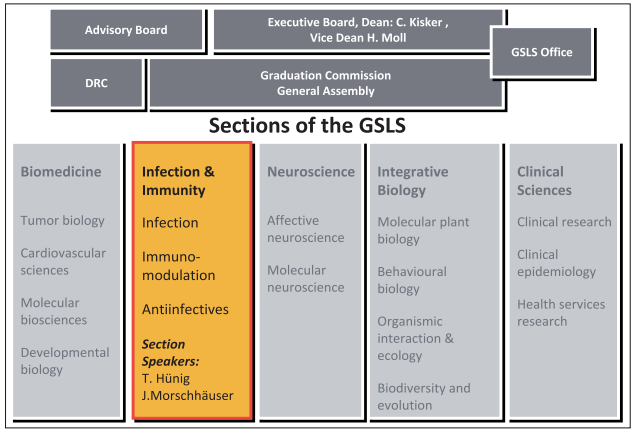


Fig. 1.: Structure of the Graduate School of Life Sciences

vestigators from all participating faculties. In 2011 the number of doctoral researchers enrolled in the doctoral study program "Life Sciences" rose to more than 300. In August of the year 2011, the GSLS submitted a renewal proposal in the framework of the 2nd phase of the Excellence Initiative. Besides establishing an international MSc program and a program for postdoctoral fellows to foster their early independence, the introduction of an excellence program for MD doctoral studies is envisaged.

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 (depending on the specific graduate school) 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)

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 students, yet provide a focus on common and converging mechanisms.

Facts of Numbers concerning the Infection and Immunity section

- 2nd largest section in GSLS
- Doctoral researchers organized in two RTGs, one IRTG, one SFB, two TR-SFB

6 Appendix
6.1 Alumni of the 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.

Chronological listing of former Young Investigator Group Leaders:

Heidrun Moll Institut für Molekulare Infektionsbiologie Josef-Schneider-Straße 2/D15 97080 Würzburg heidrun.moll@uni-wuerzburg.de www.imib-wuerzburg.de/research/moll		**Research at the ZINF** 1993-1999 *Pathogenicity of Leishmania* **Current position:** C3-Professorship at the University of Würzburg
Michael Lanzer Universitätsklinikum Heidelberg Hygiene-Institut Abt. Parasitologie Im Neuenheimer Feld 324 69120 Heidelberg michael.lanzer@med.uni-heidelberg.de www.klinikum.uni-heidelberg.de/Parasitology.6568.0.html		**Research at the ZINF** 1994-1999 *Pathogenicity of human malarial parasites* **Current position:** C4-Professorship at the University of Heidelberg
Joachim Morschhäuser Institut für Molekulare Infektionsbiologie Josef-Schneider-Straße 2/D15 97080 Würzburg joachim.morschhaeuser@uni-wuerzburg.de www.imib-wuerzburg.de/research/morschhaeuser		**Research at the ZINF** 1997-2000 *Pathogenicity of Candida* **Current position:** C3-Professorship at the University of Würzburg
Joachim Reidl Karl Franzens Universität Graz Humboldtstrasse 50/1 Institut für Molekulare Biowissenschaften joachim.reidl@uni-graz.at www.mikrobiologie.uni-graz.at/public/Reidl/Website/Home.html		**Research at the ZINF** 1996-2003 *Virulence of Gram-negative bacteria* **Current position:** Professorship at the University of Graz
Katja Becker IFZ- Biochemie der Ernährung des Menschen Heinrich-Buff-Ring 26-32 35392 GIESSEN becker.katja@gmx.de www.uni-giessen.de/cms/fbz/fb09/institute/ernaehrungswissenschaft/ag/becker/		**Research at the ZINF** 1999-2000 *Malarial parasites as targets for the development of antiparasitic drugs* **Current position:** C4-Professorship at the University of Gießen
Klaus Erb Department of Pulmonary Research, Boehringer Ingelheim Pharma GmbH & Co. KG, H91-02-01, Birkendorferstrasse 65 88397 Biberach a.d. Riss Klaus.Erb@bc.boehringer-ingelheim.com		**Research at the ZINF** 1999-2004 *Immunology of intracellular pathogens and allergic disorders* **Current position:** Head of Dept. Allergologie und Immunologie

Matthias Leippe Zoologisches Institut Abteilung Zoophysiologie Christian-Albrechts-Universität Olshausenstraße 40 24098 Kiel mleippe@zoologie.uni-kiel.de http://www.uni-kiel.de/zoologie/zoophysiologie/		**Research at the ZINF** 2001-2003 *Molecular Parasitology* **Current position:** C4-Professorship at the University of Kiel
Christof Hauck Lehrstuhl Zellbiologie Fachbereich Biologie, X908 Universität Konstanz Universitätsstraße 10 78457 Konstanz christof.hauck@uni-konstanz.de http://cms.uni-konstanz.de/hauck/		**Research at the ZINF** 2001-2006 *Pathogen-host communication* **Current position:** W3-Professorship at the University of Konstanz
Sven Hammerschmidt Interfakultäres Institut für Genetik und Funktionelle Genomforschung Jahn-Straße 15a 17489 Greifswald sven.hammerschmidt@uni-greifswald.de http://www.mnf.uni-greifswald.de/index.php?id=912		**Research at the ZINF** 2003-2007 *Pathogenicity of Streptococcus pneumoniae* **Current position:** W3-Professorship at the University of Greifswald
Ute Hentschel Julius-von-Sachs-Institut für Biowissenschaften Mikrobielle Ökologie Julius-von-Sachs-Platz 3 97082 Würzburg ute.hentschel@mail.uni-wuerzburg.de www.uni-wuerzburg.de/?id=85392		**Research at the ZINF** 2004-2008 *Novel Antiinfectives* **Current position:** W2-Professorship at the University of Würzburg
Ann-Kristin Müller Universitätsklinikum Heidelberg Hygiene-Institut Abt. Parasitologie Im Neuenheimer Feld 324 69120 Heidelberg mail@annkristinmueller.de http://www.klinikum.uni-heidelberg.de/Malaria-3-Mueller.113791.0.html		**Research at the ZINF** 2007-2008 *Biology of Rodent Malaria parasites* **Current position:** Group Leader at the Department of Parasitology
Gabriele Pradel RWTH - Institut für Molekulare Biotechnologie Worringerweg 1 42B, Room 159 52074 Aachen gabriele.pradel@molbiotech.rwth-aachen.de http://www.molbiotech.rwth-aachen.de/Groups/molmalaria/glpradel.htm		**Research at the ZINF** 2005-2011 *Malaria: Transmission blocking strategies* **Current position:** Group Leader at the RWTH Aachen
Sven Krappmann Friedrich-Alexander-Universität Erlangen-Nürnberg Wasserturmstr. 3/5 91054 Erlangen Sven.Krappmann@uk-erlangen.de http://www.mikrobiologie.uk-erlangen.de/index_ger.html		**Research at the ZINF** 2005 – 2012 *Aspects of A. fumigatus Pathogenicity* **Current position:** W2-Professorship at the University of Erlangen

6 Appendix
6.2 Meetings, Workshops and Seminars

Launch and kick-off meeting of the The International Research Training Group (IRTG) on HIV/Aids and associated Infectious Diseases in Southern Africa 1522
Stellenbosch (South Africa), February 26-28, 2009

Annual meeting of the "European Laboratory Surveillance Network of Invasive Bacterial Diseases"
Manchester, June 17, 2009

Leopoldina Symposium „Evolution of Programmed Cell Death in Infection and Immunity"
Würzburg, September 18-20, 2009

ProkaGENOMICS 2009 – "4th European Conference on Prokaryotic Genomics"
Göttingen, October 4-7, 2009

Status Seminar of the of the BMBF funding initiative "PathoGenoMik-Plus"
Göttingen, October 7, 2009

Joint PhD-student meetings of the SFB 630, SFB 544 and SFB 766
New Trends in Infectious Disease Research
Heidelberg, November 19 – 21, 2009

2nd International Symposium "Novel Agents against Infectious Diseases – an Interdisciplinary Approach
Würzburg, October 7 – 10, 2009

NGFN workshop "Small RNAs and infections"
Würzburg, May 7-8, 2010

5th Workshop on Meningococcal Diseases
Würzburg, June 18, 2010

Training workshop of the "European Laboratory Surveillance Network of Invasive Bacterial Diseases"
Würzburg, June 30 – July 2, 2010

Annual meeting of the "European Laboratory Surveillance Network of Invasive Bacterial Diseases"
Würzburg, July 1, 2010

Kick-off Meeting of the BMBF funding initiative "Medical Infection Genomics"
Würzburg, October 12 - 13, 2010

Workshop of the "European Laboratory Surveillance Network of Pneumococcal Diseases"
Stockholm, November 12, 2010

Joint PhD-student meetings of the SFB 630, SFB 544 and SFB 766
New Trends in Infectious Disease Research
Ellwangen, November 22 – 24, 2010

Course in Infection Control and Hygiene for Medical Doctors
Würzburg, November 22-26, 2010

1st International Symposium on Sponge Microbiology
Würzburg, March 21-22, 2011

Infectiological Colloquium
Multiresistant Bacteria – Therapy and Hygiene Management
Würzburg, April 6, 2011

FEMS-Leopoldina-Symposium on „Emerging Topics in Microbial Pathogenesis"
Würzburg, April 12-14, 2011

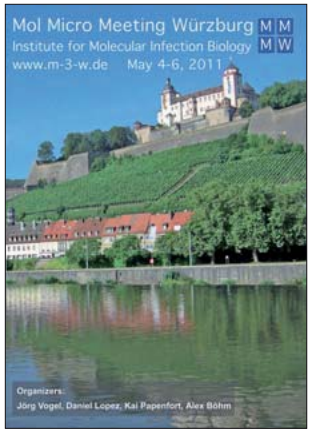
Annual meeting of the "European Laboratory Surveillance Network of Invasive Bacterial Diseases"
Ljubljana, May 17, 2011

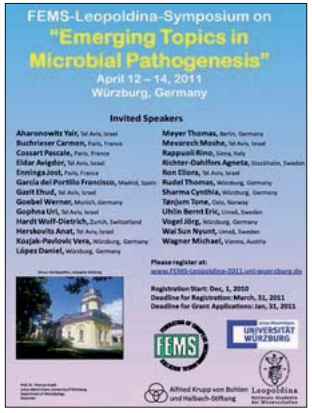
MoI Micro Meeting Würzburg
Würzburg, May 4-6, 2011

ProkaGENOMICS 2011 –"5th European Conference on Prokaryotic and Fungal Genomics"
Göttingen, September 18- 21, 2011

Status Seminar of the BMBF funding initiative "Medical Infection Genomics"
Göttingen, September, 21 – 22, 2011

Status Seminar of the DGHM section Microbial Systematics, Population Genetics and Infection - "Molecular epidemiology and microbial evolution"
Würzburg, November, 25- 26, 2011





Microbiological Colloquium
Seminar Series 2010-2011

20 Dec 2011 Andreas Bäumler | University of California, USA
Food from the fire: how the host response feeds Salmonella

13 Dec 2011 John McKinney | EPFL Lausanne, Switzerland
Individuality of bacterial responses to fluctuating environments

06 Dec 2011 Alistair Brown | Aberdeen, UK
Adapt or die - How a fungal pathogen adapts to its host

29 Nov 2011 Petra Dersch | HZI Braunschweig, Germany
How Yersiniae promote and control entry into human cells

22 Nov 2011 Martin Heisenberg | RVZ Würzburg, Germany
How behavior can be free. - Brain research on the fly Drosophila melanogaster

15 Nov 2011 Jorge Galan | Yale University, USA
Type III secreation at work - Interaction of Salmonella within host cells

08 Nov 2011 Peter Brodersen | University of Copenhagen, Denmark
Coupling of RNA silencing and innate immunity pathways in plants

25 Oct 2011 David Holden | Imperial College London, UK
Subversion of host cell functions by Salmonella

18 Oct 2011 Friedrich Götz | University of Tübingen, Germany
Staphylococcus aureus: stimulation of and response to innate immunity

26 July 2011 Kumara Ramamurthi | NIH Bethesda, USA
Morphogenesis of large structures during development

12 July 2011 Heike Broetz-Oesterheld | Universität Düsseldorf, Germany
Over-activation instead of inhibition - the novel mechanistic principle of acyldepsipeptide antibiotics

21 June 2011 Berenike Maier | Universität Münster, Germany
Force generation by bacterial pili

14 June 2011 Steffen Backert | UCD University College Dublin, Ireland
Role of the actin-binding protein cortactin in host pathogen interactions

07 June 2011 Ferric Fang | University of Washington, USA
Salmonella: A Window Into Biology

31 May 2011 Patrick Cramer | Genzentrum München, Germany
Gene transcription: molecular movies of dynamic systems

24 May 2011 Jos van Strijp | UMC Utrecht, The Netherlands
Staphylococcal immune evasion

17 May 2011 Jörg Stülke | Universität Göttingen, Germany
Virulence determinants of Mycoplasma pneumoniae, the minimal pathogen

10 May 2011 Ruth Schmitz-Streit | Universität Kiel, Germany
The nitrogen regulation in Methanoarchea: The archeal way?

08 February 2011 Dr. Franz Narberhaus | University of Bochum
Cis- and trans-acting RNAs in Prokaryotes: Here, there and everywhere

01 February 2010 Dr. Isabel Delany | Novartis Sienna, Italy
Control of antigen expression in Neisseria meningitidis

25 January 2010 Dr. Duccio Medini | Novartis Vaccines and Diagnostics Siena, Italy
Population genomics of bacteria: the role of restriction modification in the Neisseria meningitidis population structure and dynamics

6 Appendix
6.2 Meetings, Workshops and Seminars

Virology and Immunobiology Seminar Series 2010-2011

19 Dec 2011 Oliver Keppler | Heidelberg, Germany
Catch me if you can – HIV-1´s strategies to evade the intrinsic immune control

05 Dec 2011 Stephan Becker | Marburg, Germany
Replication and morphogenesis of filoviruses

28 Nov 2011 Thomas Boehm | Freiburg, Germany
The thymus: 500 million years in the making

14 Nov 2011 Claudia Berek | Berlin, Germany
Eosinophils are required for long-term survival of plasma cells

07 Nov 2011 Adrian Liston | Leuven, Belgium
Quantitative and qualitative asymmetric control immune regulation by Foxp3+ regulatory T cells

25 Jul 2011 Giulia Casorati | Milano, Italy
Leukemia immunesurveillance by CD1-restricted T cells specific for self-lipid antigens

11 Jul 2011 Manfred Kopf | Zürich, Switzerland
Latest clues in the regulation of T and B cell responses by IL-21

4 Jul 2011 Alexandra Trkola | Zürich, Switzerland
Shedding light on HIV neutralization

20 Jun 2011 Philippe Plattet | Bern, Switzerland
Insights into Morbillivirus cell entry

9 Jun 2011 Hartmut Hengel | Düsseldorf, Germany
New insights into strategies of cytomegalovirus persistency

23 May 2011 Natalio Garbi |Heidelberg, Germany
Regulation of dendritic cell development

9 May 2011 Martina Deckert | Köln
Cell type-specific immune reactions in autoimmune inflammatory diseases of the nervous system

6 May 2011 Sigrun Smola | Homburg/Saar, Germany
Innate Immunity in Human Papillomavirus-associated Carcinogenesis

24 Jan 2011 David Vöhringer | München, Germany
Regulation of allergic inflammation and protective immunity against Hookworms

31 Jan 2011 Christian Drosten | Bonn, Germany
Bats as reservoirs of emerging viruses

10 Jan 2011 Jean-François Eléouët | INRA, France
Respiratory syncytial virus RNA polymerase: structural and functional analysis and search for inhibitors

20 Dec 2010 Thomas Wekerle | Wien, Austria
Transplantation tolerance through mixed chimerism: is the glass half full or half empty

06 Dec 2010 Peter Collins | Boston NIH, USA
Human Respiratory Syncytial Virus: Immunity and pediatric vaccines

29 Nov 2010 Thomas Göbel | München, Germany
The chicken leukocyte receptor complex, a gene family gone wild

22 Nov 2010 Erich Gulbins | Düsseldorf, Germany
Ceramide in molecular medicine

08 Nov 2010 Ayalew Mergia | Gainsville, USA
Caveolin-1: Does it have any role in HIV infection?

25 Oct 2010 Gabriela Riemekasten, Berlin, Germany
Systemic lupus erythematosus: a prototypic disease of IL-2 deficiency and possible therapeutic consequences

19 Jul 2010 Marca Wauben | Utrecht, NL
Exosomal communication during dendritic cell - T cell interactions

05 Jul 2010 Stefan Kochanek | Ulm, Germany
Safety issues for the use of adenovirus vectors

28 Jun 2010 Beate Sodeik | Hannover, Germany
Herpes Simplex Virus - a hitch hiker´s guide through the cell: Viral stop-and-go along microtubules to the nuclear pore complex

21Jun 2010 Heike Hermanns | Würzburg, Germany
Pro-Inflammatory Cytokines - deciphering signaling networks

07 Jun 2010 Michaela Gack | Harvard, USA
RIG-I-mediated antiviral immune response and evasion of influenza virus

31 May 2010 Joachim Schultze | Bonn, Germany
A new player in making decisions between regulatory and effector T cells

10 May 2010 Jan Konvalinka | Prag
Structures of HIV proteases

03 May 2010 Vincenzo Bronte | Padova
Myeloid-induced tolerance in cancer: mechanisms and therapeutic perspectives

19 Apr 2010 Falk Nimmerjahn | Erlangen, Germany
Understanding and modulating the pro- and anti-inflammatory activity of IgG

01 Feb 2010 Hendrik Huthoff | London, UK
RNA-dependent oligomerization of APOBEC3G is required for restriction of HIV-1

11 Jan 2010 Joachim Schultze | Bonn, Germany
A new player in making decisions between regulatory and effector T cells

6 Appendix
6.3 Publications

2.1 Gabriele Pradel

Solyakov L, Halbert J, Alam MM, Semblat JP, Dorin-Semblat D, Reininger L, Bottrill AR, Mistry S, Abdi A, Fennell C, Holland Z, Demarta C, Bouza Y, Sicard A, Nivez MP, Eschenlauer S, Lama T, Thomas DC, Sharma P, Agarwal S, Kern S, **Pradel G**, Graciotti M, Tobin AB, Doerig C (2011)
Global kinomic and phospho-proteomic analyses of the human malaria parasite Plasmodium falciparum
Nat Commun 2:565

Humeida H, **Pradel G**, Stich A, Krawinkel MB (2011)
The effect of glucose and insulin on in vitro proliferation of Plasmodium falciparum
J Diabetol 3:6

Sologub L, Kuehn A, Kern S, Przyborski J, Schillig R, **Pradel G** (2011)
Malaria proteases mediate inside-out egress of gametocytes from red blood cells following parasite transmission to the mosquito
Cell Microbiol 13:897-912

Agarwal S, Kern S, Halbert J, Przyborski JM, Baumeister S, Dandekar T, Doerig C, **Pradel G** (2011)
Two nucleus-localized CDK-like kinases with crucial roles for malaria parasite erythrocytic replication are involved in phosphorylation of splicing factor
J Cell Biochem 112:1295-310

Coppi A, Natarajan R, **Pradel G**, Bennett BL, James ER, Roggero MA, Corradin G, Persson C, Tewari R, Sinnis P (2011)
The malaria circumsporozoite protein has two functional domains, each with distinct roles as sporozoites journey from mosquito to mammalian host
J Exp Med 208:341-356

Aminake MN, Schoof S, Sologub L, Leubner M, Kirschner M, Arndt HD, **Pradel G** (2011)
Thiostrepton and derivatives exhibit antimalarial and gametocytocidal activity by dually targeting parasite proteasome and apicoplast
Antimicrob Agents Chemother 55:1338-1348

Rupp I, Sologub L, Williamson KC, Scheuermayer M, Reininger L, Doerig C, Eksi S, Kombila DU, Frank M, **Pradel G** (2011)
Malaria parasites form filamentous cell-to-cell connections during reproduction in the mosquito midgut
Cell Res 21:683-696

Tischer M, Sologub L, **Pradel G**, Holzgrabe U (2010)
The bisnaphthalimides as new active lead compounds against Plasmodium falciparum
Bioorg Med Chem 18:2998-3003

Schoof S, **Pradel G**, Aminake MN, Ellinger B, Baumann S, Potowski M, Najajreh Y, Kirschner M, Arndt HD (2011)
Antiplasmodial thiostrepton derivatives: proteasome inhibitors with a dual mode of action
Angew Chem Int Ed Engl 49:3317-3321

Purcell LA, Leitao R, Ono T, Yanow SK, **Pradel G**, Spithill TW, Rodriguez A (2010)
A putative kinase-related protein (PKRP) from Plasmodium berghei mediates infection in the midgut and salivary glands of the mosquito
Int J Parasitol 40:979-988

Mitra BN, **Pradel G**, Frevert U, Eichinger D (2010)
Compounds of the upper gastrointestinal tract induce rapid and efficient excystation of Entamoeba invadens
Int J Parasitol 40:751-760

Nowotny B, Schneider T, **Pradel G**, Schirmeister T, Rethwilm A, Kirschner M (2010)
Inducible APOBEC3G-Vif double stable cell line as a high-throughput screening platform to identify antiviral compounds
Antimicrob Agents Chemother 54:78-87

Simon N, Scholz SM, Moreira CK, Templeton TJ, Kuehn A, Dude MA, **Pradel G** (2009)
Sexual stage adhesion proteins form multi-protein complexes in the malaria parasite Plasmodium falciparum
J Biol Chem 284:14537-14546

2.2 Sven Krappmann

Hartmann T, Cairns TC, Olbermann P, Morschhäuser J, Bignell EM, **Krappmann S** (2011)
Oligopeptide transport and regulation of extracellular proteolysis are required for growth of Aspergillus fumigatus on complex substrates but not for virulence
Mol Microbiol 82:917-935

Khanna N, Stuehler C, Conrad B, Lurati S, **Krappmann S**, Einsele H, Berges C, Topp MS (2011)
Generation of a multiple pathogen-specific T-cell product for adoptive immunotherapy based on activation-dependent expression of CD154
Blood 118:1121-1131

Stuehler C, Khanna N, Bozza S, Zelante T, Moretti S, Kruhm M, Lurati S, Conrad B, Worschech E, Stefanović S, **Krappmann S**, Einsele H, Latgé JP, Loeffler J, Romani L, Topp MS (2011)
Cross-protective TH1 immunity against Aspergillus fumigatus and Candida albicans
Blood 117:5881-2891

Morton CO, Varga J, Hornbach A, Mezger M, Sennefelder H, Kneitz S, Kurzai O, **Krappmann S**, Einsele H, Nierman W, Rogers TR, Löffler J (2011)
The temporal dynamics of differential gene expression in Aspergillus fumigatus interacting with human immature dendritic cells in vitro
PLoS One 6:e16016

Hartmann T, Dümig M, Jaber BM, Szewczyk E, Olbermann P, Morschhäuser J, **Krappmann S** (2010)
Validation of a self-excising marker in the human pathogen Aspergillus fumigatus by employing the β-rec/six site-specific recombination system
Appl Environ Microbiol 76:6313-6317

Szewczyk E, **Krappmann S** (2010)
Conserved regulators of mating are essential for Aspergillus fumigatus cleistothecia formation
Eukaryot Cell 9:774-783

Bergmann A, Hartmann T, Cairns T, Bignell EM, **Krappmann S** (2009)
A regulator of Aspergillus fumigatus extracellular proteolytic activity is dispensable for virulence
Infect Immun 77:4041-4050

2.3 Cynthia Sharma

Schmidtke C, Findeiß S, **Sharma CM**, Kuhfuß J, Hoffmann S, Vogel J, Stadler PF, Bonas U (2011)
Genome-wide transcriptome analysis of the plant pathogen Xanthomonas identifies sRNAs with putative virulence functions
NAR 40(5):2020-2031

Albrecht M, **Sharma CM**, Dittrich MT, Müller T, Reinhardt R, Vogel J, Rudel T (2011)
The Transcriptional Landscape of Chlamydia pneumoniae
Genome Biology 12(10):R98

Belair C, Baud J, Chabas S, **Sharma CM**, Vogel J, Staedel C, Darfeuille F (2011)
Helicobacter pylori interferes with an embryonic stem cell miRNA cluster to block cell cycle progression
Silence 2(1):7

Deltcheva E, Chylinski K*, **Sharma CM***, Gonzales K, Chao Y, Pirzada ZA, Eckert MR, Vogel J, Charpentier E (2011)
CRISPR RNA maturation by trans-encoded small RNA and host factor RNase III
Nature 471(7340):602-7 **Equally contributing authors*

Sharma CM, Papenfort K, Pernitzsch SR, Mollenkopf HJ, Hinton JC, Vogel J (2011)
Pervasive post-transcriptional control of genes involved in amino acid metabolism by the Hfq-dependent GcvB small RNA
Molecular Microbiology 81(5):1144-1165

Beckmann BM, Burenina OY, Hoch PG, Kubareva EA, **Sharma CM**, Hartmann RK1 (2011)
In vivo and in vitro analysis of 6S RNA-templated short transcripts in Bacillus subtilis
RNA Biology 8(5)

Berghoff BA, Glaeser J, **Sharma CM**, Zobawa M, Lottspeich F, Vogel J, Klug G (2011)
Contribution of Hfq to photooxidative stress resistance and global regulation in Rhodobacter sphaeroides
Molecular Microbiology 80(6):1479-1495

Mitschke J, Georg J, Scholz I, **Sharma CM**, Dienst D, Bantscheff J, Voß B, Steglich C, Wilde A, Vogel J, Hess WR (2011)
An experimentally anchored map of transcriptional start sites in the model cyanobacterium Synechocystis sp. PCC6803
PNAS 108(5):2124-9

Vockenhuber MP, **Sharma CM**, Statt MG, Schmidt D, Xu Z, Dietrich S, Liesegang H, Mathews DH, Suess B (2011)
Deep sequencing-based identification of small non-coding RNAs in S. coelicolor
RNA Biology 8(3)

Sharma CM, Hoffmann S, Darfeuille F, Reignier J, Findeiß S, Sittka A, Chabas S, Reiche K, Hackermüller J, Reinhardt R, Stadler PF, Vogel J (2010)
The primary transcriptome of the major human pathogen Helicobacter pylori
Nature 464(7286):250-5

Papenfort K, Bouvier M, Mika F, **Sharma CM**, Vogel J (2010)
Evidence for an autonomous 5' target recognition domain in an Hfq-associated small RNA
PNAS 107(47):20435-40

Irnov I, **Sharma CM**, Vogel J, Winkler W (2010)
Identification of regulatory RNAs in Bacillus subtilis
Nucleic Acids Research *38(19):6637-51*

Bohn C, Rigoulay C, Chabelskaya S, **Sharma CM**, Marchais A, Skorski P, Borezee-Durant B, Barbet R, Jacquet E, Jacq A, Gautheret D, Felden B, Vogel J, Bouloc P (2010)
Experimental discovery of small RNAs in Staphylococcus aureus reveals a riboregulator of central metabolism
Nucleic Acids Research 38(19):6620-36

Albrecht M, **Sharma CM**, Reinhardt R, Vogel J, Rudel T (2010)
Deep sequencing-based discovery of the Chlamydia trachomatis transcriptome
Nucleic Acids Research 38(3):868-77

Jäger D*, **Sharma CM***, Thomsen J, Ehlers C, Vogel J, Schmitz RA (2009)
Deep sequencing analysis of the Methanosarcina mazei Gö1 transcriptome in response to nitrogen availability
PNAS 106(51):21878-82 **Equally contributing authors*

Berghoff BA, Glaeser J, **Sharma CM**, Vogel J, Klug G (2009)
Photooxidative stress induced and abundant small RNAs in Rhodobacter sphaeroides
Molecular Microbiology 74(6), 1497-1512

Hoffmann S, Otto C, Kurtz S, **Sharma CM**, Khaitovich P, Vogel J, Stadler PF, Hackermüller J (2009)
Fast mapping of short sequences with mismatches, insertions and deletions using index structures
PLoS Computational Biology 5(9):e1000502

Sittka A, **Sharma CM**, Rolle K, Vogel J (2009)
Deep sequencing of Salmonella RNA associated with heterologous Hfq proteins in vivo reveals small RNAs as a major target class and identifies RNA processing phenotypes
RNA Biology 6(3):266-275

2.4 Daniel López

Böhm A, Papenfort K, **López D**, Vogel J (2011)
Microbes at their best: first Mol Micro Meeting Würzburg
Molecular Microbiology 82(4), 797-806

Romero D, Traxler MF, **López D**, Kolter R (2011)
Antibiotics as Signaling Molecules
Chemical Reviews 111: 5492-5505

López D, Kolter R (2010)
Functional Microdomains in Bacterial Membranes

Genes and Development 1;24(17):1893-902

López D, Vlamakis H, Kolter R (2010)
Biofilms
CSH Perspectives in Biology 1;2(7):a000398

López D, Kolter R (2010)
Potassium-Sensing Histidine Kinase in Bacillus subtilis
Methods In Enzymology 471: 229-251

López D, Kolter R (2010)□
Extracellular Signals that Define Distinct and Coexisting Cell Fates in Bacillus subtilis□
FEMS Microbiology Reviews 34:134-149

López D, Vlamakis H, Losick R, Kolter R (2009)
Cannibalism Enhances Biofilm Development in Bacillus subtilis□
Molecular Microbiology 74:609-618

López D, Vlamakis H, Losick R, Kolter R (2009)
Paracrine Signaling in a Bacterium
Genes and Development 23:1631-8

López D, Vlamakis H, Kolter R (2009)
Generation of Multiple Cell Types in Bacillus subtilis
FEMS Microbiology Reviews 33:152-63

López D, Fischbach M, Chu F, Losick R, Kolter R (2009)□
Structurally Diverse Natural Products that Cause Potassium Leakage Trigger Multicellularity in Bacillus subtilis□
PNAS 106:280-5

2.5 T. Nicolai Siegel

Siegel TN, Hekstra DR, Wang X, Dewell S, Cross GAM (2010)
Genome-wide analysis of mRNA abundance in two life-cycle stages of Trypanosoma brucei and identification of splicing and polyadenylation sites
Nucleic Acids Research 38(15),4946-57

Wright JR, **Siegel TN**, Cross GAM (2010)
Histone H3 trimethylated at lysine 4 is enriched at probable transcription start sites in Trypanosoma brucei
Molecular and Biochemical Parasitology 136(11), 434-50

Cliffe LJ, **Siegel TN**, Marshall M, Cross GAM, Sabatini R (2010)
Two thymidine hydroxylases differentially regulate the formation of glucosylated DNA at regions flanking polymerase II polycistronic transcription units throughout the genome of Trypanosoma brucei
Nucleic Acids Research 38(12),3923-35

DeGrasse JA, DuBois KN, Devos D, **Siegel TN**, Sali A, Field MC, Rout MP, Chait BT (2009)
Evidence for a shared nuclear pore complex architecture that is conserved from the last common eukaryotic ancestor
Molecular and Cellular Proteomics 8(9):2119-30

Siegel TN, Hekstra DR, Kemp LE, Figueiredo LM, Fenyo D, Wang X, Dewell S, Lowell JE, Cross GAM (2009)
Four histone variants mark the boundaries of polycistronic transcription units in Trypanosoma brucei
Genes and Development 23(9): 1063-76

3.1.1 Jörg Vogel

Belair C, Baud J, Chabas S, Sharma CM, **Vogel J**, Staedel C, Darfeuille F (2011)
Helicobacter pylori interferes with an embryonic stem cell micro RNA cluster to block cell cycle progression
Silence 2(1):7

Albrecht M, Sharma CM, Dittrich MT, Müller T, Reinhardt R, **Vogel J**, Rudel T (2011)
The transcriptional landscape of Chlamydia pneumoniae
Genome Biology 12(10):R98

Storz G, **Vogel J**, Wassarman KM (2011)
Regulation by small RNAs in bacteria: expanding frontiers
Molecular Cell 43(6):880-91

Sharma CM, Papenfort K, Pernitzsch SR, Mollenkopf HJ, Hinton JC, **Vogel J** (2011)
Pervasive post-transcriptional control of genes involved in amino acid metabolism by the Hfq-dependent GcvB small RNA
Molecular Microbiology 81(5):1144-65

Vogel J, Luisi B (2011)
Hfq and its constellation of RNA
Nature Reviews Microbiology 9(8):578-89

Deltcheva E, Chylinski K#, Sharma CM#, Gonzales K, Chao Y, Pirzada ZA, Eckert MR, **Vogel J**, Charpentier E (2011)
CRISPR RNA maturation by trans-encoded small RNA and host factor RNase III
Nature 471(7340):602-7

Schulte LN, Eulalio A, Mollenkopf HJ, Reinhardt R, **Vogel J** (2011)
Analysis of the host microRNA response to Salmonella uncovers the control of major cytokines by the let-7 family
EMBO J 30(10):1977-89

Gogol EB, Rhodius VA, Papenfort K, **Vogel J**#, Gross CA# (2011)
Small RNAs endow a transcriptional activator with essential repressor functions for single-tier control of a global stress regulon
PNAS 108(31):12875-80

Mitschke J, Georg J, Scholz I, Sharma CM, Dienst D, Bantscheff J, Voß B, Steglich C, Wilde A, **Vogel J**, Hess WR (2011)
An experimentally anchored map of transcriptional start sites in the model cyanobacterium Synechocystis sp. PCC 6803
PNAS 108(5):2124-9

Sharma CM, Papenfort K, Pernitzsch SR, Mollenkopf HJ, Hinton JC, **Vogel J** (2011)
Pervasive post-transcriptional control of genes involved in amino acid metabolism by the Hfq-dependent GcvB small RNA
Molecular Microbiology 81(5):1144-65

Berghoff B, Glaeser J, Sharma CM, Zobawa M, Lottspeich F, **Vogel J**, Klug G (2011)
Contribution of Hfq to photooxidative stress resistance and global regulation in Rhodobacter sphaeroides
Molecular Microbiology 80(6):1479-95

Papenfort K, **Vogel J** (2011)
Sweet business: Spot42 RNA networks with CRP to modulate catabolite repression
Molecular Cell 41(3):245-6

Eulalio A, Fröhlich KS, Mano M, Giacca M, **Vogel J** (2011)
A candidate approach implicates the secreted Salmonella effector protein SpvB in P-body disassembly
PLoS ONE 6(3):e17296

Böhm A, Papenfort K, Lopez D, **Vogel J** (2011)
Microbes at their best: First Mol Micro Meeting Würzburg
Molecular Microbiology 82(4):797-806

Corcoran CP, Rieder R, Podkaminski D, Hofmann B, **Vogel J** (2011)
Use of aptamer tagging to identify in vivo protein binding partners of small regulatory RNAs
Methods in Molecular Biology 905:177-200

Corcoran C, Papenfort K, **Vogel J** (2011)
Hfq-associated regulatory small RNAs
In: **Regulatory RNAs in Prokaryotes**, Eds. A. Marchfelder, W.R. Hess, Springer Germany

Podkaminski D, Bouvier M, **Vogel J** (2011)
Identification and characterization of small noncoding RNAs in bacteria
In: **Handbook of RNA Biochemistry** (eds. Hartmann RK, Bindereif A, Schön A, Westhof E), Wiley-VCH

Borries A, **Vogel J**, Sharma CM (2011)
Differential RNA sequencing (dRNA-seq): Deep-sequencing based analysis of primary transcriptomes
In: **Tag-based Approaches for Next-Generation Sequencing**, Eds. M. Harbers, G. Kahl, Wiley-Blackwell-VCH

Sharma CM, Hoffmann S, Darfeuille F, Reignier J, Findeiß S, Sittka A, Chabas S, Reiche K, Hackermüller J, Reinhardt R, Stadler PF, **Vogel J** (2010)
The primary transcriptome of the major human pathogen Helicobacter pylori
Nature 464(7286):250-5

Papenfort K#, Bouvier M#, Mika F#, Sharma CM, **Vogel J** (2010)
Evidence for an autonomous 5' target recognition domain in an Hfq-associated small RNA
PNAS 107(47):20435-40

Heale BS, Eulalio A, Schulte LN, **Vogel J**, O'Connell MA (2010)
Analysis of A to I editing of miRNA in Macrophages exposed to Salmonella
RNA Biology 7(5):116-22

Irnov I, Sharma CM, **Vogel J**, Winkler WC (2010)
Identification of regulatory RNAs in Bacillus subtilis
Nucleic Acids Research 38(19):6637-51

Bohn C, Rigoulay C, Chabelskaya S, Sharma CM, Marchais A, Skorski P, Borezee-Durant B, Barbet R, Jacquet E, Jacq A, Gautheret D, Felden B, **Vogel J**, Bouloc P (2010)
Experimental discovery of small RNAs in Staphylococcus aureus reveals a riboregulator of central metabolism
Nucleic Acids Research 38(19):6620-36

Albrecht M, Sharma CM, Reinhardt R, **Vogel J**, Rudel T (2010)
Deep sequencing-based discovery of the Chlamydia trachomatis transcriptome
Nucleic Acids Research 38(3):868-77

Papenfort K, **Vogel J** (2010)
Regulatory RNA in bacterial pathogens
Cell Host & Microbe 8(1):116-27

Podkaminski D, **Vogel J** (2010)
Small RNAs promote mRNA stability to activate the synthesis of virulence factors
Molecular Microbiology 78(6):1327-31

Chao Y, **Vogel J** (2010)
The role of Hfq in bacterial pathogens
Current Opinion in Microbiology 13(1):24-33

Javayel S, Papenfort K, **Vogel J** (2010)
The small RNAs of Salmonella
***Salmonella:* From Genome to Function** (Edited by S. Prowollik), Caister Academic Press; ISBN: 978-1-904455-73-8

Pfeiffer V, Papenfort K, Lucchini S, Hinton JC, **Vogel J** (2009)
Coding sequence targeting by MicC RNA reveals bacterial mRNA silencing downstream of translational initiation
Nature Structural and Molecular Biology 16(8):840-46

Jäger D , Sharma CM , Thomsen J, Ehlers C, **Vogel J**, Schmitz RA (2009)
Deep sequencing analysis of the Methanosarcina mazei Gö1 transcriptome in response to nitrogen availability
PNAS 106(51):21878-82

Papenfort K, Said N, Welsink T, Lucchini S, Hinton JC, **Vogel J** (2009)
Specific and pleiotropic patterns of mRNA regulation by ArcZ, a conserved, Hfq-dependent small RNA
Molecular Microbiology 74(1):139-58

Berghoff BA, Glaeser J, Sharma CM, **Vogel J**, Klug G (2009)
Photooxidative stress induced and abundant small RNAs in Rhodobacter sphaeroides
Molecular Microbiology 74(6), 1497-1512

Said N, Rieder R, Hurwitz R, Deckert J, Urlaub H, **Vogel J** (2009)
In vivo expression and purification of aptamer-tagged small RNA regulators
Nucleic Acids Research 37(20):e133

Albrecht M, Sharma CM, Reinhardt R, **Vogel J**, Rudel T (2009)
Deep sequencing-based discovery of the Chlamydia trachomatis transcriptome
Nucleic Acids Research 38(3):868-77

Fröhlich K, **Vogel J** (2009)
Activation of gene expression by small RNA
Current Opinion in Microbiology 12(6):674-82

Narberhaus F, **Vogel J** (2009)
Regulatory RNAs in prokaryotes: Here, there and everywhere
Molecular Microbiology 74(2):261-69

Sharma CM, **Vogel J** (2009)
Experimental approaches for the discovery and characterization of regulatory small RNA
Current Opinion in Microbiology 12(5):536-46

Vogel J (2009)
An RNA trap helps bacteria get the most of out of chitobiose
Molecular Microbiology 73(5):737–41

Hoffmann S, Otto C, Kurtz S, Sharma CM, Khaitovich P, **Vogel J**, Stadler PF, Hackermüller J (2009)
Fast mapping of short sequences with mismatches, insertions and deletions using index structures
PLoS Computational Biology 5(9):e1000502

Papenfort K, **Vogel J** (2009)
Multiple target regulation by small noncoding RNAs rewires gene expression at the post-transcriptional level
Research in Microbiology 160:278-87

Urban JH, **Vogel J** (2009)
A green fluorescent protein (GFP) based plasmid system to study post-transcriptional control of gene expression in vivo
Methods in Molecular Biology 540:301-19

Sittka A, Sharma CM, Rolle K, **Vogel J** (2009)
Deep sequencing of Salmonella RNA associated with heterologous Hfq proteins in vivo reveals small RNAs as a major target class and identifies RNA processing phenotypes
RNA Biology 6(3):266-275

Muller C, Bang IS, Velayudhan J, Karlinsey J, Papenfort K, **Vogel J**, Fang FC (2009)
Acid Stress Activation of the σ^E Stress Response in Salmonella enterica serovar Typhimurium
Molecular Microbiology 71(5):1228-38

Vogel J (2009)
A rough guide to the noncoding RNA world of Salmonella
Molecular Microbiology 71(1):1-11

3.1.2 Heidrun Moll

Ghosh S, Debnath S, Hazra S, Hartung A, Thomale K, Schultheis M, Kapkova P, Schurigt U, **Moll H**, Holzgrabe U, Hazra B (2011)
Valeriana wallichii root extracts and fractions with activity against Leishmania spp.
Parasitol Res 108(4):861-871

Bringmann G, Hertlein-Amslinger B, Kajahn I, Dreyer M, Brun R, **Moll H**, Stich A, Ioset KN, Schmitz W, Ngoc LH (2011)
Phenolic analogs of the N,C-coupled naphthylisoquinoline alkaloid ancistrocladinium A, from Ancistrocladus cochinchinensis (Ancistrocladaceae), with improved antiprotozoal activities
Phytochemistry 72(1):89-93

Schurigt U, Schad C, Glowa C, Baum U, Thomale K, Schnitzer JK, Schultheis M, Schaschke N, Schirmeister T, **Moll H** (2010)
Aziridine-2,3-dicarboxylate-based cysteine cathepsin inhibitors induce cell death in Leishmania major associated with accumulation of debris in autophagy-related lysosome-like vacuoles
Antimicrob Agents Chemother 54(12):5028-5041

Schnitzer JK, Berzel S, Fajardo-Moser M, Remer KA, **Moll H** (2010)
Fragments of antigen-loaded dendritic cells (DC) and DC-derived exosomes induce protective immunity against Leishmania major
Vaccine 28(36):5785-5793

Remer KA, Roeger B, Hambrecht C, **Moll H** (2010)
Natural killer cells support the induction of protective immunity during dendritic cell-mediated vaccination against Leishmania major
Immunology 131(4):570-582

Ponte-Sucre A, Gulder T, Gulder TA, Vollmers G, Bringmann G, **Moll H** (2010)
Alterations to the structure of Leishmania major induced by N-arylisoquinolines correlate with compound accumulation and disposition
J Med Microbiol 59(Pt 1):69-75

Pimentel-Elardo SM, Kozytska S, Bugni TS, Ireland CM, **Moll H**, Hentschel U (2010)
Anti-parasitic compounds from Streptomyces sp. strains isolated from Mediterranean sponges
Mar Drugs 8(2):373-380

Schurigt U, **Moll H** (2009)
Drug discovery and development of vaccination strategies for the treatment and prevention of cutaneous leishmaniasis
Pharm Unserer Zeit 38(6):532-537

Remer KA, Bartrow M, Roeger B, **Moll H**, Sonnenborn U, Oelschlaeger TA (2009)
Split immune response after oral vaccination of mice with recombinant Escherichia coli Nissle 1917 expressing fimbrial adhesin K88
Int J Med Microbiol 299(7):467-478

Ponte-Sucre A, Gulder T, Wegehaupt A, Albert C, Rikanovic C, Schaeflein L, Frank A, Schultheis M, Unger M, Holzgrabe U, Bringmann G, **Moll H** (2009)
Structure-activity relationship and studies on the molecular mechanism of leishmanicidal N,C-coupled arylisoquinolinium salts
J Med Chem 52(3):626-636

3.1.3 Joachim Morschhäuser

Sasse C, Schillig R, Dierolf F, Weyler M, Schneider S, Mogavero S, Rogers PD, **Morschhäuser J** (2011)
The transcription factor Ndt80 does not contribute to Mrr1-, Tac1-, and Upc2-mediated fluconazole resistance in Candida albicans
PLoS One 6(9):e25623

Schubert S, Popp C, Rogers PD, **Morschhäuser J** (2011)
Functional dissection of a Candida albicans zinc cluster transcription factor, the multidrug resistance regulator Mrr1
Eukaryot Cell 10(8):1110-1121

Schubert S, Barker KS, Znaidi S, Schneider S, Dierolf F, Dunkel N, Aid M, Boucher G, Rogers PD, Raymond M, **Morschhäuser J** (2011)
Regulation of efflux pump expression and drug resistance by the transcription factors Mrr1, Upc2, and Cap1 in Candida albicans
Antimicrob Agents Chemother 55(5):2212-2223

Neuhäuser B, Dunkel N, Satheesh SV, **Morschhäuser J** (2011)
Role of the Npr1 kinase in ammonium transport and signaling by the ammonium permease Mep2 in Candida albicans
Eukaryot Cell 10(3):332-342

Mogavero S, Tavanti A, Senesi S, Rogers PD, **Morschhäuser J** (2011)
Differential requirement of the transcription factor Mcm1 for activation of the Candida albicans multidrug efflux pump MDR1 by its regulators Mrr1 and Cap1
Antimicrob Agents Chemother 55(5):2061-2066

Dunkel N, **Morschhäuser J** (2011)
Loss of heterozygosity at an unlinked genomic locus is responsible for the phenotype of a Candida albicans sap4 sap5 sap6 mutant
Eukaryot Cell 10(1):54-62

Morschhäuser J (2010)
Regulation of multidrug resistance in pathogenic fungi
Fungal Genet Biol 47(2):94-106

Morschhäuser J (2010)
Regulation of white-opaque switching in Candida albicans
Med Microbiol Immunol 199(3):165-172

Heilmann CJ, Schneider S, Barker KS, Rogers PD, **Morschhäuser J** (2010)
An A643T mutation in the transcription factor Upc2p causes constitutive ERG11 upregulation and increased fluconazole resistance in Candida albicans
Antimicrob Agents Chemother 54(1):353-359

Dabas N, Schneider S, **Morschhäuser J** (2009)
Mutational analysis of the Candida albicans ammonium permease Mep2p reveals residues required for ammonium transport and signaling
Eukaryot Cell 8(2):147-160

3.1.4 Alex Böhm

Bergmiller T, Pena-Miller R, **Boehm A**, Ackermann M (2011)
Single-cell time-lapse analysis of depletion of the universally conserved essential protein YgjD
BMC microbiology 11:118

Spangler C, **Bohm A**, Jenal U, Seifert R, Kaever V (2010)
A liquid chromatography-coupled tandem mass spectrometry method for quantitation of cyclic di-guanosine monophosphate
J Microbiol Methods 81(3):226-231

Boehm A*, Kaiser M, Li H, Spangler C, Kasper CA, Ackermann M, Kaever V, Sourjik V, Roth V, Jenal U (2010)
Second messenger-mediated adjustment of bacterial swimming velocity
Cell 141(1):107-116

Boehm A*, Steiner S, Zaehringer F, Casanova A, Hamburger F, Ritz D, Keck W, Ackermann M, Schirmer T, Jenal U (2009)
Second messenger signalling governs Escherichia coli biofilm induction upon ribosomal stress
Mol Microbiol 72(6):1500-1516

3.1.5 Ulrich Dobrindt

Köhler CD, **Dobrindt U** (2011)
What defines extraintestinal pathogenic Escherichia coli?
Int J Med Microbiol 301(8):642-7

Schneider G, **Dobrindt U**, Middendorf B, Hochhut B, Szijártó V, Emody L, Hacker J (2011)
Mobilisation and remobilisation of a large archetypal pathogenicity island of uropathogenic Escherichia coli in vitro support the role of conjugation for horizontal transfer of genomic islands
BMC Microbiol 24;11:210

Duda KA, Lindner B, Brade H, Leimbach A, Brzuszkiewicz E, **Dobrindt U**, Holst O (2011)
The lipopolysaccharide of the mastitis isolate Escherichia coli strain 1303 comprises a novel O-antigen and the rare K-12 core type
Microbiology 157:1750-60

Krieger JN, **Dobrindt U**, Riley DE, Oswald E (2010)
Acute Escherichia coli prostatitis in previously health young men: bacterial virulence factors, antimicrobial resistance, and clinical outcomes
Urology 77(6):1420-5

Dobrindt U, Hoffmeyer B, Ruf J, Steffen IG, Zarva A, Richter WS, Furth C, Ulrich G, Grosser OS, Neumann W, Amthauer H (2010)
Blinded-read of bone scintigraphy: the impact on diagnosis and healing time for stress injuries with emphasis on the foot
Clin Nucl Med 36(3):186-9

Bielaszewska M, Middendorf B, Tarr PI, Zhang W, Prager R, Aldick T, **Dobrindt U**, Karch H, Mellmann A (2010)
Chromosomal instability in enterohaemorrhagic Escherichia coli O157:H7: impact on adherence, tellurite resistance and colony phenotype
Mol Microbiol 79(4):1024-44

Fischer H, Lutay N, Ragnarsdóttir B, Yadav M, Jönsson K, Urbano A, Al Hadad A, Rämisch S, Storm P, **Dobrindt U**, Salvador E, Karpman D, Jodal U, Svanborg C
Pathogen specific, IRF3-dependent signaling and innate resistance to human kidney infection
PLoS Pathog 23;6(9):e1001109

Zdziarski J, Brzuszkiewicz E, Wullt B, Liesegang H, Biran D, Voigt B, Grönberg-Hernandez J, Ragnarsdottir B, Hecker M, Ron EZ, Daniel R, Gottschalk G, Hacker J, Svanborg C, **Dobrindt U** (2010)
Host imprints on bacterial genomes--rapid, divergent evolution in individual patients
PLoS Pathog 26;6(8):e1001078

Dobrindt U, Hacker J (2010)
Nosocomial infections and their control
Int J Med Microbiol 300(6):341

Dobrindt U, Zdziarski J, Salvador E, Hacker J (2010)
Bacterial genome plasticity and its impact on adaptation during persistent infection
Int J Med Microbiol 300(6):363-6

Dobrindt U, Chowdary MG, Krumbholz G, Hacker J (2010)
Genome dynamics and its impact on evolution of Escherichia coli
Med Microbiol Immunol 99(3):145-54

Lehti TA, Bauchart P, Heikkinen J, Hacker J, Korhonen TK, **Dobrindt U**, Westerlund-Wikström B (2010)
Mat fimbriae promote biofilm formation by meningitis-associated Escherichia coli
Microbiology 156(Pt 8):2408-17

Gronbach K, Eberle U, Müller M, Olschläger TA, **Dobrindt U**, Leithäuser F, Niess JH, Döring G, Reimann J, Autenrieth IB, Frick JS (2010)
Safety of probiotic Escherichia coli strain Nissle 1917 depends on intestinal microbiota and adaptive immunity of the host
Infect Immun 78(7):3036-46

Moriel DG, Bertoldi I, Spagnuolo A, Marchi S, Rosini R, Nesta B, Pastorello I, Corea VA, Torricelli G, Cartocci E, Savino S, Scarselli M, **Dobrindt U**, Hacker J, Tettelin H, Tallon LJ, Sullivan S, Wieler LH, Ewers C, Pickard D, Dougan G, Fontana MR, Rappuoli R, Pizza M, Serino L (2010)
Identification of protective and broadly conserved vaccine antigens from the genome of extraintestinal pathogenic Escherichia coli
PNAS USA 18;107(20):9072-7

Dobrindt U (2010)
Virulence factors of uropathogens
Urologe 49(5):598-605 Review

Müller CM, Schneider G, **Dobrindt U**, Emödy L, Hacker J, Uhlin BE (2010)
Differential effects and interactions of endogenous and horizontally acquired H-NS-like proteins in pathogenic Escherichia coli
Mol Microbiol 75(2):280-93

Mordhorst IL, Claus H, Ewers C, Lappann M, Schoen C, Elias J, Batzilla J, **Dobrindt U**, Wieler LH, Bergfeld AK, Mühlenhoff M, Vogel U (2009)
O-acetyltransferase gene neuO is segregated according to phylogenetic background and contributes to environmental desiccation resistance in Escherichia coli K1
Environ Microbiol 11(12):3154-65

Bielaszewska M, Bauwens A, Greune L, Kemper B, **Dobrindt U**, Geelen JM, Kim KS, Schmidt MA, Karch H (2009)
Vacuolisation of human microvascular endothelial cells by enterohaemorrhagic Escherichia coli
Thromb Haemost 102(6):1080-92

Putze J, Hennequin C, Nougayrède JP, Zhang W, Homburg S, Karch H, Bringer MA, Fayolle C, Carniel E, Rabsch W, Oelschlaeger TA, Oswald E, Forestier C, Hacker J, **Dobrindt U** (2009)
Genetic structure and distribution of the colibactin genomic island among members of the family Enterobacteriaceae
Infect Immun 77(11):4696-703

Reidl S, Lehmann A, Schiller R, Salam Khan A, **Dobrindt U** (2009)
Impact of O-glycosylation on the molecular and cellular adhesion properties of the Escherichia coli autotransporter protein Ag43
Int J Med Microbiol 299(6):389-401

Brzuszkiewicz E, Gottschalk G, Ron E, Hacker J, **Dobrindt U** (2009)
Adaptation of Pathogenic E. coli to Various Niches: Genome Flexibility is the Key
Genome Dyn 6:110-25

3.1.6 Ana Eulalio

Schulte L, **Eulálio A**, Mollenkopf H, Reinhardt R, Vogel J (2011)
Analysis of the host microRNA response to Salmonella uncovers the control of major cytokines by the let-7 family
EMBO J 30(10):1977-1989

Eulálio A, Fröhlich K, Mano M, Giacca M, Vogel J (2011)
A candidate approach implicates the secreted Salmonella effector protein SpvB in P-body disassembly
PLoS One 6(3):e17296

Heale BS, **Eulálio A**, Schulte L, Vogel J, O'Connell MA (2010)
Analysis of A to I editing of miRNA in macrophages exposed to Salmonella
RNA Biology 7:116-122

Eulálio A, Tritschler F, Izaurralde E (2009)
The GW182 protein family in animal cells: new insights into domains required for miRNA-mediated gene silencing
RNA 15:1433-1442

Eulálio A, Helms S, Fritzsch C, Fauser M, Izaurralde E (2009)
A C-terminal silencing domain in GW182 is essential for miRNA function
RNA 15:1067-1077

Eulálio A, Tritschler F, Büttner R, Weichenrieder O, Izaurralde E, Truffault V (2009)
The RRM domain in GW182 proteins contributes to miRNA-mediated gene silencing
Nucleic Acids Research 37(9):2974-2983

Tritschler F, Braun J, **Eulálio A**, Truffault V, Coles M, Izaurralde E, Weichenrieder O (2009)
Structural basis for the mutually exclusive anchoring of P-body components EDC3 and Tral to the DEAD Box Protein DDX6/Me31B
Molecular Cell 33:661-668

Eulálio A, Huntzinger E, Nishihara T, Rehwinkel J, Fauser M, Izaurralde E (2009)
Deadenylation is a widespread effect of miRNA regulation
RNA 15:21-32

3.1.7 Tobias Ölschläger

Schierack P, Kleta S, Tedin K, Babila JT, Oswald S, **Oelschlaeger TA**, Hiemann R, Paetzold S, Wieler LH (2011)
E. coli Nissle 1917 Affects Salmonella adhesion to porcine intestinal epithelial cells
PLoS One 6(2):e14712

Cecil A, Rikanovic C, Ohlsen K, Liang C, Bernhardt J, **Oelschlaeger TA**, Gulder T, Bringmann G, Holzgrabe U, Unger M, Dandekar T (2011)
Modeling antibiotic and cytotoxic effects of the dimeric isoquinoline IQ-143 on metabolism and its regulation in Staphylococcus aureus, Staphylococcus epidermidis and human cells
Genome Biol 12(3):R24

Stritzker J, Weibel S, Seubert C, Gotz A, Tresch A, van Rooijen N, **Oelschlaeger TA**, Hill PJ, Gentschev I, Szalay AA (2010)
Enterobacterial tumor colonization in mice depends on bacterial metabolism and macrophages but is independent of chemotaxis and motility
Int J Med Microbio, 300(7):449-456

Oelschlaeger TA (2010)
Mechanisms of probiotic actions - A review
Int J Med Microbiol 300(1):57-62

Oelschlaeger TA (2010)
Bacteria as tumor therapeutics?
Bioeng Bugs 1(2):146-147

Gronbach K, Eberle U, Muller M, **Oelschlaeger TA**, Dobrindt U, Leithauser F, Niess JH, Doring G, Reimann J, Autenrieth IB, Frick JS (2010)
Safety of probiotic Escherichia coli strain Nissle 1917 depends on intestinal microbiota and adaptive immunity of the host
Infect Immun 78(7):3036-3046

Oelschlaeger TA, Dobrindt U, Hacker J (2010)
Cell wall structure and pathogenicity
In: Prokaryotic cell wall compounds (König, Claus and Varma, eds.) Springer-Verlag Berlin Heidelberg pp: 313-343

Remer KA, Bartrow M, Roeger B, Moll H, Sonnenborn U, **Oelschlaeger TA** (2009)
Split immune response after oral vaccination of mice with recombinant Escherichia coli Nissle 1917 expressing fimbrial adhesin K88
Int J Med Microbiol 299(7):467-478

Putze J, Hennequin C, Nougayrede JP, et al. (2009)
Genetic structure and distribution of the colibactin genomic island among members of the family Enterobacteriaceae
Infect Immun 77(11):4696-4703

Bickert T, Trujillo-Vargas CM, Duechs M, Wohlleben G, Polte T, Hansen G, **Oelschlaeger TA**, Erb KJ (2009)
Probiotic Escherichia coli Nissle 1917 suppresses allergen-induced Th2 responses in the airways
Int Arch Allergy Immunol 149(3):219-230

Oelschlaeger TA, Hacker J (2009)
Definition und Wirkmechanismen der Probiotika, Präbiotika und Synbiotika
In: Probiotika, Präbiotika und Synbiotika (Bischoff S.C. ed.) pp: 76-87 Georg Thieme Verlag Stuttgart

Oelschlaeger TA (2009)
Uropathogene Keime – Pathogenitäts- und Virulenzeigenschaften
In: Harnwegsinfektionen (Fünfstück, ed.) pp: 6-12. Dustri-Verlag Dr. Karl Feistle, München – Orlando

3.1.8 Knut Ohlsen

Depke M, Burian M, Schäfer T, Bröker BM, **Ohlsen K**, Völker U (2011)
The alternative sigma factor B modulates virulence gene expression in amurine Staphylococcus aureus infection model but does not influence kidney gene expression pattern of the host
Int J Med Microbiol 302(1):33-9

Hoffmann C, **Ohlsen K**, Hauck CR (2011)
Integrin-mediated uptake of fibronectin-binding bacteria
Eur J Cell Biol 2011 May 9 [Epub ahead of print]

Kusch K, Hanke K, Holtfreter S, Schmudde M, Kohler C, Erck C, Wehland J, Hecker M, **Ohlsen K**, Brker B, Engelmann S (2011)
The influence of SaeRS and Ïƒ(B) on the expression of superantigens in different Staphylococcus aureus isolates
Int J Med Microbiol 301(6):488-99

Hertlein T, Sturm V, Kircher S, Basse-Lüsebrink T, Haddad D, **Ohlsen K**, Jakob P (2011)
Visualization of abscess formation in a murine thigh infection model of Staphylococcus aureus by 19F-magnetic resonance imaging (MRI)
PLoS One 24;6(3):e18246

Cecil A, Rikanovi C, **Ohlsen K**, Liang C, Bernhardt J, **Oelschlaeger TA**, Gulder T, Bringmann G, Holzgrabe U, Unger M, Dandekar T (2011)
Modeling antibiotic and cytotoxic effects of the dimeric isoquinoline IQ-143 on metabolism and its regulation in Staphylococcus aureus, Staphylococcus epidermidis and human cells
Genome Biol 21;12(3):R24

Lorenz U, Lorenz B, Schmitter T, Streker K, Erck C, Wehland J, Nickel J,Zimmermann B, **Ohlsen K** (2011)
Functional antibodies targeting IsaA of Staphylococcus aureus augment host immune response and open new perspectives for antibacterial therapy
Antimicrob Agents Chemother 55(1):165-73

Lorenz U, Schäfer T, **Ohlsen K**, Tiurbe GC, Bühler C, Germer CT, Kellersmann R (2011)
In vivo detection of Staphylococcus aureus in biofilm on vascular prostheses using non-invasive biophotonic imaging
Eur J Vasc Endovasc Surg 41(1):68-75

Menzel TM, Tischer M, Francois P, Nickel J, Schrenzel J, Bruhn H, Albrecht A, Lehmann L, Holzgrabe U, **Ohlsen K** (2011)
Mode-of-action studies of the novel bisquaternary bisnaphthalimide MT02 against Staphylococcus aureus
Antimicrob Agents Chemother 55(1):311-20

Liebeke M, Meyer H, Donat S, **Ohlsen K**, Lalk M (2010)
A metabolomic view of Staphylococcus aureus and its ser/thr kinase and phosphatase deletion mutants: involvement in cell wall biosynthesis
Chem Biol 27;17(8):820-30

Ohlsen K, Lorenz U (2010)
Immunotherapeutic strategies to combat staphylococcal Infections
Int J Med Microbiol 300(6):402-10

Sibbald MJ, Winter T, van der Kooi-Pol MM, Buist G, Tsompanidou E, Bosma T, Schäfer T, **Ohlsen K**, Hecker M, Antelmann H, Engelmann S, van Dijl JM (2010)
Synthetic effects of secG and secY2 mutations on exoproteome biogenesis in Staphylococcus aureus
J Bacteriol 192(14):3788-800

Kozytska S, Stauss D, Pawlik MC, Hensen S, Eckart M, Ziebuhr W, Witte W,**Ohlsen K** (2010)
Identification of specific genes in Staphylococcus aureus strains associated with bovine mastitis
Vet Microbiol 26;145(3-4):360-5

Hoffmann C, Berking A, Agerer F, Buntru A, Neske F, Chhatwal GS, **Ohlsen K**,Hauck CR (2010)
Caveolin limits membrane microdomain mobility and integrin-mediated uptake of fibronectin-binding pathogens
J Cell Sci 15;123 (Pt24):4280-91

Herbert S, Ziebandt AK, **Ohlsen K**, Schäfer T, Hecker M, Albrecht D, Novick R, Götz F (2010)
Repair of global regulators in Staphylococcus aureus 8325 and comparative analysis with other clinical isolates
Infect Immun 78(6):2877-89

Geiger T, Goerke C, Fritz M, Schäfer T, **Ohlsen K**, Liebeke M, Lalk M, Wolz C (2010)
Role of the (p)ppGpp synthase RSH, a RelA/SpoT homolog, in stringent response and virulence of Staphylococcus aureus
Infect Immun 78(5):1873-83

Miller M, Donat S, Rakette S, Stehle T, Kouwen TR, Diks SH, Dreisbach A, Reilman E, Gronau K, Becher D, Peppelenbosch MP, van Dijl JM, **Ohlsen K** (2010)
Staphylococcal PknB as the first prokaryotic representative of the proline-directed kinases
PLoS One 4;5(2):e9057

Cuny C, Friedrich A, Kozytska S, Layer F, Nübel U, **Ohlsen K**, Strommenger B, Walther B, Wieler L, Witte W (2010)
Emergence of methicillin-resistant Staphylococcus aureus (MRSA) in different animal species
Int J Med Microbiol 300(2-3):109-17

Chlebowicz MA, Nganou K, Kozytska S, Arends JP, Engelmann S, Grundmann H, **Ohlsen K**, van Dijl JM, Buist G (2010)
Recombination between ccrC genes in a type V (5C2&5) staphylococcal cassette chromosome mec (SCCmec) of Staphylococcus aureus ST398 leads to conversion from methicillin resistance to methicillin susceptibility in vivo
Antimicrob Agents Chemother 54(2):783-91

Ohlsen K, Donat S. (2010)
The impact of serine/threonine phosphorylation in Staphylococcus aureus
Int J Med Microbiol 300(2-3):137-41

Jelsbak L, Hemmingsen L, Donat S, **Ohlsen K**, Boye K, Westh H, Ingmer H, Frees D (2010)
Growth phase-dependent regulation of the global virulence regulator Rot in clinical isolates of Staphylococcus aureus
Int J Med Microbiol 300(4):229-36

Biswas L, Biswas R, Nerz C, **Ohlsen K**, Schlag M, SchÃ¤fer T, Lamkemeyer T, Ziebandt AK, Hantke K, Rosenstein R, Götz F (2009)
Role of the twin-arginine translocation pathway in Staphylococcus
J Bacteriol 191(19):5921-9

Donat S, Streker K, Schirmeister T, Rakette S, Stehle T, Liebeke M, Lalk M,**Ohlsen K** (2009)
Transcriptome and functional analysis of the eukaryotic-type serine/threonine kinase PknB in Staphylococcus aureus
J Bacteriol 191(13):4056-69

3.1. 9 Wilma Ziebuhr

Hennig S, **Ziebuhr W** (2010)
Characterization of the transposase encoded by IS256, the prototype of a major family of bacterial insertion sequence elements
J Bacteriol 192(16):4153-63

Weisser M, Schoenfelder SMK, Orasch C, Arber C, Gratwohl A, Frei R, Eckart M, Flückiger U, **Ziebuhr W** (2010)
Hypervariability of biofilm formation and oxacillin resistance in a Staphylococcus epidermidis strain causing persistent severe infection in an immunocompromised patient
J Clin Microbiol 48(7):2407-12

Kozytska S, Stauss D, Pawlik MC, Hensen S, Eckart M, **Ziebuhr W**, Witte W, Ohlsen K (2010)
Identification of specific genes in Staphylococcus aureus strains associated with bovine mastitis
Vet Microbiol 26;145(3-4):360-5

Ziebandt AK, Kusch H, Degner M, Jaglitz S, Sibbald MJ, Arends JP, Chlebowicz MA, Albrecht D, Pantucek R, Doskar J, **Ziebuhr W**, Bröker BM, Hecker M, van Dijl JM, Engelmann S (2010)
Proteomics uncovers extreme heterogeneity in the Staphylococcus aureus exoproteome due to genomic plasticity and variant gene regulation
Proteomics 10:1634-44

Chatterjee I, Schmitt S, Batzilla CF, Engelmann S, Keller A, Ring MW, Kautenburger R, **Ziebuhr W**, Hecker M, Preissner KT, Bischoff M, Proctor RA, Beck HP, Lenhof HP, Somerville GA, Herrmann M (2009)
Staphylococcus aureus ClpC ATPase is a late growth phase effector of metabolism and persistence
Proteomics 9 :1152-76

3.2.1 Matthias Frosch

Harrison OB, Brueggemann AB, Caugant DA, van der Ende A, **Frosch M**, Gray S, Heuberger S, Krizova P, Olcen P, Slack M, Taha MK, Maiden MC (2011)
Molecular typing methods for outbreak detection and surveillance of invasive disease caused by Neisseria meningitidis, Haemophilus influenzae and Streptococcus pneumoniae, a review
Microbiology 157:2181-95

Joseph B, Schwarz RF, Linke B, Blom J, Becker A, Claus H, Goesmann A, **Frosch M**, Müller T, Vogel U, Schoen C (2011)
Virulence evolution of the human pathogen Neisseria meningitidis by recombination in the core and accessory genome
PLoS One 6:e18441

Lam TT, Elias J, **Frosch M**, Vogel U, Claus H
New diagnostic PCR for Haemophilus influenzae serotype e based on the cap locus of strain ATCC 8142
Int J Med Microbiol 301:176-9

Lam TT, Claus H, **Frosch M**, Vogel U (2011)
Sequence analysis of serotype-specific synthesis regions II of Haemophilus influenzae serotypes c and d: evidence for common ancestry of capsule synthesis in Pasteurellaceae and Neisseria meningitidis
Res Microbiol 201162:483-7

Müller S, Tappe D, **Frosch M**, Abele-Horn M, Valenza G (2011)
Resistance to ampicillin, third-generation cephalosporins, ciprofloxacin, co-trimoxazole and azithromycin in clinical isolates of Salmonella enterica subsp. enterica from Germany: real problem or sporadic circumstance
Scand J Infect Dis 43:389-91

Müller S, Oesterlein A, **Frosch M**, Abele-Horn M, Valenza G (2011)
Characterization of extended-spectrum beta-lactamases and qnr plasmid-mediated quinolone resistance in German isolates of Enterobacter species
Microb Drug Resist 17:99-103

Sako Y, Tappe D, Fukuda K, Kobayashi Y, Itoh S, **Frosch M**, Grüner B, Kern P, Ito A (2011)
Immunochromatographic test with recombinant Em18 antigen for the follow-up study of alveolar echinococcosis.
Clin Vaccine Immunol 18:1302-5

Schielke S, Schmitt C, Spatz C, **Frosch M**, Schubert-Unkmeir A, Kurzai O (2011)
The transcriptional repressor FarR is not involved in meningococcal fatty acid resistance mediated by the FarAB efflux pump and dependent on lipopolysaccharide structure
Appl Environ Microbiol 76:3160-9

Schielke S, Spatz C, Schwarz RF, Joseph B, Schoen C, Schulz SM, Hubert K, **Frosch M**, Schubert-Unkmeir A, Kurzai O (2011)
Characterization of FarR as a highly specialized, growth phase-dependent transcriptional regulator in Neisseria meningitidis
Int J Med Microbiol 301:325-33

Tappe D, Meyer M, Oesterlein A, Jaye A, **Frosch M**, Schoen C, Pantchev N (2011)
Transmission of Armillifer armillatus ova at snake farm, The Gambia, West Africa
Emerg Infect Dis 17:251-4

Valenza G, Müller S, Schmitt C, Turnwald D, Lam TT, **Frosch M**, Abele-Horn M, Pfeifer Y (2011)
Evaluation of the VITEK 2 AST-N111 card for detection of extended-spectrum beta-lactamases (ESBLs) in Escherichia coli, Klebsiella pneumoniae, and Klebsiella oxytoca compared to ESBL Etests and combination disk methods
Eur J Clin Microbiol Infect Dis 30:869-72

Zlamy M, Hofer J, Elias J, Vogel U, **Frosch M**, Jungraithmayr T, Zimmerhackl LB, Prelog M (2011)
Immunogenicity of conjugate meningococcus C vaccine in pediatric solid organ transplant recipients
Vaccine 29:6163-6

Zlamy M, Hofer J, Elias J, Vogel U, **Frosch M**, Jungraithmayr T, Zimmerhackl LB, Prelog M (2011)
Immunogenicity of meningococcus C vaccination in a patient with atypical hemolytic uremic syndrome (aHUS) on eculizumab therapy
Pediatr Transplant 4, 10-3046

Elias J, Schouls LM, van de Pol I, Keijzers WC, Martin DR, Glennie A, Oster P, **Frosch M**, Vogel U, van der Ende A (2010)
Vaccine preventability of meningococcal clone, Greater Aachen Region, Germany
Emerg Infect Dis 16:465-72

Joseph B, Schneiker-Bekel S, Schramm-Glück A, Blom J, Claus H, Linke B, Schwarz RF, Becker A, Goesmann A, **Frosch M**, Schoen C. A (2010)
Comparative genome biology of a serogroup B carriage and disease strain supports a polygenic nature of meningococcal virulence
J Bacteriol 192:5363-77

Schwarz R, Joseph B, Gerlach G, Schramm-Glück A, Engelhard K, **Frosch M**, Müller T, Schoen C (2010)
Evaluation of one- and two-color gene expression arrays for microbial comparative genome hybridization analyses in routine applications
J Clin Microbiol 48:3105-10

Slanina H, König A, Hebling S, Hauck CR, **Frosch M**, Schubert-Unkmeir A (2010)
Entry of Neisseria meningitidis into mammalian cells requires the Src family protein tyrosine kinases
Infect Immun 78:1905-14

Slanina H, König A, Claus H, **Frosch M**, Schubert-Unkmeir A (2011)
Real-time impedance analysis of host cell response to meningococcal infection
J Microbiol Methods 84:101-8

Tappe D, Zidowitz S, Demmer P, Kern P, Barth TF, **Frosch M** (2010)
Three-dimensional reconstruction of Echinococcus multilocularis larval growth in human hepatic tissue reveals complex growth patterns.
Am J Trop Med Hyg 82:126-7

Tappe D, Sako Y, Itoh S, **Frosch M**, Grüner B, Kern P, Ito A (2010)
Immunoglobulin G subclass responses to recombinant Em18 in the follow-up of patients with alveolar echinococcosis in different clinical stages
Clin Vaccine Immunol 17:944-8

Tappe D, Kern P, **Frosch M**, Kern P (2010)
A hundred years of controversy about the taxonomic status of Echinococcus species
Acta Trop 115:167-74

Valenza G, Joseph B, Elias J, Claus H, Oesterlein A, Engelhardt K, Turnwald D, **Frosch M**, Abele-Horn M, Schoen C (2010)
First survey of metallo-beta-lactamases in clinical isolates of Pseudomonas aeruginosa in a German university hospital
Antimicrob Agents Chemother 54:3493-7

Valenza G, **Frosch M**, Abele-Horn M (2010)
Antimicrobial susceptibility of clinical Campylobacter isolates collected at a German university hospital during the period 2006-2008
Scand J Infect Dis 42:57-60

Valenza G, Radike K, Schoen C, Horn S, Oesterlein A, **Frosch M**, Abele-Horn M, Hebestreit H (2010)
Resistance to tobramycin and colistin in isolates of Pseudomonas aeruginosa from chronically colonized patients with cystic fibrosis under antimicrobial treatment
Scand J Infect Dis 42:885-9

Otto-Karg I, Jandl S, Müller T, Stirzel B, **Frosch M**, Hebestreit H, Abele-Horn M (2009)
Validation of Vitek 2 nonfermenting gram-negative cards and Vitek

2 version 4.02 software for identification and antimicrobial susceptibility testing of nonfermenting gram-negative rods from patients with cystic fibrosis
J Clin Microbiol 47:3283-8

Reiter-Owona I, Grüner B, **Frosch M**, Hoerauf A, Kern P, Tappe D (2009)
Serological confirmatory testing of alveolar and cystic echinococcosis in clinical practice: results of a comparative study with commercialized and in-house assays
Clin Lab 55:41-8

Schäfer D, Lâm TT, Geiger T, Mainiero M, Engelmann S, Hussain M, Bosserhoff A, **Frosch M**, Bischoff M, Wolz C, Reidl J, Sinha B (2009)
A point mutation in the sensor histidine kinase SaeS of Staphylococcus aureus strain Newman alters the response to biocide exposure
J Bacteriol 191:7306-14

Schielke S, Huebner C, Spatz C, Nägele V, Ackermann N, **Frosch M**, Kurzai O, Schubert-Unkmeir A (2009)
Expression of the meningococcal adhesin NadA is controlled by a transcriptional regulator of the MarR family
Mol Microbiol 72:1054-67

Schoen C, Tettelin H, Parkhill J, **Frosch M** (2009)
Genome flexibility in Neisseria meningitides
Vaccine 27 Suppl 2:B103-11

Schubert-Unkmeir A, Slanina H, **Frosch M** (2009)
Mammalian cell transcriptome in response to meningitis-causing pathogens
Expert Rev Mol Diagn 9:833-42

Schubert-Unkmeir A, Schramm-Gluck A, **Frosch M**, Schoen C (2009)
Transcriptome analyses in the interaction of Neisseria meningitidis with mammalian host cells
Methods Mol Biol 470:5-27

Schubert-Unkmeir A, Konrad C, Slanina H, Czapek F, Hebling S, **Frosch M** (2009)
Neisseria meningitidis induces brain microvascular endothelial cell detachment from the matrix and cleavage of occludin: a role for MMP-8
PLoS Pathog 6:e1000874

Tappe D, **Frosch M**, Sako Y, et al. (2009)
Close relationship between clinical regression and specific serology in the follow-up of patients with alveolar echinococcosis in different clinical stages
Am J Trop Med Hyg 80:792-7

Tappe D, Grüner B, Kern P, **Frosch M** (2009)
Banding pattern indicative of echinococcosis in a commercial cysticercosis Western blot
Eur J Med Res 14:451-2

Tappe D, Müller A, **Frosch M**, Stich A (2009)
Limitations of amphotericin B and nitazoxanide in the treatment of alveolar echinococcosis
Ann Trop Med Parasitol 103:177-81

3.2.2 Klaus Brehm

Epping K, **Brehm K** (2011)
Echinococcus multilocularis: molecular characterization of EmSmadE, a novel BR-Smad involved in TGF-b and BMP signalling
Exp Parasitol 129:85-94

Förster S, Günthel D, Kiss F, **Brehm K** (2011)
Molecular characterisation of a serum-responsive, DAF-12-like nuclear hormone receptor of the fox-tapeworm Echinococcus multilocularis
J Cell Biochem 112:1630-42

Brehm K (2010)
Echinococcus multilocularis as an experimental model in stem cell research and molecular host-parasite interaction
Parasitology 137:537-55

Brehm K (2010)
The role of evolutionarily conserved signalling systems in Echinococcus multilocularis development and host-parasite interaction
Med Microbiol Immunol 199:247-59

Gelmedin V, Spiliotis M, **Brehm K** (2010)
Molecular characterisation of MEK1/2- and MKK3/6-like mitogen-activated protein kinase kinases (MAPKK) from the fox tapeworm Echinococcus multilocularis
Int J Parasitol 40:555-67

Spiliotis M, Mizukami C, Oku Y, Kiss F, **Brehm K**, Gottstein B (2010)
Echinococcus multilocularis primary cells: improved isolation, small-scale cultivation and RNA interference
Mol Biochem Parasitol 174:83-7

You H, Zhang W, Jones MK, Gobert GN, Mulvenna J, Rees G, Spanevello M, Blair D, Duke M, **Brehm K**, McManus DP (2010)
Cloning and characterisation of Schistosoma japonicum insulin receptors
PLoS One 5:e9868

Bernthaler P, Epping K, Schmitz G, Deplazes P, **Brehm K** (2009)
Molecular characterization of EmABP, an apolipoprotein A-I binding protein secreted by the Echinococcus multilocularis metacestode
Infect Immun 77:5564-71

Spiliotis M, **Brehm K** (2009)
Axenic in vitro cultivation of Echinococcus multilocularis metacestode vesicles and the generation of primary cell cultures
Methods Mol Biol 470:245-62

Tappe D, Pukall R, Schumann P, Gronow S, Spiliotis M, Claus H, **Brehm K**, Vogel U (2009)
Streptococcus merionis sp. nov., isolated from Mongolian jirds (Meriones unguiculatus)
Int J Syst Evol Microbiol 59:766-70

3.2.3 Alexandra Schubert-Unkmeir

Kobsar A, Siauw C, Gambaryan S, Hebling S, Speer C, **Schubert-Unkmeir A** (2011)
Eigenthaler M. Neisseria meningitidis induces platelet inhibition and increases vascular endothelial permeability via nitric oxide regulated pathways
Thromb Haemost 106(6):1127-38

Slanina H, König A, Claus H, Frosch M, **Schubert-Unkmeir A** (2011)
Real-time impedance analysis of host cell response to meningococcal infection
J Microbiol Methods 84(1):101-8

Schubert-Unkmeir A, Konrad C, Slanina H, Czapek F, Hebling S, Frosch M (2010)
Neisseria meningitidis induces brain microvascular endothelial cell detachment from the matrix and cleavage of occludin: a role for MMP-8
PLoS Pathog 29;6(4):e1000874

Schielke S, Schmitt C, Spatz C, Frosch M, **Schubert-Unkmeir A**, Kurzai O (2010)
The transcriptional repressor FarR is not involved in meningococcal fatty acid resistance mediated by the FarAB efflux pump and dependent on lipopolysaccharide structure
Appl Environ Microbiol 76(10):3160-9

Slanina H, König A, Hebling S, Hauck CR, Frosch M, **Schubert-Unkmeir A** (2010)
Entry of Neisseria meningitidis into mammalian cells requires the Src family protein tyrosine kinases
Infect Immun 78(5):1905-14

Schubert-Unkmeir A, Slanina H, Frosch M (2009)
Mammalian cell transcriptome in response to meningitis-causing pathogens
Expert Rev Mol Diagn 9(8):833-42

Schielke S, Huebner C, Spatz C, Nägele V, Ackermann N, Frosch M, Kurzai O, **Schubert-Unkmeir A** (2009)
Expression of the meningococcal adhesin NadA is controlled by a transcriptional regulator of the MarR family
Mol Microbiol 72(4):1054-67

Schubert-Unkmeir A, Schramm-Glück A, Frosch M, Schoen C (2009)
Transcriptome analyses in the interaction of Neisseria meningitidis with mammalian host cells
Methods Mol Biol 470:5-27

3.2.4 Ulrich Vogel

Vogel U (2011)
European efforts to harmonize typing of meningococci
Int J Med Microbiol 301(8):659-62

Zlamy M, Hofer J, Elias J, **Vogel U**, Frosch M, Jungraithmayr T, Zimmerhackl LB, Prelog M (2011)
Immunogenicity of meningococcus C vaccination in a patient with atypical hemolytic uremic syndrome (aHUS) on eculizumab therapy
Pediatr Transplant 4:10-3046

Joseph B, Schwarz RF, Linke B, Blom J, Becker A, Claus H, Goesmann A, Frosch M, Müller T, **Vogel U**, Schoen C (2011)
Virulence evolution of the human pathogen Neisseria meningitidis by recombination in the core and accessory genome
PLoS One 26;6(4):e18441

Lâm TT, Claus H, Frosch M, **Vogel U** (2011)
Sequence analysis of serotype-specific synthesis regions II of Haemophilus influenzae serotypes c and d: evidence for common ancestry of capsule synthesis in Pasteurellaceae and Neisseria meningitides
Res Microbiol 162(5):483-7

Vogel U, Claus H (2011)
Vaccine development against Neisseria meningitides
Microb Biotechnol 4(1):20-31. Review

van Alen T, Claus H, Zahedi RP, Groh J, Blazyca H, Lappann M, Sickmann A, **Vogel U** (2010)
Comparative proteomic analysis of biofilm and planktonic cells of Neisseria meningitidis
Proteomics 10(24):4512-21. doi: 10.1002/pmic.201000267

Lâm TT, Elias J, Frosch M, **Vogel U**, Claus H (2011)
New diagnostic PCR for Haemophilus influenzae serotype e based on the cap locus of strain ATCC 8142
Int J Med Microbiol 301(2):176-9

Tappe D, Schulze MH, Oesterlein A, Turnwald D, Müller A, **Vogel U**, Stich A (2010)
Panton-Valentine leukocidin-positive Staphylococcus aureus infections in returning travelers
Am J Trop Med Hyg 83(4):748-5

Vogel U (2010)
Molecular epidemiology of meningococci: application of DNA sequence typing
Int J Med Microbio 300(7):415-20 Review

Elias J, Schouls LM, van de Pol I, Keijzers WC, Martin DR, Glennie A, Oster P, Frosch M, **Vogel U**, van der Ende A (2010)
Vaccine preventability of meningococcal clone, Greater Aachen Region, Germany
Emerg Infect Dis 16:465-72

Elias J, Schoen C, Heinze G, Valenza G, Gerharz E, Gerharz H, **Vogel U** (2010)
Nosocomial outbreak of VIM-2 metallo-beta-lactamase-producing Pseudomonas aeruginosa associated with retrograde urography.
Clin Microbiol Infect 16:1494-500

Lappann M, **Vogel U** (2010)
Biofilm formation by the human pathogen Neisseria meningitidis
Med Microbiol Immunol 199(3):173-83

Lappann M, Claus H, van Alen T, Harmsen M, Elias J, Molin S, **Vogel U** (2010)
A dual role of extracellular DNA during biofilm formation of Neisseria meningitidis
Mol Microbiol 75(6):1355-71

Lewis LA, Ngampasutadol J, Wallace R, Reid JE, **Vogel U**, Ram S (2010)
The meningococcal vaccine candidate neisserial surface protein A

(NspA) binds to factor H and enhances meningococcal resistance to complement
PLoS Pathog 6:e1001027

Claus H, Matsunaga W, **Vogel U** (2010)
Molecular discrimination between Neisseria meningitidis serogroups W-135 and Y based on the nucleotide recognition domain sequence of the capsule polymerases
J Clin Microbiol 48:3459-60

Vogel U, Schoen C, Elias J (2010)
Population Genetics of Neisseria meningitides
In: Robinson, D. A., Falush, D., Feil, E. J., eds. Bacterial Population Genetics in Infectious Disease
Oxford, UK: Wiley-Blackwell pp. 247-267

Mordhorst IL, Claus H, Ewers C, Lappann M, Schoen C, Elias J, Batzilla J, Dobrindt U, Wieler LH, Bergfeld AK, Mühlenhoff M, **Vogel U** (2009)
O-acetyltransferase gene neuO is segregated according to phylogenetic background and contributes to environmental desiccation resistance in Escherichia coli K1
Environ Microbiol 11(12):3154-65

Bergfeld AK, Claus H, Lorenzen NK, Spielmann F, **Vogel U**, Mühlenhoff M (2009)
The polysialic acid-specific O-acetyltransferase OatC from Neisseria meningitidis serogroup C evolved apart from other bacterial sialate O-acetyltransferases
J Biol Chem 284:6-16

Valenza G, Veihelmann S, Peplies J, Tichy D, Roldan-Pareja Mdel C, Schlagenhauf U, **Vogel U** (2009)
Microbial changes in periodontitis successfully treated by mechanical plaque removal and systemic amoxicillin and metronidazol
Int J Med Microbiol 299(6):427-38

Tappe D, Pukall R, Schumann P, Gronow S, Spiliotis M, Claus H, Brehm K, **Vogel U** (2009)
Streptococcus merionis sp. nov., isolated from Mongolian jirds (Meriones unguiculatus)
Int J Syst Evol Microbiol 59(Pt 4):766-70

Claus H, Stummeyer K, Batzilla J, Mühlenhoff M, **Vogel U** (2009)
Amino acid 310 determines the donor substrate specificity of serogroup W-135 and Y capsule polymerases of Neisseria meningitidis
Mol Microbiol 71(4):960-71

3.3.1 Thomas Hünig

Römer PS, Berr S, Avota E, Na SY, Battaglia M, ten Berge I, Einsele H, **Hünig T**
Preculture of PBMCs at high cell density increases sensitivity of T-cell responses, revealing cytokine release by CD28 superagonist TGN1412
Blood 118(26):6772-82

Vaeth M, Gogishvili T, Bopp T, Klein M, Berberich-Siebelt F, Gattenloehner S, Avots A, Sparwasser T, Grebe N, Schmitt E, **Hünig T**, Serfling E, Bodor J (2011)
Regulatory T cells facilitate the nuclear accumulation of inducible cAMP early repressor (ICER) and suppress nuclear factor of activated T cell c1 (NFATc1)
Proc Natl Acad Sci USA 108(6):2480-5

Tabares P, Pimentel-Elardo SM, Schirmeister T, **Hünig T**, Hentschel U (2011)
Anti-protease and immunomodulatory activities of bacteria associated with Caribbean sponges
Mar Biotechnol 13(5):883-92

Pallardy M, **Hünig T** (2010)
Primate testing of TGN1412: right target, wrong cell
Br J Pharmacol 161(3):509-11

Hünig T, Lühder F, Elflein K, Gogishvili T, Fröhlich M, Guler R, Cutler A, Brombacher F (2010)
CD28 and IL-4: two heavyweights controlling the balance between immunity and inflammation
Med Microbiol Immunol 199(3):239-46

Michaelis K, Wallbrecht K, Kerstan A, Beyersdorf N, Williams C, Kerkau T, Wang XJ, **Hünig T**, Schön MP (2010)
Modulating T cell functions does not alleviate chronic inflammatory skin lesions in K5.TGF beta 1 transgenic mice
Exp Dermatol 19(5):406-15

Göbel K, Melzer N, Herrmann AM, Schuhmann MK, Bittner S, Ip CW, **Hünig T**, Meuth SG, Wiendl H (2010)
Collateral neuronal apoptosis in CNS gray matter during an oligodendrocyte-directed CD8(+) T cell attack
Glia 58(4):469-80

Beyersdorf N, Ding X, **Hünig T**, Kerkau T (2009)
Superagonistic CD28 stimulation of allogeneic T cells protects from acute graft-versus-host disease
Blood 114(20):4575-82

Na SY, Eujen H, Göbel K, Meuth SG, Martens K, Wiendl H, **Hünig T** (2009)
Antigen-specific blockade of lethal CD8 T-cell mediated autoimmunity in a mouse model of multiple sclerosis
J Immunol 182(10):6569-75

Gogishvili T, Langenhorst D, Lühder F, Elias F, Elflein K, Dennehy KM, Gold R, **Hünig T** (2009)
Rapid regulatory T-cell response prevents cytokine storm in CD28 superagonist treated mice
PLoS One 4(2):e4643

3.3.2 Thomas Herrmann

Beyersdorf N, Werner S, Wolf N, **Herrmann T**, Kerkau T (2011)
Characterization of a new mouse model for peripheral T cell lymphoma in humans
PLoS One 6(12):e28546

Elsner L, Flügge PF, Lozano J, Muppala V, Eiz-Vesper B, Demiroglu SY, Malzahn D, **Herrmann T**, Brunner E, Bickeböller H, Multhoff G, Walter L, Dressel R (2010)
The endogenous danger signals HSP70 and MICA cooperate in the activation of cytotoxic effector functions of NK cells
J Cell Mol Med 14(4):992-1002

Monzon-Casanova E, Steiniger B, Schweigle S, Clemen H, Zdzieblo D, Starick L, Müller I, Wang CR, Rhost S, Cardell S, Pyz E, **Herrmann T** (2010)
CD1d expression in paneth cells and rat exocrine pancreas revealed by novel monoclonal antibodies which differentially affect NKT cell activation
PLoS One 5(9)pii:e13089

Brandl C, Ortler S, **Herrmann T**, Cardell S, Lutz MB, Wiendl H (2010)
B7-H1-deficiency enhances the potential of tolerogenic dendritic cells by activating CD1d-restricted type II NKT cells
PLoS One 5(5):e10800

Dlaske H, Karaüzüm H, Monzon-Casanova E, Rudolf R, Starick L, Müller I, Wildner G, Diedrichs-Möhring M, Koch N, Miyoshi-Akiyama T, Uchiyama T, Wonigeit K, Fleischer B, Overbeck S, Rink L, **Herrmann T** (2009)
Superantigen-presentation by rat major histocompatibility complex class II molecules RT1.Bl and RT1.Dl.
Immunology 128:e572-81

Marx JA, Röhrborn AJ, Koelsch BU, Fischer C, **Herrmann T**, Pietsch T, Rajewsky MF, Kindler-Röhrborn A (2009)
Ablation of T cell immunity differentially influences tumor risk in inbred BD rat strains.
Cancer Immunol Immunother 58(8):1287-95

Li J, Herold MJ, Kimmel B, Müller I, Rincon-Orozco B, Kunzmann V, **Herrmann T** (2009)
Reduced expression of the mevalonate pathway enzyme farnesyl pyrophosphatesynthase unveils recognition of tumor cells by Vgamma9Vdelta2 T cells
J Immunol 182(12):8118-24

Kunzmann V, Kimmel B, **Herrmann T**, Einsele H, Wilhelm M (2009)
Inhibition of phosphoantigen-mediated gammadelta T-cell proliferation by CD4+ CD25+ FoxP3+ regulatory T cells
Immunology 126(2):256-67

3.3.3 Manfred Lutz

Oberländer U, Pletinckx K, Döhler A, Müller N, **Lutz MB**, Arzberger T, Riederer P, Gerlach M, Koutsilieri E, Scheller C (2011)
Neuromelanin is an immune stimulator for dendritic cells in vitro
BMC Neurosci 12:116

Pletinckx K, Stijlemans B, Pavlovic V, Laube R, Brandl C, Kneitz S, Beschin A, De Baetselier P, **Lutz MB** (2011)
Similar inflammatory DC maturation signatures induced by TNF or Trypanosoma brucei antigens instruct default Th2-cell responses
Eur J Immunol 41(12):3479-94

Pletinckx K, Döhler A, Pavlovic V, **Lutz MB** (2011)
Role of dendritic cell maturity/costimulation for generation, homeostasis, and suppressive activity of regulatory T cells
Front Immunol 2:39

Brandl C, Ortler S, Herrmann T, Cardell S, **Lutz MB**, Wiendl H (2010)
B7-H1-deficiency enhances the potential of tolerogenic dendritic cells by activating CD1d-restricted type II NKT cells
PLoS One 5(5):e10800

Ribechini E, Greifenberg V, Sandwick S, **Lutz MB** (2010)
Subsets, expansion and activation of myeloid-derived suppressor cells
Med Microbiol Immunol 199(3):273-81

Lutz MB, Döhler A, Azukizawa H (2010)
Revisiting the tolerogenicity of epidermal Langerhans cells
Immunol Cell Biol 88(4):381-6

Ribechini E, Leenen PJ, **Lutz MB** (2009)
Gr-1 antibody induces STAT signaling, macrophage marker expression and abrogation of myeloid-derived suppressor cell activity in BM cells
Eur J Immunol 39(12):3538-51

Lutz MB, Kurts C (2009)
Induction of peripheral CD4+ T-cell tolerance and CD8+T-cell cross-tolerance by dendritic cells
Eur J Immunol 39(9):2325-30

3.4.1 Axel Rethwilm

Matthes D, Wiktorowicz T, Zahn J, Bodem J, Stanke N, Lindemann D, **Rethwilm A** (2011)
Basic residues in the foamy virus Gag protein
J Virol 85:3986-3995

Hartl MJ, Bodem J, Jochheim F, **Rethwilm A**, Rösch R, Wöhrl BM (2011)
Regulation of foamy virus protease activity by viral RNA: a novel and unique mechanism among retroviruses
J Virol 85:4462-4469

Kasang C, Kalluvya S, Majinge C, Stich A, Bodem J, Kongola G, Jacobs GB, Mlewa M, Mildner M, Hensel I, Horn A, Preiser W, van Zyl G, Klinker H, Koutsilieri E, **Rethwilm A**, Scheller C, Weissbrich B (2011)
HIV drug resistance (HIVDR) in antiretroviral therapy-naive patients in Tanzania not eligible for WHO threshold HIVDR survey is dramatically high
PLoS One 6:e23091

Lindemann D, **Rethwilm A** (2011)
Foamy virus biology and its application for vector development
Viruses 3(5):561-85

Shityakov S, **Rethwilm A**, Dandekar T (2010)
Structural and docking analysis of HIV-1 integrase and Transportin-SR2 interaction: Ist this a more general route for retroviral nuclear import and ist regulation?
Online J Bioinform 11:19-33

Nowotny B, Schneider T, Pradel G, Schirmeister T, **Rethwilm A**, Kirschner M (2010)
Inducible APOBEC3G-Vif double stable cell line as a high throughput screening platform to identify antiviral compounds
Antimicrob Agents Chemother 54:78-87

Hartl MJ, Mayr F, **Rethwilm A**, Wöhrl BM (2010)
Biophysical and enzymatic properties of the simian and prototype foamy virus reverse transcriptases
Retrovirology 7:5

Falkowska-Hansen B, Kollar J, Grüner BM, Schanz M, Boukamp P, Siveke J, **Rethwilm A**, Kirschner M (2010)
An inducible Tet-Off-H2B-GFP lentiviral reporter vector for detection and in vivo isolation of label-retaining cells
Exp Cell Res 316:18885-18895

Rethwilm A (2010)
Das große Erbrechen
GfV Homepage-Artikel

Rethwilm A (2010)
Molecular biology of foamy viruses
Med Microbiol Immunol 199:197-207

Schulze A, Lemey P, Schubert J McClure MO, **Rethwilm A**, Bodem J (2010)
Complete nucleotide sequence and evolutionary analysis of a gorilla foamy virus
J Gen Virol 92: 582-586

Bodem J, Schied T, Gabriel R, Rammling M, **Rethwilm A**(2010)
Foamy virus nuclear RNA-export is distinct from that of other retroviruses
J Virol 85: 2333-2341

Rothenaigner I, Kramer S, Meggendorfer M, **Rethwilm A**, Brack-Werner R (2009)
Genetic engeneering of human neural progenitor cells with foamy virus vectors
Gene Ther 16:349-358

Gärtner K, Wiktorowicz T, Park J, Mergia A, **Rethwilm A**, Scheller C (2009)
Accuracy estimation of foamy virus genome copying
Retrovirology 6:32

Rohayem J, **Rethwilm A** (2009)
Caliciviren
In: Doerr/Gerlich (Eds.): **Medizinische Virologie**, 2. Auflage, Thieme, Stuttgart; ISBN-10: 3131139625

Wiktorowicz T, Peters K, Armbruster N, Steinert AF, **Rethwilm A** (2009)
Generation of an improved foamy virus vector by dissection of cis-acting sequences
J Gen Virol 90:481-487

Steinert A, **Rethwilm A** (2009)
Gentherapie des muskuloskelettalen Systems am OZMF - Die Sektion Gentherapie
In: **Muskuloskelettale Forschung 2001-2009**, von der Klinischen Forschergruppe zum Forschungszentrum; p 124 - 134 Hrsg.: F. Jakob. G.N. Duda, U. Nöth, N. Schütze, W. Sebald

Steinert AF, Proffen B, Kunz M, Hendrich C, Ghivizzani SC, Nöth U, **Rethwilm A**, Eulert J, Evans CH (2009)
Hypertrophy is induced during the in vitro chondrogenic differentiation of human mesenchymal stem cells by bone morphogenic protein-2 and bone morohogenic protein-4 gene transfer
Arthritis Res Ther 11:148

3.4.2 Sibylle Schneider-Schaulies

Avota E, Gassert E, **Schneider-Schaulies S** (2011)
Cytoskeletal dynamics: concepts in measles virus replication and immunomodulation
Viruses 3(2):102-17

Boussaad I, Varagnolo L, Hornich V, Rieger L, Krockenberger M, Stuehmer T,
Kranzfelder D, Mueller AM, **Schneider-Schaulies S** (2011)
Wild-type measles virus interferes with short-term engraftment of human CD34+ hematopoietic progenitor cells
J Virol 85(15):7710-8

Avota E, Gulbins E, **Schneider-Schaulies S** (2011)
DC-SIGN mediated sphingomyelinase-activation and ceramide generation is essential for enhancement of viral uptake in dendritic cells
PLoS Pathog 7(2):e1001290

Tran-Van H, Avota E, Börtlein C, Mueller N, **Schneider-Schaulies S** (2011)
Measles virus modulates dendritic cell/T-cell communication at the level of plexinA1/neuropilin-1 recruitment and activity
Eur J Immunol 41(1):151-63

Avota E, Gassert E, **Schneider-Schaulies S** (2010)
Measles virus-induced immunosuppression: from effectors to mechanisms
Med Microbiol Immunol 199(3):227-37

Salditt A, Koethe S, Pohl C, Harms H, Kolesnikova L, Becker S, **Schneider-Schaulies S** (2010)
Measles virus M protein-driven particle production does not involve the endosomal sorting complex required for transport (ESCRT) system
J Gen Virol 91(6):1464-72

Gassert E, Avota E, Harms H, Krohne G, Gulbins E, **Schneider-Schaulies S** (2009)
Induction of membrane ceramides: a novel strategy to interfere with T lymphocyte cytoskeletal reorganisation in viral immunosuppression
PLoS Pathog 5(10):e1000623

Abt M, Gassert E, **Schneider-Schaulies S** (2009)
Measles virus modulates chemokine release and chemotactic responses of dendritic cells
J Gen Virol 90(4):909-14

Schneider-Schaulies S, Schneider-Schaulies J (2009)
Measles virus-induced immunosuppression
Curr Top Microbiol Immunol 330:243-69

3.5.1 Thomas Rudel

Albrecht M, Sharma CM, Dittrich MT, Müller T, Reinhardt R, Vogel J, **Rudel T** (2011)
The transcriptional landscape of Chlamydia pneumonia
Genome Biol 12(10):R98

Sharma M, Machuy N, Böhme L, Karunakaran K, Mäurer AP, Meyer TF, **Rudel T** (2011)
HIF-1α is involved in mediating apoptosis resistance to Chlamydia trachomatis-infected cells
Cell Microbiol 13(10):1573-85

Karunakaran K, Mehlitz A, **Rudel T** (2011)
Evolutionary conservation of infection-induced cell death inhibition among Chlamydiales
PLoS One 6(7):e22528

Kozjak-Pavlovic V, Ott C, Götz M, **Rudel T** (2011)
Neisserial Omp85 protein is selectively recognized and assembled into functional complexes in the outer membrane of human mitochondria
J Biol Chem 286(30):27019-26

Prusty BK, Karlas A, Meyer TF, **Rudel T** (2011)
Genome-wide RNAi screen for viral replication in mammalian cell culture
Methods Mol Biol 721:383-95

Sievers C, Billig G, Gottschalk K, **Rudel T** (2010)
Prohibitins are required for cancer cell proliferation and adhesion
PLoS One 5(9):e12735

Rudel T, Kepp O, Kozjak-Pavlovic V (2010)
Interactions between bacterial pathogens and mitochondrial cell death pathways
Nat Rev Microbiol 8(10):693-705

Böhme L, Albrecht M, Riede O, **Rudel T** (2010)
Chlamydia trachomatis-infected host cells resist dsRNA-induced apoptosis
Cell Microbiol 12(9):1340-51

Prakash H, Albrecht M, Becker D, Kuhlmann T, **Rudel T** (2010)
Deficiency of XIAP leads to sensitization for Chlamydophila pneumoniae pulmonary infection and dysregulation of innate immune response in mice
J Biol Chem 285(26):20291-302

Gurumurthy RK, Mäurer AP, Machuy N, Hess S, Pleissner KP, Schuchhardt J, **Rudel T**, Meyer TF (2010)
A loss-of-function screen reveals Ras- and Raf-independent MEK-ERK signaling during Chlamydia trachomatis infection
Sci Signal 3(113):ra21

Kozjak-Pavlovic V, Ross K, Götz M, Goosmann C, **Rudel T** (2010)
A tag at the carboxy terminus prevents membrane integration of VDAC1 in mammalian mitochondria
J Mol Biol 397(1):219-32

Karlas A, Machuy N, Shin Y, Pleissner KP, Artarini A, Heuer D, Becker D, Khalil H, Ogilvie LA, Hess S, Mäurer AP, Müller E, Wolff T, **Rudel T**, Meyer TF (2010)
Genome-wide RNAi screen identifies human host factors crucial for influenza virus replication
Nature 463(7282):818-22

Albrecht M, Sharma CM, Reinhardt R, Vogel J, **Rudel T** (2010)
Deep sequencing-based discovery of the Chlamydia trachomatis transcriptome
Nucleic Acids Res 38(3):868-77

Kozjak-Pavlovic V, Dian-Lothrop EA, Meinecke M, Kepp O, Ross K, Rajalingam K, Harsman A, Hauf E, Brinkmann V, Günther D, Hermann I, Hurwitz R, Rassow J, Wagner R, **Rudel T** (2009)
Bacterial porin disrupts mitochondrial membrane potential and sensitizes host cells to apoptosis
PLoS Pathog 5(10):e1000629

Böhme L, **Rudel T** (2009)
Host cell death machinery as a target for bacterial pathogens
Microbes Infect 11(13):1063-70

Prakash H, Becker D, Böhme L, Albert L, Witzenrath M, Rosseau S, Meyer TF, **Rudel T** (2009)
cIAP-1 controls innate immunity to C. pneumoniae pulmonary infection
PLoS One 4(8):e6519

Kepp O, Gottschalk K, Churin Y, Rajalingam K, Brinkmann V, Machuy N, Kroemer G, **Rudel T** (2009)
Bim and Bmf synergize to induce apoptosis in Neisseria gonorrhoeae infection
PLoS Pathog 5(3):e1000348

Sharma M, **Rudel T** (2009)
Apoptosis resistance in Chlamydia-infected cells: a fate worse than death?
FEMS Immunol Med Microbiol 55(2):154-61

Jung M, Mollenkopf HJ, Grimm C, Wagner I, Albrecht M, Waller T, Pilarsky C, Johannsen M, Stephan C, Lehrach H, Nietfeld W, **Rudel T**, Jung K, Kristiansen G (2009)
MicroRNA profiling of clear cell renal cell cancer identifies a robust signature to define renal malignancy
J Cell Mol Med 13(9B):3918-28

Ross K, **Rudel T** Kozjak-Pavlovic V (2009)
TOM-independent complex formation of Bax and Bak in mammalian mitochondria during TNFalpha-induced apoptosis
Cell Death Differ 16(5):697-707

3.5.2 Roy Gross

Junker RR, Loewel C, **Gross R**, Dötterl S, Keller A, Blüthgen N (2011)
Composition of epiphytic bacterial communities differs on petals and leaves
Plant Biol 13(6):918-24

Ratzka C, Liang C, Dandekar T, **Gross R**, Feldhaar H (2011)
Immune response of the ant Camponotus floridanus against pathogens and its obligate mutualistic endosymbiont
Insect Biochem Mol Biol 41(8):529-36

Stoll S, Feldhaar H, Fraunholz MJ, **Gross R** (2010)
Bacteriocyte dynamics during development of a holometabolous insect, the carpenter ant Camponotus floridanus
BMC Microbiol 10:308

Gross R, Keidel K, Schmitt K (2010)
Resemblance and divergence: the „new" members of the genus Bordetella
Med Microbiol Immunol 99(3):155-63

Liang C, Schmid A, López-Sánchez MJ, Moya A, **Gross R**, Bernhardt J, Dandekar T (2009)
JANE: efficient mapping of prokaryotic ESTs and variable length sequence reads on related template genomes
BMC Bioinformatics 10:391

Gross R, Vavre F, Heddi A, Hurst GD, Zchori-Fein E, Bourtzis K (2009)
Immunity and symbiosis
Mol Microbiol 73(5):751-9

Lechner M, Schmitt K, Bauer S, Hot D, Hubans C, Levillain E, Locht C, Lemoine Y, **Gross R** (2009)
Genomic island excisions in Bordetella petrii
BMC Microbiol 9:141

Stoll S, Feldhaar H, **Gross R** (2009)
Promoter characterization in the AT-rich genome of the obligate endosymbiont "Candidatus Blochmannia floridanus"
J Bacteriol 191(11):3747-51

Stoll S, Feldhaar H, **Gross R** (2009)
Transcriptional profiling of the endosymbiont Blochmannia floridanus during different developmental stages of its holometabolous ant host
Environ Microbiol 11(4):877-88

Feldhaar H, **Gross R** (2009)
Insects as hosts for mutualistic bacteria
Int J Med Microbiol 299(1):1-8

Horvat A, **Gross R** (2009)
Molecular characterization of the BvgA response regulator of Bordetella holmesii
Microbiol Res 164(3):243-52

3.6.1 Hermann Einsele

Römer PS, Berr S, Avota E, Na SY, Battaglia M, ten Berge I, **Einsele H**, Hünig
T (2011)
Preculture of PBMCs at high cell density increases sensitivity of T-cell responses, revealing cytokine release by CD28 superagonist TGN1412
Blood 118(26):6772-82

Fuji S, Kapp M, Grigoleit GU, **Einsele H** (2011)
Adoptive immunotherapy with virus-specific T cells
Best Pract Res Clin Haematol 24(3):413-9

Bouzani M, Ok M, McCormick A, Ebel F, Kurzai O, Morton CO, **Einsele H**, Loeffler J (2011)
Human NK cells display important antifungal activity against Aspergillus fumigatus, which is directly mediated by IFN-γ release
J Immunol 187(3):1369-76

Zirkel J, Klinker H, Kuhn A, Abele-Horn M, Tappe D, Turnwald D, **Einsele H**,
Heinz WJ (2011)
Epidemiology of Candida blood stream infections in patients with hematological malignancies or solid tumors
Med Mycol 50(1):50-5

Topp MS, Kufer P, Gökbuget N, Goebeler M, Klinger M, Neumann S, Horst HA, Raff T, Viardot A, Schmid M, Stelljes M, Schaich M, Degenhard E, Köhne-Volland R, Brüggemann M, Ottmann O, Pfeifer H, Burmeister T, Nagorsen D, Schmidt M, Lutterbuese R, Reinhardt C, Baeuerle PA, Kneba M, **Einsele H**, Riethmüller G, Hoelzer D, Zugmaier G, Bargou RC (2011)
Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival
J Clin Oncol 29(18):2493-8

Kortüm M, **Einsele H** (2011)
Results of the first bortezomib-based induction therapy in the treatment of multiple myeloma
Expert Opin Pharmacother 12(10):1661-3

Muhammad K, Roll P, Seibold T, Kleinert S, **Einsele H**, Dörner T, Tony HP (2011)
Impact of IL-6 receptor inhibition on human memory B cells in vivo: impaired somatic hypermutation in preswitch memory B cells and modulation of mutational targeting in memory B cells
Ann Rheum Dis 70(8):1507-10

Ok M, **Einsele H**, Loeffler J (2011)
Genetic susceptibility to Aspergillus fumigatus infections
Int J Med Microbiol 301(5):445-52

Stuehler C, Khanna N, Bozza S, Zelante T, Moretti S, Kruhm M, Lurati S, Conrad B, Worschech E, Stevanović S, Krappmann S, **Einsele H**, Latgé JP, Loeffler J, Romani L, Topp MS (2011)
Cross-protective TH1 immunity against Aspergillus fumigatus and Candida albicans
Blood 117(22):5881-91

Kapp M, Schargus M, Deuchert T, Springer J, Wendel F, Loeffler J, Grigoleit GU, Kurzai O, Heinz W, **Einsele H**, Stuhler G (2011)
Endophthalmitis as primary clinical manifestation of fatal fusariosis in an allogeneic stem cell recipient
Transpl Infect Dis 13(4):374-9

Roll P, Muhammad K, Schumann M, Kleinert S, **Einsele H**, Dörner T, Tony HP (2011)
In vivo effects of the anti-interleukin-6 receptor inhibitor tocilizumab on the B cell compartment
Arthritis Rheum 63(5):1255-64

Flechsig C, Suezer Y, Kapp M, Tan SM, Löffler J, Sutter G, **Einsele H**, Grigoleit GU (2011)
Uptake of antigens from modified vaccinia Ankara virus-infected leukocytes enhances the immunostimulatory capacity of dendritic cells
Cytotherapy 13(6):739-52

Springer J, Loeffler J, Heinz W, Schlossnagel H, Lehmann M, Morton O, Rogers TR, Schmitt C, Frosch M, **Einsele H**, Kurzai O (2011)
Pathogen-specific DNA enrichment does not increase sensitivity of PCR for diagnosis of invasive aspergillosis in neutropenic patients
J Clin Microbiol 49(4):1267-73

Kortüm M, Knop S, **Einsele H** (2011)
Novel agents to improve outcome of allogeneic transplantation for patients with multiple myeloma
Future Oncol 7(1):135-43

Steinbrunn T, Stühmer T, Gattenlöhner S, Rosenwald A, Mottok A, Unzicker C, **Einsele H**, Chatterjee M, Bargou RC (2011)
Mutated RAS and constitutively activated Akt delineate distinct oncogenic pathways, which independently contribute to multiple myeloma cell survival
Blood 117(6):1998-2004

Mui TS, Kapp M, **Einsele H**, Grigoleit GU (2010)
T-cell therapy for cytomegalovirus infection
Curr Opin Organ Transplant epub ahead of print

Loeffler J, Ok M, Morton OC, Mezger M, **Einsele H** (2010)
Genetic polymorphisms in the cytokine and chemokine system: their possible importance in allogeneic stem cell transplantation
Curr Top Microbiol Immunol 341:83-96

Mezger M, **Einsele H**, Loeffler J (2010)
Genetic susceptibility to infections with Aspergillus fumigatus
Crit Rev Microbiol 36(2):168-77

Stühmer T, Arts J, Chatterjee M, Borawski J, Wolff A, King P, **Einsele H**, Leo E, Bargou RC (2010)
Preclinical anti-myeloma activity of the novel HDAC-inhibitor JNJ-26481585
Br J Haematol 149(4):529-36

Gattenlöhner S, **Einsele H** (2010)
Development of acute lympboblastic leukemia in a patient with increased hematogones after toxic bone marrow damage
Int J Clin Exp Pathol 3(3):310-2

Seggewiss R, **Einsele H** (2010)
Immune reconstitution after allogeneic transplantation and expanding options for immunomodulation: an update
Blood 115(19):3861-8

Einsele H (2010)
Bortezomib
Recent Results Cancer Res 184:173-87

Spinnler K, Mezger M, Steffens M, Sennefelder H, Kurzai O, **Einsele H**, Loeffler J (2010)
Role of glycogen synthase kinase 3 (GSK-3) in innate immune response of human immature dendritic cells to Aspergillus fumigatus
Med Mycol 48(4):589-97

Mezger M, Bonin M, Kessler T, Gebhardt F, **Einsele H**, Loeffler J (2009)
Toll-like receptor 3 has no critical role during early immune response of human monocyte-derived dendritic cells after infection with the human cytomegalovirus strain TB40E
Viral Immunol 22(6):343-51

Stühmer T, Chatterjee M, Grella E, Seggewiss R, Langer C, Müller S, Schoepfer J, Garcia-Echeverria C, Quadt C, Jensen MR, **Einsele H**, Bargou RC (2009)
Anti-myeloma activity of the novel 2-aminothienopyrimidine Hsp90 inhibitor NVP-BEP800
Br J Haematol 147(3):319-27

Ok M, Latgé JP, Baeuerlein C, Ebel F, Mezger M, Topp M, Kurzai O, Killian D, Kapp M, Grigoleit GU, Sennefelder H, Arroyo J, **Einsele H**, Loeffler J (2009)
Immune responses of human immature dendritic cells can be modulated by the recombinant Aspergillus fumigatus antigen Aspf1
Clin Vaccine Immunol 16(10):1485-92

Stuehler C, Mielke S, Chatterjee M, Duell J, Lurati S, Rueckert F, **Einsele H**, Bargou RC, Topp MS (2009)
Selective depletion of alloreactive T cells by targeted therapy of heat shock protein 90: a novel strategy for control of graft-versus-host disease
Blood 114(13):2829-36

Muhammad K, Roll P, **Einsele H**, Dörner T, Tony HP (2009)
Delayed acquisition of somatic hypermutations in repopulated IGD+CD27+ memory B cell receptors after rituximab treatment
Arthritis Rheum 60(8):2284-93

Kapp M, Rasche L, **Einsele H**, Grigoleit GU (2009)
Cellular therapy to control tumor progression
Curr Opin Hematol 16(6):437-43

Diekmann J, Adamopoulou E, Beck O, Rauser G, Lurati S, Tenzer S, **Einsele H**, Rammensee HG, Schild H, Topp MS (2009)
Processing of two latent membrane protein 1 MHC class I epitopes requires tripeptidyl peptidase II involvement
J Immunol 183(3):1587-97

Schoen C, Unzicker C, Stuhler G, Elias J, **Einsele H**, Grigoleit GU, Abele-Horn M, Mielke S (2009)
Life-threatening infection caused by daptomycin-resistant Corynebacterium jeikeium in a neutropenic patient
J Clin Microbiol 47(7):2328-31

Gattenlöhner S, Stühmer T, Leich E, Reinhard M, Etschmann B, Völker HU, Rosenwald A, Serfling E, Bargou RC, Ertl G, **Einsele H**, Müller-Hermelink HK (2009)
Specific detection of CD56 (NCAM) isoforms for the identification of aggressive malignant neoplasms with progressive development
Am J Pathol 174(4):1160-71

Hummel HD, Kuntz G, Russell SJ, Nakamura T, Greiner A, **Einsele H**, Topp MS (2009)
Genetically engineered attenuated measles virus specifically infects and kills primary multiple myeloma cells
J Gen Virol 90(3):693-701

Knop S, Gerecke C, Liebisch P, Topp MS, Platzbecker U, Sezer O, Vollmuth C, Falk K, Glasmacher A, Maeder U, **Einsele H**, Bargou RC (2009)
Lenalidomide, adriamycin, and dexamethasone (RAD) in patients with relapsed and refractory multiple myeloma: a report from the German Myeloma Study Group DSMM (Deutsche Studiengruppe Multiples Myelom)
Blood 113(18):4137-43

Kapp M, Stevanović S, Fick K, Tan SM, Loeffler J, Opitz A, Tonn T, Stuhler G, **Einsele H**, Grigoleit GU (2009)
CD8+ T-cell responses to tumor-associated antigens correlate with superior relapse-free survival after allo-SCT
Bone Marrow Transplant 43(5):399-410

Gattenlöhner S, Etschmann B, Kunzmann V, Thalheimer A, Hack M, Kleber G, **Einsele H**, Germer C, Müller-Hermelink HK (2009)
Concordance of KRAS/BRAF Mutation Status in Metastatic Colorectal Cancer before and after Anti-EGFR Therapy
J Oncol 2009:831626

Loeffler J, Haddad Z, Bonin M, Romeike N, Mezger M, Schumacher U, Kapp M, Gebhardt F, Grigoleit GU, Stevanovic S, **Einsele H** , Hebart H (2009)
Interaction analyses of human monocytes co-cultured with different forms of Aspergillus fumigatus
J Med Microbiol 58(1):49-58

Reimer P, Rüdiger T, Geissinger E, Weissinger F, Nerl C, Schmitz N, Engert A, **Einsele H** , Müller-Hermelink HK, Wilhelm M (2009)
Autologous stem-cell transplantation as first-line therapy in peripheral T-cell lymphomas: results of a prospective multicenter study
J Clin Oncol 27(1):106-13

Gattenlohner S, Völker HU, Etschmann B, **Einsele H**, Müller-Hermelink HK (2009)
BCR-ABL positive chronic myeloid leukemia with concurrent JAK2(V617F) positive myelodysplastic syndrome/myeloproliferative neoplasm (RARS-T)
Am J Hematol 84(5):306-7

Kunzmann V, Kimmel B, Herrmann T, **Einsele H**, Wilhelm M (2009)
Inhibition of phosphoantigen-mediated gammadelta T-cell proliferation by CD4+ CD25+ FoxP3+ regulatory T cells
Immunology 126(2):256-67

3.6.2 Hartwig Klinker

Kasang C, Kalluvya S, Majinge C, Stich A, Bodem J, Kongola G, Jacobs GB, Mlewa M, Mildner M, Hensel I, Horn A, Preiser W, van Zyl G, **Klinker H**, Koutsilieri E, Rethwilm A, Scheller C, Weissbrich B (2011)
HIV drug resistance (HIVDR) in antiretroviral therapy-naïve patients in Tanzania not eligible for WHO threshold HIVDR survey is dramatically high
PLoS One 6(8):e23091

Heinz WJ, Zirkel J, Kuhn A, Schirmer D, Lenker U, Keller D, **Klinker H** (2011)
Relevance of timing for determination of posaconazole plasma concentrations
Antimicrob Agents Chemother 55(7):3621-3

Heinz WJ, Kahle K, Helle-Beyersdorf A, Schirmer D, Lenker U, Keller D,Langmann P, **Klinker H** (2011)
High-performance liquid chromatographic method for the determination of sorafenib in human serum and peritoneal fluid
Cancer Chemother Pharmacol 68(1):239-45

Wiegand J, Neumann K, Böhm S, Weich V, Teuber G, **Klinker H**, Möller B, Rasenack J, Hinrichsen H, Gerlach T, Spengler U, Buggisch P, Sarrazin C, Berg T (2011)
Importance of minimal residual viremia for relapse prediction in patients with chronic hepatitis C genotype 1 infection
Clin Infect Dis 53(11):1111-4

Pretorius E, **Klinker H**, Rosenkranz B (2011)
The role of therapeutic drug monitoring in the management of patients with human immunodeficiency virus infection
Ther Drug Monit 33(3):265-74 Review

Manns M, Zeuzem S, Sood A, Lurie Y, Cornberg M, **Klinker H**, Buggisch P, Rössle M, Hinrichsen H, Merican I, Ilan Y, Mauss S, Abu-Mouch S, Horban A, Müller TH, Welsch C, Chen R, Faruqi R, Pedicone LD, Wedemeyer H (2011)
Reduced dose and duration of peginterferon alfa-2b and weight-based ribavirin in patients with genotype 2 and 3 chronic hepatitis C
J Hepatol 55(3):554-63

Zirkel J, **Klinker H**, Kuhn A, Abele-Horn M, Tappe D, Turnwald D, Einsele H, Heinz WJ (2011)
Epidemiology of Candida blood stream infections in patients with hematological malignancies or solid tumors
Med Mycol 50(1):50-5

Wyen C, Hendra H, Siccardi M, Platten M, Jaeger H, Harrer T, Esser S, Bogner JR, Brockmeyer NH, Bieniek B, Rockstroh J, Hoffmann C, Stoehr A, Michalik C, Dlugay V, Jetter A, Knechten H, **Klinker H**, Skaletz-Rorowski A, Fätkenheuer G,
Egan D, Back DJ, Owen A (2011)
German Competence Network for HIV/AIDS Coordinators. Cytochrome P450 2B6 (CYP2B6) and constitutive androstane receptor (CAR) polymorphisms are associated with early discontinuation of efavirenz-containing regimens
J Antimicrob Chemother 66(9):2092-8

Sarrazin C, Schwendy S, Möller B, Dikopoulos N, Buggisch P, Encke J, Teuber G, Goeser T, Thimme R, **Klinker H**, Boecher WO, Schulte-Frohlinde E, Prinzing R, Herrmann E, Zeuzem S, Berg T (2011)
Improved responses to pegylated interferon alfa-2b and ribavirin by individualizing treatment for 24-72 weeks
Gastroenterology 141(5):1656-64

Weich V, Herrmann E, Chung TL, Sarrazin C, Hinrichsen H, Buggisch P, Gerlach T, **Klinker H**, Spengler U, Bergk A, Zeuzem S, Berg T (2011)
The determination of GGT is the most reliable predictor of nonresponsiveness to interferon-alpha based therapy in HCV type-1 infection
J Gastroenterol 46(12):1427-36

Vogel M, Ahlenstiel G, Hintsche B, Fenske S, Trein A, Lutz T, Schürmann D, Stephan C, Khaykin P, Bickel M, Mayr C, Baumgarten A, Buggisch P, **Klinker H**, John C, Gölz J, Staszewski S, Rockstroh JK (2010)
The influence of HAART on the efficacy and safety of pegylated interferon and ribavirin therapy fort he treatment of chronic HCV infection in HIV-positive individuals
Eur J Med Res 15:102-111

Kahle K, Langmann P, Schirmer D, Lenker U, Keller D, Helle A, **Klinker H**, Heinz WJ (2009)
Simultaneous determination of voriconazole and posaconazole concentrations in human plasma by high-performance liquid chromatography
Antimicrob Agents Chemother 53(7):3140-2

Mocroft A, Wyatt C, Szczech L, Neuhaus J, El-Sadr W, Tracy R, Kuller L, Shlipak M, Angus B, **Klinker H**, Ross M (2009)
INSIGHT SMART Study Group. Interruption of antiretroviral therapy is associated with increased plasma cystatin C.
AIDS 23:71-82

Kahle K, Langmann P, Schirmer D, Lenker U, Keller D, Helle A, **Klinker H**, Heinz WJ (2009)
Simultaneous determination of voriconazole and posaconazole concentrations in human plasma by high-performance liquid chromatography
Antimicrob Agents Chemother 53:3140-3142

Berg T, Weich V, Teuber G, **Klinker H**, Möller B, Rasenack J, Hinrichsen H, Gerlach T, Spengler U, Buggisch P, Balk H, Zankel M, Neumann K, Sarrazin C, Zeuzem S (2009)
Individualized treatment strategy according to early viral kinetics in hepatitis C virus type 1-infected patients
Hepatology 50(2):369-77

Leyh M, Zipperich S, Winzer R, Drechsel P, Bogner J, Trein A, Schneider L, **Klinker H**, Langmann P (2009)
Pharmacokinetics of lopinavir in the LPV/r-meltrex formulation compared to the LPV/r- soft gelatine capsule in HIV infected patients
Clinical Medicine: Therapeutics 1:697-702

3.6.3 Max Topp

Topp MS, Kufer P, Gökbuget N, Goebeler M, Klinger M, Neumann S, Horst HA, Raff T, Viardot A, Schmid M, Stelljes M, Schaich M, Degenhard E, Köhne-Volland R, Brüggemann M, Ottmann O, Pfeifer H, Burmeister T, Nagorsen D, Schmidt M, Lutterbuese R, Reinhardt C, Baeuerle PA, Kneba M, Einsele H, Riethmüller G, Hoelzer D, Zugmaier G, Bargou RC (2011)
Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival
J Clin Oncol 29(18):2493-8

Stuehler C, Khanna N, Bozza S, Zelante T, Moretti S, Kruhm M, Lurati S, Conrad B, Worschech E, Stevanović S, Krappmann S, Einsele H, Latgé JP, Loeffler J, Romani L, **Topp MS** (2011)
Cross-protective TH1 immunity against Aspergillus fumigatus and Candida albicans
Blood 117(22):5881-91

Letsch M, Spahn M, Beissert M, **Topp MS**, Gerharz EW, Riedmiller H (2010)
The worst case: giant exulcerating seminoma
Urol Int 84(1):113-5

Ok M, Latgé JP, Baeuerlein C, Ebel F, Mezger M, Topp M, Kurzai O, Killian D, Kapp M, Grigoleit GU, Sennefelder H, Arroyo J, Einsele H, Loeffler J (2009)
Immune responses of human immature dendritic cells can be modulated by the recombinant Aspergillus fumigatus antigen Aspf1
Clin Vaccine Immunol 16(10):1485-92

Stuehler C, Mielke S, Chatterjee M, Duell J, Lurati S, Rueckert F, Einsele H, Bargou RC, **Topp MS** (2009)
Selective depletion of alloreactive T cells by targeted therapy of heat shock protein 90: a novel strategy for control of graft-versus-host disease
Blood 114(13):2829-36

Diekmann J, Adamopoulou E, Beck O, Rauser G, Lurati S, Tenzer S, Einsele H, Rammensee HG, Schild H, **Topp MS** (2009)
Processing of two latent membrane protein 1 MHC class I epitopes requires tripeptidyl peptidase II involvement
J Immunol 183(3):1587-97

Hummel HD, Kuntz G, Russell SJ, Nakamura T, Greiner A, Einsele H, **Topp MS** (2009)
Genetically engineered attenuated measles virus specifically infects and kills primary multiple myeloma cells
J Gen Virol 2009 90(3):693-701

Knop S, Gerecke C, Liebisch P, **Topp MS**, Platzbecker U, Sezer O, Vollmuth C, Falk K, Glasmacher A, Maeder U, Einsele H, Bargou RC (2009)
Lenalidomide, adriamycin, and dexamethasone (RAD) in patients with relapsed and refractory multiple myeloma: a report from the German Myeloma Study Group DSMM (Deutsche Studiengruppe Multiples Myelom)
Blood 113(18):4137-43

4.1 Gerhard Bringmann

Bringmann G, Zhang G, Hager A, Moos M, Irmer A, Bargou R, Chatterjee M (2011)
Antitumoral activities of dioncoquinones B and C and related naphthoquinones gained from total synthesis or isolation from plants
Eur J Med Chem 46:5778-5789

Pimentel-Elardo SM, Buback V, Gulder TAM, Bugni TS, Reppart J, **Bringmann G**, Ireland CM, Schirmeister T, Hentschel U (2011)
New Tetromycin Derivatives with Anti-Trypanosomal and Protease Inhibitory Activities
Mar Drugs 9, 1682-1697

Loesgen S, Bruhn T, **Bringmann G**, Meindl K, Dix I, Schulz B, Zeeck A (2011)
(+)-Flavipucine, the Missing Member of the Pyridione Epoxide Family of Fungal Antibiotics
Eur J Org Chem 5:156–5162

Brückner C, Götz DC, Fox SP, Ryppa C, McCarthy JR, Bruhn T, Akhigbe J, Banerjee S, Daddario P, Daniell HW, Zeller M, Boyle RW, **Bringmann G** (2011)
Helimeric Porphyrinoids: Stereostructure and Chiral Resolution of meso-Tetraarylmorpholinochlorins
J Am Chem Soc 133:8740-8752

Cecil A, Rikanović C, Ohlsen K, Liang C, Bernhardt J, **Oelschlaeger TA**, Gulder T, **Bringmann G**, Holzgrabe U, Unger M, Dandekar T (2011)
Modelling antibiotic and cytotoxic effects of the dimeric isoquinoline IQ-143 on metabolism and its regulation in S. aureus, S. epidermidis and human cells
Genome Biol 12:R24

Goel A, Verma D, Pratap R, Taneja G, Hemberger Y, Knauer M, Raghunandan R, Maulik PR, Ram VJ, **Bringmann G** (2011)
Partially Reduced 8- Oxa[5]helicenes and [5]Helicenes – Synthesis, Structure, and Dynamics
Eur J Org Chem 2940-2947

Frank H, Campanella L, Dondi F, Leitner E, Mehlich J, Rossi G, Ndjoko K, **Bringmann G** (2011)
Ethics, Chemistry and Education for the Environment
Angew Chem 123:8632-8641; Angew Chem Int. Ed. 2011, 50:8445-8458

Bergner G, Albert C, Schilling M, **Bringmann G**, Schirmeister T, Dietzek B, Schlücker S, Popp J (2011)
Quantitative CARS microscopy and Raman microspectroscopy of

C-deuterated drugs
Analyst 136:3686-369

Kugelmann E, Albert CR, **Bringmann G**, Holzgrabe U (2011)
Fenton's oxidation: a tool for the investigation of potential drug metabolites
J Pharm Biomed Anal 54:1047-1058

Bringmann G, Gulder TAM, Gulder T (2011)
Asymmetric Synthesis of (M)- 2-Hydroxymethyl-1(2-Hydroxy-4,6-dimethylphenyl)naphthalene via a Configurationally Unstable Biaryl Lactone
Org Synth 88:70-78

Liu L, Bruhn T, Guo L, Götz DC, Brun R, Stich A, Che Y, **Bringmann G** (2011)
Chloropupukeanolides C–E, Cytotoxic Pupukeanane Chlorides with a Spiroketal Skeleton from Pestalotiopsis fici
Chem Eur J 17:2604-2613

Bringmann G, Wunderlich D (2011)
Sorbicillactone A – a Chemical Paper Chase
in **Inspired by Nature** - State and Perspektives of Natural Products Research in Germany (Eds. G. Bringmann, S. Grabley, J. Piel, D. Sell, T. Spellig, C Steinbach) DECHEMA e.V., Frankfurt; 36-43

Bringmann G, Goetz D, Bruhn T (2011)
The Online Stereoanalysis of Chiral Compounds by HPLC-ECD Coupling in Combination with Quantum-Chemical Calculations
in **Comprehensive Chiroptical Spectroscopy** (N. Berova, P. Polavarapu, K. Nakanishi, R.W. Woody, Eds.), Vol. 2, John Wiley & Sons pp 355-420

Finnigan EM, Rein R, Solladié N, Dahms K, Götz DCG, **Bringmann G**, Senge MO (2011)
Synthesis and ligand binding properties of triptycene-linked porphyrin arrays
Tetrahedron 67:1126-1134

Du L, Ai J, Li D, Zhu T, Wang Y, Knauer M, Bruhn T, Liu H, Geng M, Gu Q, **Bringmann G** (2011)
Aspergiolides C and D: Spirocyclic Aromatic Polyketides with Potent Protein Kinase c-Met Inhibitory Effects
Chem Eur J 17:1319-1326

Büchold C, Hemberger Y, Heindl C, Welker A, Degel B, Pfeuffer T, Staib P, Schneider S, Rosenthal PJ, Gut J, Morschhäuser J, **Bringmann G**, Schirmeister T (2011)
New cis-Configured Aziridine-2-carboxylates as Aspartic Acid Protease Inhibitors
Chem Med Chem 6:141-152

Bringmann G, Gulder T, Gulder TA, Breuning M (2011)
Atroposelective Total Synthesis of Axially Chiral Biaryl Natural Products
Chem Rev 111:563-639

Bringmann G, Hertlein-Amslinger B, Kajahn I, Dreyer M, Brun R, Moll H, Stich A, Ioset KN, Schmitz W, Ngoc LH (2011)
Phenolic analogs of the N,C-coupled naphthylisoquinoline alkaloid ancistrocladinium A, from Ancistrocladus cochinchinensis, (Ancistrocladaceae), with improved antiprotozoal activities
Phytochemistry 72:89-93

Gebhardt K, Meyer SW, Schinko J, **Bringmann G**, Zeeck A, Fiedler HP (2011)
Phenalinolactones A–D, novel terpenoglycoside antibiotics from Streptomyces sp. Tü 6071
J Antibiot 64:229-232

Schmidt CA, Murillo R, Bruhn T, **Bringmann G**, M. Goettert, B. Heinzmann, V. Brecht, S. Laufer, I. Merfort (2010)
Catechin Derivatives from Parapiptadenia rigida with in vitro Wound-Healing Properties
J Nat Prod 73:2035–2041

Bringmann G , M Lödige , A -K Müller , M Lewis , G Pradel , H Moll , U Schurigt , L Lehmann, R Brun (2010)
Hybridverbindungen aus 4- und 8-Aminochinolinen zur prophylaktischen und therapeutischen Behandlung von Malaria und anderen parasitären Erkrankungen
German Patent Application (DE), filed 14.10.0210

Bringmann G, G Lang, Bruhn T, K Schäffler, S Steffens, R Schmaljohann, J Wiese, JF Imhoff (2010)
Sorbifuranones A-C, Sorbicillinoid Metabolites From Penicillium Strains Isolated From Mediterranean Sponges
Tetrahedron 66:9894-9901

Bringmann G , Lödige M , Kronhardt A, Beitzinger C, Barth H , Benz R (2010)
Aminoquinolinium Salts
European Patent Application (DE), filed 29.09.2010

Jindaprasert A, S Samappito, K Springob, J Schmidt, T Gulder, W De-Eknamkul, **Bringmann G**, T M Kutchan (2010)
In Vitro Plants, Callus and Root Cultures of Plumbago indica and Their Biosynthetic Potential for Plumbagin
King Mongkut's Agro-Ind J 2:53-65

Fan G , Li Z, Zeng Y, Xu M, Deng Z, Bruhn T, Bruhn H, Morschhäuser J, **Bringmann G**, Lin W (2010)
Baculiferins A-O, O-Sulfated Pyrrole Alkaloids with anti-HIV-1 Activity, from the Chinese Marine Sponge Iotrochota baculifera;
Bioorg Med Chem 18:5466–5474

Bringmann G, S K Bischof, S Müller, T Gulder, C Winter, A Stich, H Moll, M Kaiser, R Brun, J Dreher, K Baumann (2010)
QSAR guided synthesis of simplified antiplasmodial analogs of naphthylisoquinoline alkaloids
Eur J Med Chem 45:5370-5383

Bringmann G, Gulder T, Hertlein B, Hemberger Y, Meyer F (2010)
Total Synthesis of the N,C-Coupled Naphthylisoquinoline Alkaloids Ancistrocladinium A and B, and Related Analogues
J Am Chem Soc 132:1151-1158

Hansjakob A, S Bischof, **Bringmann G**, M Riederer, U Hildebrand (2010)
Very-long chain aldehydes promote in vitro prepenetration processes of Blumeria graminis in a dose and chain-length dependent manner
New Phytologist 188:1039-1054

Xu M, Bruhn T, B Hertlein, R Brun, A Stich, J Wu, **Bringmann G** (2010)
Shuangancistrotectorines A-E, Dimeric Naphthylisoquinoline Alkaloids with Three Chiral Biaryl Axes, from the Chinese Plant Ancistrocladus tectorius
Chem Eur J 16:4206-4216

Meimberg H, H Rischer, F Turini, V Chamchumroon, M Dreyer, M Sommaro, **Bringmann G**, G Heubl (2010)
Evidence for species differentiation within the Ancistrocladus tectorius complex (Ancistrocladaceae) in Southeast Asia: A molecular approach
Plant Syst Evol 284:77-98

Heubl G, F Turini, V Mudogo, I Kajahn, **Bringmann G** (2010)
Ancistrocladus ileboensis (D R.Congo), a new liana with unique alkaloids
Pl Ecol Evol 143:63-69

Rembold R, S Poppinga, O Kriesten, A Irmer, H Rischer, **Bringmann G** (2010)
Triphyophyllum peltatum (Dioncophyllaceae) an Observations on its Carnivor
Carniv Pl Newslett 39:71-77

Hentschel U, **Bringmann G** (2010)
Marine Schwämme - Füllhorne der Meere
Pharmazie uns Zeit 39:62-66

Ponte-Sucre A, Gulder T, Gulder TA, Vollmers G, **Bringmann G**, Moll H (2010)
Alterations to the structure of Leishmania major induced by N-arylisoquinolines correlate with compound accumulation and disposition
J Med Microbiol 59: 69-75

Moldenhauer J , D C G Götz, C R Albert, S K Bischof, K Schneider, R D Süssmuth, M Engeser, H Gross, **Bringmann G**, J Piel (2010)
The Final Steps of Bacillaene Biosynthesis in Bacillus amyloliquefaciens FZB42: Direct Evidence for beta,gamma-Dehydration by a trans- AT Polyketide Synthase
Angew Chem 122:1507-1509

Götz DCG , Bruhn T, O Senge, **Bringmann G** (2009)
Synthesis and Stereochemical Characterization of Highly Unsymmetric ß,meso-Linked Porphyrin Arrays
J Org Chem 74:8005–8020

Bringmann G, A Irmer, D Feineis, Gulder TAM, HP Fiedler (2009)
Convergence in the Biosynthesis of Polyketide-Derived Natural Products from Plants, Fungi, and Bacteria
Phytochemistry 70:1776-1786

Speicher A, M Groh, J Zapp, A Schaumlöffel, M Knauer, **Bringmann G** (2009)
A Synthesis-Driven Structure Revision of „Plagiochin E", a Highly Bioactive Bisbibenzyls
Synlett 1852-1858

Bringmann G, K Maksimenka, Bruhn T, M Reichert, T Harada, R Kuroda (2009)
Quantum chemical CD calculations of dioncophylline A in the solid state
Tetrahedron 65:5720-5728

Trib F, E Asan, T Arzberger, T Tatschner, E Langenfeld, HE Meyer, **Bringmann G**, P Riederer, M Gerlach, K Markus (2009)
Identification of L-ferritin in neuromelanin granules of the human substantia nigra – a targeted proteomics approach
Mol Cell Proteomics 8:1832-1838

Bunzen J, Bruhn T, **Bringmann G**, A Lützen (2009)
Synthesis and Helicate Formation of a New Family of BINOL-Based Bis(bipyridine) Ligands
J Am Chem Soc 131:3621–3630

Bringmann G, Bruhn T, K Maksimenka, Y Hemberger (2009)
The Assignment of Absolute Stereostructures by Quantum Chemical Circular Dichroism Calculations
Eur J Org Chem 17:2717 - 2727

Ponte-Sucre A, Gulder T, Wegehaupt A, Albert C, Rikanović C, Schaeflein L, Frank A, Schultheis M, Unger M, Holzgrabe U, **Bringmann G**, Moll H (2009)
Structure- Activity Relationship and Studies on the Molecular Mechanism of Leishmanicidal N,C-Coupled Arylisoquinolinium Salts
J Med Chem 52:626-636

Balaban TS, AD Bhise, **Bringmann G**, J Bürck, C Chappaz-Gillot, A Eichhöfer, D Fenske, D Götz, M Knauer, T Mizoguchi, D Mössinger, M Reichert, H Roesner, C Roussel, M Schraut, H Tamiaki, N Vanthuyne (2009)
Mimics of the self-assembling chlorosomal bacteriochlorophylls: Regio- and stereoselective synthesis and stereoanalysis of acyl-(1-hydroxyalkyl)porphyrins;
J Am Chem Soc131:14480–14492

Bringmann G, Gulder TA, Hamm A, Goodfellow M, Fiedler HP (2009)
Multiple convergence in polyketide biosynthesis: a third folding mode to the anthraquinone chrysophanol, involving a bicyclic diketone
Chem Commun 6810-6812

Yunt Z , K Reinhardt, A Li, M Engeser, H -M Dahse, M Gütschow, Bruhn T, **Bringmann G**, J Piel (2009)
Cleavage of Four Carbon-Carbon Bonds during Biosynthesis of the Griseorhodin A Spiroketal Pharmacophore
J Am ChemSoc 131: 2297-2305

4.2 Thomas Dandekar

Siegl A, Kamke J, Hochmuth T, Piel J, Richter M, Liang C, **Dandekar T**, Hentschel U (2011)
Single-cell genomics reveals the lifestyle of Poribacteria, a candidate phylum symbiotically associated with marine sponges
ISME Journal 5(1):61-70

Cecil A, Rikanovic C, Ohlsen K, Liang C, Bernhardt J, Oelschlaeger TA, Gulder T, Bringmann G, Holzgrabe U, Unger M, **Dandekar T** (2011)
Modeling antibiotic and cytotoxic effects of the dimeric isoquinoline IQ-143 on metabolism and its regulation in Staphylococcus aureus, Staphylococcus epidermidis and human cells
Genome Biol 12(3):R24

Liebeke M, Dörries K, Zühlke D, Bernhardt J, Fuchs S, Pané-Farré J, Engelmann S, Völker U, Bode R, **Dandekar T**, Lindequist U, Hecker M, Lalk M (2011)

A metabolomics and proteomics study of the adaptation of Staphylococcus aureus to glucose starvation.
Mol Biosyst 7(4):1241-53

Fuchs S, Mehlan H, Kusch H, Teumer A, Zühlke D, Berth M, Wolf C, **Dandekar T**, Hecker M, Engelmann S, Bernhardt J (2010)
Protecs, a comprehensive and powerful storage and analysis system for OMICS data, applied for profiling the anaerobiosis response of Staphylococcus aureus COL
Proteomics 10(16):2982-3000

Siegl A, Kamke J, Hochmuth T, Piel J, Richter M, Liang C, **Dandekar T**, Hentschel U (2011)
Single-cell genomics reveals the lifestyle of Poribacteria, a candidate phylum symbiotically associated with marine sponges
ISME J 5(1):61-70

Cecil A, Rikanovic C, Ohlsen K, Liang C, Bernhardt J, Oelschlaeger TA, Gulder T, Bringmann G, Holzgrabe U, Unger M, **Dandekar T** (2011)
Modeling antibiotic and cytotoxic effects of the dimeric isoquinoline IQ-143 on metabolism and its regulation in Staphylococcus aureus, Staphylococcus epidermidis and human cells
Genome Biol 21;12(3):R24

Liebeke M, Dörries K, Zühlke D, Bernhardt J, Fuchs S, Pané-Farré J, Engelmann S, Völker U, Bode R, **Dandekar T**, Lindequist U, Hecker M, Lalk M (2011)
A metabolomics and proteomics study of the adaptation of Staphylococcus aureus to glucose starvation
Mol Biosyst 7(4):1241-53

Wangorsch G, Butt E, Mark R, Hubertus K, Geiger J, **Dandekar T**, Dittrich M (2011)
Time-resolved in silico modeling of fine-tuned cAMP signaling in platelets: feedback loops, titrated phosphorylations and pharmacological modulation
BMC Syst Biol 5:178

Liang C, Liebeke M, Schwarz R, Zühlke D, Fuchs S, Menschner L, Engelmann S, Wolz C, Jaglitz S, Bernhardt J, Hecker M, Lalk M, **Dandekar T** (2011)
Staphylococcus aureus physiological growth limitations: insights from flux calculations built on proteomics and external metabolite data
Proteomics 11(10):1915-35

Ratzka C, Liang C, **Dandekar T**, Gross R, Feldhaar H (2011)
Immune response of the ant Camponotus floridanus against pathogens and its obligate mutualistic endosymbiont
Insect Biochem Mol Biol 41(8):529-36

Cecil A, Rikanović C, Ohlsen K, Liang C, Bernhardt J, Oelschlaeger TA, Gulder T, Bringmann G, Holzgrabe U, Unger M, **Dandekar T** (2011)
Modeling antibiotic and cytotoxic effects of the dimeric isoquinoline IQ-143 on metabolism and its regulation in Staphylococcus aureus, Staphylococcus epidermidis and human cells
Genome Biol 12(3):R24

Agarwal S, Kern S, Halbert J, Przyborski JM, Baumeister S, **Dandekar T**, Doerig C, Pradel G (2011)
Two nucleus-localized CDK-like kinases with crucial roles for malaria parasite erythrocytic replication are involved in phosphorylation of splicing factor
J Cell Biochem 112(5):1295-310

Shityakov S, **Dandekar T** (2010)
Lead expansion and virtual screening of Indinavir derivate HIV-1 protease inhibitors using pharmacophoric - shape similarity scoring function
Bioinformation 4(7):295-9

Friedrich T, Rahmann S, Weigel W, Rabsch W, Fruth A, Ron E, Gunzer F, **Dandekar T**, Hacker J, Müller T, Dobrindt U (2010)
High-throughput microarray technology in diagnostics of enterobacteria based on genome-wide probe selection and regression analysis
BMC Genomics 11:591

Dandekar T, Dandekar G (2010)
Pharmacogenomic strategies against microbial resistance: from bright to bleak to innovative
Pharmacogenomics 11(9):1193-6

Siegl A, Kamke J, Hochmuth T, Piel J, Richter M, Liang C, **Dandekar T**, Hentschel U (2010)
Single-cell genomics reveals the lifestyle of Poribacteria, a candidate phylum symbiotically associated with marine sponges
ISME J 5(1):61-70

Beisser D, Klau GW, **Dandekar T**, Müller T, Dittrich MT (2010)
BioNet: an R-Package for the functional analysis of biological networks
Bioinformatics 26(8):1129-30

Dittrich M, Strassberger V, Fackler M, Tas P, Lewandrowski U, Sickmann A, Walter U, **Dandekar T**, Birschmann I (2010)
Characterization of a novel interaction between vasodilator-stimulated phosphoprotein and Abelson interactor 1 in human platelets: a concerted computational and experimental approach
Arterioscler Thromb Vasc Biol 30(4):843-50

Shityakov S, Rethwilm A, **Dandekar T** (2010)
Structural and docking analysis of HIV-1 integrase and Transportin-SR2 interaction: Is this a more general and specific route for retroviral nuclear import and its regulation?
Online Journal of Bioinformatics Volume 11 (1):19-33

Dandekar T, Xiao K (2010)
New bioinformaic strategies against apicomplexan parasites
In: Katja Becker (Ed.), Apicomplexan Parasites: Molecular Approaches toward Targeted Drug Development. Wiley-VCH, Weinheim pp 21-33

Keller A, Forster F, Muller T, **Dandekar T**, Schultz J, Wolf M. Including RNA (2010)
Secondary Structures improves Accuracy and Robustness in Reconstruction of Phylogenetic Trees
Biology Direct 5(1):4

Eisenreich W, **Dandekar T**, Heesemann J, Goebel W (2010)
Carbon metabolism of intracellular bacterial pathogens and possible links to virulence
Nature Reviews Microbiology 8:401-412

Fuchs S, Mehlan H, Kusch H, Teumer A, Zühlke D, Berth M, Wolf C, **Dandekar T**, Hecker M, Engelmann S, Bernhardt J (2010)
Protecs, a comprehensive and powerful storage and analysis system for OMICS data, applied for profiling the anaerobiosis response of Staphylococcus aureus COL
Proteomics 10(16):2982-3000

Keller, A., Wolf, M., **Dandekar T** (2010)
Ribosomal RNA phylogenetics: the third dimension
Biologia 65:388-389

Schauer K, Geginat G, Liang C, Goebel W, **Dandekar T**, Fuchs TM (2010)
Deciphering the intracellular metabolism of Listeria monocytogenes by mutant screening and modelling. BMC
Genomics 18:11:573

Liang C, Wolz C, Herbert S, Bernhardt J, Engelmann S, Hecker M, Götz F, **Dandekar T** (2009)
GENOVA: A rapid genome vizualization and functional genomics software applied to strain comparisons in Staphylococcus aureus
OJB - Online Journal of Bioinformatics 10: 201-217

Zhang Q, Liang C, Yu YA, Chen N, **Dandekar T***, Szalay A A* (2009)
*corresponding authors
The highly attenuated oncolytic recombinant vaccinia virus GLV-1h68: Comparative genomic features and the contribution of F14.5L inactivation
Molecular Genetics and Genomics 282:417-435

Schwarz R, Seibel PN, Rahmann S, Schoen C, Huenerberg M, Müller-Reible C, **Dandekar T**, Karchin R, Schultz J, Müller T (2009)
Detecting species-site dependencies in large multiple sequence alignments
Nucleic Acids Res 37(18):5959-68

Keller A, Förster F, Müller T, **Dandekar T**, Schultz J, Wolf M (2009)
Including RNA secondary structures improves accuracy and robustness in reconstruction of phylogenetic trees
Biol Direct 5:4

Liang C, Schmid A, López-Sánchez MJ, Moya A, Gross R, Bernhardt J, **Dandekar T** (2009)
JANE: efficient mapping of prokaryotic ESTs and variable length sequence reads on related template genomes
BMC Bioinformatics 10:391

Förster F, Liang C, Shkumatov A, Beisser D, Engelmann JC, Schnölzer M, Frohme M, Müller T, Schill RO, **Dandekar T** (2009)
Tardigrade workbench: comparing stress-related proteins, sequence-similar and functional protein clusters as well as RNA elements in tardigrades
BMC Genomics 10:469

Philippi N, Walter D, Schlatter R, Ferreira K, Ederer M, Sawodny O, Timmer J,
Borner C, **Dandekar T** (2009)
Modeling system states in liver cells: survival, apoptosis and their modifications in response to viral infection
BMC Syst Biol 3:97

Xiao K, Jehle F, Peters C, Reinheckel T, Schirmer RH, **Dandekar T** (2009)
CA/C1 peptidases of the malaria parasites Plasmodium falciparum and P. berghei and their mammalian hosts--a bioinformatical analysis
Biol Chem 390(11):1185-97

Krüger B, **Dandekar T** (2009)
Bioinformatical approaches to detect and analyze protein interactions
Methods Mol Biol 564:401-31

Engelmann JC, Rahmann S, Wolf M, Schultz J, Fritzilas E, Kneitz S, **Dandekar T**, Müller T (2009)
Modelling cross-hybridization on phylogenetic DNA microarrays increases the detection power of closely related species
Mol Ecol Resour 9(1):83-93

Keller A, Schleicher T, Schultz J, Müller T, **Dandekar T**, Wolf M (2009)
5.8S-28S rRNA interaction and HMM-based ITS2 annotation
Gene 430(1-2):50-7

4.3 Markus Engstler

Subota I, Rotureau B, Blisnick T, Ngwabyt S, Durand-Dubief M, **Engstler M**, Bastin P (2011)
ALBA proteins are stage regulated during trypanosome development in the tsetse fly and participate in differentiation
Mol Biol Cell 22(22):4205-19

Uppaluri S, Nagler J, Stellamanns E, Heddergott N, Herminghaus S, **Engstler M**, Pfohl T (2011)
Impact of microscopic motility on the swimming behavior of parasites: straighter trypanosomes are more directional
PLoS Comput Biol 7(6):e1002058

Zaburdaev V, Uppaluri S, Pfohl T, **Engstler M**, Friedrich R, Stark H (2011)
Langevin dynamics deciphers the motility pattern of swimming parasites
Phys Rev Lett 106(20):208103

Jaé N, Preusser C, Krüger T, Tkacz ID, **Engstler M**, Michaeli S, Bindereif A (2011)
snRNA-specific role of SMN in trypanosome snRNP biogenesis in vivo
RNA Biol 8(1):90-100

Schwede A, Jones N, **Engstler M**, Carrington M (2011)
The VSG C-terminal domain is inaccessible to antibodies on live trypanosomes
Mol Biochem Parasitol 175(2):201-4

Benz C, **Engstler M**, Hillmer S, Clayton C (2010)
Depletion of 14-3-3 proteins in bloodstream-form Trypanosoma brucei inhibits variant surface glycoprotein recycling
Int J Parasitol 40(5):629-34

Field MC, Lumb JH, Adung'a VO, Jones NG, **Engstler M** (2009)
Macromolecular trafficking and immune evasion in african trypanosomes
Int Rev Cell Mol Biol 278:1-67

4.4 Ute Hentschel Humeida

Pimentel-Elardo SM, Buback V, Gulder TAM, Bugni T, Reppart J, Bringmann G, Ireland C, Schirmeister T, **Hentschel U** (2011)
New tetromycin derivatives with anti-trypanosomal and protease inhibitory activities
Mar Drugs 9(10):1682-1697

Schmitt S, **Hentschel U**, Taylor MW (2011)
Deep sequencing reveals diversity and community structure of complex microbiota in five Mediterranean sponges
Hydrobiologia DOI 10.1007/s10750-011-0799-9

Taylor MW, Hill R, **Hentschel U** (2011)
Meeting Report: 1st International Symposium on Sponge Microbiology
Mar Biotechnol 13(6):1057-1061

Tabares P, Pimentel-Elardo SM, Schirmeister T, Hünig T, **Hentschel U** (2011)
Anti-protease and immunomodulatory activities of bacteria associated with Caribbean sponges
Mar Biotechnol 13(5):883-892

Abdelmohsen UR, Ali W, Eom SH, **Hentschel U**, *Roitsch T (2011) Synthesis of distinctly different sets of antimicrobial activities by elicited plant cell suspension cultures*
Plant Cell Tissue and Organ Cult 106:105-113

Angermeier H, Kamke J, Abdelmohsen UR, Krohne G, Pawlik JR, Lindquist NL, **Hentschel U** (2011)
The pathology of sponge orange band disease affecting the Caribbean barrel sponge Xestospongia muta
FEMS Microb Ecol 75(2):218-230

Hochmuth T, Niederkrüger H, Gernert C, Siegl A, Taudien S, Platzer M, Crews P, **Hentschel U**, Piel J (2010)
Linking chemical and microbial diversity in marine sponges: possible role for Poribacteria as producers of methyl-branched fatty acids
Chembiochem 11(18):2572-2578

Siegl A, Kamke J, Hochmuth T, Piel J, Richter M, Liang C, Dandekar T, **Hentschel U** (2010)
Single cell genomics reveals the lifestyle of Poribacteria, a candidate phylum symbiotically associated with marine sponges
ISME J 5(1): 61-70

Siegl A, **Hentschel U** (2010)
PKS and NRPS gene clusters from microbial symbiont cells of marine sponges by whole genome amplification
Environ Microbiol Rep 2: 507-513

Abdelmohsen UR, Pimentel-Elardo SM, Hanora A, Radwan M, Abou-El-Ela SH, Ahmed S, **Hentschel U** (2010)
Isolation, phylogenetic analysis and anti-infective activity screening of marine sponge-associated actinomycetes
Mar Drugs 8: 399-412

Pimentel-Elardo SM, Kozytska S, Bugni TS, Ireland CM, Moll H, **Hentschel U** (2010)
Anti-parasitic compounds from Streptomyces sp. strains isolated from mediterranean sponges
Mar Drugs 8: 373-380

Hertiani T, Edrada-Ebel R, Ortlepp S, van Soest RW, de Voogd NJ, Wray V, **Hentschel U**, Kozytska S, Müller WE, Proksch P (2010)
From anti-fouling to biofilm inhibition: new cytotoxic secondary metabolites from two Indonesian Agelas sponges
Bioorg Med Chem 18 (3):1297-1311

Hentschel U, Bringmann G (2010)
Marine Schwämme: Füllhorne der Meere
Pharmazie unserer Zeit 39(1): 62-66

Seemann P, Gernert C, Schmitt S, Mebs D, **Hentschel U** (2009)
Detection of hemolytic bacteria from Palythoa caribaeorum (Cnidaria, Zoantharia) using a novel palytoxin-screening assay
Antonie Van Leeuwenhoek 96(4):405-411

Lafi FF, Fuerst JA, Fieseler L, **Hentschel U** (2009)
Widespread distribution of poribacteria in Demospongiae
Appl Environ Microbiol 75(17):5695-5699

Pimentel-Elardo SM, Scheuermayer S, Kozitska S, **Hentschel U** (2009)
Streptomyces axinellae sp. nov., a novel actinomycete isolated from the Mediterranean sponge Axinella polypoides (Porifera)
Int J Syst Evol Microbiol 59:1433-1437

4.5 Caroline Kisker

Kuper J, Wolski SC, Michels G, **Kisker C** (2011)
Functional and structural studies of the nucleotide excision repair helicase XPD suggest a polarity for DNA translocation
EMBO J 31(2):494-502

Schaefer B, **Kisker C**, Sotriffer CA (2011)
Molecular dynamics of Mycobacterium tuberculosis KasA: implications for inhibitor and substrate binding and consequences for drug design
J Comput Aided Mol Des 25(11):1053-69

Lee W, Luckner SR, **Kisker C**, Tonge PJ, Engels B (2011)
Elucidation of the protonation states of the catalytic residues in mtKasA: implications for inhibitor design
Biochemistry 50(25):5743-56

Fronczek DN, Quammen C, Wang H, **Kisker C**, Superfine R, Taylor R, Erie DA, Tessmer I (2011)
High accuracy FIONA-AFM hybrid imaging
Ultramicroscopy 111(5):350-5

Wolski SC, Kuper J, **Kisker C** (2010)
The XPD helicase: XPanDing archaeal XPD structures to get a grip on human DNA repair
Biol Chem 391(7):761-5

Luckner SR, Liu N, am Ende CW, Tonge PJ, **Kisker C** (2010)
A slow, tight binding inhibitor of InhA, the enoyl-acyl carrier protein reductase from Mycobacterium tuberculosis
J Biol Chem 285(19):14330-7

Breuning A, Degel B, Schulz F, Büchold C, Stempka M, Machon U, Heppner S, Gelhaus C, Leippe M, Leyh M, **Kisker C**, Rath J, Stich A, Gut J, Rosenthal PJ, Schmuck C, Schirmeister T (2010)
Michael acceptor based antiplasmodial and antitrypanosomal cysteine protease inhibitors with unusual amino acids
J Med Chem 53(5):1951-63

Roth HM, Tessmer I, Van Houten B, **Kisker C** (2009)
Bax1 is a novel endonuclease: implications for archaeal nucleotide excision repair
J Biol Chem 284(47):32272-8

Luckner SR, Machutta CA, Tonge PJ, **Kisker C** (2009)
Crystal structures of Mycobacterium tuberculosis KasA show mode of action within cell wall biosynthesis and its inhibition by thiolactomycin
Structure 17(7):1004-13

Dietzel U, Kuper J, Doebbler JA, Schulte A, Truglio JJ, Leimkühler S, **Kisker C** (2009)
Mechanism of Substrate and Inhibitor Binding of Rhodobacter capsulatus Xanthine Dehydrogenase
J Biol Chem 284(13):8768-76

4.6 Heike Walles (Mertsching)

Heine J, Schmiedl A, Cebotari S, Karck M, **Mertsching H**, Haverich A, Kallenbach K (2011)
Tissue engineering human small-caliber autologous vessels using a xenogenous decellularized connective tissue matrix approach: preclinical comparative biomechanical studies
Artifi Organs 35(10):930-940

Pusch J, Votteler M, Göhler S, Engl J, Hampel M, **Walles H**, Schenke-Layland K (2011)
The physiological performance of a three-dimensional model that mimics the microenvironment of the small intestine
Biomaterials 32(30):7469-78

Pudlas M, Koch S, Bolwien C, Thude S, Jenne N, Hirth T, **Walles H**, Schenke-Layland K (2011)
Raman Spectroscopy: A Noninvasive Analysis Tool For The Discrimination of Human Skin Cells
Tissue Eng Part C Methods 17(10):1027-1040

Schanz J, Pusch J, Hansmann J, **Walles H** (2010)
Vascularised human tissue models: A new approach for the refinement of biomedical research
J Biotechnol 1;148(1):56-63

Kluger PJ, Wyrwa R, Weisser J, Maierle J, Votteler M, Rode C, Schnabelrauch M, **Walles H**, Schenke-Layland K (2010)
Electrospun poly(D/L-lactide-co-L-lactide) hybrid matrix: a novel scaffold material for soft tissue engineering
J Mater Sci Mater Med 21(9):2665-71

Pudlas M, Koch S, Bolwien C, **Walles H** (2010)
Raman spectroscopy as a tool for quality and sterility analysis for tissue engineering applications like cartilage transplants
Int J Artif Organs 33(4):228-37

Frühauf JH, **Mertsching H**, Giri S, Frühauf NR, Bader A (2009)
Porcine endogenous retrovirus released by a bioartificial liver infects primary human cells
Liver Int 29(10):1553-61

Kallenbach K, Sorrentino S, **Mertsching H**, Kostin S, Pethig K, Haverich Md A, Cebotari S (2009)
A Novel Small Animal Model for Accelerated Investigation of Tissue Engineered Aortic Valved Conduits
Tissue Eng Part C Methods 16(1):41-50

Mertsching H, Walles T (2009)
Europe's advanced therapy medicinal products: chances and challenges
Expert Rev Med Devices 6(2):109-10

Mertsching H, Schanz J, Steger V, Schandar M, Schenk M, Hansmann J, Dally I, Friedel G, Walles T. (2009)
Generation and transplantation of an autologous vascularized bioartificial human tissue
Transplantation. 27;88(2):203-10

Schanz J, Hampel M, **Mertsching H**, *Walles T (2009) Experimental tracheal patching using extracellular matrix scaffolds*
Ann Thorac Surg 87(4):1321-2

Mertsching H, Hansmann J (2009)
Bioreactor technology in cardiovascular tissue engineering
Adv Biochem Eng Biotechnol 112:29-37

4.7 August Stich

Kasang C, Kalluvya S, Majinge C, **Stich A**, Bodem J, Kongola G, Jacobs GB, Mlewa M, Mildner M, Hensel I, Hom A, Preiser W, van Zyl G, Klinker H, Koutsilieri E, Rethwilm A, Scheller C, Weissbrich B (2011)
HIV drug resistance (HIVDR) in antiretroviral therapy-naïve patients in Tanzania not eligible for WHO threshold HIVDR survey is dramatically high
PLoS One 6(8):e23091

Rogoll D, Schauber J, Mheta KK, **Stich A**, Scheppach W (2011)
Differential cathelicidin expression in duodenal and gastric biopsies from Tanzanian and German patients
PLoS One *2011;6(7):e22049*

Tappe D, Schulze MH, van der Linden M, Ziegler U, Müller A, **Stich A** (2011)
Travel-related Streptococcal toxic shock syndrome caused by emm type 78 Streptococcus pyogenes
J Clin Microbiol 49(8):3094-5

Schulze MH, Keller C, Müller A, Ziegler U, Langen HJ, Hegasy G, **Stich A** (2011)
Rickettsia typhi infection with interstitial pneumonia in a traveler treated with moxifloxacin.
J Clin Microbiol 49(2):741-3

Bringmann G, Hertlein-Amslinger B, Kajahn I, Dreyer M, Brun R, Moll H, **Stich A**, Ioset KN, Schmitz W, Ngoc LH (2011)
Phenolic analogs of the N,C-coupled naphthylisoquinoline alkaloid ancistrocladinium A, from Ancistrocladus cochinchinensis (Ancistrocladaceae), with improved antiprotozoal activities
Phytochemistry 72(1):89-93

6 Appendix
6.3 Publications

Tappe D, Schulze MH, Oesterlein A, Turnwald D, Müller A, Vogel U, **Stich A** (2010)
Panton-Valentine leukocidin-positive Staphylococcus aureus infections in returning travelers
Am J Trop Med Hyg 83(4):748-50

Bringmann G, Bischof SK, Müller S, Gulder T, Winter C, **Stich A**, Moll H, Kaiser M, Brun R, Dreher J, Baumann K (2010)
QSAR guided synthesis of simplified antiplasmodial analogs of naphthylisoquinoline alkaloids
Eur J Med Chem 45(11):5370-83

Waag T, Gelhaus C, Rath J, **Stich A**, Leippe M, Schirmeister T (2010)
Allicin and derivates are cysteine protease inhibitors with antiparasitic activity
Bioorg Med Chem Lett 15;20(18):5541-3

Tappe D, Schmidt-Chanasit J, Günther S, Schulze MH, **Stich A** (2010)
Chikungunya and dengue virus antibodies in a traveller with severe arthralgia returning from
India J Clin Virol 49(3):148-50

Tappe D, Schulze MH, Ziegler U, Müller A, **Stich A** (2010)
Maculo-papular exanthema after travel to Hong Kong
J Travel Med 17(3):215-6

Xu M, Bruhn T, Hertlein B, Brun R, **Stich A**, Wu J, Bringmann G (2010)
Shuangancistrotectorines A-E, dimeric naphthylisoquinoline alkaloids with three chiral biaryl axes from the Chinese plant Ancistrocladus tectorius
Chemistry 12;16(14):4206-16

Tappe D, Müller A, Ziegler U, Weissbrich B, Schubert J, Günther S, Schmidt-Chanasit J, **Stich A** (2010)
Positive hepatitis E and Epstein Barr virus serology in a patient with jaundice after travel
J Clin Virol 48(2):78-81

Breuning A, Degel B, Schulz F, Büchold C, Stempka M, Machon U, Heppner S, Gelhaus C, Leippe M, Leyh M, Kisker C, Rath J, **Stich A**, Gut J, Rosenthal PJ, Schmuck C, Schirmeister T (2010)
Michael acceptor based antiplasmodial and antitrypanosomal cysteine protease inhibitors with unusual amino acids
J Med Chem 11;53(5):1951-63

Tappe D, Müller A, **Stich A** (2010)
Resolution of cutaneous old world and new world leishmaniasis after oral miltefosine treatment
Am J Trop Med Hyg 82(1):1-3

Stich A (2010)
Staying healthy during travel is more than happiness. Travel pharmacy for the tropics
Pharm Unserer Zeit 39(1):68-71. Review. German.

Stich A, Gottschalk R (2010)
Are we prepared? Highly contagious diseases
Pharm Unserer Zeit 39(1):12-6. Review. German

Stich A (2009)
The most important tropical infectious disease. Malaria
Pharm Unserer Zeit 38(6):508-11. Review. German

Stich A (2009)
African sleeping sickness. An ancient threat returns
Pharm Unserer Zeit 38(6):546-50. Review. German

Tappe D, Dobler G, **Stich A** (2009)
Tache noire in African tick bite fever.
Am J Trop Med Hyg 81(5):733-4

Tappe D, Schmidt-Chanasit J, Ries A, Ziegler U, Müller A, **Stich A** (2009)
Ross River virus infection in a traveller returning from northern Australia
Med Microbiol Immunol 198(4):271-3

Tappe D, Müller A, Frosch M, **Stich A** (2009)
Limitations of amphotericin B and nitazoxanide in the treatment of alveolar echinococcosis
Ann Trop Med Parasitol 103(2):177-81

Images:

2.3 Figure1; provided by Volker Bringmann, Max-Planck Institute for Infection Biology

2.5 Figure 1: Courtesty of Thierry Blisnick, Phillippe Bstin laboratory, Institut Pastuer, Paris

3.1.2 Figure1: published in: Schnitzer et al. (2010), Vaccine 28:5785-5793

3.1.2 Figure 2: published in: Ponte-Sucre et al. (2010) J Med Microbiol 59:69-75

3.1.6 Figure1: published in: Eulalio et al. (2011) PLoS One 6(3): e17269

Impressum:

Herausgeber:
Zentrum für Infektionsforschung
Josef-Schneider-Straße 2/D15
97080 Würzburg
http://www.zinf.uni-wuerzburg.de

Redaktion:
Jörg Vogel
Stan Gorski
Hilde Merkert

Layout und Druck:
Schimmel Satz & Graphik GmbH
Im Kreuz 9
97076 Würzburg

Cover photo:
False-colored scanning electron microscopy image of innate immune cells and the parasite *Trypanosoma brucei* in an infected mouse liver. Image: Gilles Vanwalleghem, Daniel Monteyne, Etienne Pays, and David Pérez-Morga, Laboratory of Molecular Parasitology and Center for Microscopy and Molecular Imaging, Université Libre de Bruxelles, Gosselies, Belgium

ZINF - Research Center
for Infectious Diseases

Josef-Schneider-Straße 2/D15 · 97080 Würzburg
http://www.zinf.uni-wuerzburg.de